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Concise Textbook of PHYSIOLOGY

THIRD EDITION

Indu Khurana
Arushi Khurana

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Concise Textbook of Physiology

Concise Textbook of Physiology

Third Edition

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Registered Office: 818, Indraprakash Building, 8th Floor, 21, Barakhamba Road, New Delhi-110001
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Concise Textbook of Physiology, Third Edition, Indu Khurana and Arushi Khurana

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ISBN: 978-81-312-5299-4
e-ISBN: 978-81-312-5300-7

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First Printed in India 2018, Reprinted 2019

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Typeset by GW Tech India

Printed and bound in India at EIH Limited – Unit Printing Press, IMT Manesar, Gurgaon (Haryana).

To

My parents and teachers for their blessings

PREFACE

A sound knowledge of human physiology is most essential for all medical and health profession practices. Now in this third edition this book is aptly named *Concise Textbook of Physiology* and an effort has been made to provide the essential text in a thorough, yet concise manner. This book fulfills the needs of dental, nursing, and physiotherapy students. Its conciseness makes it the preferred book for students of alternative medical sciences (Ayurveda, Homeopathy, etc.) and allied health sciences. This book will also be very useful for students pursuing Masters in Physiology. Care has been taken to update the book as per syllabi prescribed by the health universities across the country.

In this text core and applied aspects of human physiology have been skillfully intermingled for students to apply their learning in clinical situations. The text has been organized systematically into eleven sections. Each section has been subdivided into various chapters.

Salient features of this book

- A brief overview given in each section highlighting the topics covered.
- Chapter outline given in the beginning of each chapter provides the clear layout of the text included.
- Relevant functional anatomy included in each chapter will be quite useful in conceptualizing the subject.
- Various levels of headings, subheadings, boldface and italics given in the text makes the easy understanding of the subject.
- Plenty of clear line diagrams, tables and flow charts provide vivid and lucid details and are thus useful for assimilation and quick revision of the subject.
- In order to emphasize the clinical significance of physiology, the relevant applied aspects have been covered adequately in each chapter and highlighted separately.
- Additional important information has been highlighted in the form of 'Important Notes'.
- For 'Self-assessment', the frequently asked questions during examinations, are given at the end of each chapter.

It is hoped that the book will be helpful in providing in depth understanding of the subject and thus will be useful in laying a strong foundation. Sincere efforts have been made to verify the correctness of the text, however, in spite of best efforts some inaccuracies, ambiguities and typographical mistakes are likely to be noticed by the readers. Therefore, feedback and suggestions from the teachers and students are invited for improving the future edition. Feedbacks received will be highly appreciated and duly acknowledged.

Indu Khurana
Arushi Khurana

ACKNOWLEDGEMENTS

Third edition of *Concise Textbook of Physiology* has been possible as a result of active criticism, suggestions, feedback and generous help of many faculty members and students. Surely, I owe sincere thanks to them all. Having Dr. Arushi Khurana, MD, former chief resident, Department of Internal Medicine, University of Connecticut, USA and Fellow, Hematology–Oncology, Massey Cancer Center, Virginia Commonwealth University, Richmond, VA, USA, as a co-author has been very useful in updating the text, especially the applied aspects. I bow with reverence to my teachers for grooming me for this task. I wish to express indebtedness to my husband, Dr. AK. Khurana, Sr. Professor Regional Institute of Ophthalmology, PGIMS, Rohtak; my son, Aruj K Khurana, Vitreoretinal Surgeon, NEI, Rishikesh; daughter-in-law Dr. Bhawna Piplani Khurana, Oculoplastic Surgeon, NEI Rishikesh; and Son-in-law Dr. Gurukripa Kowlgi, MD Internal Medicine, University of Connecticut, USA and Fellow, Cardiovascular Diseases Pauley Heart Center, Virginia Commonwealth University Richmond, VA.

I am highly thankful to Dr. (Mrs.) Ritu Singh, Trustee; and Dr. Narender Singh, Chairman World College of Medical Sciences and Research, Jhajjar, Haryana for encouragement and infusing academic atmosphere.

It's my special pleasure to acknowledge with gratitude the most assured co-operation and skill received from the staff of RELX India Pvt. Ltd., especially Nimisha Goswami (Manager–Content Strategy), Shabina Nasim (Head of Content Project Management), and Goldy Bhatnagar (Content Project Manager).

Indu Khurana

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SECTION 1

General Physiology

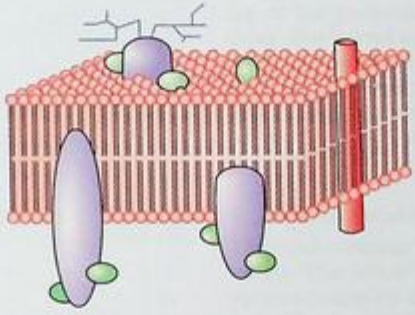
SECTION OUTLINE

1.1 Functional Organization, Composition and Internal Environment of Human Body

1.2 The Cell Physiology

1.3 Transport through Cell Membrane

1.4 Membrane Potential



Physiology, in simple terms, refers to the study of normal functioning of the living structures. The *human physiology* is concerned with the way the various systems of the human body function and the way each contributes to the functions of the body as a whole. In other words, the human physiology is concerned with specific characteristics and mechanisms of the human body that make it a living being and the mechanisms that help in adaptation and homeostasis, which are the two fundamental features of life.

The *general physiology* envisages the general concepts and principles that are basic to the functions of all the systems. As we know, the fundamental unit of human body is a cell; therefore, this section includes a short review of fundamental aspect of the cell physiology. Before studying the general biophysiological processes and the cell physiology, it will be worthwhile to have a brief knowledge about the functional organization, composition and internal environment of the human body.

1.1 Functional Organization, Composition and Internal Environment of Human Body

CHAPTER OUTLINE

Functional Organization of the Human Body
Skin and its Appendages
Skeletal System
Muscular System
Nervous System
Cardiovascular System
Respiratory System
Digestive System
Excretory System
Reproductive System
Endocrine System
Blood and Immune System

Body Composition
Total Body Water
Body Electrolytes

Internal Environment and Homeostasis
Internal Environment
Homeostasis
Mode of Action of Homeostatic Control System

FUNCTIONAL ORGANIZATION OF THE HUMAN BODY

The human body is actually a social order of about 100 trillion cells organized into different functional structures, some of which are called organs; some organs combinedly form a system. For convenience of description, the human body can be considered to be functionally organized into various systems.

1. Skin and its Appendages

Skin is the outermost covering of the human body. Its appendages include hairs, nails, sebaceous glands and sweat glands. The skin performs the following important functions:

- It acts as a physical barrier against entry of microorganisms and other substances.
- It prevents loss of water from the body.
- It is a very important sensory organ containing receptors for touch and related sensations.
- It plays an important role in regulating body temperature.

2. Skeletal System

The basic framework of the body is provided by a large number of bones that collectively form the *skeleton*. At joints, the bones are united to each other by fibrous bands called *ligaments*. In addition to the bones and joints, the skeletal system also includes the *cartilages* present in the body.

3. Muscular System

Overlying and usually attached to the bones are various muscles. Muscles are composed of many elongated cells called *muscle fibres*, which are able to contract and relax. Three distinct types of muscles can be identified: skeletal muscles, smooth muscles and cardiac muscles.

4. Nervous System

The specialized cells that constitute the functional units of the nervous system are called *neurons*. The *nervous* system may be divided into (i) the *central nervous system*, made up of brain and spinal cord, and (ii) the *peripheral nervous system*, consisting of the peripheral nerves and the ganglia associated with them. The nerves supplying the body wall and limbs are often called *cerebrospinal* nerves. The nerves supplying the viscera, along with the parts of the brain and spinal cord related to them, constitute the *autonomic nervous system*. The autonomic nervous system is subdivided into two major parts: the *sympathetic* and the *parasympathetic* nervous systems.

5. Cardiovascular System

The cardiovascular system consists of the *heart* and the *blood vessels*. The blood vessels that take blood from the heart to various tissues are called *arteries*. The smallest arteries are called *arterioles*. Arterioles open into a network of *capillaries* that perfuse the tissues. Exchange of various substances between the blood and the tissues takes place through the walls of capillaries. In some situations, capillaries are replaced by slightly different vessels called *sinusoids*. Blood from capillaries (or from sinusoids) is collected by small *venules*, which join to form veins. The veins return blood to the heart.

6. Respiratory System

The respiratory system consists of the lungs and the passages through which air reaches them. The passages are nasal cavities, the pharynx, the trachea, the bronchi and their intrapulmonary continuations.

7. Digestive System

The digestive or the alimentary system includes all those structures that are concerned with eating, and with digestion and absorption of food. The system consists of an alimentary canal, which includes the oral cavity, pharynx, esophagus, stomach, small intestine and large intestine. Other structures included in the digestive system are the liver, the gall bladder and the pancreas.

8. Excretory System

Excretion is the removal of waste products of metabolism from the body. *Egestion* (or defaecation) is the removal of undigested

food from the gut and is not regarded as excretion because the material taken into the gut through the mouth is not made by the body itself. The organs forming excretory system are the kidney, the ureters, the bladder and the urethra.

9. Reproductive System

Reproduction is the production of a new generation of individuals of the same species. It involves the transmission of genetic material from one generation to the next. *The male reproductive organs* are the testes, the epididymis, the ductus deferens, the seminal vesicles, the prostate, the male urethra and the penis. *The female reproductive organs* are the ovaries, uterine tubes, the uterus, the vagina, the external genitalia and the mammary glands.

10. Endocrine System

Endocrine tissue is made up essentially of cells that produce secretions, which are poured directly into blood called *hormones*. Some organs are entirely endocrine in function. They are referred to as *endocrine glands* (or *ductless glands*), e.g. the hypophysis cerebri (pituitary gland), the pineal gland, the thyroid gland, the parathyroid glands and the suprarenal (adrenal) glands. Groups of endocrine cells may be present in the organs that have other functions. These include the *islets of Langerhans* of pancreas, the interstitial cells of the testis, and the follicles and corpora lutea of the ovaries. Hormones are also produced by some cells in the kidney, the thymus and the placenta.

11. Blood and Immune System

Blood is regarded as a modified connective tissue because the cellular elements in it are separated by a considerable amount of 'intercellular substance' and because some of the cells in it have close affinities to cells in general connective tissue.

Circulating blood normally contains three main types of cells, which perform their respective physiologic functions: (i) the red cells (*erythrocytes*) are largely concerned with oxygen transport, (ii) the white cells (*leucocytes*) play various roles in the body defence against infection and tissue injury and (iii) platelets (*thrombocytes*), which are primarily involved in maintaining the integrity of blood vessels and in preventing blood loss. Detailed physiology of each organ system is considered in the relevant chapters.

BODY COMPOSITION

The normal body in an average adult male is composed of *water* (60%), *minerals* (7%), *protein* and related substances (18%) and *fat* (15%). The water denoted by the term total body water (TBW) and the electrolytes need special emphasis.

Total Body Water

Water is the principal and essential constituent of the human body. TBW is about 10% less in a normal young adult female (average 50%) than that in an average adult male (60%) due to relatively greater amount of adipose tissue in the females. In both sexes the value tends to decrease with age.

The Body Fluid Compartments

The TBW is distributed into two main compartments of the body fluids separated from each other by membranes freely permeable to water (Fig. 1.1-1; Table 1.1-1).

1. Intracellular Fluid Compartment

The intracellular fluid (ICF) compartment is composed of about 40% of the body weight, the bulk of which is contained in the muscles.

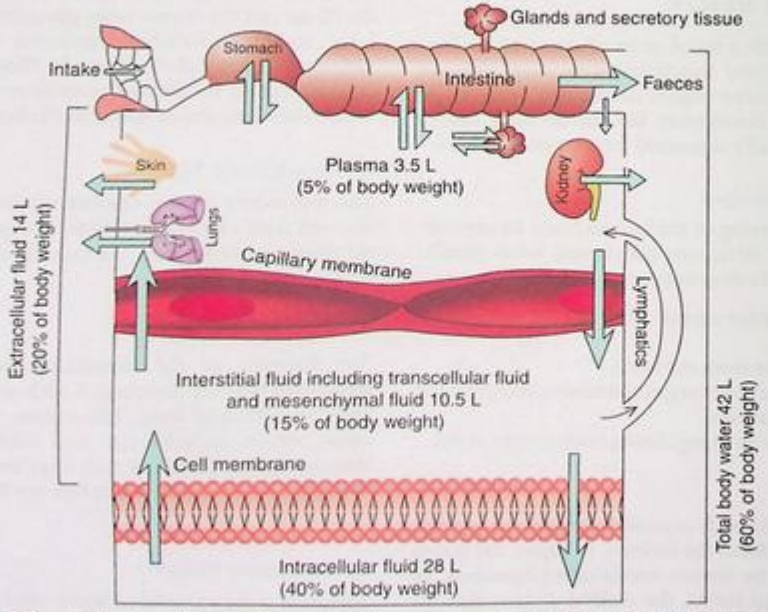


Figure 1.1-1 Distribution of total body water in different compartments. Arrows indicate fluid movement.

TABLE 1.1-1 Distribution of Total Body Water in a Normal 70-kg Person

Compartment	Volume (L)	Body Weight (%)	Body Water (%)
Total body water	42	60	100
Intracellular fluid	28	40	67
Extracellular fluid (ECF)	14	20	33
• Plasma (25% of ECF)	3.5	5	8
• Interstitial fluid, transcellular fluid and mesenchymal tissue fluid (75% of ECF)	10.5	15	25

TABLE 1.1-2 Distribution of Ions in the Extracellular Fluid and Intracellular Fluid (Values are in mEq/L of H_2O)

Ion	Extracellular Fluid	Intracellular Fluid
Cations		
Na^+	142	10
K^+	4	140
Ca^{2+}	2.4	<1 (0.0001)
Mg^{2+}	1.2	58
Anions		
Cl^-	103	4
HCO_3^-	28	10
PO_4^{3-}	4	75
Protein	1 g/dL	>5 g/dL

2. Extracellular Fluid Compartment

The extracellular fluid (ECF) compartment constitutes about 20% of the body weight. The ECF compartment is composed of the following:

(i) Plasma It is the fluid portion of the blood (*intravascular fluid*) and is composed of about 5% of the body weight (i.e. 25% of ECF). On an average, of 5 L of total blood volume 3.5 L is plasma.

(ii) Interstitial fluid including lymph It constitutes the major portion (about three-fourth) of ECF. The composition of interstitial fluid is the same as that of plasma except it has little protein. Thus, interstitial fluid is an ultrafiltrate of plasma.

(iii) Transcellular fluid It is the fluid contained in the secretions of the secretory cells and cavities of the body, e.g. saliva, sweat, cerebrospinal fluid, intraocular fluids (aqueous humour and vitreous humour), pericardial fluid, bile, fluid present between the layers (pleura, peritoneum and synovial membrane), lacrimal fluid and luminal fluids of the gut, thyroid and cochlea.

Transcellular fluid volume is relatively small, about 1.5% of the body weight, i.e. 15 mL/kg body weight (about 1 L in a person of 70 kg).

(iv) Mesenchymal tissue fluid The mesenchymal tissues such as dense connective tissue, cartilage and bones contain about 6% of the body water.

The interstitial fluid, transcellular fluid and mesenchymal tissue fluid combinedly form 75% of ECF.

The normal distribution of TBW in the fluid compartments is kept constant by two opposing sets of forces: osmotic and hydrostatic pressure.

Body Electrolytes

The electrolytes constitute about 7% of the total body weight. The distribution of electrolytes in various compartments differs markedly. Table 1.1-2 shows the distribution of electrolytes in two major compartments of body fluid: ECF and ICF.

From Table 1.1-2, it may be noted that in ICF the principal cations are K^+ and Mg^{2+} and the principal anions are PO_4^{3-} and proteins, whereas in ECF the predominant cation is Na^+ and the principal anions are Cl^- and HCO_3^-. Besides these, a small proportion of nondiffusible proteins, nutrients and metabolites such as glucose and urea are also present in ECF.

The essential difference between the two main subdivisions of ECF is the higher protein content in plasma than in the interstitial fluid, which plays an important role in maintaining fluid balance.

It is Important to Note the Following:

- Essentially all of the body K^+ is in the exchangeable pool.
- Only 65%–70% of the body Na^+ is exchangeable.
- Almost all of the body Ca^{2+} and Mg^{2+} are nonexchangeable.
- Only the exchangeable solutes are osmotically active.

Functions of Electrolytes

1. Electrolytes are the main solutes in the body fluids for the maintenance of acid–base balance.
2. Electrolytes maintain the proper osmolality and volume of body fluids.
3. The concentration of certain electrolytes determines their specific physiologic functions, e.g. the effect of calcium ions on neuromuscular excitability.

INTERNAL ENVIRONMENT AND HOMEOSTASIS

Internal Environment

Claude Bernarde (1949), the great French physiologist, introduced the term *internal environment* of the body or the *milieu interieur* for the ECF of the body. He said so because all the body cells essentially depend on ECF for maintenance of cellular life. Cells are capable of living, growing and performing their special functions as long as the proper concentration of oxygen, glucose, different ions, amino acids, fatty substances and other constituents are available in the internal environment.

Homeostasis

Homeostasis, a term introduced by W.B. Cannon, refers to the mechanism by which the constancy of the internal environment is maintained and ensured. For this purpose, living membranes with varying permeabilities such as vascular endothelium and cell membrane play important role.

The factors involved in the maintenance of internal environment can be summarized as follows:

- Transport of ECF
- Maintenance of pH of ECF (acid–base balance)

- Regulation of temperature
- Maintenance of water and electrolyte balance
- Supply of nutrients, oxygen, enzymes and hormones
- Removal of metabolic and other waste products
- Reproduction

Mode of Action of Homeostatic Control System

The homeostasis is a complex phenomenon. The mode of operation of all the systems, which are involved in the homeostasis is through 'feedback' mechanism and the adaptive control system. Feedback mechanism is of two types: negative feedback mechanism and positive feedback mechanism.

Negative Feedback Mechanism

Most control systems of the body act by the negative feedback. In general, if the activity of a particular system is increased or decreased, a control system initiates a negative feedback, which consists of a series of changes that return the activity towards normal.

Examples of feedback mechanism

1. When the blood pressure suddenly rises or lowers, it initiates a series of reactions that tries to bring the blood pressure to normal levels.
2. When thyroxine secretion is more, it inhibits the secretion of thyroid-stimulating hormone from pituitary so that thyroxine is not secreted from the thyroid gland.

Positive Feedback Mechanism

Positive feedback is better known as a vicious cycle. Usually it is harmful and in some instances even death can occur due to positive feedback. For example, as shown in Fig. 1.1-2, when a person suddenly bleeds 2 L of blood, a vicious cycle of progressively weakening of the heart is set, which ultimately causes death.

A mild degree of feedback can be overcome by the negative feedback control mechanisms of the body, and a vicious cycle fails to develop. For example, when a patient bleeds 1 L of blood instead of 2 L, the negative feedback mechanisms of controlling the blood pressure may overcome the positive feedback, and the blood pressure will return to normal, as shown in Fig. 1.1-2.

Furthermore, sometimes positive feedback can serve useful purposes, e.g. under the following circumstances:

- ***Clot formation*** followed by rupture of vessels is accelerated by the vicious cycle of thrombin formation (for details see page 94). This stops the bleeding.
- ***Childbirth*** during labour is facilitated by progressively increasing uterine contractions due to positive feedback from stretching of the cervix by head of the baby (for details see page 376).

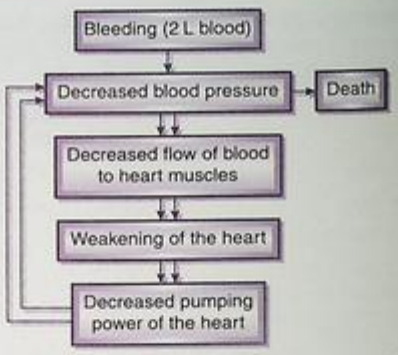


Figure 1.1-2 Flowchart showing how a positive feedback mechanism can cause death.

- ***Generation of nerve signals*** by the vicious cycle of progressive leakage of Na^+ ions from the channels set up further stimulation of membrane of nerve fibre is due to the positive feedback.

Adaptive Control System

Adaptive control system refers to a delayed type of negative feedback mechanism. This is seen in the nervous system. For example, when some movements of the body occur very rapidly, there is not enough time for the nerve signals to travel from the peripheral parts of the body all the way to the brain and then back to the periphery again in time to control the movements. Under such circumstances brain uses a principle called *feed-forward control* to cause the required muscle contraction, which retrospectively is conveyed to the brain by the sensory nerve signals from the moving part. If the movement performed is found incorrect, then the brain corrects the *feed-forward signals* that it sends to the muscle the next time the movement is required. Such a correction made by successive retrospective feedback mechanism is called *adaptive control.*

SELF-ASSESSMENT

1. Describe briefly:
   - Total body water and its distribution
   - Body electrolytes
2. Define internal environment and its significance.
3. Define homeostasis. Briefly discuss its regulatory mechanisms.
4. What do you understand by feedback control mechanisms?

1.2 The Cell Physiology

CHAPTER OUTLINE

Cell Structure
Cytoplasm
Nucleus

The Cell Membrane
Fluid Mosaic Model
Arrangement of Different Molecules in Cell Membrane

Intercellular Junctions
Tight Junction
Adherens Junction
Gap Junction

CELL STRUCTURE

The cell is the smallest structural and functional unit of the body. The human body contains about 100 trillion cells. Different types of cells of the body possess features which distinguish one type from the other, and are specially adapted to perform particular functions, e.g. the red blood cells transport oxygen from lungs to the tissues, and muscle cell is specialized for the function of contraction.

A typical cell, as seen by the light microscope, consists of three basic components (Fig. 1.2-1):

- Cell membrane
- Cytoplasm
- Nucleus

THE CELL MEMBRANE

Cell membrane or the plasma membrane is the protective sheath enveloping the cell body. It separates the contents of cell from the external environment and controls exchange of materials between the fluid outside the cell (extracellular fluid) and the fluid inside the cell (intracellular fluid). A detailed knowledge of its structure (Fig. 1.2-2) is essential for the understanding of cell functions.

Structure

Electron microscopy has shown that cell membrane/plasma membrane has a *trilayer* structure having a total thickness of 7–10 nm (70–100 Å) and is known as *unit membrane*. The three layers consist of two *electron-dense layers* separated by an *electron-lucent layer* (clear zone). Biochemically, the cell membrane is composed of a complex mixture of lipids (40%), proteins (55%) and carbohydrates (5%).

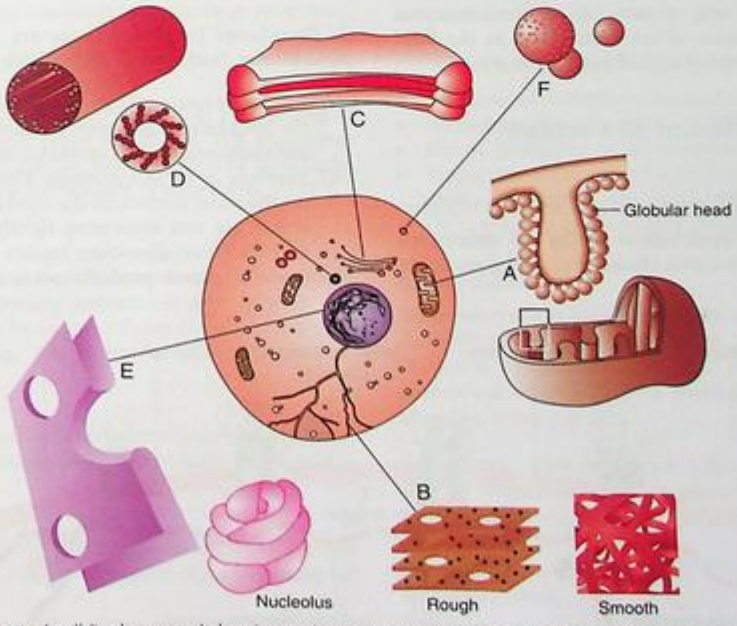


Figure 1.2-1 Structure of a typical cell (in the centre) showing various organelles: A, mitochondrion; B, endoplasmic reticulum (rough and smooth); C, Golgi apparatus; D, centrosome; E, nucleus and F, secretory granules.

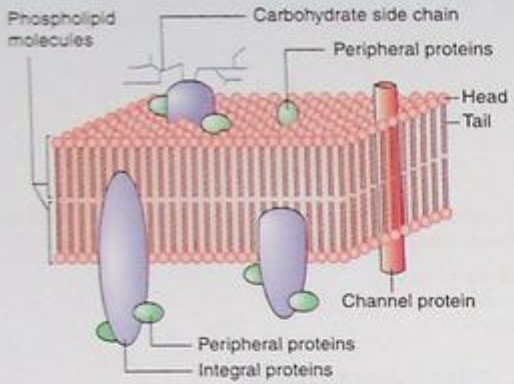


Figure 1.2-2 Fluid mosaic model of the structure of cell membrane.

A few hypotheses have been proposed to explain the distribution of various biochemical components in the cell membrane. The most important hypothesis is the fluid mosaic model of Singer and Nicholson.

FLUID MOSAIC MODEL

In 1972, Singer and Nicholson put forward the fluid mosaic model of membrane structure (Fig. 1.2-2), which is presently most accepted. According to this model:

- *Phospholipid bilayer* is the basic continuous structure forming the cell membrane. The phospholipids are present in fluid form. This fluidity makes the membrane quite flexible and thus allows the cells to undergo considerable changes in the shape without disruption of structural integrity.
- *The protein molecules* are present as a discontinuous mosaic of globular proteins which float about in the fluid phospholipid bilayer forming a *fluid mosaic pattern.*

Arrangement of Different Molecules in Cell Membrane

Arrangement of Lipid Bilayer of the Cell Membrane

Each lipid molecule in the lipid bilayer of the cell membrane primarily consists of phospholipid, cholesterol and glycolipids. The lipid molecule is clothespin shape and consists of a *head end* and a *tail end.*

The head end or the globular end of the molecule contains phosphate moiety of phospholipid or hydroxyl radical of cholesterol. It is positively charged and quite soluble in water (i.e. *polar or hydrophilic*). The tail end consists of two chains of fatty acids or steroid radicle of cholesterol. It is quite insoluble in water (*nonpolar* or *hydrophobic*). These lipid molecules are arranged as bilayer in such a way that their nonpolar hydrophobic tail ends are directed towards the centre of the membrane, whereas their polar hydrophilic head ends are directed outwards on either side of the membrane (Fig. 1.2-2). In this way, head ends of molecules face the aqueous phase, i.e. extracellular fluid on outside and the intracellular fluid (cytoplasm) on inner side. The major types of phospholipids are phosphatidyl choline, phosphatidyl ethanolamine, glycosphingolipids, sphingomyelin and cholesterol.

Functional Significance of the Lipid Bilayer. The lipid bilayer of the cell membrane makes it a semipermeable membrane which constitutes the major barrier for the water-soluble molecules such as electrolytes, urea and glucose. On the contrary, fat-soluble substances such as oxygen, fatty acids and alcohol can pass through the membrane with ease.

Arrangement of Proteins in the Cell Membrane

Most protein molecules float about in the phospholipid bilayer forming a fluid mosaic pattern. The two types of proteins recognized in the cell membrane are as follows:

- *Lipoproteins*, i.e. the proteins containing lipids which function as enzymes and ion channels and
- *Glycoproteins*, i.e. the proteins containing carbohydrates which function as receptors for hormones and neurotransmitters.

The proteins in the cell membrane are described below.

1. Peripheral Proteins. These are present peripheral to the lipid bilayer, both inside and outside to it.

(i) *Intrinsic proteins.* These are located on the inner surface of the lipid bilayer and serve mainly as enzymes. Some of these are anchored to the cytoskeleton of the cell (Fig. 1.2-3).

(ii) *Extrinsic or surface proteins.* These are the proteins located on the outer surface of the lipid bilayer. These protein molecules are not associated tightly with the cell membrane and thus can dissociate readily from the cell membrane. Some of these proteins serve as *cell adhesion molecules*

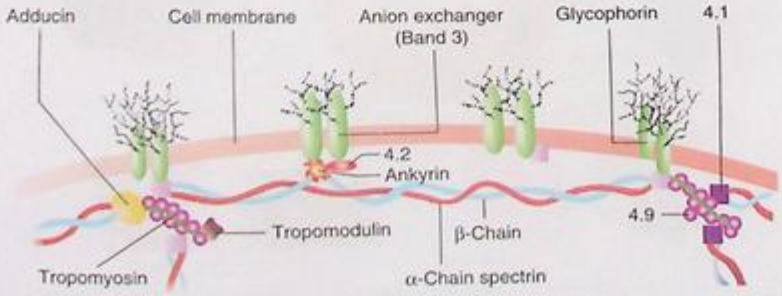


Figure 1.2-3 Cytoskeleton showing various proteins.

(CAMs) that anchor cells to the neighbouring cells and basal lamina.

2. Integral Proteins or Transmembrane Proteins. These are the proteins which extend into the lipid bilayer (Fig. 1.2-3). Some proteins penetrate only part of the way into the membrane, whereas others penetrate all the way through. The integral proteins on the basis of functions they serve are discussed below.

- *Channel proteins* serve as channels for water-soluble substances such as glucose and electrolytes.
- *Carrier proteins* help in transport of substances across the cell membrane by means of active and passive (facilitated diffusion) transport.
- *Receptor proteins.* Some of the proteins function as receptors that bind neurotransmitters and hormones, initiating physiologic changes inside the cell.
- *Antigens.* Some proteins in the cell membrane also act as antigens.
- *Pumps.* There are certain proteins in the cell membrane which act as pumps and form active transport system of the cell, e.g. Na^+–K^+ ATPase pump, K^+–H^+ ATPase pump and Ca^{2+} pump.

Arrangement of Carbohydrates in the Cell Membrane

The carbohydrates are attached either to the proteins (glycoproteins) or the lipids (glycolipids). Throughout the surface of cell membrane, carbohydrate molecules form a thin loose covering called *glycocalyx*.

Functions of Cell Membrane Carbohydrates

- Being negatively charged, the carbohydrate molecules of the cell membrane do not allow the negatively charged particles to move out of the cell.
- The glycocalyx helps in tight fixation of the cells with one another.
- Some of the carbohydrate molecules also serve as *receptors*.

Cytoplasm

Cytoplasm is an aqueous substance (cytosol) containing a variety of cell organelles and other structures. The structures dispersed in the cytoplasm can be broadly divided into three groups: organelles, inclusion bodies and cytoskeleton.

A. Organelles

The organelles are the permanent components of the cells which are bounded by limiting membrane and contain enzymes; hence they participate in the cellular metabolic activity. These include the following.

1. Mitochondria

Mitochondria are the major sites for aerobic respiration. These are oval structures and more numerous in metabolically active cells.

Structure. The mitochondria consist of

- *Membrane.* There are two layers of the membrane. The outer smooth and inner folded into incomplete septa called cristae (Fig. 1.2-1A).
- *Matrix* of the mitochondria contains enzymes required in Krebs' cycle by which products of carbohydrate, fat and protein metabolism are oxidized to produce energy that is stored in the form of ATP in the lollipop-like globular structures.

Functions. In addition to their role as power-generating units, the mitochondria may have a role in synthesizing membrane-bound proteins since they also possess deoxyribonucleic acid (DNA) and ribosomes.

2. Endoplasmic Reticulum

Endoplasmic reticulum (ER) is a system of flattened membrane-bound vesicles and tubules called *cisternae* (Fig. 1.2-1B). It is continuous with the outer membrane of the nuclear envelop, Golgi apparatus and possibly with the cell membrane. Morphologically, two types of ER can be identified: rough or granular and smooth or agranular.

(i) Rough Endoplasmic Reticulum. The rough ER is characterized by the presence of a number of ribosomes on its surface and transports proteins made by the ribosomes through the cisternae. Thus, the rough ER is especially well developed in cells active in protein synthesis, e.g. Russell's bodies of plasma cells, Nissl granules of nerve cells and acinar cells of pancreas.

(ii) Smooth Endoplasmic Reticulum. Smooth ER is devoid of ribosomes on its surface. It is a site of lipid and steroid synthesis. Therefore, it is found in abundance with the Leydig cells and cells of the adrenal cortex. In the skeletal and cardiac muscles, smooth ER is modified to form sarcoplasmic reticulum which is involved in the release and sequestration of calcium ions during muscular contraction.

3. Golgi Apparatus

The Golgi apparatus or complex is a collection of membranous vesicles, sacs or tubules which is generally located close to the nucleus. It is continuous with the ER. Golgi apparatus is particularly well developed in exocrine glandular cells (Fig. 1.2-1C).

Functions. Its principal functions are as follows:

- Synthesis of carbohydrates and complex proteins.
- Packaging of proteins synthesized in the rough ER into vesicles.
- Site of formation of lysosomal enzymes.
- Transport of the material to the other parts of cell or to the cell surface membrane and secretion.
- Glycosylation of proteins to form glycoproteins.

4. Ribosomes

Ribosomes are spherical particles which contain 80%–85% of the cell's ribonucleic acid (RNA). They may be present in the cytosol as free (unattached) or in bound form (attached to the membrane of ER). Slightly smaller form of ribosomes is also found in mitochondria.

Functions. They are the site of protein synthesis. They synthesize all transmembrane proteins, secreted proteins and most proteins that are stored in the Golgi apparatus, lysosomes and endosomes.

5. Lysosomes

Lysosomes are rounded to oval membrane-bound organelles containing powerful lysosomal digestive (hydrolytic) enzymes.

They are formed by the Golgi apparatus. As many as 40 different lysosomal enzymes have been synthesized. Lysosomes are particularly abundant in cells involved in phagocytic activity, e.g. neutrophils and macrophages. There are three forms of lysosomes:

Primary Lysosomes or Storage Vacuoles are formed from the various hydrolytic enzymes synthesized by rough ER and packaged in the Golgi apparatus.

Secondary Lysosomes or Autophagic Vacuoles are formed by fusion of primary lysosomes with parts of damaged or worn-out cell components.

Residual Bodies are undigestible materials in the lysosomes.

6. Peroxisomes

Peroxisomes, also known as microbodies, are spherical structures enclosed by a single layer of unit membrane. These are predominantly present in hepatocytes and tubular epithelial cells.

Functions. They essentially contain two types of enzymes:

- *Oxidases* which are active in oxidation of lipid.
- *Catalases* which act on hydrogen peroxide to liberate oxygen.

7. Centrosome

The centrosome consists of two short cylindrical structures called centrioles (Fig. 1.2-1D). It is situated near the centre of the cell close to the nucleus. The centrioles are responsible for movement of chromosomes during cell division.

B. Cytoplasmic Inclusions

The cytoplasmic inclusions are the temporary components of certain cells. These may or may not be enclosed in the membrane. A few examples of cytoplasmic inclusions are given below.

- *Lipid droplets.* These are seen in the cells of adipose tissue, liver and adrenal cortex.
- *Glycogen.* It is seen in the cells of liver and skeletal muscles.
- *Proteins as secretory granules* are seen in the secretory glandular cells (Fig. 1.2-1F).
- *Melanin pigment* is seen in the cells of epidermis, retina and basal ganglia.
- *Lipofuscin.* It is a yellow–brown pigment believed to be derived from secondary lysosomes and is seen in the cardiac muscle and brain cells of elderly people.

C. Cytoskeleton

The cytoskeleton is a complex network of fibres that maintains the structure of the cell and allows it to change shape and move. It primarily consists of the following (Fig. 1.2-3).

1. Microtubules

Microtubules are long, hollow, tubular structures without limiting membrane about 25 nm in diameter. These are made up of two globular protein subunits α- and β-tubulin. The bundles of tubulin give structural strength to the cells. Microtubules form the transport system of the cells. Some of the other organelles and protein molecules move to a different part of the cell through the microtubules. *Kinesin* and *dynein* known as molecular motors help in the movement of molecules through the microtubules.

The *cilia* and *flagella* which project from surface of certain cells (spermatozoa, respiratory mucosa and fallopian tubes) are also composed of microtubules enclosed in the plasma membrane and are active in the locomotion of the cells.

2. Intermediate Filaments

Intermediate filaments are filamentous structures about 10 nm in diameter. Some of these filaments connect the nuclear membrane to the cell membrane. Their principal function is to mechanically integrate the cell organelles within the cytoplasm. In their absence, cells rupture more easily, and when they are abnormal in human, blistering of the skin is common.

3. Microfilaments

Microfilaments are long, solid, filamentous structures having a diameter of 6–8 nm. These are made up of contractile proteins, actin and myosin. Actin is the most abundant protein in the mammalian cell. It attaches to various parts of cytoskeleton by other proteins (anchor proteins). These are identified by numbers as 4.1, 4.2 and 4.9. Extension of microfilaments along with the plasma membrane on the surface of the cells form *microvilli*, which increase the absorptive surface of the cells (e.g. intestinal epithelium). In the skeletal muscle, presence of actin and myosin filaments is responsible for their contractile property.

Molecular Motors Molecular motors help in the movement of different proteins, organelles and other cell parts (their cargo) to all parts of the cell. These can be divided into two types:

1. Microtubule-Based Molecular Motors. This is a super family of molecular motors that produce motion along microtubules. Two important molecular motors are

(i) Conventional kinesin and
(ii) Dynein.

2. Actin-Based Molecular Motors. This is a superfamily of molecular motors that produce motion along the actin. The important example of this group is myosin.

Nucleus

Nucleus is present in all the eukaryotic cells. It controls all the cellular activities including reproduction of the cell. Most of the cells are uninucleated except few types of cells like skeletal muscle cells which are multinucleated. The nucleus consists of the following (Fig. 1.2-1E).

1. Nuclear Membrane

The nuclear membrane is double-layered porous structure having a 40–70 nm wide space called *perinuclear cistern*, which is continuous with the lumen of ER. The outer layer of the nuclear membrane is continuous with ER. The exchange of

materials between the nucleoplasm and cytoplasm occurs through the nuclear membrane.

2. Nucleoplasm

The nucleoplasm or the nuclear matrix is a gel-like ground substance containing a large quantity of genetic material in the form of DNA. When a cell is not dividing the nucleoplasm appears as dark staining thread-like material called nuclear *chromatin*. During cell division, the chromatin material is converted into rod-shaped structures, the chromosomes. There are 46 chromosomes (23 pairs) in all the dividing cells of the body except the gamete (sex cells) which contains only 23 chromosomes (haploid number). Each chromosome is composed of two chromatids connected at the centromere to form 'X' configuration having variation of the location of centromere. The chromosomes are composed of three components: DNA, RNA and other nuclear proteins. The nuclear DNA carries the genetic information which is passed via RNA into the cytoplasm for synthesis of proteins of similar composition.

3. Nucleolus

The nucleus may contain one or more rounded bodies called nucleoli. The nucleoli are the site of synthesis of ribosomal RNA. The nucleoli are more common in growing cells or in cells that actively synthesize proteins.

INTERCELLULAR JUNCTIONS

The cell membranes of the neighbouring cells are connected with one another through the *intercellular junctions* or the junctional complexes, which are of three types.

Types of Intercellular Junctions

1. Tight Junction This is also called *zona occludens* or the *occluding zone* (Fig. 1.2-4A). In this type of intercellular junction, the outer layer of the cell membrane of the neighbouring cells fuse with each other, thus obliterating the space between the cells. Such junctions form a barrier to the movement of ions and other solutes from one cell to another. A few examples of the cells where tight junctions are present as follows:

- Apical margins of epithelial cells, like the intestinal mucosa.
- The renal tubular epithelial cells.
- Capillary endothelium in the brain forming blood–brain barrier.

2. Adherens Junction This is also called *zonula adherens*. In this type of junction, cell membranes of the adjacent cells are separated by a 15–20 nm wide space which is at focal places obliterated by the dense accumulation of the proteins at the cell surface. Bundles of intermediate filaments project from the intercellular junctional areas and radiate into the cytoplasm. This holds the adjacent cells at these focal places. These are of two types:

- *Desmosomes* are the adherens junctions where thickened focal areas are formed on both the apposing cell membranes (Fig. 1.2-4B).
- *Hemidesmosomes* are the adherens junctions where focal thickening is seen only on the membrane of one of the two adjacent cells. So, this is also known as half desmosome. Adherens junctions are seen in the cells of epidermis. Focal adhesions attach the cell to the basal lamina and also to actin filaments present inside the cell and thus help in cell movement.

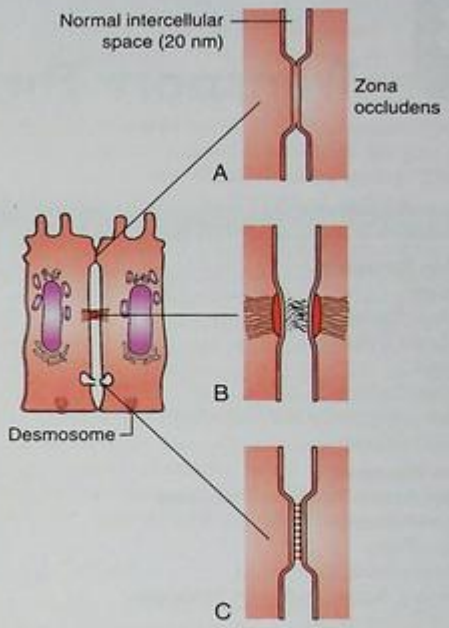


Figure 1.2-4 Schematic diagram of a cell to show various intercellular junctions: A, tight junction; B, adherens junction and C, gap junction.

3. Gap Junction The gap junctions or the nexus are the channels on the lateral surfaces of the two adjacent cells through which the molecules are exchanged between the cells (Fig. 1.2-4C). Each half of the channel is surrounded by six subunits of proteins (the *channel proteins*). The intercellular space is reduced from the usual size of 15–20 nm to 2–3 nm at such junction. The gap junctions are seen in the heart and basal part of epithelial cells of intestinal mucous membrane. Gap junctions serve the following functions:

- These permit the intercellular passage of glucose, amino acids, ions and other substances which have a molecular weight of about 1000.
- These permit rapid propagation of electrical potential changes from one cell to another as seen in cardiac muscle and other smooth muscle cells.
- These help in the exchange of chemical messengers between the cells.

SELF-ASSESSMENT

1. Describe briefly:
   - The structure of a cell membrane
   - The composition of cell membrane and significance of its components
2. How the proteins are distributed in a plasma membrane. Describe their functions.
3. Describe the structure, types and functions of intercellular junctions.

1.3 Transport Through Cell Membrane

CHAPTER OUTLINE

Passive Transport
Diffusion
Simple Diffusion
Facilitated Diffusion
Osmosis
Osmotic Pressure
Osmole, Osmolality and Osmolarity
Tonicity of Fluids

Active Transport
Primary Active Transport Processes
Sodium–Potassium Pump
Calcium Pump
Potassium–Hydrogen Pump
Secondary Active Transport Processes
Sodium Cotransport
Sodium Countertransport

Vesicular Transport
Endocytosis
Pinocytosis
Phagocytosis
Receptor-Mediated Endocytosis
Exocytosis
Transcytosis

Other Transport Processes
Transport Across Epithelial Membrane
Ultrafiltration

The physiological activities of a cell depend on the substances such as nutrients, oxygen and water, which must be transported into the cell, and at the same time metabolic waste must be transported out of the cell. Various processes involved in the transport of substances across the cell membrane may be grouped as follows:

- Passive transport,
- Active transport and
- Vesicular transport.

PASSIVE TRANSPORT

Passive transport refers to the mechanism of transport of substances along the gradient without expenditure of any energy. It depends on the physical factors such as concentration gradient, electrical gradient and pressure gradient. Since the transport of substances occurs along the gradient, this process is also called *down-hill movement*. The passive transport mechanisms operating at the cell membrane level are diffusion and osmosis.

Diffusion

Diffusion refers to passive transport of molecules from areas of higher concentration to areas of lower concentration. Diffusion through cell membrane is divided into two subtypes: simple diffusion and facilitated diffusion.

Simple Diffusion

In simple diffusion, there occurs a net flux of the molecules from the areas of high concentration to areas of low concentration due to constant random movement. Quantitatively, the net movement of the molecules across a permeable membrane is expressed by *Fick's law of diffusion*, which states that rate of diffusion (J) is directly proportional to the difference in the concentration of the substance in two regions [concentration gradient, i.e. $(C_1 - C_2)$] and cross-sectional area (A) and inversely proportional to the distance to be travelled, i.e. thickness of the membrane (T).

Thus, $J = D, \frac{A(C_1 - C_2)}{T}$, where D is the diffusion coefficient.

The diffusion of molecules across the biological membranes differs depending on the lipid solubility, water solubility, type of electrical charge and size of the molecules. Furthermore, selective permeability of the semipermeable cell membrane also affects the diffusion of different molecules. How the different molecules diffuse across a cell membrane is discussed below.

Simple Diffusion of Lipid-Soluble Substances through the Cell Membrane

The rate of diffusion through the lipid bilayer of the cell membrane is directly proportional to the solubility of a substance in lipids. Therefore, molecules of substances, such as oxygen, nitrogen, carbon dioxide, alcohol, steroid hormones and weak organic acids and bases, are lipid soluble and diffuse very rapidly through the lipid bilayer of the cell membrane.

Simple Diffusion of Water and Other Lipid-Insoluble Molecules through the Cell Membrane

Astonishingly, water and other lipid-insoluble substances can also pass easily through the cell membrane. It has been shown that it is possible due to the presence of the so-called *protein channels* (made from transmembrane proteins) in the cell membrane.

Diffusion through Protein Channels

The protein channels are tube-shaped channels which extend in the cell membrane from the extracellular to the intracellular ends (Fig. 1.3-1). Therefore, even the highly lipid-insoluble substances can diffuse by simple diffusion directly through these channels of the cell membrane.

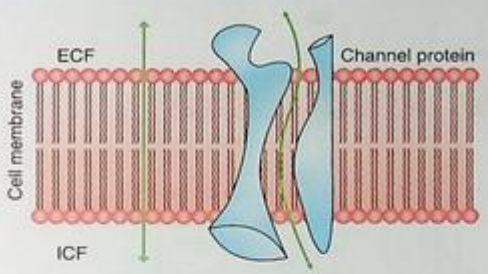


Figure 1.3-1 Simple diffusion.

The protein channels have been equipped with following characteristics:

- Selective permeability and
- Gating mechanism.

Selective Permeability of Protein Channels The protein channels are highly selective, i.e. each channel can permit only one type of ion to pass through it. This results from the characteristics of the channel itself, such as its diameter, its shape and nature of electrical charges along its inside surfaces. Examples of some selective channels are given below:

- *Sodium channels* are specifically selective for the passage of sodium ions. These are 0.3' 0.5 nm in size and their inner surfaces are *strongly negatively charged* (Fig. 1.3-2).
- *Potassium channels* are specifically selective for the passage of potassium ions. These are 0.3' 0.3 nm in size and are *not negatively charged.*

Gating Mechanism in Protein Channels Some protein channels are continuously open, whereas most others are 'gated', i.e. they are equipped with actual gate-like extensions of the transport protein molecule which can open and close as per requirement. This gating mechanism is a means of controlling the permeability of the channels. The opening and closing of gates are controlled by three principal ways:

1. ***Voltage-gated channels.*** These respond to the electrical potential across the cell membrane. As shown in Fig. 1.3-2 in the case of sodium channels, the gates are located at the outer end of the channels and remain tightly closed when there is a strong negative charge on the inside of cell membrane. When the inside of cell membrane loses its negative charge, these gates open and there occurs a tremendous inflow of sodium ions. This is the basis of occurrence of action potentials in nerves that are responsible for nerve signals.
2. ***Ligand-gated channels.*** Gates of these channels open when some other chemical molecule binds with the gate proteins that is why this is also called *chemical gating.* The ligand (binding molecules) may be internal or *external.*
   - The external or extracellular ligands are also called *first messengers.* One of the most important examples of external ligand channel gating is the effect of acetylcholine on the so-called *acetylcholine channels.* This gate plays an important role in transmission of nerve signals from one nerve cell to another and from nerve cells to muscle cells.
   - The internal or the intracellular ligands are also called *second messengers.* The examples include intracellular Ca^{2+}, cAMP or G protein produced in the cells. The second messenger generally activates protein kinases.
3. ***Mechanical-gated channels.*** Some protein channels are opened by mechanical stretch. These mechanosensitive channels play an important role in cell movements.

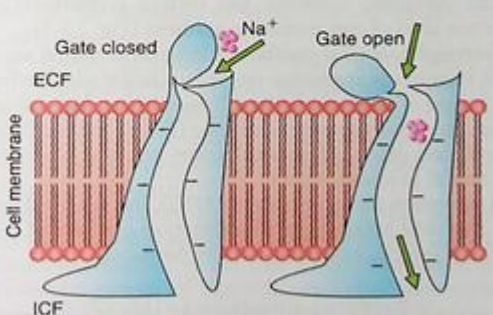


Figure 1.3-2 Voltage-gated sodium channels.

Facilitated Diffusion

The water-soluble substances having larger molecules such as glucose cannot diffuse through the protein channels by simple diffusion. Such substances diffuse through the cell membrane with the help of some carrier proteins. Therefore, this type of diffusion is called facilitated or the carrier-mediated diffusion. There are many types of carrier proteins in the cell membrane, each type having binding sites that are specific for a particular substance. Among the most important substances that cross cell membranes by facilitated diffusion are *glucose* and most of the *amino acids.*

Mechanism of Facilitated Diffusion

Postulated mechanism for facilitated diffusion is shown in Fig. 1.3-3. As shown in the figure, a conformational change occurs in the carrier protein after the molecule to be transported is bound at the receptor site. The repetitive spontaneous configurational changes allow the diffusion of the molecule.

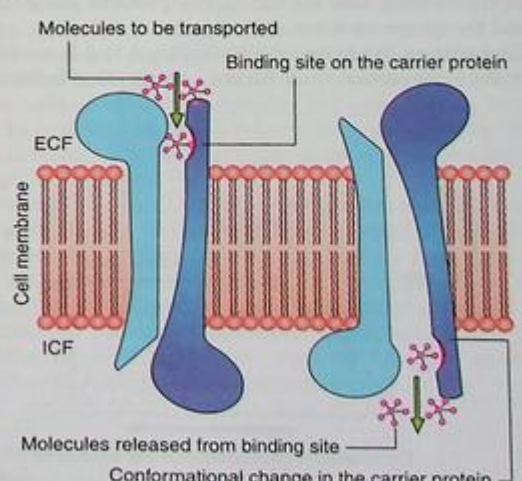


Figure 1.3-3 Postulated mechanism of facilitated diffusion.

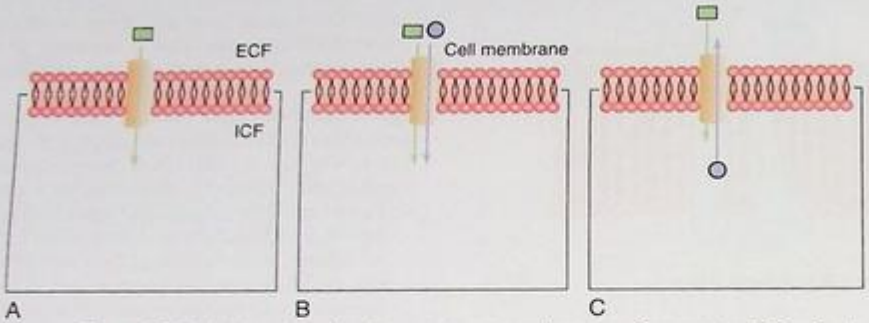


Figure 1.3-4 Various types of carrier protein systems: A, uniport; B, symport and C, antiport.

Types of Carrier Protein Systems Three types of carrier protein systems are known: uniport, symport, and antiport (Fig. 1.3-4). The symports and antiport are together known as cotransport.

1. ***Uniport.*** In this system, the carrier proteins transport only one type of molecules (Fig. 1.3-4A).
2. ***Symport.*** In this system, transport of one substance is linked with transfer of another substance. For example, facilitated diffusion of glucose in the renal tubular cells is linked with the transport of sodium (Fig. 1.3-4B).
3. ***Antiport.*** In this system, the carrier proteins exchange one substance for another. For example, Na^+–K^+ exchange or Na^+–H^+ exchange in the renal tubules (Fig. 1.3-4C).

Differences between Simple and Facilitated Diffusion

1. ***Specificity.*** The carrier proteins are highly specific for different molecules.
2. ***Saturation.*** As shown in Fig. 1.3-5, in simple diffusion the rate of diffusion increases proportionately with the increase in the concentration of the substance and there is no limit to it. However, in facilitated diffusion the rate of diffusion increases with increase in concentration gradient to reach a limit beyond which a further increase in the diffusion cannot occur. This is called *saturation* point, and here all the binding sites on the carrier proteins are occupied and the system operates at its maximum capacity.
3. ***Competition.*** When two molecules, say A and B, are carried by the same protein, there occurs a competition between the two molecules for the transport. Thus, an increase in the concentration of 'A' molecule will decrease the transport of molecule 'B' and vice versa. No such competition is known to occur in simple diffusion.

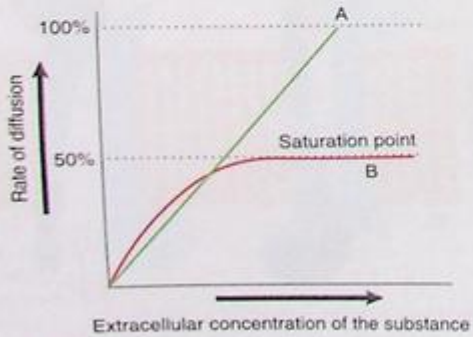


Figure 1.3-5 Effect of concentration of substance on rate of diffusion in: A, simple diffusion and B, facilitated diffusion.

Factors Affecting Net Rate of Diffusion The diffusion of the substance can occur either way, i.e. extracellular fluid (ECF) to intracellular fluid (ICF) or vice versa, depending on the prevailing environment. The factors which affect the net rate of diffusion in the desired direction are given below.

1. ***Cell membrane permeability.*** Permeability of the cell membrane (P) is the major determining factor for the net diffusion, which in turn depends on the following factors:
   - *Thickness of the membrane.* The diffusion is inversely proportional to the thickness of the cell membrane.
   - *Lipid solubility.* Diffusion is directly proportional to the lipid solubility of the substance.
   - *Distribution of protein channels in the cell membrane.* The rate of diffusion of lipid-insoluble substance is directly proportional to the number of channels per unit area of the cell membrane.
   - *Temperature.* Rate of diffusion increases with an increase in the temperature. This is due to the increased motion of the molecules and ions of the solution with increase in temperature.
   - *Size of the molecules.* Rate of simple diffusion is inversely proportional to the size of molecules.
   - *Area of the membrane. The* net diffusion of the substance is directly proportional to the total area of the membrane.
2. ***Concentration gradient.*** The simple diffusion is directly proportional to the concentration gradient, but the facilitated diffusion, however, has certain limitations beyond certain level of concentration gradient (Fig. 1.3-5).
3. ***Electrical potential gradient.*** Electrical potential across the cell membrane is another important factor which affects the diffusion of ions across the cell membrane. Net diffusion of any ion across the cell membrane (J) will be the resultant of combined effect of concentration gradient and electrical potential gradient.

   At normal body temperature (37°C), the electrical gradient that will balance the concentration gradient of a univalent ion can be determined by *Nernst equation*:

$$\text{EMF (in millivolts)} = \pm 61 \log \frac{C_o}{C_i}, \text{ where}$$

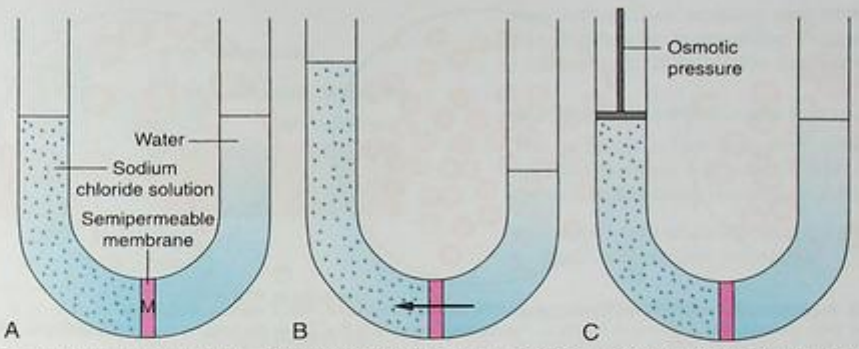


Figure 1.3-6 Diagrammatic representation of phenomenon of osmosis: A, semipermeable membrane 'M' separates sodium chloride solution from pure water; B, net movement of water occurs through M from pure water to the sodium chloride solution and C, demonstration of osmotic pressure (net movement of water from pure water to sodium chloride solution is prevented by applying appropriate pressure on the solution).

EMF is the electromotive force between outside and inside of the membrane

C_0 is the concentration of ion outside the membrane

C_1 is the concentration of ion inside the membrane

This equation is extremely important in understanding the membrane potential, and hence is discussed in detail in the relevant section (page 21).

4. ***Pressure gradient.*** It has been observed that the increased amount of energy is available to cause net movements of molecules from the high-pressure side towards the low-pressure side.

Osmosis

Osmosis refers to diffusion of water or any other solvent molecules through a semipermeable membrane (i.e. membrane permeable to solvent but not to the solute) from a solution containing lower concentration of solutes towards the solution containing higher concentration of solutes; Fig. 1.3-6 shows osmosis across a selective permeable membrane. When a sodium chloride solution is placed on one side of the membrane and water on the other side (Fig. 1.3-6A), then the net movement of water occurs from the pure water into the sodium chloride solution (Fig. 1.3-6B).

Osmotic Pressure

Osmotic pressure refers to the minimum pressure which when applied on the side of higher solute concentration prevents the osmosis. Figure 1.3-6C shows that when appropriate pressure is applied, the net diffusion of water into the sodium chloride solution is prevented.

The osmotic pressure in the body fluids refers to the pressure exerted by the solutes dissolved in water or other solvents. The osmotic pressure exerted by the colloidal substances in the body is called *colloidal osmotic pressure*. The colloidal osmotic pressure due to plasma colloids (proteins) is called *oncotic pressure*.

The osmotic pressure depends on the number of molecules or ions dissolved in a solution rather than their size, type, or chemical composition. In the case of nondissociated solutes, 1-g molecular weight of any substance shall contain similar number of molecules and hence exerts similar degree of osmotic pressure, i.e. equal to 22.4 atm, whereas in the case of dissociated solutes the osmotic pressure depends on the number of ions resulting from its dissociation.

Osmole, Osmolality and Osmolarity

Osmole is the unit used in place of grams to express the concentration in terms of number of osmotically active particles in a given solution. One osmole is equal to the molecular weight of a substance in grams divided by the number of freely moving particles liberated in solution by each molecule. Thus,

- A molar solution of glucose contains 1 mole and exerts osmotic pressure of 1 atm.
- A molar solution of NaCl contains 2 osmoles (1 mole of Na^+ and 1 mole of Cl^-) and exerts osmotic pressure of 2 atm.
- A molar solution of $CaCl_2$ contains 3 osmoles (1 mole of Ca^{2+} and 2 moles of Cl^-) and thus exerts osmotic pressure of 3 atm.
- One milli osmole (mOsm) is 1/1000 of an osmole.

Osmolality of a solution refers to the number of osmotically active particles (osmoles) per kilogram (kg) of a solution, whereas *osmolarity* refers to the number of osmoles per litre (L) of a solution. Therefore, osmolarity is affected by the volume of the various solutes in the solution and the temperature, whereas the osmolality is not. The osmotic pressure is determined by the osmolality and not the osmolarity. However, the quantitative differences between the osmolarity and osmolality are less than 1%. In practice, *osmolarity* is more frequently used in physiological studies, since it is far more easier to measure osmolarity vis-a-vis osmolality.

Normal Plasma Osmolality. The normal osmolality of the extracellular and intracellular fluids is 290 milliosmoles per kilogram (mOsm/kg). In the plasma of the total osmolality, 270 mOsm are contributed by Na^+, Cl^- and HCO_3^-. The remaining 20 mOsm are contributed by glucose and urea. Because of the large molecular weight and hence lesser number of particles, plasma proteins (70 g/L) contribute 2 mOsm to the total plasma osmolality.

Tonicity of Fluids

In clinical practice, the word tonicity always refers to tonicity of a solution with respect to that of plasma (290 mOsm). In other

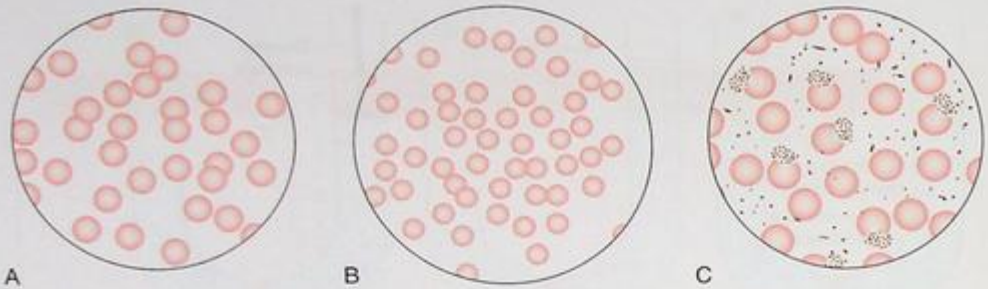


Figure 1.3-7 Tonicity of fluids: A, isotonic fluid (0.9% NaCl) has osmolarity similar to plasma, RBCs neither shrink nor swell in it; B, hypertonic fluid (2% NaCl) has osmolarity higher than plasma, RBCs shrink in it and C, hypotonic fluid (0.3% NaCl) has osmolarity lower than plasma, RBCs swell in it.

words, it is the red blood cell (RBC) membrane across which the tonicity is tested. Thus,

- *Isotonic fluids* are those which have osmolality similar to plasma. RBCs neither shrink nor swell in such solution (Fig. 1.3-7A). A solution of 0.9% NaCl is isotonic with plasma.
- *Hypertonic fluids* have osmolality higher than the plasma. The RBCs shrink in such solutions by losing water by osmosis (Fig. 1.3-7B).
- *Hypotonic fluids* are those whose osmolality is lower than that of plasma. The RBCs swell up in hypotonic solutions by gaining water by osmosis (Fig. 1.3-7C).

APPLIED ASPECTS

- The total plasma osmolality may increase in patients having severe dehydration.
- Increased blood glucose levels in patients with severe diabetes also increase the plasma osmolality.
- Excessive intravenous administration of 5% glucose decreases plasma osmolality leading to swelling of the body tissues.
- Hyperosmolality can cause coma by causing water to flow out of the brain cells (hyperosmolar coma).
- Raised plasma levels of urea in patients with renal diseases also cause hyperosmolality.

ACTIVE TRANSPORT

Active transport refers to the mechanism of transport of substances against the chemical and/or electrical gradient. Active transport involves expenditure of energy which is liberated by breakdown of high-energy compounds like adenosine triphosphate (ATP). Since the transport of substances occur against the chemicoelectrical gradient, this process is also called *uphill movement.*

Mechanism of Active Transport

The active transport is also carrier-mediated, since the carrier proteins are involved in the transport mechanism; so like facilitated diffusion the active transport also shows specificity, saturation and competition.

Since the active transport mechanism involves the expenditure of energy, the transporting carrier protein system is also called the *active pump mechanisms.*

Substances transported actively across the cell membrane include

- *Ionic substances* such as Na^+, K^+, Ca^{2+}, Cl^- and I^- and
- *Nonionic substances* such as glucose, amino acids and urea.

Types of Active Transport

The active transport is of two types:

- Primary active transport and
- Secondary active transport.

Primary Active Transport Processes

In primary active transport process, the energy is derived directly from the breakdown of ATP or some other high-energy phosphate compound. Some of the important pumps involved in the primary active transport processes are as follows:

- Sodium–potassium pump,
- Calcium pump and
- Potassium–hydrogen pump.

1. Sodium–Potassium Pump

Sodium–potassium (Na^+–K^+) pump is present in all the cells of the body. It is involved with the active transport of sodium ions outwards through the cell membrane and potassium ions inwards simultaneously. Thus, this pump is responsible for maintaining the Na^+ and K^+ concentration differences across the cell membrane and for establishing a negative electrical potential inside the cells.

Structure of Na^+–K^+ Pump (Fig. 1.3-8). The carrier protein involved in Na^+–K^+ pump is a complex consisting of two separate protein units: a larger α subunit (molecular weight approximately 100,000) and a smaller β subunit (molecular weight approximately 55,000). The α subunit is mainly concerned with Na^+–K^+ transport. It obtained the following binding sites:

- Three intracellular sites—one each for binding sodium ions ($3Na^+$) and ATP, and one phosphorylation site.
- Two extracellular sites—one each for binding potassium ions ($2K^+$) and ouabain.

Mechanism of Operation of Na^+–K^+ Pump (Fig. 1.3-9). The functioning of Na^+–K^+ pump involves the use of enzyme ATPase. The enzyme ATPase is activated when three sodium

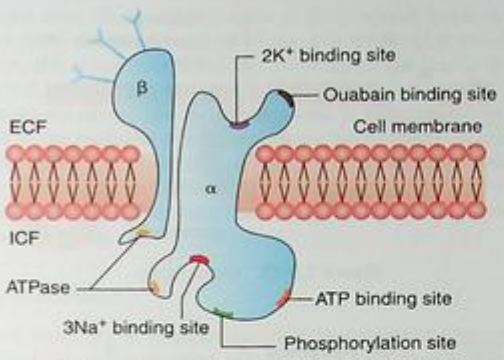


Figure 1.3-8 Structure of sodium–potassium ATPase pump.

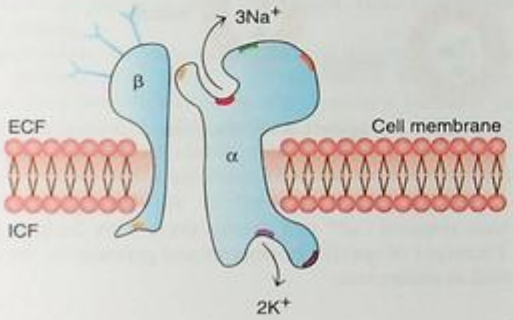


Figure 1.3-9 Mechanism of operation of sodium–potassium ATPase pump.

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ions and one ATP molecule bind to their respective binding sites. The activated ATPase catalyses the hydrolysis of ATP to ADP and liberates a high-energy phosphate bond of energy (phosphorylation). The energy so liberated is believed to cause a conformational change in the carrier protein molecule extruding sodium into the ECF. This is followed by binding of two potassium ions to the receptor site on extracellular surface of the carrier protein and dephosphorylation of a subunit which returns to its previous conformation, releasing potassium into the cytoplasm.

Functions of Na^+–K^+ Pump. The Na^+–K^+ pump subserves two principal functions:

1. ***Controlling the cell volume.*** It is the most important function of the Na^+–K^+ pump, without which most of cells of the body will swell up until they burst. When the Na^+–K^+ pump fails the cells swell up and burst.
2. ***Electrogenic activity.*** Na^+–K^+ pump acts as an electrogenic pump since it produces a net movement of positive charge out of the cell ($3Na^+$ out and $2K^+$ in), thus creating electrical potential across the cell membrane. This is basic requirement in nerves and muscles to transmit the signals.

2. Calcium Pump

The calcium pump forms another important active transport mechanism. Like Na^+–K^+ pump, it also operates through a carrier protein which has ATPase activity. But the difference from Na^+–K^+ pump is that the carrier protein binds calcium ions rather than sodium and potassium ions. The calcium pump helps in maintaining extremely low concentration of calcium in the ICF (10,000 times less than the ECF).

3. Potassium–Hydrogen Pump

The primary active transport system of hydrogen ion also operates through ATPase (K^+–H^+ ATPase) activity. These are present at following two places in the human body:

- Parietal cells of gastric glands (see page 262) and
- Renal tubules (see page 233).

Secondary Active Transport Processes

In secondary active transport processes, the energy is derived secondarily from the energy which has been stored in the form of ionic concentration differences between the two sides of a membrane, created in the first place by primary active transport. At many areas in the body transport of some other substance is coupled with the active transport of Na^+, i.e. the same carrier protein which is involved in the active transport of Na^+ also secondarily transports some other substance. The secondary active transport of substance may occur in the form of sodium cotransport or sodium countertransport.

Sodium Cotransport

The carrier protein here acts as a symport, i.e. transports some other substance along with the sodium. Substances carried by sodium cotransport include glucose, amino acids, chloride and iodine (Fig. 1.3-10).

Sodium Countertransport

The carrier protein involved here acts as an *antiport*, i.e. sodium ion is exchanged for some other substance. Some of the sodium countertransport mechanisms occurring in the body are *sodium–calcium countertransport*, *sodium–hydrogen countertransport* and *other countertransport* systems (Fig. 1.3-11).

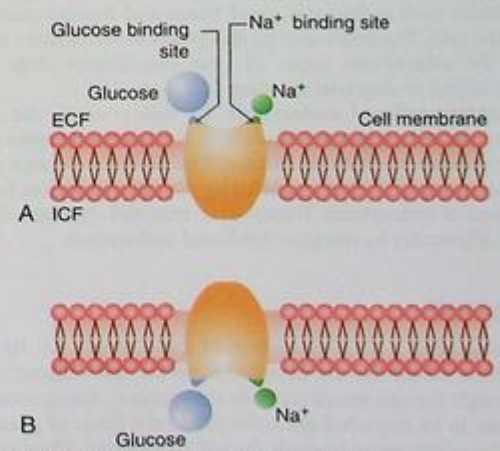

Figure 1.3-10 Postulated mechanism of sodium cotransport of glucose (secondary active transport): A, carrier protein has two receptor sites, one for sodium and one for glucose and B, conformational change in carrier proteins causes transport of both glucose and sodium inside the cell simultaneously.

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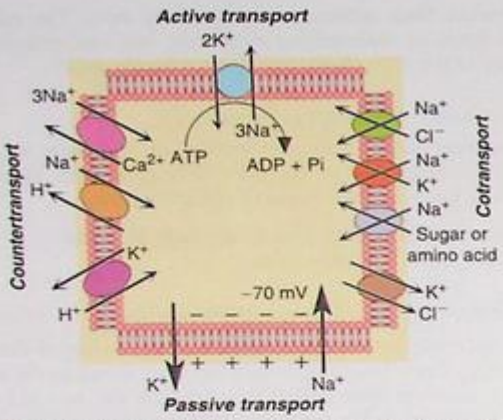


Figure 1.3-11 Composite diagram of the cell showing the various cotransport and countertransport mechanisms and maintenance of membrane potential as an effect of primary active transport of Na^+ and K^+.

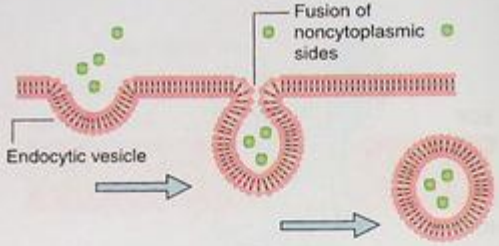


Figure 1.3-12 Endocytosis.

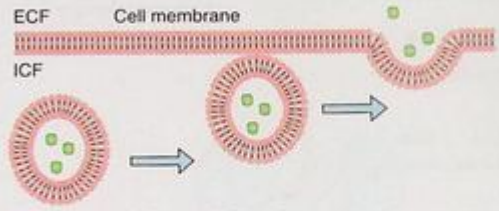


Figure 1.3-13 Exocytosis.

VESICULAR TRANSPORT

Vesicular transport mechanisms are involved in the transport of macromolecules such as large protein molecules which can neither pass through the membrane by diffusion nor by active transport mechanisms. The vesicular transport mechanisms include endocytosis, exocytosis and transcytosis.

Endocytosis

Endocytosis is the process in which the substance is transported into the cell by infolding of the cell membrane around the substance and internalising it (Fig. 1.3-12). It is further categorized into three types.

1. ***Pinocytosis,*** i.e. cell drinking, refers to the process of engulfing liquid substances by the enfolding of cell membrane, e.g. reabsorption by renal tubular epithelial cells.
2. ***Phagocytosis,*** i.e. cell eating, is the process of engulfing solid particles such as bacteria, dead tissue and foreign particles by the cells. The process of phagocytosis involves three steps: (i) the attachment stage, (ii) the engulfment stage and (iii) killing or degradation stage (see page 77).
3. ***Receptor-mediated endocytosis.*** In this process, the substance to be transported binds with the special receptor protein present on the cell surface. The receptor protein-substance complex is then engulfed by the cell membrane by the process of endocytosis. Transport of iron and cholesterol into the cells occurs by receptor-mediated endocytosis.

Exocytosis

Exocytosis (Fig. 1.3-13) is reverse of endocytosis, i.e. by this process the substances are expelled from the cell without passing through the cell membrane. In this process, the substances which are to be extruded are collected in the form of granules or vesicles which move towards the cell membrane. Their membrane then fuses to the cell membrane. The area of fusion breaks down releasing the contents to the exterior and leaving the cell membrane intact. Release of hormones and enzymes by secretory cells of the body occurs by exocytosis. The process of exocytosis requires Ca^{2+} and energy along with docking proteins. Excretion of specific hormones and granules by the cells is termed as *emiocytosis.*

Transcytosis

Vesicular transport within the cell is called transcytosis or cytopempsis. It is quite similar to exocytosis and endocytosis. Three basic steps involved in this process are (i) vesicle formation, (ii) vesicle transportation and (iii) docking in the cell.

OTHER TRANSPORT PROCESSES

So far, we have considered transport across the cell membrane, i.e. movement of substances between the ICF and the ECF through the cell membrane. In addition to this, there are many situations in the body where transport of substances occurs through the epithelia and the capillary endothelial cell membrane. Some of these processes discussed briefly are as follows:

- Transport across epithelia and
- Ultrafiltration.

Transport Across Epithelia

Transport across epithelia involves movement of the substances from one side of the epithelium to the other. The transepithelial transport occurs in body cavities lined by continuous sheet of cells such as in gastrointestinal tract, renal tubules, pulmonary airways and other structures. For transepithelial transport to occur the cells need to be bound by tight junctions, and have different ion channels and transport protein in different parts of their membrane. Transport across epithelia may occur in two ways:

1. ***Transport through the cells proper.*** In gastrointestinal tract and in urinary tubules substances are transferred from the

lumen into the epithelial cells at their apical borders and then from the basal borders of the cells into interstitial fluid. From the interstitial fluid the substances are finally transported into the blood through the capillaries.

2. ***Transport across the tight junctions.*** It has been identified that in the epithelia of small intestine, proximal renal tubules and gall bladder, most of the sodium chloride passes through the tight junctions (areas of tight adherence between the two adjacent cells) rather than traversing the whole length of the epithelial cells.

Ultrafiltration

When a solution of protein and salt is separated from plain water or a less-concentrated salt solution by a membrane permeable to salt and water and not to the protein, there will be a net movement of water on the protein side by diffusion and a movement of salt away from the protein side. This process is called dialysis.

Ultrafiltration. Refers to occurrence of dialysis under hydrostatic pressure (Fig. 4.4-12). Ultrafiltration is occurring at the capillary level in the body. The capillary blood is under hydrostatic pressure. The pressure is 35 mm Hg near the arteriolar end and gradually declines to 12 mm Hg near the venous end of the capillary. Through the capillaries, there occurs ultrafiltration of all the constituents of the plasma except the proteins into the interstitial spaces. Ultrafiltration plays important role in the formation of body fluids (see page 142) (Fig. 4.4-12).

SELF-ASSESSMENT

1. Describe the mode of transport of water soluble substances across the cell membrane.
2. Describe the gating mechanism of protein channels.
3. Mechanism of action of Na^+–K^+ ATPase.
4. Differentiate between:
   - Active and passive transport
   - Simple and facilitated diffusion
   - Osmotic and oncotic pressure
   - Exocytosis and endocytosis
   - Transcytosis and pinocytosis
   - Isotonic and hypertonic solution
   - Primary active and secondary active transport
5. Define the followings terms:
   - Diffusion
   - Osmosis
   - Osmotic pressure
   - Endocytosis
   - Exocytosis
   - Transcytosis
   - Ultrafilterate

1.4 Membrane Potential

CHAPTER OUTLINE

Introduction
Genesis of Membrane Potential
Selective Permeability of the Cell Membrane
Gibbs–Donnan Membrane Equilibrium
Nernst Equation
Goldmann–Hodgkin–Katz Equation
Role of Na^+–K^+ ATPase Pump
Recording of Membrane Potential
Instruments Used for Recording
Technique of Recording

INTRODUCTION

There exists a potential difference across the membrane of all living cells with the inside being negative in relation to the outside. This potential difference is called *membrane potential*, because the cations and anions arrange themselves along the outer and inner surfaces of the cell membrane. The magnitude of membrane potential varies from cell to cell and in a particular cell varies according to its functional status. For example, a nerve cell has a membrane potential of −70 mV (inside negative) at rest, but when it gets excited the membrane potential becomes about +30 mV (inside positive). The membrane potential at rest is called *resting membrane potential* or resting transmembrane potential or simply resting potential. The term rest does not imply that cell is metabolically quiescent but that it is not undergoing any electrical change. The membrane potential measured during excited state of the cell is called *action potential.*

GENESIS OF MEMBRANE POTENTIAL

Membrane potential is basically due to unequal distribution of ions across the cell membrane, which in turn results due to the combined effect of various forces acting on the ions. The factors involved in genesis of membrane potential are as follows:

- Selective permeability of the cell membrane,
- Gibbs–Donnan membrane equilibrium,
- Nernst equation,
- Constant field Goldmann's equation and
- Sodium–potassium ATPase pump.

Selective Permeability of the Cell Membrane

The cell membrane is selectively permeable, i.e. to some ions it is freely permeable, to others impermeable and to some others it has variable permeability as follows:

- Ions such as Na^+, K^+, Cl^- and HCO_3^- are diffusible ions. The cell membrane is freely permeable to K^+ and Cl^- and moderately permeable to Na^+.
- The cell membrane is practically impermeable to intracellular proteins and organic phosphate which are negatively charged ions.
- Presence of gated channels in the cell membrane is responsible for the variable permeability of certain ions in different circumstances.

Gibbs–Donnan Membrane Equilibrium

According to Gibbs–Donnan membrane equilibrium, when two ionized solutions are separated by a semipermeable membrane at equilibrium:

- Each solution shall be electrically neutral, i.e. total charges on cations will be equal to total charges on anions.
- The product of diffusible ions on one side of the membrane will be equal to product of diffusible ions on the other side of the membrane.

To understand, let us consider 'M' is a semipermeable membrane separating two ionized solutions of sodium chloride A and B (Fig. 1.4-1). Then according to the *Gibbs–Donnan equilibrium:*

1. Each solution is electrically neutral, i.e.

$$(\text{cations})_A = (\text{anions})_A \text{ and } (\text{cations})_B = (\text{anions})_B$$

OR

$$(Na^+)_A = (Cl^-)_A \text{ and } (Na^+)_B = (Cl^-)_B$$

2. The product of diffusible ions on both sides will be equal, i.e.

$$(\text{diffusible cations})_A \times (\text{diffusible anions})_A = (\text{diffusible cations})_B \times (\text{diffusible anions})_B$$

OR

$$[(Na^+)_A \times (Cl^-)_A] = [(Na^+)_B \times (Cl^-)_B]$$

From the above equation, the ratio of diffusible ions at equilibrium is as follows:

$$\frac{(\text{diffusible cations})_A}{(\text{diffusible cations})_B} = \frac{(\text{diffusible anions})_B}{(\text{diffusible anions})_A}$$

OR

$$\frac{[Na^+]_A}{[Na^+]_B} = \frac{[Cl^-]_B}{[Cl^-]_A}$$

Thus, there will be symmetrical distribution of ions at equilibrium. But if one or more nondiffusible ions 'X^-' are present on one side (A side) of the membrane, then according to Gibbs–Donnan equilibrium the distribution of diffusible ions is as follows:

1. Both solutions will be electrically neutral, i.e.

$$(Na^+)_A = (Cl^-)_A + (X^-)_A \text{ and } (Na^+)_B = (Cl^-)_B$$

Therefore,

$$(Na^+)_A + (Cl^-)_A + (X^-) > (Na^+)_B + (Cl^-)_B \quad \text{(i)}$$

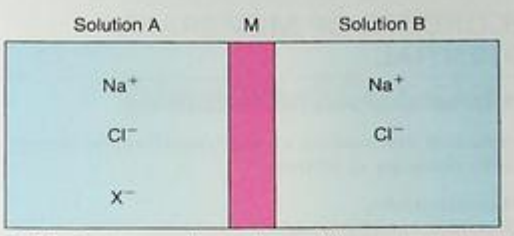


Figure 1.4-1 Semipermeable membrane 'M' separates ionic solutions of sodium chloride A and B.

2. The product of diffusible ions on two sides will be equal, i.e.

$$(Na^+)_A \times (Cl^-)_A = (Na^+)_B \times (Cl^-)_B \qquad \text{(ii)}$$

From the relationship of (1) and (2), it is found that

- $(Na^+)_A > (Na^+)_B$ and
- $(Cl^-)_A < (Cl^-)_B$.

Hence, there is unequal distribution of diffusible ions (asymmetrical). At equilibrium, Na^+ being greater on the side which contains nondiffusible anions 'X^-' (side A) and anion Cl^- is greater on the other side (side B). However, their concentration ratios are equal.

Since the intracellular fluid (ICF) contains nondiffusible anions such as proteins and organic phosphate, so, according to Gibbs–Donnan equilibrium there should be an asymmetrical distribution of diffusible ions across the cell membrane with cations being more inside than the outside. However, in reality interior of the cell is negatively charged, which will be explained in the ensuing discussion.

Nernst Equation

The asymmetrical distribution of diffusible ions across the cell membrane in the form of excess diffusible cation inside due to the Gibbs–Donnan equilibrium (as explained above) results in concentration gradient. As a result of which diffusible cations (K^+) will try to diffuse back into the extracellular fluid (ECF) from ICF, but it is counteracted by the electrical gradient, which will be created due to the presence of nondiffusible anions inside the cell. Thus, equilibrium will be reached between the concentration gradient and the electrical gradient, resulting in diffusion potential (equilibrium potential) across the cell membrane. The magnitude of this equilibrium potential can be determined by the Nernst equation as:

$$E_{(m)} = -\frac{RT}{ZF} \ln \frac{(Conc)_i}{(Conc)_o}$$

where

$E_{(m)}$ = Equilibrium potential (in millivolts) of the ions at which efflux and influx of the ions are equal

R = The natural gas constant and its value is 8.316 J/degree

T = The absolute temperature

F = The Faraday constant and its value is represented as:

$$\frac{\text{No. of Coulomb}}{\text{mole of charge}} = 96{,}500 \text{ Coulomb/mole}$$

Z = The valency of the ion

ln = Symbol for natural logarithm

$(Conc)_i$ = The concentration of the ions in the intracellular fluid (inside)

TABLE 1.4-1 Equilibrium Potential, $E_{(m)}$, for Important Ions in a Mammalian Spinal Motor Neuron

Ion	Concentration (mmol/L of H_2O)		Equilibrium Potential (mV)
	Outside the Cell	Inside the Cell	
Na^+	150	15	+60
K^+	4	140	−90
Cl^-	125	09	−70
Ca^{2+}	2.4	<1	+130

$(Conc)_o$ = The concentration of the ions in the extracellular fluid (outside)

At normal body temperature (37°C), converting from the natural log to the base 10 log and replacing some of the constants with numerical values, the equation can be simplified to

$$E_{(m)} = \pm 61 \log \frac{(Conc)_i}{(Conc)_o}$$

The equilibrium potential, $E_{(m)}$, for some of the important ions in the mammalian spinal motor neuron calculated from the simplified Nernst equation is shown in Table 1.4-1.

Goldmann–Hodgkin–Katz Equation

The Nernst equation helps in calculating the equilibrium potential for each ion individually. However, the magnitude of the membrane potential at any given time depends on the distribution of Na^+, K^+ and Cl^- and the permeability of each of these ions. The integrated role of different ions in the generation of membrane potential can be described accurately by the *Goldmann's constant field equation* or the so-called Goldmann–Hodgkin–Katz (GHK) equation:

$$V = \frac{RT}{F} \ln \frac{P_{k^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o}{P_{k^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}$$

where

V = The membrane potential

R = The gas constant

T = The absolute temperature

F = The Faraday constant

P_{k^+}, P_{Na^+} and P_{Cl^-} = The permeabilities of the membrane to K^+, Na^+ and Cl^-, and brackets signify concentration and i and o refer to inside and outside of the cell, respectively.

Inferences of the Goldmann's Constant Field Equation

The following important inferences can be drawn from the Goldmann's constant field equation:

1. Most Important Ions for Development of membrane potentials in nerve and muscle fibres are sodium, potassium and chloride. The voltage of membrane potential is determined by the concentration gradient of each of these ions.

2. Degree of Importance of each of the ions in determining the voltage depends on the membrane permeability of the individual ion. For example, if the membrane is impermeable to K^+ and Cl^-, then the membrane potential will be determined by the Na^+ gradient alone and the resulting potential will be equal to the Nernst potential for sodium.

3. Positive Ion Concentration from Inside the Membrane to Outside is responsible for electronegativity inside the membrane. This is because of the fact that due to concentration gradient, the positive ions diffuse outside leaving the nondiffusible negative ions inside the cell.

4. Signal Transmission in the nerves is primarily due to change in the sodium and potassium permeability because their channels undergo rapid change during conduction of the nerve impulse and not much change is seen in the chloride channels.

Role of Na^+–K^+ ATPase Pump

The role of Na^+–K^+ ATPase lies in building the concentration gradient. It serves to pump back the Na^+ that diffuses into the cell and K^+ that diffuses out of the cell. In the resting membrane, these diffusions are negligible, so the Na^+–K^+ pump works very feebly in this stage. Furthermore, although the Na^+–K^+ pump is potentially electrogenic (since it pumps out $3Na^+$ ions for $2K^+$ ions), at no stage the pump is able to build up a significant membrane potential. This is because of the fact that as soon as the pump creates a negative potential inside the cell, chloride ions rush out of the cell and restore electroneutrality. Thus, in other words, the pump pumps out $3Na^+$ ions and one Cl^- ion for every $2K^+$ ions it pumps in.

RECORDING OF MEMBRANE POTENTIAL

Instruments Used for Recording

The essential instruments used in recording the activity of an excitable tissue are as follows:

- Microelectrodes,
- Electronic amplifiers and
- Cathode ray oscilloscope (CRO).

Basic principles of the functioning of these instruments are described on page 32.

Technique of Recording

Technique of recording of membrane potential is described on page 33.

SELF-ASSESSMENT

1. Define resting membrane potential and its genesis.
2. What is the significance of Gibbs–Donnan membrane equilibrium, Nernst equation and Goldman–Hodgkin–Katz equation?

SECTION 2

Nerve Muscle Physiology

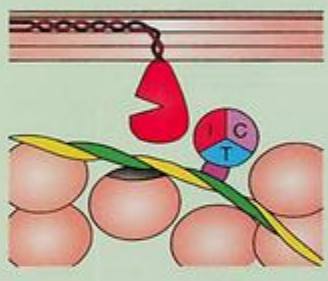
SECTION OUTLINE

2.1 The Nerve

2.2 Neuromuscular Junction

2.3 Skeletal Muscle

2.4 Smooth Muscle and Cardiac Muscle



The nerve and muscle cells are *excitable*, i.e. capable of generation of electrical impulses at their membranes. For this very reason, the physiological aspects of these excitable tissues are discussed together in this section.

The electrical impulses generated in the excitable tissues, in most instances, can be used to transmit signals along the membranes. A neuron is the basic unit of nervous tissue. It is responsible for reception, integration and transmission of information in the body. Muscles, like neurons, are excitable tissues but are characterized by the fact that a mechanical contraction follows an action potential.

To understand the physiological aspects, it is imperative to have knowledge about the *functional anatomy* and physiological properties of the nerve, the muscle and the neuromuscular junction.

2.1 The Nerve

CHAPTER OUTLINE

Functional Anatomy
Neuron
Neuroglia
Peripheral Nerve

Biological Activities
Protein Synthesis

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FUNCTIONAL ANATOMY

Neuron

Neuron, or the nerve cell, is the structural and functional unit of the nervous system. The nervous system of humans is made up of innumerable neurons. The total number of estimated neurons in the human brain is more than 10^{12}. The neurons are linked together in a highly intricate manner. It is through these connections that the body is made aware of changes in the environment or of those inside the body itself, and then appropriate responses to such changes are produced.

Structure

Neurons vary considerably in size, shape and other features. However, most of them have some major features in common. The basic structure of a neuron is best studied in a spinal motor neuron. A neuron primarily consists of the cell body and processes called *neurites*, which are of two kinds: dendrites and axon (Fig. 2.1-1).

Cell Body The cell body of a neuron is also called the *soma* or *perikaryon* and may be round, stellate, pyramidal or fusiform in shape. Like any other cell, it consists of a mass of cytoplasm with all its principal constituents surrounded by a cell membrane. The cell body contains a large nucleus with one or two nucleoli, but there is no centrosome. The absence of centrosome indicates that the neuron has lost its ability for division. Thus, neurons once destroyed are replaced only by neuroglia. In addition to the general features of a typical cell (page 7), the cytoplasm of a neuron has the following distinctive characteristics (Fig. 2.1-1):

Nissl Granules/Bodies These are basophilic granules that seem to be composed of rough-surfaced endoplasmic reticulum. The Nissl bodies are present in the dendrites as well but are usually absent from the axon hillock and the axon.

Neurofibrillae These consist of microfilaments and microtubules. In certain degenerative diseases like Alzheimer disease, the neurofilament protein gets altered, resulting in the formation of *neurofibrillary tangles*.

Pigment Granules These are seen in some neurons. For example, *neuromelanin* is present in the neurons of substantia nigra. Ageing neurons contain a pigment called *lipofuscin*.

Dendrites

The dendrites are multiple, small branched processes. Dendrites contain Nissl bodies and neurofibrillae.

Dendrites are the *receptive processes* of the neuron, receiving signals from other neurons via their synapses with axon terminals.

Axon

The axon is the single long process of the nerve cell. It varies in length from a few microns to a metre. It originates from the conical extension of the cell body called *axon hillock*, which is devoid of the Nissl bodies. The part of the axon between the axon hillock and the beginning of myelin sheath is called the *initial segment*. In the axon, the cell membrane continues as *axolemma* and the cytoplasm as *axoplasm*. The axon terminates

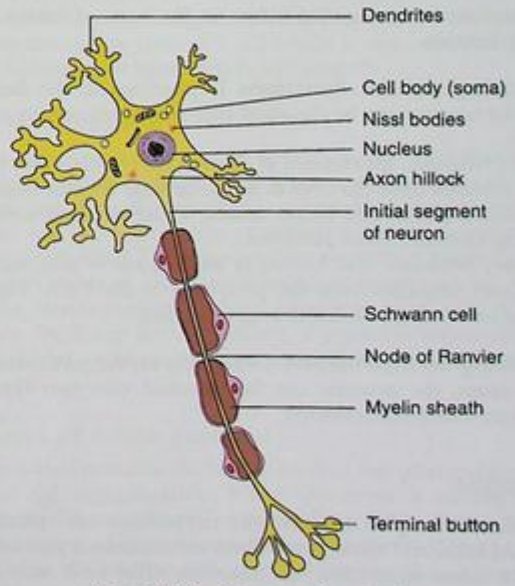


Figure 2.1-1 Structure of a typical neuron.

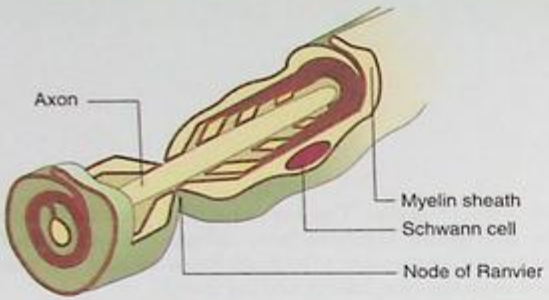


Figure 2.1-2 Structure of a myelinated neuron. *Note:* Schwann cell encircles the axon to form myelin sheath.

by dividing into a number of branches, each ending in a number of *synaptic knobs* that are also known as *terminal buttons* or axon telodendria. Synaptic knobs contain microvesicles in which chemical neurotransmitters are stored. *Myelin sheath* is present around the axon in the so-called *myelinated nerve fibres* (Fig. 2.1-2).

Myelin sheath, which consists of a protein–lipid complex, is produced by glial cells called *Schwann cells*, which encircle the axons, forming around it a thin sleeve. Each Schwann cell provides the myelin sheath for a short segment of the axon. At the junction of any two such segments, there is a short gap, i.e. periodic 1 μm constrictions at about a distance of 1 mm. These gaps are the *nodes of Ranvier*. There are some axons which are devoid of myelin sheath.

Myelination of axons increases the speed of conduction, but greatly increases their diameter.

Axons perform the specialized function of conducting impulses away from the cell body. They transmit propagated impulses (all-or-none transmission).

Types of Neurons

Neurons have been classified below on the basis of functions and myelination.

Depending on the Functions Depending on the functions, the neurons can be classified into two types: motor and sensory.

1. Motor Neurons, also known as efferent nerve cells, carry the motor impulses from the CNS to the peripheral effector organs like muscles, glands and blood vessels. These neurons have a very long axon and short dendrites.

2. Sensory Neurons, also known as afferent nerve cells, carry the sensory impulses from the periphery to the CNS. These neurons have a short axon and long dendrites.

Depending on Myelination Depending on the myelination of the axons, the neurons can be classified into two types: myelinated and nonmyelinated.

Neuroglia

Neuroglia or the glial cells are the supporting cells present within the brain and spinal cord. There are numerous glial cells, about 10 times more than the neurons. Glial cells may be divided into two major categories (Fig. 2.1-3):

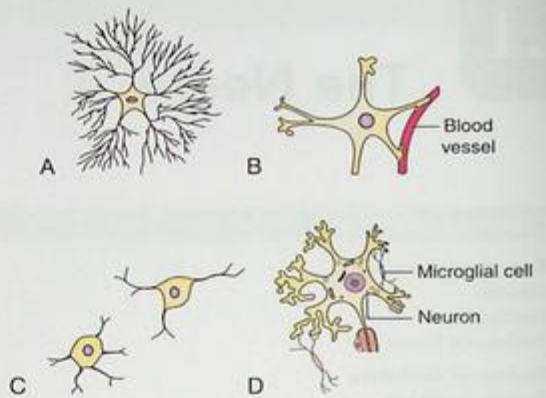


Figure 2.1-3 Different types of glial cells: (A) fibrous astrocyte; (B) protoplasmic astrocyte; (C) oligodendrocyte; and (D) microglial cells.

1. Macroglia Macroglia or large glial cells are ectodermal in origin. These are of two types:

- *Astrocytes*, which may be subdivided into fibrous and protoplasmic astrocytes
- *Oligodendrocytes*

2. Microglia Microglia or the small glial cells are mesodermal in origin. These are the smallest neuroglial cells having a flattened cell body and short processes. These are more in number in the grey matter than in the white matter. These act as phagocytes and become active after damage to nervous tissue by trauma or disease.

Peripheral Nerve

A compact bundle of axons located outside the CNS is called a nerve. In a nerve, the axons are arranged in different bundles called fasciculi (Fig. 2.1-4).

- Each axon or the nerve fibre is covered by *endoneurium*, which is bounded internally by basal lamina around the Schwann cells and externally by the relatively impermeable inner basal lamina of the perineurium.
- Each fasciculus is covered by *perineurium*. The cells of the perineurium are highly adherent and act as a barrier to the

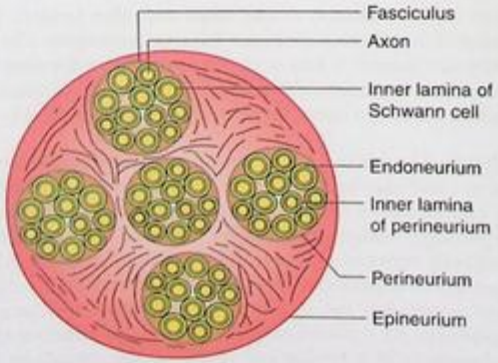


Figure 2.1-4 Cross-section of a peripheral nerve.

passage of particulate traces, dye molecules or toxins into the endoneurium.
- The whole nerve is covered by *epineurium*, which is a tubular sheath formed by an areolar membrane. It limits the extent to which the nerve can be stretched by body movements or external pressure, thereby protecting the fragile axons inside the nerve.

BIOLOGICAL ACTIVITIES

Protein Synthesis

The cell bodies (soma) of all the neurons contain a cellular apparatus required for the protein synthesis, i.e. the ribosomes and the Golgi apparatus. The axons do not have these organelles, so all the proteins, including the neurotransmitters, are synthesized in the cell body and then transported along the axon to the synaptic knobs by the process of *axoplasmic flow*, as discussed below.

Axoplasmic Transport

Axoplasm, the cytoplasm of the neurons, stays in constant motion. The axoplasmic transport is vital to nerve cell functions because movements of various materials occur through it. The axoplasmic transport is of two types:

1. Anterograde Transport Anterograde transport means the transport of materials away from the cell body. Some materials travel 100–400 mm a day along the axoplasm. Microtubules play an important role in this form of transport.

2. Retrograde Transport Retrograde transport, i.e. axoplasmic flow towards the cell body, may also carry tetanus toxin and neurotropic viruses (e.g. polio, herpes simplex and rabies) along the axon into the neuronal cell bodies in the CNS. It has also been employed by the neuroanatomists for charting out neural pathways.

ELECTRICAL PROPERTIES OF NERVE FIBRE

The main electrical properties of the nerve fibres are as follows:

- ***Excitability***, i.e. the capability of generating electrical impulses (action potential)
- ***Conductivity***, i.e. the ability of propagating the electrical impulses generated along the entire length of nerve fibres

Excitability

Excitability is that property of the nerve fibre by virtue of which it responds by generating a nerve signal (electrical impulses or the so-called action potentials) when it is stimulated by a suitable stimulus, which may be mechanical, thermal, chemical or electrical. In experimental studies, electrical stimulus is more frequently employed because its strength and frequency can be accurately controlled.

Before discussing the excitability (production of action potential), it will be useful to know about the electrical potential in the nerve fibre at rest, i.e. before it is stimulated (*resting membrane potential*).

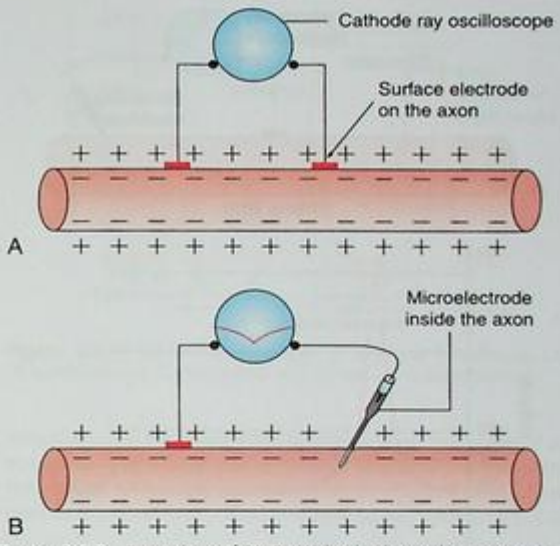


Figure 2.1-5 Recording of RMP: (A) both electrodes are on the surface of axon, no potential difference is recorded and (B) one electrode on the surface and other inserted inside the axon, potential difference (–70 mV) is recorded.

Resting Membrane Potential

The study of electrical activity of a tissue has been made possible due to advances in the method of recording electrical potentials, especially the development of microelectrodes and the 'cathode ray oscilloscope' (CRO).

As shown in Fig. 2.1-5, when two electrodes are placed on the surface of a nerve fibre and connected to a CRO, no potential difference is observed. However, if one of the microelectrodes is inserted inside the nerve fibre (Fig. 2.1-5), a steady potential difference of −70 mV (inside negative) is observed on the CRO. This is resting membrane potential (RMP) and indicates the resting state of a cell which is also called the *state of polarization*. For more details, see page 20.

Action Potential

The *action potential* may be defined as the brief sequence of changes which occur in RMP when stimulated by a threshold stimulus. When the stimulus is subminimal or subthreshold, it does not produce action potential, but does produce some changes in RMP. There is slight depolarization for about 7 mV, which cannot be propagated, because propagation occurs only if the depolarization reaches a firing level of 15 mV (–55 mV). Once the firing level is reached, it produces action potential, i.e. abrupt depolarization with propagation (action potential) occurs.

Phases of Action Potential

The action potential basically occurs in two phases: depolarization and repolarization. When the nerve is stimulated, the polarized state (–70 mV) is altered, i.e. RMP is abolished and the interior of the nerve becomes positive (+35 mV) as compared to the exterior. This is called the *depolarization phase*. In no time reverse occurs to the nearly original potential, and this

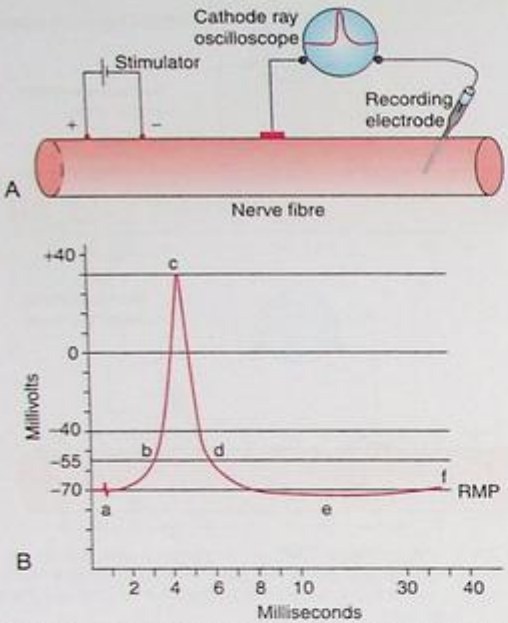


Figure 2.1-6 Recording of action potential of a large mammalian myelinated nerve fibre: (A) arrangement for recording action potential and (B) various phases (components) of action potential (a, stimulus artefact; b, firing level; b and c, depolarization; c and d, repolarization; d and e, after depolarization; e and f, after hyperpolarization).

second phase of action potential is called the *repolarization phase*.

An action potential curve is obtained when RMP is being recorded on a CRO and the nerve fibre is stimulated at a short distance away from the recording electrode (Fig. 2.1-6A). It has the following components (Fig. 2.1-6B):

1. Resting Membrane Potential is recorded as a straight baseline at −70 mV.

2. Stimulus Artefact is recorded as a mild deflection of the baseline as soon as the stimulus is applied. The stimulus artefact occurs due to leakage of current from the stimulating electrode to the recording electrode.

3. Latent Period is recorded as a short isoelectric period (0.5–1 ms) following the stimulus artefact. It represents the interval between the application of stimulus and the onset of action potential. It depends on the distance between the site of stimulation, and the point of recording and the velocity of action potential along the particular axon.

4. Firing Level After the latent period, the phase of depolarization starts. To begin with, depolarization proceeds relatively slow up to a level called the *firing level* (–55 mV), at which depolarization occurs very rapidly.

5. Overshoot From the firing level, the curve reaches the zero potential rapidly and then *overshoots* the zero line up to +35 mV.

6. Spike Potential After reaching the peak (+35 mV), the phase of depolarization is completed and the phase of repolarization starts, and the potential descends quickly near the firing level. The phase of rapid rise of potential in depolarization and the phase of rapid fall of potential in repolarization combinedly constitute the so-called *spike potential*. Its duration is approximately 1 ms in an axon.

7. After Depolarization is the slow repolarization phase, which follows a rapid fall in spike potential and extends up to attainment of the RMP level. It is called the phase of *negative after potential* and lasts for about 4 ms.

8. After Hyperpolarization After reaching the resting level (–70 mV), the potential further falls and becomes more negative (–72 mV). This phase is called *after hyperpolarization* or the phase of *positive after potential*. It lasts for a prolonged period (35–40 ms). Finally, RMP is restored.

Ionic Basis of Action Potential

1. Polarization Phase RMP (–70 mV) is due to the distribution of more cations outside the cell membrane and more anions inside the cell membrane. At this point, though Na^+ ions are more in extracellular fluid (ECF), they cannot enter the cell due to the impermeability of the membrane.

2. Depolarization Phase When threshold stimulus is applied to the cell membrane, at the point of stimulation (Fig. 2.1-7), the permeability of the membrane for Na^+ ions increases. At first, the rise of permeability for Na^+ ions is slow till it reaches the *firing level*. When the membrane depolarizes, the Na^+ channels start opening up. The opening of the Na^+ channels depolarizes the membrane further, leading to the opening of a greater number of Na^+ channels. As the concentration gradient and electrical gradient of this ion are directed inwards, there occurs a rapid influx of Na^+ ions into the cell. This rapid entry of Na^+ is sufficient to overwhelm the repolarizing forces.

3. Repolarization Phase Repolarization occurs due to further decrease in Na^+ influx and K^+ efflux through the voltage-gated K^+ channels, which open later than Na^+ channels but remain activated for a prolonged period.

4. After Depolarization This is due to the fact that the rate of K^+ efflux slows down as the electrical gradient responsible for initial rapid diffusion declines. This last phase of slow repolarization due to slow efflux of K^+ is called *after depolarization*.

5. After Hyperpolarization The slow efflux of K^+ continues even after RMP is reached, resulting in a prolonged phase of *hyperpolarization*, during which the membrane potential falls up to −72 mV. However, little after, the voltage-gated K^+ channels also shut down. The final ionic distribution is brought to the resting state by the action of the Na^+–K^+ pump and the leak channels (K^+, Cl^-).

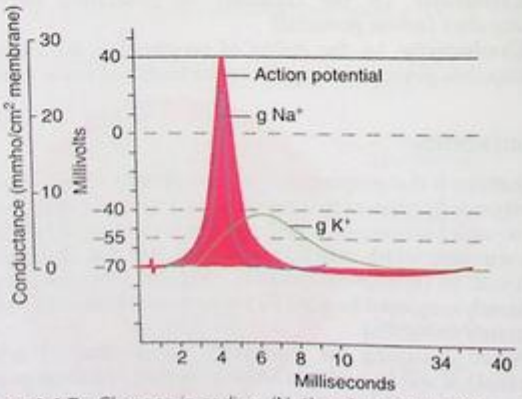


Figure 2.1-7 Changes in sodium (Na^+) and potassium (K^+) conductance during action potential.

Characteristics of Nerve Excitability Vis-à-Vis Characteristics of the Stimulus

1. Strength–Duration Curve

The relationship between the strength and duration of a stimulus has been studied by varying the duration of a stimulus and finding out the threshold strength for each duration. The results plotted on a semilog graph paper give the *strength–duration* curve (Fig. 2.1-8). The following inferences can be drawn from the strength–duration curve:

- *Rheobase (R)* refers to the minimum intensity of stimulus which if applied for adequate time (utilization time) produces a response.
- *Chronaxie (C)* refers to the minimum duration for which the stimulus of double the rheobase intensity must be applied to produce a response. Within limits, the chronaxie of a given excitable tissue is constant. In other words, the chronaxie is an index of the excitability of a tissue and can be used to compare the excitability of various tissues. For example, a nerve fibre has a far smaller chronaxie value than a muscle fibre, indicating greater excitability of the former.
- When a stimulus of weaker intensity than the rheobase is applied, it will not produce a response, no matter how long the stimulus is applied.
- Stimulus of an extremely short duration will not produce any response, no matter how intense that may be.

2. All-or-None Response

A single nerve fibre always obeys the 'all-or-none law', i.e. (Fig. 2.1-9):

- When a stimulus of subthreshold intensity is applied to the axon, then no action potential is produced (*none response*).
- A response in the form of spike of action potential is observed when the stimulus is of threshold intensity.
- There is no increase in the magnitude of action potential when the strength of stimulus is more than the threshold level (all response).

This all-or-none relationship observed between strength of stimulus and response achieved is known as *all-or-none* law.

3. Membrane Excitability During Action Potential

When a stimulus is applied to the nerve fibre membrane during the stage of action potential (produced by a previous threshold stimulus), the response elicited depends on the stage of action potential. Depending on the response elicited to the stimulus, the period of action potential can be divided into refractory period, supernormal period and subnormal period (Fig. 2.1-10).

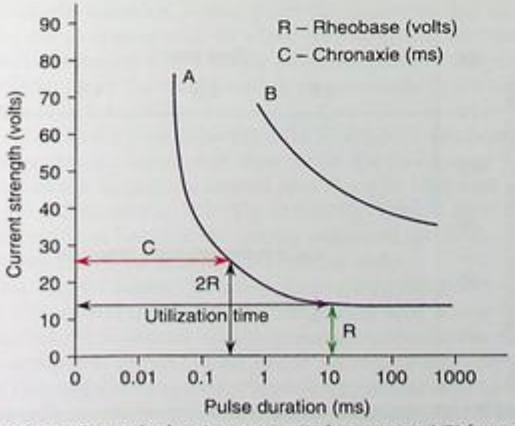


Figure 2.1-8 Strength–duration curves: (A) for nerve and (B) for muscle.

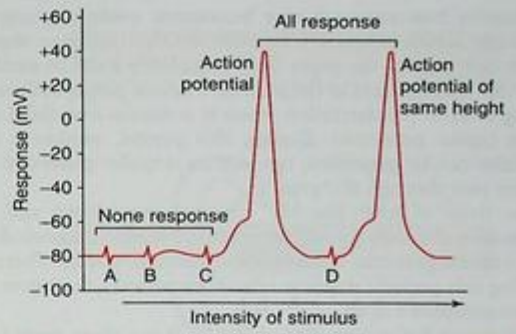


Figure 2.1-9 All-or-none response in a single nerve fibre: (A) and (B) subthreshold; (C) threshold; and (D) suprathreshold stimuli.

(i) Refractory Period Refractory period refers to the period following action potential (produced by a threshold stimulus) during which a nerve fibre either does not respond or responds subnormally to a stimulus of threshold intensity or greater than threshold intensity. It is of two types:

(a) Absolute Refractory Period (ARP) It is a short period following action potential during which the second stimulus,

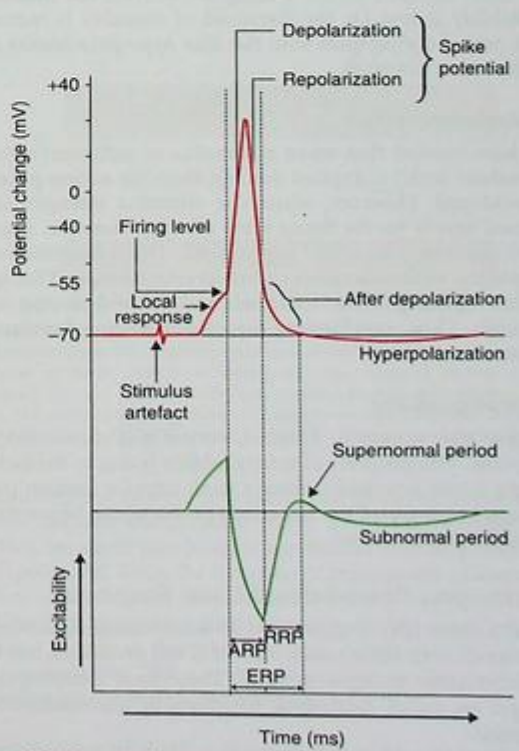


Figure 2.1-10 Membrane excitability during different phases of action potential: ARP (absolute refractory period), RRP (relative refractory period) and ERP (effective refractory period).

no matter how strong it may be, cannot evoke any response (another action potential). In other words, during an absolute refractory period, the nerve fibre completely loses its excitability. ARP corresponds to the period of action potential from the firing level to repolarization when it is almost one-third complete (spike potential). During this period, neither a fresh impulse can be generated, nor can an impulse generated elsewhere pass through this area.

Ionic Basis of ARP The Na^+ channels are closed and slow potassium channels are not yet opened. Sodium channels do not open unless potential comes back to the resting level. Therefore, during this period (absolute refractory period), the nerve fibre is not stimulated at all.

(b) Relative Refractory Period (RRP) It is a short period during which the nerve fibre shows response, if the strength of stimulus is more than normal. It extends from the end of ARP to the start of *after depolarization* of the action potential.

Ionic Basis of RRP During this stage, the Na^+ channels are coming out of an inactivated stage and voltage-gated potassium channels are still opened. The stronger stimulus (suprathreshold) at this stage is able to open more Na^+ channels and thus excite a response. The action potential elicited during this period, however, has a lower upstroke.

(ii) Supernormal Period During the supernormal period, the membrane is hyperexcitable, i.e. the threshold of stimulus is decreased. This period corresponds with the *after depolarization* phase of the action potential.

(iii) Subnormal Period During this period, the membrane excitability is low, i.e. the threshold of stimulus is increased. This period corresponds with the *after hyperpolarization* stage of the action potential.

4. Accommodation

We have studied that when a stimulus of sufficient strength (threshold level) is applied quickly, then the action potential is produced. However, when the stimulus strength is increased slowly to the firing level (during constant application), no *action potential is produced.* This phenomenon of adaptation to the stimuli is called *accommodation.* This is due to slow opening of Na^+ channels and delayed closing of K^+ channels. Thus, repolarizing forces overwhelm depolarizing forces.

5. Infatiguability

A nerve fibre cannot be fatigued, even if it is stimulated for a long time. This property of infatiguability is due to the fact that during action potential neither a fresh impulse (action potential) can be generated nor the action potential can be conducted through the nerve fibre.

Electrotonic Potential and Local Response

When a nerve fibre is stimulated by subminimal or subthreshold stimuli, then the action potential is not produced, but there do occur some changes in RMP. These local nonpropagated changes are called *electrotonic potentials* or *acute subthreshold potentials.*

Types of Electrotonic Potentials Depending on the nature (negative or positive) of subthreshold level current used to stimulate (Fig. 2.1-11), the electrotonic potentials can be classified into two types:

1. Catelectrotonic Potential Catelectrotonic potentials are localized depolarizing potential changes in the membrane potential produced when the stimulus of subthreshold strength is applied with a cathode. This potential change rises sharply and then decays exponentially with time.

2. Anelectrotonic Potential Anelectrotonic potentials are the localized hyperpolarizing potential changes in the membrane potential when anodal subthreshold current is applied.

Graded Potentials As shown in Fig. 2.1-11, the electrotonic potentials produced by varying intensities of stimuli are proportionate to the magnitude of stimulation. Therefore, these are also known as *graded potentials.* The graded response is achieved both at the cathode and at the anode up to 7 mV of depolarization or hyperpolarization.

Differences between graded potentials and action potential are summarized in Table 2.1-1.

Inhibition of Excitability

There are certain factors which inhibit the excitability of the nerve fibres. Some of the factors or the conditions which lead to inhibition or decrease in excitability are given below:

1. High Extracellular Calcium Concentration A high extracellular Ca^{2+} concentration decreases membrane permeability to Na^+ ions, thereby decreasing the membrane excitability.

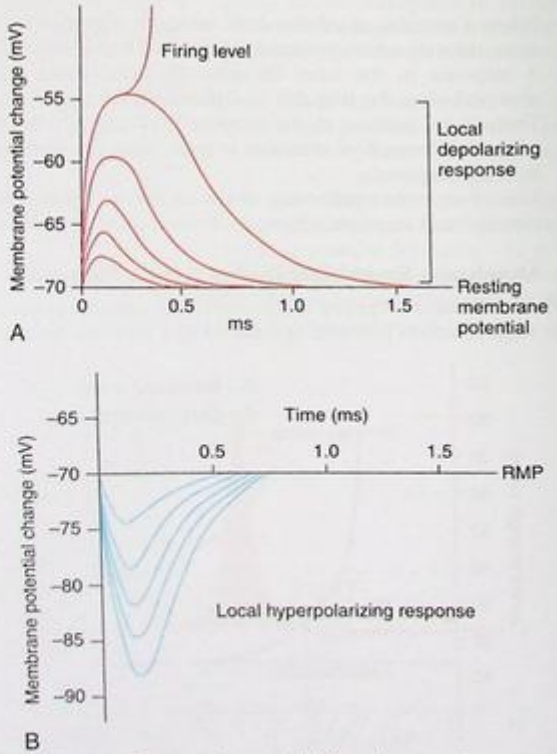


Figure 2.1-11 Electrotonic potential: (A) catelectrotonic potential and (B) anelectrotonic potential.

TABLE 2.1-1 Differences Between Graded Potential and Action Potential

Graded Potential	Action Potential
1. The amplitude of graded potential is proportionate to the intensity of the stimulus and can get summated.	The amplitude of action potential remains constant with increasing intensity of stimulus, therefore it cannot be summated.
2. Graded potentials can be either depolarizing or hyperpolarizing.	Action potential is always depolarizing.
3. Graded potential can be generated either spontaneously or in response to either physical or chemical stimuli.	Action potential is generated only in response to membrane depolarization.
4. Graded potentials cannot conduct impulse.	Action potential can conduct impulses.
5. Examples are as follows: • Receptor potential at sensory nerve endings. • Motor end plate potential.	Examples are as follows: • Action potential of a nerve fibre, skeletal muscle and cardiac muscle.

2. Local Anaesthetics Local anaesthetic agents like *procaine*, tetracaine and lidocaine block the Na^+ channels, thus reducing the membrane excitability.

Conductivity

Conductivity refers to the propagation of nerve impulse (action potential) in the form of a wave of depolarization through the nerve fibre. The mechanism of conduction of action potential along an unmyelinated nerve fibre and a myelinated nerve fibre is described below.

Propagation of Action Potential in an Unmyelinated Axon

The steps involved in the propagation of action potential along an unmyelinated axon are as follows:

- In the resting phase (polarized state), the axonal membrane is outside positive and inside negative (Fig. 2.1-12A).
- When an unmyelinated axon is stimulated at one site by a threshold stimulus, action potential occurs at that site, i.e. the site is depolarized. In other words, at that site outside becomes negative and inside becomes positive (reversal of polarity), but the neighbouring areas remain in a polarized state (Fig. 2.1-12C).
- As ECF and intracellular fluid (ICF) are both conductive to electricity, a current will flow from the positive polarized area to the negative activated area through ECF and in the reverse direction in ICF (Fig. 2.1-12C). Thus, a *local circuit current* flows between the resting polarized site to the depolarized site of the membrane (current sink).
- This circular current flow depolarizes the neighbouring area of the membrane up to the firing level, and a new action potential is produced, which, in turn, depolarizes the neighbouring area ahead. Thus, due to successive depolarization of the neighbouring area, the action potential is propagated along the entire length of the axon (Fig. 2.1-12D). This type of conduction is known as *electrotonic conduction*. Once initiated, the moving impulse cannot spread to reverse direction because the proximal site is in a *refractory state*, and, thus, the distal sites being in a polarized state keep on getting depolarized. Thus, the direction of propagation of impulse is that of the current flow inside the nerve fibre (Fig. 2.1-12E).
- The depolarization remains at any site for some length of time; therefore, the portion which depolarizes first also repolarizes first. Thus, the repolarization is also propagated following the depolarization (Fig. 2.1-12F).

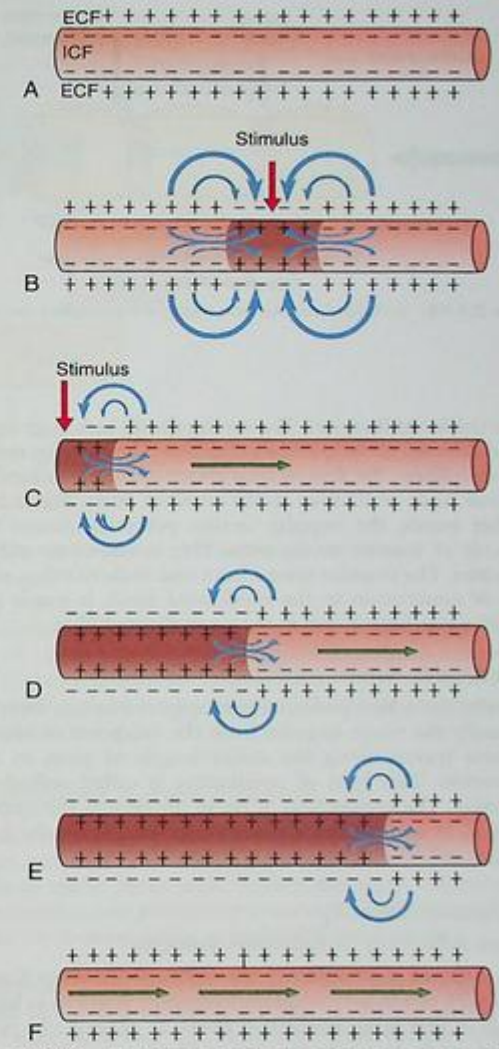


Figure 2.1-12 Electrotonic conduction of impulse in an unmyelinated nerve fibre: (A) resting phase (polarized state); (B) conduction of impulse in both directions when stimulus applied at the middle of nerve fibre; (C) when stimulus applied at one end of the nerve fibre; (D) and (E) propagation of impulse in one direction along the nerve fibre; and (F) repolarization (occurs in the same direction).

Propagation of Action Potential in a Myelinated Axon

The myelinated nerve fibres have a wrapping of myelin sheath with gaps at regular intervals, which are devoid of myelin

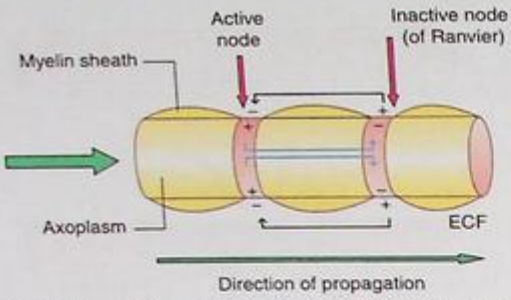


Figure 2.1-13 Saltatory conduction along a myelinated nerve fibre.

sheath (nodes of Ranvier). The myelin sheath acts as an insulator and does not allow the flow of current. Therefore, in myelinated nerve fibres, the flow of *local circuit of current* occurs only from one node of Ranvier to the adjacent node (Fig. 2.1-13). In other words, the impulse (action potential) jumps from one node of Ranvier to the next. This is known as *saltatory conduction*. The impulse jumps from one node to other, so the speed of conduction in the myelinated fibres is much more (50–100 times faster) than in the unmyelinated fibre.

Orthodromic Versus Antidromic Conduction

Normally, the action potential is propagated in one direction, i.e. usually the nerve impulse from the receptors or synaptic junctions travels along the entire length of axon to their termination. This type of conduction is called *orthodromic conduction*. The conduction of nerve impulse in the opposite direction, as seen in the sensory nerve supplying the blood vessels, is called *antidromic conduction*.

Conduction Velocity

Factors Affecting Conduction Velocity

The velocity of conduction in the nerve fibres varies from as little as 0.25 m/s in very small unmyelinated fibres to as high as 100 m/s in very large myelinated fibres. In general, the factors affecting conduction velocity are as follows:

1. Temperature A decrease in temperature delays conduction, i.e. slows down the conduction velocity.

2. Axon Diameter affects the conduction velocity through the *resistance offered by the axoplasm* (Ri) to the flow of axoplasmic current. If the diameter of the axon is more, the axoplasmic resistance (Ri) is lesser and hence the velocity of conduction is higher.

3. Myelination increases conduction velocity by the following effects:

- By increasing the axon diameter
- By the saltatory conduction produced due to its insulating effect (as discussed above)

Recording of Membrane Potentials and Action Potentials

The recording of membrane excitation and action potentials is made possible by the use of highly sophisticated equipment. The mammalian axons are about 20 μm or less in diameter; so being relatively small, it is very difficult to separate them out from other axons. Certain invertebrate species like crab (carcinus), cuttlefish (sepia) and squid (loligo) have giant cells. The largest axon found in the neck region of loligo is about 1 mm in diameter. The fundamental properties are quite similar to the human axons. Therefore, these animals can be used for recording various events.

Instruments Used for Recording

The instruments used in recording the activity of excitable tissue are as follows:

- Microelectrodes
- Electronic amplifiers
- CRO

The basic principles behind the functioning of these instruments are as follows:

1. Microelectrodes Microelectrodes are usually a very small pipette (micropipette) of tip size less than 1 μm in diameter. The tip of a micropipette electrode is impaled through the cell membrane of the nerve fibre. Another electrode called an *indifferent electrode* is placed in ECF (Fig. 2.1-14).

The microelectrode can be connected to the CRO through a suitable amplifier for recording rapid changes in membrane potential during nerve impulse transmission.

2. Electronic Amplifier This device can magnify the potential changes of the tissue to more than thousand times so that these can be recorded on the oscilloscope screen.

3. Cathode Ray Oscilloscope CRO is almost an inertialess instrument, which can record and measure the electrical events of living tissues instantaneously. CRO primarily consists of a glass tube with a cathode, fluorescent surface (screen) and two sets of electrically charged plates (Fig. 2.1-14).

The Cathode is in the form of an electronic gun. When connected to a suitable anode and electric current, the electronic gun emits electrons.

Fluorescent Surface (the face of glass tube coated with fluorescent material) acts as a screen. The electrons emitted from the cathode are directed into a beam which hits this screen.

Electrically Charged Plates are arranged in the following two sets:

Horizontal Deflection Plates are placed on either side of the electron beam. These are connected to a sweep generator (*electronic sweep circuit*). When a voltage is applied across these plates, the beam of electrons (being negatively charged) is attracted towards the positively charged plate and repelled away by the negatively charged plate. If saw-tooth voltage (i.e. voltage is increased slowly, then suddenly reduced and again slowly increased) is applied, then the electron beam will steadily move towards the positively charged plate (with slowly increasing voltage), then back to its original position (with a sudden reduction in voltage) and then again move towards the positively charged plate. In this way, the electron beam is made to sweep across the fluorescent screen horizontally, which will give a continuous marking of the line of glowing light.

Vertical Deflection Plates are placed above and below the electron beam. These are connected to recording electrodes placed

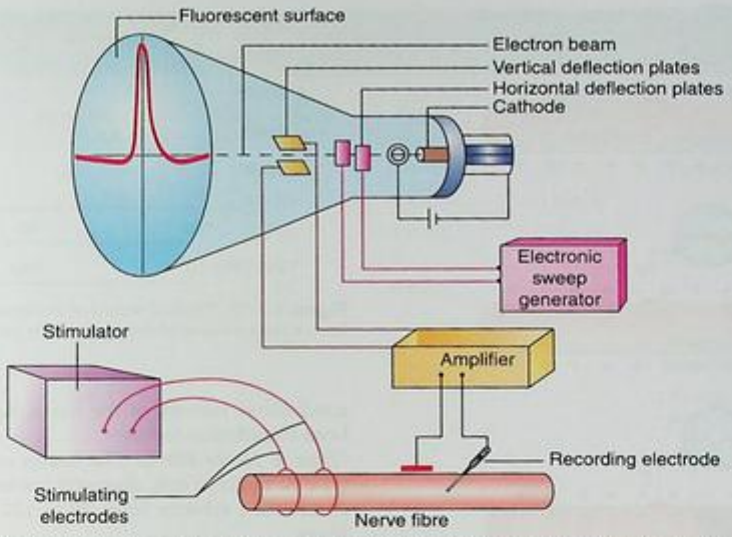


Figure 2.1-14 Cathode ray oscilloscope and simplified diagram to record action potential from a nerve fibre.

on the nerve through an electronic amplifier. The potential change occurring in the nerve will charge these plates, which will cause vertical (upward and downward) deflection of the electron beam. The magnitude of deflection will be proportional to the potential difference between the two plates. Thus, action potential is recorded as vertical deflection of the beam as it moves across the fluorescent screen of the CRO.

Recording of Resting Membrane Potential

The arrangement of electrodes for recording membrane potential is shown in Fig. 2.1-5. The electrical potential recorded at the surface of the membrane (exterior) when both the electrodes (indifferent and microelectrodes) are on the surface (outside) of the nerve fibre membrane, then no potential difference is recorded (zero potential), which is the potential of ECF. However, when the microelectrode is made to penetrate into the interior of cell, a constant potential difference (–70 mV) is observed. This is known as RMP (Fig. 2.1-5B).

Recording of Action Potential

Monophasic Recording of Action Potential For monophasic recording of action potential, one microelectrode is placed inside the nerve fibre and the other electrode on the outside surface. These electrodes are then connected to the CRO (Fig. 2.1-14). When the nerve is stimulated, a typical monophasic record of action potential obtained has the following components:

- Depolarization
- Repolarization

It has been described in detail on page 27.

Biphasic Recording of Action Potential For biphasic recording of action potential, both the exploring electrodes (x and y) are placed on the outside surface of nerve fibre and are connected to a CRO (Fig. 2.1-15). When the nerve is stimulated, the excitation of one electrode causes deflection opposite to that of another during the passage of impulse. A recording of this alternate deflection of one negative below the baseline and one positive above the baseline (called *biphasic action potential*) is depicted in Fig. 2.1-16.

Compound Action Potential

Compound action potential is the monophasic recording of action potential from a *mixed* nerve, which contains different types of nerve fibres with varying diameters. Therefore, the compound action potential represents an algebraic summation of the all-or-none action potentials of many axons.

Response of a Mixed Nerve to Stimulus Response of a mixed nerve to a stimulus depends on the thresholds of the individual axons in the nerve and their distance from the stimulating electrode (Fig. 2.1-17):

Features of a Compound Action Potential

- It has a unique shape (multiple peaks) because a mixed nerve is made up of different fibres with various speeds of conduction.
- The number and size of the peaks vary with the types of fibres in the particular nerve being studied.
- When fewer than maximal stimuli are used, the shape of compound action depends on the number and type of fibres stimulated.

NERVE FIBRE TYPES

Various schemes for the classification of the nerve fibres on the basis of their diameter and their conduction velocity have been proposed.

Classification of Nerve Fibres

1. Letter Classification of Erlanger and Gasser This is the best known classification based on the diameter and

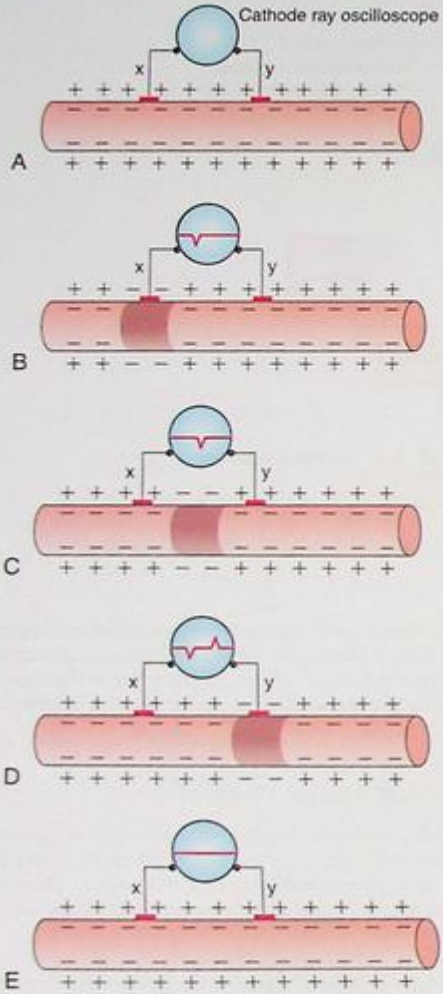


Figure 2.1-15 Arrangement for recording biphasic action potential (recording electrodes x and y are on the surface of the nerve fibre connected to cathode ray oscilloscope): (A) resting state; (B) on stimulation when the wave of excitation reaches at electrode 'x'; (C) when impulse passes beyond electrode 'x'; (D) when impulse reaches at electrode 'y'; and (E) when impulse passes away from electrode 'y'.

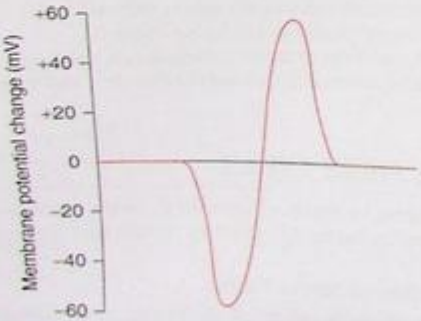


Figure 2.1-16 Typical complete record of biphasic action potential.

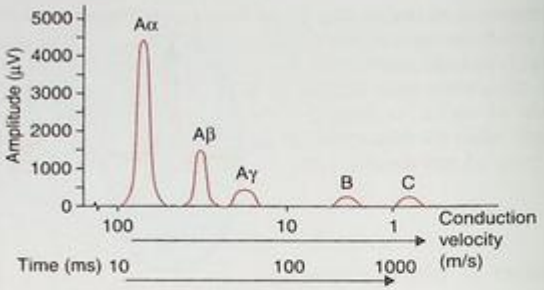


Figure 2.1-17 Typical record of compound action potential (recorded from a mixed nerve) showing multiple peaks.

conduction velocity of the nerve fibres. The nerve fibres have been classified as follows:

'Type A' Nerve Fibres The fastest conducting fibres are called type A fibres. Their diameter varies from 12 to 20 μm and conduction velocity from 70 to 120 m/s. They are myelinated fibres.

Type A fibres have been further subdivided into α, β, γ and δ. Type A fibres subserve both motor and sensory functions.

'Type B' Nerve Fibres These fibres are myelinated, have a diameter of less than 3 μm and their conduction velocity varies from 4 to 30 m/s. They form preganglionic autonomic efferent fibres, afferent fibres from skin and viscera, and free nerve endings in the connective tissue of muscle.

'Type C' Nerve Fibres These are unmyelinated, have a diameter of 0.4–1.2 μm and their conduction velocity varies from 0.5 to 4 m/s. They form the postganglionic autonomic fibres, some sensory fibres carrying pain sensations, some fibres from thermoreceptors and some from viscera.

The salient features of type A, B and C nerve fibres are summarized in Table 2.1-2.

2. Numerical Classification

Some physiologists have classified sensory nerve fibres by a numerical system into type Ia, Ib, II, III and IV. A comparison of the numerical classification and the letter classification is given in Table 2.1-3.

3. Susceptibility of Nerve Fibres to Hypoxia, Pressure and Local Anaesthetics

Hypoxia As given in Table 2.1-4, the type B fibres are most susceptible to hypoxia.

Pressure Type A fibres are most susceptible to pressure and type C the least.

Local Anaesthetics Type C fibres (conducting pain, touch and temperature sensations generated by cutaneous receptors) are most susceptible to local anaesthetics. This fact is useful for surgical interventions under local anaesthesia.

DEGENERATION AND REGENERATION OF NEURONS

When the axon of neuron is injured, a series of degenerative changes are seen at three levels:

- In the axon distal to injury
- In the axon proximal to injury
- In the cell body

TABLE 2.1-2 Salient Features of Type A, B and C Nerve Fibres

Fibre Type	Myelinated/ Nonmyelinated	Fibre Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)	Function	
						Efferent	Afferent
A	α Myelinated	12–20	70–120	0.4–0.5	0.4–1	Somatic motor	Proprioception
	β Myelinated	5–12	30–70	0.4–0.5	0.4–1	–	Touch, pressure
	γ Myelinated	3–6	15–30	0.4–0.5	0.4–1	Motor to muscle spindles	–
	δ Myelinated	2–5	12–30	0.4–0.5	0.4–1	–	Pain, cold, touch
B	Myelinated	<3	3–15	1.2	1.2	Preganglionic autonomic	–
C	Nonmyelinated	0.4–1.2	0.5–2	2	2	Postganglionic autonomic	Pain, temperature, some mechanoreception reflex responses

TABLE 2.1-3 Numerical Vis-à-Vis Letter Classification of Sensory Nerve Fibres

Types of Nerve Fibre		
Numerical Classification	Letter Classification	Origin
Ia	Aα	Muscle spindle (annulospiral endings)
Ib	Aα	Golgi tendon organ
II	Aβ	Muscle spindle (flower spray endings), touch and pressure
III	Aδ	Pain and cold receptors, some touch receptors
IV	C	Pain, temperature and other receptors

TABLE 2.1-4 Susceptibility of Nerve Fibres to Hypoxia, Pressure and Local Anaesthetics

	Type of Nerve Fibre		
Sensitivity to	Most Susceptible	Intermediate Susceptible	Least Susceptible
Hypoxia	B	A	C
Pressure	A	B	C
Local anaesthetics	C	B	A

Along with the degenerative changes, the reparative process (regeneration) also starts soon if the circumstances are favourable. The effects of injury to a nerve and the occurrence of regenerative changes thereafter will depend on the degree and type of damage.

Stage of Degeneration

The degenerative changes which occur in the part of axon distal to the site of injury are referred to as an *anterograde degeneration* or Wallerian degeneration (after the discoverer A. Waller, 1862). The degenerative changes occurring in the neuron proximal to the injury are referred to as retrograde degeneration. These changes take place in the cell body and in the axon proximal to injury.

Changes in the Part of Axon Distal to Injury

The degenerative changes start within few hours of injury and continue for about 3 months and include the following (Fig. 2.1-18):

Axis Cylinder Axis cylinder becomes swollen and irregular in shape within a few hours of injury. After a few days, it breaks up into small fragments, the neurofibrils within it break down into granular debris and are seen in the space occupied by the axis cylinder.

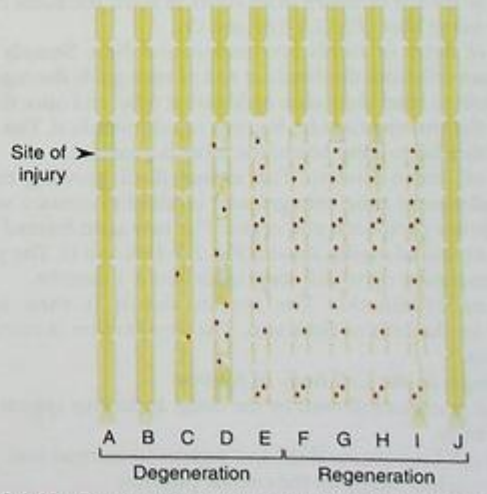


Figure 2.1-18 Degenerative changes (Wallerian degeneration) in a distal part of a nerve fibre after injury (A–E) and subsequent regenerative changes (F–J).

Changes in the Cell Body of Neuron Changes in the cell body of injured neuron start within 48 hours and continue up to 15–20 days. The changes are as follows:

- Nissl substances undergo disintegration and dissolution (chromatolysis).
- Golgi apparatus, mitochondria and neurofibrils are fragmented and eventually disappear.
- Cell body draws in more fluid, enlarges and becomes spherical.
- Nucleus is displaced to the periphery (towards cell membrane). Sometimes the nucleus is extruded out of the cell, in which case the neuron atrophies and finally disappears completely.

Stage of Regeneration

The stage of degeneration is followed by the stage of regeneration under favourable circumstances (listed below). It starts within 4 days of injury but becomes more active after 30 days, and may take several months to a year for complete recovery.

Factors Affecting Regeneration

- Regeneration occurs more rapidly when a nerve is crushed than when it is severed and the cut ends are separated.
- Chances of regeneration of a cut nerve are considerably increased if the two cut ends are near each other (gap does not exceed 3 mm) and remain in the same line.
- Presence of neurilemma is a must for regeneration to occur. Therefore, axons in the CNS once degenerated never regenerate as these nerve fibres have no neurilemma.
- Presence of nucleus in the neuron cell body is also must for regeneration to occur. If it is extruded, the neuron is atrophied and the regeneration does not occur.

Regenerative Changes

Anatomical Regeneration

1. Changes in the Axon

Stage of Fibre Formation Axis cylinder from the proximal cut end of the axon elongates and gives out fibrils up to 100 in number in all directions. These branches grow into the connective tissue at the site of injury in an effort to reach the distal cut end of the nerve fibre (Fig. 2.1-18F and G).

Stage of Entry of Fibrils into Endoneural Tube Strands of the Schwann cells from the distal cut end of axon guide the regenerating fibrils to enter their axon endoneural tube, and once the fibril enters the endoneural tube, it grows rapidly within it. The axonal fibrils that fail to enter one of the tubes degenerate.

Stage of Active Growth The axonal fibril growing through the endoneural tube enlarges and establishes contact with an appropriate peripheral end organ. The new axon formed in this way is devoid of myelin sheath (Fig. 2.1-18H and I). The process of regeneration up to this stage takes about 3 months.

Stage of Myelination The myelin sheath is then formed slowly by the cells of Schwann. The myelination is completed in 1 year.

2. Changes in the Cell Body of Neuron

- Nissl granules followed by the Golgi apparatus appear in the cell body.
- The cell loses excess fluid and regains its normal size.
- The nucleus occupies the central position.

The above changes in some of the neurons start within 20 days of injury and are completed in 80 days.

Functional Regeneration The above-mentioned regenerative changes constitute the anatomical regeneration. The functional (physiological) recovery, however, occurs after a long period.

FACTORS PROMOTING NEURONAL GROWTH

Various factors affecting neuronal development, growth and survival have been isolated and studied. These can be broadly arranged into two groups:

- Neurotrophins
- Other factors affecting neuronal growth

Neurotrophins

Neurotrophins are the proteins which provide trophic support to the neurons, i.e. they promote nerve growth and survival. They also have a role in neuronal plasticity.

Production The neurotrophins are produced by the muscles or other structures, especially the glands that the neurons innervate. Some of the neurotrophins are produced by the astrocytes.

Established neurotrophins include the following:

- Nerve growth factor (NFG)
- Brain-derived neurotrophic factor
- Neurotrophin-3 (NT-3) and 4/5

1. Nerve Growth Factor NGF is probably the first neurotrophin recognized. It promotes the growth of *sympathetic nerves* and some sensory nerves.

- It is found in various tissues in human beings and many species of animals. NGF is particularly found in high concentration in the submaxillary salivary glands of the male mice.
- NGF is made up of 2α, 2β and 2γ subunits.
  - The α subunits have trypsin-like activity.
  - The β subunits are similar in structure to insulin and possess all the nerve growth–promoting activities.
- The γ subunits are serine proteases. Their functions are unknown.
  - Receptor of NGF is Trk A (tyrosine kinase activity A).

2. Brain-Derived Neurotrophic Factor Brain-derived neurotrophic factor (BDNF) has a growth-promoting role for peripheral sensory nerves.

3. Neurotrophin-3 and 4/5 NT-3 and 4/5 play a growth-promoting role in cutaneous mechanoreceptors.

Other Growth-Promoting Factors

Factors, other than neurotrophins, which promote nerve growth include:

- Insulin-like growth factor-I
- Transforming growth factor
- Fibroblast growth factor
- Platelet-derived growth factor

SELF-ASSESSMENT

1. Draw the structure of a neuron and briefly describe the types of neurons.
2. Discuss the property of excitability and its ionic basis in a neuron.
3. How is the nerve impulse conducted in myelinated and nonmyelinated nerve fibres?
4. Differentiate between the following:
   - Chronaxie and rheobase
   - Graded potential and action potential
   - Monophasic and biphasic recording of action potential
   - Catelectrotonic and anelectrotonic potentials
5. What is the significance of the following?
   - Strength duration curve
   - All-and-none response
   - Property of refractory period
   - Infatiguability
6. Write notes on the following:
   - Compound action potential
   - Basis of classification of nerve fibres
   - Wallerian degeneration
   - Phases of action potential
   - Cathode ray oscilloscope

2.2 Neuromuscular Junction

CHAPTER OUTLINE

Structure of Neuromuscular Junction
Terminal Button
Presynaptic Membrane
Synaptic Cleft
Postsynaptic Membrane

Neuromuscular Transmission
Release of Acetylcholine by the Nerve Terminals
Effect of Acetylcholine on the Postsynaptic Membrane
Development of End Plate Potential
Removal of Acetylcholine by Cholinesterase

Drugs Affecting and Disorder of Neuromuscular Junction
Drugs Affecting Neuromuscular Junction
Neuromuscular Blockers
Neuromuscular Stimulators
Disorder of Neuromuscular Junction
Myasthenia Gravis

STRUCTURE OF NEUROMUSCULAR JUNCTION

Neuromuscular junction refers to the intimate contact of the nerve endings with the muscle fibre to which they innervate. Characteristics of the nerve and muscle fibre at and near the neuromuscular junction are as follows (Fig. 2.2-1):

Terminal Button The axon of a neuron supplying a skeletal muscle loses its myelin sheath and divides into a number of fine branches, which end in small swellings (knobs) called *terminal buttons* or end feet, which form a neuromuscular junction at the centre of muscle fibre (Fig. 2.2-1A). The nerve terminal or the so-called synaptic knob contains a large number of vesicles (about three lakhs) containing acetylcholine and mitochondria. The acetylcholine is synthesized by the mitochondria and is stored in the vesicles (Fig. 2.2-1B).

Presynaptic Membrane This refers to the axonal membrane lining the *terminal buttons* of the nerve endings.

Synaptic Cleft It is a 50–100 nm wide space between the presynaptic and the postsynaptic membranes. It is filled by extracellular fluid (ECF) with reticular fibres forming the matrix.

Postsynaptic Membrane (Fig. 2.2-1B) This is the name given to the muscle fibre membrane (sarcolemma) in the region of neuromuscular junction. The muscle membrane in this region is thickened and depressed to form the *synaptic trough*, in which the terminal button fits. This thickened portion of the muscle membrane is also called the *motor end plate*. Furthermore, the postsynaptic membrane is thrown into a large number of folds called *subneural clefts* or pallisades. These increase the surface area. The postsynaptic membrane near the junction folds contains *receptor sites* for acetylcholine called the *nicotinic receptors*. The matrix of subneural cleft contains the enzyme cholinesterase, which can degrade acetylcholine.

NEUROMUSCULAR TRANSMISSION

The skeletal muscle is stimulated only through its nerve. The neuromuscular junction transmits the impulses from the nerve to muscle. The *sequence of events* that causes transmission of impulse through the neuromuscular junction is as follows:

- Release of acetylcholine by the nerve terminals
- Effect of acetylcholine on the postsynaptic membrane
- Development of end plate potential
- Miniature end plate potential
- Removal of acetylcholine by cholinesterase

Release of Acetylcholine by the Nerve Terminals

When the nerve impulse (action potential) travelling in the nerve fibre (axon) reaches the terminal buttons, the voltage-gated Ca^{2+} channels present on the presynaptic membrane open up, increasing its permeability to Ca^{2+} ions. Consequently, the Ca^{2+} ions present in the ECF of synaptic cleft enter the terminal buttons. The elevated Ca^{2+} levels in the cytosol of terminal buttons trigger a marked increase in exocytosis of vesicles, releasing acetylcholine in the synaptic cleft (Fig. 2.2-2).

Effect of Acetylcholine on the Postsynaptic Membrane

The acetylcholine so released diffuses in the synaptic cleft and binds to the nicotinic–acetylcholine receptors located mainly

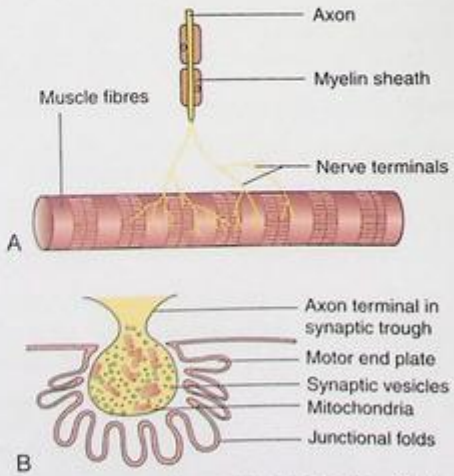


Figure 2.2-1 Structure of neuromuscular junction: (A) the axon of the neuron loses its myelin sheath and divides into fine branches and (B) structure of terminal button and motor end plate.

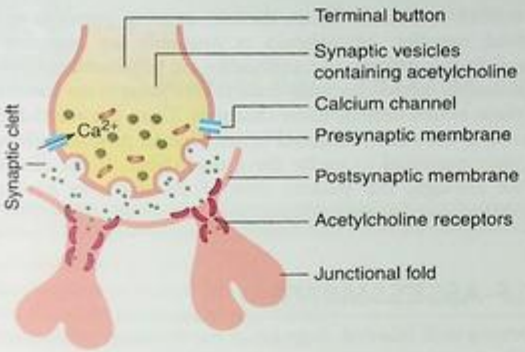


Figure 2.2-2 Detailed structure of neuromuscular junction showing Ca^{2+} channels on the presynaptic membrane and ACh receptors on the postsynaptic membrane.

on the junctional folds of the motor end plate (postsynaptic membrane).

Development of End Plate Potential Due to opening of the acetylcholine-gated channels in the end plate membrane, a large number of Na^+ ions from the ECF enter the muscle fibre following the electrochemical gradient.

The resting membrane potential at the postsynaptic membrane is about −80 to −90 mV. When sodium ions carrying large numbers of positive charges enter, there occurs depolarization, causing a local positive potential change inside the muscle fibre membrane called the *end plate potential.*

The end plate potential is nonpropagative, but when a critical level of −60 mV is reached, the end plate potential triggers the development of action potential in the muscle fibre (Fig. 2.2-3). The action potentials are generated on either side of the end plate and conducted away from the end plate in both the directions along the muscle fibres, thus causing muscle contraction.

Miniature End Plate Potential Even at rest, small quanta of acetylcholine are released randomly from the nerve terminal.

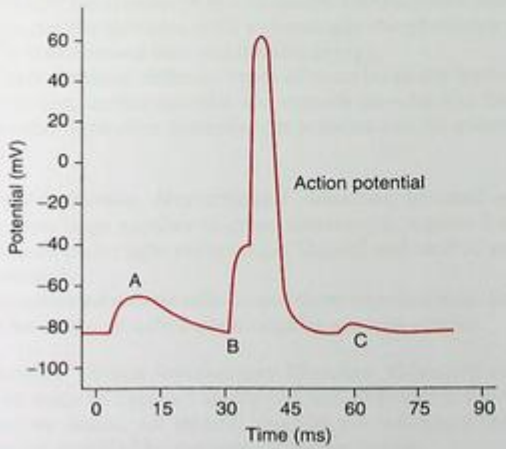


Figure 2.2-3 End plate potential and development of action potential in muscle fibre: (A) weak end plate potential (<60 mV); (B) end plate potential triggers propagating action potential (>60 mV); and (C) miniature end plate potential.

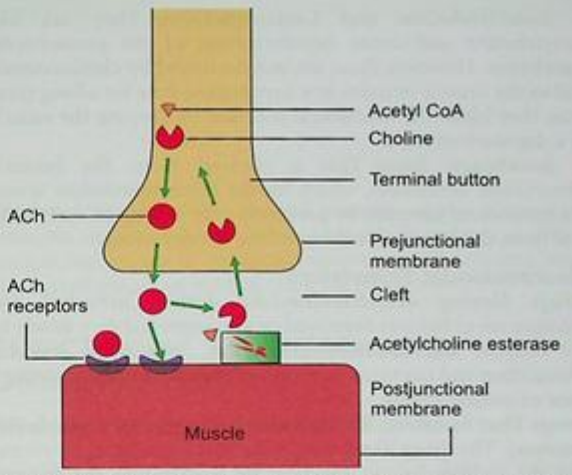


Figure 2.2-4 Removal of acetylcholine from the synaptic cleft of neuromuscular junction.

Each quantum of acetylcholine produces a weak end plate potential of about 0.5 mV in magnitude. This is called the *miniature end plate potential.*

Removal of Acetylcholine by Cholinesterase The acetylcholine released in the synaptic cleft stays for a short period and is removed within 1 ms in two ways as detailed below (Fig. 2.2-4):

- Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase, which is present in the matrix of synaptic cleft.
- A small amount of the acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fibre membrane.

It is important to note that the rapid removal of acetylcholine prevents the repeated excitation of muscle fibre.

DRUGS AFFECTING AND DISORDER OF NEUROMUSCULAR JUNCTION

Drugs Affecting Neuromuscular Junction

Neuromuscular Blockers Neuromuscular blockers are the drugs that block transmission at the neuromuscular junction. Some of the common neuromuscular blockers that are commonly used in clinical practice for producing muscle relaxation during surgery are as follows:

1. Curare Curare prevents the neuromuscular transmission by competitive inhibition. Tubocurarine and ACh both compete for nicotinic ACh receptors; therefore, if the amount of *tubocurarine* is more, then receptor sites occupied by *tubocurarine* will not be available for ACh. The acetylcholine thus released cannot combine with the receptors and so end plate potential does not develop.

2. Bungarotoxin This is found in the venom of deadly snakes, which blocks neuromuscular transmission by binding with the acetylcholine receptors.

3. Succinylcholine and Carbamylcholine They act like acetylcholine and cause depolarization of the postsynaptic membrane. However, these are not destroyed by cholinesterase and so the muscle remains in a depolarized state for a long time; thus, they block the myoneural junction by keeping the muscle in a depolarized state.

4. Botulinum Toxin This is derived from the bacteria *Clostridium botulinum*, which blocks the transmission across the myoneural junction by preventing the release of acetylcholine from the terminal buttons of the nerve endings.

Neuromuscular Stimulators

Drugs Having Acetylcholine-Like Action Carbachol and nicotine are either not destroyed or are destroyed very slowly by the enzyme acetylcholinesterase. Thus, they cause repeated stimulation and continuous action of muscle, thereby causing a state of muscle spasm.

Drugs That Inactivate the Enzyme Cholinesterase (Anticholinesterase) The drugs like neostigmine and physostigmine stimulate the neuromuscular junction by inactivating the enzyme acetylcholinesterase.

Disorder of Neuromuscular Junction

Myasthenia Gravis Myasthenia gravis is a disorder in which the myoneural junction is unable to transmit signals from the nerve fibre to muscle fibres, thereby causing paralysis of the involved muscles. Myasthenia is probably an autoimmune disease. In this disease, the antibodies are produced against the acetylcholine-gated channels (receptors) present on the motor end plate, which destroy these channels. Thus, the acetylcholine released at the nerve terminal is not able to produce adequate end plate potential to excite the muscle fibre. If the disease is intense enough, the patient dies of paralysis, in particular paralysis of respiratory muscles.

SELF-ASSESSMENT

1. Draw a well-labelled diagram of the structure of neuromuscular junction.
2. Write short notes on the following:
   - Endplate potential
   - Myasthenia gravis
   - Acetylcholinesterase

2.3 Skeletal Muscle

CHAPTER OUTLINE

Introduction
Striated Versus Nonstriated Muscles
Voluntary Versus Involuntary Muscles
Skeletal Muscles

Functional Anatomy and Organization
Structural Organization of Muscle
Structure of a Muscle Fibre
Sarcotubular System

Process of Muscle Excitability and Contractility
Process of Muscle Excitation
Process of Excitation–Contraction Coupling
Process of Muscle Contraction
Sequence of Events during Muscle Contraction and Relaxation when Stimulated by a Nerve

Characteristics of Muscle Contractility
Contractile and Elastic Components of a Muscle
Concepts About Muscle Length
Motor Unit
Contractile Response
Muscle Tone

Electromyography

INTRODUCTION

The muscle cell, like the neuron, is an excitable tissue, i.e. an action potential (AP) is generated when it is stimulated either chemically, electrically or mechanically. Furthermore, the muscle is a contractile tissue with a chemically stored energy which can be transformed into mechanical energy.

There are three different types of muscles in the body: skeletal muscles, cardiac muscles and smooth muscles. On the basis of certain distinctive features, the muscles can be grouped as follows.

Striated Versus Nonstriated Muscles ***Striated muscle cells*** show large number of cross-striations at regular intervals when seen under light microscope. Skeletal and cardiac muscles are striated.

Nonstriated muscle cells do not show any striations. Smooth muscles or the so-called plain muscles are nonstriated.

Voluntary Versus Involuntary Muscles ***Voluntary muscles*** can be made to contract under our will to perform the movements we desire. All skeletal muscles are voluntary muscles. These are supplied by the somatic motor nerves.

Involuntary muscles' activities cannot be controlled at will. Cardiac and all smooth muscles are involuntary muscles. These are innervated by the autonomic nerves.

Skeletal Muscles The skeletal muscles, as the name indicates, are attached with the bones of the body skeleton and their contraction results in the body movements. The skeletal muscles constitute about 40% of the total body mass.

FUNCTIONAL ANATOMY AND ORGANIZATION

Structural Organization of Muscle

Structurally, the skeletal muscle consists of a large number of muscle fibres and a connective tissue framework is organized as follows (Figs 2.3-1 and 2.3-2):

- Each *muscle fibre* is surrounded by a delicate connective tissue called *endomysium*, which contains large quantity of elastic tissue arranged longitudinally.
- The muscle fibres are grouped into a number of bundles called *fasciculi.* Each fasciculus is surrounded by a stronger sheath of connective tissue called *perimysium.*
- All the fasciculi collectively form the *muscle belly.* The connective tissue that surrounds the entire muscle belly is called *epimysium.*
- At the junction of the muscle with its tendon, the fibres of endomysium, perimysium and epimysium become continuous with the fibres of the tendon.
- *Tendons* are fibrous terminal ends of the muscles composed of collagen fibres.

Structure of a Muscle Fibre

Each muscle fibre is basically a long (1–40 mm), cylindrical (10–100 μm in diameter), multinucleated cell. Its cell membrane is called *sarcolemma* and the cytoplasm is called *sarcoplasm.* Like any other cell, in the sarcoplasm are embedded many structures, the nuclei, Golgi apparatus, mitochondria, sarcoplasmic reticulum, ribosomes, and glycogen and occasional lipid

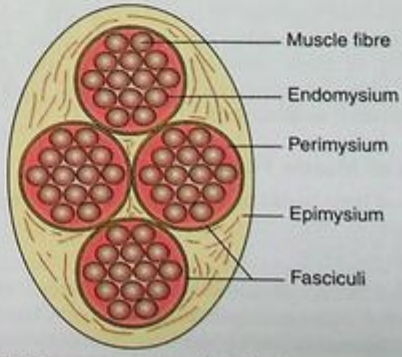


Figure 2.3-1 Transverse section of skeletal muscle as seen under light microscope.

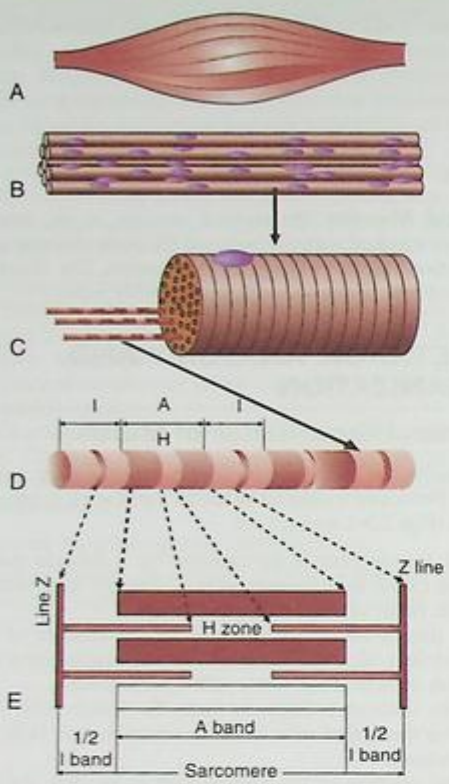


Figure 2.3-2 Schematic diagram showing structural organization of skeletal muscle: (A) muscle belly; (B) muscle fibres grouped into fasciculi; (C) muscle fibre; (D) myofibril; and (E) arrangement of thick and thin filaments.

droplets. In addition, the sarcoplasm mainly contains number of *myofibrils* which form the principal structure of a muscle fibre. The sarcolemma along with the sarcoplasmic reticulum forms the so-called *sarcotubular system.*

Myofibril

Each muscle fibre consists of a large number of myofibrils which are arranged parallel to each other and run along the entire length of the muscle fibre.

Each myofibril consists of many thick and thin filaments (myofilaments) composed of contractile proteins. The peculiar arrangement of these myofilaments when seen under *light microscope* gives an appearance of alternate dark and light bands (striations) as described.

Striations of Muscle Fibres

The dark and light bands result from a difference in the refractive index of its different parts. The arrangement is given as follows (Fig. 2.3-2D):

- The dark band is called *A band* (anisometropic to polarized light). It is 1.5 μm in length. In the area of A band, the thick (myosin) filaments line up the thin filaments.
- In the centre of each A band, there is a lighter H zone where thin filaments do not overlap the thick filaments. (The word H either represents the discoverer, Henson, or the hell which in German means light.)
- In the centre of each H zone is seen an *M line*, which is more pronounced during muscle contraction.
- The light band is called *I band* because it is isotropic to polarized light. It is about 1 μm in length. This area contains only thin (actin) filaments.
- Each I band is bisected by a narrow dark *Z line* (the word Z has been taken from Zwischenscheibe, which in German means between discs).
- The portion of myofibril between two successive Z lines is called a *sarcomere.* Thus, a sarcomere includes ½ I band, + 1A band and ½ I band, and is about 2.5 μm in length at rest. The sarcomere is the structural and functional unit of the muscle fibre. During muscle contraction the sarcomere reduces in length to 1.5 μm and during stretching of the muscle it increases in length to 3.5 μm.

Thick and Thin Filaments

The thick and thin filaments (Fig. 2.3-2E) form the contractile apparatus of a striated muscle.

Thick Filament Thick filaments are about twice the diameter of thin filaments. Each thick filament is surrounded by six thin filaments arranged in a regular hexagonal manner. A thick filament is composed of hundreds of molecules of a complex actin-binding contractile protein called *myosin.*

Structure of Myosin Molecule. The myosin molecule has a molecular weight of 480,000 and is composed of six polypeptide chains: two heavy chains and four light chains. The two heavy chains wrap around each other to form a double helix, which constitutes the *tail and body* of the myosin molecule (Fig. 2.3-3B). The light chains combine with the terminal part of the heavy chains to form the globular *head* of myosin molecule. The myosin molecule present in the skeletal muscle has two heads and is called *myosin II* (Fig. 2.3-3C). During muscle contraction, the head forms the *cross-bridging* (as described later).

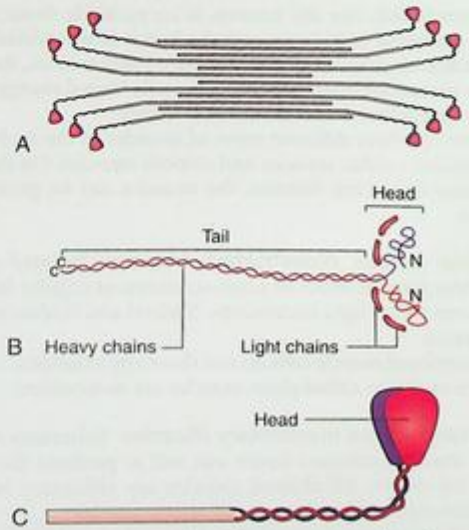


Figure 2.3-3 Myosin molecules: (A) arrangement of myosin molecules in thick filament; (B) structure of myosin molecule; and (C) molecule of myosin II (with two heads).

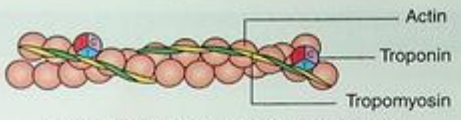


Figure 2.3-4 Structure of a thin filament.

Arrangement of myosin molecules in a thick filament. In a thick filament, half of the myosin molecules are oriented with their heads in one direction and the remaining half in opposite direction (Fig. 2.3-3A). Because of this arrangement, the central portion of a thick filament is devoid of the head portions of the myosin molecules. This accounts for the comparatively lighter H zone seen in the centre of dark A band.

Thin Filament Each thin actin filament is composed of contractile protein molecules (actin) and two types of regulatory protein molecules (tropomyosin and troponin) (Fig. 2.3-4).

Actin. About 300–400 actin molecules are present in each thin filament. The actin molecules form a long double helix consisting of two chains of globular units. The globular molecules are *G-actin*, and the chain formed by them is designated as *F-actin*.

Tropomyosin. About 40–60 tropomyosin molecules are present in each thin filament. The tropomyosin molecules are long filaments which lie in the groove between the two chains of actin molecules. It covers the binding site of actin where myosin head comes in contact with actin. Thus, it is a regulatory protein which prevents the interaction between actin and myosin filaments.

Troponin. Troponin molecules are small globular units located at intervals along the tropomyosin molecule. The troponin molecule has three subunits:

- ***Troponin-T*** binds the other troponin components to tropomyosin.
- ***Troponin-I*** prevents the interaction of myosin heads with the active sites on actin.
- ***Troponin-C*** contains binding site for Ca^{2+} that initiates muscle contraction. Each molecule of troponin-C binds to four molecules of Ca^{2+} ions.

Sarcotubular System

The sarcolemma (cell membrane of muscle cell) along with the sarcoplasmic reticulum (the endoplasmic reticulum of muscle cell) forms a highly specialized system called sarcotubular system. This plays an important role in the internal conduction of depolarization within the muscle fibre. The sarcotubular system is primarily formed by a transverse tubular system (T-system) and a longitudinal sarcoplasmic reticulum (Fig. 2.3-5).

Transverse Tubular System (T-System) The T-system of transverse tubules is formed by the thorough and thorough invagination of sarcolemma into the muscle fibre in the region of junction of A and I bands (Fig. 2.3-5). The T-tubules are formed by the invagination of sarcolemma, so their lumen contains ECF which surrounds the muscle cell. These T-tubules facilitate rapid transmission of the impulse in the form of AP from sarcolemma to the myofibrils. The membrane of T-tubules contains voltage-gated Ca^{2+} channels called *dihydropyridine* (DHP) receptors (as they get blocked by the drug DHP), through which they activate the longitudinal sarcoplasmic reticulum.

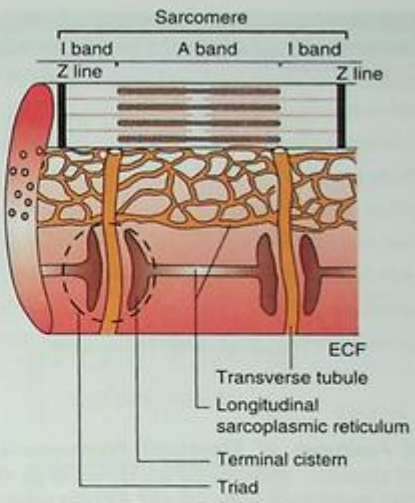


Figure 2.3-5 Sarcotubular system showing transverse tubules and longitudinal sarcoplasmic reticulum.

Longitudinal Sarcoplasmic Reticulum (L-Tubules) The longitudinal sarcoplasmic reticulum is the name given to the *sarcoplasmic* tubules of the sarcoplasmic reticulum which run in long axis of the muscle fibre forming a closed tubular system around each myofibril. These L-tubules do not open to the exterior like T-tubules. The longitudinal sarcoplasmic tubules on either side of the T-tubule are dilated to form the so-called terminal cisterns. A single T-tubule with the two terminal cisterns lying in close proximity (contiguity) constitutes a *triad*, which is found at the junction of A and I bands. Thus, there are two triads in each sarcomere.

The longitudinal tubules store a large quantity of calcium ions. When the AP reaches the cisterns of L-tubules, these Ca^{2+} ions are released into the sarcoplasm through the calcium channels present on their membrane. These are called *ryanodine receptors* (RYRs) as they are kept in open position by ryanodine alkaloid.

PROCESS OF MUSCLE EXCITABILITY AND CONTRACTILITY

As we know, the muscle is an excitable tissue, i.e. when stimulated an AP is produced (*electrical phenomenon*). The skeletal muscle responds to stimulus by contracting (*mechanical phenomenon*). The events which link the electrical phenomenon with the mechanical phenomenon is called *excitation–contraction coupling phenomenon*. These three phenomena which mark the excitability and contractility of the muscle when stimulated by the nerve innervating it are discussed.

Process of Muscle Excitation

As discussed in the transmission across neuromuscular junction (page 38), an end plate potential (EPP) is developed at the motor end plate by the nerve impulse travelling across the innervating axon. The EPP, as discussed earlier (page 39), is localized and nonpropagated. However, when EPP reaches a threshold level it produces an *AP* which propagates over muscle fibre surface and into the muscle fibre along the transverse tubules.

TABLE 2.3-1 Essential Features of Electrical Phenomena in the Skeletal Muscle Fibre and the Nerve Fibre

Features	Skeletal Muscle Fibre	Nerve Fibre
1. Resting membrane potentia	−90 mV	−70 mV
2. Initial excitation threshold leve	30–40 mV	15 mV
3. Magnitude of action potentia	120–130 mV	100–105 mV
4. Duration of spike potentia	2–4 ms	0.4–2 ms
5. Absolute refractory period	1–3 ms	0.4–2 ms
6. Maximum number of impulses conducted	Less (100–200/s)	More (1000/s)
7. The excitability	Less (chronaxie is longer)	More (chronaxie is shorter)
8. Conduction velocity of action potentials	Low (3–5 m/s)	Variable, directly proportional to its diameter. In a myelinated nerve fibre it is up to 120 m/s

Essential Features of Electrical Phenomena Essential features of electrical phenomena which occur in the muscle fibre (resting membrane potential and AP) are similar to those occurring in a nerve fibre. However, there are some quantitative differences between the electrical phenomenon occurring in a skeletal muscle fibre and a nerve fibre which are summarized in Table 2.3-1.

Process of Excitation–Contraction Coupling

The sequence of events by which an AP in the plasma membrane of a muscle fibre leads to cross-bridge activity (excitation–contraction coupling) is as follows:

- AP initiated in the plasma membrane of a muscle fibre spreads rapidly on the surface as well as into the interior of the muscle fibre through the T-tubules.
- When the AP reaches the tip of T-tubule, it activates the voltage-gated channels called DHP receptors, which are located on the T-tubule membrane (Fig. 2.3-6).
- Activated DHP receptors, in turn, trigger the opening of Ca^{2+} release channels located on the terminal cisterns, the so-called RYR.
- Due to opening of calcium release channels (RYR), calcium ions diffuse into the cytoplasm. The concentration of Ca^{2+} in the intracellular fluid is increased by some 2000 times.
- The Ca^{2+} ions get attached to troponin-C and start a chain of events (discussed below) which produce contraction. Thus, the calcium ions act as linking or coupling material between the excitation and the contraction of the muscle. Hence, the calcium ions are said to form the basis of excitation–contraction coupling.

Process of Muscle Contraction

Molecular Basis of Muscle Contraction

The process of muscle contraction is initiated by the calcium ions as discussed above. A.F. Huxley and H.E. Huxley in 1954 put forward the *sliding theory* or *ratchet theory* to explain how the actin filaments slide over myosin filaments and form the actin–myosin complex during muscular contraction. This theory explains that the sliding of filaments is brought about by a repeated cycle of formation of the *cross-bridges* between the head of myosin and actin molecules.

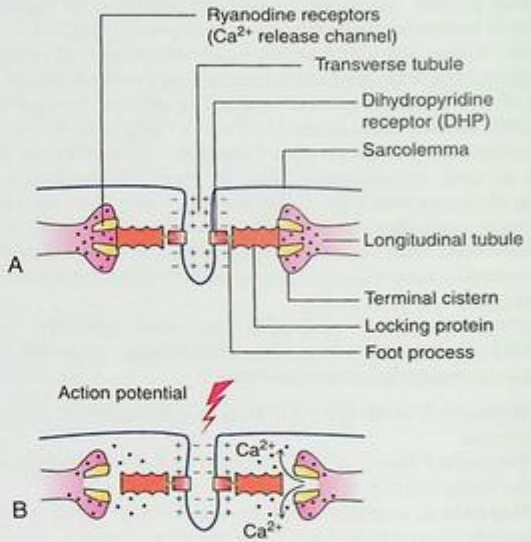


Figure 2.3-6 Mechanism of release of calcium ions from terminal cistern of longitudinal tubules: (A) in resting state Ca^{2+} release channels (RYR) remain closed due to mechanical interlocking between DHP and RYR and (B) during activation state (depolarization of T-tubule). Conformational change in DHP results in opening of RYR and release of Ca^{2+}.

Steps of Cross-Bridge Cycling

1. Initiation of Cross-Bridge Cycling

- During resting stage, troponin-I is lightly bound to actin and the tropomyosin molecules are located in the groove between the strands of actin filaments in such a way that they block the myosin binding sites on actin. Thus, during resting stage, no actin–myosin cross-bridges are formed. Thus, the *troponin–tropomyosin complex*, the so-called *relaxing proteins*, inhibits the interaction between actin and myosin (Fig. 2.3-7A).
- When activation takes place, the Ca^{2+} ions released into the cytosol from the terminal cisterns of the sarcoplasmic reticulum get attached to *troponin-C* subunit of the protein troponin. It results in a conformation change which causes the tropomyosin molecule to move laterally, uncovering the binding sites on the actin molecules for head of the myosin molecules. Seven myosin binding sites on the actin filament are uncovered for each molecule of troponin that

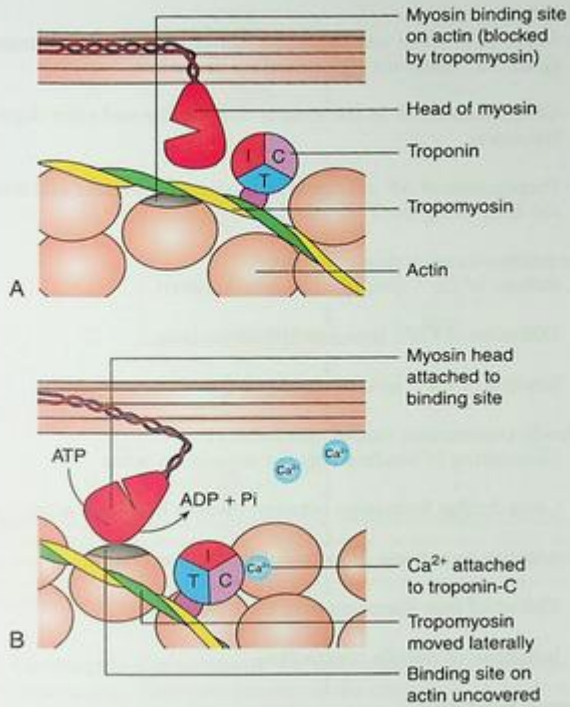


Figure 2.3-7 Initiation of cross-bridge cycling: (A) resting state (myosin binding site on actin is covered by the troponin–tropomyosin complex) and (B) on activation Ca^{2+} binds to troponin-C subunit, which results in conformational change and lateral displacement of tropomyosin causing uncovering of binding site for myosin (head of myosin) on actin (initiation of cross-bridge cycle).

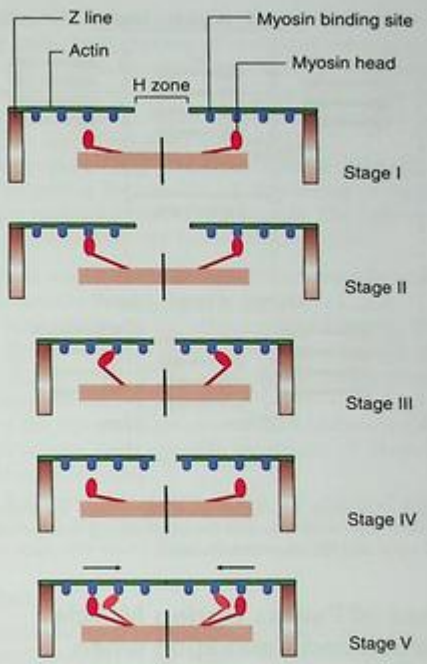


Figure 2.3-8 Stages of cross-bridge cycling.

binds a Ca^{2+} ion. Thus, the cross-bridge cycle is switched on (initiated) by the lateral movement of the tropomyosin (Fig. 2.3-7B).

2. Formation of Actin–Myosin Complex (i.e. Attachment of Myosin Head to Active Site of Actin Filament)

- The head of myosin molecule binds with adenosine triphosphate (ATP). The ATPase activity of myosin head immediately causes breaking of ATP to adenosine diphosphate (ADP) and Pi cleavage products which remain bound to the myosin head. The head of myosin therefore becomes energized. The activated myosin head extends perpendicularly (at 90° conformation) towards the actin filament and gets attached to actin filament (Fig. 2.3-8) (Stages I and II).
- Formation of the *actin–myosin–ADP Pi* complex triggers the following events:
  - Release of the Pi and ADP from the complex.
  - A conformational change in the myosin head causing it to flex towards the arm of the cross-bridge. The flexion of the myosin head from the high-energy 90° conformation to low-energy 45° conformation generates mechanical force (the power stroke).

3. Detachment of Head of a Cross-Bridge from Active Site of an Actin Filament The release of ADP and Pi allows a fresh ATP molecule to bind to the myosin head. The *myosin–ATP complex* has a low affinity for actin and, therefore, it results in the dissociation of myosin head from the actin filament (Fig. 2.3-8) (Stage IV).

4. Reactivation of Myosin Head The freshly bound ATP molecule splits again and myosin head is reactivated for the next cycle to begin.

Thus with each cross-bridge cycle, there is movement of the actin filament towards the centre of myosin to a small degree. Repeated cross-bridge cycling causes the movement of actin filaments of either side towards the centre of myosin filament of the sarcomere leading to muscle contraction (Fig. 2.3-8) (Stage V).

Changes Produced by Sliding of Thin Filaments over Thick Filaments During Muscle Contraction

Figure 2.3-9 shows the following changes produced by sliding of thin filaments over thick filaments during muscle contraction:

1. The width of A band remains constant.
2. H zone disappears.
3. I band width decreases.
4. The Z lines move closer.
5. The sarcomere shortens.
6. The actin filaments from the opposite end of the sarcomere approach each other and when the muscle shortening is marked, these filaments apparently overlap.

Steps in Muscle Relaxation Within a few milliseconds of the AP, the calcium pump transports Ca^{2+} ions present in the sarcoplasm during contraction, back into the longitudinal portion of the sarcoplasmic reticulum, from where the Ca^{2+} ions are discharged into the terminal cistern for storage.

Removal of calcium from troponin restores blocking action of the troponin–tropomyosin complex. Myosin cross-bridge cycle closes and muscle relaxes.

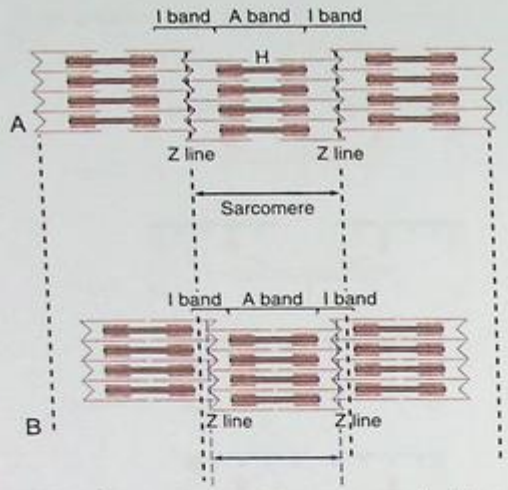


Figure 2.3-9 Changes produced in a sarcomere by sliding of thin filament (actin) over thick filament (myosin) during muscle contraction: (A) relaxed state and (B) contracted state.

Sequence of Events During Muscle Contraction and Relaxation when Stimulated by a Nerve

The events which occur during contraction and relaxation in a skeletal muscle when excited by a nerve are summarized in sequence.

Nerve excitation
- Stimulation of motor neuron
- ↓
- Initiation of AP in motor neuron's axon

Nerve conduction
- Propagation of AP in the motor nerve
- ↓
- Impulse reaching at nerve ending (at synaptic button)

Neuromuscular transmission
- Increased permeability of presynaptic membrane to Ca^{2+} ions
- ↓
- Inflow of Ca^{2+} ions from extracellular fluid (ECF) into the nerve terminals
- ↓
- Release of acetylcholine (ACh) from the microvesicles present at the nerve terminal
- ↓
- Diffusion of ACh into the synaptic cleft
- ↓
- Binding of ACh to receptors on the motor end plate (post-synaptic membrane)
- ↓
- Opening of ACh-gated channels in the motor end plate membrane
- ↓
- Entry of mainly Na^+ ions and to a lesser extent Ca^{2+} ions through these channels into the muscle fibre
- ↓
- Development of EPP

Muscle excitation
- Local EPP when reaches a threshold magnitude, voltage-gated Na^+ channels are opened up at the site
- ↓
- Generation of AP in the muscle fibre by the end plate depolarization
- ↓
- Propagation of AP in muscle fibre along the surface and into the fibre along the T-tubules
- ↓

Excitation–contraction coupling
- Release of Ca^{2+} ions from terminal cistern
- ↓
- Diffusion of Ca^{2+} ions into the sarcoplasm
- ↓
- Binding of Ca^{2+} ions to troponin-C
- ↓

Muscle contraction (molecular theory)
- Uncovering of binding sites for myosin on actin
- ↓
- Cross-bridge formation between myosin head and actin
- ↓
- Angular movement of cross-bridges (power stroke)
- ↓
- Sliding of thin filaments over thick filaments
- ↓
- Initiation of muscle contraction
- ↓

Muscle relaxation
- Active transport of Ca^{2+} into sarcoplasmic reticulum
- ↓
- Decreased concentration of Ca^{2+} in sarcoplasm
- ↓
- Removal of Ca^{2+} ions from troponin-C
- ↓
- Cessation of cross-bridge cycling
- ↓
- Relaxation of muscle fibre

CHARACTERISTICS OF MUSCLE CONTRACTILITY

Contractility

To understand contractile response and its characteristics, it is essential to have knowledge about the following elementary aspects in relation to skeletal muscle:

- Contractile and elastic components of a muscle
- Concept about muscle length
- Motor unit
- Contractile response

Contractile and Elastic Components of a Muscle

To understand certain facts associated with muscle contraction such as shortening, contraction without shortening and effect of passive stretch, a *three-component model* has been proposed. According to this model, the skeletal muscle as a whole consists of three components (Fig. 2.3-10A):

- Contractile component (CC)
- Series elastic component (SEC)
- Parallel elastic component (PEC)

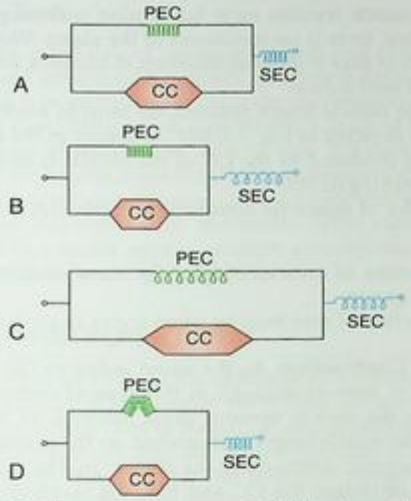


Figure 2.3-10 Three component model of skeletal muscle consisting of contractile component (CC), series elastic component (SEC) and parallel elastic component (PEC): (A) when muscle is at normal length; (B) during isometric contraction; (C) when muscle is passively stretched; and (D) in isotonic contraction.

1. Contractile Component CC represents the thick (myosin) and thin (actin) filaments present in the myofibrils. It offers no resistance to stretch and is unable to return to its original length after it has shortened.

2. Series Elastic Component SEC refers to that elastic tissue of the muscle which is present in series with the CC of the muscle. It consists of the elastic tendon of the muscle. In resting condition, the SEC offers resistance to passive stretch and explains how muscle is able to contract even when its external length does not change, i.e. isometric contraction (Fig. 2.3-10B). It also explains how the muscle regains its original length after contracting isometrically.

3. Parallel Elastic Component PEC refers to the elastic tissue of the muscle which is attached parallel to the CC. The PEC is represented by the structural elastic tissue of the muscle such as connective tissue sheaths of the muscle, sarcolemma and filaments. Presence of this component explains why the muscle regains its original length after it is passively stretched (Fig. 2.3-10C and D). In isotonic contraction, this component gets folded up. It also offers some resistance to passive stretch.

Concepts about Muscle Length

The following concepts about muscle length will be useful in understanding certain characteristics about muscle contraction:

Optimum length. It refers to the length of the muscle at which it will develop *maximum active tension. At optimum length,* there is optimum overlapping between the actin and myosin filaments, so maximum cross-bridges are formed between them.
Resting length. It represents the length of the muscle during relaxed state under natural conditions in the body. The resting length of many muscles in the body is optimum length.
Equilibrium length. It refers to the length of a relaxed muscle cut free from its bony attachments.
Initial length. It is the length of the muscle before it contracts.

Effect of afterload. Afterload refers to the load which acts on the muscle after the beginning of muscular contraction. Thus, the afterload opposes the force produced by muscle contraction. The work done in an afterloaded muscle is less than that of a free-loaded muscle. An example of afterload in an intact body is lifting any object from the ground.
Force–velocity relationship The force–velocity curve (Fig. 2.3-11) is plotted by noting the velocity of shortening of muscle with progressively increasing load on the muscle. The following inferences can be drawn from the force–velocity curve:

- When load is zero, the muscle contracts rapidly and the velocity of muscle shortening is maximum (V_{max}).
- As the load increases, the velocity of shortening decreases. With a further increase in the load, a stage comes when the muscle is unable to lift the load. At this point, muscle contracts isometrically.
- Between the two extremes of zero load and immovable load, all contractions have variable durations of isometric and isotonic contractions.
- In the force–velocity curve, **mt** is the point of maximum efficiency of the muscle. It lies about one-third of the abscissa and one-third from the ordinate.

Motor Unit

Motor unit is the functional unit of muscle contraction in the intact body. It consists of the single-motor neuron cell body, its axon fibres and the muscle fibres innervated by it (Fig. 2.3-12).

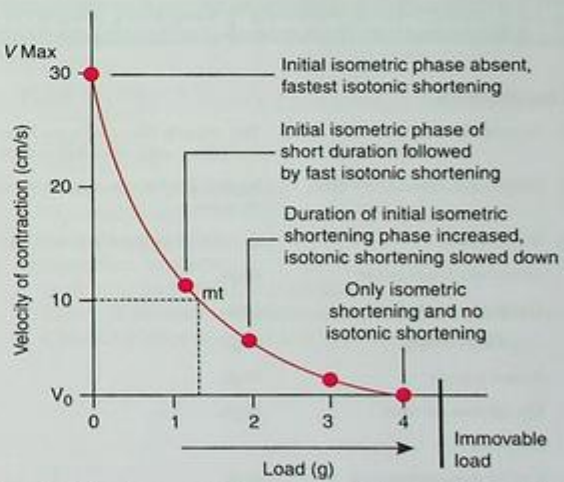


Figure 2.3-11 Force–velocity curve plotted by recording velocity of the shortening of skeletal muscle with progressively increasing load.

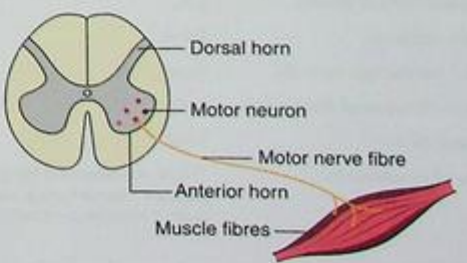


Figure 2.3-12 Structure of a motor unit.

The cell bodies of the motor neurons (α motor neuron) supplying the skeletal muscle fibres lie in the ventral horn of the spinal cord or the motor cranial nerve nuclei.

Type of motor units. Each motor neuron innervates only one type of muscle fibre. In other words, in a single-motor unit the muscle fibres supplied by it are of the same type. Therefore, depending on the type of muscle fibres, the motor units are also of two types:

- *Type I* (red or slow) motor units (fast or slow type)
- *Type II* (white or fast) motor units. The characteristic features of each type of motor units are given in Table 2.3-2.

Contractile Response

Contractile response is the characteristic feature of a skeletal muscle. An AP is developed in the muscle fibres on stimulation, which is followed by the muscle contraction. The muscle contraction is manifested by either shortening (*isotonic contraction*) or development of tension (*isometric contraction*) or both. The contractile response of a skeletal muscle can be discussed under the following headings:

- Isometric versus isotonic contraction
- Factors affecting force of contraction

Isometric Versus Isotonic Contraction

Isometric Contraction As the name indicates (iso = same, metric = measure, i.e. length), in this type of contraction the length of muscle remains same but tension is developed in the muscle. Thus, there is no movement of the object. Work done is the product of *force* × *distance*; therefore, in isometric contraction, *no external work is done.*

How the muscle length remains the same in isometric contraction is depicted in Fig. 2.3-10B. As shown in the figure, the shortening produced by the CC of the muscle is compensated by the stretching of SEC.

Examples of isometric contraction of muscles are given as follows:

- Contraction of muscles which help in maintaining posture against gravity
- Contraction of arm muscles when trying to push a wall

Isotonic Contraction As the name indicates (iso = same, and tonic = tone or tension), in this type of contraction the tension in the muscle remains same, whereas its length decreases. The muscle length is shortened, so the *external work is done* in isotonic contraction. As shown in Fig. 2.3-10D, in isotonic contraction the CC and PEC are shortened, but the SEC does not stretch further, producing a visible shortening of the muscle.

Examples of isotonic muscle contraction are as follows:

- Contraction of leg muscles during walking and running
- Contractions of muscles while lifting a weight
- Contraction of muscles during flexion of arm

TABLE 2.3-2 Characteristic Features of Type I and Type II Motor Units

Characteristics	MOTOR UNIT	
	Type I	Type II
1. Muscle fibre type	The muscle fibres of type I motor units are slow, red (slow) and involved in tonic activity	The muscle fibres of type II motor unit are fast, white (fast) and involved in phasic activity
2. Motor unit innervation ratio	High (120–160 muscle fibres/axon), e.g. postural muscles	Low (six muscle fibres/axon), e.g. extraocular muscles
3. Metabolism	Aerobic, low glycolytic and high oxidative capacity	Anaerobic, high glycolytic and low oxidative capacity
Mitochondria number	High	Low
Glycogen contents	Low	High
Capillary density	High	Low
Blood supply	High	Normal
Myoglobin content	High	Low
Enzymes:		
NADH dehydrogenase	High	Low
Phosphorylase activity	Low	High
Myosin ATPase activity	Low	High
4. Axon diameter	Smal	Large
5. Axon conduction velocity	Slow	Fast
6. Twitch duration of the muscle	Long	Brief
7. Tetanic tension	Smal	Large
8. Type of movements	These are adapted for tonic contraction, i.e. for posture maintenance and are first to be recruited during muscle contraction	These are adapted for phasic contractions, e.g. fine and skilled movements and these remain inactive during contraction and recruited only when brief and powerful contraction is required
9. Fatiguability	Fatigue resistant	Easily fatiguable

Muscle Tone

Muscle tone is the state of slight contraction with certain degree of vigour and tension. All the skeletal muscles exhibit muscle tone. However, it is more marked in the antigravity muscles, i.e. extensors of the lower limbs, trunk muscles and muscles of the neck.

Maintenance of muscle tone. Muscle tone is a state of partial tetanus of the muscle maintained by asynchronous discharge of impulses from γ motor neurons in the anterior grey horn of the spinal cord concerned with the motor nerve supply of the muscles. The γ motor neurons, in turn, are controlled by some higher centres in brain (see page 430).

ELECTROMYOGRAPHY

Electromyography refers to the technique of recording the total electrical activity of the motor nerve and the muscle under study. The machine used to record the said electrical activity is called *electromyograph* and the record obtained is called the *electromyogram* (Fig. 2.3-13). The potential changes recorded during muscle contraction is called motor unit potential (MUP). The electromyographic records obtained *during different grades* of muscle contraction have the following characteristics:

1. ***On minimal voluntary contraction,*** only a single or two smaller motor units in the vicinity of needle electrode give off electrical discharge (Fig. 2.3-13A).
2. ***With the progressive increase in the voluntary contraction,*** the firing rate of small units increases until it reaches a certain frequency, when larger units are recruited. Fig. 2.3-13B shows the recruitment pattern with moderate force of contraction.
3. ***During maximal contraction*** so many motor units are recruited and thus the so many rhythmically recurring MUPs become superimposed on one another on the oscilloscope screen that it is impossible to determine their individual characteristics. The resulting appearance of the EMG is designated as normal interference pattern (Fig. 2.3-13C).

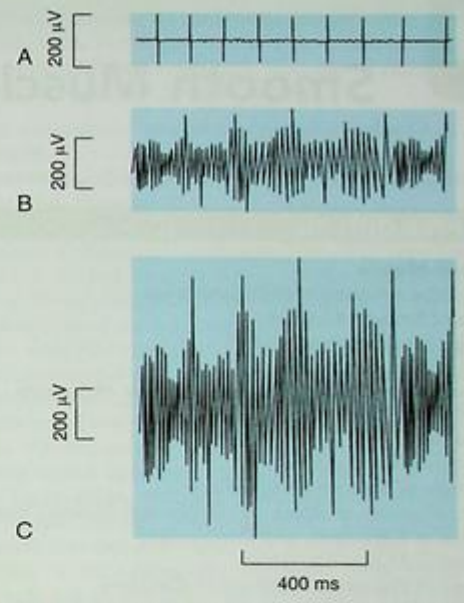


Figure 2.3-13 Electromyogram during voluntary muscle activity on: (A) minimal contraction; (B), moderate contraction (recruitment pattern); and (C) maximum contraction (normal interference pattern).

SELF-ASSESSMENT

1. Draw a labelled diagram of:
   - Structural organization of skeletal muscle
   - Sarcotubular system
2. Draw a flow diagram to describe the sequence of events during muscle contraction and relaxation when stimulated by a nerve.
3. Write note on:
   - Sarcomere
   - Motor unit
   - Muscle tone
   - Force velocity relationship
   - Optimal length
   - Electromyography
4. Differentiate between:
   - Isometric and isotonic contraction
   - Effect of preload and afterload on muscle contraction
   - Characteristics of type I and type II motor units

2.4 Smooth Muscle and Cardiac Muscle

CHAPTER OUTLINE

Smooth Muscle
Functional Anatomy and Organization
Types of Smooth Muscles
Single-Unit Smooth Muscles
Multiunit Smooth Muscles
Innervation and Neuromuscular Junction of Smooth Muscles
Nerve Supply
Neuromuscular Junction
Structure of Smooth Muscle Fibre
Salient Features of Structure of a Smooth Muscle Fibre
Process of Excitability and Contractility
Process of Muscle Excitation
Process of Excitation–Contraction Coupling
Process of Smooth Muscle Contraction
Characteristics of Smooth Muscle Excitation and Contraction
Plasticity
Latch Phenomenon
Excitation and Inhibition of Smooth Muscles
Excitation of Smooth Muscles
Inhibition of Smooth Muscles

Cardiac Muscle
Functional Anatomy
Process of Excitability and Contractility
Properties of Cardiac Muscle

Comparison of Skeletal, Smooth and Cardiac Muscles

SMOOTH MUSCLE

Functional Anatomy and Organization

Smooth muscles (nonstriated muscles), as the name indicates, are characterized by absence of the typical cross-striated pattern seen in the skeletal muscles. Because of their spontaneous activity or activity through the autonomic nervous system, they are also called *involuntary muscles.*

The smooth muscle cells are long fusiform in shape and are aggregated to form bundles or *fasciculi.* The fasciculi are aggregated to form layers of variable thickness. Thus, smooth muscles exist either in sheet or bundles of fibres. In each layer, the cells are so arranged that thick central part of one cell is opposite to the thin tapering ends of adjoining cells (Fig. 2.4-1).

Figure 2.4-1 Arrangement of smooth muscle fibres.

Types of Smooth Muscles

Smooth muscles are of two types: single-unit and multiunit smooth muscles.

1. Single-Unit Smooth Muscles (Fig. 2.4-2) Single-unit smooth muscles are also called *visceral smooth muscles* because they are present in the walls of hollow viscera such as gastrointestinal tract, uterus, ureters, urinary bladder and respiratory tract.

2. Multiunit Smooth Muscles Multiunit smooth muscles, as the name indicates, are made up of multiple individual units without interconnecting bridges, i.e. *nonsyncytial in* character (Fig. 2.4-1). These are *located* in most blood vessels, epididymis, vas deferens, iris, ciliary body and piloerector muscles.

Innervation and Neuromuscular Junction of Smooth Muscles

Nerve Supply Smooth muscles are innervated by the autonomic nerves, both sympathetic as well as parasympathetic. The two have opposite effects. In some organs, sympathetic stimulation causes contraction and parasympathetic stimulation causes relaxation of smooth muscles. However, in some other organs a reverse action is seen.

Neuromuscular Junction The postganglionic nerve fibres, as approach the smooth muscles, branch extensively and come in close contact with large number of smooth muscle fibres (Fig. 2.4-3). The neuronal network so formed has a beaded appearance due to the large enlargements called *varicosities.* These *varicosities* contain the chemical neurotransmitter (acetylcholine or norepinephrine).

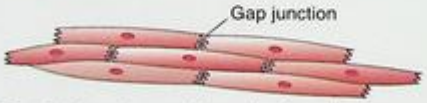


Figure 2.4-2 Single-unit smooth muscle fibre showing gap junctions between two adjacent cells.

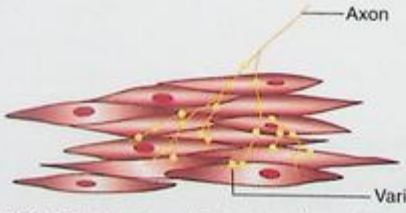


Figure 2.4-3 The nerve supplying to smooth muscle showing varicosities (beaded appearance).

In the smooth muscle, the nerve fibres are not ending in *motor end plates* (as seen in skeletal muscles), i.e. the nerve fibres do not make any direct contact with the muscle fibres. Instead, the nerve fibres release its neurotransmitter from each varicosity into the interstitial fluid close to the muscle fibres. The neurotransmitter so released diffuses into a large number of cells and causes activation of all muscle fibres up to where it is forming a syncytium.

Excitatory Junctional Potential (EJP) or Inhibitory Junction Potential (IJP), i.e. either a depolarizing or a hyperpolarizing response may be recorded from a smooth muscle in response to an appropriate nerve stimulus. These potentials summate with repeated stimuli. The EJP and IJP are *local responses* like those seen in a synapse [excitatory and inhibitory postsynaptic potential (EPSP and IPSP)].

Structure of Smooth Muscle Fibre

Each smooth muscle fibre is a long spindle-shaped cell (myocyte) having a broad central part and tapering ends (Fig. 2.4-4A). The length of smooth muscle fibre is highly variable (15–500 μm) depending on the organ in which they are present. For example,

- *Digestive tract* fibres are 30–40 μm long and 5 μm in diameter.
- Fibres in *blood vessels* are 15–20 μm long and 2–3 μm in diameter.
- Fibres in *uterus* are 300 μm long and 10 μm in diameter.

Salient Features of Structure of a Smooth Muscle Fibre

Plasma Membrane which binds the smooth muscle is surrounded by an external lamina. Adjacent smooth muscle cells communicate through gap junctions.

Nucleus is oval or elongated and lies in the central part of the cell.

Sarcoplasm, in addition to a single nucleus, contains other cell organelles like mitochondria (source of energy), a Golgi complex, some granular endoplasmic reticulum and free ribosomes. Apart from these, sarcoplasm also contains myofibrils and intermediate filaments.

Sarcoplasmic Reticulum (SR), similar to that in skeletal muscle, is present, but is not as developed.

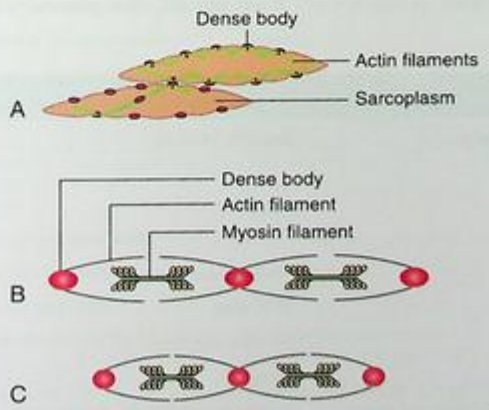


Figure 2.4-4 Structure of smooth muscle: (A) arrangement of thin (actin filaments attached to dense bodies) and thick (myosin) filaments; (B) position of dense bodies in relaxed state; and (C) the dense bodies are drawn closer to each other in contracted state.

Myofibrils are made of contractile proteins, the myosin and actin filaments. The *longitudinal striations* seen on light microscopy are due to these myofibrils. The salient differences from the skeletal muscle are given as follows:

- The *sarcotubular system* is not well developed in smooth muscles.
- Smooth muscles contain relatively less *thick filaments* and more *thin filaments.*
- *Z line* is not well defined in smooth muscles.
- *Myosin* is chemically different from that seen in skeletal muscles. It binds to actin only if its light chain is phosphorylated. Thus, phosphorylation of myosin is necessary for the contraction of smooth muscles.
- *Thin actin filaments* are also different from those in skeletal muscle due to absence of the troponin protein molecules.
- *Dense bodies* (Fig. 2.4-4B) attached to the cell membrane and scattered all over the body of the fibres are seen under electron microscope. The actin filaments are attached to these dense bodies. In between the actin filaments, the thick myosin filaments are situated. There are cross bridges between actin and myosin, which help in sliding mechanism of muscle contraction. When the muscle contracts then the points on the cell membrane, where dense bodies are attached, are drawn closer to each other. This converts an oblongated smooth muscle in one that is oval (Fig. 2.4-4C).

Process of Excitability and Contractility

Process of Muscle Excitation

Process of muscle excitation basically includes the electrical activity in smooth muscles, which differs in a multiunit smooth muscle than that in a single-unit muscle, and so is discussed separately.

Electrical Activity in Single-Unit (Visceral) Smooth Muscles

Resting Membrane Potential The resting membrane potential (RMP) in a visceral smooth muscle ranges between −50 and −75 mV. Sometimes it may reach as low as −25 mV. Thus, the peculiarity of the resting membrane potential is its *unstability*, i.e. there is no true resting value rather it keeps on oscillating between −55 and −35 mV (Fig. 2.4-5). These oscillations in the RMP occur due to superimposition by the *pacemaker potentials*, which, in turn, occur due to rhythmic changes in either $Ca2^+$ channel permeability and/or the activity of Na^+–K^+ pump.

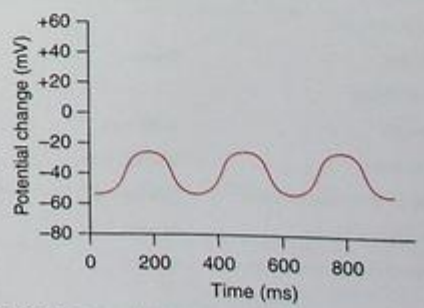


Figure 2.4-5 Resting membrane potential (fluctuating type) in visceral smooth muscle.

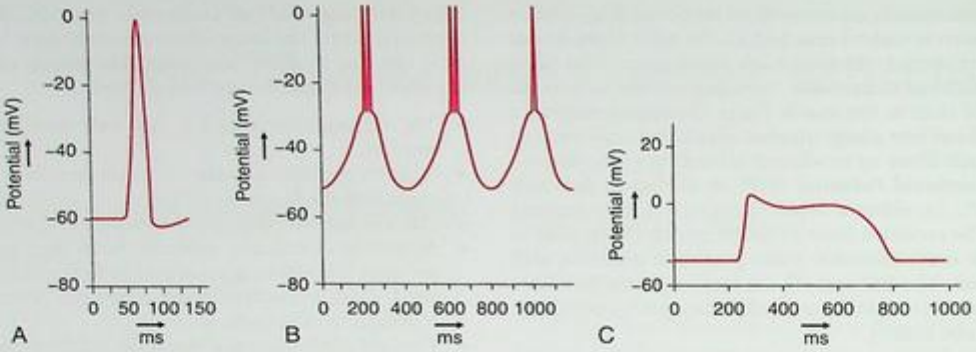


Figure 2.4-6 Three types of action potentials recorded from smooth muscles: (A) spike potential; (B) spike potential superimposed over slow wave potentials; and (C) action potential with plateau.

Action Potential When depolarization reaches threshold potential, an action potential is generated which is transmitted to the adjacent muscle cells through the gap junction. Three types of action potentials are known to occur in the visceral smooth muscle fibres, viz. spike potential, spike potential superimposed over pacemaker potential and action potential with plateau.

1. Spike Potential A typical spike potential similar to that seen in the skeletal muscles is also observed in most, if not all, single-unit smooth muscles (Fig. 2.4-6A).

2. Spike Potential Superimposed Over Slow Wave Potentials In self-excitatory smooth muscles the slow waves can initiate action potential. When the potential of slow waves rises above the level of about −35 mV (the approximate threshold for eliciting action potential in most visceral smooth muscles), an action potential develops and spreads over the muscle mass. Such a spike potential appears rhythmically at a rate of about one or two spikes superimposed at the peak of each slow wave (Fig. 2.4-6B) and cause rhythmic contractions of the self-excitatory smooth muscles.

3. Action Potential with Plateau is seen in some types of vascular smooth muscles, e.g. ureter and uterus. As shown in Fig. 2.4-6C, this type of action potential starts with rapid depolarization as is seen in the skeletal muscles, but the repolarization is delayed by 100 to 1000 ms.

Ionic Basis of Action Potential In smooth muscles, the depolarization occurs due to entry of Ca^{2+} ions from extracellular fluid (ECF) to inside the cell rather than Na^{+} ions (as seen in skeletal muscles). The smooth cell membrane has far more *voltage-gated calcium channels* than does skeletal muscle has, but few voltage-gated sodium channels.

Electrical Activity in Multiunit Smooth Muscles

The multiunit smooth muscles (such as the muscles of iris and piloerector muscles) usually respond to nerve stimuli. The nerve endings secrete neurotransmitter (acetylcholine or norepinephrine), which causes depolarization of the smooth muscle membrane. Fibres are too small, so they do not generate action potential. The local depolarization called the EJP. However, the EJP spreads electrotonically over the entire fibre and is sufficient to cause the muscle contraction.

Process of Excitation–Contraction Coupling

Three different mechanisms of excitation–contraction coupling known in smooth muscles are given as follows:

1. Electromechanical Coupling It occurs when the smooth muscle is excited through sarcolemmal depolarization. Due to depolarization of the membrane the *voltage-gated Ca^{2+} channels* present on it are opened and the Ca^{2+} ions from the ECF move into the sarcoplasm. These Ca^{2+} ions, in turn, stimulate the release of more Ca^{2+} from the SR, this process is called

TABLE 2.4-1 Comparison of Skeletal, Smooth and Cardiac Muscles

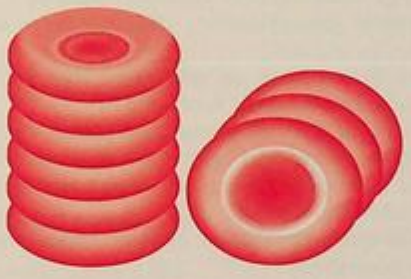
Feature	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Structural features			
• Striations	Present	Present	Absent
• Size of fibres			
– Length	1–40 mm	80 mm	50–500 mm
– Diameter	50–500 mm	15 mm	2–10 mm
• Shape of the muscle fibre	Cylindrical	Ribbon like	Spindle shaped
• Branching of fibres	Absent	Present	Absent
• Connection between fibres	Absent	Functional connections present forming functional syncytium	In single-unit muscle, functional c onnections are present; in multiunit muscles, no connections
• Nucleus	Single or multiple at periphery	Single, central with many nuclei	Single

SECTION 3

Blood and Immune System

SECTION OUTLINE

3.1 Plasma and Plasma Proteins
3.2 Red Blood Cells and Anaemias
3.3 White Blood Cells
3.4 Immune Mechanisms
3.5 Platelets, Haemostasis and Blood Coagulation
3.6 Blood Groups and Blood Transfusion



Blood is a fluid connective tissue, which transports substances from one part of the body to another. It provides nutrients and hormones to the tissues and removes their waste products. Blood, confined in the cardiovascular system, constitutes a major part of the extracellular fluid of the body.

Some of the important physical characteristics of blood are as follows:

- *Colour* of the blood is opaque red due to the pigment haemoglobin in the red blood cells (RBC). The arterial blood is bright red and venous blood is dark red in colour.
- *Volume* of blood in an average adult is about 5–6 L (8% of the body weight or 80 mL/kg body weight).
- *Viscosity* of blood is five times more than that of water.
- *Specific gravity* of blood is 1.050–1.060. Specific gravity of RBC is greater (1.090) than that of plasma (1.030).
- *pH* of blood is about 7.4 (ranges from 7.38 to 7.42), i.e. it is alkaline in nature. In acidosis pH of blood falls below 7.38 and in alkalosis pH is more than 7.42.

Blood is composed of two principal components, plasma and cellular elements.

Plasma constitutes about 55% of the blood volume. It is a clear straw coloured fluid portion of blood. *Plasma proteins*, an important constituent of plasma, form about 7% of its volume.

Cellular elements of blood are about 45% of the total blood volume and constitute the so-called packed cell volume. Blood cells are

1. Erythrocytes or RBC (5 million/μL)
2. Leucocytes or white blood cells (4000–11,000/μL)
3. Platelets or thrombocytes (1.5–4 lakh/μL).

Functions of Blood

1. *Nutritive function.* Blood carries the nutritive substances like glucose, amino acids, fatty acids, vitamins, electrolytes and others from the gut to the tissues where they are utilized.
2. *Respiratory functions.* Blood picks up oxygen from the lungs and delivers it to the various tissues. Most important function of the blood is the uninterrupted delivery of O_2 to heart and brain. It also carries away CO_2 from the tissues to the lungs from where it is expelled out in the expired air.
3. *Excretory function.* Blood transports various metabolic waste products such as urea, uric acid and creatinine to excretory organs (kidney, skin, intestine and lungs) for their disposal.
4. *Transport function.* The various hormones produced by endocrine glands, the biological enzymes and antibodies are transported by the blood to the target tissue to modulate metabolic process.
5. *Protective function.* Blood plays an important role in the defence mechanism of the body:
   - Neutrophils and monocytes engulf the microorganisms entering the body by phagocytosis.
   - Lymphocytes and γ globulins initiate immune response.
   - Eosinophils accomplish detoxification, disintegration and removal of foreign proteins.
6. *Homeostatic function.* Blood plays an important role in maintaining the internal environment of the body (homeostatic function):
   - The water content of blood is freely interchangeable with the interstitial fluid and helps in maintaining the water and electrolyte balance of the body.
   - Plasma proteins and haemoglobin act as buffers and help in maintaining the acid–base balance and pH of the body fluids.
7. *Maintenance of body temperature.* Blood plays an important role in regulation of the body temperature, as described:
   - *Specific* heat of blood is high, which is useful in buffering the sudden changes in body temperature.
   - *High heat conductivity* of blood renders it possible for distribution of heat from deep organs to the skin and lungs for dissipation.
   - Due to *high latent heat of evaporation* of blood, a large amount of heat is lost from the body by evaporation of water from the lungs and skin.
8. *Storage function.* Blood serves as a ready-made source of substances stored in it (such as glucose, water, proteins and electrolytes for use in emergency conditions like starvation, fluid loss and electrolyte loss).

Immune System

The immune system which constitutes the body's defence system consists of immunological cells distributed in two principal components: mononuclear phagocytic system and lymphoid component. The immune system of the body responds to an antigen by two ways:

- *Humoral* or *antibody-mediated immunity* (AMI) which is mediated by antibodies produced by plasma cells.
- *Cell-mediated immunity* (CMI) which is mediated directly by the sensitized lymphocytes.

3.1 Plasma and Plasma Proteins

CHAPTER OUTLINE

Plasma
Composition
Serum

Plasma Proteins
Classification of Plasma Proteins
Properties of Plasma Proteins
Functions of Plasma Proteins
Synthesis of Plasma Proteins
Site of Synthesis
Factors Affecting the Synthesis
Changes in Plasma Proteins in Health and Disease

PLASMA

Plasma is the clear, straw-coloured fluid (with dissolved solid substances) portion of the blood minus its cellular elements. It constitutes about 55% of the blood volume.

Composition

Plasma contains the following constituents:

Water. Water is the principal constituent of plasma, forming 91% of it.

Solids. The solids dissolved in the plasma constitute a total of 9% of the plasma. The solid constituents of plasma are given as follows:

Plasma proteins form 7% of the solids in plasma. Their normal value ranges from 6.4 to 8.3 g/dL. They include albumin, globulins, fibrinogen and others.

Other organic molecules which form 1% of the solids include the following:

- *Carbohydrates*, mainly glucose (100–120 mg/dL).
- *Fats* are neutral fats (30–150 mg/dL), phospholipids (150–300 mg/dL) and cholesterol (150–240 mg/dL).
- *Nonprotein nitrogenous* (NPN) *substances* (28–40 mg/dL) are ammonia (traces), amino acids, creatine (1–2 mg/dL), creatinine (0.6–1.2 mg/dL), xanthine (traces), hypoxanthine (traces), urea (20–40 mg/dL) and uric acid (2–4 mg/dL).
- *Hormones, enzymes and antibodies.*

Inorganic substances which constitute 1% of the solids in plasma include sodium, potassium, calcium, magnesium, chloride, iodide, iron, phosphates and copper.

Gases. Gases present in the plasma are oxygen, carbon dioxide and nitrogen.

Serum

Plasma from which fibrinogen and clotting factors (II, V and VIII) have been removed is called serum. Serum is formed when the blood is allowed to clot in a test tube and the clot is retracted. Serum has a higher serotonin (5HT) content because of the breakdown of platelets during clotting.

PLASMA PROTEINS

Classification of Plasma Proteins

Plasma proteins form the major solid constituent of the plasma. The total plasma protein concentration is 7.4 g/dL (ranges from 6.4 to 8.3 g/dL). The major forms of plasma proteins are albumin, globulins and fibrinogen. Serum is plasma minus clotting protein (fibrinogen); therefore, the albumin and globulins are usually referred to as serum albumin and serum globulins. Presently, more than 100 types of plasma proteins have been identified. The original classification is based on the classical method of precipitation of salts as described by Howe (1922). By electrophoretic techniques the globulins have been further subclassified. On the basis of these, the important fractions of plasma proteins are given as follows:

- Albumin (4.8 g/dL)
- Globulins (2.3 g/dL)
  - Alpha 1 (α_1) globulin
  - Alpha 2 (α_2) globulin
  - Beta (β) globulin
  - Gamma (γ) globulin
- Fibrinogen (0.3 g/dL)

Electrophoretic protein patterns. On the basis of paper electrophoresis, the following classes of serum proteins (Fig. 3.1-1) are identified:

- Albumin (55%)
- α1 globulins (5%)
- α2 globulins (9%)

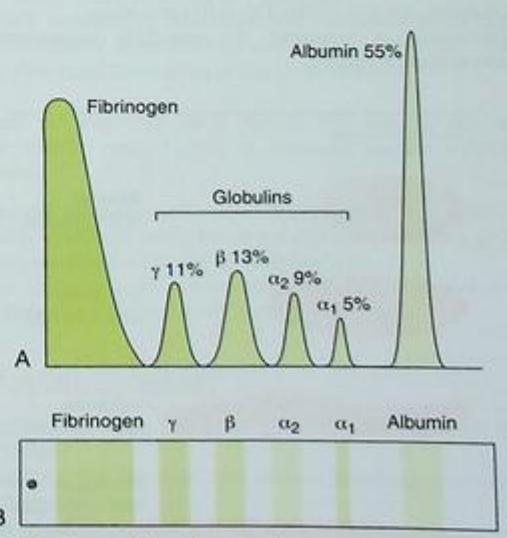


Figure 3.1-1 Paper electrophoresis showing: (A) relative amount of plasma proteins and (B) bands of different plasma proteins.

- β globulins (13%)
- γ globulins (11%)

Properties of Plasma Proteins

1. Molecular Weight. Plasma proteins are large molecules with the following molecular weight:

- Albumin: 69,000
- Globulins: 90,000–156,000
- Fibrinogen: 500,000

Thus, the fibrinogen has got highest molecular weight. Relative size and shape of different plasma proteins are shown in Fig. 3.1-2.

2. Osmotic Pressure. The plasma proteins exert an osmotic pressure of about 25 mm Hg.

3. Specific Gravity. The specific gravity of plasma proteins is 1.026.

4. Isoelectric Point. Proteins can ionize either as acids or as bases owing to the fact that the side chains of their constituent amino acids contain a selection of amino group (NH_2) and carboxyl groups (–COOH). At an intermediate pH (specific for each protein), the protein molecules carry equal number of positive and negative charges and hence have a zero net charge. This pH value for electrical neutrality of the molecule is known as the *isoelectric point.*

5. Electrophoretic Mobility. The proteins act as *anions* in alkaline solutions and *cations* in acidic solutions. Because of this property, they possess electrophoretic mobility.

6. Precipitation by Salts. Proteins can be precipitated by different concentrations of salts. This property of proteins is utilized for their separation by the precipitation method.

Ammonium sulphate solution is utilized to precipitate the plasma protein fractions in different strengths:

- *Albumin* is precipitated by full saturation.
- *Globulins* are precipitated by half saturation.
- *Fibrinogen* is separated by one-fifth saturation with ammonium sulphate.

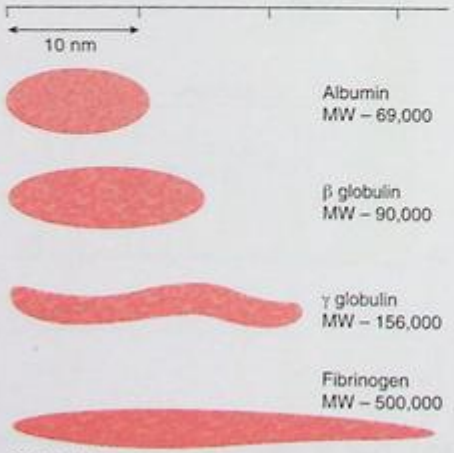


Figure 3.1-2 Molecular weights and shapes of different plasma proteins.

7. Water Solubility. The protein molecules are soluble in water because of the presence of polar residues like NH_2 and COOH.

8. Amphoteric Nature. Protein molecules are amphoteric in nature because of the presence of NH_2 and COOH groups. By virtue of their amphoteric nature, the plasma proteins act as efficient buffers.

Functions of Plasma Proteins

1. Exert Osmotic Pressure. The protein molecules are unable to pass across the capillary membrane and consequently exert colloid osmotic pressure of about 25 mm Hg on the capillary membrane. About 70%–80% of the osmotic pressure is contributed by the albumin fraction. The colloid osmotic pressure plays an important role in exchange of water between the blood and tissue fluid.

2. Contribution to Blood Viscosity. Fibrinogen and globulins are significant contributors to blood viscosity because of their asymmetrical shape. The blood viscosity plays an important role in the maintenance of blood pressure by providing resistance to flow of blood in blood vessels.

3. Role in Coagulation of Blood. The fibrinogen, prothrombin and other coagulation proteins present in the plasma play an important role in the coagulation of blood.

4. Role in Defence Mechanism of the Body. The γ globulins are antibodies which play an important role in the immune system meant for defence of the body against the microorganisms.

5. Role in Maintaining Acid–Base Balance of the Body. Plasma proteins act as buffers and contribute for about 15% of the buffering capacity of blood. Because of their amphoteric nature, plasma proteins can combine with acids and bases as explained below:

- *In acidic pH*, the NH_2 group of the proteins acts as base, accepts proton and is converted to NH_4.
- *In alkaline pH*, the COOH group of the proteins acts as acid, can donate a proton and thus becomes COO^-.
- *At normal pH of blood* proteins act as acids and combine with cations (mainly sodium).

6. Transport Function. Plasma proteins combine easily with many substances and play an essential role in their transport, as explained below:

- *Carbon dioxide* is transported by the plasma proteins in the form of carbamino compound.
- *Thyroxine* is transported by an α globulin called thyroxine-binding protein (TBP).
- *Cortisol* is transported by transcortin, which is a mucoprotein.
- *Vitamin A, D and E* are transported by the high- and low-density lipoproteins (HDL and LDL).
- *Vitamin B_{12}* is bound to transcobalamin for transport.
- *Bilirubin* is associated with albumin and also with fractions of the α globulin.
- *Drugs* of various types are transported after combining with the albumin.
- *Calcium* of the plasma is partly (50%) bound to the proteins for transport.
- *Copper* is bound to ceruloplasmin (α_2 globulin) for transport.
- *Free haemoglobin* in the vessels is bound by haptoglobin and carried to reticuloendothelial system.

7. Role as Reserve Proteins. Plasma proteins serve as reserve proteins and are utilized by the body tissues during conditions like:

- Fasting
- Inadequate protein intake
- Excessive catabolism of body proteins

8. Role in Suspension Stability of Red Blood Cells. Suspension stability refers to the property of RBCs by virtue of which they remain uniformly suspended in the blood. Globulins and fibrinogen accelerate this property.

9. Fibrinolytic Function. The enzymes of the fibrinolytic system digest the intravascular clot (thrombus) and thus save from the disastrous effects of thrombosis.

10. Role in Genetic Information. Many plasma proteins exhibit *polymorphism*. Polymorphism is a Mendelian trait that exists in the population with differing prevalence. They serve as valuable tool for the studies of population genetics. Plasma proteins that show polymorphism are haptoglobin, transferrin, ceruloplasmin and immunoglobulins.

Synthesis of Plasma Proteins

Site of Synthesis. *In embryo*, the plasma proteins are synthesized by the mesenchymal cells. First, the albumin is produced and then the other proteins are synthesized.

In adults, plasma proteins are synthesized as described below:

- The albumin and fibrinogen are synthesized mostly by the reticuloendothelial cells of the liver.
- α and β globulins are synthesized by the liver, spleen and bone marrow.
- γ globulins are synthesized by the B-lymphocytes.

Factors Affecting Synthesis of Plasma Proteins

1. Dietary Proteins. Dietary proteins play the most essential role in the synthesis of plasma proteins.

- *Essential amino acids* must be present in the diet for the satisfactory synthesis of plasma proteins.
- *Dietary proteins of animal origin* favour albumin synthesis.
- *Dietary proteins of plant origin* favour globulin synthesis.

2. Other Factors. Other factors which affect plasma protein synthesis in the body are the following:

- *Presence of infection* in the body reduces plasma protein synthesis.
- *Exposure to some antigen* stimulates formation of antibodies.
- *Inflammatory conditions* promote the synthesis of a number of proteins.
- *Variation in colloid osmotic pressure* influences the albumin synthesis.
- *Interleukin-1*, a material released by the activated macrophages in the body, stimulates the synthesis of many acute-phase proteins in the liver.
- *Prostaglandins* are also reported to increase the synthesis of acute phase proteins, possibly through stimulation of macrophage release of interleukin-1.

Changes in Plasma Proteins in Health and Disease

Physiological Variations

- *In infants*, the total protein level is low (about 5.5 g/dL) due to low γ globulins.
- *In old age*, there is a tendency for the albumin level to fall and the total globulin level to rise.
- *In pregnancy*, during first 6 months, the albumin and globulin levels decrease, whereas the fibrinogen level increases.

Abnormalities of Plasma Protein Levels

Hypoproteinaemia. Hypoproteinaemia refers to generalized decrease in the levels of plasma proteins.

Causes of Hypoproteinaemia include:

- *Dietary deficiency* and starvation.
- *Malabsorption syndrome* due to intestinal diseases.
- *Liver diseases* reduced synthesis of proteins in the liver.
- *Renal diseases* like nephrotic syndrome cause hypoproteinaemia due to more loss of proteins in the urine.
- *Haemorrhage and extensive burns* are associated with acute hypoproteinaemia.
- *Hereditary analbuminaemia* is an inborn defect in the genetic level where there is no synthesis of albumin.
- *Congenital afibrinogenaemia* is a rare condition characterized by defective blood clotting.

Effects of Hypoproteinaemia. Low levels of plasma proteins are associated with a decrease in the plasma osmotic pressure, which causes water retention and oedema of the body tissue.

Hyperproteinaemia. Hyperproteinaemia, i.e. increase in the plasma protein levels, is seen in following conditions:

- *Acute inflammatory conditions* are associated with increased synthesis of the so-called *acute phase proteins*, which include C-reactive proteins, α antitrypsin, haptoglobin, fibrinogen and ceruloplasmin.
- *Acute tissue destruction* as in myocardial infarction is also associated with raised levels of acute phase proteins.
- *Chronic inflammation and malignancies* are also associated with raised levels of C-reactive proteins.
- *Multiple myeloma* is associated with increased levels of the so-called *Bence Jones* proteins and myeloma globulin due to their abnormal formation in the bone marrow.

Reversal of Normal A/G Ratio. The normal albumin: globulin (A/G) ratio (1.7:1) is reversed in the following conditions:

- When the albumin synthesis is decreased, as occurs in liver diseases (globulin levels being normal because many globulins are synthesized by the B-lymphocytes).
- When globulin levels are increased (as occurs in most of the conditions) associated with hyperproteinaemia.

SELF-ASSESSMENT

1. Describe different types of plasma proteins and their functions.
2. Discuss briefly the sites and factors affecting synthesis of plasma proteins.
3. Write notes on:
   - Variations in plasma proteins
   - Isoelectric point
   - Reserve proteins
   - A/G ratio

3.2 Red Blood Cells and Anaemias

CHAPTER OUTLINE

Characteristic Features of Red Blood Cells
Functional Morphology
Normal Size, Shape and Counts of RBCs
Variations in Counts of RBCs
Packed Cell Volume and Red Cell Indices
Rouleaux Formation and Erythrocyte Sedimentation Rate

Formation of Red Blood Cells
Sites of Haemopoiesis
Blood Cell Precursors
Stages of Erythropoiesis
Regulation of Erythropoiesis
Factors Necessary for Erythropoiesis

Haemoglobin
Normal Blood Haemoglobin
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Varieties of Haemoglobin
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Red Cell Fragility
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Anaemias
Definition and Classification
General Clinical Features of Anaemia
Iron-Deficiency Anaemia
Megaloblastic Anaemia

CHARACTERISTIC FEATURES OF RED BLOOD CELLS

Functional Morphology

The red blood cells (RBCs) (mature erythrocytes) form one of the important constituent of the cellular elements of the blood. Each RBC like any other cell in the body is bounded by a *cell membrane* but is *non-nucleated* and lacks the usual cell organelles. The cytoplasm of the RBC contains a special pigmented protein called the *haemoglobin* (Hb), which forms 90% of the weight of the erythrocytes. The red colour of the RBCs and thus of the blood is due to the presence of Hb.

Normal Size, Shape and Counts of RBCs

Normal Size

- *Diameter* of each RBC is 7.2 μm (range 6.9–7.4 μm).
- *Thickness* in the periphery is 2 μm and in the centre is 1 μm.
- *Surface area* of each RBC is about 120–140 μm^2.
- *Volume* is about 80 μm^3 (range 78–86 μm^3).

Normal Shape

The RBCs are circular, biconcave discs (Fig. 3.2-1).

Advantages of biconcave shape are as follows:

- It renders the red cells quite flexible so that they can pass through the capillaries whose minimum diameter is 3.5 μm (Fig. 3.2-2).
- The biconcavity provides greater surface area as compared to volume, which allows considerable alterations in the cell volume. Thus, the RBCs can withstand considerable changes of osmotic pressure. In this way, the RBCs can resist haemolysis to certain extent when placed in the hypotonic solution.

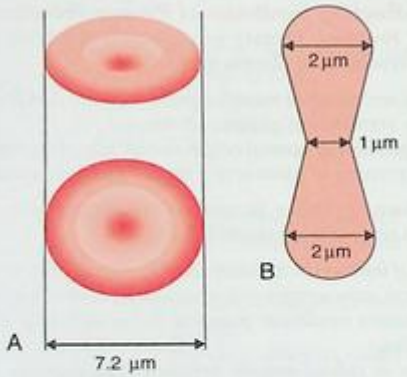


Figure 3.2-1 Size and shape of a normal red blood cell: (A) biconcave disc (diameter 7.2 μm) and (B) thickness (2 μm at the periphery and 1 μm in the centre).

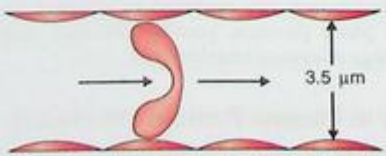


Figure 3.2-2 Diagram showing how flexibility of red blood cell allows it to pass through smaller capillaries (diameter 3.5 μm).

- Greater surface area allows easy exchange of O_2 and CO_2, and rapid diffusion of other substances.

Normal Counts

- *At birth*, normal RBC count is 6–7 million/mm^3.
- *In adult males*, the normal count varies from 5 to 6.5 million/mm^3 (average 5.5 million/mm^3).
- *In females*, it varies from 4.5 to 5.5 million/mm^3 (average 4.8 million/mm^3).
- *Clinically*, a count of 5 million/mm^3 is considered as 100%.

Variations in Counts of RBCs

Physiological increase in the RBC count (physiological polycythaemia) is seen in the following circumstances:

- *Age.* At birth, the RBC count is 6–7 million/mm^3 of blood. After about 10 days of birth, the count decreases due to the destruction of cells. This is the cause of *physiological jaundice* of newborn. In infants, the RBC count is slightly more than the adults.
- *Sex.* RBC count in the adult females (average 4.8 million/mm^3) is lower than the adult males (average 5.5 million/mm^3).
- *High altitude.* RBC count of the individuals residing in high altitude areas (above 10,000 feet from the sea level) have high RBC count (7 million/mm^3) because of the hypoxic stimulation of erythropoiesis.
- ***Excessive exercise.*** Mild hypoxia and spleen contraction causes temporary increase in the RBC count.
- ***Emotional conditions*** like anxiety are associated with the temporary increase in the RBC count due to sympathetic stimulation.
- ***Increase in atmospheric temperature*** causes a temporary elevation of RBC count.
- ***After meals***, the RBC count is raised slightly.

Polycythaemia or pathological increase in the RBC count (above 7 million/μL) is of two types:

- *Primary polycythaemia or polycythaemia vera* occurs in myeloproliferative disorder-like malignancies of the bone marrow. The RBC count is persistently above 14 million/mm^3 and is always associated with high white blood cell (WBC) count.
- *Secondary polycythaemia* occurs due to certain conditions producing a state of chronic hypoxia in the body such as:
  - congenital heart disease
  - chronic respiratory disorders like emphysema

Physiological Decrease in RBC Count is seen in the following conditions:

- *At high barometric pressure*, the RBC count is decreased slightly due to high O_2 tension of the blood.
- *After sleep*, the RBC count is decreased slightly.
- *In pregnancy*, there occurs relative reduction in RBC count due to haemodilution caused by increase in the plasma volume.

Anaemia. In anaemia, there may occur marked reduction in the RBC count or the Hb level or both (see page 71).

Packed Cell Volume and Red Cell Indices

Packed Cell Volume

Packed cell volume (PCV) refers to the percentage of the cellular elements (RBCs, WBCs and platelets) in the whole blood. The volume of WBCs and platelets is very less, so for all practical purposes the PCV is considered equivalent to the volume of packed red cells or the so-called *haematocrit value.* The normal values of the PCV in males are about 45% and in females about 42%. The PCV is increased in polycythaemia and decreased in anaemia.

Red Cell Indices

The red cell indices defined below are calculated taking normal values of the RBC count 5 million/μL, PCV 45% and Hb level of 15 g%.

1. Mean Corpuscular Volume. The mean corpuscular volume (MCV) refers to the average volume of a single RBC. It is calculated by dividing the PCV by the red cell count.

$$\text{MCV} = \frac{\text{PCV in 1000 mL of blood, i.e. (PCV} \times 10)}{\text{RBC count/mm}^3} = \frac{45 \times 10}{5} = 90\ \mu\text{m}^3$$

- Normal value of the MCV is 90 μm^3 (range 78–94 μm^3). When the MCV value is normal then it is referred as *normocytosis.*
- Decreased value of the MCV occurs in *microcytosis.*
- Increased value of the MCV occurs in *macrocytosis.*

2. Mean Cell Haemoglobin. Mean cell haemoglobin (MCH) refers to the average weight of the Hb contained in each RBC. It is calculated by dividing the amount of Hb in 1 L of blood by the red cell count in 1 L of blood:

$$\text{MCH} = \frac{\text{Hb g/L}}{\text{RBC count/L}} = \frac{\text{Hb g\%} \times 10}{\text{RBC count/mm}^3 \times 10^{12}} = \frac{15 \times 10}{5 \times 10^{12}} = 30 \times 10^{-12}\ \text{g} = 30\ \text{pg [since } 10^{-12}\ \text{g} = \text{one picogram (pg)]}$$

- *Normal value of MCH* is 30 (range 27–33) pg.
- *Increased values of MCH* occur in the spherocytosis and in the megaloblastic anaemia.
- MCH is not used to find out the type of anaemia.

3. Mean Cell Haemoglobin Concentration. The MCH concentration (MCHC) refers to the amount of Hb expressed as a percentage of the volume of an RBC. It is calculated by dividing the amount of Hb in g% by the volume of packed cells in 100 mL of blood and then multiplying by 100:

$$\text{MCHC} = \frac{\text{Hb g\%}}{\text{PCV/100 mL}} \times 100 = \frac{15}{45} \times 100 = 33.3\%$$

- *Normal value of MCHC* is 33.3% (range 30–38%). RBCs with normal values of MCHC are called *normochromic.*
- *In hypochromic RBCs* the values of MCHC are less than the normal, as is seen in the iron-deficiency anaemia.
- *Hyperchromia* is very rare, high levels of MCHC (>38%) cannot occur, because the RBCs cannot hold Hb beyond the saturation point.

Figure 3.2-3 Rouleaux formation.

- MCHC is independent of the RBC count and the size of RBCs, so it is considered to be of greater clinical significance as compared to other absolute values.

Rouleaux Formation and Erythrocyte Sedimentation Rate

Rouleaux Formation

- Rouleaux formation refers to the tendency of the RBCs to pile one over the other like a pile of coins (Fig. 3.2-3). The discoid shape and protein coating of red cells play a major role in the rouleaux formation. Rouleaux formation does not occur in the normal circulation under physiological conditions, as the moving cells show little or no tendency to adhere.
- This is a reversible phenomenon, but it promotes sedimentation of the RBCs. It should not be confused with agglutination where the cells are irreversibly clumped.
- Albumin decreases the rouleaux formation, whereas fibrinogen, globulin and other products of tissue destruction increase rouleaux formation.

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) is the rate at which the RBCs sediment (settle down) when the blood containing an anticoagulant is allowed to stand in a vertically placed tube. It is expressed in millimetre at the end of first hour.

Clinical Significance of ESR

- *Normal values* of ESR by Westergren's method vary from 3 to 7 mm in males and from 5 to 9 mm in females in first hour.
- Values of ESR are raised in a large number of pathological conditions, so it has got no specific diagnostic value. However, raised levels of ESR do suggest presence of some chronic inflammatory conditions in the body.
- Estimation of ESR is more useful as a *prognostic test*, i.e. to judge the progress of the disease in patients under treatment.

Factors Affecting ESR

- *Rouleaux formation.* Increased tendency of the rouleaux formation raises the ESR. Fibrinogen and the proteins, which enter the plasma in inflammatory (globulins) and neoplastic diseases, favour rouleaux formation and thus increase the ESR.
- *Size of the RBCs.* Increase in the size of the RBCs (macrocytosis) raises the ESR.
- *Number of RBCs.* When the number of RBCs is increased, the ESR is decreased and when the number of RBCs is decreased (as in anaemia), the ESR is increased.
- *Viscosity of blood.* ESR is increased when the viscosity of blood is decreased and vice versa.
- *Sex.* ESR is greater in the females (5–9 mm) than the males (3–7 mm).
- *Menstruation.* ESR is slightly raised during menstruation in the females.
- *Pregnancy.* ESR is raised in pregnancy from third month to parturition, and returns to normal after 3–4 weeks of delivery.

Pathological Variations in ESR *Increase in the ESR* is seen in the following pathological conditions:

- Tuberculosis
- Malignant diseases
- Collagen diseases
- All anaemias (except sickle cell anaemia)
- Chronic infections

Decrease in the ESR occurs in the following pathological conditions:

- Polycythaemia
- Decreased fibrinogen levels
- Sickle cell anaemia
- Allergic conditions

FORMATION OF RED BLOOD CELLS

Formation of RBCs is a part of the process of development of blood cells (RBCs, WBCs and platelets) called *haemopoiesis*, which includes:

- Erythropoiesis, i.e. development of RBCs
- Leucopoiesis, i.e. development of WBCs
- Thrombopoiesis or megakaryocytopoiesis, i.e. development of platelets

Sites of Haemopoiesis

- ***In the first two months of gestation,*** the *yolk sac* is the main site of haemopoiesis.
- ***From third months of gestation,*** liver and spleen become the main sites of blood formation and continue to do so till birth. Spleen makes small contribution as compared to the liver.
- ***From 20th week of gestation,*** haemopoiesis begins in the bone marrow and by seventh or eighth month it becomes the main site.
- ***At birth*** **(in normal full-term),** (in normal full-term), almost whole of the haemopoiesis occurs in the bone marrow.
- ***In young children,*** active haemopoietic bone marrow is found in both axial skeleton and bones of extremities. The active haemopoietic bone marrow is red in colour due to marked cellularity, and hence is called *red bone marrow.* However, during this period there occurs a progressive fatty replacement throughout the long bones converting red bone marrow into the so-called *yellow bone marrow.*
- ***In adults,*** therefore, haemopoietic (red) bone marrow is confined to the *axial skeleton* (skull, vertebrae, sternum, ribs, sacrum and pelvis) and the *proximal ends of long bones* (humerus, femur and tibia). Even in these haemopoietic areas, about 50% the bone marrow consists of fat.

APPLIED ASPECTS

- *In adults, during pathological conditions,* when there is an increased demand of blood cells, the *nonhaemopoietic (yellow) marrow* is capable of reverting back to active haemopoiesis.
- *During pathological conditions,* when the increased demand of blood cells cannot be met by the hyperactivity of bone marrow alone, even the liver and spleen resume their fetal role of haemopoiesis, as the stem cell retains its potential haemopoietic activity. Such a situation is referred as *extramedullary haemopoiesis.*

Blood Cell Precursors

Stem Cells The *monophyletic theory* of haemopoiesis is now widely accepted, according to which all blood cells originate from the *pluripotent* or *multipotent stem cell.* Stem cells possess two *fundamental properties*:

- *Self-replication,* i.e. stem cells are capable of cell division to give rise to more stem cells.
- *Differentiation and commitment,* i.e. the stem cells have ability to differentiate into specialized cells called progenitor cells.

Progenitor Cells The stem cells after a series of divisions differentiate into progenitor cells.

Pluripotent progenitor cells, which can give rise to any type of blood cells.

Lymphoid (immune system) stem cells, which ultimately develop into lymphocytes.

Myeloid (trilineage) stem cells, which later differentiate into three types of cell lines.

- *Granulocyte–monocyte progenitors,* which produce all leucocytes except the lymphocytes.
- *Erythroid progenitors,* which produce RBCs.
- *Megakaryocyte progenitors,* which produce platelets.

Features of Progenitor Cells Morphologically the progenitor cells present in the bone marrow cannot be differentiated from the stem cells, as they both look alike. However, they can be differentiated by immunological techniques, taking advantage of the different types of molecules present on their cell membrane.

Progenitor cells possess the ability to give rise to *clones* (group of cells), so they are also called *colony forming cells* or *colony forming units* (CFUs). The three types of progenitor cells are given:

- ***CFU–GEMM*** (colony forming unit–granulocyte, erythroid, megakaryocyte and macrophage) refers to a multipotent progenitor cell, i.e. myeloid progenitor cells.
- ***BFU–E*** (burst forming unit–erythroid) form large colonies of erythroid series.
- ***CFU–E*** (colony forming unit–erythroid) develop into erythrocytes.
- ***Ba–CFU*** refers to the basophil colony forming units.
- ***Eo–CFU*** are the eosinophil colony forming units.
- ***M–CFU*** refers to the monocyte colony forming units.
- ***G–CFU*** are the neutrophil forming units.

The broad outlines of haemopoiesis discussed above are summarized in Fig. 3.2-4. Further details of erythropoiesis are discussed in this chapter and details of development of other blood cells are discussed in the relevant chapters.

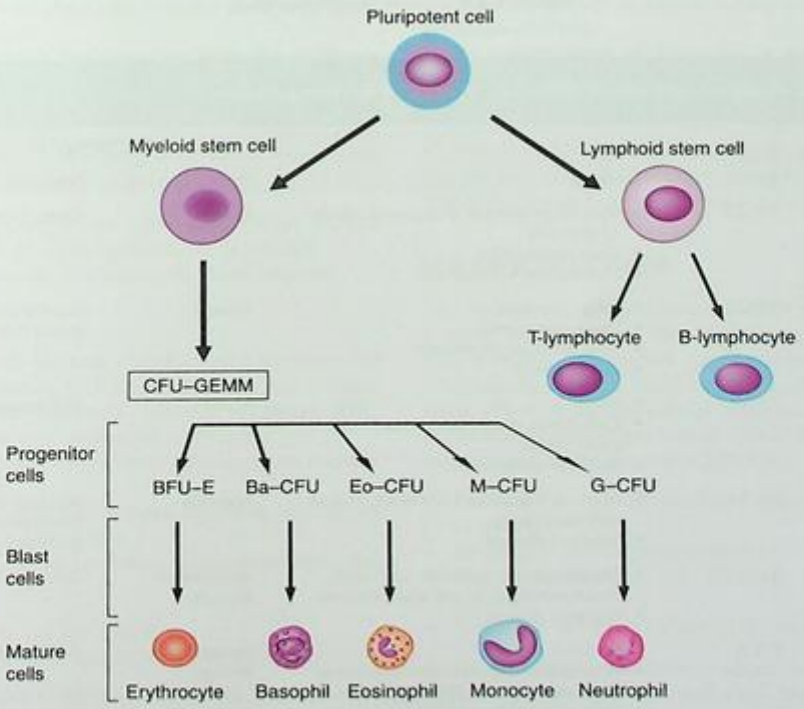


Figure 3.2-4 Schematic broad outline of haemopoiesis.

Stages of Erythropoiesis

The RBCs develop from the burst forming unit–erythrocyte (BFU–E) and colony forming unit–erythrocyte (CFU–E), which are derived from the committed progenitor cells.

The well-defined and readily recognisable lineage of nucleated red cells (erythroid series), which form different stages of erythropoiesis (Fig. 3.2-5), are summarized in Table 3.2-1.

Maturation of a Reticulocyte into an Erythrocyte A reticulocyte spends 1–2 days in bone marrow and circulates for 1–2 days in the peripheral blood before maturing in the spleen to become a biconcave red cell. The mature red cell has lost its nucleus as well as the ribosomes and mitochondria. It thus cannot synthesize Hb and any other protein. Normally only mature blood cells are able to enter the circulation. The reticulocytes are also found normally in the peripheral blood. Normal range of the reticulocytes in healthy adults is 0.5%–2% and in infants it is 2%–6%. Abnormal increase in the circulating reticulocytes is called *reticulocytosis*. This is seen when the rate of erythropoiesis is very high, as it occurs in the haemolytic anaemia and following the treatment of deficiency anaemias.

Reticulocytes can be counted in the laboratory by vital staining with dyes, such as new methylene blue or brilliant cresyl blue.

Summary of Changes Occurring in the Cells of Erythroid Series during Maturation It takes 7 days for the formation and maturation of RBCs. Till the stage of reticulocyte, it takes 5 days and to become matured red cell from reticulocyte, it takes 2 days. Various changes which occur during maturation from the stage of pronormoblast to erythrocyte are summarized below:

Size of the cell (from 15–20 μm of pronormoblast) goes on decreasing with subsequent stages till it reaches about 7 μm.
Nucleus first condenses, then becomes pyknotic and finally disappears at the stage of reticulocyte formation.
Hb synthesis starts at the stage of intermediate normoblast and then its content increases progressively.
Cytoplasm staining. Initially, before the appearance of Hb the cytoplasm is basophilic. When Hb starts appearing cytoplasm becomes polychromatic, i.e. stained both by acidic and basic dyes. In the stage of late normoblast when Hb synthesis is almost completed, cytoplasm is stained by an acidic dye.
Mitosis is seen up to the stage of intermediate normoblast. During these stages, 3–5 cell divisions occur. In this way, each pronormoblast gives rise to 8–320 late normoblasts. From the stage of late normoblast onwards, the mitosis ceases and cell only matures.

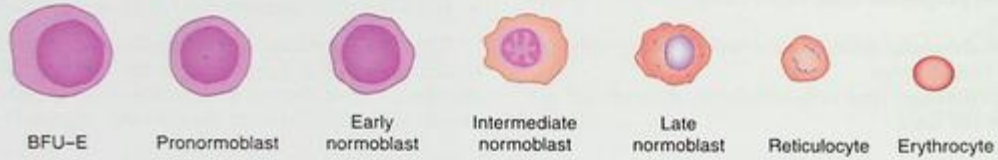


Figure 3.2-5 Stages of erythropoiesis.

TABLE 3.2-1 Characteristic Features of Cells at Different Stages of Erythropoiesis

Stage	Size (μm)	Nucleus	CYTOPLASM		Mitosis
			Hb	Staining	
1. Homocytoblast (stem cell)	19–23	• Very large (almost occupying whole of the cell) • Deep basophilic • Containing 4–5 nucleoli	Absent	Deep basophilic	Present ++
2. Pronormoblast (proerythroblast)	15–20	• Large (central) • Deep basophilic • Fine reticular chromatin • 2–3 nucleoli	Absent	Scanty and deep basophilic	++
3. Early normoblast	12–16	• Large • Chromatin strand becomes thicker and coarser • Nucleoli disappears	Absent	Still basophilic	++
4. Intermediate normoblast (polychromatic normoblast)	10–14	• Nucleus becomes condense, coarse and basophilic • Nucleoli absent	Appears	Acidophilic with basophilic hue (polychromatic)	+
5. Late normoblast (orthochromatic normoblast)	8–10	• Nucleus small, pyknotic with dark chromatin (cart-wheel appearance) • Nucleoli absent	Increased in amount	Acidophilic	Absent
6. Reticulocyte	7–7.5	• Nucleus absent • With supravital stain (brilliant cresyl blue) remnants of RNA appear in the form of reticulum in the cytoplasm	Increased in amount	Acidophilic	Absent

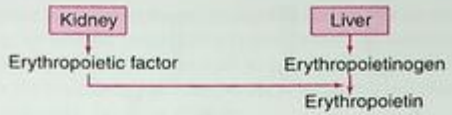


Figure 3.2-6 Mechanism of erythropoietin secretion.

Regulation of Erythropoiesis

Erythropoietin *Erythropoietin* is a hormone, which regulates the process of erythropoiesis. It is a glycoprotein having molecular weight of 34,000.

Site of Formation. Erythropoietin is mainly (85%) produced by the juxta glomerular apparatus of kidney. Extrarenal sources like liver and cells of tissue macrophage system produce about 15% of erythropoietin, especially when hypoxia is marked.

Stimulus for Secretion. A certain basal level of the hormone is necessary for the normal rate of erythropoiesis. The main function of the RBCs is to supply oxygen to the tissues. Therefore, whenever, there is hypoxia or decrease in the number of RBCs (e.g. after haemorrhage or in haemolytic anaemia), there occurs a release of renal erythropoietic factor from juxta glomerular cells of kidney. Renal erythropoietic factor acts on the plasma alpha globulin called erythropoietinogen to form the erythropoietin (Fig. 3.2-6). Thus the levels of erythropoietin vary with degree of hypoxia or number of circulating RBCs. This explains how polycythaemia (increased RBC count) is observed in hypoxic states, such as in normal individuals residing at high altitude or in patients suffering from cardiopulmonary disorder.

Actions of Erythropoietin. Erythropoietin increases erythropoiesis because of the following actions:

- Erythropoietin exerts its chief effect on the stem cells causing them to differentiate.
- It promotes Hb synthesis by increasing globulin synthesis and potentiating δ-amino laevulinic acid synthetase.
- It also promotes every stage of maturation from pronormoblast to the mature red cells.
- Erythropoietin also promotes release of RBCs from bone marrow into the peripheral circulation.

Factors Increasing Erythropoietin Secretion. Other factors which increase secretion of erythropoietin are as follows:

1. Hormones which increase erythropoietin secretion are:

- Androgens
- Thyroxine
- Other hormones which increase erythropoietin secretion are growth hormone, prolactin, ACTH and adrenocortical steroids.

2. Haemolysates, i.e. the products released following RBC destruction, also increase erythropoietin secretion.

3. Nucleotides which enhance erythropoietin secretion include cAMP, NAD and NADP.

4. Vasoconstrictor Drugs produce renal hypoxia, which, in turn, affects erythropoietin secretion.

Factors Decreasing Erythropoietin Secretion **are the following:**

- Adenosine Antagonists, e.g. theophylline.
- Oestrogen decreases erythropoietin secretion by:

- decreasing the synthesis of globin in liver and
- depressing the erythropoietic response to hypoxia.

Factors Necessary for Erythropoiesis

Factors necessary for erythropoiesis can be divided into three groups:

- General factors
- Special maturation factors
- Factors necessary for haemoglobinization

I. General Factors The main general factors necessary for the process of erythropoiesis are optimum level of the hormone *erythropoietin*, and the efficient *feedback mechanism* controlling the secretion of *erythropoietin* have been discussed in the regulation of erythropoiesis.

II. Special Maturation Factors Special factors which are essential for maturation of RBC include vitamin B_{12}, intrinsic factor of Castle and folic acid.

Vitamin B_{12} and Intrinsic Factor of Castle Vitamin B_{12} (cyanocobalamin), also known as extrinsic factor, is essential for maturation of red cells.

Daily requirement of vitamin B_{12} in adults is 1–2 µg. Its deficiency causes pernicious anaemia, so it is also called antipernicious factor.

Daily requirement. It is required for the synthesis of DNA and maturation of nucleus and cell. Deficiency of vitamin B_{12} leads to:

- Failure of maturation of nucleus.
- Cells remain large (megaloblasts) and become more fragile. Normally during maturation, cell size decreases progressively.
- There occurs reduction in the cell division.

Folic Acid Folic acid (pteroylglutamic acid) and related compounds are known as folates – play an important role in the synthesis of DNA.

Daily requirement of folate for a normal healthy adult is 100 µg.

Folate deficiency causes megaloblastic anaemia (see page 72).

III. Factors Necessary for Haemoglobinization Various factors necessary for Hb formation in the RBCs are proteins, minerals (specially iron) and vitamins.

HAEMOGLOBIN

The cytoplasm of erythrocytes (RBCs) contains an *oxygen-binding protein* called Hb. Erythrocyte precursors synthesize Hb, whereas the mature erythrocytes lose the property of synthesizing Hb. The inclusion of Hb within the erythrocytes is most effective for functional purposes because it avoids the following *disadvantages* which would have occurred if the Hb was present in the plasma as free Hb:

- Increase in blood viscosity causing a rise in blood pressure.
- Increase in the osmotic pressure.
- Rapid destruction of Hb by the reticuloendothelial system.
- Excretion of Hb by kidney (Hb urea).

In pathologic states, e.g. acute haemolytic disorder, Hb appears in the plasma and may lead to above-mentioned consequences.

Normal Blood Haemoglobin

The normal blood Hb concentration at different ages is given below:

- ***In fetus,*** just before birth, the Hb concentration of blood from the umbilical cord ranges from 16.5 to 18.5 g/dL.
- ***After birth,*** the Hb concentration increases rapidly and may reach up to 23 g/dL. This occurs due to the transfusion of cells from the placenta to infant.
- ***At the end of 3 months.*** After 2 days of birth, the Hb levels start falling and stabilize at the end of 3 months to 10.5 g/dL.
- ***At 1 year of age.*** The concentration then rises gradually to reach 12 g/dL at 1 year of age.
- ***In adult males*** the mean blood Hb concentration is 15.5 g/dL (range 14–18 g/dL).
- ***In adult females*** the mean Hb concentration is 14 g/dL (range 12–15.5 g/dL).

IMPORTANT NOTES

- The normal Hb becomes 100% saturated when blood is equilibrated with 100% oxygen (PO_2, 760 mm Hg).
- One gram of Hb when fully saturated combines with 1.34 mL oxygen. Thus Hb concentration is an index of oxygen carrying capacity of blood. Thus, normal values of oxygen carrying capacity in males is 1.34 × 15.5 = about 21 mL% and in females is 1.34 × 14 = about 18.5 mL%.
- *Clinically,* irrespective of the age, a level of 14.8 g/dL is considered as 100% Hb.

Structure of Haemoglobin

Hb is a globular molecule having a molecular weight of 68,000. It consists of the protein *globin* combined with iron-containing pigment called *haem.*

Structure of Globin The protein globin, present in the Hb, is made of four polypeptide chains. Haemoglobin A (HbA) consists of the following four polypeptide chains:

- *Two α chains,* each containing 141 amino acid residues.
- *Two β chains,* each containing 146 amino acid residues.

Therefore, the normal adult HbA is written as HbA ($\alpha_2\beta_2$).

Structure of Haem The haem is an iron–porphyrin complex called *iron–protoporphyrin IX,* i.e. it consists of a porphyrin nucleus and the iron. The structural characteristics of the haem (iron–protoporphyrin IX) are given below (Fig. 3.2-7A–C):

Porphyrin Nucleus

- The porphyrin nucleus consists of four *pyrrole rings* numbered I, II, III and IV, i.e. porphyrins are tetrapyrroles.
- The pyrrole rings are joined together by four *methine bridges* (=CH⁻). The carbon atoms of methine bridges are labelled α, β, γ and δ.
- Eight *side chains* are attached to the pyrrole ring at positions labelled 1–8. These are as follows:
  - Four *methyl* (CH_3) side chains at position 1, 3, 5 and 8.
  - Two *vinyl* ($-CH = CH_2$) side chains at position 2 and 4.
  - Two *propionic* acid ($-CH_2 - CH_2 - COOH$) side chains at position 6 and 7.

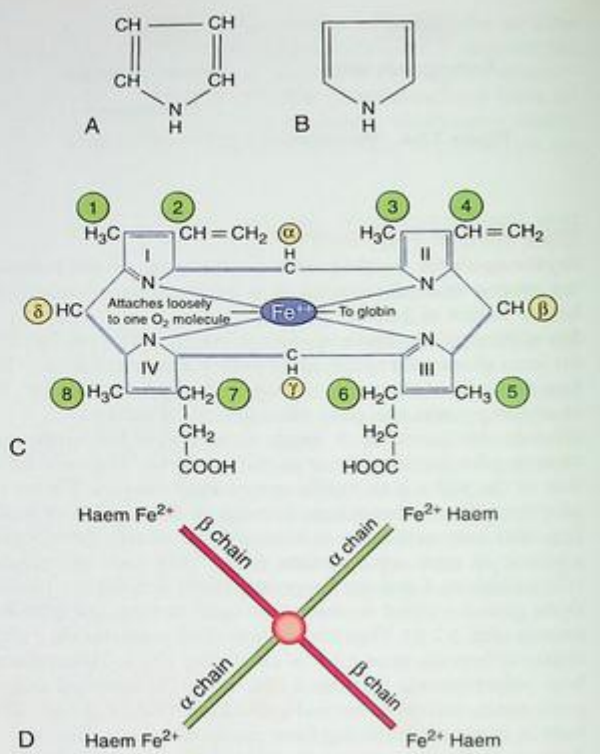


Figure 3.2-7 Chemistry of haemoglobin: (A) structure of a pyrrole ring; (B) conventional outline of a pyrrole ring; (C) arrangement of pyrrole rings in one unit of haem (iron protoporphyrin IX); and (D) arrangement of four units of haem in one molecule of haemoglobin.

The Iron

- The iron in the haem is in *ferrous* (Fe^{2+}) form.
- The iron is attached to the nitrogen atom of each pyrrole ring.
- On the iron (Fe^{2+}) a bond is available for loose union, where:
  - In oxyhaemoglobin, O_2 is attached.
  - In carboxyhaemoglobin, CO is attached, and so on (see derivatives of Hb).

Attachment of Haem to Globin One molecule of Hb contains four units of haem, each attached to one of the four polypeptide chains constituting globin (Fig. 3.2-7D). As there are four units of haem in one molecule of Hb, so there are four iron atoms in one molecule of Hb, which can carry four molecules (eight atoms) of oxygen.

Functions of Haemoglobin

1. Transport of O_2 from Lungs to Tissues

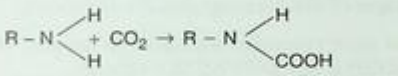
- *In the lungs,* one molecule of O_2 is attached loosely and reversibly at the sixth covalent bond of each iron atom of the Hb to form *oxyhaemoglobin* represented as HbO_2:

Hb	+	O_2	→	HbO_2
Deoxygenated (reduced) haemoglobin				Oxygenated haemoglobin

- Oxygenation of first haem molecule in the Hb increases the affinity of second haem for oxygen, which, in turn, increases the affinity of third haem and so on. In this way, the affinity of Hb for fourth oxygen molecule is many times that for the first molecule. Because of this:
  - Hb reacts with oxygen very rapidly taking less than 0.01 s. Similarly, deoxygenation of Hb is also very rapid.
  - The oxygen–Hb dissociation curve becomes sigmoid shape (see page 194).
- The affinity of Hb for oxygen is influenced by pH, temperature and concentration of 2,3-biphosphoglycerate, i.e. 2, 3-BPG (a product of metabolism of glucose) in the RBCs.

2. Transport of CO_2 from the Tissues to the Lungs Hb also transports CO_2 from the tissues to the lungs.

- It is important to note that the CO_2 from the tissues is transported by combining with amino acids of the globin part as shown below and not in combination with Fe^{2+} atom like O_2.



Haemoglobin Carbaminohaemoglobin

- Deoxygenated Hb forms carbamino-Hb more readily than oxygenated Hb. That is why venous blood becomes more suitable for the transport of CO_2 from the tissues to the lungs.

3. Control pH of the Blood The Hb constitutes the most important acid–base buffer system of blood. Hb has six times the buffering capacity as compared to the plasma proteins.

Varieties of Haemoglobin

Several varieties of Hb occur in human beings. In all varieties of Hb the haem moiety remains the same. It is the composition of polypeptide chains of globin part of the Hb which differs in various varieties of Hb. Various varieties of Hb can be grouped as under:

- Physiological varieties of Hb
- Haemoglobinopathies

Physiological Varieties of Haemoglobin

Adult Haemoglobin (Adult Hb) is of two types.

(i) ***Haemoglobin A*** **[HbA ($\alpha_2\beta_2$)]**. It is the main form of normal adult Hb. As described on page 66, its globin part consists of two α and two β polypeptide chains.

(ii) ***Haemoglobin A_2*** **[HbA_2 ($\alpha_2\delta_2$)]**. It is a minor component (about 2.5% of the total Hb) in normal adults. Its globin part consists of two α and two δ polypeptide chains. δ chains have slightly different amino acid composition (out of 146, 10 amino acids are different) as compared to β chains.

Fetal haemoglobin or haemoglobin F [HbF ($\alpha_2\gamma_2$)], as the name indicates, refers to the Hb present in the fetal RBCs and gradually disappears 2–3 months after birth.

Structure of HbF is similar to that of HbA, except that its globin part consists of two α and two γ polypeptide chains (in place of β chains). γ chains also have 146 amino acids but its 37 amino acids are different than that of β chains.

Special Features of HbF are given below:

- ***Affinity for oxygen*** in case of HbF is more than that of HbA, i.e. it can take more oxygen than HbA at low oxygen pressure. It is owing to poor binding of 2,3-BPG by the γ polypeptide chain. Because of this, movement of oxygen from maternal to fetal circulation is facilitated. At PO_2 20 mm Hg, HbF is 70% saturated whereas HbA is only 30%–35% saturated.
- ***Resistance to action of alkalies*** is more in HbF than HbA. This property is used in a photoelectric calorimetric method to estimate HbF in the presence of HbA.

Haemoglobinopathies Haemoglobinopathies, i.e. abnormal formation of Hb occurs due to the disorders of globin synthesis; haem synthesis being normal. Disorders of the globin synthesis are of two main types:

- *Formation of abnormal polypeptide chains* due to substitution of an abnormal amino acid chain in the HbA. Example of such a disorder is haemoglobin S (HbS).
- *Suppression* of synthesis of polypeptide chain of globin as seen in thalassaemia.

1. Sickle Cell Haemoglobin or HbS is the most important haemoglobinopathy.

- It occurs in 10%–20% of Negroes. Sickle cell gene has originated in the black population in Africa.
- Sickle trait is inherited as Mendelian dominant trait but the full blown disease is autosomally recessive. Heterozygous individual with sickle cell trait rarely has severe symptoms but homozygous develop full blown disease.
- HbS is formed due to substitution of valine for glutamic acid at position 6 in the β chain of HbA.
- When HbS is reduced (e.g. in low-O_2 tension or when pH at tissue level is low), it becomes much less soluble and precipitates into crystals within the RBCs. The crystals elongate producing changes in shape of the cells from biconcave to sickle-shaped cells (sickling) (Fig. 3.2-8).
- The cells containing HbS are less flexible as compared to the RBCs containing HbA, hence leading to a blockade of microcirculation.
- Sickle-shaped cells greatly increase blood viscosity, thereby decreasing the blood flow to tissues.
- Sickle-shaped cells are more fragile and are very liable to undergo haemolysis producing the so-called sickle cell anaemia.
- The individual with sickle cell trait has resistance to one type of malaria.

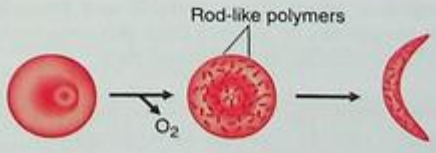


Figure 3.2-8 Mechanism of sickling of red blood cell containing haemoglobin S (HbS).

TABLE 3.2-2 Main Differentiating Features of β-Thalassaemia – Major and Minor

S. No.	β-Thalassaemia major	β-Thalassaemia minor
1.	Thalassaemia major is also called Mediterranean anaemia or Cooley anaemia and is less common.	Thalassaemia minor is more common.
2.	It is inherited as a homozygous transmission (i.e. abnormal genes are inherited from both the parents); therefore:	It is inherited as a heterozygous transmission (i.e. abnormal gene is inherited from one parent); therefore:
	• There is complete absence of β chain synthesis.	• The synthesis of β chain is not completely absent (partial).
	• Absence of β chain synthesis results in moderate to severe anaemia.	• Anaemia is of mild type.
	• HbF level is markedly increased.	• HbF level is either normal or slightly elevated.
3.	The individual suffering from thalassaemia major has short lifespan, i.e. (dies young 17–18 years).	The individuals suffering from thalassaemia minor comparatively survive longer (up to adult) and transmit abnormal gene to their offsprings.

2. *Thalassaemia* (Mediterranean anaemia) is a haemoglobinopathy characterized by the following features:

- ***Cause.*** Thalassaemia results due to defect in the synthesis of polypeptide chain α and β of HbA.
- ***Types.*** Depending on whether α or β chains are not synthesized, α-thalassaemia or β-thalassaemia may occur, respectively. B-thalassaemia is more common and is further of two types: thalassaemia major and thalassaemia minor.
- ***Features*** of thalassaemia major and minor are depicted in Table 3.2-2.

Derivatives of Haemoglobin (Reactions of Haemoglobin)

Hb has the property to readily react with any gas, other substance to form the so-called derivatives of Hb. These include the following:

1. *Oxyhaemoglobin* Hb reacts readily with oxygen to form oxyhaemoglobin, which is an unstable and reversible compound, i.e. oxygen can be released from this compound. In this compound iron remains in the ferrous state.

2. *Reduced Haemoglobin* or deoxygenated Hb is formed when oxygen is released from the oxyhaemoglobin.

$$\underset{\text{(Oxyhaemoglobin)}}{HbO_2} \rightarrow \underset{\text{(Reduced haemoglobin)}}{Hb} + O_2$$

3. *Carbaminohaemoglobin* is a compound of Hb with carbon dioxide.

$$HbNH_2 + CO_2 \rightarrow HbNHCOOH$$

4. *Carboxyhaemoglobin* or carbon monoxyhaemoglobin is a compound of Hb with carbon monoxide (CO):

$$Hb + CO \rightarrow COHb$$

The affinity of Hb for CO is much more (200–250 times) than its affinity for oxygen. Because of this, the CO displaces oxygen from Hb, thereby reducing the oxygen carrying capacity of the blood.

5. *Methaemoglobin* When reduced or oxygenated Hb is treated with an oxidizing agent, e.g. potassium ferricyanide, the ferrous Fe^{2+}, is oxidized to ferric (Fe^{3+}); the sixth bond is attached to OH to form the compound methaemoglobin. Methaemoglobin is represented as HbOH.
Disadvantages of methaemoglobin are as follows:

- It cannot unite reversibly with gaseous oxygen; the O_2 of the attached OH is not given off in a vacuum.

6. *Glycosylated Haemoglobin* is a derivative of HbA present in very small amount, e.g. *haemoglobin* A_{1C} (HbA_{1C}), in which glucose is attached to terminal valine in the β chains. The level of glycosylated Hb in the blood increases in poorly controlled patients of diabetes mellitus.

Synthesis of Haemoglobin

Hb is synthesized in the cytoplasm of intermediate normoblasts.

Synthesis of Haem Haem is synthesized in the mitochondria.

- Succinyl-CoA (derived from the citric acid cycle in mitochondria) and glycine are the starting substances in the synthesis of haem. Steps of synthesis are shown in Fig. 3.2-9.
- The *protoporphyrin IX* is then formed after a series of reactions promoted by other enzymes.
- Finally, ferrous ion is introduced into the protoporphyrin IX molecule to form *haem* in a reaction catalysed by the enzyme haem synthetase.

Synthesis of Globin Globin, the protein part of the Hb, is synthesized in the ribosomes.

Factors Controlling Haemoglobin Formation Whipple's standard anaemic dog studies show that iron as well as dietary proteins, both play very important role in synthesis of Hb. In addition, certain other minerals and vitamins also control the Hb formation.

1. Role of Proteins. First class proteins provide amino acids required for the synthesis of globin part of the Hb. A low protein intake retards Hb regeneration even in the presence of excess iron; the limiting factor being lack of globin.

2. Role of Iron. Iron is necessary for formation of the haem part of Hb. In addition to dietary iron, the iron released by degradation of RBCs is also reused for the synthesis of Hb.

3. Role of other Metals

- ***Copper*** is essential for the Hb synthesis, as it promotes the absorption, mobilization and utilization of iron.

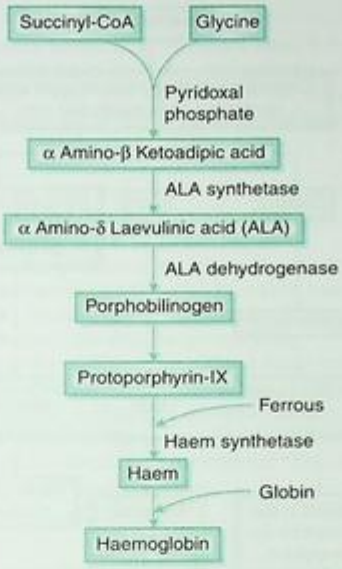


Figure 3.2-9 Steps of synthesis of haemoglobin.

- ***Cobalt.*** Its role in humans is not evidenced, but in some species cobalt increases the production of erythropoietin, which, in turn, stimulates RBC formation.
- ***Calcium*** reported to help indirectly by conserving iron and its subsequent utilization.

4. Role of Vitamins. Vitamin B_{12}, folic acid, and vitamin C help in synthesis of nucleic acid which, in turn, is required for the development of RBCs. Vitamin C also helps in absorption of iron from the gut.

5. Role of Bile Salts. Presence of bile salts in the intestine is necessary for proper absorption of metals like copper and nickel which, in turn, are essential factors for synthesis of Hb.

RED CELL FRAGILITY

Red cell fragility refers to the susceptibility of red cell membrane to get broken or bursted. The process of breaking of RBCs and release of Hb into the plasma is called haemolysis. Red cell fragility depending on the underlying mechanism is of two types:

- Osmotic red cell fragility
- Mechanical red cell fragility

Osmotic Red Cell Fragility

Osmotic red cell fragility refers to the susceptibility of red cell membrane to get lysed due to changes in the osmotic pressure of the solution in which they are suspended (see page 16).

Effect of Osmotic Pressure of Solution on the RBCs

- *Isotonic solutions* have tonicity as that of plasma. These include 0.9% NaCl, 5% glucose, 10% mannitol and 20% urea. When RBCs are placed in these solutions, they remain suspended in them, i.e. neither swell nor shrink. This is because the osmotic pressure of the isotonic solutions is equal to the osmotic pressure within the RBCs.
- *Hypertonic solutions* (e.g. >0.9% NaCl, 20% mannitol) have osmotic pressure more than the osmotic pressure within the RBCs. Therefore, when the RBCs are placed in such solutions, fluid goes out of the cells and they shrink.
- *Hypotonic solutions* (e.g. <0.9% NaCl) have osmotic pressure less than the osmotic pressure within the RBCs. Therefore, when the RBCs are placed in such solutions, they swell up by absorbing water from outside and finally burst, i.e. get haemolysed.

Normal Values (Index of Fragility)

- ***Onset of haemolysis*** (fragility) in normal RBCs occurs in 0.48% NaCl.
- ***Completion of haemolysis*** (ending of fragility) occurs in 0.35% NaCl.
- ***Explanation.*** Normally only the older red cells with comparative fragile membrane are haemolysed in around 0.48% of NaCl solution because these cells cannot withstand this hypotonicity. But, younger cells are not affected. In 0.35% NaCl even the youngest cells are haemolysed and so haemolysis is completed.

Abnormal Osmotic Fragility Increase in osmotic fragility index occurs in the following conditions:

- Congential spherocytosis
- Autoimmune haemolytic anaemia
- Deficiency of glucose 6-phosphate dehydrogenase (G6PD).

Decrease in osmotic fragility index occurs when the RBCs become slender, e.g. in iron-deficiency anaemia. In this condition the onset of haemolysis occurs at 0.36% NaCl and is completed at 0.24% NaCl solution.

Mechanical Red Cell Fragility

The red cells are subjected to a mechanical stress and trauma as they pass through the capillaries and trabeculae of spleen some 300,000 times during their lifespan of 120 days. They are made more brittle due to unusual mechanical stress. The red cells can become more rigid as a result of the pathological changes in the membrane or in the cell contents caused by a number of red cell disorders. The cells thus become mechanically more fragile, i.e. less liable to tolerate deforming stresses than the normal healthy red cell.

LIFESPAN AND FATE OF RED BLOOD CELLS

Lifespan of RBCs

Normally, the average lifespan of RBCs is 120 days.

Fate of RBCs

The cell membrane of old RBCs (after about 120 days) becomes more fragile due to decreased NADPH activity. The younger RBCs can easily pass through the capillaries which have diameter smaller than the red cells. The older cells with fragile membrane are destroyed when the cells try to squeeze through the capillaries. The destruction of red cells occurs mostly in the capillaries of spleen because they have very thin lumen. Because of this, spleen is also called the graveyard of RBCs. The Hb released after the haemolysis of red cells is taken up by the tissue macrophages.

The tissue macrophage system (reticuloendothelial system) includes the following phagocytic cells:

- *In the bone marrow* these cells form part of the lining of the blood sinuses (littoral cells).
- *In the liver* they lie at intervals along the vascular capillaries (Kupffer cells).
- *In the spleen* they are found in the pulp.
- *In the lymph nodes* they line the lymphatic paths.

Fate of Haemoglobin (Fig. 3.2-10)

- In the macrophages, the haem part of the Hb molecule is altered by oxidation of one of its methine (=CH) bridges. As a result of this chemical change, the green iron- containing compound *choleglobin is formed*. As the name implies, the choleglobin molecule still contains the original globin.
- Next, the *choleglobin splits off* into globin, iron and biliverdin (tetrapyrrole straight chain gets free from globin and iron).
- *Globin* is degraded into amino acids, joins the amino acid pool of plasma and is released.
- *Iron* released into the circulation is
  - carried into the bone marrow for reutilization, and
  - in the other tissues it combines with apoferritin to form the ferritin (storage form of iron).
- *Biliverdin* (tetrapyrrole straight chain free from globin and iron) is converted into bilirubin (by the enzyme biliverdin reductase) and is released into the blood.

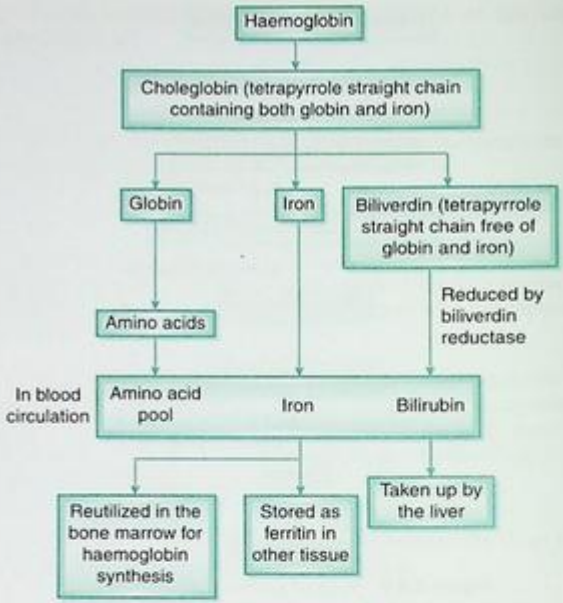


Figure 3.2-10 Fate of haemoglobin.

BILIRUBIN AND JAUNDICE

Bilirubin Formation and Its Fate

As discussed above, the bilirubin is formed in the macrophages. It undergoes the following changes (Fig. 3.2-11):

1. Uptake of Bilirubin. Macrophages release the bilirubin into circulation. This bilirubin is called free or *unconjugated bilirubin*. It is lipid soluble, in the plasma it is bound to the albumin (protein conjugated), which prevents its excretion by the kidneys.

2. Conjugation of Bilirubin. The unconjugated bilirubin (bound to albumin) from the circulation is taken up by the liver. In the liver the bilirubin is split off from the albumin and enters the hepatic cells. In the hepatic cells, it is conjugated with uridine diphosphate glucuronic acid (UDP-glucuronic acid) making it a water-soluble conjugated *bilirubin*.

3. Excretion of Bilirubin. The conjugated bilirubin from the hepatic cells is excreted and enters the intestine. Some of it escapes into general circulation and is excreted by the kidneys in urine as *urine bilirubin*.

4. Formation and Excretion of Urobilinogen. The conjugated bilirubin which enters the intestine is degraded by the intestinal bacteria in the terminal ileum and the large intestine. The bacterial enzyme β-glucuronidase splits off the glucuronide and converts bilirubin into the *urobilinogen* (stercobilinogen), which is a colourless compound.

- Some urobilinogen (20%) from the intestine is reabsorbed and goes via the portal system to the liver. From the liver some urobilinogen escapes into general circulation and some are re-excreted into the bile (enterohepatic circulation).
- From general circulation, the urobilinogen is filtered off by the kidney and is excreted in the urine.

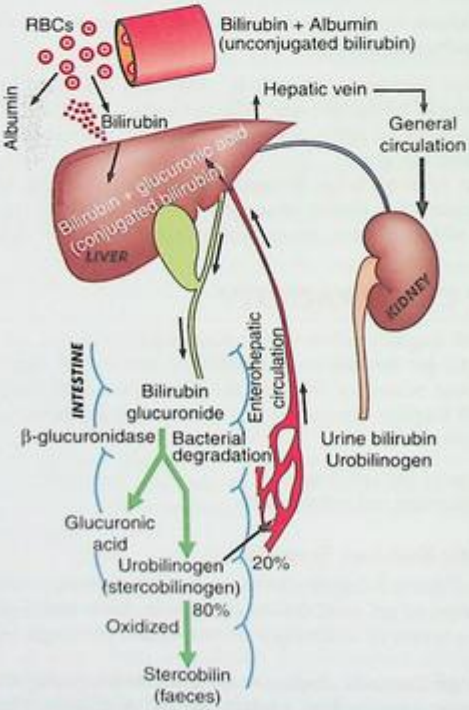


Figure 3.2-11 State of bilirubin in the body.

Bilirubin

The normal serum bilirubin level ranges from 0.3 to 1.0 mg/dL. The total serum bilirubin includes conjugated as well as unconjugated bilirubin. The Van den Bergh test described below is helpful in determining the type of bilirubin present in the serum.

Van den Bergh Test Van den Bergh test is performed using the diazo reagent (mixture of sulphanilic acid, hydrochloric acid and sodium nitrite). It is of two types:

Direct Van den Bergh Reaction. When diazo reagent is added to the serum containing conjugated bilirubin (water soluble) a reddish brown colouration is obtained within 30 s. This is called direct positive Van den Bergh reaction.

Indirect Van den Bergh Reaction. When diazo reagent is added to the serum containing mainly unconjugated bilirubin (water insoluble), no colour is obtained. However, if some solvent like alcohol (which dissolves the unconjugated bilirubin) is added, the reddish brown colouration is obtained. This is called indirect positive Van den Bergh reaction.

Jaundice

Jaundice (icterus) refers to the yellow appearance of the skin, sclera and mucous membranes resulting from an increased bilirubin concentration *(hyperbilirubinaemia)* in the body fluids. Clinically, jaundice is detectable when the plasma bilirubin exceeds 2–3 mg/dL.

Mechanisms Producing Jaundice Hyperbilirubinaemia producing jaundice can result from the following mechanisms:

1. Excessive Breakdown (Haemolysis) of RBCs produces the so-called haemolytic jaundice or prehepatic jaundice. *Unconjugated* hyperbilirubinaemia occurs because it is being produced in excess of what can be conjugated by the liver.

2. Damage to the Liver Cells (infective or toxic) produces the so-called hepatic or hepatocellular jaundice. *Both unconjugated* as well as *conjugated* bilirubin is increased in serum.

3. Obstruction to Bile Ducts produces the obstructive or posthepatic or cholestatic jaundice. *Conjugated hyper*bilirubinaemia results due to impaired flow of bile.

Physiological Jaundice of Newborn Physiological jaundice of newborn is also called neonatal jaundice.

Mechanism of Production. A hyperbilirubinaemia producing jaundice may be seen normally in the newborn. It appears within 2–5 days of birth and usually disappears in 2 weeks. Its mechanism of production includes:

Excessive Destruction of RBCs occurs in first few days after birth causing increase in the serum bilirubin.

Hepatic Immaturity in the first few (7–10) days after birth also contributes to increased serum bilirubin.

Prevention and Treatment

Prevention. Neonatal jaundice can be prevented by the administration of hepatic microsomal enzyme inducers (e.g. phenobarbital) to the pregnant mother or newborn. The microsomal enzyme inducers increase the activity of glucuronyl transferase in liver.

Treatment. Neonatal jaundice can be effectively treated by *phototherapy*. Exposure of the skin to white light causes photoisomerization of bilirubin to water-soluble *lumirubin*, which can be rapidly excreted in bile without requiring any conjugation.

ANAEMIAS

Definition and Classification

Definition

Anaemia is not a single disease but a group of disorders in which Hb concentration of blood is below the normal range for the age and sex of the subject. Therefore, anaemia is labelled when the Hb concentration is less than:

- 13 g/dL in adult males
- 11.5 g/dL in adult females
- 15 g/dL in newborn
- 9.5 g/dL at 3 months of age

Low RBC count (less than 4 million/mm^3) is usually, but not always, associated with low Hb levels in anaemia.

Grading of anaemia depending on the level of Hb has somewhat arbitrarily been made as:

- Mild anaemia – Hb 8–10 g/dL
- Moderate anaemia – Hb 6–8 g/dL
- Severe anaemia – Hb below 6 g/dL

Classification

Aetiological (Whitby's) Classification Types of anaemia depending on the causative mechanism are as follows:

A. Deficiency Anaemias

- Iron-deficiency anaemia
- Megaloblastic anaemia (pernicious anaemia) due to deficiency of vitamin B_{12}
- Megaloblastic anaemia due to deficiency of folic acid
- Protein and vitamin C deficiency can also cause anaemia.

B. Blood Loss Anaemias or haemorrhagic anaemias are commonly known and can be:

- Acute posthaemorrhagic anaemia as in accidents
- Chronic posthaemorrhagic anaemia

C. Haemolytic Anaemias. These are relatively uncommon and occur in conditions associated with increased destruction of RBCs. These can be:

1. Hereditary haemolytic anaemias, e.g. as seen in:

- Thalassaemia
- Sickle cell anaemia
- Hereditary spherocytosis
- Glucose 6-phosphate dehydrogenase (G6PD) deficiency

2. Acquired haemolytic anaemias such as Immunohaemolytic anaemia (due to antibodies against RBCs):

- Haemolytic anaemia due to direct toxic effects (e.g. in malaria, snake venom and toxic effects of drugs and chemicals)
- Haemolytic anaemia in splenomegaly
- Haemolytic anaemia in paroxysmal nocturnal haemoglobinuria (PNH)

D. Aplastic Anaemia. It occurs due to the failure of bone marrow to produce RBCs.

E. Anaemia Due to Chronic Diseases. It is seen in tuberculosis, chronic infections, malignancies, chronic lung diseases, etc.

Morphological (Wintrobe's) Classification Based on the mean cell volume (MCV), i.e. cell size and the MCHC, i.e. Hb saturation of RBCs, the anaemias can be classified as:

1. Normocytic Normochromic Anaemias. These are characterized by normal MCV (78–94 μm^3 or 78–94 μL) and normal MCHC (30%–38%). Such a morphological picture is seen in:

- Acute posthaemorrhagic anaemia
- Haemolytic anaemias
- Aplastic anaemias

2. Microcytic Hypochromic Anaemias. These are characterized by reduced MCV (<78 μm^3) and reduced MCHC (<30%). Examples of such anaemias are as follows:

- Iron-deficiency anaemia
- Chronic posthaemorrhagic anaemia
- Thalassaemia

3. Macrocytic Normochromic Anaemia. It is characterized by increased MCV (>94 μm^3) and normal MCHC (30–38%). Examples are as follows:

- Megaloblastic anaemia (pernicious anaemia) due to deficiency of vitamin B_{12}
- Megaloblastic anaemia due to deficiency of folic acid

General Clinical Features of Anaemia

General Clinical Manifestations of Anaemia which occur either due to tissue hypoxia or due to compensatory mechanisms are as follows:

- *Generalized muscular weakness*
- *Pallorness of skin and mucous membranes*
- *Breathlessness*
- *Palpitation*
- *Visual disturbances*
- *Anorexia, atrophy of papillae on tongue*
- *In females* menstrual disturbances occur such as amenorrhoea and menorrhagia.

Iron-Deficiency Anaemia

Iron-deficiency anaemia is the commonest nutritional deficiency disorder present throughout the world, but its prevalence is higher in the developing countries. In India, iron-deficiency is the commonest cause of anaemia. Iron-deficiency anaemia is much more common:

- In women between 20 and 45 years than in men
- At periods of active growth in infancy, childhood and adolescence

Daily Requirement. Only 10% of the dietary intake of iron is absorbed. Therefore, daily requirement in the adult males is 5–10 mg/day and in females is 20 mg/day (to compensate the menstrual loss). Pregnant and lactating women require about 40 mg of iron per day.

Causes of Iron-Deficiency Anaemia

Causes of iron-deficiency vary with age, sex and country of residence of patient. In general, the causes of iron- deficiency anaemia can be grouped as follows:

1. Inadequate Dietary Intake of Iron as in:

- Milk fed infants
- Poor economic status individuals
- Anorexia, e.g. in pregnancy
- Elderly individuals due to atrophy and poor dentition

2. Increased Loss of Iron (as blood loss) from the body, e.g.

- *Uterine bleeding in females* in the form of excessive menstruation, repeated miscarriages, postmenopausal bleeding, etc.
- *Gastrointestinal bleeding* due to peptic ulcer, haemorrhoids, ulcerative colitis, etc.
- *Renal tract bleeding*, e.g. haematuria
- *Nasal bleeding*, i.e. repeated epistaxis
- *Bleeding from lungs* as haemoptysis

3. Increased Demand of Iron as in:

- Infancy, childhood and adolescence
- Menstruating females
- Pregnant females

4. Decreased Absorption of Iron, as seen in:

- Partial or total gastrectomy
- Achlorhydria
- Intestinal malabsorption diseases

Clinical Features, Laboratory Findings and Treatment

Clinical Features of Anaemia

1. ***General features of anaemia.*** As described above.
2. ***Characteristic features of iron-deficiency anaemia*** are in the form of following epithelial tissue changes:
   - *Nails* become dry, soft and spoon shaped (koilonychia)
   - *Tongue* becomes angry red (atrophic glossitis)
   - *Mouth* may show angular stomatitis
   - *Oesophagus* may develop their membranous webs at the postcricoid area leading to dysphagia (Plummer–Vinson syndrome)

Laboratory Findings

1. Blood Picture and Red Cell Indices

- *Hb* concentration is decreased.
- RBCs are hypochromic (deficient in Hb) and microcytic (smaller in size). They show anisocytosis and poikilocytosis.
- *Red cell indices* like MCV, MCH and MCHC are decreased.

2. Bone Marrow Findings

- Marrow cellularity: Erythroid hyperplasia
- Erythropoiesis: Normoblastic
- Marrow iron: Deficient

3. Biochemical Findings

- Serum iron decreases, often under 50 mg/dL (normal 60–160 mg/dL)
- Serum billirubin is less than 0.4 mg/dL
- Serum ferritin is very low, indicating poor tissue iron stores
- Total iron binding capacity (TIBC) is increased

Treatment Treatment of iron-deficiency anaemia consists of:

- Oral administration of Fe^{2+} salts
- Correction of causative factor, if possible

Megaloblastic Anaemia

Megaloblastic anaemias are characterized by the abnormally large cells of erythrocyte series. These are caused by defective DNA synthesis due to deficiency of vitamin B_{12} and/or folic acid (folate).

I. Megaloblastic Anaemia due to Vitamin B_{12} Deficiency

Causes of Vitamin B_{12} Deficiency are as follows:

1. *Inadequate dietary intake* may occur in:
   - Strict vegetarians
   - Breast-fed infants
2. *Malabsorption of vitamin B_{12}* is more often the cause of deficiency and may be due to the deficiency of intrinsic factors such as an autoimmune cause of failure of secretion of intrinsic factor (Addisonian pernicious anaemia), gastrectomy and congenital lack of intrinsic factor.

Addisonian Pernicious Anaemia Addisonian pernicious anaemia is the term which is used specifically for the megaloblastic anaemia due to vitamin B_{12} deficiency occurring as a result of failure of secretion of intrinsic factor by the stomach owing to an autoimmune atrophy of gastric mucosa.

II. Megaloblastic Anaemia due to Folate Deficiency

Causes of folate deficiency *are as follows:*

1. *Inadequate dietary intake*
2. *Malabsorption*, e.g. in coeliac disease, tropical sprue and Crohn disease.
3. *Increased demand* that occurs in conditions such as pregnancy, lactation and infancy.
4. *Effect of drugs* such as contraceptive pills and certain cytotoxic drugs (e.g. methotrexate).

Clinical Features of Megaloblastic Anaemia

A. General Features of Anaemia See page 72.

B. Characteristic Features of Megaloblastic Anaemia

1. Blood Picture and Red Cell Indices

- *Hb* level is low.
- RBCs are larger in size (macrocytosis) but contain a normal concentration of Hb (normochromia).
- *MCV* increases to 95–160 μm^3 (normal 78–94 μm^3).
- *MCH* increases to 50 pg (normal 28–32 pg).
- *MCHC* usually normal (35 ± 3%) because both MCV and MCH increase. In late stages MCHC may decrease.
- *Peripheral smear* shows nucleated RBCs.
- *Reticulocyte count* increases to more than 5% (normal less than 1%).
- *Lifespan of RBCs* is decreased.
- *WBCs and platelets* decrease because of encroachment of megaloblastic tissue.

2. Bone Marrow Picture Bone marrow shows *megaloblastic hyperplasia* characterized by presence of:

- 70% proerythroblasts and early normoblasts (normal 30%)
- 30% intermediate and late normoblasts (normal 70%)

3. Biochemical Finding

- *Serum bilirubin* increases more than 1 mg/dL (normal 0.2–0.8 mg/dL) due to excessive destruction of RBCs in spleen, liver and bone marrow, and jaundice occurs.
- *Urine urobilinogen* excretion may increase due to increased serum bilirubin.
- *Serum iron and* ferritin is usually increased because iron is not utilized by the immature RBCs.
- *Serum vitamin B_{12}* levels are decreased (normal 200–900 pg/mL) in patients with megaloblastic anaemia due to vitamin B_{12} deficiency.
- *Serum folate levels* are decreased in the patients with megaloblastic anaemia due to folic acid deficiency.

SELF-ASSESSMENT

1. Describe the stages of erythropoiesis and its regulation.
2. Describe the characteristics features of different phases of erythropoiesis and factors necessary for erythropoiesis.
3. What is the structure and functions of haemoglobin?
4. Describe the factors controlling formation of haemoglobin.
5. What is the lifespan and fate of RBCs?
6. Short note on:
   - Pernicious anaemia
   - Bilirubin
   - Osmotic fragility
   - Thalassaemia
   - Sickle cell haemoglobin
   - Erythropoietin
7. Differentiate between:
   - Red and yellow bone marrow
   - Intravascular and extravascular erythropoiesis
   - Blood picture of iron and vitamin B_{12} deficiency anaemia
   - Haemoglobin A and fetal haemoglobin
   - Prehapatic and posthepatic jaundice
8. Give normal value of:
   - Size of a erythrocyte
   - RBC counts
   - Lifespan of RBC
   - MCV
   - MCHC
   - ESR
   - Reticulocyte count
   - Haemoglobin

3.3 White Blood Cells

CHAPTER OUTLINE

Types of White Blood Cells and Their Counts
Types of White Blood Cells
Normal WBC Counts
Total Leucocyte Count
Differential and Absolute Leucocyte Count
Variations in WBC Count
Leucocytosis
Leucopenia

Formation of White Blood Cells
Formation of Granulocytes and Monocytes
Monocyte–Macrophage Series
Formation of Lymphocytes
Lymphoid Series
Regulation of Leucopoiesis

Morphology, Functions, Lifespan and Variations in Counts of WBCs
Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes

TYPES OF WHITE BLOOD CELLS AND THEIR COUNTS

Types of White Blood Cells

The white blood cells (WBCs) or leucocytes are so named because they are colourless in contrast to the red colour of red blood cells (RBCs). These are nucleated cells and play an important role in the defence mechanism of the body. The leucocytes of the peripheral blood are of two principal varieties, distinguished by the presence or absence of granules. These are granulocytes and agranulocytes (nongranulocytes).

Granulocytes The WBCs with granules in their cytoplasm are called granulocytes. Depending on the colour of granules, granulocytes are further divided into three types:
Neutrophils. They contain granules which take both acidic and basic stain.
Eosinophils. They contain granules which take acidic stain.
Basophils. They contain granules which take basic stain.

Agranulocytes WBCs which do not contain granules in their cytoplasm are called agranulocytes. These are of two types:

- *Lymphocytes*
- *Monocytes*

Normal WBC Counts

Total Leucocyte Count Total leucocyte count (TLC) varies with age.

Adults: 4000–11,000/mm^3 of blood.
At birth, in full-term infant: 10,000–25,000/mm^3 of blood.
Infants up to 1 year of age: 6000–16,000/mm^3 of blood.
Children, 4–7 years of age: 5000–15,000/mm^3 of blood.
Children, 8–12 years of age: 4500–13,500/mm^3 of blood.

Differential and Absolute Leucocyte Count Differential leucocyte count (DLC) and absolute count in normal adults are shown in Table 3.3-1.
Clinical Significance of Differential and Absolute Counts The DLC determines if there is an increase or decrease in a particular type of leucocyte because in different diseases one or the other type of cells show an increase or decrease in its numbers. The differential count is done in 100 or 200 cells and shows only a relative increase or decrease in particular variety of cells. DLC alone is not of much importance and so never done as an isolated test, but always it is a part of full blood counts including TLC and then calculating absolute count.

Variations in WBC Counts

Leucocytosis Leucocytosis refers to an increase in total WBC count above 11,000/mm^3.
Physiological Causes of Leucocytosis

1. Age
2. Exercise
3. After food intake
4. Mental stress
5. Pregnancy
6. Exposure to low temperature also causes leucocytosis

Pathological Causes of Leucocytosis

1. Acute bacterial infections especially by the pyogenic organisms
2. Acute haemorrhage
3. Burns
4. Postoperative period
5. Tuberculosis
6. Glandular fever

TABLE 3.3-1 Differential Leucocyte Count and Absolute Count in Normal Adults

WBCs	Differential Count (%)	Absolute Count (per mm^3)
Granulocytes		
• Neutrophils	40–75	2000–7500
• Eosinophils	1–6	40–440
• Basophils	0–1	0–100
Agranulocytes		
• Lymphocytes	20–40	1500–4000
• Monocytes	2–10	500–800

Leucopenia Leucopenia refers to a decrease in the total WBC count below 4000/mm³.

Causes of Leucopenia

1. Infections by the nonpyogenic bacteria, especially typhoid fever and paratyphoid fever
2. Viral infections, such as influenza, smallpox and mumps
3. Protozoal infections
4. Starvation and malnutrition
5. Aplasia of bone marrow
6. Bone marrow depression due to:
   - Drugs such as chloromycetin and cytotoxic drugs used in malignant diseases
   - Repeated exposure to X-rays or radiations
   - Chemical poisons like arsenic, dinitrophenol and antimony

FORMATION OF WHITE BLOOD CELLS

The process of development and maturation of WBCs (leucocytes), called *leucopoiesis*, is a part of haemopoiesis (formation of blood cells). All the blood cells develop from the so-called pluripotent *haemopoietic stem cells* (*PHSCs*). The stem cells after a series of divisions differentiate into *progenitor cells*, which are also called colony forming units (CFUs) (for details, see page 63). The leucopoiesis can be discussed under two headings:

- Formation of granulocytes (granulopoiesis) and monocytes.
- Formation of lymphocytes (lymphopoiesis).

Formation of Granulocytes and Monocytes

The granulocytes and monocytes are formed in the bone marrow from the colony forming unit called CFU-GM (colony forming unit granulocytes and monocytes): The progenitor cells (CFU-GM) forming different cells are further named as follows:

- CFU-G are neutrophil forming units.
- CFU-EO refers to eosinophil forming units.
- CFU-Ba are basophil forming units.
- CFU-M refers to monocyte forming units.

The development of granulocytes through various stages is called *myeloid series* and development of monocytes through various stages is called *monocyte–macrophage series.*

Features of the Cells of Myeloid Series (Fig. 3.3-1)

These characteristic features of myeloid series cells are summarized in Table 3.3-2.

Formation of Lymphocytes

The lymphocytes are formed from the *lymphocyte stem cells*, which are formed from the PHSCs in the bone marrow (Fig. 3.2-5). The lymphocyte stem cells migrate into the thymus and the peripheral lymphoid tissues, where they proliferate and mature into lymphocytes. In humans, the bone marrow and thymus form the primary lymphopoietic *organs*, where lymphoid stem cells undergo spontaneous division independent of antigenic stimulation. The tissues which actively produce lymphocytes from the germinal centres of lymphoid follicles as a response to antigenic stimulation constitute the so-called *secondary or reactive lymphoid tissue.* It is composed of the following:

- Lymph nodes
- Spleen
- Gut-associated lymphoid tissue (GALT)

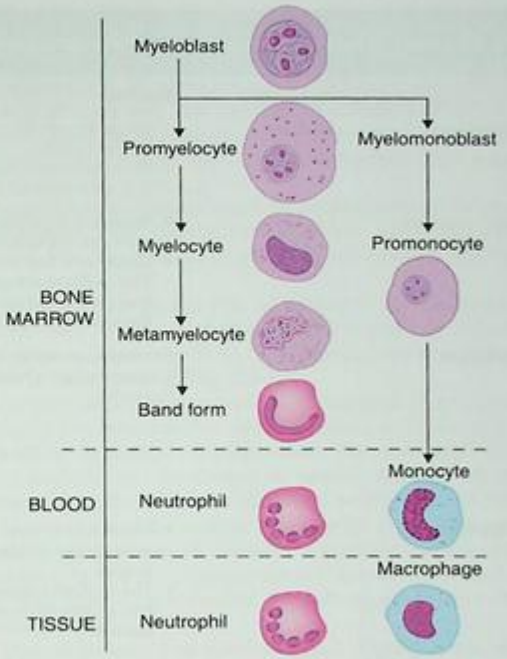


Figure 3.3-1 Granulopoiesis and features of the cells of myeloid series and monocyte–macrophage series.

Lymphoid Series

The maturation stages of lymphoid series are (Fig. 3.3-2) discussed below.

1. Lymphoblast. It is the earliest recognizable cell of the lymphoid series. It is actively dividing cell and resembles the myeloblast morphologically.

2. Prolymphocyte. It is the intermediate stage between the lymphoblast and mature lymphocyte.

3. Lymphocytes. Prolymphocytes mature successively into a large lymphocyte and a small lymphocyte, both of which are found in circulation.

- Then some lymphocytes enter thymus where they are processed and come out as T-lymphocytes. In thymus, a factor called *thymosin* plays an important role in the processing.
- Some lymphocytes are processed in liver (in fetal life) and bone marrow (after birth). These come out as B-*lymphocytes.* The word B comes from 'bursa of Fabricius', which is the site of B cell processing in birds. Morphological features of large and small lymphocytes are described on page 79.

TABLE 3.3-2 Characteristic Features of Cells of Myeloid Series

Cells	Size (μm)	Nucleus	Cytoplasm	Mitosis
1. *Myeloblast*	16–20	• Large (nearly filling the cells), round to oval • Fine chromatin and contains 2–5 well-defined pale nucleoli	Basophilic, present as a thin rim around the nucleus Granules absent	Marked (+++)
2. *Promyelocytes*	14–18	• Round or oval, slightly smaller than the nucleus of myeloblast • Chromatin fine and condensed • The nucleoli are present but are less prominent and fewer than those in the myeloblast	Amount increases and is characterized by the presence of *azurophil granules;* these granules are also called *primary nonspecific granules* and give a positive reaction with the peroxidase stain	Marked (+++)
3. *Myelocyte*	12–16	Eccentric, round to oval Coarse nuclear chromatin and no nucleoli	*Specific (secondary) granules present* and accordingly the cell can be identified at this stage as: • Neutrophil myelocyte • Eosinophil myelocyte • Basophil myelocyte The primary granules are also present at this stage, but their formation is stopped	Continues up to this stage; multiplication of these cells is maximum
4. *Metamyelocyte*	10–14	• Decreases in size, becomes indented and lobed (horseshoe shape) • The nuclear chromatin is dense and clumped; nucleoli are absent	Amount increases and becomes more liquid Both primary and secondary granules are present; depending on the features of secondary granules the metamyelocytes are distinguished as: • Neutrophil metamyelocyte • Eosinophil metamyelocyte • Basophil metamyelocyte	Stops at this stage
5. *Band or stab form* (juvenile granulocytes)	Size is slightly smaller than metamyelocyte	• Further condensation of chromatin, nucleus becomes band shaped (deeply indented, V shaped)	Pink and contains fine evenly distributed granules	Absent
6. *Mature granulocytes* (neutrophils, eosinophils and basophils)				

Note: Morphological features of different granulocytes are described at page 77.

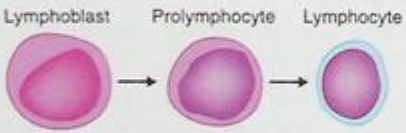


Figure 3.3-2 Formation of lymphoid series cells.

Regulation of Leucopoiesis

The constancy of leucocyte count suggests an efficient feedback mechanism to control their production and release (Fig. 3.3-3). During tissue injury and inflammation, bacterial toxins, products of injury, etc., cause a great increase in the rate of production and release of leucocytes. Thus, unlike erythropoiesis, the products of dead and dying white cells themselves control leucopoiesis. The substances which stimulate or inhibit the process of leucopoiesis are complex and include the following:

- The cytokines which control the formation of different types of granulocytes are called *colony stimulating factors*

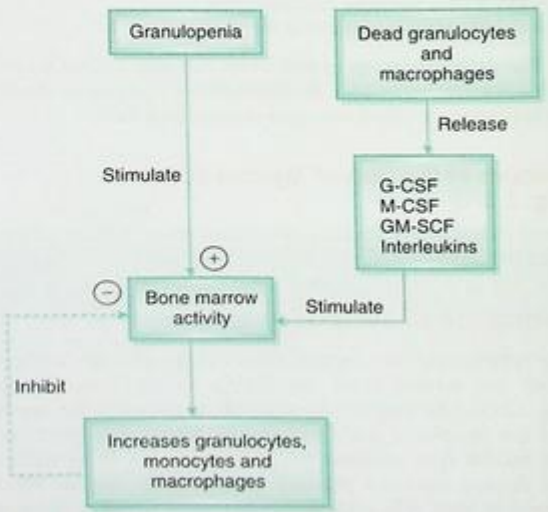


Figure 3.3-3 Schematic diagram of regulation of leucopoiesis.

(*CSFs*). The CSFs are glycoproteins formed by monocytes and T-lymphocytes.
- The cytokines that control lymphocyte formation are called *interleukins*, e.g. IL-1 and IL-3. The interleukins are formed by monocytes, macrophages and endothelial cells.

MORPHOLOGY, FUNCTIONS, LIFESPAN AND VARIATIONS IN COUNTS OF WBCS

Morphological features of various types of WBCs as studied under microscope with Leishman's staining and haematoxylin–eosin stain (Fig. 3.3-4) are summarized below along with their functions and variations in their counts.

Neutrophils

Morphological Features

The polymorphonuclear neutrophils, commonly called polymorphs or neutrophils, have the following morphological features (Fig. 3.3-4A):

Diameter. Diameter of a neutrophil varies from 10 to 14 μm.
Nucleus. A young neutrophil has a single horseshoe-shaped nucleus, which becomes lobed as the cell grows. Nucleus of a mature neutrophil is purple in colour and multilobed (two to six lobes); that is why a neutrophil is also called polymorphonuclear leucocytes. The lobes of the nucleus are connected by the chromatin filaments, seen clearly through the cytoplasm.
Cytoplasm. Cytoplasm of neutrophil is pale bluish in colour and full of fine (pinpoint) granules. Granules take both acidic and basic stain, and look violet-pink in colour.

Functions

The neutrophils along with the monocytes constitute the first line of defence against the microorganisms, viruses and other injurious agents that enter the body. Neutrophils subserve this role by the following mechanisms:

1. **Phagocytosis.** The neutrophils engulf the foreign particles or bacteria, digest them and ultimately may kill them by a process called phagocytosis. Various steps of phagocytosis are described below in detail.

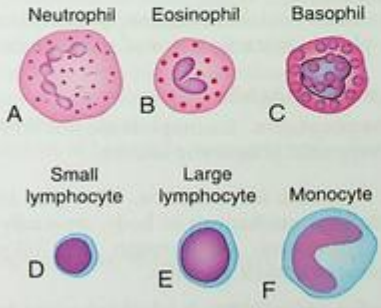


Figure 3.3-4 Morphological features of white blood cells: (A) neutrophil; (B) eosinophil; (C) basophil; (D) small lymphocyte; (E) large lymphocyte; and (F) monocyte.

2. **Reaction of inflammation.** The neutrophils also release leukotrienes, prostaglandins, thromboxanes, etc., that bring about the reactions of inflammation like vasodilatation and oedema.
3. **Febrile response.** The neutrophils contain a fever-producing substance called *endogenous pyrogen*, which is an important mediator of febrile response to the bacterial pyrogens.

Phagocytosis Phagocytosis (cell eating) refers to the process of engulfment and destruction of solid particulate material by the cells. The process of phagocytosis involves the following steps:
1. Margination. In the area of infection the neutrophils gets *marginated*, i.e. get attached towards the capillary endothelium and start rolling along its surface. This process is called *margination* or *pavementing* (Fig. 3.3-5A).
2. Emigration and Diapedesis. The marginated neutrophils are emigrated in large number from the blood at the site of *infection* caused by the foreign microorganism. They are motile and move by diapedesis into the tissues by passing through the junction between endothelial cells of the blood vessels (Fig. 3.3-5B).
3. Chemotaxis. Chemotaxis refers to the process by which the neutrophils are attracted towards bacteria at the site of inflammation (Fig. 3.3-5C). The process of chemotaxis is mediated by the chemotactic agents called *chemokines*, which are released at the infected area.
4. Opsonization (Attachment Stage). Opsonization refers to the process of coating of bacteria by the *opsonins* by which bacteria become tasty to the phagocytes (Fig. 3.3-5D). The principal opsonins are the naturally acting factors in the serum and include IgG opsonin and opsonin fragment of the complement protein.
5. Engulfment Stage. The neutrophils project *pseudopodia* in all directions around the opsonized particle, which is bound to the surface of neutrophil (Fig. 3.3-5E). Pseudopodia meet each other on opposite side and fuse. This creates an enclosed chamber with the engulfed material. It breaks away from the membrane to form a *phagocytic vesicle*. Then the lysosomes of the cell fuse with the phagocytic vesicle to form *phagolysosome* or phagosome (Fig. 3.3-5F).
6. Secretion (Degranulation) Stage. Once the bacteria are engulfed, the lysosomes pour their enzymes into the vesicle and also in interstitial space (Fig. 3.3-5G). This process is called degranulation. There are large numbers of proteolytic enzymes especially geared up for digesting bacteria. In addition, lysosomes of macrophages also contain lipases which can digest the thick lipid membranes possessed by certain bacteria.
7. Killing or Degradation Stage. The neutrophils and macrophages contain *bactericidal agents* (defensins α and β) which can kill most of the bacteria.

IMPORTANT NOTES

- A neutrophil can usually phagocytose 5–20 bacteria before it itself becomes inactivated or dead.
- Neutrophils killed by the toxins released from the bacteria are collected in the centre of infected area. These are called pus cells and together with plasma leaked from the blood vessels, liquefied tissue cells and RBCs escaped from the damaged capillaries constitute the pus.

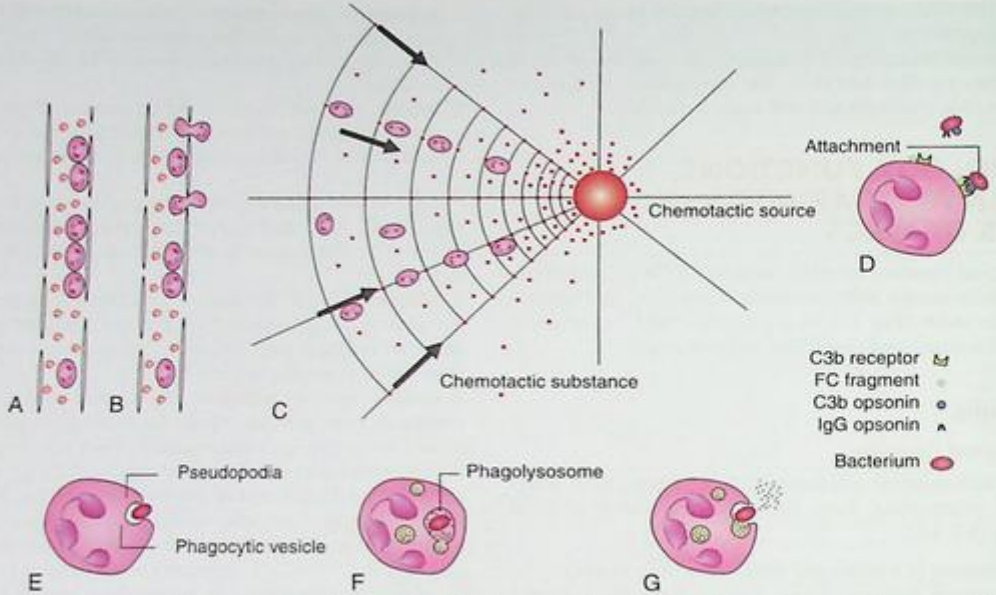


Figure 3.3-5 Stages of phagocytosis: (A) margination; (B) diapedesis; (C) chemotaxis; (D) opsonization; (E) engulfment; (F) formation of phagolysosome; and (G) degranulation.

Variations in Counts

Neutrophilia. Neutrophilia refers to increase in the circulating neutrophil counts (absolute count > 10,000/mm^3). It is the commonest cause of leucocytosis.

Causes. *Physiological causes* of neutrophilia are as follows:

- Newborn babies
- After exercise
- After meals
- Pregnancy, menstruation, parturition and lactation
- Mental stress and emotional stress
- After injection of epinephrine

Pathological causes of neutrophilia are as follows:

- Acute pyogenic bacterial infections
- Noninfective inflammatory conditions like gout, acute rheumatic fever
- Acute tissue destruction as in:
  - Burns
  - Postoperatively
  - Myocardial infarction

Neutropenia. Decrease in the neutrophil count is known as neutropenia (absolute count <2500/mm^3).

Causes of Neutropenia *are as follows:*

- Typhoid and paratyphoid fever
- Malaria
- Aplasia of bone marrow
- Bone marrow depression due to:
  - Drugs, such as chloromycetin and cytotoxic drugs used in the malignant diseases
  - Repeated exposure to X-rays and radiations
  - Chemical poisons like arsenic

Eosinophils

Morphological Features

Morphological features of eosinophils (Fig. 3.3-4B) are given below.

Diameter. Diameter of eosinophils is similar to neutrophils, i.e. 10–14 µm.

Nucleus. Nucleus is purple in colour and is bilobed in 85% of the cells. The two lobes are connected by the chromatin strands and thus look *spectacle shaped*. The remaining 15% of the eosinophils have a trilobed nucleus.

Cytoplasm. Cytoplasm is acidophilic and appears bright pink in colour.

- It contains coarse, deep red staining granules which do not cover the nucleus.
- The granules in eosinophils contain basic protein and stain more intensely for peroxidase than granules in the neutrophils.
- The granules contain histamine, lysosomal enzymes and eosinophil chemotactic factor of anaphylaxis (ECF-A).

Functions of Eosinophils

1. Mild Phagocytosis. Eosinophils are not very motile and thus have a very mild phagocytic activity.

2. Role in Parasitic Infestations. They play an important role in the defence mechanism of body, especially *in parasitic infestations.* Eosinophils act through the following lethal substances present in their granules:

- ***Major basic protein (MBP).*** It is highly larvicidal polypeptide. Because of this, eosinophils are able to damage the parasitic larvae which are large to be engulfed by phagocytosis.

- ***Eosinophil cationic protein (ECP)*** is a potent bactericidal and major destroyer of helminths.
- ***Eosinophil peroxidase*** is capable of destroying helminths, bacteria and tumour cells.

3. Role in Allergic Reaction. The eosinophils increase in number in allergic conditions like bronchial asthma and hay fever.

- They are capable of *detoxifying* inflammation-inducing substances (released by mast cells and basophils), like histamine and bradykinin.
- They inhibit mast cell degranulation.
- They phagocytose and destroy antigen–antibody complexes and thus prevent spread of local inflammatory process.

4. Role in Immunity. The eosinophils are present in abundance in the mucosa of respiratory tract, gastrointestinal tract and urinary tract, where they probably provide mucosal immunity.

Variations in Counts

Eosinophilia. Eosinophilia refers to increase in the eosinophil count (absolute count > 500/mm^3).

Causes of eosinophilia are as follows:

- Allergic conditions like bronchial asthma and hay fever
- Parasitic infestation, e.g. intestinal worms like hookworm, roundworm and tapeworm
- Skin diseases like urticaria
- Scarlet fever

Eosinopenia Eosinopenia is the decrease in the eosinophil count (absolute count < 50/mm^3).

Causes of eosinopenia are as follows:

- Adrenocorticotrophic hormone (ACTH) and steroid therapy
- Stressful conditions
- Acute pyogenic infections

Basophils

Morphological Features (Fig. 3.3-4C)

Diameter. Diameter of a basophil is similar to neutrophil and eosinophil, i.e. 10–14 μm.

Nucleus. Nucleus of basophils is irregular, may be bilobed or trilobed, and its boundary is not clearly defined because of overcrowding with the coarse granules.

Cytoplasm. Cytoplasm of basophils is slightly basophilic and appears blue. It is full of granules.

- Granules of basophils are very coarse and stain deep purple or blue with basic (methylene) dye.
- Granules are in plenty and completely fill the cell and overload the nucleus.
- The granules of basophils contain heparin, histamine and 5-HT.

Functions

1. Mild Phagocytosis. Basophils have very mild phagocytic function.

2. Role in Allergic Reaction. Basophils release histamine, bradykinin, slow reacting substances of anaphylaxis (SRS-A) and serotonin (5HT). These substances, in turn, cause local vascular and tissue reactions that cause many allergic manifestations.

3. Role In Preventing Spread of Allergic Inflammatory Process. Basophils also release eosinophil chemotactic factor that causes eosinophils to migrate towards the inflamed allergic tissue. Eosinophils then phagocytose and destroy antigen–antibody complexes and prevent spread of local inflammatory process.

4. Release of Heparin. Basophils release heparin in the blood which:

- Prevents clotting of the blood
- Activates the enzyme lipoprotein lipase, which removes fat particles from the blood after a fatty meal

Variations in Counts

Basophilia. Basophilia refers to increase in the basophil count (absolute count > 100/mm^3).

Causes of basophilia are as follows:

- Viral infections, e.g. influenza, small pox and chickenpox
- Allergic diseases
- Chronic myeloid leukaemia

Basopenia. Decrease in the basophil count is called basopenia.

Causes of basopenia are as follows:

- Corticosteroid therapy,
- Drug-induced reactions and
- Acute pyogenic infections.

Mast Cells

Mast cells are large tissue cells resembling the basophils. These are present in bone marrow and immediately outside the capillaries in the skin. These do not enter the blood circulation.

Functions. Mast cells play role in the allergic reactions similar to the basophils.

Lymphocytes

Morphological Features

There are two types of lymphocytes, large and small, having almost similar structure. Morphological features of lymphocytes are given below.

Diameter. Diameter of large lymphocytes varies from 12 to 16 μm and that of small lymphocytes from 7 to 10 μm (Fig. 3.3-4D and E).

Nucleus. Lymphocytes have a large, round, single nucleus, which almost completely fills the cell. It stains blue very deeply giving *ink-spot appearance.* Nuclear chromatin is coarsely clumped and shapeless.

Cytoplasm. The cytoplasm is scanty, i.e. its amount is always less than that of the nucleus. It is seen as a crescent of clear light blue colour around the nucleus. Cytoplasm does not contain visible granules.

Functional Subtypes. On the basis of their developmental background, lifespan and functions, the small lymphocytes have been broadly classified into three subtypes (Fig. 3.3-6).

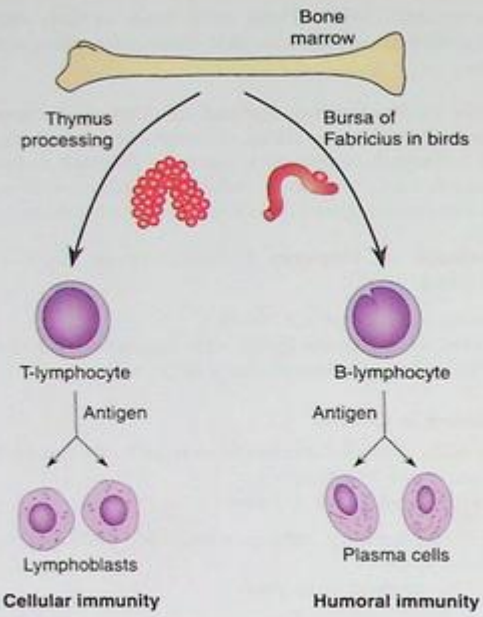


Figure 3.3-6 Processing of stem cells in thymus and bone marrow to become immunocompetent T- and B-lymphocytes.

1. ***B-lymphocytes*** which are processed in the bone marrow and concerned with the humoral immunity.
2. ***T-lymphocytes*** which are processed in the thymus and concerned with cellular immunity.
3. ***Natural killer (NK) cells*** are lymphocyte-like cells that non-specifically kill any cell that is coated with immunoglobulin IgG. This phenomenon is called *antigen-dependent cell-mediated cytotoxicity (ADCC)*. Thus, NK cells provide *innate immunity*. The NK cells lack identifying surface markers.

Kinetics, Lifespan and Fate of Lymphocytes

- After processing, the T-lymphocytes (processed in the thymus) and B-lymphocytes (processed in the bone marrow (B stands for 'bursa of Fabricius', the site of B cell processing in birds) enter the circulation.
- Many of the lymphocytes remain in circulation for a few hours, and then leak out through the venules and settle in the *peripheral lymphoid tissues* which include lymph nodes, spleen, gut-associated lymphoid tissue (GALT) and lymphoid tissue associated with respiratory and urinary tracts. At any given time, only about 2% of the body lymphocytes are in the peripheral lymphoid tissue.
- Some of the lymphocytes re-enter the blood circulation through the lymphatics draining the peripheral lymphoid tissues. In this manner, they re-circulate for months or years. Thus, the lymphocytes have a lifespan of months or a year depending on body's need for these cells.

Functions

Lymphocytes play an important role in immunity. *Immunity* is the capacity of human body to resist all types of microorganisms and toxins that tend to damage the tissue or organ. For details see page 84.

Variations in Counts

Lymphocytosis. Lymphocytosis refers to increase in the lymphocyte count (absolute count > 4000/mm^3).

Causes. Physiological causes of lymphocytosis are as follows:

- *In healthy infants and young children,* the lymphocytes count is usually high (about 60% in DLC), whereas the TLC is normal (relative lymphocytosis).
- *In females,* during menstruation lymphocytes are increased.

Pathological causes of lymphocytosis are as follows:

- Chronic infections like tuberculosis, hepatitis and whooping cough
- Viral infections like chickenpox
- Autoimmune diseases like thyrotoxicosis
- Infectious mononucleosis
- Lymphatic leukaemia (most common cause of lymphocytes > 10,000/mm^3)

Lymphopenia Lymphopenia or lymphocytopenia refers to decrease in lymphocyte count (absolute count below 1500/mm^3).

Causes of lymphopenia are as follows:

- Patients on corticosteroid and immunosuppressive therapy
- Hypoplastic bone marrow
- Widespread irradiation
- Acquired immunodeficiency syndrome (AIDS, see page 90)

Monocytes

Morphological Features (Fig. 3.3-4F)

Diameter. The monocyte is the largest mature leucocyte in the peripheral blood measuring some 12–20 μm in diameter.

Nucleus. The nucleus of a monocyte is large, single and eccentric in position, i.e. present on one side of the cell. It may be notched or indented, i.e. horseshoe or kidney shaped.

Cytoplasm. The cytoplasm is abundant, pale blue and usually clear (no granules); sometimes, it may contain fine, purple, dust-like granules called *azure granules*, which may be few or numerous.

Kinetics, Lifespan and Fate of Monocytes

- After release from the bone marrow, the monocytes remain in circulation for 10–20 to over 40 hours and then leave the blood to enter the extravascular tissues.
- In the tissues, the monocytes get converted to macrophages and form the part of so-called *tissue–macrophage system* (reticuloendothelial system). In the tissues, they can live for months or even years unless destroyed while performing the phagocytic function.

Functions

1. Role in Defence Mechanism. Monocytes along with the neutrophils play an important role in the body's defence mechanism. Their principal function *is phagocytosis.*

2. Role in Tumour Immunity. Monocytes may also kill tumour cells after sensitization by the lymphocytes.

3. Synthesis of Biological Substances. Monocytes synthesize complement and other biologically important substances.

Variations in Counts

Monocytosis A rise in the blood monocytes above 800/mm³ is termed monocytosis.

Causes of monocytosis are as follows:

1. *Certain bacterial infections* such as tuberculosis, syphilis and subacute bacterial endocarditis
2. *Infectious mononucleosis* or the so-called glandular fever
3. *Viral infections*
4. *Protozoal* and rickettsial infections, e.g. malaria and kalaazar

Monocytopenia Monocytopenia refers to decrease in the monocyte count.

Causes. Monocytopenia is rare. It may be seen in the hypoplastic bone marrow.

Leukaemias

Leukaemias constitute a group of malignant diseases of the blood in which there occurs an increase in the total WBC count associated with presence of immature WBCs in the peripheral blood. The total WBC count is usually above 50,000/mm³ and may be as high as 100,000–300,000/mm³.

Types of Leukaemias Leukaemias account for 4% of all cancer deaths. Leukaemias are classified on the basis of cell types predominantly into *myeloid* (involving cells derived from the myeloid stem cells) and *lymphoid* (involving the cells derived from lymphoid stem cells). On the basis of natural history of disease, each variety can be divided into *acute* and *chronic* types. In this way, the principal types of leukaemias are as follows:

1. Acute myeloblastic leukaemia (AML)
2. Acute lymphoblastic leukaemia (ALL)
3. Chronic myeloid leukaemia (CML)
4. Chronic lymphoid leukaemia (CLL)

SELF-ASSESSMENT

1. Describe the different types of leucocytes and their characteristic features.
2. Describe the regulation of leucopoiesis.
3. Write notes on:
   - Variations of leucocyte counts
   - Phagocytosis
   - Functions of eosinophils
   - Functions of lymphocytes
   - Functions of monocytes

3.4 Immune Mechanisms

CHAPTER OUTLINE

Architecture of Immune System
Mononuclear–Phagocytic System
Lymphoid Component
Central Lymphoid Organs
Peripheral Lymphoid Organs

Immunity
Innate Immunity
Acquired Immunity
Active Immunity
Passive Immunity

Antigens
Definition
Histocompatibility Antigens

Antibodies
Structure of Antibody
Functions of Immunoglobulins

Development of Immune Response
Development of Humoral Immunity
Types of Humoral Immune Response
Stages of Humoral Immune Response
Role of Humoral Immunity
Development of Cellular Immune Response
Role of Cellular Immunity
Types of Cellular Immune Response
Stages of Cellular Immune Response
Cytokines

Other Immune Mechanism-Related Aspects
Immune Tolerance
Autoimmunity
Hypersensitivity
Immunodeficiency Diseases

ARCHITECTURE OF IMMUNE SYSTEM

The immune system, which constitutes the body's defence system, consists of immunological cells distributed between the following two main components:

1. Mononuclear–phagocytic system (MPS)
2. Lymphoid component

Mononuclear–Phagocytic System

MPS, also known as the *tissue–macrophage system*, is the new name given to the system, previously called the *reticuloendothelial system* (RES).

Formation of Mononuclear–Phagocytic System The monocytes enter the blood from the bone marrow and circulate for about 3 days. From the blood, the monocytes migrate into the tissue, where they attain maturity and acquire the ability to phagocytose and thus get converted into macrophages. These tissue macrophages scattered in different parts of the body collectively constitute the *tissue–macrophage system* or the so-called MPS. The tissue–macrophage system includes the macrophages present at the following sites in the body:

- Macrophages lining the sinusoids of liver (Kupffer cells)
- Spleen
- Bone marrow (littoral cells)
- Lymph nodes
- Lungs (pulmonary alveolar macrophages [PAM], also called dust cells)
- Connective tissue (histiocytes)
- Pleura and peritoneum
- Subcutaneous tissue
- Bones (osteoclasts)
- Central nervous system (microglial cells)

Functions of Mononuclear–Phagocytic System The MPS plays the following roles in the body:

1. *Role in inflammation and healing*
2. *Role in defence against the bacteria invading the body tissues*
3. *Role in the immune response*
4. *Role in removal of old RBCs, WBCs and platelets*

Lymphoid Component

The lymphoid component of the immune system consists of a network of lymphoid organs, tissues and cells, and the product of these cells. Lymphoid organs can be classified as follows:

A. *Central or primary lymphoid organs*, which include the following:
   I. Thymus
   II. Bursa equivalent (fetal liver and bone marrow)
B. *Peripheral lymphoid organs*, which include the following:
   I. Lymph nodes
   II. Spleen
   III. Mucosa-associated lymphoid tissue (MALT)

A. Primary (Central) Lymphoid Tissues

I. Thymus

The thymus gland is located in mediastinum just above the heart. It consists of many lobules. Histologically, each lobule consists of an outer *cortex* and an inner *medulla*. Both cortex and medulla contain two types of cells.

- ***Epithelial cells:*** These cells form a network in which thymocytes and macrophages are found.
- ***Thymocytes:*** They refer to the immature lymphocytes predominantly present in the cortex and mature lymphocytes mainly present in the medulla. Lymphocytes produced in the

thymus are called thymus-derived lymphocytes, T-lymphocytes or simply T-cells.

Role of Thymus in the Immune System

- The main function of the thymus is to confer immunological competence on the lymphocytes during their stay in the organ so that they become capable of mounting cell-mediated immune response against appropriate antigens.
- The *immunologically competent lymphocytes* from the thymus migrate into peripheral lymphoid organs after attaining maturity and are selectively seeded into the paracortical areas of the peripheral lymph nodes and into the white pulp of the spleen around the central arterioles. These regions are known as *thymus-dependent* areas.

II. Bursa Equivalent

In the human being, the fetal liver and bone marrow appear to be the equivalent of avian bursa of Fabricius. *Bursa of Fabricius* in birds is also a site of lymphocytic proliferation and differentiation. Immunocompetent lymphocytes produced in the bursa are called bursa lymphocytes or B-lymphocytes or B-cells. The mature B-cells migrate into germinal follicles, medullary cords of lymph nodes and lymphoid follicles of spleen. These sites are known as *bursa-dependent* or *thymus-independent* areas. Following appropriate antigenic stimulation, B-lymphocytes transform into plasma cells and secrete antibodies, which constitute the humoral immunity or *antibody-mediated immunity* (AMI).

B. Peripheral Lymphoid Organs

I. Lymph Nodes

The lymph nodes are small, bean-shaped or oval structures that form part of the lymphatic network distributed throughout the body.

Structural Characteristics of Lymph Node (Fig. 3.4-1)

- *Capsule* of connective tissue covers each lymph node. From the capsule, trabeculae penetrate into the lymph node.
- *Microscopically*, the lymph node consists of two parts: peripheral cortex and central medulla.
- *Cortex* of the lymph node consists of several rounded aggregates of lymphocytes called *lymphoid follicles*, representing the *B-cell area* of the node.
- *Paracortex* is a deeper part of cortex, i.e. the zone between the peripheral cortex and the inner medulla, and represents the *T-cell area* (the *bursa-independent area*).
- *Medulla* is predominantly composed of cords (*medullary cords*). The medullary cords contain B-lymphocytes and along with the lymphoid follicles constitute the *bursa-dependent areas* of the lymph node.

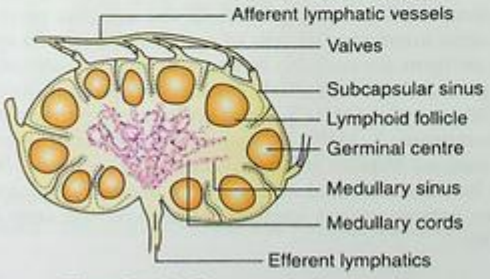


Figure 3.4-1 Structure of a lymph node.

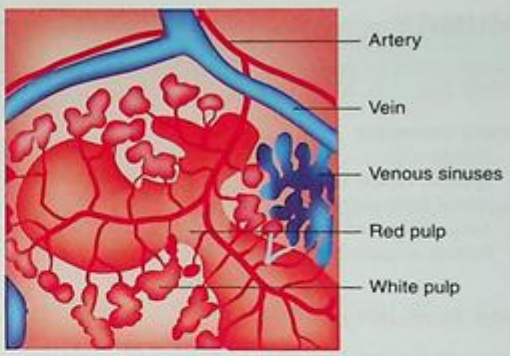


Figure 3.4-2 Structure of spleen.

Functions of Lymph Nodes

1. ***To mount immune response in the body:*** The bulk of antigens are processed, and antibody production occurs in the lymphoid follicles (for details see page 86).
2. ***The lymph nodes constitute a series of inline filters:*** Lymph must pass through at least one lymph node before mixing with the blood stream. Over 99% of the lymph passes through the lymph sinuses and only 1% penetrates the lymphoid follicles.

II. Spleen

The spleen is the largest lymphoid organ of the body. Under normal conditions, the average weight of the spleen is about 150 g.

Structural Characteristics (Fig. 3.4-2)

Capsule of the connective tissue surrounds the spleen. From the capsule, the connective tissue *trabeculae* extend into the pulp of the organ and serve as a supportive network.

Grossly, on a cut section, the spleen consists of homogeneous, soft, dark-red mass called *red pulp*. In the red pulp are seen scattered white nodules called *white pulp* (malpighian bodies).

Microscopically, the structural characteristics are as follows:

- *Red pulp* consists of the thin-walled *blood sinuses* with *splenic cords* between them. The splenic cords consist of a collection of lymphocytes and macrophages.
- *White pulp* consists of lymphocytes surrounding an eccentrically placed central artery. These periarteriolar lymphocytes are mainly *T-lymphocytes*. In addition, the white pulp also contains the lymphoid follicles composed principally of *B-lymphocytes*.

Functions of Spleen

1. *Role in immune response*: For details, see page 86.
2. *Role in removal of old RBCs, WBCs and platelets*: For details, see page 69.
3. *Role in haematopoiesis*: During the fourth and fifth months of fetal life, erythropoiesis occurs in the spleen.

III. Mucosa-associated Lymphoid Tissue

MALT, including tonsils, adenoids and Peyer's patches of small intestine, is known as gut-associated lymphoid tissue (GALT).

IMMUNITY

Immunity refers to resistance of the body to pathogens and their toxic products. It can be classified as follows:

I. ***Innate immunity***
   1. Nonspecific
   2. Specific innate immunity

II. ***Acquired immunity***
   1. Active acquired immunity
   2. Passive acquired immunity

Innate Immunity

- *Innate or natural immunity* is the inborn capacity of the body to offer resistance to pathogens and their toxic products. It is due to the genetic and constitutional make-up of an individual.
- It may be *specific* (against a particular organism) or *nonspecific.*

Mechanisms of Innate Immunity

1. Mechanical Barrier against invading microorganisms is provided by the intact skin and mucosa in the body.

2. Surface Secretions constitute one of the important mechanisms of innate immunity. These include the following:

- *Secretions* from the sebaceous glands of skin contain both saturated and unsaturated fatty acids that kill many bacteria and fungi.
- *Saliva*, constantly produced in the mouth cavity, has an inhibitory effect on many microorganisms.
- *Gastric juice* and highly acidic environment of the stomach may hydrolyse microbial invaders.
- *Tears* poured in the conjunctival sac mechanically wash away the particles, and a hydrolytic enzyme, lysozyme, present in the tears can destroy most of the microorganisms.

3. Humoral Defence Mechanisms provide innate immunity through the nonspecific microbicidal substances present in the body fluids. A few examples are given below:

- *Lysozyme* is found in high concentration in most tissue fluids except cerebrospinal fluid, sweat and urine. It is a mucolytic enzyme that kills microorganisms by splitting sugars of the structural mucopeptide of their cell wall.
- *C-reactive protein (CRP)*: Foreign substances (antigen) increase the concentration of plasma proteins, especially CRP, which coats the invading substance.
- *Complements* have lytic and several other effects on the foreign substances (see page 87).
- *Interferons* (IFNs) are antiviral substances produced by the cells stimulated by live or killed viruses.

4. Cellular Mechanisms of Defence, which provide nonspecific innate immunity, are as follows:

- *Phagocytes*, i.e. neutrophils and the monocyte–macrophage system cells constitute the most important nonspecific cellular defence against the invading microorganisms.
- *Natural killer* (NK) *cells* refer to a subpopulation of lymphocytes that provide nonspecific cellular defence against viruses, tumour cells and other infected cells.
- *Eosinophil* granules contain enzymes and toxic molecules that act against larvae of helminths.

Acquired Immunity

The resistance that an individual acquires during his lifetime is known as acquired immunity. It is antigen-specific and may be antibody-mediated or cell-mediated. It is of two types: active and passive.

1. Active Immunity

Active immunity is acquired by the synthesis of antibodies (humoral immunity) and production of immunocompetent cells (cell-mediated immunity) by the individual's own immune system in response to an antigenic stimulation. Active immunity can be induced by vaccines, e.g.:

- Bacterial product vaccines
  - Tetanus toxoid
  - Diphtheria toxoid
- Viral vaccines
  - Live: Sabin vaccine for poliomyelitis, MMR vaccine for measles, mumps and rubella
  - Killed: Salk vaccine for poliomyelitis, neural and non-neural vaccines for rabies

2. Passive Immunity

Passive immunity refers to the immunity that is transferred to a recipient in a ready-made form. Here the individual's immune system does not play an active role.

Differences between Active and Passive Immunity

Differences between active and passive immunity are summarized in Table 3.4-1.

ANTIGENS

Definition

Antigen: Antigens are substances that can stimulate an immune response in the body. Most antigens are proteins, but some are carbohydrates, lipids and nucleic acids. The specificity of an antigen is due to specific areas of its molecule called *determinant sites* or *epitopes.*

Histocompatibility Antigens

Histocompatibility antigens refer to the antigens present on the plasma membrane of cells of each individual of a species. These antigens are encoded by genes known as histocompatibility genes, which collectively constitute the major histocompatibility complex (MHC). These are located on the short arm of chromosome 6. MHC present on the surface of leucocytes is known as human leucocyte-associated antigens (HLA). These have been studied extensively in organ transplantation. No two persons except identical twins have the same MHC proteins.

TABLE 3.4-1 Differences Between Active and Passive Immunity

Active Immunity	Passive Immunity
1. ***Production:*** Antibodies are produced by the body's own immune system in response to antigens introduced naturally or artificially in the body.	Received passively by the host. No participation of the host's immune system. It is conferred by administration of ready-made antibodies naturally or artificially in the body.
2. ***Negative phase:*** Negative phase is present in the development of active immunity, during which the immunity is transiently lowered. This is due to antigens combining with the preexisting antibodies and lowering their level.	There is no negative phase in passive immunity as antigens are not injected.
3. ***Latent period:*** Active immunity develops after a latent period varying from 4 days to 4 weeks. This is the time required for the generation of antibodies and immunocompetent cells.	There is no latent period. Passive immunity is effective immediately.
4. ***Secondary response:*** Due to immunological memory, the secondary response, i.e. response to antigen introduced. Second time is more enhanced.	There is no immunological memory. Rather subsequent administration of antibodies is less effective due to immune elimination.
5. ***Duration:*** Active immunity is long-lasting.	Passive immunity is short-lasting.
6. ***Effectivity:*** Active immunity is more effective and confers better protection.	Passive immunity is less effective and provides inferior immunity.
7. ***Applicability in immunodeficient individuals:*** Active immunity is not applicable in the immunodeficient individuals.	Passive immunity is applicable in the immunodeficient hosts.

There are two subclasses of MHC genes: class I and class II.

MHC class I Molecules are found on the surface of virtually all the cells of the body excluding RBCs (Fig. 3.4-3).

MHC class II In men, MHC class II antigens are found only in immunologically reactive cells, such as B-lymphocytes, macrophages, monocytes and activated T-lymphocytes.

HLA Tissue Typing Histocompatibility typing or the so-called HLA tissue typing refers to the detection of the MHC class I and MHC class II antigens. HLA typing is used to determine HLA compatibility prior to organ/tissue transplantation from one individual to another within a species.

ANTIBODIES

Antibodies or immunoglobulins (Igs) are gamma globulins that are produced in response to an antigenic stimulation. These react specifically with the antigens that stimulate their production. All antibodies are Igs, but all Igs are not antibodies. Igs have been divided into five distinct classes or isotypes: IgG, IgA, IgM, IgD and IgE.

Structure of Antibody

IgG has been studied extensively and serves as a model of basic structural unit of all Igs. An Ig is a Y-shaped molecule made of four polypeptide chains: two heavy (H) and two light (L). These are held together by the disulphide bonds (Fig. 3.4-4).

Heavy Chains

- Heavy (H) chains have a molecular weight of 50,000 Da.
- H chains are structurally and antigenically distinct for each class of Ig and are named as follows:
  - α (alpha) in IgA
  - δ (delta) in IgD

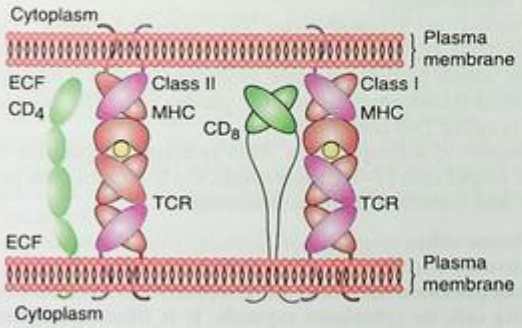


Figure 3.4-3 Structure of MHC proteins and their relation to CD_4 and CD_8.

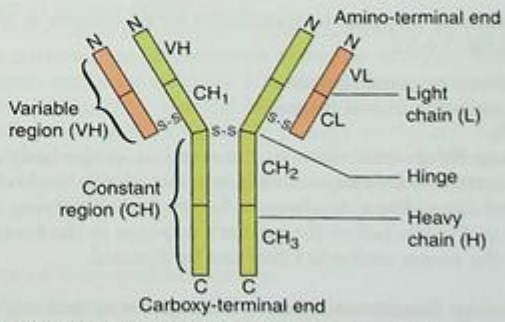


Figure 3.4-4 Basic structure of an antibody showing the arrangement of heavy and light chains, and its variable and constant domains.

- ϵ (epsilon) in IgE
- γ (gamma) in IgG
- μ (mu) in IgM

- The amino acid (NH_2) terminal half of each chain has a variable sequence of amino acids and is called the *variable region*. In a heavy chain, it is designated as VH.
- The carboxy (COOH) terminal of each chain has a relatively constant sequence and is called the *constant region*. In a heavy chain, it is designated as CH.
- Two H chains are always identical in a given molecule. In IgG, each H chain contains 440 amino acids.

Light Chains

- Molecular weight of light (L) chains is 25,000 Da.
- Similar to H chains, the variable region of L chains is designated VL and constant region is designated CL.

Functions of Immunoglobulins

From the available information, the specific functions of various Igs are as follows:

- ***IgG*** protects the body fluids.
- ***IgA*** protects the body surfaces.
- ***IgM*** protects the blood stream.
- ***IgE*** mediates type I hypersensitivity.
- ***IgD's*** role is not clearly known.

DEVELOPMENT OF IMMUNE RESPONSE

Development of immune response implies *development of acquired active immunity* in the body. The immune system of the body responds to an antigen in the following two ways:

1. Humoral or AMI
2. Cell-mediated immunity (CMI)

Development of Humoral Immunity

The humoral immunity is mediated by antibodies and so also called AMI. The antibodies are produced by the plasma cells, which, in turn, are produced by the B-lymphocytes.

Types of Humoral Immune Response

The antibody response to stimulation by an antigen is of two types (Fig. 3.4-5):

- Primary humoral response
- Secondary humoral response

Primary Response refers to the response of the body's immune system to an antigen that is introduced into the body for the first time. There is always a latent period varying from 4 days to 4 weeks before the primary response in the form of a rise in the serum antibodies titre can be detected.

Secondary Response refers to the response of the body's immune system to an antigen that is introduced into the body on a second occasion. Such a response occurs more quickly and more abundantly. This is because of the fact that the immune system is liable to retain the memory of a prior antigenic exposure for long periods (immunological memory) and produce enhanced response when encountered with the same antigen for the second time.

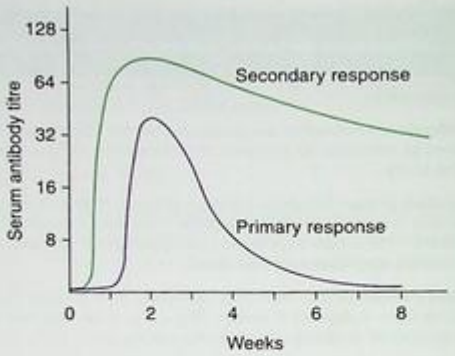


Figure 3.4-5 Time course of antibody production in primary versus secondary response of body immune system to an antigen.

Stages of Humoral Immune Response *(Fig. 3.4-6)*

1. Antigen Processing and Presentation Once the antigen enters the body, it is phagocytosed by the macrophages (nonspecific response). Phagocytosed material is broken down into polypeptide fragments. The antigen polypeptide fragments then combine with the MHC II present in the macrophages and move to the cell surface. This is called *processing of antigen*. The processed antigen is then presented to immunocompetent lymphocytes by the macrophages. So, the macrophages are also called *antigen-presenting cells*.

2. Recognition of Antigen by Lymphocytes The lymphocytes possess the antigen-recognition receptors. The process of binding of processed antigen to specific receptors on the surface of lymphocytes is called *recognition of antigen by* lymphocytes. Thus, millions of different T- and B-lymphocytes, each with the ability to respond to a particular antigen, are present in the body.

3. Lymphocyte Activation The lymphocytes that have combined with an antigen are activated, i.e. the lymphocytes become larger and look like a lymphoblast. This is known as *blast transformation*.

Activation of T-lymphocytes The activated helper T-cells (T_H cells) (CD_4) secrete interleukins 2 (IL-2) and B-cell growth factor, which further promote proliferation of B-lymphocytes and their transformation into the plasma cells. This phenomenon is called *T–B cooperation*.

Activation of B-lymphocytes After receiving cooperation from the T helper cells (T–B cooperation), the B-lymphocytes proliferate and transform into the following:

- Plasma cells
- Memory B-cells

Role of plasma cells: When a B-lymphocyte is converted into a plasma cell, its cytoplasm expands. It is filled with granular endoplasmic reticulum. The plasma cells secrete antibodies.

Each plasma cell produces about 2000 molecules of antibodies per second. A plasma cell secretes an antibody of a single specificity of a single antibody class.

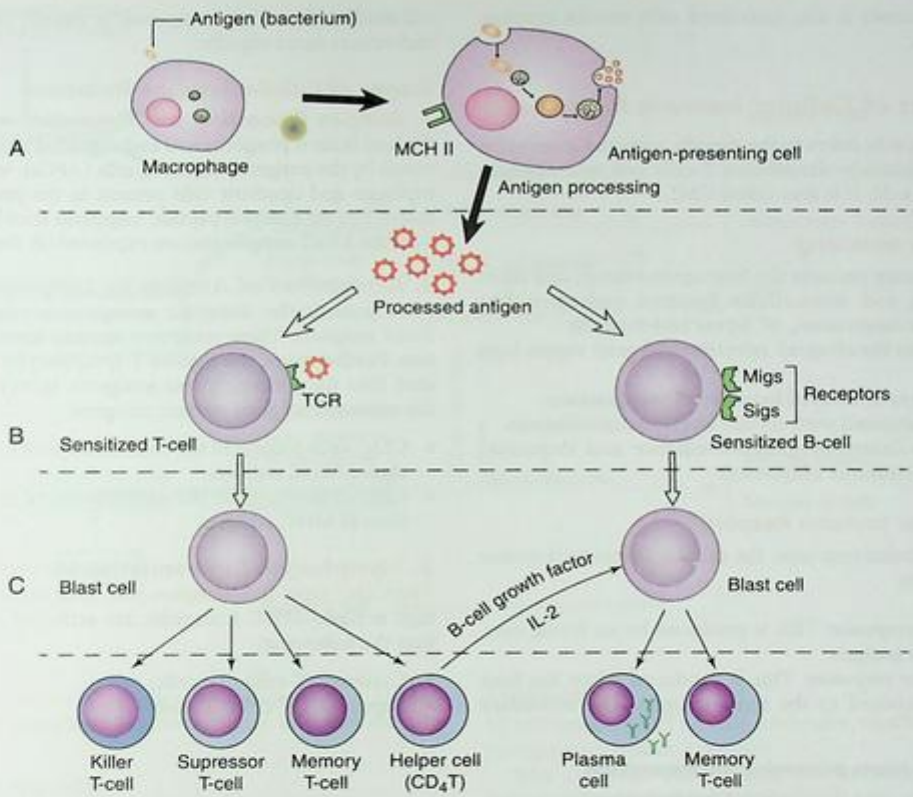


Figure 3.4-6 Broad outline of development of humoral immune response: (A) antigen processing and presentation to immunocompetent cells; (B) recognition of antigen by the lymphocytes; and (C) activation of lymphocytes (blast transformation).

Role of memory B-cells: Only a small portion of the activated B-lymphocytes proliferate and transform into small-sized memory B-cells, which occupy the lymphoid tissue throughout the body. Memory B-cells have a long lifespan and remain inactive. When the body is exposed to the same antigen for the second time, they are able to recognize it and become active, i.e. they are responsible for secondary response of antibodies.

4. Inactivation of Antigen or Attack Phase or Effector Phase of Immune Response This is the last phase of immune response and involves the inactivation of antigen by the antibodies. Antibodies act on the invading antigen in the following two ways:

(i) Direct Attack on the Invading Agents Antibodies can inactivate the invading agent by the following reactions:

Agglutination: By this reaction, a large number of particles (bacteria or red cells) with antigens on their surface are bound together to form a clump. Clumping increases the susceptibility to phagocytosis.

Precipitation: In this reaction, the antigen–antibody complex forms an insoluble precipitate.

Neutralization: Antibodies cover the toxic sites of antigens and neutralize them.

Cytolysis: Antibodies attach the membranes of cellular agents, thereby causing rupture of cells.

(ii) Attack on the Antigen through Complement System The complement system includes 11 enzymatic proteins, which are named C1–C9, B and D. All these are present in the blood as plasma proteins.

These are also present in the tissue fluid. The complement system acts in the following two ways:

(a) Classical Pathway This is activated by the antigen–antibody reaction. When an antibody binds with an antigen, a specific reactive site on the constant portion of the antibody becomes uncovered, where the protein C1 binds and thus gets activated. The activated C1, in turn, activates the other complements in a series of cascade reactions.

(b) Alternative Pathway or Properdin Pathway In the alternative pathway, the complement system is activated without an antigen–antibody reaction. The alternative or properdin pathway is initiated by binding of the protein in circulation (properdin) with a polysaccharide present in the cell wall of the invading organism, i.e. bacteria (endotoxin) and yeast cell wall (zymogen). This binding triggers reactions that activate C3 and C5, which ultimately attack the antigenic products of invading organisms.

Role of Humoral Immunity

1. The humoral immunity provides defence against most extracellular bacterial pathogens and viruses that infect through the respiratory and intestinal tract.
2. It participates in immediate hypersensitivity reactions of types I, II and III.

3. Humoral immunity is also associated with certain autoimmune diseases.

Development of Cellular Immune Response

The cellular immunity refers to the specific acquired immunity, which is accomplished by the effector T-cells and macrophages (Figs 3.4-7 and 3.4-8). It is also called CMI.

Role of Cellular Immunity

1. Cellular immunity protects the host against fungi, and most of the viruses and intracellular bacterial pathogens like *Mycobacterium tuberculosis, M. leprae* and *Brucella*.
2. It participates in the allograft rejection and graft versus host reaction.
3. CMI participates in delayed hypersensitivity reaction.
4. CMI is also associated with certain autoimmune diseases.
5. It provides an immunological surveillance and immunity against cancer (tumour immunity).

Types of Cellular Immune Response

Like humoral immune response, the cellular immune response is also of two types:

Primary cellular response: This is produced by an initial contact with a foreign antigen.
Secondary cellular response: This is produced when the host is subsequently exposed to the same antigen. The secondary cell-mediated immune response is usually more pronounced and occurs more rapidly.

Stages of Cellular Immune Response

1. Antigen Processing and Presentation Antigen entering the host body is phagocytosed and degraded into polypeptide fragments by the antigen-processing cells (APCs), which include macrophages and dendritic cells present in the peripheral lymphoid tissue. The antigen polypeptide fragments then become associated with the MHC antigen and are expressed on the surface of APC.

2. Recognition of Antigen by Lymphocytes T-lymphocytes possess the antigenic recognition receptors known as *T-cell receptors*. These receptors serve as specific surface receptors. Furthermore, the mature T-lymphocytes can be differentiated into the following two antigenic subtypes depending on the ensemble of their surface antigens:

- CD_8^+ cells recognize the combination of foreign antigen and class I MHC antigen.
- CD_4^+ cells recognize the combination of foreign antigen and class II MHC antigen.

3. T-lymphocyte Differentiation (Activation) The CD_8^+ type of T-lymphocytes after combining with a foreign antigen–MHC I complex are activated and differentiated into the following:

- Cytotoxic T-cells (T_C-cells)
- Suppressor T-cells (T_S-cells)

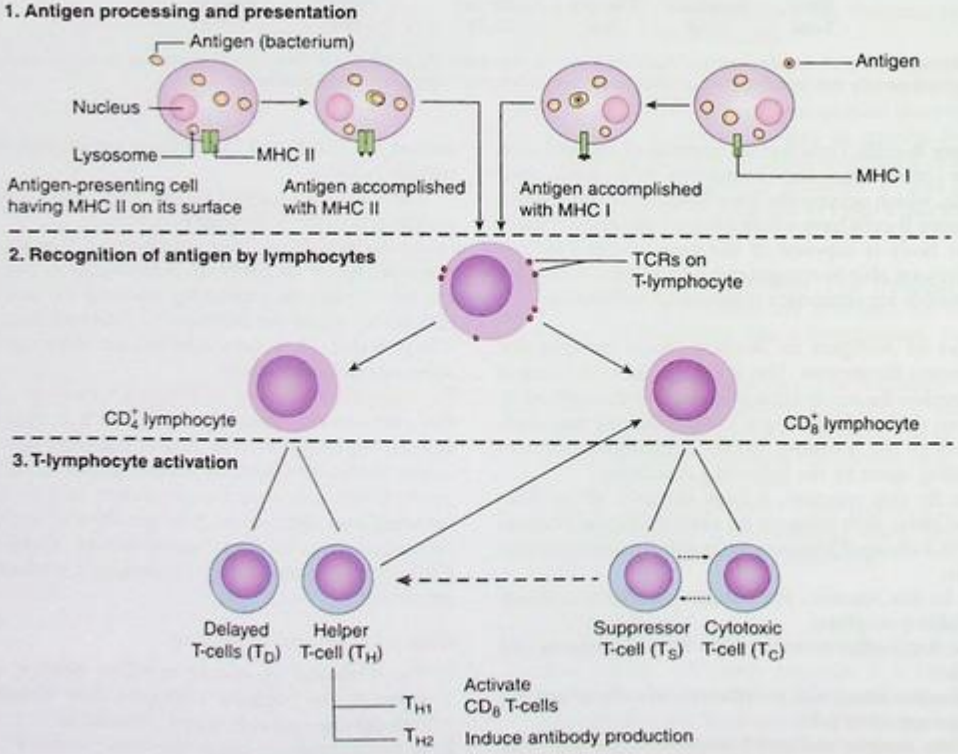


Figure 3.4-7 Development of cellular immune response.

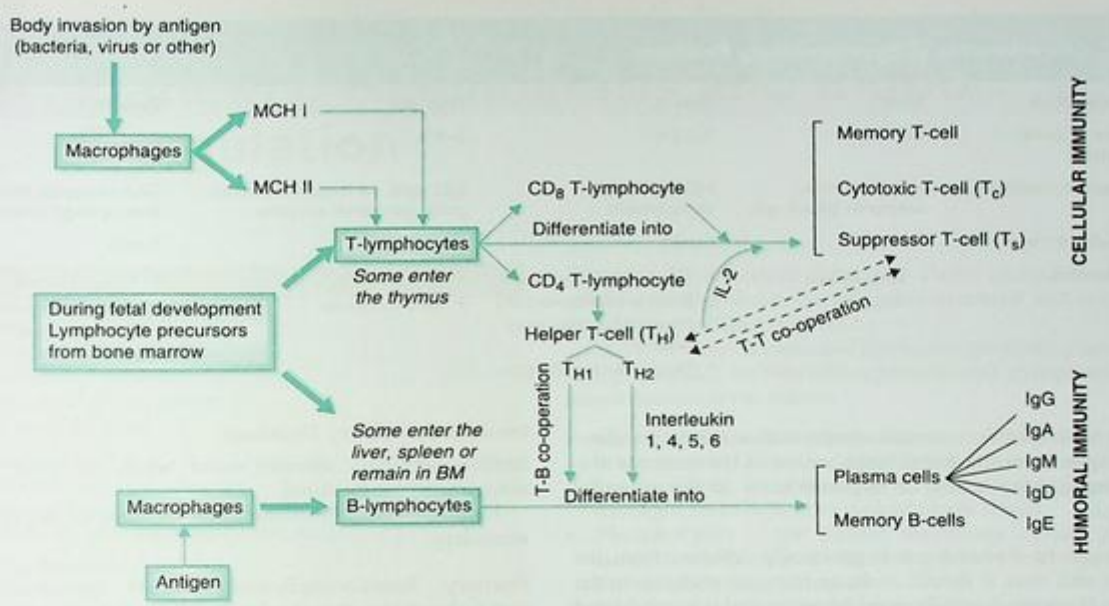


Figure 3.4-8 Summary of the immune system.

CD_4^+ type of T-lymphocytes after combining with a foreign antigen–MHC II complex are activated and differentiate into the following:

- Helper T-cells (T_H-cells)
- Delayed-type hypersensitivity T-cells (T_D-cells)

T–T cooperation The differentiation of T-lymphocytes into T_H-, T_C-, T_S- and T_D-cells is interdependent. This interdependence is called T–T cooperation.

Release of Differentiated T-cells The differentiated T-lymphocytes so formed are released into the lymph and then enter the blood, through which they are distributed throughout the body.

Note: T-lymphocyte memory cells are also formed. These spread throughout the lymphoid tissues of the entire body. Therefore, on subsequent exposure to the same antigen, release of T-cells occurs far more rapidly and much more powerfully than in the first response (secondary response).

4. Attack Phase of Cell-Mediated Immunity

Role of Cytotoxic T-cells ***Cytotoxic T-cells*** (T_C-cells) and NK cells are responsible for the attack phase of cell-mediated immunity.

Role of helper T-cells (T_H-cells) Helper T-cells are of two types: T_{H1} and T_{H2}.

Helper T-cells (antigen-bearing cells) play their roles by secreting cytokines and interlukins.

Role of Suppressor T-lymphocytes (T_S-cells)

- Suppressor T-cells regulate the activity of cytotoxic T-cells.
- Suppressor T-cells also play an important role in preventing the cytotoxic T-cells from destroying the body's own tissue along with the invading organism.
- Suppressor T-cells also suppress the activities of helper T-cells.

Cytokines

Cytokines are small protein molecules, which act like hormones to regulate immune response.

The cytokines are secreted not only by lymphocytes and macrophages, but also by endothelial cells, neuroglial cells and other types of cells. Broadly, cytokines can be grouped into ILs and others.

Interleukins: These are the principal cytokines and include IL-1 to IL-13.

Other cytokines include the following:

- Chemokines
- Growth factors
- Colony stimulating factors (CSF)
- Tumour necrosis factors (TNF-α and TNF-β)
- IFNs

Mechanism of Action and Functions The cytokines act in an *autocrine* (i.e. on the cell that produced them) or *paracrine* (i.e. on the cell close by) manner through their specific receptors.

OTHER IMMUNE MECHANISM–RELATED ASPECTS

Immune Tolerance

Types of Immune Tolerance Immune tolerance may be defined as a state of unresponsiveness to an antigen. It occurs in two forms: natural and acquired.

1. Natural Tolerance refers to the nonresponsiveness to a self-antigen. During embryonic development, when the immune system is immature, any antigen that comes in contact with the immature immune system is recognized as a self-antigen. Therefore, it does not evoke any response in later life when the body is exposed to the same antigen.

TABLE 3.4-2 Characteristics of Hypersensitivity Reactions

Characteristics	Type I	Type II	Type III	Type IV
1. Time of onset of reaction	1/2–8 h	5–12 h	3–8 h	24–48 h
2. Reaction mediators	IgE, histamine, serotonin SRS-A, etc.	IgG, IgM and complement	IgG, IgM, neutrophils, eosinophils, lysosomal enzymes	T-lymphocytes and macrophage lymphokines
3. Passive transfer with	Serum	Serum	Serum	T-cells
4. Examples	• Anaphylaxis • Asthma	• Transfusion reactions (incompatibility reaction) • Haemolytic disease of newborn • Drug induced allergies	• Arthus reaction • Serum sickness	• Tuberculin test • Contact dermatitis • Graft rejection

2. Acquired Tolerance means unresponsiveness to a potential antigen. It results due to impairment of the immune system; hence, there is lack of responsiveness to the potential antigens.

Tolerance to Fetus Fetus is genetically different from the mother, and, thus, it should evoke an immune response in the mother. However, it usually never happens, and it is considered to be the best example of immune tolerance.

Autoimmunity

During fetal life, when many antigens are presented to the immune system, they are recognized as self-antigens and antibodies, and cytotoxic T-cells are not produced.

Therefore, tolerance to self-antigens is produced. However, sometimes the body starts producing antibodies or T-cells against self-antigens (own cells or tissue), leading to an autoimmune disease. Therefore, autoimmunity may be defined as immune response to self-antigens.

Autoimmune Diseases Common autoimmune diseases include the following:

- *Haemolytic anaemia*: Antibodies react with its own RBCs.
- *Pernicious anaemia*: Antibodies react against gastric mucosa.
- *Thrombocytopenic purpura*: Autoantibodies react with self-platelets.
- *Graves disease*: Autoantibodies bind to the thyroid cells and stimulate them.
- *Insulin-dependent diabetes mellitus*: Antibodies damage the β-cells (insulin-producing cells) of the pancreas.
- *Rheumatoid arthritis*: Antibodies damage the joints.

Hypersensitivity

Hypersensitivity is an abnormal response that produces physiological or histopathological damage in the host. There are four types of hypersensitivity reactions:

- Type I (anaphylaxis or IgE mediated)
- Type II (antibody-mediated cytotoxicity)
- Type III (immune complex-mediated disorders)
- Type IV (delayed type or T-cell-mediated hypersensitivity)

The characteristic features of each hypersensitivity reaction are given in Table 3.4-2.

Immunodeficiency Diseases

Immunodeficiency diseases occur when the body defence mechanisms are impaired.

Immunodeficiency diseases may be classified as primary or secondary.

Primary Immunodeficiency Primary immunodeficiency occurs due to defect in the development of the immune system.

X-linked agammaglobulinaemia is the first immune deficiency disorder recognized by Bruton in 1952, hence also known as Bruton disease.

Secondary Immunodeficiency Acquired deficiencies of immunological response mechanisms can occur secondarily to a number of diseases. Secondary immunodeficiency is more common than the primary immunodeficiency. Acquired immunodeficiency syndrome (AIDS) is the most important.

Acquired Immunodeficiency Syndrome **AIDS,** i.e. acquired immunodeficiency syndrome, is characterized by reduction in the number of T_H-cells because of infection by the human immunodeficiency virus (HIV). AIDS was first detected in the USA in 1981.

Spread of Disease AIDS is a major worldwide life-threatening disease spreading rapidly. On a daily basis, about 8500 persons get infected with HIV. The high-risk groups include sex workers, drug addicts, homosexual males, persons with extramarital relations and recipients of unscreened blood transfusion.

SELF-ASSESSMENT

1. Describe the role of thymus in the immune system.
2. Describe the cellular immune response.
3. Describe the humoral immune response.
4. Write notes on:
   - Histocompatibility antigen
   - Structure of IgG antibody
   - Functions of immunoglobulins
   - Cytokines
   - Autoimmunity and immune tolerance
   - Complement system
5. Differentiate between
   - Active and passive immunity
   - Humoral and cell-mediated immunity
   - Classical and alternative pathway of complement system
   - Primary and secondary response of immune system

3.5 Platelets, Haemostasis and Blood Coagulation

CHAPTER OUTLINE

Platelets
Structure and Composition
Properties and Functions
Normal Count and Variations
Formation of Platelets

Haemostasis
Vasoconstriction
Formation of Temporary Haemostatic Plug
Formation of Definitive Haemostatic Plug

Blood Coagulation
Clotting Factors
Mechanism of Coagulation
Blood Clot Retraction
Role of Calcium in Blood Coagulation
Role of Vitamin K, Liver and Vascular Wall in Haemostasis and Coagulation
Why Circulating Blood does not Clot?
Thrombosis

Antihaemostatic Mechanisms
Factors Preventing Platelet Aggregation
Circulatory Anticoagulants
Fibrinolytic Mechanism
Anticoagulants

Bleeding Disorders
Purpura
Haemophilia
Disseminated Intravascular Coagulation
Laboratory Tests in Bleeding Disorders

PLATELETS

Structure and Composition

Platelets (small plates), also known as thrombocytes (thrombo = clot; cytes = cells), have the following features:

- ***Size:*** Platelets are the smallest blood cells varying in diameter from 2 to 4 μm with an average volume of 5.8 μm^3.
- ***Shape and colour:*** Platelets are colourless, spherical, or oval discoid structures.
- ***Leishman staining*** shows a platelet consisting of faint bluish cytoplasm containing reddish purple granules.
- ***Nucleus*** is absent in the platelets and therefore these cannot be reproduced.

Electron Microscopic Structure Under an electron microscope, a platelet shows the following structural and compositional characteristics (Fig. 3.5-1):

1. Cell Membrane It consists of lipids (phospholipids, cholesterol and glycolipids), carbohydrates, proteins and glycoproteins. Its salient features are as follows:

- ***Glycoproteins*** forming the surface coat of the platelet membrane prevent adherence of platelets to normal endothelium but accelerate the adherence of platelets to collagen and damaged endothelium in injured blood vessels.
- ***Phospholipids*** of the platelet membrane contain platelet factor-3, which plays an activating role at several points in the blood-clotting process.
- ***Invagination*** of the surface membrane forms the so-called *canalicular system* or the *surface connecting system.*
- ***Receptors*** present on the platelet membrane are meant for combining with specific substances like collagen and fibrinogen.
- ***Precursors*** of various substances like thromboxane A_2, prostaglandins, leukotrienes and platelet factors 3 and 4 are also present in the platelet membrane.

2. Microtubules The microtubules are made up of polymerized proteins called tubulins. These form a compact bundle, which is present immediately beneath the platelet membrane. These are responsible for maintenance of the discoid shape of the circulating platelets.

3. Cytoplasm The cytoplasm of the platelets contains the following:

- ***Endoplasmic reticulum and Golgi apparatus*** These structures synthesize various enzymes and store large quantities of calcium.
- ***Mitochondria*** These are capable of forming ATP and ADP.
- ***Contractile proteins*** include actin, myosin and thrombosthenin. Contractile proteins can cause the platelet to contract and are thus responsible for the clot retraction.
- *Other proteins* present in the cytoplasm are as follows:
  Fibrin stabilizing factor
  Platelet-derived growth factor (PDGF)
  von Willebrand factor (VWF)

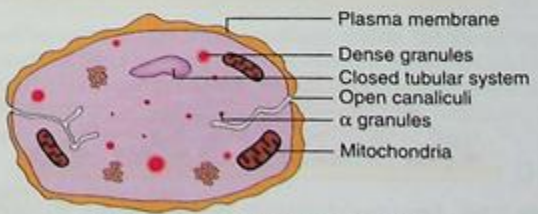


Figure 3.5-1 Ultrastructure of a platelet.

- ***Granules*** present in the cytoplasm of platelets contain substances like phospholipids, triglycerides, cholesterol, ATP, ADP and serotonin (5HT).
- ***Enzymes*** present in the cytoplasm of platelets include adenosine triphosphatase and the enzyme necessary for the synthesis of prostaglandins.

Properties and Functions

Properties of Platelets (Fig. 3.5-2)

1. Adhesiveness Platelets possess the property of adhesiveness, i.e. when they come in contact with any wet surface or rough surface, they get activated and stick to the surface. Factors responsible for adhesiveness are collagen, thrombin, ADP, thromboxane A_2, calcium ions and VWF.

2. Aggregation Platelets have the property to aggregate, i.e. they stick to each other. This is due to ADP and thromboxane A_2.

3. Agglutination Clumping together of platelets is called agglutination. This occurs due to the actions of some platelet agglutinins.

Functions of Platelets When activated, platelets perform the following functions:

1. Role in Haemostasis Haemostasis refers to the spontaneous arrest of bleeding from an injured blood vessel. The roles of platelets in haemostasis are described on page 94.

2. Role in Clot Formation Process of clot formation involves a complex series of events (described on page 94). Platelets play an important role in the formation of the intrinsic prothrombin activator, which is responsible for the onset of blood clotting.

3. Role in Clot Retraction Contraction of contractile proteins (actin, myosin and thrombosthenin) present in the platelets plays an important role in clot retraction.

4. Role in Repair of Injured Blood Vessels The PDGF present in the cytoplasm of platelets plays an important role in the repair of endothelium and other structures of the injured/damaged blood vessels.

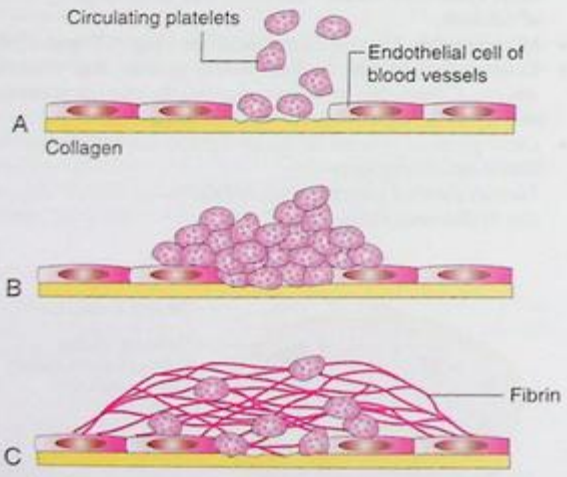


Figure 3.5-2 Properties of platelets: (A) adhesiveness; (B) aggregation; and (C) formation of haemostatic plug.

5. Role in Defence Mechanism Platelets, due to their property of agglutination, are capable of phagocytosis. These are particularly helpful in phagocytosis of carbon particles, viruses and immune complexes.

6. Transport and Storage Function The 5HT is stored in the platelets and transported to the site of injury where it is released.

Normal Count and Variations

Normal Count Normal platelet count ranges from 150,000 to 450,000/mm^3, with an average count of 2.5 lakhs/mm^3.

Physiological Variations

1. ***Age:*** Platelet count is less in infants (1–2 lakhs/mm^3). Adult levels are reached by third month of age.
2. ***Sex:*** Normally, there is no difference in the platelet counts of males and females. However, during menstruation the count is reduced in females.
3. ***After meals***, the platelet count is slightly increased.
4. ***After severe muscular exercise***, platelets may increase.
5. ***At high altitude***, platelet count is increased.

Pathological Variations

A. Thrombocytosis An increase in the number of platelets more than 4.5 lakhs/mm^3 is called thrombocytosis.

Causes of thrombocytosis: Platelet count is increased in the following cases:

1. After splenectomy
2. After the following events:
   - Haemorrhage
   - Severe injury
   - Major surgical operation
   - Parturition
3. In myeloproliferative disorders such as that given below:
   - Chronic myeloid leukaemia
   - Polycythaemia vera
   - Myelofibrosis

B. Thrombocytopenia Decrease in the number of platelets below 1.5 lakhs/mm^3 is called thrombocytopenia.

Causes of thrombocytopenia

1. Idiopathic thrombocytopenic purpura
2. Bone marrow depression due to the following:
   - Effects of various cytotoxic drugs
   - Whole body irradiation
   - Hypoplastic and aplastic anaemia
3. Acute leukaemia or secondary deposits of malignancy in the bone marrow
4. In infections like smallpox, chickenpox, typhoid and dengue fever
5. In hypersplenism
6. In toxaemia, septicaemia and uraemia

Formation of Platelets

Formation or development of platelets is called *thrombopoiesis*. The platelets are produced in the bone marrow. The pluripotent stem cell destined to form platelets is converted into colony-forming units called Meg-CFU, which develop into platelets after passing through various stages.

Stages in Platelet Production *(Fig. 3.5-3)*

1. Megakaryoblast The earliest recognizable precursor of platelets in the bone marrow is megakaryoblast. It arises from the Meg-CFU by a process of differentiation.

- *Diameter* of megakaryoblast is about 20–30 μm.
- *Cytoplasm* is small, blue and nongranular.
- *Nucleus* is large, oval or kidney shaped with several nucleoli.

2. Promegakaryocyte Promegakaryocyte is formed from the megakaryoblast. A megakaryoblast undergoes endoreduplication of nuclear chromatin, i.e. nuclear chromatin replicates repeatedly in multiples of two without division of the cell. Ultimately, a large cell containing up to 32 times the normal diploid content of nuclear DNA is formed when further nuclear replication ceases and cytoplasm becomes granular. The granules are intensely basophilic.

3. Megakaryocyte A promegakaryocyte matures into a megakaryocyte with the following features:

- *Diameter*: Mature megakaryocyte is a large cell of diameter 30–90 μm.
- *Nucleus*: Megakaryocyte has a single multilobed (4–16 lobes) nucleus with coarsely clumped chromatin.
- *Cytoplasm* is abundant, light blue in colour and contains red-purple granules.
- *Cell margin* is irregular and shows many pseudopodia. Platelets are formed from pseudopodia of megakaryocyte cytoplasm, which get detached into the blood stream. Each megakaryocyte may form up to 4000 platelets. The formation of platelets from the stem cell takes about 10 days.

Control of Thrombopoiesis Thrombopoiesis seems to be regulated by the following humoral factors:

- Thrombopoietin
- Megakaryocyte colony stimulating activity (Meg-CSA)

The factors stimulating the synthesis and release of these agents are not yet known.

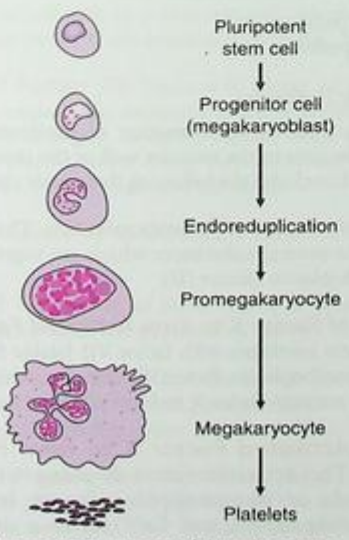


Figure 3.5-3 Stages of thrombopoiesis.

Lifespan and Fate of Platelets Lifespan of platelets varies from 8 to 12 days with an average of 10 days. Platelets are destroyed by the tissue macrophage system in spleen. Therefore:

- *Splenomegaly* causes reduction in the platelet count.
- *Splenectomy* is followed by an increase in the platelet count.

HAEMOSTASIS

Haemostasis refers to the spontaneous arrest or prevention of bleeding from the injured/damaged vessels by the physiological process. It involves the following three main steps (Fig. 3.5-4):

- Vasoconstriction
- Formation of temporary haemostatic plug
- Formation of the definitive haemostatic clot

1. Vasoconstriction Initial vasoconstriction is caused by a direct effect of injury on the vascular smooth muscles. The initial vasoconstriction is transient but is maintained for several minutes or even hours by humoral facilitation due to release of 5HT and other vasoconstrictors.

2. Formation of Temporary Haemostatic Plug Formation of a temporary haemostatic plug by the platelets at the site of injury involves the following steps:

Platelet Adhesion Following injury, platelets become sticky and therefore adhere to the collagen of the damaged cell wall and to the damaged endothelium.

Platelet Activation The platelets secrete large quantities of ADP and thromboxane A_2, which act on the nearby platelets and cause their activation. Stickiness of these additional platelets causes them to adhere to originally activated platelets. In this way, a vicious cycle is initiated, which leads to activation and adherence of a large number of platelets.

Platelet Aggregation The large numbers of activated sticky platelets stick to each other, forming platelet aggregation. Platelet aggregation is also increased by the *platelet-activating factor* (PAF), a cytokine secreted by neutrophils, monocytes and platelet cell membrane lipids.

The platelet adherence and aggregation ultimately leads to the formation of a platelet plug. At first, it is a fairly loose plug but is successful in blocking the blood loss if the vascular opening is small.

3. Formation of Definitive Haemostatic Plug The temporary platelet plug is converted into the definitive haemostatic plug by the process of clot formation (blood coagulation). Platelets play an important role in the formation of the intrinsic prothrombin activator, which is responsible for initiating the process of clot formation (page 94).

BLOOD COAGULATION

Blood remains in the fluid condition within the blood vessels throughout life. However, when the blood is shed from the blood vessels or collected in a container, it loses its fluidity within a few minutes and gets converted into a jelly-like mass called clot. This phenomenon is called *coagulation* or clotting of blood.

Clotting Factors

The process of coagulation essentially involves a stepwise activation of certain substances, mostly proteins, present in the blood

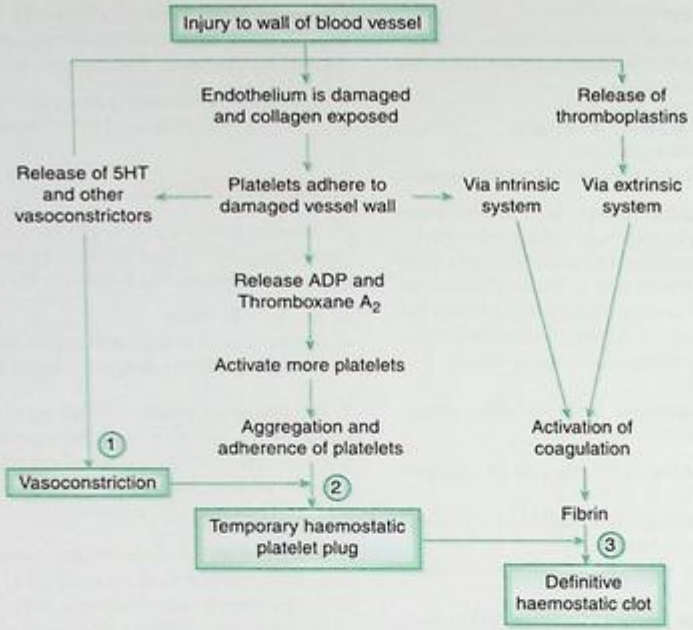


Figure 3.5-4 Steps of haemostasis.

and/or tissue fluids. These substances are called clotting factors and have been conferred Roman numerals for identification:

- Factor I (fibrinogen)
- Factor II (prothrombin)
- Factor III (thromboplastin)
- Factor IV (calcium)
- Factor V (labile factor or proaccelerin or accelerator globulin)
- Factor VI (nonexistent)
- Factor VII (stable factor or proconvertin)
- Factor VIII (antihaemophilic factor A [AHF] or antihaemophilic globulin [AHG])
- Factor IX (Christmas factor or plasma thromboplastic component [PTC or antihaemophilic factor B])
- Factor X (Stuart–Prower factor)
- Factor XI (plasma thromboplastin antecedent, i.e. PTA or antihaemophilic factor C)
- Factor XII (Hageman factor or glass factor or contact factor)
- Factor XIII (fibrin-stabilizing factor or fibrinase or Laki–Lorand factor)
- PL (platelet phospholipid)

Mechanism of Coagulation

Normally, blood circulates in the blood vessels and does not clot spontaneously. Clot formation is initiated under the following situations:

- Trauma to the vascular wall and adjacent tissues
- Trauma to blood
- Contact of blood with damaged endothelial cells or collagen or other tissue elements outside the vessel

The process of coagulation involves a *cascade* of reactions in which activation of one factor leads to activation of the next clotting factor (Fig. 3.5-5). This enzyme cascade reaction is also called the *water fall sequence*. The process of coagulation can be divided into three main steps:

A. Formation of prothrombin activator
B. Conversion of prothrombin into thrombin
C. Conversion of fibrinogen into fibrin

A. Formation of Prothrombin Activator

Two different mechanisms involved in the formation of prothrombin activator are as follows:

1. Extrinsic pathway
2. Intrinsic pathway

1. Extrinsic Pathway

The extrinsic pathway of formation of prothrombin activator begins with trauma to the vascular wall or the tissues outside the blood vessel. It includes the following three basic steps (Fig. 3.5-5):

Release of Tissue Thromboplastins The traumatized tissues release several substances which are together known as *tissue thromboplastin (factor III)*.

Activation of Factor X to form Activated Factor X Tissue thromboplastin combines with factor VII (stable factor) to form the tissue thromboplastin–factor VII complex, which in the presence of Ca^{2+} activates factor X to form activated factor X (Xa).

Effect of Activated Factor X to form Prothrombin Activator The activated factor X along with the tissue phospholipids or phospholipids released from platelets, factor V (labile factor) and Ca^{2+} forms a complex called prothrombin activator.

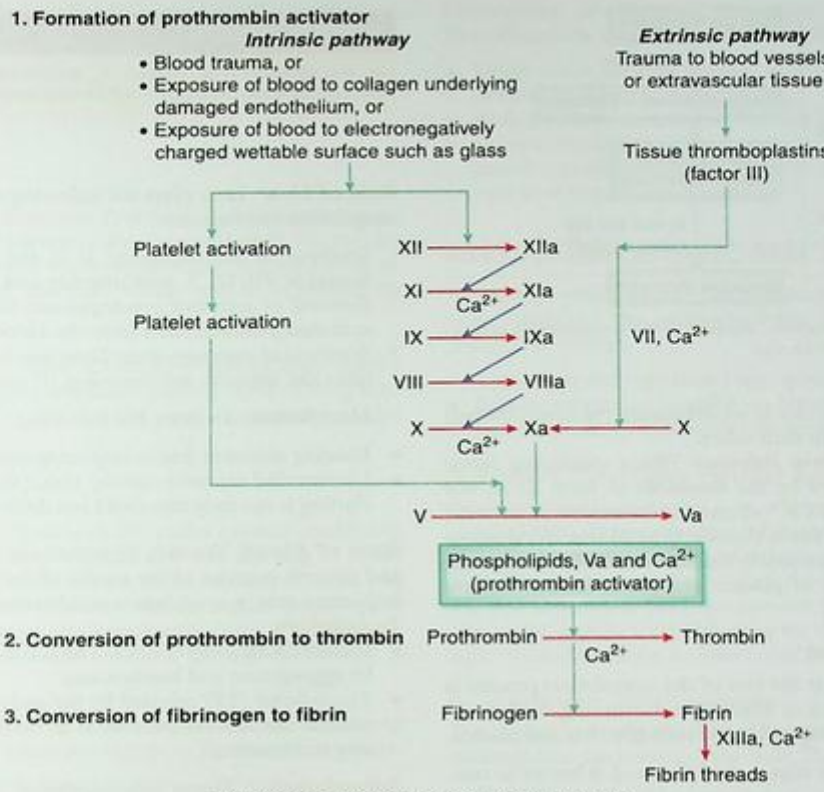


Figure 3.5-5 Mechanism of blood coagulation.

2. Intrinsic Pathway

The intrinsic pathway of formation of prothrombin activator begins in the blood itself following trauma to blood or exposure of blood to collagen in a traumatized vascular wall. The steps of intrinsic pathway are summarized in Fig. 3.5-5.

Activation of Factor XII Trauma to blood or exposure to collagen fibres underlying damaged vascular endothelium (or electronegatively charged wettable surface such as glass, in vitro) activates plasma factor XII to form XIIa and initiates the intrinsic pathway. Platelets are also activated.

Activation of Factor XI to form XIa is caused by the activated factor XII.

Activation of Factor IX to form IXa is, in turn, caused by the activated factor XI in the presence of Ca^{2+}.

Activation of Factor X Factor IXa in the presence of the activated factor VIII, Ca^{2+} and phospholipids (released by activated platelets) activates factor X to form Xa.

Formation of Prothrombin Activator The activated factor X along with the phospholipids released by the activated platelets, activated factor V and Ca^{2+} forms a complex called prothrombin activator.

B. Conversion of Prothrombin into Thrombin

Conversion of Prothrombin into Thrombin is caused by the prothrombin activator in the presence of Ca^{2+}. This occurs at the surface of platelets, which form the platelet plug at the site of injury.

Thrombin

Thrombin so formed acts as a proteolytic enzyme. The roles played by thrombin are as follows:

- It *converts fibrinogen into fibrin* (discussed below).
- *Positive feedback role of thrombin*: It accelerates the rate of formation of prothrombin activator by the activating factors VIII, V and XIII. In this way, thrombin itself can cause further conversion of prothrombin into thrombin (amplification effect).
- It also activates protein C (which is an anticoagulant).

C. Conversion of Fibrinogen into Fibrin

Conversion of fibrinogen into fibrin involves the following three reactions (Fig. 3.5-6):

1. Proteolysis Thrombin acting as a proteolytic enzyme removes four low-molecular-weight peptide chains from each molecule of fibrinogen to convert it into a fibrin monomer.

2. Polymerization Fibrin monomer polymerizes with another monomer to form *long fibrin* threads, which form the reticulum

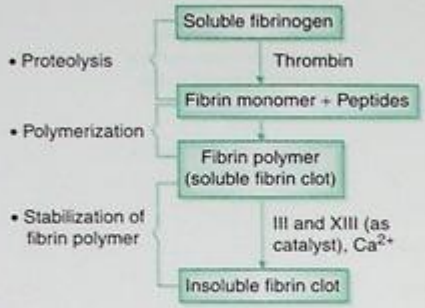


Figure 3.5-6 Types of reactions involved in the conversion of soluble fibrinogen into insoluble fibrin clot.

of the clot. Initially, the clot is weak because the fibrin threads are not cross-linked with each other.

3. Stabilization of Fibrin Polymers Fibrin stabilizing factor (factor XIII) is activated by the thrombin to form XIIIa, but XIIIa in the presence of Ca^{2+} causes the formation of covalent cross-linkages between fibrin threads, thus adding tremendous strength to the fibrin meshwork. The fibrin meshwork traps the remaining components of plasma and blood cells to form a solid mass called clot.

Blood Clot Retraction

The blood clot formed at the end of the coagulation process is composed of a meshwork of fibrin threads running in all directions along with the entrapped blood cells, platelets and plasma.

- Within a few minutes after a clot is formed, it begins to contract and usually squeeze out most of the fluid called *serum* (plasma without fibrinogen and other clotting factors) within 30–60 minutes.
- *Platelets are essential* for the clot retraction. The contractile proteins (platelet thrombosthenin, actin and myosin) present in the cytoplasm of platelets cause strong contraction of platelet spicules attached to fibrin fibres. This contraction is activated by thrombin and calcium ions.
- If a blood clot is kept for several hours, the clot retracts to about 40% of its original volume.

Role of Calcium in Blood Coagulation

From the study of mechanism of blood coagulation, it is quite clear that except for the first two steps in the intrinsic pathway, calcium ions are required for the promotion of all the reactions. Therefore, in the absence of calcium ions, blood clotting will not occur. Thus, coagulation of blood can be prevented in vitro (e.g. for storage in the blood bank or for separation of plasma) by removal of calcium ions. The use of oxalates and citrates as in vitro anticoagulants is based on this principle.

Role of Vitamin K, Liver and Vascular Wall in Haemostasis and Coagulation

Role of Vitamin K Dietary vitamin K and that synthesized by the bacterial flora is absorbed from the gut and reaches the liver. In the liver, the synthesis of the following factors is dependent upon vitamin K:

- Coagulant like prothrombin
- Factors VII, IX and X
- Circulatory anticoagulant protein

APPLIED ASPECTS

In the deficiency of vitamin K, prothrombin time and blood clotting time are prolonged and serious haemorrhages may occur.

Role of Liver Liver plays the following significant roles in the coagulation mechanism:

1. *Synthesis of procoagulants:* It is the site of synthesis of factors V, VII, IX, X, prothrombin and fibrinogen.
2. *Removal of activated procoagulants*: Liver also removes the activated procoagulants from the blood.
3. *Synthesis of anticoagulants*: Liver also synthesizes anticoagulants like heparin, antithrombin III and protein C.

Liver failure can cause the following:

- *Bleeding disorders* due to hypocoagulability of the blood
- *Uncontrolled extensive clotting* inside the blood vessels where clotting is not only unwanted but dangerous as well

Role of Blood Vessels Endothelium, subendothelial tissue and smooth muscles of the media of the blood vessels play an important role in coagulation and haemostasis mechanisms.

Endothelium

- Endothelium secretes VWF: The plasma VWF initiates platelet aggregation and haemostasis.
- *Tissue factor* (TF) released by the endothelial cells following trauma initiates the process of an extrinsic pathway of clotting mechanism.

Subendothelial Tissue Subendothelial tissue, which chiefly consists of collagen fibres, plays the following roles in coagulation:

- *Platelet aggregation* is initiated when blood comes in contact with the subendothelial collagenous tissue.
- *Intrinsic coagulation pathway* is initiated when factor XII is activated following contact of blood with subendothelial collagenous tissue.

Vascular Smooth Muscle Smooth muscles of the vascular wall play a role in haemostasis by causing vasoconstriction initiated by a mechanical injury to muscles.

Why Circulating Blood Does Not Clot?

We all know that blood circulating in the blood vessels does not clot and that the fluidity of the blood is essential for life. The factors responsible for the fluidity of the blood are as follows:

1. Velocity of Circulation Blood is pumped into the vessels and circulated at a constant velocity, which contributes to its fluidity. That is why decrease in circulation velocity in certain conditions is associated with the intravascular clotting.

2. Surface Effects of Endothelium

- Smoothness of the endothelial lining inhibits platelet adhesion.
- A layer of glycocalyx (mucopolysaccharide) adsorbed to the inner surface of endothelium being negatively charged repels clotting factors (anion proteins) and platelets, and thereby prevents clotting.
- Intact endothelium acts as a barrier between the thrombogenic subendothelial collagenous tissue and the blood.

3. Circulatory Anticoagulants or the so-called natural anticoagulants present in the blood which prevent clotting are as follows:

- Heparin
- Antithrombin III
- α_2 Macroglobulin
- Protein C

4. Fibrinolytic Mechanism Protein C is a naturally occurring anticoagulant which inactivates factors V and VIII and also inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin, which acts as a fibrinolytic system.

5. Removal of Activated Clotting Factors Liver plays a role in preventing the intravascular clotting by removing activated clotting factors in the event of onset of spontaneous clot formation.

Thrombosis

We have studied that physiologically, under normal conditions, the circulating blood does not clot and that clotting of blood occurs only extravascularly when a vessel has been injured and bleeding has occurred. However, under certain pathological conditions, the intravascular clotting may occur. The intravascular clotting is called *thrombosis* and the clot so formed is called thrombus.

Predisposing Factors Virchow described the following three primary events which predispose to the thrombus formation (*Virchow's triad*):

1. Endothelial Injury Endothelial injury may occur in atherosclerosis, haemodynamic stress in hypertension, arterial disease, diabetes mellitus and hypercholesterolaemia.

2. Alterations in Flow of Blood Both in turbulence as well as in stasis of blood, normal axial flow of blood is disturbed and platelets come in contact with the endothelium, initiating thrombus formation. Stasis of blood is commonly associated with venous thrombosis, especially in the leg veins after major operations on the abdomen (postoperative thrombosis) or otherwise bedridden patients.

3. Hypercoagulability of Blood This may occur due to:

- Increase in coagulation factors such as fibrinogen, prothrombin, factors VIa, VIIa and Xa
- Increase in the platelet count and their adhesiveness
- Decreased levels of coagulation inhibitors such as antithrombin III and fibrinogen degradation products

Effects of Thrombi Intravascular thrombi may be even life-threatening depending upon their size and site.

1. Ischaemia and Infarction Thrombi may decrease or stop the blood supply to a part of an organ and cause ischaemia, which may subsequently result in infarction. For example, thrombus formation in coronary arteries may cause myocardial ischaemia and infarction.

2. Thromboembolism The thrombus or its part may get dislodged and carried along in the blood stream as *embolus* to get lodged in a distant vessel. Examples of emboli formation are as follows:

- *Pulmonary embolism*
- *Cerebral embolism*

Prevention of Thrombi Formation and/or extension of a thrombus can be prevented by the administration of the following:

- *Drugs which decrease platelet adhesiveness*, such as aspirin, dextran or dipyridamole
- *Anticoagulants*, such as low doses of heparin and dicoumarol
- *Intermittent compression* or electrical stimulation of the calf muscles in addition to the above drugs for preventing postoperative venous thrombosis

ANTIHAEMOSTATIC MECHANISMS

The factors which balance the tendency of the blood to clot in vivo constitute the *antihaemostatic factors*. These can be grouped as follows:

- Factors preventing platelet aggregation
- Factors preventing coagulation (circulatory anticoagulants)
- Factors causing fibrinolysis (fibrinolytic mechanism)

A. Factors Preventing Platelet Aggregation

Prostacyclin Prostacyclin is an endogenous factor which prevents platelet aggregation by inhibiting the thromboxane A_2 formation (which promotes platelet aggregation).

Note. The drug *aspirin* also inhibits the formation of thromboxane and thus when used can prevent platelet plug formation. This makes aspirin a valuable drug for the prevention of thrombosis in patients prone to myocardial infarction and stroke.

B. Circulatory Anticoagulants

The natural anticoagulants circulating in the blood constitute the anticoagulant mechanism of the body. These include the following:

- Heparin
- Antithrombin III or heparin co-factor II
- Protein C

1. Heparin Heparin is a powerful naturally acting anticoagulant since it was first isolated from liver, so it is named heparin (hepar = liver). However, it is also present in many other organs. It is a polysaccharide containing many sulphate groups. Its molecular weight is 15,000–18,000 Da.

Mechanism of action: It acts as an anticoagulant by the following mechanisms:

- Preventing activation of prothrombin to thrombin
- Inhibiting the action of thrombin on fibrinogen
- Facilitating the action of antithrombin III, i.e. acts as its cofactor and, thereby, inhibiting the active forms of clotting factors IX, X, XI and XII

2. Antithrombin III Antithrombin III is present in plasma as well as vascular endothelium. It inactivates a number of coagulation factors, including thrombin.

3. Protein C Protein C is a plasma protein synthesized in liver. It, along with *thrombomodulin* and protein S, constitutes an important negative feedback pathway that keeps the coagulatory process under control. The steps of protein C pathway are given in Fig. 3.5-7.

C. Fibrinolytic Mechanism

Fibrinolysis refers to the process that brings about the dissolution of fibrin. The important component of the fibrinolytic

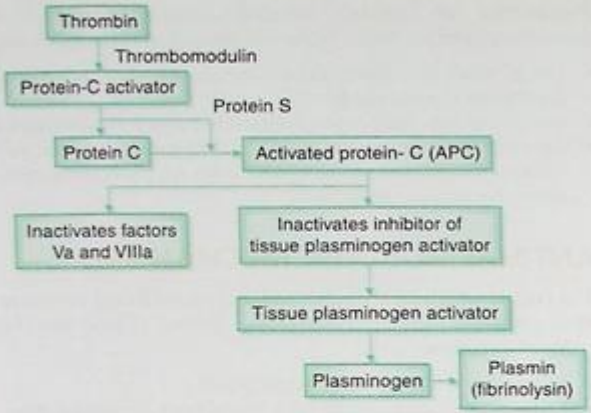


Figure 3.5-7 Steps of protein C pathway in inhibiting coagulation and promoting fibrinolysis.

system is *plasmin* or fibrinolysin, which is present in the blood in an inactive form called *plasminogen* or profibrinolysin.

Physiological Role of Fibrinolysis System Plasmin of the fibrinolysis system plays the following physiological roles:

- ***Cleaning the minute clots of tiny vessels:*** The fibrinolytic system is constantly in action to prevent fibrin formation.
- ***Promote normal healing process:*** Lysis of clot formed as a result of tissue injury helps to promote normal healing process.
- ***Liquefaction of menstrual clot*** in the vagina is carried out by the fibrinolytic system.
- ***Liquefaction of sperms in the epididymis*** when seminal ejaculation does not occur is caused by the fibrinolysin system.
- ***Role in inflammatory response:*** In addition to its fibrinolytic activity, plasmin can form plasma kinins (bradykinins, kallidin) and thus contribute to the vascular and sensory features (pain) of the inflammatory response to injury.

Anticoagulants

Anticoagulants refer to the substances which delay or prevent the process of coagulation of blood.

Types: Anticoagulants may be divided into endogenous and exogenous anticoagulants.

A. Endogenous Anticoagulants Endogenous anticoagulants are those which are present inside the blood naturally:

- Heparin
- Antithrombin III
- Protein C

B. Exogenous Anticoagulants Exogenous anticoagulants are administered from outside or are used in vitro. These include the following:

- Heparin
- Calcium sequesters
- Vitamin K antagonist
- Defibrination substances

1. Heparin: Heparin, a naturally acting anticoagulant, can also be synthesized. It inhibits blood coagulation both in vivo and in vitro.

2. Calcium Sequesters or Decalcifying Agents: In vitro, blood clotting can be prevented by substances which sequester (remove) calcium from the blood. These include two types of agents:

- Substances which form insoluble salts with calcium, such as sodium citrate and sodium oxalate.
- Calcium chelators which bind calcium, such as ethylene diamine tetraacetic acid (EDTA).

3. Vitamin K Antagonists: These are used orally and thus can prevent coagulation in vivo effectively. These include the following:

- Coumarin derivatives, e.g. Dicoumarol and Warfarin
  Mechanism of action: These agents occupy vitamin K receptor sites in the liver and prevent vitamin K to carry out its normal physiological function, hence the name vitamin K antagonists. Thus, these substances inhibit synthesis of vitamin K dependent factors, i.e. factors VII, IX and X.

4. Defibrination Substances: Defibrination substances are those which cause destruction of fibrinogen.

- Malaysian pit viper venom.
- Arvin or ancord: It is purified preparation of snake venom. It is a glycoprotein in nature and is administered by injection.

5. Cold: Keeping blood cold (at 5–10°C) can retard the process of coagulation but cannot absolutely prevent it. This is the reason why blood is stored in blood banks at a low temperature, but some anticoagulant agent is always used (while cold delays coagulation); in fact, when ice is applied on the surface, it prevents bleeding by inducing reflex vasoconstriction.

BLEEDING DISORDERS

Bleeding disorders are characterized by spontaneous escape of blood from blood vessels (in the tissues, inside the body cavities or on a few surfaces like skin and mucous membrane) or persistent and/or excessive bleeding following minor injuries like tooth extraction, etc.

Classification Of Bleeding Disorders

I. Platelet Disorders

A. *Deficiency of blood platelets: Thrombocytopenic purpura* (see page 99)
B. *Functional disorder of platelets*

II. Coagulation Disorder or Defective Coagulation Mechanism

1. Deficiency of clotting factors (see Table 3.5-1)
2. Vitamin K deficiency (see page 96)
3. Anticoagulant overdose
4. Disseminated intravascular clotting (DIC)

TABLE 3.5-1 **Deficiency of Clotting Factors**

Deficiency of Factor	Clinical Syndrome	Cause
• Factor I	Fibrinogenopenia, afibrinogenaemia	Depletion during pregnancy with premature separation of placenta; congenital (rare)
• Factor II	Hypoprothrombinaemia (haemorrhagic tendency in liver disease)	Decreased hepatic synthesis, usually secondary to vitamin K deficiency
• Factor V	Parahaemophilia	Congenital
• Factor VII	Hypoconvertinaemia	Congenital
• Factor VIII	Haemophilia A or classical haemophilia	Congenital defect due to abnormal gene on X chromosome
• Factor IX	Haemophilia B or Christmas disease	Congenital
• Factor X	Stuart–Prower factor deficiency	Congenital
• Factor XI	PTA deficiency	Congenital
• Factor XII	Hageman trait (does not produce bleeding)	Congenital
• von Willebrand factor	von Willebrand disease	Congenital

III. Vascular Disorders: Damage of Capillary Endothelium (Nonthrombocytopenic Purpura)

- Due to infection by bacteria and their toxins
- Due to toxic effects of drugs and chemicals
- Due to avitaminosis C
- Due to allergic purpura
- Due to connective tissue diseases

Only a few important bleeding disorders, the purpura and haemophilia, are described briefly.

Purpura

The term purpura is derived from purple-coloured petechial haemorrhages and bruises in the skin. The blood that leaks out changes colour from red to blue to dark blue and green over a period of time.

Causes and Types of Purpura

I. Platelet Disorders Platelet disorders are associated with bleeding disorders. Platelet disorders include the following:

1. Deficiency of Platelets Decrease in the platelet count below 1.5 lakhs/mm^3 is called thrombocytopenia. Thrombocytopenic purpura is of the following types:

- ***Primary thrombocytopenic purpura*** (idiopathic, cause not known): In many of the idiopathic cases, antibodies develop against platelets (immune thrombocytopenic purpura, ITP).
- ***Secondary causes of platelet deficiency*** (secondary thrombocytopenic purpura) are as follows:
  - Bone marrow depression due to effects of various cytotoxic drugs, whole body irradiations, hypoplastic and aplastic anaemia
  - Hypersplenism

2. Functional Disorders of Platelets (Thrombocytopenic Purpura) Functional disorders of platelets include the following:

- ***Drug-induced defects*** occur with aspirin, large doses of penicillin and other drugs.
- ***von Willebrand disease:*** It is inherited as an autosomal dominant trait. This condition is associated with a deficiency of factor VIII related antigen (VIII R:Ag), also called VWF. This factor acts as a carrier of factor VIII, so its deficiency results in diminished adherence of platelets to collagen fibres in a damaged vessel.

II. Vascular Disorders Bleeding tendencies seen in patients with vascular disorders (damage to capillary endothelium) are referred to as *nonthrombocytopenic purpura.* In all cases of purpura due to vessel wall defects, the platelet counts are normal, but the bleeding time is prolonged and capillary fragility test is positive.

Causes of Nonthrombocytopenic Purpura

1. *Drug-induced damage to capillary wall*
2. *Deficiency of vitamin C (scurvy)*
3. *Allergic purpura*
4. *Infections*
5. *Senile purpura*
6. *Connective tissue diseases*

Haemophilia

Haemophilia is the name given to a group of disorders occurring due to *hereditary deficiency of coagulation* and characterized by bleeding tendencies associated with increased clotting time. The haemophilia includes the following:

- Haemophilia A (83% cases)
- Haemophilia B (15% cases)
- Haemophilia C (2% cases)

1. Haemophilia A

- Haemophilia A, also known as true or classical haemophilia, occurs due to *deficiency of factor VIII*, i.e. AHG.
- It is the most common hereditary coagulation disorder. Being sex-linked recessive disease, it affects males exclusively, and females act as carriers (Fig. 3.5-8). The carrier female shows no symptoms due to the presence of an X chromosome, which is dominant over X. Only mating of a haemophilic male with a carrier female will produce a haemophilic female, which is a very rare occurrence.
- Clinical features (bleeding tendency) are not apparent since birth but generally start early in life (within first 3 years).

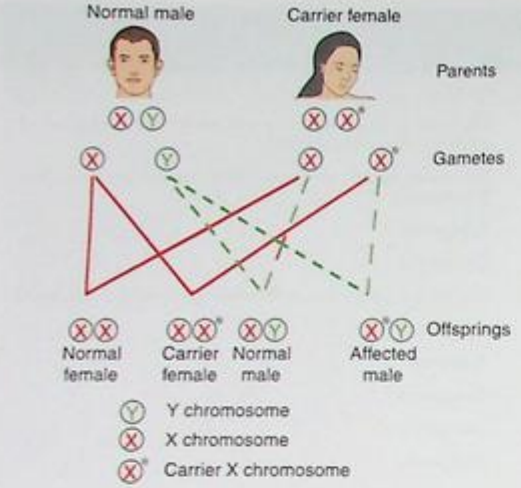


Figure 3.5-8 Sex-linked inheritance of haemophilia A.

- Haemophilics have a normal bleeding time, platelet count and prothrombin time. Coagulation time is increased, and, typically, the patients have prolonged PTT.
- Haemophilia A can be treated by transfusion of the following:
  - Factor VIII concentrate commercially available as cryoprecipitated antihaemophilic factor for intravenous infusion.

2. Haemophilia B

- Haemophilia B, also known as *Christmas disease*, occurs due to deficiency of factor IX (Christmas factor or plasma thromboplastin component [PTC]). It was discovered in a family with surname Christmas.
- Like haemophilia A, haemophilia B is also a recessive X-linked disease that occurs in males and is transmitted by females.
- Clotting time in this condition may be prolonged or may be within normal limits.

Disseminated Intravascular Coagulation

- Disseminated intravascular coagulation (DIC), as the name indicates, refers to the condition when the clotting mechanism becomes activated in widespread areas of the circulation.
- Due to widespread intravascular coagulation, there occurs plugging of small vessels with clots, resulting in decreased O_2 and nutrient supply to its tissues, causing multiple organ damage.

Laboratory Tests in Bleeding Disorders

Bleeding Time

Definition: Bleeding occurs from the skin when it is pricked with a needle, which normally stops of its own within a few minutes. The time lapse between the skin prick and the arrest of bleeding is called *bleeding time* (BT).

Normal BT *by* Duke's method varies from 1 to 6 minutes. Normal BT indicates that the platelet count and their function as well as health of capillaries are normal.

Prolonged BT occurs in purpura, while it is normal in haemophilia.

Platelet Count

Normal Platelet Count varies from 1.5 to 4.5 lakhs/mm^3 with an average of 2.5 lakhs/mm^3. Platelet count is decreased in primary and secondary thrombocytopenic purpura (page 99).

Coagulation Time (CT)

Definition: Coagulation time refers to the time taken by the fresh fluid blood to get coagulated (demonstrated) by the formation of fibrin threads.

Normal clotting time: By capillary tube method varies from 3-6 min., by modified Lee-White method 8-12 min. (for glass tube) and 20-60 min. (for siliconized tube).

Importance of Clotting Time (CT): The CT is prolonged in haemophilia and other clotting disorders because thrombin cannot be normally generated; however, the BT reflects vasoconstriction and platelet plug formation independently of clot formation.

- *Physiologically*, clotting time is reduced during menstruation, and before and during parturition.
- *Pathologically, CT is prolonged in* haemophilia, liver diseases, afibrinogenaemia, Christmas disease, vitamin K deficiency and disseminated intravascular coagulation (DIC).

SELF-ASSESSMENT

1. Describe the structure of thrombocyte, its composition and functions of its constituents.
2. Describe the functions of platelets.
3. Describe the process of formation of thrombocytes.
4. Describe the mechanism of coagulation.
5. Write notes on:
   - Haemostasis
   - Role of calcium in blood coagulation
   - Thrombosis
   - Heparin
   - Significance of fibrinolytic mechanism
   - Calcium sequester
   - Purpura
   - Haemophilia
   - Disseminated intravascular coagulation
   - von Willebrand factor
   - Clot retraction
6. Explain the following:
   - Blood does not clot in circulation.
   - Bleeding time is normal in haemophilia.
   - Uncontrolled bleeding occurs in liver failure.

3.6 Blood Groups and Blood Transfusion

CHAPTER OUTLINE

Blood Groups
Introduction
Classical ABO Blood Grouping System
Agglutinogens
Agglutinins
Types of ABO Blood Groups
Population Distribution of ABO Blood Groups
Inheritance of ABO Blood Groups
Determination of ABO Blood Groups
Rhesus (Rh) Blood Grouping System
Rh Antigens
Rh Antibodies
Inheritance of Rh Antigens
Haemolytic Disease of Newborn
Clinical Applications of Blood Grouping

Blood Transfusion
Indications
Donor and Recipient
Precautions during Blood Transfusion
Autologous Blood Transfusion

BLOOD GROUPS

Introduction

Agglutinogens and Agglutinins

Agglutinogens refer to the antigens present on the cell membranes of red blood cells (RBCs). A variety of antigens are present on the cell membrane, but only a few of them are of practical significance.
Agglutinins refer to the antibodies against the agglutinogens. These are present in the plasma.
Agglutination of RBCs can be caused by the antigens present on their cell membranes in the presence of suitable agglutinins (antibodies). That is why these antigens are called agglutinogens.

Blood Grouping Systems Depending on the type of agglutinogen present or absent on the red cell membranes, various blood grouping systems are known, which can be classified as follows:
Major blood group systems are based on the presence of agglutinogens, which are widely prevalent in the population and are known to cause worst transfusion reactions. These include the following:

- The classical ABO blood grouping system
- Rhesus (Rh), (CDE) blood grouping system

Minor blood group systems are based on the presence of agglutinogens, which are found only in a small proportion of the population and occasionally produce mild transfusion reactions. These include the following:

- MNS blood group system
- P blood group system

Note: From clinical point of view, only major blood group systems are important, so will be discussed.

Landsteiner Law Karl Landsteiner in 1900 framed a law in relation to agglutinogens and agglutinins, which states that:

1. ***If an agglutinogen is present*** on the red cell membrane of an individual, the corresponding agglutinin must be absent in the plasma.
2. ***If an agglutinogen is absent*** from the cell membrane of RBCs of an individual, the corresponding agglutinin must be present in the plasma.

It is important to note that:

- The Landsteiner law is applicable only to the ABO blood group system.
- The law is not applicable to other blood group systems because there are no naturally occurring agglutinins in these systems.

Classical ABO Blood Grouping System

A and B Agglutinogens

- The classical ABO blood grouping system is based on the presence of A and B agglutinogens on the cell membrane of RBCs.
- A and B agglutinogens are complex oligosaccharides differing in their terminal sugars.
- The A and B antigens present on the membranes of RBCs are also present in many other tissues like salivary glands, pancreas, kidney, liver, lungs and testis, and also in body fluids like saliva, semen and amniotic fluid. The antigens on the RBC's membrane are glycolipids, while in the tissues and body fluids they are soluble glycoproteins.

Anti-A and Anti-B Agglutinins

- Anti-A (or α) agglutinin and anti-B (or β) agglutinin refer to the antibody, i.e. which reacts with or acts on the antigen A and antigen B, respectively.
- There are two types of α agglutinins: the α_1 and α proper.
- The α and β agglutinins are globulins of IgM type and *cannot cross the placenta.*
- The α and β agglutinins act best at a low temperature (5–20°C) and are therefore also called cold antibodies.

Types of ABO Blood Groups

Depending on the presence or absence of A and B agglutinogens and α and β agglutinins, there are four types of blood groups:
Blood Group A is characterized by the following:

- Presence of A agglutinogen and absence of B agglutinogen on the cell membrane of RBCs.
- Presence of anti-B agglutinin and absence of anti-A agglutinin from the plasma.
- Group A has two subgroups: A_1 and A_2. The α_1-agglutinin agglutinates with subgroup A_1 only, while α-proper agglutinin agglutinates with both A_1 and A_2 subgroups.

Blood Group B is characterized by the following:

- Presence of B agglutinogen and absence of A agglutinogen on the cell membrane of RBCs
- Presence of anti-A agglutinin and absence of anti-B agglutinin from the plasma

Blood Group AB is characterized by the following:

- Presence of both A and B agglutinogens on the cell membrane of RBCs.
- Absence of both anti-A and anti-B agglutinins from the plasma.
- Blood group AB has two subgroups: A_1B and A_2B.

Blood Group O is characterized by the following:

- Absence of both A and B agglutinogens on the red cell membrane
- Presence of both anti-A and anti-B agglutinins in the plasma

Population Distribution of ABO Blood Groups (Table 3.6-1)

TABLE 3.6-1 Population Distribution of ABO Blood Groups in India Vis-á-Vis Britain

Blood Group	India (%)	Britain (%)
A	20	42
B	40	9
AB	8	3
O	32	46

Inheritance of ABO Blood Groups

Agglutinogens A and B or the nonantigenic substances which determine the blood groups are genetically inherited as Mendelian dominant in the classical Mendelian pattern.

The ABO phenotypes and possible genotypes are as follows:

Phenotype	Genotype	
Blood group A	AA	AO
Blood group B	BB	BO
Blood group AB	AB	
Blood group O	OO	

The genes that determine A and B phenotypes are located on chromosome 9P. The enzymes glycosyltransferases are the gene products which confer enzymatic ability for addition of specific antigenic carbohydrates. Therefore, individuals who lack 'A' and 'B' transferases are 'O' type, while those who inherit both 'A' and 'B' are 'AB' type, and Individuals who lack the H gene (responsible for coding fructose transferase) cannot produce H substance. Such individuals are homozygous for silent h allele (hh) and are known as *Bombay phenotype*, i.e. (Oh), but are rare.

Determination of ABO Blood Groups

The ABO blood group of an individual can be determined by mixing one drop of suspension of the red cells (in isotonic saline) with a drop each of antiserum A (containing α agglutinins) and antiserum B (containing β agglutinins) separately on a glass slide. The antiserum A will cause agglutination or clumping of RBCs having A antigens, and antiserum B will cause agglutination of RBCs having B antigens. The blood group of the individual will be shown by the presence of agglutination with one, both or none of the sera (Table 3.6-2 and Fig. 3.6-1).

Note: The antisera A and B are available commercially. For a quick identification, the anti-A serum is tinted blue and anti-B serum is tinted yellow.

Rhesus (Rh) Blood Grouping System

Rh Antigens

- The antigens responsible for this blood grouping system are called Rh antigens or Rh agglutinogens or Rh factor because these were first discovered in the RBCs of rhesus monkeys. On the basis of presence of Rh antigen, two types of blood groups are described:
  - Rh positive blood group
  - Rh negative blood group

TABLE 3.6-2 Determination of Blood Group of an Individual

	AGGLUTINATION WITH	
Blood Group of RBC Suspension	Antiserum A (Containing α Agglutinins)	Antiserum B (Containing β Agglutinins)
A	+	–
B	–	+
AB	+	+
O	–	–

Note: + sign indicates agglutination and – sign indicates no agglutination.

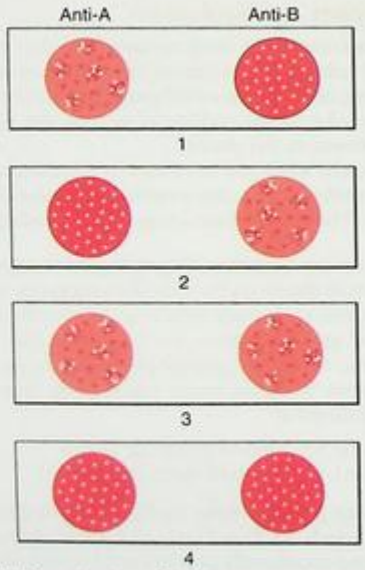


Figure 3.6-1 Determination of blood groups – the RBCs showing agglutination with antisera are as follows: (1) of blood group 'A' with antisera A; (2) of blood group B with antisera B; (3) of blood group 'AB' with antisera A and B (both); and (4) of blood group 'O' with none.

- The Rh antigens were discovered by Landsteiner and Weiner in 1940. They noticed that when RBCs of rhesus monkey (monkey with red ischial callosity) were injected into a rabbit, antibodies were formed against these RBCs. When such rabbit's serum was tested against human red blood cells, agglutination occurred in 85% of the cases, i.e. these persons' RBCs contained antigen, which reacted with antibodies formed against rhesus monkey RBCs. They labelled this antigen *Rh antigens* and such persons were laboured Rh +ve. The remaining 15% were labelled Rh −ve.
- Three types of Rh antigens, i.e. C, D and E, have been recognized. However, D antigen is the most common and produces the worst transfusion reactions. Therefore, for all practical purposes, the term Rh antigen refers to D antigen.
- Rh antigens are integral membrane proteins. These are *not found* in tissues other than RBCs.

Rh Antibodies

- There are no natural antibodies of Rh antigens, while in the ABO system of blood grouping α or β antibodies are always present naturally if the appropriate antigen is absent.
- Rh antibodies (also called anti-D) are produced only when an Rh −ve individual is transfused with Rh +ve blood or when an Rh −ve mother gives birth to an Rh +ve baby (Rh +ve RBCs of fetus enter into the maternal circulation); Rh antibodies are of IgG type and can cross the placenta. These react best at body temperature, so are also called warm antibodies.
- Once produced, the Rh antibodies persist in the blood for years and can produce serious reactions during the second transfusion.

Inheritance of Rh Antigens

- The Rh antigen (D antigen) is inherited as dominant gene D. When gene D is absent from a chromosome, its place is occupied by the alternate form (allelomorph) called 'd' Rh gene, which is inherited from both the father and the mother.
- An Rh +ve individual may have two genotypes: DD (homozygous) or Dd (heterozygous). Of 85% Rh +ve individuals, about 35% have DD genotype and 50% have Dd genotype.
- The genotype of an Rh −ve individual is dd.
- Therefore, the genotype (gene composition) of offspring will be as follows:
  - DD, when gene D is carried by both sperm and ovum
  - Dd, when one gamete carries D and other d
  - dd, when both the gametes carry gene d

  Inheritance of Rh antigen is summarized in Fig. 3.6-2.

Haemolytic Disease of Newborn

Haemolytic disease of newborn occurs as a result of incompatibility of Rh blood groups between the mother and the fetus.

IMPORTANT NOTE

It is important to note that incompatibility of ABO blood groups between the mother and fetus is very common, but there is seldom any complication because the α and β agglutinins, i.e. antibodies against antigen A and B, are of IgM type, which cannot cross the placental barrier.

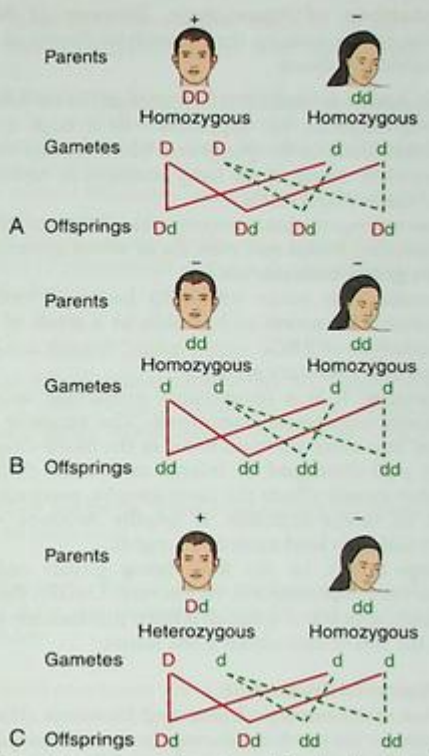


Figure 3.6-2 Inheritance of Rh antigen: (A) when the father is homozygous Rh +ve and mother is homozygous Rh −ve, then all the offspring are heterozygous Rh +ve; (B) when the father and mother both are homozygous Rh −ve, then all the offspring are homozygous Rh −ve; and (C) when the father is heterozygous Rh +ve and mother is homozygous Rh −ve, then 50% of the offspring are Rh +ve (heterozygous) and the remaining 50% are Rh −ve (homozygous).

Mechanism of Haemolytic Disease of Newborn in Rh Incompatibility Mechanism of development of haemolytic disease of the newborn can be described under the following steps:

1. Entrance of Rh +ve Fetal RBCs into Rh −ve Mother's Circulation during First Pregnancy When an Rh −ve mother (genotype dd) bears an Rh +ve child (genotype Dd) with father being Rh +ve (genotype DD or Dd) at the time of delivery, the fetal RBCs enter maternal circulation because of severance of the umbilical cord. Before delivery, usually the fetal and maternal circulation do not mix. Rh +ve RBCs enter maternal circulation during delivery, so the first child is usually normal.

2. Production of Rh Antibodies (anti-D) in Mother During the postpartum period, i.e. within a month after delivery, the mother develops Rh antibodies in her blood. As mentioned earlier, the Rh antibodies are of IgG type and are able to cross the placental barrier. Once formed, the Rh antibodies persist for a long period in the mother's blood.

3. Rh Incompatibility Reaction during Second Pregnancy When the Rh −ve mother in the second pregnancy also bears an Rh +ve child, the Rh antibodies present in the mother's blood enter the fetal circulation by crossing the placental barrier and cause agglutination of fetal RBCs, leading to a haemolytic disease of the newborn.

Manifestations of Haemolytic Disease of Newborn

Depending on the severity, the haemolytic disease of newborn may manifest as follows:

1. **Erythroblastosis fetalis:** It is characterized by the following:
   - *Erythroblastosis*, i.e. appearance of a large number of erythroblasts in the peripheral blood, occurs as the haemopoietic tissue of the baby attempts to rapidly replace the haemolysed RBCs.
   - *Anaemia* occurs due to excessive haemolysis of RBCs by Rh antibodies. Infant may even die of severe anaemia.
2. **Icterus gravis neonatorum**
   - *Jaundice* may occur within 24 hours of birth due to excessive formation of bilirubin as a result of excessive haemolysis of RBCs.
   - *Liver and spleen* are enlarged.
3. **Kernicterus:** It is a neurological syndrome occurring in newborns with severe haemolysis. The excessive bilirubin formed may enter the brain tissue as the blood–brain barrier is not well developed in infants and cause damage. The bilirubin mostly affects the basal ganglia, producing disturbance of motor activities. It usually develops when the serum bilirubin level exceeds 18 mg/dL.
4. **Hydrops fetalis**, i.e. the fetus being grossly oedematous, occurs when haemolysis is very severe. Usually, there occurs intrauterine death of fetus, or if born prematurely or even at term, the infant dies within a few hours.

Prevention and Treatment

Prevention of Haemolytic Disease of Newborn The haemolytic disease in the newborn during the second pregnancy can be prevented by injecting a single dose of Rh antibodies (anti-D) in the form of Rh-immunoglobulin to the mother soon after child birth. These antibodies will destroy the Rh +ve RBCs of the fetus, which have gained access to maternal circulation. In this way, active antibodies will not be formed by the mother.

Treatment of Haemolytic Disease of Newborn Treatment of haemolytic disease of the newborn is replacement of the baby's Rh +ve blood with Rh −ve blood through exchange transfusion.

Clinical Applications of Blood Grouping

1. In Blood Transfusion Before blood transfusion, cross-matching is always done; blood grouping, however, does help in narrowing down the choice of compatible blood.

2. In Preventing Haemolytic Disease in newborn due to Rh incompatibility (as discussed above).

3. In Paternity Disputes The ABO, Rh and MNS blood grouping is helpful in settling cases of disputed paternity. Antigens A and B are dominant, whereas O is recessive. It is possible to prove that a person could not have been the father but not that he was or is father, e.g.:

- If the child's blood group is O, whatever the blood group of the mother, a person with blood group AB cannot be the father.
- If the child's blood group is AB, whatever the blood group of the mother, a person with blood group O cannot be the father (Table 3.6-3). DNA fingerprinting can prove or disprove fatherhood with 100% certainty.

TABLE 3.6-3 Predictive Blood Groups of Parents in Paternity Disputes

Blood Group of the Child	Parents Must Have Given Blood Group	Mother's Blood Group	Father Not Have Been of Blood Group
O	O + O	No matter which	AB
AB	A + B	No matter which	O
A	A + O or A + A	B or O	B or O
B	B + O or B + B	A or O	A or O

Note: The child's true ABO typing may not be set until 1 year of age.

4. In Medicolegal Cases Any red stain on clothing may be claimed to be blood by a supposed victim. Therefore, it is first confirmed that it really is blood by preparing hemin crystals from the stain extract.

5. In Knowing Susceptibility to Diseases The incidence of certain diseases is related to blood groups, e.g.:

- Individuals with blood group O (nonsecretors) are said to be more susceptible to duodenal ulcer (peptic ulcer) than the individuals with blood groups A and B (secretors).
- Individuals with blood group A are more susceptible to carcinoma of stomach, pancreas and salivary glands.
- To some extent, incidence of diabetes mellitus is more in individuals with blood group A.

BLOOD TRANSFUSION

Indications

Blood transfusion is a life-saving measure and should be carried out only when it is absolutely essential. Common situations in which blood transfusion is indicated are as follows:

1. Blood Loss Severe blood loss is the most important indication for blood transfusion.

2. For Quick Restoration of Haemoglobin in patients with severe anaemia, which is required in situations like pregnancy and emergency surgery.

3. Exchange Transfusion It is required in haemolytic disease of newborn.

4. Blood Diseases Blood diseases like aplastic anaemia, agranulocytosis, leukaemias, haemophilia, purpura and clotting defects may require blood transfusion.

5. Acute Poisoning, e.g. carbon monoxide poisoning.

Donor and Recipient

Donor refers to a person who donates the blood, and the person who receives blood is a recipient.

Universal Donor Blood of the individuals with blood group O does not contain any agglutinogen. So, when this blood is transfused to a person with any blood group (A, B, AB or O), theoretically, its RBCs will not be agglutinated. Because of this fact, an individual with blood group O is called a universal donor. However, practically, this term is no longer valid, as it ignores the complications produced by existence of Rh factor and other blood group systems.

Universal Recipient Blood of an individual with blood group AB does not contain any agglutinins. So, theoretically, when such an individual receives blood from an individual with any blood group (A, B, AB or O), there should be no transfusion reaction. Because of this fact, an individual with blood group AB is called a universal recipient. However, practically, this term is no more valid because it ignores the complications produced by the existence of Rh factor and other blood group systems.

Precautions to be Observed during Blood Transfusion

1. Absolute Indication should always be there for the transfusion of blood.

2. Cross-matching should always be done before the blood transfusion. For it, the blood is collected from the donor as well as the recipient. Plasma and RBCs are separated in each. The cross-matching involves two steps: major and minor cross-matching.

- *Major cross-matching involves mixing of the donor's cells with recipient's plasma*: This is called major cross-matching because of the fact that when mismatched blood is transfused in a recipient, the donor's cells get agglutinated, as against their agglutinogen there is a sufficiently high concentration of agglutinins present in the recipient's plasma.
- *Minor cross-matching involves mixing of recipient's cells with donor's plasma*: This is called minor cross-match due to the fact that the reaction of the donor's plasma and recipient's cells usually does not occur or is very, very mild on giving mismatched blood transfusion because of the following:
  - Firstly, the donor's plasma in the transfusion (about 250 mL) is usually so diluted by the much larger volume of the recipient's blood (about 5 L) that it rarely causes agglutination even when the titre of agglutinins against the recipient's cell is high.
  - Secondly, the donor's agglutinins are also neutralized by soluble agglutinogen, which is found free in the recipient's body fluid.

3. Rh +ve Blood Should Never be Transfused to an Rh −ve Person It is particularly essential for females of any age before menopause because once she is sensitized by the Rh antigen the anti-D antibodies are formed, and she will not be able to bear an Rh +ve fetus. In other words, Rh +ve transfusion may make a woman permanently childless.

4. Donor's Blood Should Always be Screened for diseases which are spread through blood, such as AIDS, hepatitis B, malaria and syphilis.

5. Blood Bag/Bottle Should be Checked for the name of recipient and blood group on the label before starting blood transfusion.

6. Blood Transfusion Should be done at a Slow Rate If the transfusion is rapid, the citrate present in stored blood may cause chelation of calcium ions, leading to decreased serum calcium level and tetany.

7. Proper Aseptic Measures must be taken during transfusion of blood.

8. Careful Watch on the Recipient's Condition is must for the first 10–15 minutes of starting the transfusion and then periodically later.

Autologous Blood Transfusion

Autologous blood transfusion refers to transfusion of an individual's own blood, which has been withdrawn and stored. Autologous transfusion is done under the following situations:

For Elective Surgery, a self-predonation is a common practice in some hospitals.

During Surgery, the cell-saver machine when used sucks up the blood from the wound, recycles it and returns it to the patient's body.

Some Sportspersons are also known to sue autologous transfusion a few days before an important event to enhance their performance.

SELF-ASSESSMENT

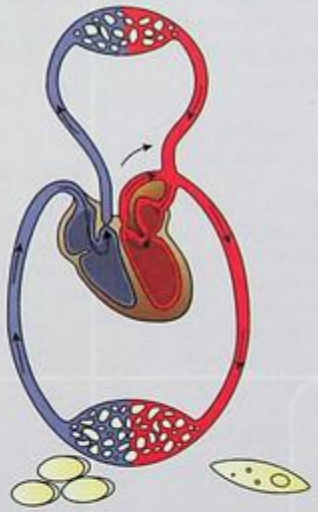
1. Describe briefly the basis of ABO grouping.
2. Describe briefly the basis of Rh grouping.
3. Write notes on:
   - Landsteiner's law
   - Rh incompatibility
   - Significance of blood groups
   - Kernicterus
   - Hydrops fetalis
   - Autologous blood transfusion
   - Haemolytic disease of newborn
   - Cross-matching
   - Precautions during blood transfusion

SECTION 4

Cardiovascular System

SECTION OUTLINE

4.1 Functional Anatomy of Heart and Physiology of Cardiac Muscle
4.2 Origin and Spread of Cardiac Impulse and Electrocardiography
4.3 Heart as a Pump: Cardiac Cycle, Cardiac Output and Venous Return
4.4 Dynamics of Circulation: Pressure and Flow of Blood and Lymph
4.5 Cardiovascular Regulation
4.6 Regional Circulation
4.7 Cardiovascular Homeostasis in Health and Disease



The cardiovascular system (CVS) consists of the heart and the blood vessels. The *heart* acts as a system of two pumps working in series and forms the driving force for blood flow. The blood vessels that take blood from the heart to various tissues are called arteries. The smallest arteries are called *arterioles*. Arterioles open into a network of *capillaries* which constitute the microcirculation. The most important function of blood vessels, i.e. the rapid exchange of materials between the blood and extracellular fluid bathing the tissue cells is served by the capillaries. In other words, capillaries serve as the *exchange region*. In some situations, capillaries are replaced by slightly different vessels called *sinusoids*. Blood from capillaries (or from sinusoids) is collected by small *venules* which join to form *veins*. Veins serve as the blood reservoir and return the collected blood to the heart.

Functions of Cardiovascular System

Primary functions of the CVS are as follows:

1. Distribution of nutrients and oxygen (O_2) to all body cells
2. Collection of waste products and CO_2 from different body cells, and to carry them to excretory organs for excretion

Secondary functions that are subserved by the CVS are as follows:

1. Thermoregulation
2. Distribution of hormones to the target tissues
3. Delivery of antibodies, platelets and leucocytes to aid body defence mechanism

Physiology of Cardiovascular System

Physiology of CVS includes various aspects of physiology of heart as a pump and physiology of two principal divisions of blood circulation—the pulmonary and systemic circulation.

- The heart consists of two pumps in series (right and left halves) that are connected by pulmonary and systemic circulation.
- In systemic circulation the various systemic organs receive blood through parallel distribution channels. The parallel arrangement of vessels supply the body organs with blood of the same arterial composition (i.e. same O_2 and CO_2 tension, pH, glucose level) and essentially the same arterial pressure.
- The pulmonary and systemic circulation divisions are arranged in series, so both ventricles must pump the same amount of blood over any significant time period. Such a balanced output is achieved by an intrinsic property of cardiac muscle known as *Frank–Starling* mechanism.

4.1 Functional Anatomy of Heart and Physiology of Cardiac Muscle

CHAPTER OUTLINE

Functional Anatomy of Heart
Chambers of Heart
Valves of Heart
Structure of the Walls of Heart
Physiology of Cardiac Muscle
Structural Organization of Cardiac Muscle
Structure of a Cardiac Muscle Fibre
Sarcotubular System
Process of Excitability and Contractility
Electrical Potentials in Cardiac Muscle
Excitation–Contraction Coupling Phenomenon in Cardiac Muscles
Process of Cardiac Muscle Contraction
Relaxation of Cardiac Muscle
Properties of Cardiac Muscle
Excitability
Contractility

FUNCTIONAL ANATOMY OF HEART

The heart is a muscular pump designed to ensure the circulation of blood through the tissues of the body. The human heart weighs approximately 300 g and consists of two halves, right and left. The right heart circulates blood through the lungs for the purpose of oxygenation (i.e. through pulmonary circulation). The left heart circulates blood to the tissues of the entire body (i.e. through the systemic circulation).

Chambers of Heart

Each half of the heart consists of an inflow chamber called the *atrium* and an outflow chamber called the *ventricle* (Fig. 4.1-1). Thus, there are four chambers in the heart.

Atria

Interatrial septum separates the right and left atria which are thin-walled chambers.

Right atrium receives deoxygenated blood from the tissues of the entire body through the *superior and inferior vena cavae*. This blood passes into the right ventricle through the right *atrioventricular orifice*, which is guarded by a *tricuspid valve*. The right atrium has got the pacemaker known as *sinoatrial (SA) node* that produces cardiac impulses and *atrioventricular (AV) node* that conducts these impulses to the ventricles.

Left atrium receives oxygenated blood from the lungs through the four *pulmonary veins* (two right and two left). This blood passes into left ventricle through the *left atrioventricular orifice*, which is guarded by the mitral valve.

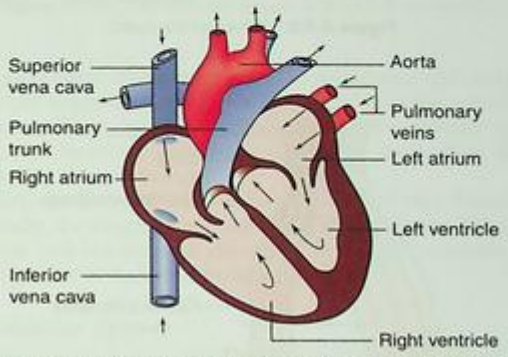


Figure 4.1-1 Schematic diagram of the heart to show its chambers.

Ventricles

Interventricular septum separates the right ventricle from the left ventricle.

Right ventricle receives blood from the right atrium and pumps through the pulmonary trunk (which divides into right and left pulmonary arteries) into the lungs. The *pulmonary valve* is present at the junction of right ventricle and pulmonary trunk.

Left ventricle receives blood from the left atrium and pumps out into systemic circulation through the aorta. *Aortic* valve is present at the junction of left ventricle and the *ascending aorta*.

Valves of Heart

There are four valves in a human heart, two AV valves and two semilunar valves. Valves allow unidirectional flow of blood.

Atrioventricular Valves The AV valves open towards the ventricles and close towards the atria. They allow blood to flow from atria to ventricles. But when ventricles contract, they remain closed and thus prevent backflow of blood from ventricles to atria.

- The ***right AV valve*** is known as *tricuspid valve* and is made of three cusps: anterior, posterior and septal (Fig. 4.1-2).
- The ***left AV valve*** is called *mitral valve* or *bicuspid valve* and is made of two cusps: anterior and posterior (Figs 4.1-2 and 4.1-3).
- At the periphery the cusps (flaps) of the AV valves are attached to the *AV ring*, which is the fibrous connection between the atria and ventricles. The free edges of the cusps are attached to

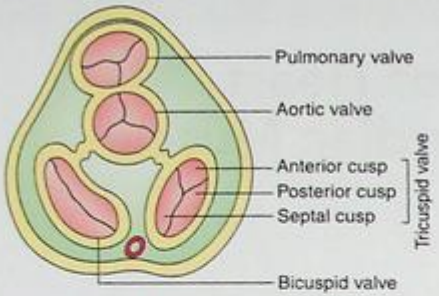


Figure 4.1-2 Valves of the heart.

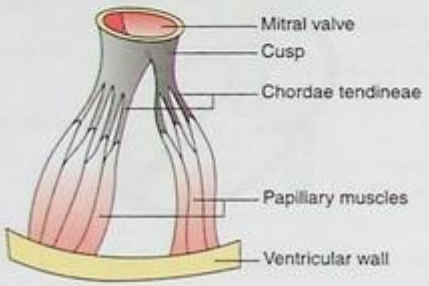


Figure 4.1-3 Bicuspid valve attached with papillary muscles and chordae tendineae.

the *papillary muscles* through the cord-like structures called the *chordae tendineae* (Fig. 4.1-3).

- ***Papillary muscles*** arise from the inner surface of ventricles and contract when the ventricular walls contract. They prevent the bulging of the valves into the atria when ventricles contract.

Semilunar Valves

- ***Semilunar valves open*** away from the ventricles and close towards the ventricles. These valves open when ventricles contract allowing the blood to flow from the left ventricle to aorta and from the right ventricle to the pulmonary trunk.
- ***Semilunar valves*** close when ventricles relax, thus preventing backflow of blood from aorta or pulmonary trunk into the ventricles.
- ***Aortic valve*** is the semilunar valve present at the opening of aorta in the left ventricle. It is made of three semilunar cusps: one anterior and two posterior (Fig. 4.1-2).
- ***Pulmonary valve*** is the semilunar valve present at the opening of pulmonary trunk into the right ventricle. It is also made of three semilunar cusps: one posterior and two anterior (Fig. 4.1-2).

Structure of the Walls of Heart

Walls of the heart are composed of thick layer of cardiac muscle, the *myocardium* (see page 111), covered externally by the epicardium and lined internally by the *endocardium*.

- Walls of the atrial portion of the heart are thin.
- Walls of the ventricular portion of the heart are thick.

Skeleton of the heart consists of fibrous rings that surround the AV, pulmonary and aortic orifices, and are continuous with the membranous part of the ventricular septum.

Pericardium Pericardium consists of two layers: outer fibrous and inner serous (Fig. 4.1-4).

Fibrous pericardium surrounds the heart like a bag and is attached with the surrounding structures.

Serous pericardium has parietal and visceral layers. The *parietal layer* of serous pericardium lines the fibrous pericardium and is reflected around the roots of the great vessels to become continuous with the *visceral layer of serous pericardium* that closely covers the heart and is often called the *epicardium*. The slit-like space between the parietal and the visceral layers of the serous pericardium is called *pericardial cavity*, which contains small amount of *pericardial fluid* that acts as a lubricant to facilitate movement of the heart.

Myocardium The myocardium (muscular tissue of the heart) is the principal tissue constituting the walls of the heart. It consists of three types of muscle fibres:

- ***Cardiac muscles*** forming the walls of the atria and ventricles.
- ***Muscle fibres*** forming the *pacemaker*, which is the site of origin of cardiac impulse.
- ***Muscle fibres*** forming the conducting system which transmits the impulse to the various parts of the heart.

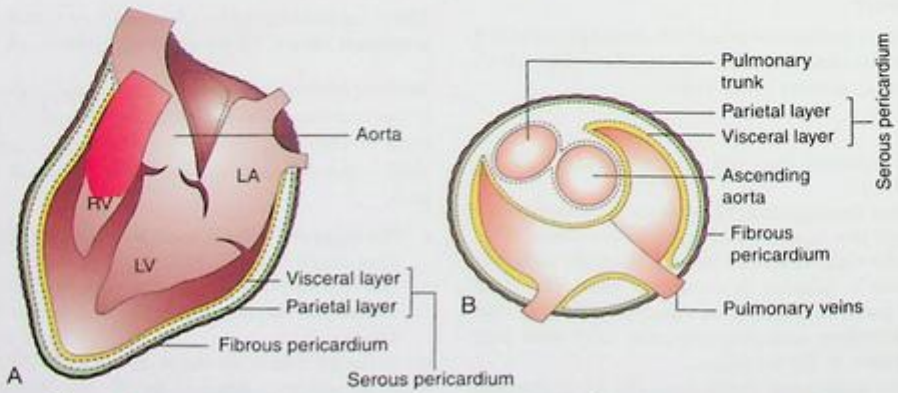


Figure 4.1-4 Schematic sagittal section of the heart showing fibrous and serous pericardium.

Endocardium Endocardium is thin, smooth and glistening membrane lining the myocardium internally. It consists of a single layer of endothelial cells. The endocardium continues as the endothelium of great vessels opening in the heart.

PHYSIOLOGY OF CARDIAC MUSCLE

Structural Organization of Cardiac Muscle

- The cardiac muscle fibres are *striated* and resemble quite a lot to the skeletal muscle fibres in structure. However, unlike the skeletal muscles, the cardiac muscles are *involuntary* (like smooth muscles). Thus, cardiac muscles share some characteristics with the skeletal muscles and others with the smooth muscles.
- The cardiac muscle fibres are *ribbon-like* rather than cylindrical. These are *branched* and interdigitate freely with each other, but each fibre is a completely separate unit. The branches from the neighbouring fibres join together. At the point of contact of two muscle fibres, the membranes of both the muscle fibres are fused together and thrown into an extensive infolding forming the so-called *intercalated disc* (Fig. 4.1-5). These discs form tight junctions between the muscle fibres and do not allow the ions to pass through. However, the intercalated discs provide a strong union between fibres and thus play an important role during the contraction of muscle fibres by transmitting pull of one contractile unit along its axis to the next, thereby increasing force of contraction.
- Along the sides near the outer border of intercalated disc, the two adjacent muscle fibres are connected with each other through the *gap junctions*. The action potential passes from one cardiac muscle cell to the other through gap junctions, which provide *low-resistance bridges* and thus the cardiac muscle acts as *a functional syncytium* of many cardiac cells. In this way, the cardiac impulse spreads throughout the muscle mass quickly resulting in a coordinated contraction of the whole tissue. In the heart, the cardiac muscle forms two separate syncytia, i.e. the *atrial syncytium* (walls of two atria) and the *ventricular syncytium* (walls of the two ventricles). Action potential is conducted from the atrial syncytium to the ventricular syncytium by way of specialized conducting system. Each syncytium obeys all-or-none law. The atrial and the ventricular syncytium are two separate syncytia; therefore, atria contract a short time ahead of the ventricular contraction.
- The cardiac muscle fibres are richly supplied by the capillaries (one capillary/fibre).

Structure of a Cardiac Muscle Fibre

Each muscle fibre is about 80 μm long and about 15 μm broad. Its cell membrane is called *sarcolemma* and the cytoplasm is called *sarcoplasm*. The sarcoplasm is in abundance and contains all the cell organelles, a well-developed sarcoplasmic reticulum and a centrally placed nucleus. Each muscle fibre is made up of number of *myofibrils*, which lie parallel to each other. Each myofibril is 2 μm is diameter.

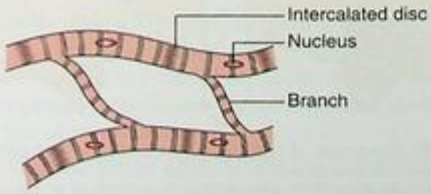


Figure 4.1-5 Structure of cardiac muscle.

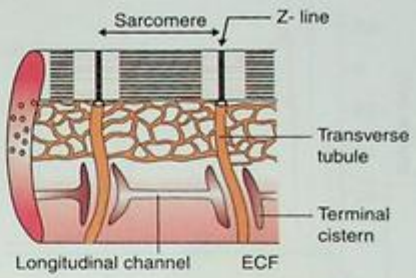


Figure 4.1-6 Sarcotubular system in the cardiac muscle.

Myofibril. Each myofibril consists of thick and thin filaments. Essentially, the structure and striations as seen under light microscope and the detailed electron microscopic structure are similar to that of a skeletal muscle (see page 42).

Sarcotubular System

The sarcotubular system in the cardiac muscles is well developed like that of the skeletal muscle. However, the tubules of the T-system penetrate the sarcomere at Z line (Fig. 4.1-6). Therefore, in cardiac muscles, there is only one triad per sarcomere as compared to two in skeletal muscle (page 43).

Process of Excitability and Contractility: An Electromechanical Phenomenon

The cardiac muscle being an excitable tissue produces an action potential *(electrical phenomenon)* when stimulated and responds by contracting.

Electrical Potentials in Cardiac Muscle

Resting Membrane Potential The resting membrane potential of a normal cardiac muscle fibre is −85 to −95 mV (negative interior with reference to exterior).

Action Potential When stimulated, each cardiac muscle fibre shows an electrical activity known as propagated action potential.

The action potential recorded from a single cardiac muscle fibre is unusually long and can be divided into five distinct phases (Fig. 4.1-7).

Phase 0: Rapid Depolarization. Phase 0 (upstroke) is characterized by the depolarization which proceeds rapidly, an overshoot is present, as in skeletal muscle and nerve. In mammalian heart, depolarization lasts about 2 ms. In this phase, amplitude of potential reaches up to +20 to +30 mV (positive interior with reference to exterior).

Ionic basis. The initial rapid depolarization and the overshoot are due to the rapid opening of voltage-gated Na^+ channels and rapid influx of Na^+ ions similar to that occurring in the nerve and the skeletal muscle.

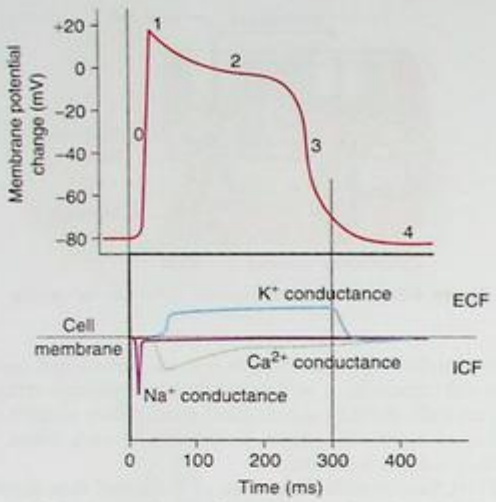


Figure 4.1-7 Various phases of action potential and ion conductance: phase 0, depolarization; phase 1, rapid repolarization; phase 2, plateau phase; phase 3, late rapid repolarization and phase 4, resting potential.

At −30 to −40 mV membrane potential the calcium channels also open up and influx of Ca^{2+} ions also contributes in this phase.

Phase 1: Initial Rapid Repolarization. Rapid depolarization is followed by a very short-lived, slight, rapid repolarization. The membrane potential reaches from +30 to −10 mV during this phase.

Ionic basis. The initial rapid repolarization is due to closure of Na^+ channels and opening of K^+ channels resulting in transient outward current.

Phase 2: Plateau. During plateau phase, the cardiac muscle fibre remains in the depolarized state. The membrane potential falls very slowly only to −40 mV during this phase. The plateau lasts for about 100−200 ms. This plateau in action potential explains the 5–15 times longer contraction time of the cardiac muscle as compared to skeletal muscle.

Ionic basis. Very slow repolarization during the plateau phase is due to:

- Slow influx of Ca^{2+} ions resulting from opening of sarcolemmal *L-type* Ca^{2+} channels.
- Closure of a distinct set of K^+ channels called the inward rectifying K^+ channels.

Phase 3: Repolarization. During this phase, complete repolarization occurs and the membrane potential falls to the approximate resting value −80 mV. This phase lasts for about 50 ms.

Ionic basis. The slow repolarization results from the closing of Ca^{2+} channels and opening of following two types of K^+ channels:

- *Delayed outward rectifying* K^+ channels, which are voltage-gated and are activated slowly.
- Ca^{2+} *activated channels*, which are activated by the elevated sarcoplasmic Ca^{2+} levels.

Phase 4: Resting Potential. In this phase of resting membrane potential (also called polarized state) the potential is maintained at −90 mV by activation of Na^+–K^+ ATPase pump.

Duration of Action Potential. The duration of action potential is about 250 ms at a heart rate of 75 beats/min. The duration of action potential decreases with increased heart rate (150 ms at a heart rate of 200 beats/min). This type of action potential found in contractile myocardial cells of the ventricles is referred to as *fast response.*

Spread of Action Potential through Cardiac Muscle. The cardiac muscle acts as a physiological syncytium due to the presence of gap junctions amongst the cardiac muscle fibres. Because of this the action potential spreads through the cardiac muscles very rapidly. Furthermore, as there are two syncytia (the atrial and the ventricular) in the heart, so the action potential is transmitted from atria to ventricles only through the fibres of specialized conductive system.

Excitation–Contraction Coupling Phenomenon in Cardiac Muscles Excitation–contraction coupling refers to the sequence of events by which an excited plasma membrane of a muscle fibre leads to cross-bridge activity by increasing sarcoplasmic calcium concentration.

The sequence of events during excitation–contraction coupling in the cardiac muscle is similar to those observed in a skeletal muscle (see page 44) with the following exception:

In cardiac muscle (as against that in skeletal muscle), extra calcium ions diffuse into the sarcoplasm from T-tubules (Fig. 4.1-8) without which the contraction strength would be considerably

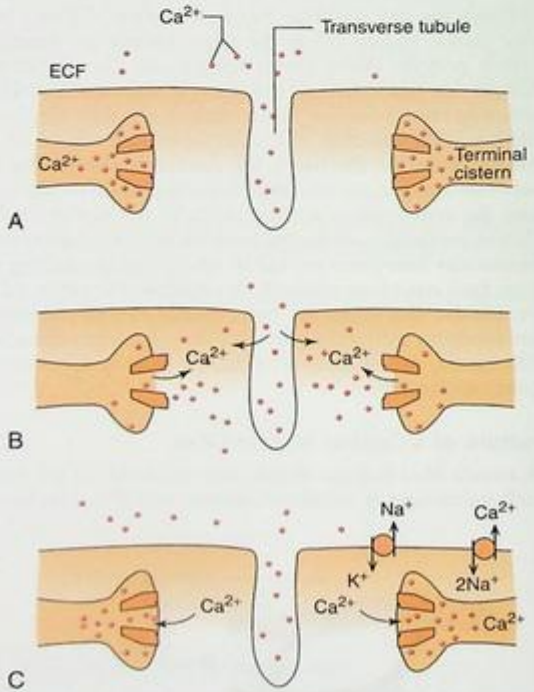


Figure 4.1-8 Dynamics of Ca^{2+} during excitation–contraction coupling phenomenon and relaxation in cardiac muscle: (A) in resting state; (B) calcium-induced calcium release during excitation and contraction state; and (C) during relaxation state.

reduced, whereas skeletal muscle contraction is hardly affected by calcium concentration in ECF.

Process of Cardiac Muscle Contraction

The molecular mechanism of cardiac muscles contraction by cross-bridge cycling and sliding of filaments is primarily similar to that of skeletal muscles (page 44) and smooth muscles. However, in cardiac muscle:

- Troponin–tropomyosin complex controls the onset and offset of cross-bridge cycling, similar to that in the skeletal muscles.
- Like smooth muscles, the contractility of cardiac muscle is sensitive to *phosphorylation.*

Relaxation of Cardiac Muscle

Relaxation of cardiac muscle (diastole) occurs when levels of Ca^{2+} ions fall in the cardiac muscle fibres. During diastole, the Ca^{2+} ions are extruded out of the cardiac muscle fibre by a carrier system operating at the sarcolemma in which two Na^+ ions are exchanged for each Ca^{2+} ion extruded (Fig. 4.1-8C). Thus, the rate of Ca^{2+} ion extrusion depends on the gradient of Na^+ created by Na^+–K^+ ATPase.

IMPORTANT NOTE

Digitalis or other cardiac glycosides raises the intracellular Ca^{2+} concentration and thereby increases myocardial contractility by inhibition of this secondary active transport of Ca^{2+} ions. This effect is utilized in patients with congestive heart failure.

Properties of Cardiac Muscle

The basic properties of a cardiac muscle include:

- Automaticity
- Rhythmicity (chronotropism)
- Conductivity (dromotropism)
- Excitability (bathmotropism)
- Contractility (inotropism)

Some of the properties of cardiac muscle, such as automaticity, rhythmicity and conductivity, are discussed in Chapter 4.2 (see page 116).

The characteristics of excitability and contractility are described here.

Excitability

Excitability (bathmotropism) is the property by which tissues respond to stimuli. The cardiac muscle responds by the development of action potential. The essential features of the resting membrane potential and action potential of cardiac muscle have been discussed on page 117.

The characteristic of a cardiac muscle excitability which needs a special emphasis is its refractory period.

Refractory Period Refractory period refers to the period following action potential during which the cardiac muscle does not respond to a stimulus. Cardiac muscle has a long refractory period (250–300 ms in ventricles and about 150 ms in atria). It is of two types.

*1. **Absolute Refractory Period (ARP).*** During this period, the cardiac muscle does not show any response at all. It extends from phase 0 to half of phase 3 of action potential, i.e. until the membrane potential reaches approximately −50 mV during repolarization (Fig. 4.1-9). Normal duration of ARP in the ventricles is about 180–200 ms.

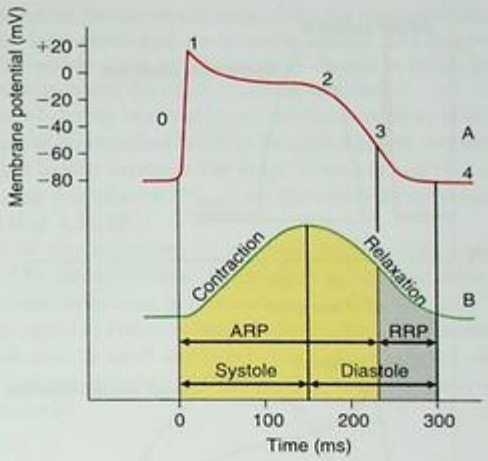


Figure 4.1-9 Record of action potential (A) and mechanical response (B) from the cardiac muscle fibre shown on the same time scale depicting the significance of long refractory period. ARP, absolute refractory period; RRP, relative refractory period.

*2. **Relative Refractory Period.*** During this period, the muscle shows response if the strength of stimulus is increased to maximum. It extends from second half of phase 3 to phase 4 of the action potential. Normal duration of relative refractory period in ventricles is about 50 ms.

Significance of Long Refractory Period in Cardiac Muscle. As shown in Fig. 4.1-9, the cardiac muscle is refractory to any stimulus during the contraction phase (systole); therefore, the complete summation of contractions and thus tetanus cannot be produced in the cardiac muscle. This property is very useful. The heart has to function as a pump, so it must relax, get filled up with blood and then contract to pump out the blood. A tetanized heart would be useless as a pump.

Contractility

Contractility is the ability of the cardiac muscle to actively generate force to shorten and thicken to do work when sufficient stimulus is applied.

Mechanical response in cardiac muscle fibre begins just after the start of depolarization and lasts about 1.5 times as long as the action potential (Fig. 4.1-10B). Thus, the mechanical response (300 ms) overlaps the electrical response (200 ms) for the whole period. This is in contrast to the skeletal muscle, where the mechanical response begins a few milliseconds after the end of repolarization and lasts for 30−50 ms in the mammalian skeletal muscle and 100 ms in the amphibian skeletal muscle (Fig. 4.1-10A).

Characteristic features of myocardial contractility *and factors affecting are as follows:*

- All-or-none law
- Effect of preload
- Effect of afterload

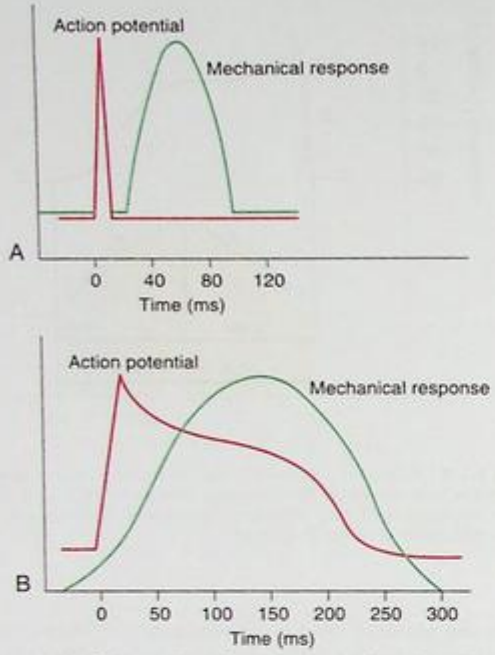


Figure 4.1-10 Relationship of action potential and mechanical response: (A) in skeletal muscle and (B) in cardiac muscle.

1. All-or-None Law The response of a cardiac muscle to a stimulus is all-or-none in character, i.e. when a stimulus is applied either the heart does not contract at all (none response) or contracts to its maximum ability (all response). This is because of the syncytial arrangement of the cardiac muscle fibres. Therefore, the 'all-or-none' law in heart is applicable to whole of functional syncytial unit, i.e. the entire atria or entire ventricle. However, in skeletal muscle it is applicable only to a single-muscle fibre.

2. Effect of Preload A load which starts acting on a muscle before it starts to contract is called *preload*. The preload increases the initial length of the muscle. According to Starling's law, the force of contraction is the function of the initial length of the muscle fibres, and up to physiological limits the greater the initial length, greater is the force of contraction. In the case of heart muscle, the end-diastolic volume forms the preload. The effect of changing end-diastolic volume on force of cardiac contraction has been studied by Frank and Starling in 1910. *The Frank–Starling law of heart* states that within physiological limits the force of cardiac contraction is proportional to its end-diastolic volume.

Length–Tension Relationship. Length–tension relationship, i.e. the relation between the initial fibre length and total tension in cardiac muscle, is basically similar to that in the skeletal muscle. In cardiac muscle, the length–tension relationship graph is plotted with the end-diastolic volume in mL (representing initial length) along the horizontal axis and the pressure developed in the ventricle in mm Hg (representing tension)

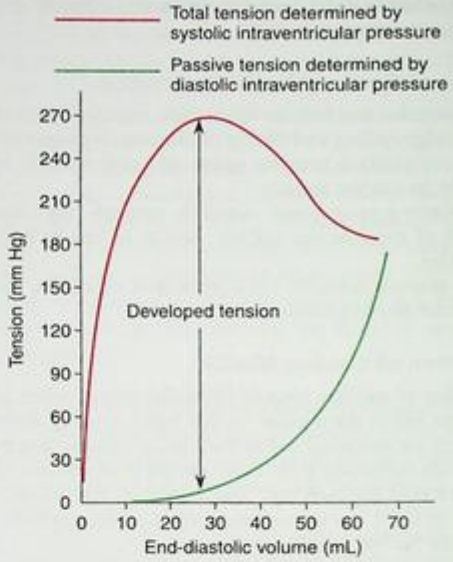


Figure 4.1-11 Length–tension relationship in cardiac muscle.

along the vertical axis (Fig. 4.1-11). The following inferences can be drawn from this graph (Starling's curve).

Diastolic intraventricular pressure represents the passive tension and it increases with the increase in end-diastolic volume (i.e. with the passively increased muscle length). It is important to note that the pressure–volume curve for ventricles in diastole is initially quite flat, indicating that large increase in volume can be accommodated with only a small increase in pressure.

Systolic ventricular pressure represents the active tension developed (isometric tension), which is proportionate to the degree of diastolic filling of the heart (initial length of muscle fibres). The graph (Fig. 4.1-11) shows that the developed tension increases as the diastolic volume increases until it reaches a maximum (ascending limb of Starling curve), then tends to decrease (descending limb of Starling's curve). The descending limb is instead due to the beginning of disruption of the myocardial fibres.

Clinical Significance of the Frank–Starling Law of Heart and its role in control of cardiac output is discussed in Chapter 4.3 'Heart as a Pump' (see page 132).

3. Effect of Afterload Afterload refers to the load which acts on the muscle after the beginning of muscular contraction. The afterload affecting the force of contraction of cardiac muscle is represented by the resistance against which the ventricles pump the blood. The afterload (resistance) for right ventricle is low in pulmonary artery due to its intrathoracic location. The afterload (resistance) for the left ventricle is high in the aorta due to resistance to blood flow through the aortic valves and systemic blood vessels called *peripheral resistance.*

Force–Velocity Relationship. The force–velocity curve is plotted by noting the velocity of muscle contraction with progressively increasing load on the muscle. In the heart, load is represented by the resistance against which the ventricles pump the blood and velocity of muscle contraction is represented by the

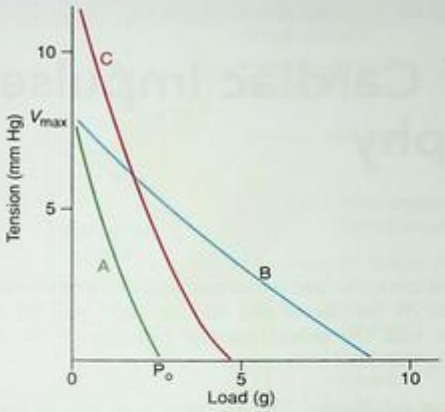


Figure 4.1-12 Force–velocity curve in cardiac muscle (A), effect of change of initial length (B) and effect of catecholamines or increased Ca^{2+} concentration in ECF (C) on it.

stroke output. Following inferences can be drawn from the force–velocity curve (Fig. 4.1-12A).

- When the load is zero, the muscle contracts rapidly and the velocity of muscle shortening is maximum (V_{max}).
- As the load increases progressively, the velocity of shortening decreases till it reaches zero. At this point, force developed is called maximum isometric force and is represented by P_o.

Therefore, during muscle contraction the velocity of shortening and force developed are inversely related. The force–velocity relationship curve is influenced by change in initial length of the muscle and the effect of catecholamines.

Effects of change in initial length on force–velocity relationship curve. An increase in change in the initial length (within physiological limits) increases the force of contraction (P_o) without changing the velocity (V_{max}), i.e. the relationship shifts to the right (Fig. 4.1-12B).

Effect of catecholamines or increased calcium concentration in ECF. The catecholamines or increased Ca^{2+} concentration in ECF both cause an increase in P_o as well as V_{max} (Fig. 4.1-12C).

Significance of Force–velocity Relationship. The cardiac muscle can alter its work and power (rate of working) at any given load and muscle length by nature of its changing force–velocity relationship.

SELF-ASSESSMENT

1. Draw a well-labelled diagram to show phases of action potential of cardiac muscle fibre and their ionic basis.
2. Describe briefly the Starling law of heart and its significance.
3. Describe briefly:
   - The property of refractory period and its significance in cardiac muscle
   - All-or-none law

4.2 Origin and Spread of Cardiac Impulse and Electrocardiography

CHAPTER OUTLINE

Origin and Spread of Cardiac Impulse
Introduction
Anatomic Consideration
Conducting System of the Heart
Innervational Characteristics of the Heart
Mechanism of Origin of Rhythmic Cardiac Impulse
Pacemaker
Electrical Potential in Pacemaker Tissue
Role of Autonomic Nervous System in Controlling Heart Rhythm
Spread of Cardiac Impulse

Heart Rate
Factors Affecting Heart Rate
Regulation of Heart Rate

Electrocardiography
Introduction
Recording of ECG
ECG Leads
Electrocardiograph
Normal Electrocardiogram
Waves of ECG
Intervals and Segments of ECG
Characteristic Features of ECG Complex in Unipolar Chest Leads and Limb Leads
Clinical Applications of ECG

ORIGIN AND SPREAD OF CARDIAC IMPULSE

Introduction

The cardiac muscle possesses special properties which include autorhythmicity, conductivity, excitability and contractility.

Autorhythmicity refers to the property of the cardiac muscle which enables the heart to initiate its own impulse at constant rhythmical intervals. Because of this property, the heart continues to beat even after all nerves to it are sectioned. This is because of the presence of a specialized *pacemaker tissue* in the heart that can initiate repetitive action potentials. The pacemaker tissue makes a *conduction system* that normally spreads impulses through the heart.

Anatomic Consideration

Conducting System of the Heart

The conducting system of the heart consists of specialized fibres of the heart muscle present as the sinoatrial (SA) node, the interatrial tract, the internodal tracts, the atrioventricular (AV) node, the AV bundle of His and its right and left terminal branches, and the subendocardial plexuses of the Purkinje fibres (Fig. 4.2-1).

1. Sinoatrial Node. The SA node is located in the wall of right atrium, just right to the opening of superior vena cava. Spontaneous rhythmical electrical impulses arise from the SA node and spread in all directions to:

- Cardiac muscles of atria
- Interatrial tract to left atrium
- Internodal tracts to AV node

2. Interatrial tract (Bachman's Bundle). It is a band of specialized muscle fibres that run from the SA node to the left atrium. It causes simultaneous depolarization of the atria.

3. Internodal Conduction Pathway. Three internodal conduction paths have been described as follows (Fig. 4.2-2):

- *Anterior internodal pathway of Bachman*
- *Middle internodal pathway of Wenckebach*
- *Posterior internodal pathway of Thorel*

4. Atrioventricular (AV) Node. The AV node is located just beneath the endocardium on the right side of lower part of the atrial septum, near the tricuspid valve. It is stimulated by the excitation wave that travels through the internodal tracts and the atrial myocardium. From it, the cardiac impulse is conducted to the ventricles by the AV bundle.

5. Atrioventricular Bundle of His. The AV bundle arises from the AV node, descends through the fibrous skeleton of the heart and divides into right bundle branch for the right ventricle and the left bundle branch for the left ventricle. The branches break up and become continuous with the plexus of Purkinje fibres.

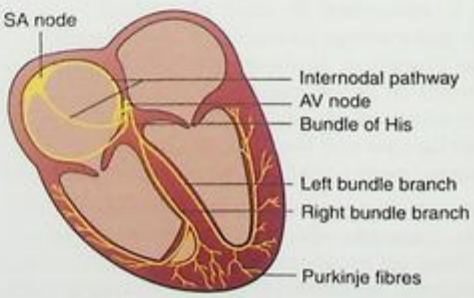


Figure 4.2-1 Specialized conducting tissues of the heart.

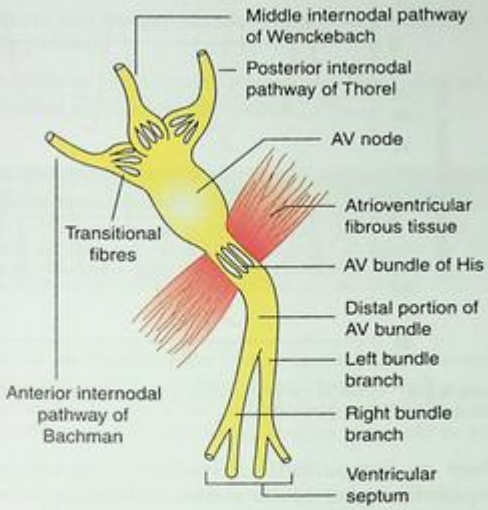


Figure 4.2-2 Internodal conduction pathways.

6. Purkinje Fibres. These are spread out deep to the endocardium and reach all parts of the ventricles including the bases of papillary muscles.

Innervational Characteristics of the Heart

- Both SA node and AV node are richly supplied by the sympathetic as well as the parasympathetic nerves. Parasympathetic fibres come from the vagus nerve and most sympathetic fibres come from the stellate ganglion.
- The SA node is supplied by the right vagus nerve and right-sided sympathetics.
- The AV node is supplied by the left vagus and left-sided sympathetic nerves.

Mechanism of Origin of Rhythmic Cardiac Impulse

Pacemaker

The part of the heart from which rhythmic impulses for heart beat are produced is called *pacemaker.* In mammalian heart, though the other parts of the heart like AV node, atria and ventricle can also produce the impulse but *SA node acts as a pacemaker* because the rate of impulse generation by the SA node is highest. However, when there occurs blockage of transmission of impulse from the SA node to the AV node, the pacemaker activity may shift from the SA node to other sites, e.g. the AV node. When pacemaker is other than the SA node, it is called as *ectopic pacemaker.* Ectopic pacemaker causes abnormal sequence of contraction of different parts of the heart.

Rate of production of rhythmic impulses by different parts of the heart is as follows:

- SA node: 70–80/min
- AV node: 40–60/min
- Atrial muscle: 40–60/min
- Ventricular muscles: 20–40/min

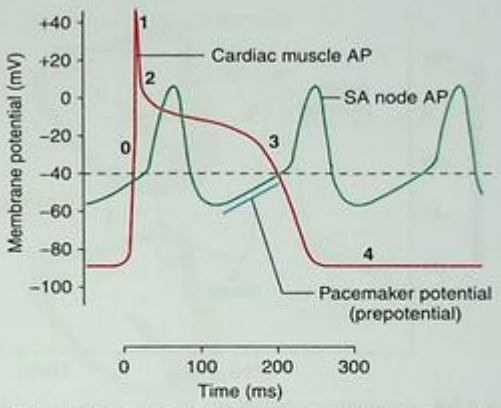


Figure 4.2-3 Phases of action potential in a cardiac muscle fibre (0, 1, 2, 3, 4) and sinoatrial node showing pacemaker potential. AP, action potential.

Electrical Potential in Pacemaker Tissue

The electrical potential in a cardiac muscle (contractile myocardial cells—CMCs) has been described on page 111. As shown in Fig. 4.1-7 in phase 4 of action potential of cardiac muscle (CMC), there exists a constant resting membrane potential of −85 to −90 mV. In pacemaker (SA node) fibres, however, the resting membrane potential is only of −55 to −60 mV, and that this is not steady, i.e. it shows a slow rise in the resting membrane potential due to slow depolarization (Fig. 4.2-3). Due to this slow depolarization the threshold level of −40 mV is reached very slowly. Once the threshold level of −40 mV is reached, there occurs a rapid depolarization up to +5 mV followed by a rapid repolarization, i.e. there occurs action potential and generation of an impulse. After a rapid repolarization (phase 3 of action potential) once again the resting membrane potential (phase 4 of action potential) is reached, which is not stable and starts rising slowly to again reach at threshold level to produce the second impulse. This slow-rising resting membrane potential in between the action potentials is called *prepotential* or *pacemaker* potential (Fig. 4.2-3). Presence of this unique feature in the cells of pacemaker tissue is the underlying mechanism responsible for self-generation of rhythmic impulses (autorhythmicity).

Ionic Basis of Pacemaker Potential and Action Potential in SA Node. The myocardial cells present in the SA node and the AV node are called *slow fibres* (Fig. 4.2-4).

- The slow fibres of the pacemaker tissue have a unique feature, i.e. leakage of resting membrane for sodium (whereas the resting membrane of fast fibres is relatively impermeable to Na^+). This causes *slow diffusion of Na^+ into the SA nodal fibres under* resting condition. This slow entry of Na^+ in the cells slowly raises the potential to *−55 mV* (i.e. causes slow depolarization). This slow depolarization forms the initial part of pacemaker potential (Fig. 4.2-4).
- Then the 'T (transient) calcium channels' open up and there is slow influx of Ca^{2+} causing further depolarization in the same at slower rate till a threshold level of −40 mV is reached. Thus, calcium current (Ica) due to opening of 'T calcium channels' forms the later part of the pacemaker potential.

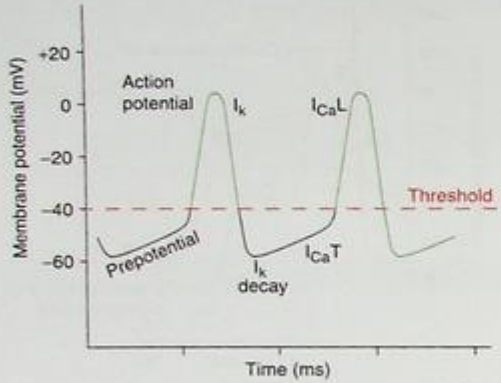


Figure 4.2-4 Pacemaker potential and its ionic basis. $I_{Ca}T$: Ca^{2+} conductance through transient channels; $I_{Ca}L$: Ca^{2+} conductance through long-lasting channels; I_k: potassium conductance.

- At the threshold level (−40 mV) the long-lasting calcium channels open up and the action potential starts with a rapid depolarization due to influx of Ca^{2+}. Thus, it is important to note that the depolarization in SA node is mainly due to influx of Ca^{2+} rather than Na^+. Consequently, the depolarization is not as sharp as in the other myocardial fibres.
- At the end of depolarization, potassium channels open up and calcium channels close. This causes K^+ to diffuse out of the fibres resulting in a rapid repolarization from −55 to −60 mV.
- Again, due to an unique feature of slow fibres of the SA node (i.e. *leakage of resting membrane to* Na^+) the resting potential does not become stable but slow depolarization starts due to slow influx of Na^+ making initial part of prepotential. Ultimately, due to repetition of the above-described steps, another action potential is initiated. In this way, impulses are generated at regular intervals of time *(autorhythmicity)*.

Role of Autonomic Nervous System in Controlling Heart Rhythm

Vagal Tone. SA node is richly innervated by the parasympathetic fibres from the right vagus. Normal activity of vagus liberates acetylcholine from its nerve endings, which increases the permeability of the SA nodal fibres for potassium producing hyperpolarization (due to rapid efflux of K^+). This hyperpolarization slows the firing rate of the SA node from its automatic rate of 90–120 impulses/min to the actual heart rate of about 72 beats/min. The normal vagal activity is called vagal tone.

Effect of Parasympathetic Stimulation. Parasympathetic stimulation causes release of acetylcholine at the vagal nerve endings and by the above described mechanism causes (Fig. 4.2-5A):

- Decrease in the heart rate by decrease in the rate of sinus rhythm and
- Decrease in the rate of transmission of impulses to ventricles due to decreased excitation of the conducting system. Strong parasympathetic stimulation may even completely block the transmission and ventricles may stop beating for 4–10 seconds. If it happens, the Purkinje system initiates the rhythm causing the ventricular contraction at a rate of 15–40/min. This phenomenon is called *vagal escape.*

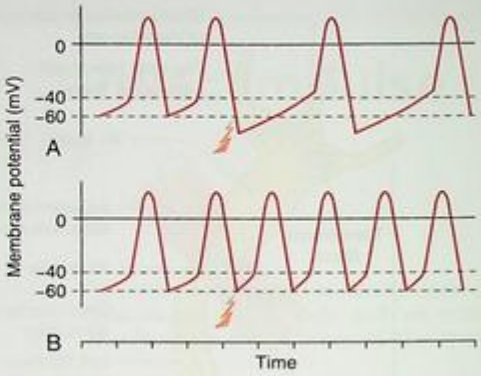


Figure 4.2-5 Effect of parasympathetic (A) and sympathetic (B) stimulation on pacemaker potential.

Effect of Sympathetic Stimulation. Stimulation of the sympathetic nerves causes release of norepinephrine at the nerve endings. Probably, this increases permeability of cardiac muscle fibres to calcium by opening up L calcium channels. This increases the rate of sinus rhythm and rate of conduction of impulse as well as excitability in all the portions of heart. Force of contraction of atria and ventricles also increases greatly (Fig. 4.2-5B).

Spread of Cardiac Impulse

The cardiac impulse which originates in the SA node in the form of action potential spreads throughout the heart through the conduction system (properties of which are summarized in Table 4.2-1) in the sequence given:

SA node and atria. The impulse travels over the muscle fibres of atria from the SA nodal fibres and through the interatrial tract to the left atrium. Conduction through these fibres causes simultaneous depolarization of both the atria. Atrial depolarization is completed in about 0.1 second. The impulse reaches to AV node from SA node within 0.03 second after its origin.

AV node. *Conduction through AV node* is slow, and there is a delay of about 0.1 second. The causes of *AV nodal delay* are given as follows:

- Transitional fibres connecting internodal tracts and the AV node are very small and conduct the impulse at a very slow rate.

TABLE 4.2-1 Properties of the Conduction System

Tissue	Fibres Diameter (μm)	Resting Membrane Potential (mV)	Conduction Velocity (m/s)
SA node	—	–40 to –50	0.05
Atrial muscle	8–10	–70 to –80	0.3–0.5
Interatrial and internodal tract	15–20	–80 to –90	1
AV node	Variable	–50	0.02–0.05
Purkinje fibres	70–80	–70	2–4
Ventricular muscle	10–16	–80	<1

- There are very few gap junctions connecting successive fibres in the pathway.

The ability of the AV node to slow and block the rapid impulse is called *detrimental contraction.*

IMPORTANT NOTE

This *AV nodal delay is useful,* for it provides time for completion of the atrial contraction and their emptying (i.e. ventricular filling), before the ventricles contract.

Ventricular conduction. The impulses conducted through the AV node are distributed to ventricles through bundle of His, its branches and Purkinje fibres in 0.08–0.15 second. In humans, depolarization of the ventricular muscle proceeds as follows (Fig. 4.2-6):

- Starts at the left side of the interventricular septum.
- Moves first to the right across the middle portion of the septum.
- The wave of depolarization then spreads down the septum to apex of the heart.
- It, then, returns along the ventricular walls to the AV groove, proceeding from the endocardial to the epicardial surface.
- The last parts of the heart to be depolarized are the posterobasal portion of the left ventricles, the pulmonary conus and the upper most portion of the septum.

The total time required for conduction from the SA node to the endocardial surface is 0.22 second.

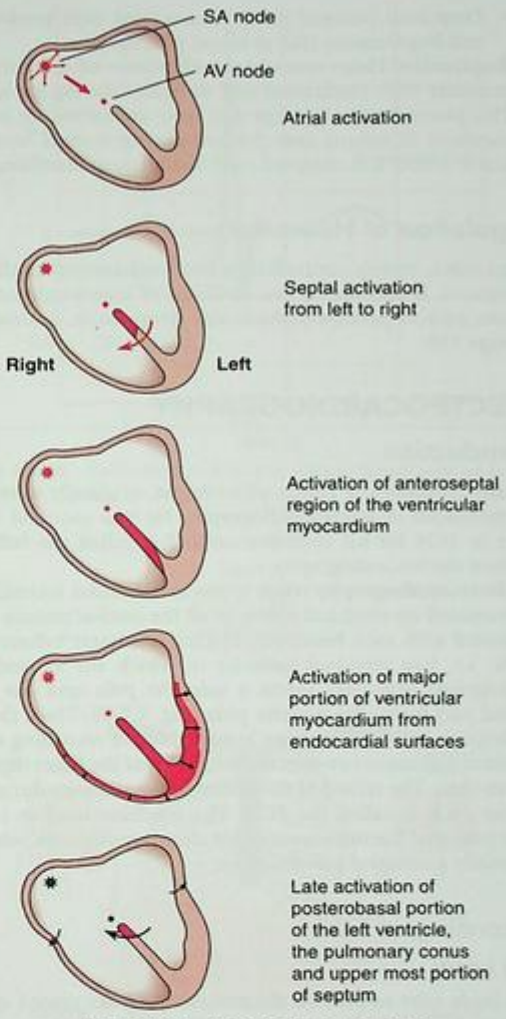


Figure 4.2-6 Spread of cardiac impulse.

HEART RATE

The normal heart rate in an adult male is 70–80 beats/min.

Factors Affecting Heart Rate

The factors that affect heart rate are given as follows:

1. ***Age.*** Heart rate varies with age, i.e. it decreases as the age increases due to increase in the degree of vagal tone. The normal range of heart rate with different age groups is shown in Table 4.2-2.
2. ***Sex.*** In females the resting heart rate is comparatively higher than in males of same age group.
3. ***Temperature.*** Heart rate increases with rise in body temperature. For each 1°F rise in body temperature, the heart rate increases by 10 beats/min.
4. ***Blood pressure.*** Heart rate is inversely related to the arterial pressure; this is referred as *Marey's law.*
5. ***Emotions.*** Tachycardia occurs in emotions such as anxiety, anger and fear. Bradycardia is associated with sudden shock and grief. The emotional effects on heart rate are mediated through corticohypothalamic pathways.
6. ***Exercise.*** During muscular exercise heart rate increases. For details see page 217.
7. ***Painful stimuli***
   - *Superficial pain* causes tachycardia and hypertension (rise in blood pressure).

TABLE 4.2-2 **Heart Rate Values in Relation to Age**

Age	Heart Rate (beats/min)
Birth	140–150
1 month	130–140
1 year	110–115
5 years	105–110
10 years	95–100
15 years	80–85
Adults	70–80
Old age	Up to 100

- *Deep pain* (visceral pain) is associated with bradycardia and hypotension (fall in blood pressure).

8. ***Respiration.*** Heart rate varies with phases of respiration; it increases with inspiration and decreases during expiration. This phenomenon is referred as *sinus arrhythmia*. It is quite common in infants and children during normal breathing but in adults it is observed only during deep breathing.

Regulation of Heart Rate

Heart rate is mainly controlled by two mechanisms: cardiac innervations. It consists of two divisions of autonomic nervous system, such as parasympathetic and sympathetic, as described on page 118.

ELECTROCARDIOGRAPHY

Introduction

Willem Einthoven, a Dutch physiologist, originally developed the technique of electrocardiography. He was awarded Nobel Prize in 1924 for his contribution and is called the father of modern electrocardiography.

Electrocardiography refers to the extracellular recording of the summed-up electrical events of all the cardiac muscle fibres generated with each heartbeat. Electrically, heart behaves as a *dipole*, i.e. two terminal batteries in which the excited part (depolarized segment) forms a negative pole and the non-excited part forms the positive pole (Fig. 4.2-7). Thus, electrocardiogram (ECG) is nothing but the surface recording of the potential difference between the two poles of the heart dipole at a given time. The record of the potential fluctuations during the cardiac cycle is called the *ECG*. The machine used to record these potential fluctuations is called *electrocardiograph*, which is essentially a sensitive galvanometer.

Recording of ECG

ECG Leads

ECG leads refer to the two electrodes which are placed on the body surface and connected to ECG machine for measuring the potential fluctuations between only two points. ECG is recorded using two types of lead systems, the bipolar leads and unipolar leads.

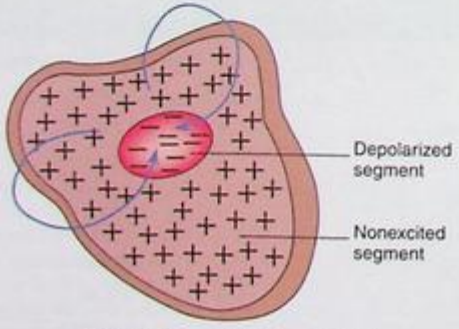


Figure 4.2-7 The heart as a dipole.

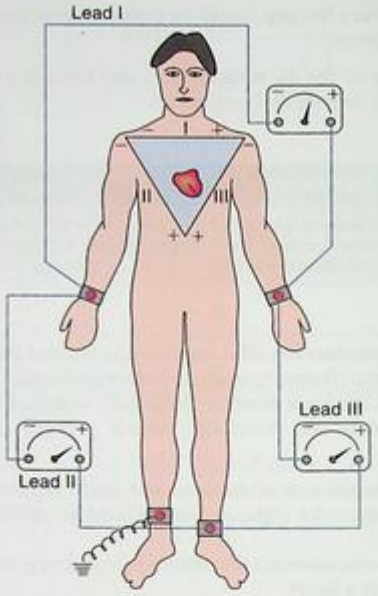


Figure 4.2-8 Einthoven's triangle and position of electrodes for standard limb leads (I, II and III).

Bipolar Leads In bipolar recording, *both the electrodes are active*, and one of the active electrodes is connected to negative terminal of the ECG machine and the other to the positive terminal. Three standard limb leads are used in the bipolar recording.

In three standard limb leads, the two active electrodes are connected as shown in Fig. 4.2-8.

Lead I (LI). In lead I, the two active electrodes are connected to left arm to the positive and right arm to the negative.

Lead II (LII). In lead II, the electrodes are connected to right arm to the negative and left leg to the positive terminals.

Lead III (LIII). In lead III, the electrodes are connected to left arm to the negative and left leg to the positive terminals.

Unipolar Leads In unipolar recording one electrode is an *active* or the *exploring* electrode and the other is an *indifferent electrode* at zero potential. Since the potential at the indifferent electrode remains zero, so in unipolar recording the records obtained represent the potential fluctuations occurring at the site of exploring electrode.

In clinical electrocardiography, two types of unipolar leads are used.

Unipolar Chest Leads. There are six unipolar chest leads (precordial leads) designated V_1–V_6. The indifferent electrode is obtained as described above and the active electrode is placed on six points on the chest as shown in Fig. 4.2-9.

Lead V_1: In the right-fourth intercostal space, just near the sternum.

Lead V_2: In the left-fourth intercostal space, just near the sternum.

Lead V_3: Halfway between V_2 and V_4.

Lead V_4: In the left-fifth intercostal space at mid-clavicular line.

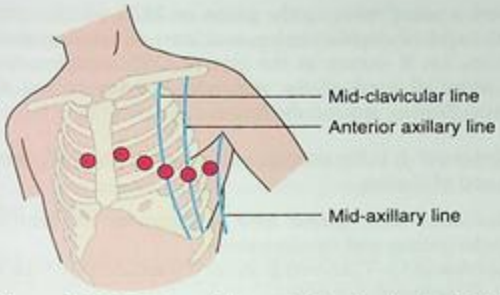


Figure 4.2-9 Position of electrodes for chest leads (V_1–V_6).

Lead V_5: In the left-fifth intercostal space at anterior axillary line.
Lead V_6: In the left-fifth intercostal space at mid-axillary line.

Unipolar Limb Leads. These include lead VL, VF and VR. In unipolar limb leads one *exploring* (active) *electrode* is placed over a limb (in lead VL over the left arm, VF over the left foot and lead VR over the right arm) and is connected to the positive terminal of the electrocardiograph. These leads are not used and have been replaced by the augmented limb leads.
Augmented Unipolar Limb Leads. Generally, augmented unipolar limb leads designated as aVR, aVL and aVF are used. In augmented leads the size of potential is increased by 50% without any change in the configuration from the non-augmented record.

Electrocardiograph

The electrocardiograph (ECG machine) is essentially a sophisticated string galvanometer. A modern electrocardiograph amplifies and records the potential fluctuations on a moving strip of paper. Special paper is used which turns black on exposure to heat. The stylus (recording pen) is made hot by the electrical current flowing through its tip.

Calibration of Time and Voltage on ECG Paper

- The special ECG paper having 1 mm and 5 mm squares (Fig. 4.2-10) is used. The tracing is usually made at a standard recording speed of 25 mm/s.
- On horizontal axis, therefore, each millimetre represents 0.04 second (1/25).
- The sensitivity of ECG is adjusted in such a way that a potential fluctuation of 1 mV causes a vertical deflection of 1 cm. Thus, on vertical axis, each millimetre represents 0.1 mV magnitude of potential.

Normal Electrocardiogram

ECG refers to the record of the potential fluctuations during the cardiac cycle. As a result of sequential spread of the excitation in the atria, the interventricular septum and the ventricular walls (Fig. 4.2-6) and finally repolarization of the myocardium, a series of positive and negative waves designated as P, Q, R, S and T are recorded during each cardiac cycle. Depolarization moving towards an active electrode in a volume conductor produces a positive deflection, whereas depolarization moving in the opposite direction produces a negative deflection.

Therefore, the shape and polarity of P, Q, R, S and T waves will vary in different leads due to differences in the orientation

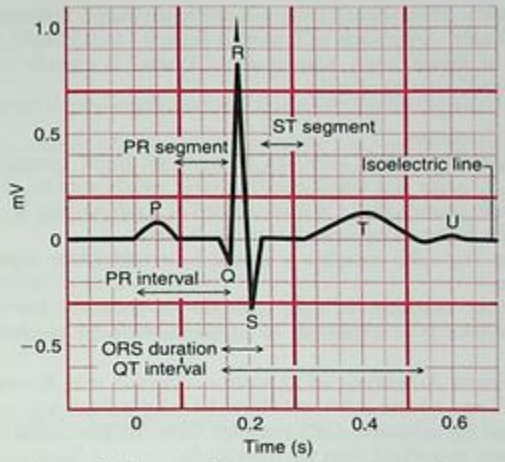


Figure 4.2-10 Calibration of time and voltage (amplitude) on special ECG paper.

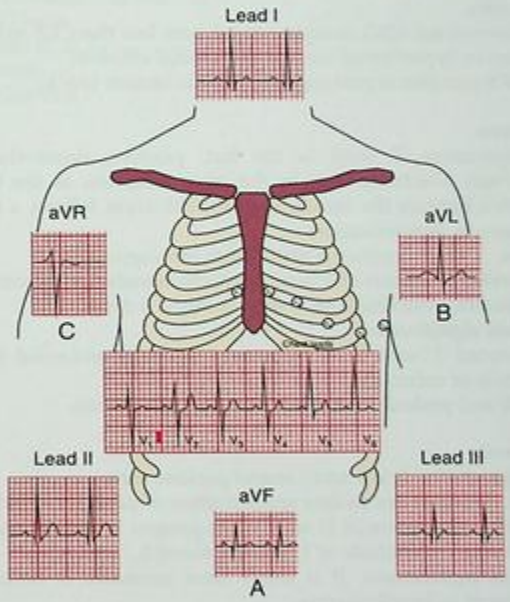


Figure 4.2-11 The electrocardiographic complexes recorded from different leads.

of each lead with respect to the heart (Fig. 4.2-11). *Configuration of a typical ECG* from a bipolar limb lead II (L II) is described as follows (Fig. 4.2-10).

Waves of ECG

P Wave

Configuration. P wave is the positive (upright rounded) deflection.
Cause. It is produced by the depolarization of the atrial musculature, therefore it is also called atrial complex.

Duration. Duration of P wave is not more than 0.1 second.
Amplitude. Amplitude of P wave is from 0.1 to 0.12 mV.
Clinical Significance. Magnitude of P wave is a guide to the functional activity of atria.

QRS Complex

Configuration. QRS complex consists of three consecutive waves. Q wave is a small negative wave which may be absent normally (quite often). It is continued as a tall positive R wave which is followed by a small negative S wave.
Cause. The QRS complex is caused by a ventricular depolarization.
Duration. Duration of QRS complex is normally less than 0.08 second. It is a measure of an intraventricular conduction time.
Amplitude. Amplitude of Q wave is 0.1−0.2 mV, R wave is 1.0 mV and S wave is 0.4 mV (total 1.5−1.6 mV).
Clinical Significance. QRS complex from the precordial leads are more important than the limb leads.

- Deep Q wave (more than 0.2 mV) along with other changes is an important sign of myocardial infarction.
- Tall R wave (more than 1.3 mV) is seen in ventricular hypertrophy.
- Low-voltage QRS complex (total sum less than 1.5 mV) is seen in hypothyroidism and pericardial effusion.
- QRS complex is prolonged in bundle branch block.

T Wave

Configuration. T wave is the last, positive, dome-shaped deflection. Normally, it is in the same direction as the QRS complex because the ventricular repolarization follows a path opposite to depolarization.
Cause. T wave represents ventricular repolarization.
Duration. Duration of T wave is approximately 0.27 second.
Amplitude. Amplitude of T wave is about 0.3 mV.
Clinical significance.

- Inverted T wave is an important sign of myocardial ischaemia or infarction.
- Tall and peaked T wave occurs in hyperkalaemia.

U Wave

Configuration. It is a small round positive wave.
Cause. It occurs due to slow repolarization of papillary muscle.
Duration. Duration of U wave when present is 0.08 second.
Amplitude. Amplitude of U wave is about 0.2 mV.
Clinical significance. It is rarely seen normally. It becomes prominent in hypokalaemia.

Note. Since atrial repolarization coincides with ventricular depolarization, so it is merged with the QRS complex and thus not recorded as a separate wave.

Intervals and Segments of ECG

P–R Interval It is measured from the onset of P wave to the onset of the QRS complex. Actually, it is P–Q interval but Q wave is frequently absent; therefore, it is called P–R interval.

- It measures the *AV conduction time*, including the AV nodal delay.
- Its *duration* varies from 0.12 to 0.21 second depending on the heart rate.
- *Clinical significance.* Prolonged P–R interval indicates AV conduction block.

J Point J point refers to the point on ECG which coincides with the end of depolarization and start of repolarization of ventricles, i.e. it occurs at the end of QRS complex. At this point, since all parts of the ventricles are depolarized so no current is flowing around the heart.

Q–T Interval It is the time from the start of the QRS complex to the end of T wave.

- It indicates total *systolic time of ventricles*, i.e. ventricular depolarization and repolarization.
- ***Duration*** of Q–T interval is about 0.4 second (QRS duration and ST segment duration).
- ***Clinical significance.*** Ischaemia and any ventricular conduction defects prolong the Q–T interval. In hypocalcaemia also Q–T interval is prolonged.

T–P Interval It is measured from the end of T wave to the beginning of P wave.

- It measures the *diastolic period* of the heart.
- Variable T–P interval indicates AV dissociation.

P–P Interval P–P interval is the interval between two successive P waves. Equal P–P intervals indicate rhythmic depolarization of the atria.

ST Segment It is an isoelectric period between the end of the QRS complex and the beginning of T wave.

- ***Duration*** is about 0.32 second.
- It corresponds with the *ventricular repolarization.*
- ***Clinical significance.*** ST segment is elevated in the patients with myocardial infarction.

Characteristic Features of ECG Complex in Unipolar Chest Leads and Limb Leads

The ECG complex produced in unipolar chest leads (V_1–V_6) represents the electrical activity of the part of the heart, which lies nearest to the active electrode (Fig. 4.2-12).

P Wave is positive in all the leads because the excitation wave moves from the SA node to the AV node, i.e. posterior to anterior.

QRS Complex It represents the electrical activity of ventricles and so its configurational changes in different leads are as follows:

- *In V_1 and V_2* (which reflect right ventricular activity), the principal QRS complex is *negative.*

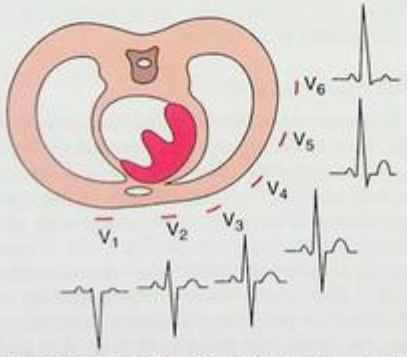


Figure 4.2-12 Pattern of QRS complex in chest leads (V_1–V_6).

- *In* V_3 and V_4 (which reflect activity of both ventricles including interventricular septum), the principal QRS complex is *biphasic.*
- *In* V_5 and V_6 (which reflect left ventricular activity) mainly the principal QRS complex is *positive,* as shown in Fig. 4.2-12.

R Wave gradually increases in size from V_1 to V_6 leads. In leads V_1, R wave represents the activity of right ventricle and in V_6 of left ventricle.

S Wave gradually decreases in size from lead V_1 to V_6. In lead V_1, S wave represents activity of left ventricle and in lead V_6 of right ventricle.

Lead VF and aVF These leads reflect the electrical activity of inferior surface of the heart, which is formed by parts of both right and left ventricles and interventricular septum. Therefore, the QRS complex in these leads like that of V_3 and V_4 is predominantly *biphasic* (Fig. 4.2-11A).

Lead VL and aVL These leads reflect the electrical activity of left outer side of the heart, which is mainly formed by the left ventricle. Therefore, the QRS complex in these leads like that of V_6 is predominantly *positive* (Fig. 4.2.11B).

Lead VR and aVR These leads reflect the activity of the cavity of the ventricles, irrespective of the position of heart. Therefore, *P wave, QRS complex and T wave* all have *negative deflection* (Fig. 4.2-11C).

Clinical Applications of Electrocardiography

Electrocardiography is an indispensable tool in the diagnosis, prognosis and planning treatment of most of the cardiac disorders. The important applied aspects which need special mention are as follows:

- Cardiac arrhythmias
- Myocardial infarction
- Hypertrophy of various cardiac chambers
- Effects on ECG of changes of the ionic composition of blood

SELF-ASSESSMENT

Describe briefly:

- Conducting system of heart
- Pacemaker potential
- Vagal tone
- Factors affecting heart rate
- ECG leads
- Waves of ECG
- J point
- PR interval

4.3 Heart as a Pump: Cardiac Cycle, Cardiac Output and Venous Return

CHAPTER OUTLINE

Cardiac Cycle
Introduction
Phases of Cardiac Cycle
Atrial Cycle
Ventricular Cycle
Events during Cardiac Cycle
Duration of Systole and Diastole Vis-á-Vis Heart Rate
Arterial Pulse

Cardiac Output and Venous Return
Definition of Cardiac Output and Related Terms
Measurement of Cardiac Output
Variations in Cardiac Output
Regulation of Cardiac Output
Heart–Lung Preparation

CARDIAC CYCLE

Introduction

The ***heart as a pump*** can be considered actually comprising of two separate pumps in the series: a *right heart* that pumps the blood through the lungs and a *left heart* that pumps the blood through the peripheral organs. To act as a pump, the heart contracts and relaxes rhythmically. The terms *systole* (contractile phase) and *diastole* (relaxation phase) usually refer to the ventricular events but may be prefixed by 'atrial' to refer to the atrial contraction and relaxation, respectively. As discussed in Chapter 4.2 the cardiac impulse arising from the SA node spreads in the whole heart. The electrocardiogram (ECG) records the *electrical events* that precede and initiate the corresponding *mechanical events* as:

- *P wave*, which is caused by spread of depolarization through the atria, and this is followed by *atrial contraction.*
- *QRS waves*, which appear 0.16 second after the onset of P wave, are caused by depolarization of the ventricles, which initiates *contraction of the ventricles.*
- *T wave* represents the stage of repolarization of the ventricles at which time the ventricular muscle fibres begin to relax. Therefore, T wave occurs slightly before the end of ventricular contraction.

The cardiac cycle thus includes both electrical and mechanical events that occur from the beginning of one heart beat to the beginning of the next.

Cardiodynamics is the study of the mechanical events associated with the contraction and relaxation of the heart. These include:

- Pressure changes in the ventricles
- Pressure changes in the atria
- Pressure changes in the aorta
- Volume changes in the ventricles
- Valvular events, i.e. production of heart sounds

Phases of Cardiac Cycle

Duration of each cardiac cycle at a normal heart rate (HR) of 75 beats/min is 60/75 = 0.8 second.

During each cardiac cycle, both atria contract *(atrial systole)* and relax *(atrial diastole)*, and both ventricles contract *(ventricular systole)* and relax *(ventricular diastole)*.

Therefore, each cardiac cycle can be considered to consist of simultaneously occurring atrial and ventricular cycles with following phases (Figs 4.3-1 and 4.3-2).

Atrial Cycle

1. Atrial systole or atrial contraction phase (0.1 second).
2. Atrial diastole (0.7 second).

Ventricular Cycle

Ventricular systole (0.3 second) consisting of:

1. Isovolumic (isometric) contraction phase (0.05 second)
2. Phase of ventricular ejection, which can be further divided into rapid ejection phase (0.1 second) and slow ejection phase (0.15 second)

Ventricular diastole (0.5 second) consisting of:

1. Protodiastole (0.04 second)
2. Isovolumic (isometric) relaxation phase (0.06 second)
3. Rapid passive filling phase (0.11 second)
4. Reduced filling phase or diastasis (0.19 second)
5. Last rapid filling phase which coincides with the atrial systole (0.1 second)

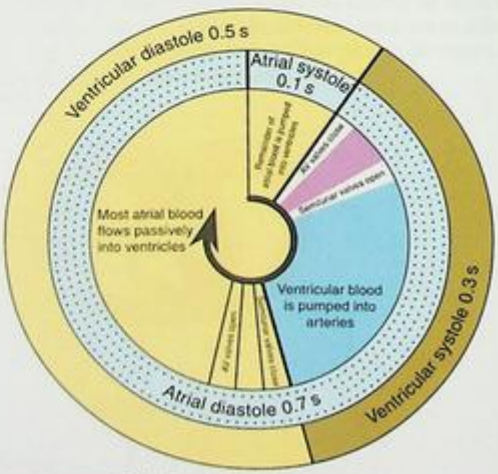


Figure 4.3-1 Duration of phases of cardiac cycle.

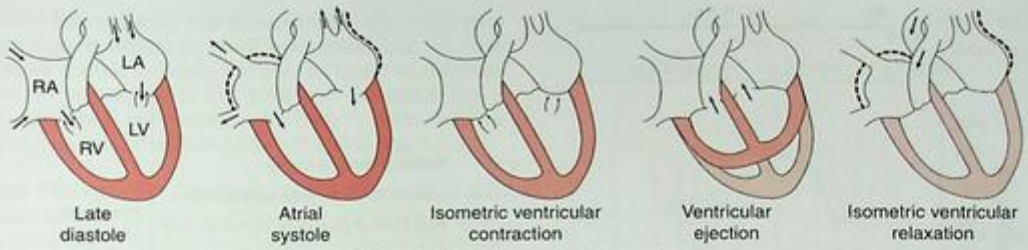


Figure 4.3-2 Phases of cardiac cycle.

Atrial Cycle

Atrial Systole

- Atrial systole or the atrial contraction phase lasts for 0.1 second and coincides with the last rapid filling phase of ventricular diastole (Figs 4.3-1 and 4.3-2).
- Before the beginning of atrial systole, the ventricles are relaxing, the atrioventricular (AV) valves are open and the blood is flowing from the great veins into the atria and from the atria into the ventricles. Thus, the atria and ventricles are forming a continuous cavity.

*The **contraction of atria causes** the following.*

- *Increase in the intra-atrial pressure.* During atrial systole there occurs a sharp rise in intra-atrial pressure by 4–6 mm Hg in right atrium and by 7–8 mm Hg in left atrium, and causes a pressure wave recorded as *a-wave* from the jugular vein ('a' stands for atrial systole).
- *Increase in the ventricular pressure.* The intraventricular pressure (about 6–7 mm Hg in right ventricle and about 7–8 mm Hg in left ventricle) due to pumping of blood in the ventricles. In the intraventricular pressure curve (Fig. 4.3-3), the segment AB represents the pressure changes during atrial systole. The point A denotes the onset of atrial systole and the point B denotes the closure of AV valve.
- When the atrial contraction begins about 105 mL (75%) of the blood has already flown into the ventricles. The atrial contraction causes additional 25 mL (25%) filling of the ventricles. Thus at the end of atrial systole, i.e. at the end of ventricular diastole, the ventricular volume is about 130 mL. This is called *end-diastolic volume (EDV).*
- During atrial systole the pressure in the aorta is about 80 mm Hg.

Atrial Diastole

After the atrial systole, there occurs atrial diastole (0.7 second). This period coincides with the ventricular systole and most of the ventricular diastole (Fig. 4.3-1).

During the atrial diastole, the atrial muscles relax and there occurs gradual filling of the atria due to continuous venous return and the pressure gradually increases in the atria and drop down to almost zero with the opening of AV valves (Fig. 4.3-3). Then the pressure again rises and follows the ventricular pressure during the rest of atrial diastole.

Ventricular Cycle

Ventricular Systole

After the atrial contraction phase is over, the ventricles get excited by the impulse travelling along the conduction system and start contracting. The ventricular systole lasts for 0.3 second and has following phases.

1. Phase of Isovolumic (Isometric) Contraction

- With the beginning of ventricular contraction the ventricular pressure exceeds the atrial pressure very rapidly causing closure of AV valves (this event is responsible for the production of first heart sound).
- AV valves have closed and semilunar valves have not opened, so the ventricles contract as a closed chamber and the pressure inside the ventricles rises rapidly to a high level.
- In the intraventricular pressure curve (Fig. 4.3-3), this phase is represented by the segment BC. The point C denotes the opening of semilunar valves and commencement of ventricular ejection phase.
- As the ventricles contract, the volume of blood in the ventricles does not change, so this phase is called *isovolumic contraction phase.*
- During this phase, due to sharp rise in the ventricular pressure, there occurs bulging of AV valves into the atria producing a small but sharp rise in the intra-atrial pressure called *c-wave.* ('c' stands for contraction of the ventricle.)
- This phase lasts for 0.05 second, until the pressure in the left and right ventricles exceeds the pressure in the aorta (80 mm Hg) and pulmonary artery (10 mm Hg), and the aortic and pulmonary valves open.

2. Phase of Ventricular Ejection The ventricular ejection phase begins with the opening of semilunar valves and lasts for about 0.25 second. It can be further divided into two phases.

Rapid Ejection Phase. As soon as the semilunar valves open, the blood is rapidly ejected out for about 0.1 second. About two-thirds (89 mL of blood) of the stroke volume (SV) is ejected out by each ventricle in this phase.

The ventricles contract at a rate greater than the rate at which blood is ejected so that a great rise in the pressure occurs. Pressure rises to maximum of 120 mm Hg in the left ventricle and 25 mm Hg in the right ventricle. In the intraventricular pressure curve (Fig. 4.3-3), this phase is denoted by the segment CD. The point D denotes the peak point of intraventricular pressure after which it starts declining.

Slow Ejection Phase. It refers to the latter two-third of systole (about 0.15 second) during which the rate of ejection declines. There is no further ventricular contraction and the pressure starts declining (Fig. 4.3-3, segment DE). About one-third of the SV is ejected during this phase. The intraventricular pressure starts declining and falls to a value slightly lower than in the aorta, but for a short period momentum keeps the blood flowing forward.

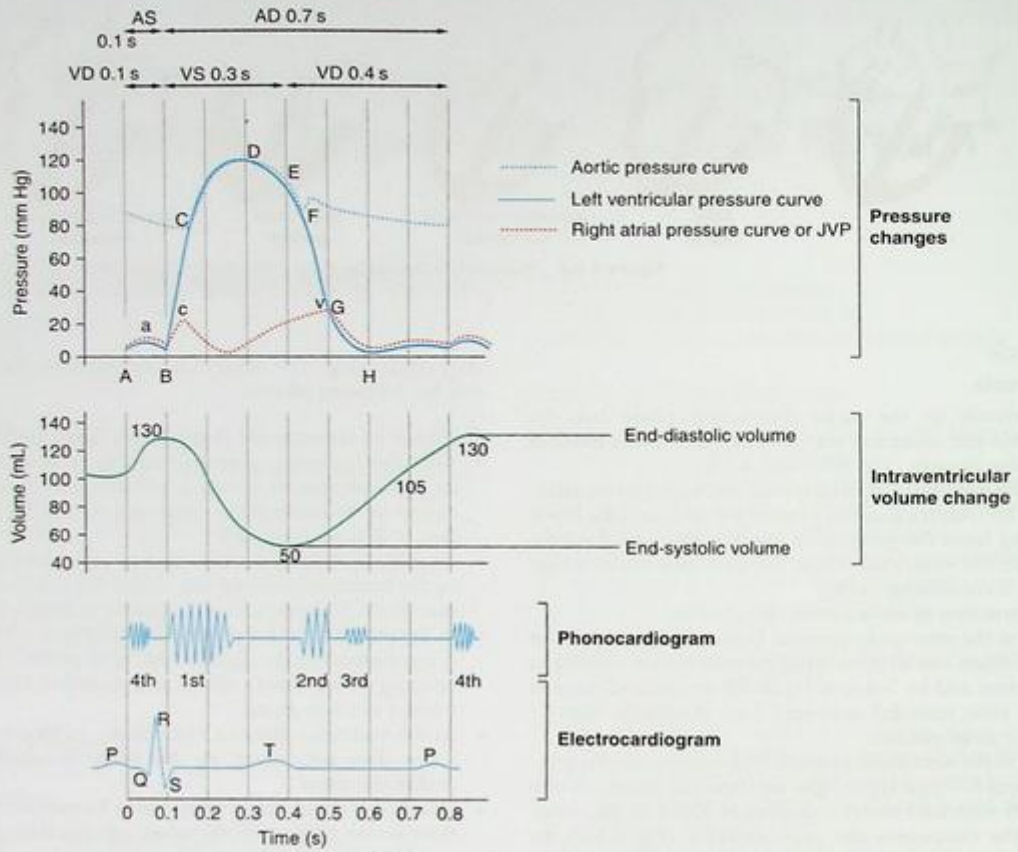


Figure 4.3-3 Phases and events during cardiac cycle.

The aortic pressure starts rising along with the intraventricular pressure during rapid ejection phase and reaches maximum (120 mm Hg) at the end of rapid ejection phase. During reduced ejection phase the aortic pressure starts falling along with the ventricular pressure.

The percentage of the EDV that is ejected out with each stroke during systole (about 65%) is called *ejection fraction*. Thus, about 50 mL of the blood in each ventricle at the end of ventricular systole is called *end-systolic volume*.

Ventricular Diastole

1. Protodiastole When the ventricular systole ends, the ventricles start relaxing and intraventricular pressure falls rapidly. This phase lasts for 0.04 second. During this phase, the elevated pressure in the distended arteries (aorta and pulmonary artery) immediately pushes the blood back towards ventricles, which snaps the semilunar valves to close. Closure of semilunar (i.e. aortic and pulmonary) valves prevents the movement of blood back into the ventricles and produces the *second heart sound* (S_2). It also causes a *dicrotic notch* in the down slope of aortic pressure called the *incisura*.

In the intraventricular pressure curve (Fig. 4.3-3), this phase is represented by the segment EF and the point F denoted the closure of semilunar valves.

2. Isovolumic or Isometric Relaxation Phase

- This phase begins with the closure of the semilunar valves and lasts for about 0.06 second.
- Semilunar valves have closed and the AV valves have not yet opened, so the ventricles continue to relax as closed chambers in this phase. This causes rapid fall of pressure inside the ventricles (from 80 to about 2−3 mm Hg in the left ventricle).
- As in this phase the ventricular volume remains constant, so this phase is called isovolumic or isometric relaxation phase.
- In the intraventricular pressure curve (Fig. 4.3-3), the segment FG represents this phase and the point G coincides with the opening of AV valve.
- During rest of the diastole the aortic pressure smoothly declines. By the time the aortic pressure declines to about 80 mm Hg, another ventricular systole boosts the aortic pressure again.
- This phase ends when the AV valves open, as indicated by the peak of *v-wave* on the atrial pressure tracing (Figs 4.3-2 and 4.3-3).

3. Rapid Passive Filling Phase (0.11 second)

- During ventricular systole, the atria are in diastole and venous return continues so that the atrial pressure is high. When the AV valves open, the high atrial pressure causes a

rapid, initial flow of blood into the ventricles. The rapid passive filling phase produces the *third heart sound* (S_3), which is not normally audible in adults but may be heard in children.
- Once the AV valves open, the atria and ventricles are a common chamber and pressure in both cavities falls as ventricular relaxation continues (segment GH in Fig. 4.3-3).

4. Reduced Filling and Diastasis (0.19 second) In this phase pressure in the atria and ventricles reduces slowly and remains little above zero. This decreases the rate of blood flow from the atria to ventricle causing a very slow filling called *diastasis*.
Note. It is important to note that about 75% of blood passes from the atria to the ventricles during rapid filling and reduced filling phases of the ventricular diastole.

5. Last Rapid Filling Phase (0.1 second) The last rapid filling phase of ventricular diastole coincides with the atrial systole. As described in the beginning, the atrial systole brings about the last rapid filling phase and pushes the additional 25% of the blood in the ventricles. With this phase the ventricular cycle is completed.

Events During Cardiac Cycle

The events associated with contraction and relaxation of the heart during a cardiac cycle include pressure changes in the ventricles, atria and aorta as well as volume changes in the ventricles and valvular events. Most of these have been described during various phases of cardiac cycle.

Pressure Changes in the Pulmonary Artery

Pressure curve in the pulmonary artery is similar to that of the aorta but pressures are low (about one-sixth of that in aorta). Pulmonary artery systolic pressure averages 15–18 mm Hg and its pressure during diastole is 8–10 mm Hg.
During Ventricular Ejection Phase about 80 mL of the blood is ejected out.

Valvular Events (Heart Sounds)

A total of four heart sounds (first, second, third and fourth) are produced by certain mechanical activities during each cardiac cycle.

First Heart Sound (HS_1)

Cause. First heart sound is produced by the vibrations set up by the sudden closure of AV valves at the start of ventricular systole during phase of isovolumic contraction (Fig. 4.3-3).
Characteristics. The first heart sound is long and soft when HR is low and loud when the HR is high. Its duration is about 0.15 second and frequency is 25–45 Hz. It sounds like the spoken word 'LUBB'.
Site for Auscultation. It can be heard by auscultation of the chest with stethoscope. It is best heard over mitral and tricuspid areas. *Mitral area* is located in the fifth intercostal space just internal to mid-clavicular line. *Tricuspid area* is located in the fifth intercostal space near the sternum (Fig. 4.3-4).

Second Heart Sound (HS_2)

Cause. It is caused by the vibrations associated with closure of the semilunar valves just at the onset of ventricular diastole.
Characteristics. The second heart sound is short, loud, high-pitched sound. Its duration is 0.12 second and frequency is 50 Hz. It sounds like the spoken word 'DUBB'.

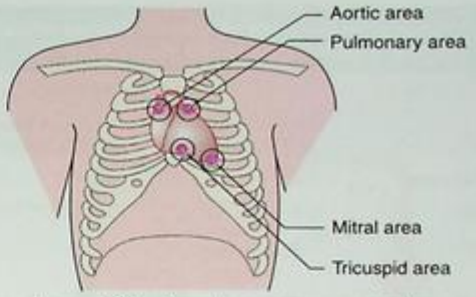


Figure 4.3-4 Auscultatory areas over the chest.

Site for Auscultation. It can be heard by auscultation of the chest with stethoscope. It is best heard over the aortic and pulmonary areas. *Aortic area* lies in the right second intercostal space near the sternum, *pulmonary area* is in the left second intercostal space close to sternum (Fig. 4.3-4).
Correlation with ECG. Second heart sound usually coincides with the end of T wave in ECG.

Third Heart Sound (HS_3)

Cause. Third heart sound is caused by the vibrations set up in the cardiac wall by inrush of blood during *rapid filling phase* of the ventricular diastole.
Characteristics. Third heart sound is a short, soft and low-pitched sound. Its duration is 0.1 second. Normally, it cannot be heard by auscultation with stethoscope.
Correlation with ECG. The third heart sound appears between T and P waves of ECG.

Fourth Heart Sound (HS_4)

Cause. It is caused by the vibrations set up during the atrial systole which coincides with last rapid filling phase of the ventricular diastole. It is normally not audible.

Duration of Systole and Diastole vis-á-vis Heart Rate

Effect of Heart Rate

- Cardiac muscle has the unique property of contracting and repolarizing faster when the HR is high.
- Therefore, when the HR increases the total duration of cardiac cycle decreases, e.g. at an HR of 200 beats/min the total duration of cardiac cycle is 60/200 = 0.3 second.
- It is important to note that though the duration of all phases of the cardiac cycle decreases at high HR, the *duration of diastole* decreases much more than the duration of systole. For example, when the HR increases from 75 to 200 beats/min, the duration of systole decreases from 0.3 to 0.16 second, whereas that of diastole decreases from 0.5 to 0.14 second (Table 4.3-1).

This fact has *clinical implications:*

- It is during diastole that the heart muscle rests and coronary blood flow to the subendocardial portion of the left ventricle occurs only during diastole. Therefore, at a very high rate there occurs reduction in cardiac perfusion and there are chances of myocardial ischaemia.

TABLE 4.3-1 Change in Duration of Various Events of Cardiac Cycle with Increase in the Heart Rate

Event	DURATION (SECOND)	
	At Heart Rate of 75 beats/min	At Heart Rate of 200 beats/min
Cardiac cycle	0.8	0.3
Systole	0.3	0.16
Diastole	0.5	0.14

- Furthermore, most of the ventricular filling occurs in the diastole. Therefore at very high HR filling may be compromised to such a degree that cardiac output (CO) per minute falls and symptoms of the heart failure develop.

Arterial Pulse

Arterial pulse is also an event related to the cardiac cycle. The blood forced into the aorta during the systole not only moves the blood in the vessels forward, but also sets up a pressure wave that is transmitted along the *arteries to the* periphery. The pressure wave expands the arterial walls as it travels and expansion is palpable as the *pulse.*

Methods of Recording Arterial Pulse The tracings of arterial pulse can be made by the following techniques of recording.
1. Manometric Technique. It is used in animals. In this technique a cannula is inserted into the dissected artery and is connected to manometer or any other recording device to obtain the arterial pulse tracing.
2. Electronic Transducer Method. The electronic transducer is placed on the skin overlying any artery.

Interpretation of Arterial Pulse Tracing The pulse tracing recorded from the carotid artery shows the following characteristics (Fig. 4.3-5):

Ascending limb, also known as *anacrotic limb* or primary limb, is due to the rise in pressure during systole.
Descending limb, also known as *catacrotic limb*, represents the fall in pressure during diastole.
Percussion wave (P) corresponds to the ejection phase of the ventricular systole.
Tidal wave (T) is due to falling blood column during slow ejection phase.
Dicrotic notch (N) is due to the closure of aortic valve and marks end of the ventricular systole.
Dicrotic wave (D) is due to rebound of blood column from the closed aortic valve.

When the record is taken from the peripheral arteries at a distant place from the heart, e.g. femoral or radial arteries, the contour or shape of record changes. In arterioles and capillaries, the waves disappear.

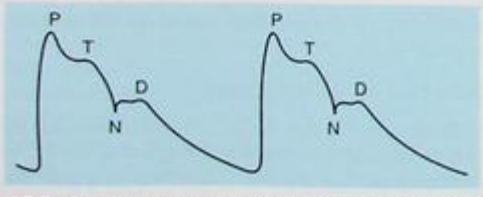


Figure 4.3-5 Record of arterial pulse from a carotid artery: P, percussion wave; T, tidal wave; N, dicrotic notch; and D, dicrotic wave.

Examination of Arterial Pulse Examination of the arterial pulse is an essential feature of a clinical examination. Arterial pulse can be palpated from any superficial artery, e.g. radial, femoral, dorsalis pedis and carotid. Most frequently, pulse is examined from the radial artery because it is conveniently approached without exposing the body and can be easily palpated as it is placed superficially against the bone.

Examination of the pulse should include following aspects.
1. Pulse Rate refers to the number of pulses per minute. It is a convenient method of determining the HR.

- *Normal pulse rate* varies with age being 150–180 minutes in foetus, 130–140 minutes at birth, about 90 minutes at the age of 10 years and about 72/min in adults.
- *Increased pulse rate* represents tachycardia and occurs during exercise, in anxiety, fever, hyperthyroidism, and atrial and ventricular tachycardias.
- *Decreased pulse rate* represents bradycardia and is seen in hypothyroidism and incomplete heart blocks.

2. Volume of Pulse, also known as strength of arterial pulse or amplitude or impact, can be felt. It represents SV or the pulse pressure (i.e. systolic–diastolic pressure).

- *Rapid and thready pulse* occurs in hypovolaemia as in severe haemorrhage and there is marked reflex vasoconstriction.
- *Increased volume pulse* is seen during exercise and in ventricular hypertrophy.

3. Rhythm of Pulse is noted as regular or irregular. Under normal conditions and during sinus bradycardia or sinus tachycardia pulse appears at regular intervals.

- *Irregular pulse rhythm* is a feature of extra systole, atrial fibrillation and other cardiac arrhythmias; type of arrhythmia is confirmed only on ECG. The irregular pulse rhythm may be regularly irregular or irregularly irregular.

4. Character of Pulse is felt on palpation. It denotes the tension and waves in the pulse. Feeling of different characters of the pulse can be learnt by the subjective experience.

- *Normal character* of the pulse is sinuous on examination, i.e. an upstroke is followed by a downstroke. Normally, it is not possible to feel the different waves of the pulse or slight variations in the character. However, in certain heart diseases and valvular defects the normal character is altered and can be easily felt while palpating the peripheral arterial pulse.

CARDIAC OUTPUT AND VENOUS RETURN

Definition of Cardiac Output and Related Terms

The principal function of the heart is to pump blood to meet the metabolic needs of the body. The measure of the heart's ability to pump blood is cardiac output.

The cardiac output refers to the amount of blood ejected by each ventricle per minute.

The stroke volume is the amount of blood pumped out by each ventricle per beat or per contraction. Therefore, CO can be calculated by multiplying the SV by the HR:

$$CO = SV \times HR$$

Under normal conditions, the average HR is about 70 beats/min and SV is about 80 mL, and thus CO is $80 \times 70 = 5.6$ L.

The CO is expressed in litres per minute and normally varies from 5–6 L/min. Thus, each ventricle pumps about 5–6 L of blood into the circulation per minute. This is made possible because of the fact that the right and the left side of pumps act in series.

Cardiac index is the CO expressed in relation to the body surface area. The normal cardiac index is about 3.2 L/min/m^2.

Distribution of the Cardiac Output Of the total CO about 75% is distributed to the vital organs of the body and rest of 25% to the skeletal muscle, other organs of the body and skin.

Measurement of Cardiac Output

Cardiac output, in experimental animals, can be measured directly with the help of an electromagnetic flowmeter placed on the ascending aorta. However, in humans only indirect methods are possible and include:

- Methods based on Fick's principle
- Indicator or dye dilution method
- Thermodilution method
- Physical methods

Methods Based on Fick's Principle

Fick's Principle The Fick's principle states that the amount of a substance taken up by an organ (or by the whole body) per unit of time is equal to the arterial level of the substance (A) minus the venous level (V) times the blood flow (F), i.e.

$$Q = (A - V)\,F$$

or

$$F = \frac{Q}{(A - V)}$$

This principle can be, of course, only in situations in which the arterial blood is the sole source of the substance taken up.

In this method (Fig. 4.3-6) CO is determined by measuring the pulmonary blood flow. As we know:

- Pulmonary blood flow/min = right ventricular output.
- Right ventricular output = left ventricular output (CO).

Measurement of pulmonary blood flow can be made by measuring the amount of O_2 taken by the blood from the lungs, O_2 concentration of the venous blood from pulmonary artery (PAO_2) and O_2 concentration of the arterial blood from the pulmonary vein (PVO_2).

- Amount of O_2 uptake/min is determined with the help of a spirometer.
- PAO_2 is measured from the venous blood sample taken from the pulmonary artery directly with the help of a cardiac catheter. The cardiac catheter is inserted into a vein at the forearm and is then guided up under fluoroscopic control through the venous channels into the right atrium, right ventricle and pulmonary artery.
- PVO_2, because of practical difficulty in taking sample from pulmonary vein, is measured from the arterial blood sample taken from any peripheral artery, e.g. brachial artery (the O_2 content of all the major arteries is same as that of pulmonary veins). According to Fick's principle:

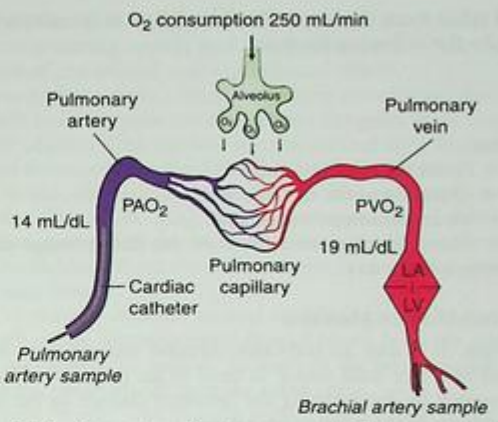


Figure 4.3-6 Estimation of cardiac output by Fick's principle. PAO_2, oxygen content of pulmonary artery blood; PVO_2, oxygen content of pulmonary vein blood.

$$\text{Pulmonary blood flow} = \frac{\text{Amount of } O_2 \text{ taken by the lungs/min}}{PVO_2 - PAO_2}$$

$$\text{Cardiac output} = \frac{O_2 \text{ taken by the lungs/min}}{PVO_2 - PAO_2}$$

For example, if O_2 uptake is 250 mL/min, PVO_2 is 19 mL/ 100 mL and PAO_2 is 14 mL/dL, then

$$\text{Cardiac output} = \frac{250 \times 100}{19 - 14} = \frac{25{,}000 \text{ mL/min}}{5} = 5000 \text{ mL/min} = 5 \text{ L/min}$$

Disadvantages of Fick's Principle

- It is an invasive technique, so there are risks of infection and haemorrhage.
- The CO estimated may be somewhat higher than normal as the patient becomes conscious of the whole technique.
- A fatal complication like ventricular fibrillation may occur if the indwelling catheter irritates the ventricular walls, especially when the CO is being measured during heavy exercise.

Indicator or Dye Dilution Method

Principle In this method, a known amount of the dye is injected into a large vein or preferably into the right atrium by cardiac catheterization. By its passage through heart and pulmonary circulation it will be evenly distributed in the blood stream. Its mean concentration during the first passage through an artery can be determined from the successive samples of

blood taken from the artery. The blood flow in litres/min (F) is given by the following formula:

$$F = \frac{Q}{Ct}$$

where
F = Blood flow in litres/min
Q = Quantity of the dye injected
C = Mean concentration of dye
t = Time duration in second of the first passage of dye through the artery

Thermodilution Method

Principle. It is also an indicator dilution technique in which instead of a dye 'cold saline' is used as an indicator. The CO is measured by determining the resultant change in the blood temperature in the pulmonary artery.

Physical Methods

Physical methods developed to measure the CO include the following.

Echocardiography Echocardiography refers to the ultrasonic evaluation of cardiac functions. It is a noninvasive technique that does not involve injections or insertion of a catheter. It involves B-scan ultrasound at a frequency of 2.25 MHz using a transducer, which also acts as a receiver of the reflected waves. The recording of the echoes displayed against time on an oscilloscope provides a record of:

- The movement of the ventricular wall and septum, and valves during the cardiac cycle.
- When combined with the Doppler techniques, echocardiography can be used to measure velocity and volume of flow through the valves.
- Thus, it is particularly useful in evaluating EDV, end-systolic volume, CO and valvular defects.

Ballistocardiography Method This method is not used practically. Ballistocardiography refers to the graphical record of the pulsations created due to ballistic recoil of the pumping heart.

Variations in Cardiac Output

Physiological Causes of Variations in Cardiac Output

- ***Age.*** Because of less body surface area the children have more cardiac index than adults.
- ***Sex.*** The body surface area is less in females, so they have more cardiac index than the males.
- ***Diurnal variation.*** In the early morning CO is low, which increases in the day time depending on the basal condition of the individual.
- ***Environmental temperature.*** Moderate change in the environmental temperature does not cause any change in CO. A high environmental temperature is associated with an increase in the CO.
- ***Anxiety and excitement*** are reported to increase the CO by 50%–100%.
- ***Eating*** is associated with an increase in CO approximately by 30%.
- ***Exercise*** may increase the CO up to 700% depending on the vigorousness of exercise.
- ***Pregnancy.*** An increase in CO to the tune of 45%–60% is reported during the later months of the pregnancy.
- ***Highaltitude.*** The CO is increased at a high altitude due to release of adrenaline as a consequence to hypoxia.
- ***Posture change.*** Sitting or standing from lying down position may decrease the CO by 20%–30% because of pooling of blood in the lower limbs.

Pathological Causes of Variations in Cardiac Output

Increase in cardiac output is seen in the following conditions:

- *Fever*, due to increased oxidative processes.
- *Anaemia*, due to hypoxia.
- *Hyperthyroidism*, due to increased metabolism.

Decrease in cardiac output may occur in the following conditions:

- *Rapid arrhythmias*, due to incomplete filling.
- *Congestive cardiac failure*, due to weak contractions of heart.
- *Cardiac shock*, due to poor pumping and circulation.
- *Incomplete heart block*, owing to defective pumping action of the heart.
- *Haemorrhage* because of decreased blood volume.
- *Hypothyroidism*, due to decreased basal metabolism.

Regulation of Cardiac Output

The CO increases or decreases in various physiological and pathological conditions as described above. The variations in the CO are brought out by certain factors operating through certain mechanisms by an integrated role.

The CO, as we know, is the product of SV and HR, i.e. CO = SV × HR. Therefore, variations in the CO can be produced by the factors which change SV or HR or both. The principal factors affecting CO are venous return, myocardial contractility, peripheral resistance and HR (Fig. 4.3-7).

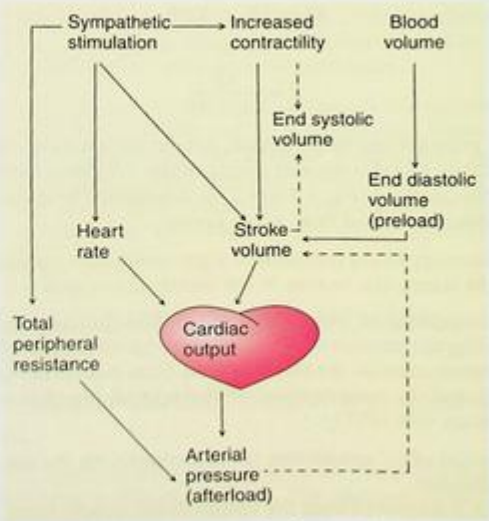


Figure 4.3-7 Interaction between the factors that regulate cardiac output and arterial pressure. Solid lines indicate increase and dotted lines indicate a decrease.

Cardiac Output Control Mechanisms

The CO is regulated by two mechanisms: intrinsic and extrinsic.

A. Intrinsic Autoregulation (Frank–Starling Mechanism)

The force of contraction of cardiac muscle fibres like that of the skeletal muscle fibres depends on its preload. The preload determines the initial length (resting length) of the muscle fibres. According to *Frank–Starling law* of heart, 'within physiological limits' the force of contraction of *cardiac muscle* is proportionate to the initial length of muscle fibres. In the heart, EDV forms the preload. Therefore, precisely the Frank–Starling law of heart can be stated as, within physiological limits the force of cardiac contraction is proportional to its EDV. This fact was demonstrated about a century ago by Frank and Starling on the heart–lung preparation in a dog. In this intrinsic regulation mechanism, cardiac muscle fibres are stretched to increase their initial length, so it is also termed as *heterometric mechanism*.

The relationship between the ventricular SV and EDV is called the *Frank–Starling curve* (Fig. 4.3-8). Details of the effect of preload on the force of myocardial contraction including the *length–tension relationship* are described in detail on page 114.

Factors Affecting End-Diastolic Volume The EDV refers to the *venous return* to the heart during diastole.

Up to physiological limits, the CO is directly proportional to the venous return. Thus, over any significant period of time, venous return must be equal to CO. For individual at rest, the CO and venous return are approximately 5 L/min. Factors affecting venous return are given as follows (Fig. 4.3-8).

1. Respiratory Pump. Normally the intrapleural (intrathoracic) pressure at the end of expiration is about −2 mm Hg. During inspiration, the intrathoracic pressure becomes more negative (about −5 mm Hg) due to which the diameter of inferior vena cava is increased and pressure inside it is reduced; and there occurs descent of diaphragm which increases the intra-abdominal pressure. The decreased pressure inside the inferior vena cava coupled with increased intra-abdominal pressure during inspiration results in the increased flow of blood into the right atrium. This mechanism of increased blood flow during inspiration is called *respiratory pump*. This respiratory pump operates strongly in the forced respiration and in severe muscular exercise increasing the venous return.

2. Cardiac Pump. The cardiac pump influences the venous return by two kinds of forces the 'vis-a-tergo' and 'vis-a-fronte'.

- ***Vis-a-tergo*** refers to the forward push from behind, i.e. the propelling force which pushes the blood from veins into the right atrium. Vis-a-tergo results from the myocardial contraction during systole and is supplemented by the elastic recoil of the arterial wall (Windkessel effect).
- ***Vis-a-fronte*** refers to the suction force acting from the front which basically pulls the blood from the great veins into the right atrium. This suction force is created by a ventricular contraction and has the following two components:
  - *Ventricular systolic suction* results from pulling down of the fibrous AV ring causing enlargement of the atrial lumen and thus decreasing the intra-atrial pressure which sucks blood from the inferior vena cava and the superior vena cava.
  - *Ventricular diastolic suction* results from the opening of AV valves allowing rapid flow of blood from the atria to ventricles. The sudden decrease in the atrial pressure, in turn, sucks blood from the great veins.

3. Muscle Pump. The muscle pump mechanism is responsible for flow of blood from the veins of the limbs to the heart.

Working of muscle pump. Two types of veins are present in the limbs: superficial and deep veins.

Blood flows from the superficial veins into the deep veins through communicating veins. Due to the presence of valves in the limb veins, the blood flows in one direction, i.e. from periphery towards heart and not in the reverse direction.

- *When the skeletal muscles contract*, the deep veins present in between the muscles are compressed and due to increased pressure the valve present proximal to the contracting muscle is opened up while the valve present on distal end is tightly closed, and in this way the blood is propelled up towards the heart (Fig. 4.3-9A).
- *When the skeletal muscle relaxes*, a negative pressure is created in the segment of veins. So due to back flow the proximal valve is closed, distal valve is opened and blood is sucked up (Fig. 4.3-9B).
- *With rhythmic contractions of skeletal muscles* in this way the blood is squeezed out of the limbs towards the heart.

APPLIED ASPECTS

In certain professions (e.g. nurses and traffic police) the individuals have to keep standing for a long time of a day. In such persons, veins of lower limbs become large, tortuous and bulbous. This condition is called *varicose veins*.

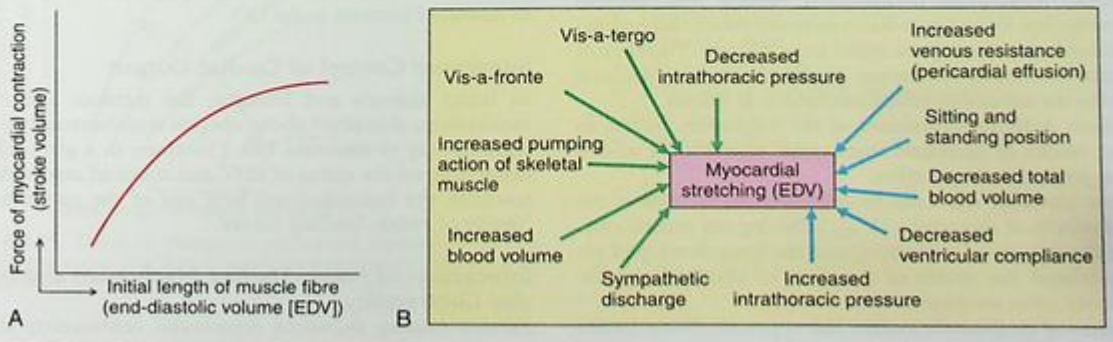


Figure 4.3-8 Frank–Starling curve and factors affecting end-diastolic volume. Green arrows indicate increase and blue arrows indicate decrease.

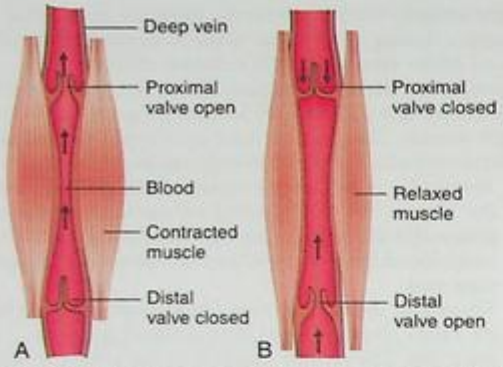


Figure 4.3-9 Mechanism of muscle pump: (A) during contraction of muscles and (B) during relaxation of muscles.

4. Blood Volume. The increased blood volume increases the venous return and a decreased blood volume decreases the venous return.
5. Sympathetic Discharge. On sympathetic stimulation there occurs increase in the venous tone, which decreases the capacity of the venous system (veins are capacitance vessels).
6. Standing Body Position. It is associated with a decreased venous return due to peripheral pooling of the blood.
7. Resistance to Venous Return. Decrease in the resistance to venous return increases the venous return, whereas an increase in the resistance to venous flow decreases the venous return.

Clinical Significance of Frank–Starling Mechanism

Maintenance of Constant SV When the Peripheral Resistance is Increased is Carried Out by Intrinsic Mechanism. When the peripheral resistance (blood pressure) is increased, initially the heart is unable to pump all the blood that it normally does. The accumulated blood in the ventricle stretches the muscle fibres leading to great force of contraction, and thus the SV is restored to normal in spite of greater resistance to the outflow.

Intrinsic Control Mechanism Serves as a Life-saving Device in a Cardiac Failure. Left ventricular failure causes accumulation of blood within the left ventricle, thereby decreases blood supply to the vital organs. Soon accumulation of blood in the left ventricle increases the initial length of muscle fibres leading to greater CO according to Frank–Starling mechanism. However, when accumulation of blood is too great, the Frank–Starling law will fail to operate leading to decrease in the blood supply to the vital organs and ultimately death may occur.

B. Extrinsic Regulation (Autonomic Neural Mechanism)

In this mechanism SV increases due to *increased myocardial contractility* without any increase in the initial muscle length. Therefore, it is also called *homometric mechanism*. The homometric regulation is governed by the autonomic neural mechanism as follows.

Sympathetic Activity *Stimulation of the sympathetic nerves* to the heart results in increased myocardial contractility and is known as *positive inotropic effect.*

Positive inotropic effect can be defined as an increase in the *maximal velocity* of shortening (V'_{max}). During any muscle contraction, the velocity of shortening and the force developed are inversely related. For details of the effect of afterload and the *force–velocity curve* see page 114.

Inhibition of sympathetic system has opposite effects. Under normal conditions there is continuous slow rate of discharge through sympathetic fibres to the heart. Therefore, when sympathetic activity is inhibited the ventricular force of contraction decreases.

In intact animals, stimulation of sympathetic nerves produces a marked increase in the HR and a moderate increase in the SV, leading to a manifold increase in the CO.

Characteristics of Increased Myocardial Contractility

Characteristics of Homometric Regulation. The increased myocardial contractility achieved by homometric regulation differs from the increase in force of contraction of myocardium achieved by heterometric regulation. Its characteristic features are the following.

- The ventricles contract more forcefully and more rapidly, i.e. velocity of shortening of muscle is increased. As a result the ventricles are able to do more work per stroke, i.e. ejection fraction increases at the same EDV (without increase in venous return).
- Due to more complete emptying of ventricles during each systole the *end-systolic volume is decreased.*
- Due to increased stroke output *arterial pressure is increased.*

Mechanism of Effects of Sympathetic Stimulation. Sympathetic stimulation increases the myocardial contractility by causing *activation of* β_1 adrenergic receptors, which, in turn, increases the concentration of Ca^{2+} within the myocardial cells causing a more rapid and forceful contraction.

Parasympathetic Activity There is a negative inotropic effect of parasympathetic (vagal) stimulation. This effect, however, is not much because vagal fibres are mainly distributed to the atria and not much to the ventricles.

Role of Heart Rate in Control of Cardiac Output

The CO and HR both are increased during exercise proportionate to its severity. CO is the product of SV and HR; therefore, it is tempting to attribute the increase in CO to increase in the HR. However, in fact it is not so. It has been seen that when HR alone is increased, e.g. by change in the frequency of discharge of an artificial cardiac pacemaker, the CO does not increase at all. As shown in Fig. 4.3-10, the progressive increase in the HR is associated with a proportionate decrease in the SV because of reduced diastole time and thus reduced EDV. Conversely, when the HR is reduced the ventricular diastole is prolonged leading to more ventricular filling and thus an increased SV.

During exercise, the sympathetic stimulation produces a marked increase in the HR due to positive chronotropism and moderate increase in the SV due to positive inotropism leading to manifold increase in the CO.

Integrated Control of Cardiac Output

In intact animals and humans, the intrinsic and extrinsic mechanisms described above operate simultaneously in an integrated way to maintain CO. Therefore, in a given situation, depending on the status of EDV and status of myocardial contractility, the individual will have one of the curves from the 'family of Frank–Starling curves'.

Interaction of Frank–Starling Mechanism and Myocardial Contractility

Factors causing increased myocardial contractility shift the Frank–Starling curve to the left (Fig. 4.3-11). The increased

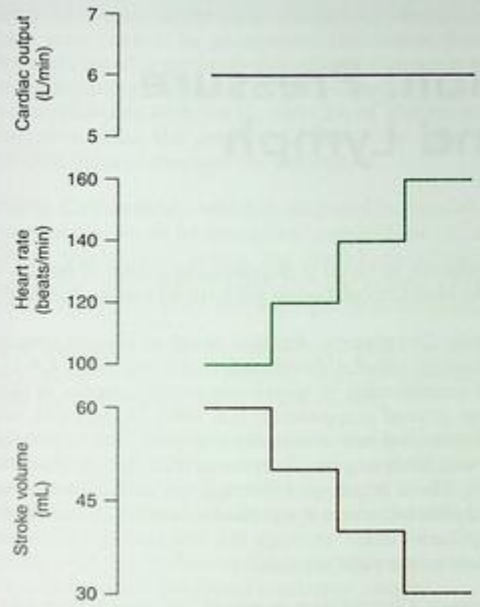


Figure 4.3-10 Effect of increase in heart rate through an artificial pacemaker on stroke volume and cardiac output.

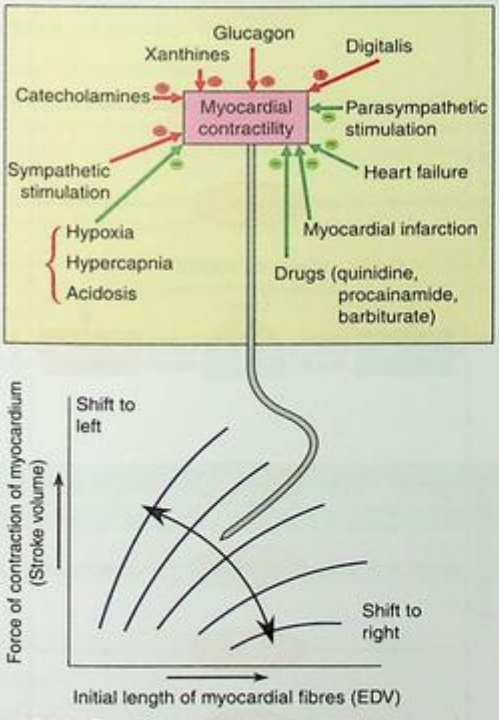


Figure 4.3-11 Effect of changes in myocardial contractility on the Frank–Starling curve. The factors which increase the contractility shift the curve to left and those that decrease the contractility shift the curve to right.

contractility (positive inotropism) refers to the greater contraction force at a given preload or EDV. The factors increasing myocardial contractility are as follows:

- *Sympathetic stimulation,*
- *Catecholamines,*
- *Xanthines* such as caffeine and theophylline,
- *Glucagon* and
- *Digitalis and related drugs.*

Factors Causing Decreased Myocardial Contractility shift the Frank–Starling curve to the right (Fig. 4.3-11). The decreased contractility (negative inotropism) represents a decrease in the force of contraction at any fibre length or ventricular volume. The factors decreasing myocardial contractility are as follows:

- Parasympathetic (vagal) stimulation,
- Heart failure,
- Myocardial infarction,
- Hypercapnia, hypoxia and acidosis and
- Drugs such as quinidine, procainamide and barbiturates.

Heart–Lung Preparation

The Frank–Starling's heart–lung preparation is an experimental set up in a dog, devised to demonstrate the effects of various factors on the activities of heart. In this preparation, as the name suggests, blood does not flow to any part of the body except the heart and the lungs. The animal is actually dead and heart is functionally denervated.

SELF-ASSESSMENT

1. Draw a labelled diagram of normal cardiac cycle to show various phases and their durations.
2. Define regulation of cardiac output.
3. Describe briefly:
   - Heart sounds
   - Arterial pulse
   - Left ventricular pressure changes in cardiac cycle
4. Differentiate between:
   - First and second heart sound
   - Isovolemic and rapid ejection phase of ventricular systole.
5. Write notes on:
   - Fick's principle
   - End-diastolic volume
   - Jugular venous pulse
   - Respiratory pump
   - Cardiac pump
   - Muscle pump
   - Vis-a-tergo force
   - Principle of indicator dilution method
6. Define the following:
   - Cardiac output
   - Stroke volume
   - Ejection fraction

4.4 Dynamics of Circulation: Pressure and Flow of Blood and Lymph

CHAPTER OUTLINE

Introduction

Functional Organization and Structure of Vascular System
Organization of Vascular System
Structure of Blood Vessels

Haemodynamics
General Principles Governing Blood Flow
Flow–Pressure–Resistance Relationship
Blood Flow and Pressure Gradient Relationship
Flow and Resistance Relationship
Velocity of Blood Flow
Blood Flow: Types and Distribution

Pressure and Flow in Various Functional Segments of Systemic Vascular Tree
Pressure and Flow Functions of Elastic Arteries
Pressure and Flow Functions of Muscular Arteries
Pressure and Flow Functions of Arterioles
Microcirculation
Lymphatic Circulation
Venous Circulation

Blood Pressure
Definitions (Terminology)
Determinants of Arterial Blood Pressure
Variations in Blood Pressure
Measurement of Blood Pressure
Regulation of Blood Pressure

INTRODUCTION

Dynamics of circulation is concerned with flow of blood and lymph and also the pressure in the various segments of the vascular system of the body. For descriptive purposes, the 'dynamics of circulation' is discussed under the following headings:

- Functional organization and structure of vascular system
- Haemodynamics
- Blood flow and pressure in different segments of circulatory system
- Blood pressure

FUNCTIONAL ORGANIZATION AND STRUCTURE OF VASCULAR SYSTEM

Organization of Vascular System

The vascular system is organized into two separate circulations, systemic and pulmonary, arranged in series. In addition, parallel to the circulation of blood is disposed circulation of lymph, which helps the blood circulation to perform its various functions.

Systemic Circulation supplies blood to various systemic organs through parallel distribution channels (Fig. 4.4-1). This parallel arrangement of vessels ensures the supply of blood of the same arterial composition (i.e. same O_2 and CO_2 tension, pH, glucose level and essentially the same arterial pressure) to the various body organs. In systemic circulation, from the left ventricle, blood is pumped through the arteries and arterioles to the capillaries, where it equilibrates with the interstitial fluid. The capillaries drain through the venules into the veins and ultimately to the right atrium.

Pulmonary Circulation is meant for oxygenation of blood. Pulmonary circulation is arranged in series with systemic

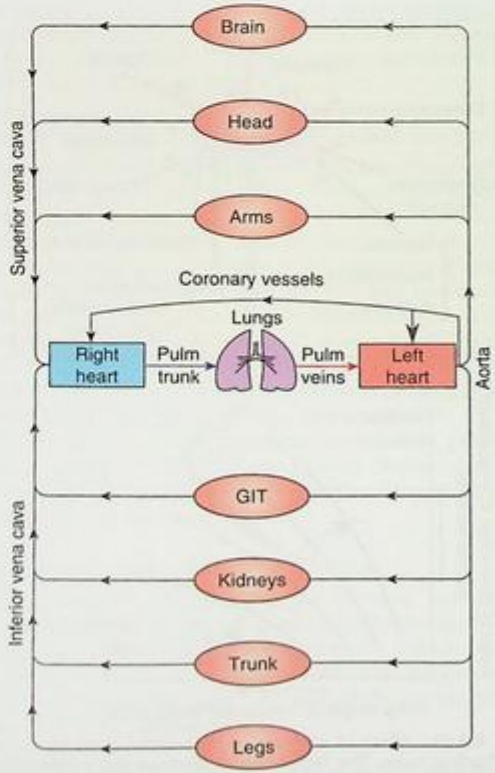


Figure 4.4-1 A schematic illustration of the organization of cardiovascular system depicting in series arrangement of pulmonary and systemic circulation and parallel arrangement of vessels supplying blood to the organs.

circulation, so it receives the same amount of blood over any significant time period. In pulmonary circulation, from the right ventricle, blood is pumped through the pulmonary arteries to the pulmonary capillaries. In the pulmonary capillaries, the blood equilibrates with the O_2 and CO_2 of alveolar air. The capillaries then drain the oxygenated blood through venules and then pulmonary veins into the left atrium.

Lymphatic Circulation, which is disposed in parallel to the circulation of blood can be considered a third type of circulation. Some tissue fluid enters the lymphatic channels as lymph, which is ultimately drained into the venous system via the thoracic lymphatic duct and the right lymphatic duct.

Systemic Vascular Tree For descriptive purposes and from functional point of view, the systemic vascular tree can be divided into the following types of blood vessels:

- *Large elastic arteries* (windkessel vessels) include aorta and its principal branches, such as carotid, iliac and axillary arteries.
- *Large muscular* arteries (distribution vessels) which include most of the arteries of the body, e.g. arteries like radial, ulnar, popliteal.
- Arterioles and precapillary sphincters (resistance vessels).
- Meta-arterioles and capillaries (exchange vessels).
- Venules (postcapillary resistance vessels).
- Veins (capacitance vessels).
- Arteriovenous anastomoses (shunt or thoroughfare vessels).

Structure of Blood Vessels

Structural Characteristics

General Structural Characteristics Histologically, walls of most of the blood vessels except the capillaries consist of three coats. General structural characteristics of a large artery are as follows (Fig. 4.4-2).

1. Tunica Intima. It is the innermost coat of the vessel wall. In large arteries, from inside to outside, it consists of:

- *Endothelial lining,* which is very smooth and silky, and consists of a single layer of cells. It lies in contact with the blood.
- *Basal lamina* is a thin layer of glycoprotein which lines the external aspect of the endothelium.

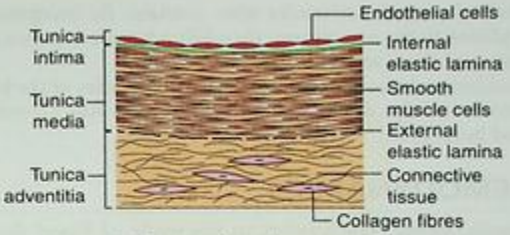


Figure 4.4-2 Histological structure of an artery.

- *Subendothelial connective tissue* is a delicate layer of connective tissue which lies outside the basal lamina.
- *Internal elastic lamina* is a thin membrane formed by the elastic fibres.

2. Tunica Media. It is the middle, thickest coat of the vessel wall. It consists of smooth muscles and elastic tissue. The ratio of these two tissues varies from vessel to vessel. On the outside, tunica media is limited by a membrane formed by the elastic fibres called the *external elastic lamina.*

3. Tunica Adventitia. It is the outermost coat of the vessel wall. It is made of connective tissue in which collagen fibres are prominent. This layer prevents undue stretching or distension of the blood vessel.

Essential Characteristics Essential characteristics of blood vessels like lumen diameter, wall thickness, approximate total cross-sectional area and percentage of blood volume contained are shown in Table 4.4-1.

Innervational Characteristics

- Smooth muscles of the blood vessels are innervated by the sympathetic fibres. These muscles contain α adrenergic receptors. Therefore, noradrenaline causes contraction of muscle fibres leading to vasoconstriction.
- Sympathetic fibres exert tonic effect even at rest, resulting in the existence of vasomotor tone in the blood vessels.
- Stimulation of sympathetics increases the vasomotor tone; as a result the vessels are constricted and narrowed.
- Inhibition of sympathetic discharge results in a decreased vasomotor tone and hence vasodilatation.

TABLE 4.4-1 Essential Characteristics of Various Types of Blood Vessels

Types of blood vessels	Lumen diameter	Cross-sectional area (cm^2)	Velocity of blood flow	Pressure as cumulative blood volume %
• Aorta	2.5 cm	4.5	20 cm/s	2
• Arteries	0.4 cm	20	4 cm/s	8
• Arterioles	30 μm	400	2 mm/s	1
• Capillaries	05 μm	4500	0.2 mm/s	5
• Venules	20 μm	4000	0.2 mm/se	
• Vein	0.5 cm	40	2 cm/s	54
• Vena cava	3 cm	18	4.5 cm/s	

- Skeletal muscle arterioles also contain β_2 receptors in addition to the α receptors; therefore adrenaline causes dilatation of these vessels.
- Besides α adrenergic receptors, smooth muscles of the blood vessels are also stimulated by other agents like O_2 tension and lactic acid.

HAEMODYNAMICS

Haemodynamics, which refers to the study of blood flow in various segments of the vascular system, can be discussed under the following headings:

- General principles governing (factors affecting) blood flow
- Types of blood flow
- Measurement of blood flow
- Distribution of blood flow to various regions of the body
- Regulation of blood flow in different situations

General Principles Governing (Factors Affecting) Blood Flow

Flow–Pressure–Resistance Relationship

Relationship between the flow of a fluid with the pressure and resistance offered to it through a rigid tube was studied by a French physiologist Poiseuille in 1842 and Hagen. This relationship is known as Poiseuille's law or Poiseuille–Hagen law.

Poiseuille's Law

Poiseuille's law expressing the relation between the flow (Q) and pressure gradient (ΔP) in a long narrow tube of length (L), the viscosity of fluid (η) and the radius (r) of the tube is as:

$$Q = \frac{\Delta P \pi r^4}{8\eta l}$$

Thus, according to the Poiseuille's law, the flow (Q) of a Newtonian fluid through a rigid tube is determined by the following.

1. Pressure Gradient (ΔP), i.e. difference in the pressure between the two ends of the tube. In other words, fluid always flows from an area of high pressure (P_1) to one of lower pressure (P_2), and rate of flow (Q) is determined by the pressure gradient ($P_1 - P_2$), i.e. $Q \propto \Delta P$ or ($P_1 - P_2$).
2. Radius of Tube. The flow of fluid varies directly as the fourth power of radius (r^4). Thus if the radius is halved, the flow will decrease by 16 times and vice versa. Thus, this factor is very important for the flow of blood through the blood vessels.
3. Viscosity of Fluid (η). The flow of fluid varies inversely with the viscosity of fluid, i.e. greater the viscosity, lesser the flow and vice versa.
4. Length of the Tube (L). The flow is inversely proportional to the length of the tube. This is easily understandable, as every segment of the tube is offering resistance to the flow; therefore, longer the length greater will be the total resistance offered.

Resistance (R). According to mathematical calculation in principles of physics, resistance (R) is represented by $8\,Ln/\pi r^4$. By replacing $8\,Ln/\pi r^4$ with R in the Poiseuille's law, it becomes:

$$Q = \frac{\Delta P}{R}$$

Thus, the Poiseuille's law can be considered analogous to the Ohm's law of current in which:

$$\text{Current (flow)} = \frac{\text{Voltage (pressure gradient)}}{\text{Resistance}}$$

Hence, the rate of flow (Q) is inversely proportional to the R.

The Poiseuille's law is valid for straight rigid tubes with Newtonian fluid flowing through them. The blood vessels are not rigid and the blood is not a Newtonian fluid; therefore, strictly speaking the Poiseuille's law does not apply to flow of blood through the vascular system. Nevertheless, the important principles relating flow, pressure gradient and resistance remain applicable, so they are discussed in relation to blood flow as:

- Blood flow and pressure gradient relationship
- Blood flow and resistance relationship

Blood Flow and Pressure Gradient Relationship

According to the Poiseuille's law, fluid always moves from an area of higher pressure to the one of lower pressure. This downhill movement of blood (i.e. along the pressure gradient) occurs in the vascular system. In the systemic circulation, pressure at the beginning of aorta is about 100 mm Hg and is nearly zero near the terminal portion of inferior vena cava (Fig. 4.4-3). Therefore, $P_1 - P_2 = (100 - 0) = 100$ mm Hg. Note the progressive decrease in pressure from the left ventricle through the systemic circulation until the blood enters the right ventricle. It is important to note that greatest pressure drop occurs in the arterioles, which represent the highest resistance segment of the systemic circulation.

Critical Closing Pressure

The flow–pressure relationship in a rigid tube is linear, so flow will cease only if the pressure is zero (Fig. 4.4-4A). However, in a blood vessel the flow ceases when the blood pressure is 20 mm Hg or even more (Fig. 4.4-4B). The pressure value at which the vessel collapses, its lumen closes and flow ceases is called *critical*

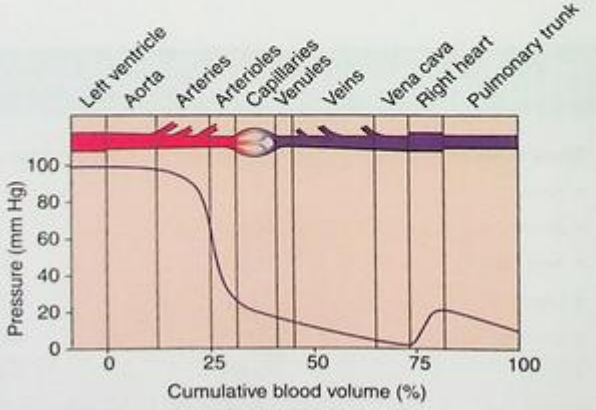


Figure 4.4-3 Mean lateral pressure in various components of vascular system and cumulative blood volume.

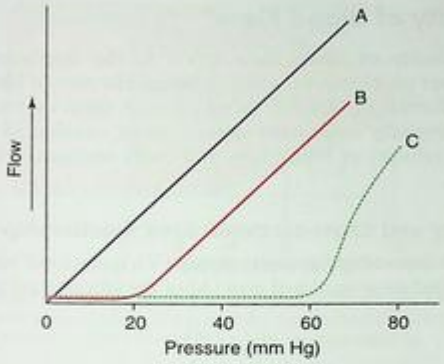


Figure 4.4-4 Relationship of pressure and flow in a rigid tube (A) in a blood vessel; (B) on sympathetic stimulation; and (C) depicting critical closing pressure.

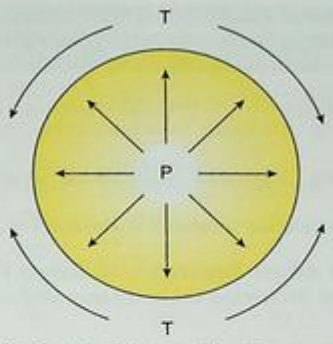


Figure 4.4-5 Relationship between distending pressure (*P*) and wall tension (*T*) in a hollow viscus.

closing pressure (CCP). The blood flow ceases when the blood pressure falls below the CCP because:

- Certain amount of intramural pressure is essentially required to push the RBCs (with average diameter of 7.5 μm) through the capillaries (average diameter 5 μm).
- Furthermore, the tissue pressure exerted over the vessels also causes their collapse. So, certain amount of intramural pressure is must to counteract the tissue pressure and thus to keep the vessels patent and maintain the blood to flow.
- On sympathetic inhibition, value of CCP falls to 0 mm Hg.

Equilibrium of Factors at Critical Closing Pressure

- In general, vasomotor tone of the blood vessels tries to constrict the vessels.
- Intramural pressure tries to dilate the blood vessels up to a certain limit. When a point is reached where the intramural pressure (P) is not able to maintain an equilibrium with tension (T) in the vessel wall. At this point, the blood vessel closes and the pressure at which it occurs is called CCP. Laplace law described below helps to explain this equilibrium relationship.

Law of Laplace Law of Laplace governs the relation between the distending pressure and tension in the wall of a distensible viscus including blood vessels (Fig. 4.4-5). According to this law, the distending pressure (*P*) in a distensible hollow object is equal at equilibrium to the tension in wall (T) divided by the two principal radii of curvature of the object (r_1 and r_2):

$$P = T\left(\frac{1}{r_1} + \frac{1}{r_2}\right), \text{ where}$$

T is expressed in dynes/cm
r_1 and r_2 are in cm
So, P is expressed in dynes/cm^2

- *In a sphere*, $r_1 = r_2$. Therefore,

$$P = \frac{T}{r}$$

- *In a cylinder* such as a blood vessel, one radius is infinite. Therefore,

$$P = \frac{T}{r}$$

Physiological Applications of Law of Laplace This law applies to all the hollow viscous structures in the body. Some of its important applications are discussed below.
In Vascular System. As described above, for the blood vessels Laplace equation is P = T/r. This equation shows that smaller is the radius of a blood vessel, lesser is the tension (T) on the walls of the blood vessel required to balance the distending pressure or force (P). For example:

- *In aorta* the tension at normal pressure is 170,000 dynes/cm.
- *In inferior vena cava* it is about 21,000 dynes/cm.
- But in the capillaries, it is approximately 16 dynes/cm. This explains, why capillaries being so thin walled and delicate are not prone to rupture.

In Heart. *Law of Laplace also explains* the disadvantage faced by a dilated heart. When the radius of a cardiac chamber is increased, a greater tension must be developed in the myocardium to produce any given pressure; consequently, a dilated heart must do more work than a nondilated heart.

Flow and Resistance Relationship From the Poiseuille's law, it can be derived that the flow is inversely proportional to the resistance, i.e. $Q \propto 1/R$; and that resistance is represented by $8\,L\,\eta/\pi r^4$, i.e. resistance depends on the length (L) and fourth power of radius (r^4) of the tube and viscosity of the fluid (η).

Peripheral Resistance Unit (PRU) As discussed above, the Poiseuille's law can be considered analogous to the Ohm's law, so:

$$\text{Flow, i.e. } Q(\text{mL/s}) = \frac{P_1 - P_2 (\text{mm of Hg})}{\text{Resistance (R)}}$$

$$\text{Thus, } R = \frac{P_1 - P_2 \text{ (mm of Hg)}}{Q \text{ (mL/s)}}$$

Therefore, in vascular system, *PRU* is mm Hg/mL/s.

Total Peripheral Resistance (TPR) At rest, the resistance (R) of the entire systemic circulation is called 'total peripheral resistance'. Its values are as follows:

- At rest, TPR is 1 PRU (1 mm Hg/mL/s).
- TPR, during maximum vasoconstriction may increase to 4 PRU.
- TPR during maximum vasodilation may decrease to 0.2 PRU.
- Pulmonary vascular resistance is about 0.1–0.2 PRU.

Factors that Affect Resistance to Blood Flow The major factors that determine the resistance to flood flow are as follows:

I. The viscosity of blood
II. The radius of vessels

I. Blood Viscosity and Resistance

Definition and Unit of Viscosity *Viscosity* was described by Isaac Newton in 1713 as an internal friction to flow in a fluid or lack of slipperiness. These terms emphasize that when fluid moves along a tube, laminae in the fluid slip on one another and move at different speeds thereby causing a velocity gradient in a direction perpendicular to the wall of the tube. Thus, resistance met by the fluid moving through a tube in a streamlined flow is due to the friction between adjacent laminae and not due to the friction between vessel wall and fluid. Thus, greater the internal friction, greater is difference in velocity (shear rate) between two laminae and greater the coefficient of viscosity.

***Unit of viscosity* is *Poise* (after Poiseuille).** A fluid of 1 poise viscosity has a force of 1 dyne/cm^2 of contact between layers when flowing with a velocity gradient of 1 cm/s. One Poise is considered to be consisting of 100 centipoise (CP). *Viscosity of water* at 21°C is 0.01 poise or 1 centipoise.

Relative viscosity is a more often used term and refers to the viscosity of a fluid relative to the viscosity of water at body temperature (37°C).

- Water has a viscosity of 0.695 centipoise at body temperature.
- Plasma, which has a viscosity of 1.2 centipoise at 37°C, thus has a relative viscosity of 1.7.
- Blood (plasma plus cells), which has a viscosity of 2.8–3 centipoise at 37°C, thus has a relative viscosity of about 4–5.

II. Radius of Blood Vessels and Resistance As mentioned earlier, the rate of flow is proportional to the fourth power of the radius (r^4) of the blood vessels. Thus, even a small change in the calibre of the blood vessels will produce a marked change in the blood flow. For example, at a pressure head of 100 mm Hg, the change in the flow rate with change in the radius:

Radius	Flow Rate
1 mm	1 mL/min
2 mm	16 mL/min
4 mm	256 mL/min

Among the blood vessels, in aorta and large arteries, there is little resistance. Arterioles are the major seat of vascular resistance.

Velocity of Blood Flow

The velocity of blood flow refers to the displacement of blood per unit time, i.e. cm/s, whereas the rate of blood flow is the amount of blood flowing per unit time, i.e. cm^3/s. The physiologically important aspects to be considered in relation to velocity of blood flow and cross-sectional area are as follows.

Velocity and Cross-sectional Area Relationship

- The relationship between velocity (V), quantity of blood flow (Q) and cross-sectional area (A) of the blood vessel is:

$$V = \frac{Q}{A}$$

- Thus, if quantity of blood flow (Q) remains constant and the cross-sectional area (A) increases, then the velocity of blood flow will decrease.
- The cross-sectional area of capillaries is 1000 times as that of the aorta, so the velocity of blood flow in the capillaries is approximately 1 mm/s as compared to 40 cm/s in the aorta.
- The total cross-sectional area of various types of blood vessels, the velocity of blood flow and pressure in the various segments of the cardiovascular system plotted as a function of the cumulative blood volume is shown in Fig. 4.4-6 and Table 4.4-1.

Blood Flow: Types and Distribution

Types of Blood Flow

Blood flow in the vascular system is of two types:

- Laminar blood flow
- Turbulent blood flow

Laminar Blood Flow Blood flow in the blood vessels is normally in streamline, like the flow of liquids in narrow rigid tubes. Such a blood flow is called laminar blood flow and is

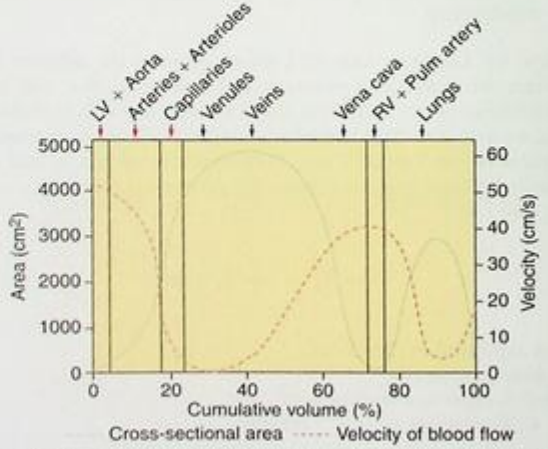


Figure 4.4-6 Relationship between the cross-sectional area, velocity of blood flow and pressure as a function of cumulative blood volume.

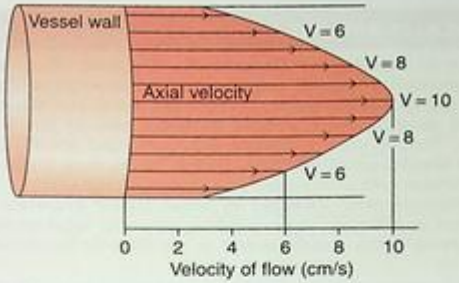


Figure 4.4-7 Laminar blood flow showing different velocities of the different laminae resulting in a parabolic distribution of velocities. Note that the central core of blood stream has greatest velocity.

considered to consist of a series of thin laminae slipping over one another.

- The outermost lamina, i.e. an infinitely thin layer of blood in contact with the wall of the blood vessel, does not move and the next lamina has some velocity. The subsequent inner layers have progressively increasing velocity, and thus the innermost lamina, i.e. the core of the blood stream, has the maximum velocity (Fig. 4.4-7).
- The laminar blood flow being streamlined is noiseless and within physiological limits shows a linear relationship with the pressure.

Turbulent Blood Flow The above described laminar blood flow occurs up to a certain velocity, at or above which the blood flow becomes turbulent. The velocity of flow at which blood flow becomes turbulent is called critical velocity.

- In turbulent blood flow, the blood moves in an irregular varying paths continuously mixing within the vessel and colliding with the vessel wall. This causes a greater energy loss as compared to the laminar flow.
- The turbulent blood flow is noisy and does not show a typical linear relationship with the pressure.
- Normally, none of the small vessels show turbulent flow. In humans, the critical velocity sometimes exceeds in the aorta at the peak of systole.

Probability of Turbulence The chances of blood flow becoming turbulent are determined by the *probability of turbulence*, which is denoted as Re (Reynold number), named after the person who described it.

- Directly proportional to the:
  - density of blood (ρ, i.e. rho) equal to 1
  - diameter of the vessel (D) in cm
  - velocity of blood flow (V) in cm/s
- Indirectly proportional to:
  - viscosity of the blood (η, i.e. eta) in poises

$$\text{thus Re} = \frac{\rho DV}{\eta}$$

- Blood flow is usually not turbulent when Re is less than 2000.
- Chances of blood flow becoming turbulent are increased when Re exceeds 2000.

When Re is more than 3000, turbulence is almost always present.

TABLE 4.4-2 Distribution of Blood Flow to Various Organs of the Body

Organs	BLOOD FLOW PER ORGAN (ml/min)		BLOOD FLOW (ml/100 g/min)	
	At Rest	During Maximum Activity	At Rest	During Maximum Activity
Heart	250	1200	80	400
Brain	750	2100	55	150
Liver	1500	3000	58	120
Skeletal muscles	150	1800	04	70
Kidney	1200	1400	400	450
Skin	200	3500	08	150

Conditions Associated with Turbulent Blood Flow

- Constriction of the artery by an atherosclerotic plaque or by any other cause, e.g. application of external pressure while measuring the blood pressure with a sphygmomanometer is associated with a blood flow velocity, which exceeds critical velocity and thus causes the turbulent blood flow. The turbulent flow generates vibrations (sounds) which can be heard over the artery by a stethoscope, e.g. *Korotkoff sounds* heard while recording the blood pressure or the *murmur* heard over a constricted artery.
- *Anaemia.*

Distribution of Blood Flow to Various Regions of the Body

At rest, about 5 L of blood enters aorta per minute. In terms of tissue weight, blood flow to liver, brain and heart is very high. Kidney has a high blood flow because it is related to the excretory function rather than the metabolic requirement. The distribution of blood flow to various organs and regions of the body during resting conditions and during maximum activity conditions is shown in Table 4.4-2.

- At rest, at least 50% of the circulating blood volume is in the systemic veins.
- Twelve percent is in the heart cavities, and 18% in the lower pressure pulmonary circulation. Only 2% in the aorta, 8% in the arteries, 1% in the arterioles and 5% in the capillaries.
- When extra blood is administered by transfusion, less than 1% of it is distributed in the arterial system (the high pressure system) and all the rest in the systemic veins, pulmonary circulation and heart chambers other than the left ventricle (the 'low pressure system').

PRESSURE AND FLOW IN VARIOUS FUNCTIONAL SEGMENTS OF SYSTEMIC VASCULAR TREE

Pressure and Flow Functions of Elastic Arteries

The large elastic arteries (windkessel vessels) include aorta and its principal branches, such as carotid, iliac and axillary arteries.

These vessels contain elastic tissue in their walls in abundance, which provides them two properties of distensibility and elastic recoil. The effect of these two properties of the elastic arteries on pressure and flow of blood is given below.

Distensibility

As we know, the heart acts as a pump and ejects about 70 mL of blood into the aorta with each systole. The distensibility (compliance) of the elastic arteries allows them to accommodate the stroke volume of heart with only a moderate increase in pressure (from 80 to 120 mm Hg) (Fig. 4.4-8A). Due to distension of these vessels a part of energy released from the heart is stored as the potential energy in the wall of aorta.

Elastic Recoil

During diastole, the stretched elastic wall of the aorta recoils and the potential energy stored in the wall is released onto the blood. This causes the blood to flow during diastole also; in this way the pressure in the aorta does not fall below 80 mm Hg (Fig. 4.4-8B). In other words, the elastic recoil of big arteries acts as a subsidiary pump for a continuous blood flow. This recoil effect is called *windkessel effect*. Windkessel is a German word meaning elastic reservoir.

Functions of Elastic Vessels

1. They reduce the velocity of blood flow to some extent during the ventricular contraction (systole) due to property of distensibility.
2. They cause increase in the velocity of blood flow to some extent during the ventricular diastole by elastic recoil. Thus, the windkessel effect reduces the energy expenditure of heart.
3. Pumping action of the heart along with the elastic recoil of aorta together constitutes a driving force for blood to move forward (towards periphery). This force is called *vis-a-tergo force* and is an important determinant for the venous return.
4. Conversion of pulsatile blood flow from the heart to a steady continuous flow. The elastic vessels act together with arterioles (resistance vessels) to convert this pulsatile flow into a steady continuous flow in the tissue capillaries, which allows maximum exchange between the blood and tissues.

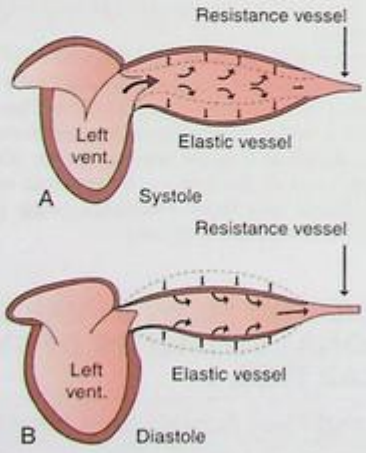


Figure 4.4-8 Distensibility (A) and elastic recoil (B) seen in aorta, and its principal branches maintain arterial pressure and flow during diastole.

CLINICALLY APPLIED ASPECTS

1. Due to Age-Related Degenerative Changes, the elasticity of large vessels is decreased and so is the windkessel effect. Therefore, in old age systolic blood pressure increases due to loss of distensibility and diastolic blood pressure decreases (due to loss of elastic recoil). Thus, in normal healthy individual aged about 70 years, typical blood pressure is 160/70 mm Hg. That is, there occurs *systolic hypertension* with an *increased pulse pressure* (SBP-DBP).

2. Atherosclerotic Changes in Small Blood Vessels are also common in old age. These produce *essential hypertension, i.e.* an increase in the systolic as well as the diastolic blood pressure.

Pressure and Flow Functions of Muscular Arteries

The muscular arteries composed of most of the named arteries in the body, such as radial artery, facial artery and ophthalmic artery. These arteries serve as the *distributing channels* to the organs.

Pressure and Flow Functions of Arterioles

Structural Characteristics

Each arteriole is only a few millimetre long and branches many a times to supply about 10–100 capillaries. The characteristic features of arterioles are given below.

- A thick muscular wall having a profuse vasomotor (sympathetic) innervations.
- A relatively narrow lumen (30 μm) because of which these vessels are considered the major site of peripheral resistance (PR). The arterial pressure drops by about 50 mm Hg while passing through a few millimetre long arterioles.

Functions of Arterioles

1. Control of Blood Flow to the Organs The arterioles play a major role in the control of blood flow to the organs or tissues. So, they are considered *stopcocks (valves) of circulation.* The constriction of the arterioles increases the resistance and decreases the blood flow, whereas dilation of arterioles decreases the resistance and increases the blood flow. The arterioles control blood flow to the organs by the following two mechanisms.

Control of Blood Flow during Alterations in Blood Pressure (Autoregulation)

Autoregulation. It is the ability of an organ or tissue to adjust its vascular resistance and maintain a relatively constant blood flow over a wide range of arterial pressure (Fig. 4.4-9). Autoregulation is well developed in the kidney, brain, heart, skeletal muscle and mesentery. Two theories have been put forward to explain the phenomenon of autoregulation.

Metabolic theory proposed that an increased arterial blood pressure initially increases the blood flow to a tissue or organ. This increased blood flow washes out the vasodilator substances such as CO_2, H^+, nitric oxide, adenosine, prostaglandins, K^+, phosphate ions and low oxygen levels in the area. As a result, the arterioles constrict, the vascular resistance increases and the blood flow returns to normal.

Myogenic theory. According to this theory, the vascular smooth muscle (VSM) responds to wall tension. An increase in the

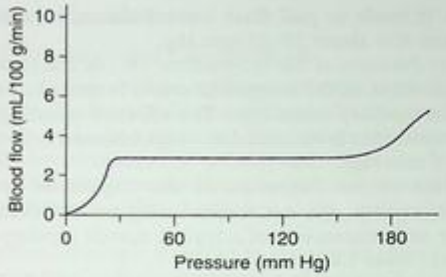


Figure 4.4-9 Autoregulation of blood flow. *Note:* The blood flow remains relatively constant over a wide range of arterial pressure. This is accomplished by change in resistance proportionate to change in arterial pressure.

arterial pressure initially stretches the smooth muscle fibres, in response to which the VSM contracts, increases the resistance and compensates for the higher arterial pressure, returning the blood flow to control levels.

2. Conversion of Pulsatile Flow from the Heart to a Steady Continuous Flow As described in the function of the elastic vessels, the arterioles along with the elastic vessels convert the pulsatile flow in the arteries to a steady flow in the capillaries.

Microcirculation

Architecture of Microcirculation

The microcirculation involves a meshwork of vessels that are less than 100 μm in diameter. These include small arterioles, meta-arterioles, capillaries, postcapillary venules and arteriovenous shunts (Fig. 4.4-10).

Meta-arterioles. The arterioles divide into smaller muscles walled vessels, sometimes called meta-arterioles, and these, in turn, feed into capillaries.

Precapillary sphincters refer to a cuff of smooth muscle cells that surround the origin of capillaries. These determine the size of the capillary exchange area at one particular moment in the tissue. For example, increase in the sphincter patency increases number of open capillaries. Precapillary sphincters respond to local or circulating vasoconstrictor substances.

Capillaries arise directly from the arterioles or meta-arterioles. These vessels allow easy exchange of gases and nutritive substances across them and so are also called *exchange vessels.* Capillaries constitute the most important segment of the circulatory system.

Postcapillary venules, which measure 20–60 μm in diameter, are the *most permeable part* of the microcirculation.

Arteriovenous anastomosis *(shunt or thoroughfare vessels).* These are short, low-resistance connections between the arterioles and veins, bypassing the capillaries. These are abundantly innervated by the vasomotor sympathetic fibres. These vessels are especially found in the skin of fingers, toes and ear lobes, where they are involved in the regulation of body temperature.

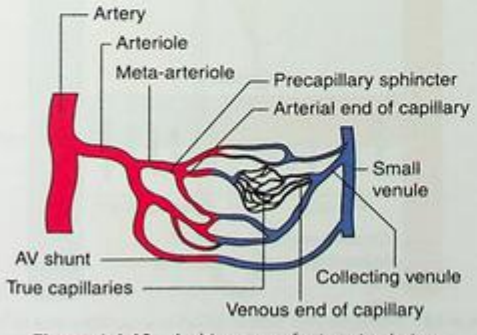


Figure 4.4-10 Architecture of microcirculation.

Structural Characteristics of Capillaries

Each capillary has an average diameter of 5 μm, length of 50 μm, wall thickness of 1 μm and cross-sectional area of 40 μm^2.

The capillary wall essentially consists of a single layer of endothelial cells which are lined on the outside by a basal lamina (glycoprotein), overlying the basal lamina there may be isolated branching perivascular cells called *pericytes.*

The endothelial structure of capillaries varies in different organs depending on the function of the particular tissue. Under the electron microscope, three types of capillaries have been identified.

1. Continuous Capillaries are characterized by a single layer of endothelial cells which are almost continuous, except for small clefts of 6–7 nm in size in between the cells. It is believed that most of the water-soluble ions (Fig. 4.4.11A) and molecules pass across the capillary through these clefts (or *slit pores).* These are the most common type of capillaries and are found in most of the body tissues, e.g. skeletal muscle, adipose tissue, connective tissue and pulmonary circulation.

2. Fenestrated Capillaries consist of thin endothelial cells with large fenestrations (20–100 nm in diameter) in between, which are bridged by a thin basement membrane that surrounds the endothelial cells (Fig. 4.4-11B). The fenestrations permit the passage of relatively large molecules and make the capillaries porous. Fenestrated capillaries are found in the renal glomeruli, intestinal villi and most endocrinal glands.

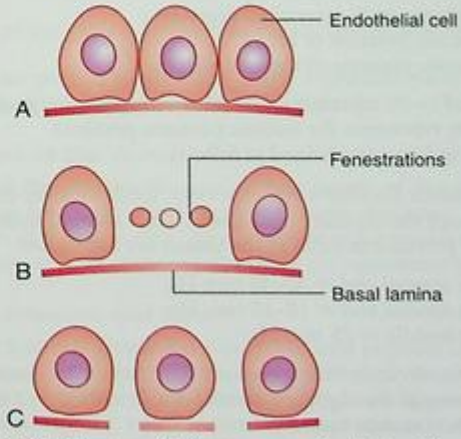


Figure 4.4-11 Structure of different types of capillaries: (A) continuous; (B) fenestrated; and (C) discontinuous.

3. Discontinuous Capillaries are characterized by large gaps (600–3000 nm in diameter) between endothelial cells that are not closed by the basement membrane (Fig. 4.4-11C). Through these gaps even formed elements of blood can pass freely. Such capillaries are also called sinusoids and are found in the bone marrow, liver and spleen.

Functions of Capillaries

The primary function of circulation is to transport nutrients to the tissues and remove waste products – occur in the capillaries. About 10 billion capillaries which have a total surface area 500–700 m^2 provide this function for the body. The cross-sectional area of capillary bed when fully patent is 2800 times that of aorta.

In active tissues, the meta-arterioles and the precapillary sphincters dilate and the blood flows through all the capillaries (active capillaries).

The opening and closing of the precapillary sphincters is controlled mostly by the local metabolic vasodilators and possibly also through sympathetic innervation.

Transcapillary Exchange

The capillary blood brings oxygen, electrolytes and nutrients to the tissues and removes the waste products of cellular metabolism. The exchange of these substances occurs across the thin membrane formed by the endothelial cells.

Mechanisms of Transcapillary Exchange Exchange of substances occurs primarily in the capillaries and postcapillary venules. The major mechanisms of exchange are diffusion and filtration (bulk flow). Some substances also pass through the cells by the *vesicular transport.*

Filtration and Reabsorption across Microvascular Endothelium The rate of filtration and absorption at any point along the capillary wall depends on the balance of forces known as *Starling forces.* According to the Starling hypothesis, the filtration absorption is expressed as follows:

$$K(P_c + \pi_i) - (P_i + \pi_c),$$

K = the permeability-surface area coefficient
P_c = the hydrostatic capillary pressure
P_i = the hydrostatic interstitial pressure
π_c = oncotic pressure of blood
π_i = oncotic pressure of the interstitium

Thus, $P_c - P_i$, represents the hydrostatic pressure gradient
$\pi_c - \pi_i$ represents the oncotic pressure gradient.
Starling forces are defined as follows.

1. Hydrostatic Capillary Pressure (Pc) tends to force the fluid out through the capillary membrane. The values of hydrostatic capillary pressure in most of the tissues are as follows:

- At the arterial end = 30–40 mm Hg
- At the venous end = 10–15 mm Hg
- In the middle = 25 mm Hg

2. Hydrostatic Interstitial Pressure (P_i) tends to force fluid inward through the capillary membrane. It is about −2 mm Hg in the subcutaneous tissue.

3. Oncotic Pressure of Blood or Plasma Colloid Osmotic Pressure (π_c) results from the osmotic pressure of plasma proteins. It tends to pull fluid inward through the capillary membrane. It is about 25–27 mm Hg.

4. Oncotic Pressure of the Interstitium (π_i) is due to the presence of proteins in the interstitial space. It tends to pull fluid out of the capillary membrane. The effective oncotic pressure in the interstitium is estimated to range between 5–10 mm Hg (average 8 mm Hg).

Calculation of Net Filtration at the Capillaries From the above description, the net forces acting on the fluid at the arteriolar and venous end of a typical muscle *capillary* can be calculated (Table 4.4-3).

However, over the length of the capillary, the hydrostatic pressure gradually declines to zero near the middle of capillary. From here the inward forces become dominant and reabsorption process starts to reach its maximum at the venular end (Fig. 4.4-12).

TABLE 4.4-3 Calculation of Net Filtration Force at the Capillaries

	At the Arteriolar End (mm Hg)	At the Venous End (mm Hg)
• **Forces tending to move fluid outward**		
• Capillary hydrostatic pressure (P_c)	35	10
• Interstitial oncotic pressure (π_i)	3	3
Total outward force ($P_c + \pi_i$)	38	13
• **Forces tending to move fluid inward**		
• Oncotic pressure of blood (π_c)	25	25
• Interstitial hydrostatic pressure (P_i)	−2	−2
Total inward force ($\pi_c + P_i$)	23	23
• **Filtering force**	(38 – 23) 15	(13 – 23) −10
• **Net filtering force of the whole capillary**	= (15 – 10) = 5	

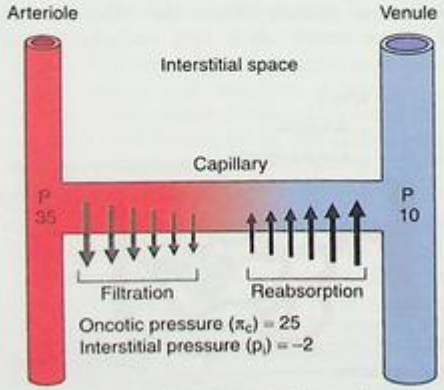


Figure 4.4-12 Filtration and reabsorption in a capillary due to balance of the Starling forces.

Lymphatic Circulation

Lymph: Formation and Composition

Formation As discussed in capillary exchange, most (90%) of the fluid filtered at the arterial end of the capillary is reabsorbed at its venous end, the remaining 10% enters the circulation through the lymphatics and is called lymph. Thus, the lymph is a transudate formed from the blood in the tissue spaces, i.e. it is derived from the interstitial fluid.

Composition of lymph is similar to the plasma except that its protein content is usually lower than that of the plasma (2–5 g%).
Protein content of the lymph varies with the region it drains:
Fat content. The lymphatic system also provides a route of absorption of long-chained fatty acids and cholesterol from the intestine (in the form of *chylomicrons);* therefore, after a fatty meal these fat globules may be so numerous that lymph becomes milky and is then called *chyle.*
Cellular content. Suspended in the lymph are cells that are chiefly lymphocytes. Most of these lymphocytes are added to the lymph as it passes through the lymph nodes.

Lymphatic Vessels

The lymphatic system constitutes an accessory route for the removal of interstitial fluid. The small lymph vessels are called lymph capillaries, the large lymph vessels are called lymphatic trunks and the largest lymph vessel is thoracic duct.

Lymph Capillaries The lymph capillaries *originate* as closed endothelial tubes that are permeable to fluid and high-molecular weight compounds.

Lymph capillaries (Fig. 4.4-13) are basically similar to that of the blood capillaries. The junctions between endothelial cells are open. In fact, the edges of the endothelial cells overlap in such a way that they form minute flap valves.

Larger Lymph Vessels The lymphatic capillaries join to form larger lymph vessels which ultimately form lymphatic trunks and lymphatic ducts as:

Thoracic duct is the largest lymph vessel in the body. It carries lymph from both sides of the body below the diaphragm and from the left side above the diaphragm.

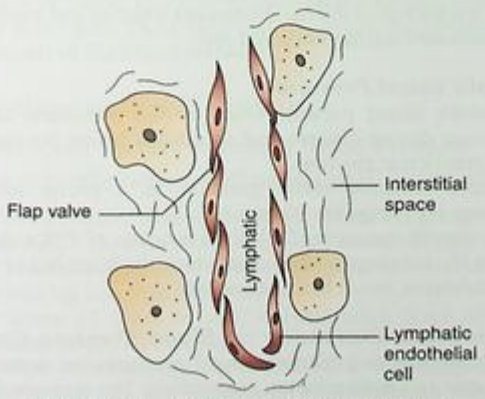


Figure 4.4-13 Structure of a lymphatic capillary.

The thoracic duct ends by opening into the junction of the left subclavian vein and the internal jugular vein.
Right lymphatic duct drains lymph from the right half of the body above the diaphragm. It ends by opening into the right subclavian vein.

Structure of Larger Lymph Vessels is similar to that of the veins:

- *Three coats,* i.e. tunica intima, tunica media and tunica adventitia can be distinguished.
- *Valves* similar to those in veins are present in abundance in small as well as in large lymphatic vessels. The valves often give lymph vessels a beaded appearance.

Lymph Flow

Functions of Lymph Flow

1. Returns Proteins from Tissue Spaces to Blood. The lymphatic system recovers approximately 200 g of protein daily that has been lost from the microcirculation.
2. Absorption of Nutrients, especially fats from the gastrointestinal tract.
3. Acts as a Transport Mechanism to remove red blood cells that have lost into the tissues as a result of haemorrhage.
4. Supplies Nutrients and Oxygen to those parts where blood cannot reach.
5. Role in Defence Mechanism. Lymph nodes associated with lymphatic system act as efficient filters. They have sinuses lined with phagocytic cells that engulf bacteria, red cells and other particulate material.

Normal Lymph Flow

Normal lymph flow is 2–4 L/day (80–150 mL/h) for the entire body.

Venous Circulation

Structural Characteristics of Veins

Walls of veins, as compared to arteries, at equivalent levels in the vascular tree are thin walled and contain small amount of elastic tissue and smooth muscle, and have larger lumen. Because of their structural characteristics, they are more distensible and collapsible.

Lumen of the veins is larger than the equivalent arteries.

Valves are present in the veins of the dependent parts of the body (Fig. 4.3-9) that prevent the back flow of venous blood.

Functions of the Veins

1. Blood Reservoirs Because of their feature of *distensibility and collapsibility,* the veins serve as blood reservoirs. About 60%–70% of the circulating blood is present in the venous system. Due to this property, veins are also called the *capacitance vessels.*

Venous Pressure and Flow

Central Venous Pressure Central venous pressure refers to the pressure in the right atrium because all the systemic veins open into the right atrium. The normal right atrial pressure is about 0 mm Hg, (i.e. equal to atmospheric pressure) but it can rise to as high as 20–30 mm Hg under abnormal conditions, such as heart failure and massive blood transfusion. The right

atrial pressure can decrease to as low as −3 to −5 mm Hg when the heart (right atrium) is pumping with vigour or when venous return is greatly depressed.

Peripheral Venous Pressure The pressure in the venules is about 10 mm Hg. As the veins approach the heart, there is a gradual decrease in the venous pressure. In the great veins near the heart, venous pressure is approximately 5 mm Hg.

Factors Affecting Peripheral Venous Pressure

1. Effect of Gravitational Pressure. Peripheral venous pressure, like arterial pressure, is affected by this gravitational hydrostatic pressure. When an adult person stands absolutely still the pressure in the body veins because of the effect of hydrostatic pressure is (Fig. 4.4-14):

- At the level of heart, it is 0 mm Hg.
- At the level of ankles, it is approximately 180 mm Hg.
- At other levels in the body, from heart to feet, the venous pressure varies between 0 and 80 mm Hg. It increases by 0.77 mm Hg for each centimetre below the right atrium. Therefore, if the venous valves are incompetent, as in *varicose veins*, it results in venous pooling, i.e. accumulation of blood in the lower parts of the body.
- Pressure in the veins above the right atrium decreases by 0.77 mm Hg for each centimetre. Therefore, *neck veins* completely collapse due to atmospheric pressure on the outside of neck, and pressure inside the vein almost remains zero.
- Subdural venous sinuses in the skull cannot collapse because of the tough noncollapsible nature of dura mater; therefore, a negative hydrostatic pressure (−10 mm Hg) exists in them. Because of this reason, if a dural sinus is opened during a neurosurgical procedure with the patient seated, air is sucked into the sinus, resulting in *air embolism*.

2. Effect of Venous Resistance. Increased venous resistance can raise peripheral venous pressure to some extent. This is especially useful in postural changes. For example, sudden change of posture from lying down to standing position results in peripheral pooling of the blood in veins of legs and feet due to effect of gravity. Therefore, venous return to heart decreases, systemic blood pressure falls and may cause dizziness. However, normally the compensatory mechanism operated via baroreceptor reflex prevents any fall in blood pressure (see page 155).

3. Effect of Central Venous Pressure. Peripheral venous pressure to a great extent depends upon the central venous pressure. Therefore, any factor that increases central venous pressure (i.e. right atrial pressure) will also increase the peripheral venous pressure. Common causes associated with rise in right atrial pressure are as follows:

- Increased blood volume (massive blood transfusion)
- Heart failure

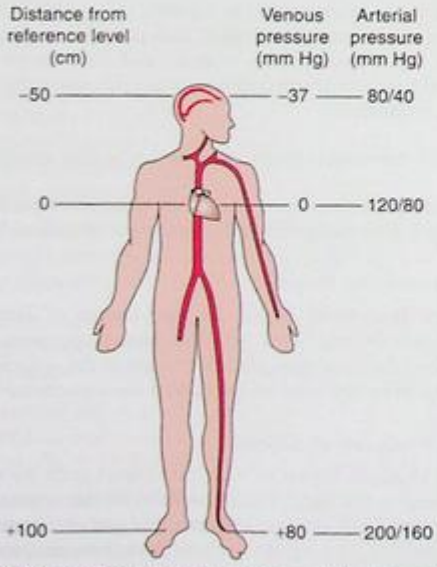


Figure 4.4-14 Effect of hydrostatic pressure of blood on arterial and venous pressure in an upright position.

Venous Flow and Venous Return

As we know, the blood flows in the veins towards the heart due to a pressure gradient which exists between the right atrial pressure (0 mm Hg) and the peripheral veins (6–7 mm Hg).

Venous return has been discussed in detail on page 131.

BLOOD PRESSURE

Definitions (Terminology)

Blood Pressure

Blood pressure is the lateral pressure exerted by the flowing blood on the walls of the vessels. It is usually measured in mm Hg. Without any further qualification the term blood pressure denotes the *arterial pressure*. While describing the pressure exerted by the blood column in other types of blood vessels, the type of vessels is also mentioned, e.g. *capillary pressure* and *venous pressure*.

Systolic Blood Pressure

- The maximum arterial pressure during the systole is called *systolic blood pressure* and occurs during the ventricular ejection.
- The systolic blood pressure is a function of the cardiac output (CO), i.e. it represents the extent of work done by the heart.
- Normal systolic blood pressure in a young adult is 120 mm Hg (range: 105–135 mm Hg).
- Systolic blood pressure undergoes considerable fluctuations, e.g. it is increased during excitement, exercise and meals, and is decreased during sleep and rest.

Diastolic Blood Pressure

- Diastolic blood pressure refers to the minimum arterial pressure during diastole and occurs just before the onset of the ventricular ejection.
- Normal diastolic blood pressure in a young adult is 80 mm Hg (range 60–90 mm Hg).
- The diastolic pressure (DP) is the function of TPR and indicates the constant load against which the heart has to work. It undergoes much less fluctuations.

Conventional Expression of Blood Pressure Conventionally, systolic and diastolic blood pressures are denoted as numerator and denominator, respectively. For example, blood pressure of a normal person is written as 120/80 mm Hg.

Pulse Pressure

- Pulse pressure (PP) is the arithmetic difference between the systolic and the diastolic blood pressures.
- Normally, average PP is 40 mm Hg.
- PP determines the pulse volume.
- The high PP is an indicative of the systolic hypertension and indirectly determines a decrease in elasticity of blood vessels.

Mean Arterial Pressure

- Mean arterial pressure (MAP) is the average of all pressure measured millisecond by millisecond throughout the cardiac cycle.
- The duration of cardiac systole is shorter than the duration of diastole, so the MAP is not equal to the algebraic mean of the systolic and diastolic blood pressures, i.e. it is not equal to (systolic pressure + diastolic pressure/2).
- Practically, MAP is roughly equal to the DP plus one-third of PP, i.e.

$$DP + \frac{1}{3}pp$$

- MAP is same for each organ and determines the pressure head. Thus, the regional blood flow through an organ depends on it.
- All cardiovascular reflexes are sensitive to MAP.
- Normal value of MAP is 93 mm Hg (range: 90–100 mm Hg).

Determinants of (Factors Affecting) Arterial Blood Pressure

- The arterial blood pressure is a function of the product of cardiac output (CO) and TPR, i.e.

$$\text{Arterial blood pressure} = CO \times PR$$

- Therefore, the arterial blood pressure is affected by conditions that affect either cardiac output or peripheral resistance.
- Changes in the cardiac output affect the systolic pressure more than the DP while changes in the peripheral resistance affect DP more than the systolic pressure.
- As discussed in the section on cardiac output (page 129), the cardiac output is a function of *heart rate* and *stroke volume*, so these two are important determinants of the blood pressure.
- The peripheral resistance (page 138) depends upon the viscosity of blood, elasticity of the vessel wall and velocity of the blood flow. Thus, these factors are also important determinants of the blood pressure.

Variations in Blood Pressure

Physiological Factors Affecting Blood Pressure

1. Age. In healthy humans, both systolic and DPs rise with age.

- *At birth*, systolic blood pressure is 40 mm Hg (range: 20–60 mm Hg). It then rises rapidly up to 1 month of age.
- *At 1 month* of age, the systolic blood pressure becomes about 80 mm Hg and then rises slowly.
- *At about 17 years* of age, normal adult level of blood pressure is 120/80 mm Hg.
- *At about 70 years of age*, the normal value of blood pressure is 160/90 mm Hg. The increase in blood pressure associated with advancing age is due to increase in rigidity of vessel wall.

2. Sex. *Before menopause*, females have little lower (4–6 mm Hg) systolic blood pressure than males of corresponding age. *After menopause*, systolic blood pressure in females is little higher (4–6 mm Hg) than males of same age group.
3. Effect of Meals. *Systolic blood pressure* increases by 4–6 mm Hg after meals and this effect lasts for about 1 hour. *Diastolic blood pressure* either remains unchanged or decreases slightly due to the vasodilatation in splanchnic vessels.
4. Emotions. Increased sympathetic activity during emotional situations leads to increase in the systolic blood pressure.
5. Climatic Temperature. *Exposure to cold* produces rise in the blood pressure, whereas *exposure to hot temperature* lowers the blood pressure.
6. Diurnal Variation. Systolic blood pressure shows a diurnal variation of about 6–10 mm Hg – the values being lower in the morning and higher in the afternoon. In night workers, however, a reverse rhythm is observed.
7. Exercise. In muscular exercise, generally systolic blood pressure rises and diastolic blood pressure falls.
8. Effect of Gravity. In standing position, due to hydrostatic (gravitational) effect of the blood column, the pressure in the vessels below heart level is increased and in the vessels above heart level it is decreased (Fig. 4.4-14). For every centimetre below or above the heart level the pressure increases or decreases by 0.77 mm Hg, respectively. Therefore, for clinical recording blood pressure should always be checked at the heart level.
9. Effect of Change in Posture. Immediately on standing, there occurs peripheral pooling of blood in dependent parts leading to decreased venous return and decreased cardiac output, and momentary fall in the systolic blood pressure. Fall in systolic pressure immediately decreases baroreceptor discharge via vasomotor centre leading to an increased *diastolic blood pressure*. On standing, there also occurs an increase in the peripheral resistance and momentary increase in diastolic blood pressure. Thus, immediately after standing from lying down posture a rise in diastolic blood pressure can be recorded for about 30–60 seconds. Later on due to decrease in baroreceptor discharge, the blood pressure comes back to normal and no symptoms are experienced by the normal individuals. The sequences of events are summarized in Fig. 4.4-15.
10. Sleep. In complete relaxed state during early hours of sleep there occurs fall in blood pressure up to 15–20 mm Hg. However, in disturbed sleep blood pressure increases due to increased sympathetic discharge.
11. Body Built. Systolic blood pressure is slightly higher in obese individuals as compared to thin-built individuals. This usually occurs because there is more tissue between the cuff and artery and so, some of the cuff pressure is dissipated. Therefore, use of a cuff that is wider than the standard arm cuff is recommended in the obese individuals.

Pathological Variations in Blood Pressure

Hypertension **Definition.** Hypertension (HT) refers to a condition in which value of systolic blood pressure is persistently more than 140 mm Hg and/or that of diastolic blood pressure is above 90 mm Hg. If there is increase only in the systolic blood pressure, it is called *systolic hypertension* in which pulse pressure is raised.

Types of hypertension It is of two types: primary and secondary hypertension.

1. ***Primary hypertension,*** also known as *essential hypertension*, is characterized by a raised blood pressure without

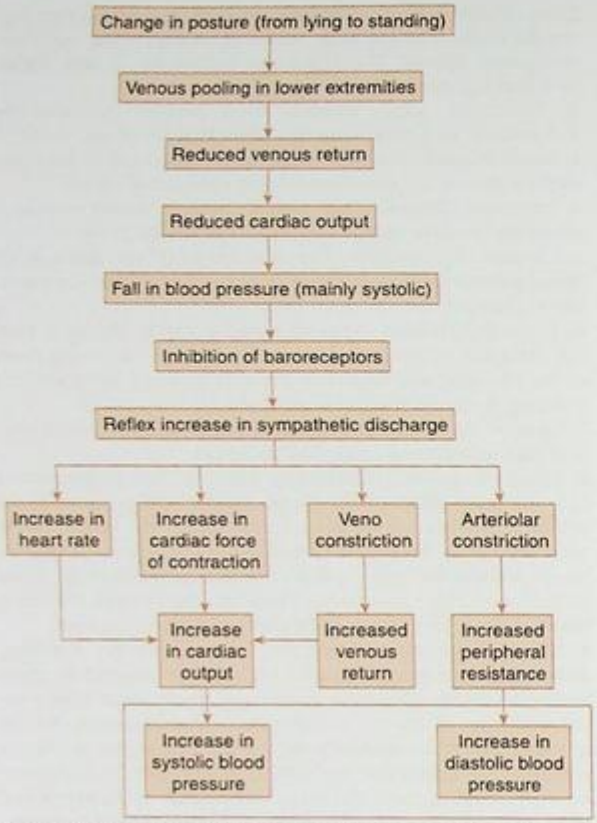


Figure 4.4-15 Summary of events maintaining normal blood pressure during change of posture from lying to standing.

any underlying disease. Risk factors for primary HT include heredity, obesity, mental tension and smoking.

2. ***Secondary hypertension*** refers to a condition in which blood pressure is raised due to some other underlying disease. Common causes of secondary hypertension are as follows:
   - *Cardiovascular diseases*, e.g. atherosclerosis.
   - *Renal diseases*, e.g. glomerulonephritis and tumour of juxtaglomerular cells leading to formation of excess of angiotensin II.
   - *Endocrinal disorders* like hyperaldosteronism (excessive secretion of aldosterone from adrenal cortex), phaeochromocytoma (tumour of adrenal medulla) and Cushing syndrome (excessive secretion of glucocorticoids from adrenal cortex).
   - *Neurologic disorders* which may produce hypertension include raised intracranial pressure.
   - *Pregnancy-induced hypertension (PIH)* is noticed in some of the pregnant women. Its exact cause is not known.

Hypotension Hypotension refers to a condition in which values of blood pressure are below the normal range. Clinically, when the systolic blood pressure is less than 90 mm Hg, it is considered hypotension. It is of the following types:

- ***Primary hypotension***, also known as essential hypotension, is a disorder of unknown aetiology.
- ***Secondary hypotension*** occurs secondary to some other underlying diseases, such as myocardial infarction, neurogenic shock, haemorrhagic shock, hypoactivity of pituitary gland and hypoactivity of adrenal glands.
- ***Postural hypotension*** refers to the sudden fall in blood pressure when patients stand up from lying down posture. It occurs due to some dysfunction of autonomic nervous system.

Measurement of Blood Pressure

Direct Method

Direct method of measuring blood pressure is used in the experimental studies. In it, a cannula or T-tube is inserted into an artery and connected to either

- *Mercury manometer* and pressure is recorded on the kymograph or
- *Pressure transducer* (strain gauge) which, in turn, is connected to Polyrite for recording

The record will show fluctuations as depicted in Fig. 4.4-16, upper level of which indicates systolic blood pressure and lower level indicates diastolic blood pressure.

Indirect Method

In human beings, blood pressure is measured indirectly by using sphygmomanometer.

Sphygmomanometer Commonly called blood pressure apparatus, it is the instrument used to measure blood pressure (Fig. 4.4-17).

Procedure The blood pressure may be tested with subject lying supine or sitting, but should be physically and mentally relaxed and free from excitation.

The blood pressure can be measured by an auscultatory method described by Korotkoff in 1905, is the most useful technique.

- The cuff of the blood pressure apparatus is applied on the upper arm with the centre of the rubber bag lying over the brachial artery, which lies medially, and its lower edge should be about 3 cm above the elbow.
- Raise the pressure in the cuff by 30–40 mm above the level, when the radial artery pulse disappears.

Figure 4.4-16 Record of arterial blood pressure obtained by direct arterial cannulation method.

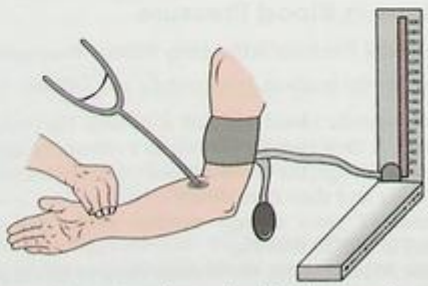


Figure 4.4-17 Procedure of recording blood pressure by an auscultatory method.

- Then diaphragm of stethoscope is placed on the brachial artery in the cubital space and is kept in a position with the help of thumb and fingers of left hand.
- Pressure in the cuff is lowered slowly by opening the leak valve of the air pump with right hand. While doing so, initially no sound is heard.

However, when mercury column is lowered further a tap sound is heard. The character and quality of sound goes on changing while further lowering the mercury column by deflating the cuff, and ultimately the sound disappears. These sounds are called Korotkoff sounds and from these the levels of systolic and diastolic blood pressure are noted.

Mechanism of Korotkoff's Sounds

- Normally, the blood flow through the arteries is streamlined or laminar, and no sounds are heard over them when auscultated.
- While testing blood pressure, when the cuff pressure is raised above the expected systolic pressure level, the blood flow in the brachial artery completely ceases and no sounds are heard. When the cuff pressure is reduced gradually, a time comes when, at the peak of each systole, the intra-arterial pressure just exceeds the cuff (extra-arterial) pressure. The small amounts of blood that are ejected at a high velocity (exceeding the critical velocity) through the partially narrowed artery result in *intermittent turbulence* which produces the sounds. These sounds are called *Korotkoff sounds.*
- As the cuff pressure falls further, the blood flow becomes laminar once again and the sounds disappear.

Regulation of Blood Pressure

Arterial blood pressure is controlled by several mechanisms which under physiological conditions maintain the normal MAP within a narrow range of 95–100 mm Hg. The different mechanisms concerned with regulation of blood pressure have been discussed in detail in Chapter 4.5 on Cardiovascular Regulation and have been briefed here just for orientation about control of blood pressure. Each mechanism performs a specific function. Various mechanisms controlling arterial pressure can be grouped as follows:

A. Rapid blood pressure control mechanism
B. Intermediate blood pressure control mechanisms
C. Long-term blood pressure control mechanisms

Rapid Blood Pressure Control Mechanism (Nervous Regulating Mechanism)

Rapid blood pressure control mechanism or the so-called short-term control mechanism primarily includes the following three nervous reflexes:

1. Baroreceptor reflexes (see page 154)
2. Central nervous system ischaemic response (see page 157)
3. Chemoreceptor reflexes (see page 156)

Salient Features. The salient features of the nervous reflexes are discussed below.

- These *act very rapidly,* i.e. within seconds to few minutes of alterations in the blood pressure.
- These are *short-term mechanisms,* i.e. these act for few hours to few days and are thus insignificant in the long-term regulation of blood pressure.
- These are useful in preventing *acute decreases in blood pressure* (e.g. during severe haemorrhage) as well as in preventing *excessive increases in blood pressure* (e.g. as might occur in response to excessive blood transfusion).

Intermediate Blood Pressure Control Mechanisms

The intermediate blood pressure control mechanisms that are important in the blood pressure control after several minutes of acute pressure changes are as follows:

- Renin–angiotensin vasoconstrictor mechanism (for details see page 157).
- Stress relaxation and reverse stress relaxation mechanism.
- Capillary fluid shift mechanism.

Salient features of intermediate blood pressure control mechanisms are as follows:

- These mechanisms come into play after several minutes of acute pressure changes and reach full function within a few hours.
- These mechanisms play their role from few days to few weeks.
- All these mechanisms basically try to control the alterations in the blood pressure by altering the blood volume.

Stress Relaxation and Reverse Stress Relaxation Mechanisms

Stress Relaxation Mechanism refers to vasodilatation occurring due to stress on the vascular smooth muscles. When pressure in the vessels become too high (e.g. following massive slow intravenous transfusion), the vessels become stretched and continue to stretch for minutes or hours. This causes relaxation of blood vessels simply by a vascular tone adjustment. This leads to an increase in the capacity of the arterial system with a concomitant fall in blood pressure.

Reverse Stress Relaxation Mechanism operates when the blood pressure is low due to less stress on the vessels walls and tries to restore it back to normal. For example, when blood pressure falls due to prolonged slow bleeding, there occurs tightening of blood vessel walls by vascular tone adjustment secondary to less stress on the vessel wall (reverse stress relaxation mechanism). This mechanism tries to restore the blood pressure back to normal. This mechanism can correct up to 15% change in blood volume below normal.

Capillary Fluid Shift Mechanism Capillary fluid shift mechanism helps in restoring both low and high blood pressure back to normal.

When blood pressure is raised, the mean capillary pressure is also high resulting in shift of fluid from circulation to the interstitial fluid compartments. This reduces the blood volume to restore the arterial pressure.

When blood pressure is lowered, the mean capillary pressure is also low, resulting in absorption of fluid from the interstitial compartments to circulation. Thus the blood volume is increased which helps to return the blood pressure back to normal.

The capillary fluid shift mechanism is about two times more effective than baroreceptor reflex mechanism in controlling the blood pressure, but it acts much more slowly (intermediate acting mechanism) than baroreceptor mechanism (rapid acting mechanism).

Long-Term Blood Pressure Control Mechanisms

Kidneys play principal role in the long-term control of blood pressure by the following mechanisms.

1. ***Direct mechanism***, i.e. 'Renal-body fluid feedback mechanism'.
2. ***Indirect mechanisms*** control kidney functions indirectly via the following hormonal mechanisms:
   (i) Aldosterone system
   (ii) Renin–angiotensin system

For details see page 157.

Renal-Body Fluid System for Arterial Pressure Control

The most important mechanism for the long-term control of blood pressure is linked to control of circulatory volume by the kidney, a mechanism known as the *renal-body fluid feedback system*. In fact, it is similar to the capillary fluid shift mechanism except that only the renal glomerular capillaries are involved in the process.

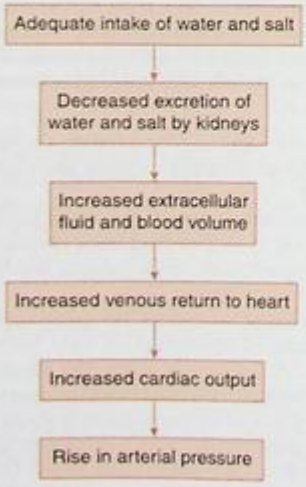
Modes of Operation of Renal-Body Fluid Feedback System

The renal-body fluid system corrects the blood pressure by causing appropriate changes in the blood volume through *diuresis* and *natriuresis*.

When blood pressure rises too high, the kidneys excrete increased quantities of sodium and water because of *pressure natriuresis* and *pressure diuresis*, respectively. As a result of increased renal excretion, the extracellular fluid volume and blood volume both decrease until blood pressure returns to normal and the kidneys excrete normal amounts of sodium and water.

When the blood pressure falls too low, the kidneys reduces the rate of sodium and water excretion, and over a period of hours to days, if the person drinks enough water and eats enough salt to increase blood volume, the blood pressure will return to its previous level. This mechanism, being very slow to act, is not of major importance in the acute control of arterial pressure. However, it is by far the most potent of all long-term arterial pressure controllers.

The sequence of events in order of occurrence during control of blood pressure by this mechanism is summarized as follows:



Salient Features of Renal-Body Fluid Feedback Mechanism

The salient features of the renal-body fluid feedback mechanism can be summarized as:

- The renal-body fluid feedback mechanism takes several hours to show any significant response.
- These mechanisms operate very powerfully to control arterial pressure over days, weeks and months.
- The effectiveness of these mechanisms becomes steadily greater with time.
- These mechanisms, if given sufficient time, control arterial pressure at the level that provides normal output of salt and water by the kidneys.

SELF-ASSESSMENT

1. Describe briefly the Poiseuille's law governing haemodynamics.
2. What is peripheral resistance? Discuss a brief account of factors affecting peripheral resistance.
3. Define blood pressure. What are the determinants, factors affecting and its regulation?
4. Write notes on:
   - Critical closing pressure
   - Law of Laplace
   - Windkessel vessels and their significance
   - Mechanism of autoregulation of blood flow
   - Microcirculation
   - Central venous pressure
   - Korotkoff sounds
   - Capillary fluid shift mechanism
5. Differentiate between:
   - Laminar and turbulent blood flow
   - Central and peripheral venous pressure
   - Mean and pulse pressure
   - Capillary fluid shift and renal-body fluid system is control of blood pressure

4.5 Cardiovascular Regulation

CHAPTER OUTLINE

Introduction
Need for Cardiovascular Control
Circulatory Adjustments
Cardiovascular Control Mechanisms

Neural Control Mechanisms
Medullary Cardiovascular Control Centres
Autonomic Nerve Supply to Heart and Blood Vessels
Afferent Impulses to Medullary Cardiovascular Control Centres
Afferent Impulses from Higher Centres Controlling Vasomotor Centre and Cardiac Vagal Centre
Afferent Impulses from Respiratory Centres
Cardiovascular Reflex Mechanisms Affecting Medullary Control Centres
Direct Effects on Vasomotor Area

Humoral Control Mechanisms
Circulating Vasodilators
Circulating Vasoconstrictors
Ions and Other Chemical Factors

Local Control Mechanisms

INTRODUCTION

Cardiovascular control makes *circulatory adjustments* which are essential to cope up with the timely needs of each and every organ of the body, and is thus of fundamental importance for survival.

Need for Cardiovascular Control

Functions served by cardiovascular control are as follows:

- *To increase the blood supply* to active tissues, e.g. during exercise to skeletal and cardiac muscles.
- *Redistribution of blood* to increase or decrease the heat loss from the body as per requirements.
- *Circulatory adjustments* during routine cardiovascular stresses like change in posture, hours of excitement, fear, anxiety, meals and sleep, etc.
- *Maintenance of adequate flow to vital organs,* such as brain, heart and kidney, all the times including emergencies such as shock and haemorrhage, even at the expense of the circulation to the rest of the body, as the vital organs may develop irreversible changes in no time. For example, the brain is irreversibly damaged within 3 minutes of ischaemia, whereas skin, skeletal muscle and gastrointestinal tract can tolerate reduction of blood for a longer duration.

Circulatory Adjustments

Circulatory adjustments which ensure that all of the organs receive sufficient blood flow are (1) control of blood volume and (2) control of arterial pressure. These circulatory adjustments are made by the cardiovascular control mechanisms primarily by regulating the following parameters.

A. Regulation of Cardiac Performance, i.e. alterations in the activities of heart which include the following.

1. ***Chronotropic action,*** i.e. effect on heart rate which may be in the form of:
   - Increased heart rate (tachycardia) or positive chronotropic effect.
   - Decreased heart rate (bradycardia) or negative chronotropic effect.
2. ***Inotropic action,*** i.e. effect on force of contraction which may be in the form of:
   - Increase in the force of contraction (positive inotropic effect) or
   - Decrease in the force of contraction (negative inotropic effect).

B. Regulation of performance of blood vessels, which primarily includes the following.

1. *Alterations in diameter of arterioles,* which change the peripheral resistance and also the hydrostatic pressure in the capillaries.
2. *Alterations in diameter of veins,* which change the venous pressure and thus the venous return and the cardiac output.

Cardiovascular Control Mechanisms

The cardiovascular control mechanisms which play their role in making circulatory adjustments during the routine and emergency cardiovascular stresses can be grouped as:

- Neural control mechanism,
- Humoral control mechanism and
- Local control mechanisms.

NEURAL CONTROL MECHANISMS

Neural regulation of circulation is of fundamental importance because it responds within seconds. The nervous regulation mainly controls systemic functions of circulatory system (whenever required) such as:

- Redistribution of blood flow to different parts of the body.
- Increasing pumping activity of heart.
- Rapid control of arterial pressure.

Components of Neural Control Mechanism The neural cardiovascular regulating mechanism consists of the following.

A. Medullary Cardiovascular Control Centres. These are the prime centres concerned with neural control of circulation. These include the following:

- Medullary sympathetic centre (vasomotor centre [VMC]).
- Medullary parasympathetic centre (nucleus ambiguus).
- Medullary relay centre for cardiorespiratory and afferents (nucleus of tractus solitarius [NTS]).

B. Autonomic Nervous System Supplying the Heart and Blood Vessels. The regulation of circulation by medullary control centres is exerted almost entirely through the autonomic nervous system (ANS). The sympathetic component of ANS is most important for controlling circulation and the parasympathetic component mainly contributes to the regulation of heart functions.

C. Afferent Impulses to Medullary Centres. The VMC is influenced by afferent impulses from the higher centres and a large number of other areas.

D. Role of Skeletal Nerves and Muscles in Controlling Blood Pressure.

Medullary Cardiovascular Control Centres

1. Vasomotor Centre

Though popularly known as VMC, more appropriately it should be called *medullary sympathetic centre.* It is the primary cardiovascular regulatory centre located in the medulla oblongata of brainstem. It consists of groups of neurons situated bilaterally in the reticular substance of medulla at the floor of fourth ventricle. The medullary cardiovascular centre is constituted by the following different areas (Fig. 4.5-1).

Pressor Area Pressor area is located in the rostral ventrolateral medulla (RVLM). It contains glutaminergic neurons which exert *excitatory* effect on the thoracolumbar spinal sympathetic neurons.

Continuous sympathetic vasoconstrictor tone. Normally, the neurons forming pressor area of the VMC show *inherent tonic activity,* i.e. they discharge rhythmically (at a rate of about 1 impulse per second) in a tonic fashion to excite sympathetic preganglionic neurons present in the intermediolateral grey column of the spinal cord. In this way, the continuous signals are passed to the sympathetic vasoconstrictor nerves fibres over the entire body. Sympathetic vasoconstrictor tone.

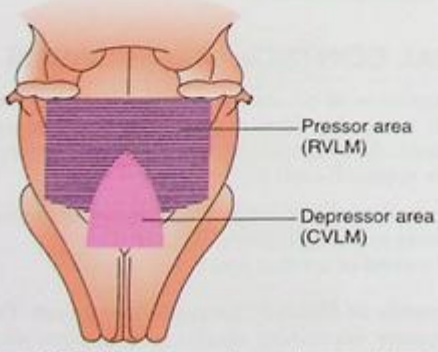


Figure 4.5-1 Medullary cardiovascular control centres.

Stimulation of pressor area produces:

- *Arteriolar constriction,* which increases the systemic blood pressure.
- *Venoconstriction,* which decreases blood stored in the venous reservoir and increases venous return.
- *Increase in heart rate* or positive chronotropic effect.
- *Increase in force of contraction* or positive inotropic effect.

Depressor Area Depressor area is situated bilaterally in the *caudal ventrolateral medulla* (CVLM). Stimulation of neurons forming depressor area produces decrease in the sympathetic activity due to inhibition of the tonically discharging impulses of the pressor area causing:

- *Arteriolar dilation,* which decreases systemic blood pressure.
- *Venodilatation,* which increases storage of blood in the venous reservoir and decreases venous return and cardiac output.
- *Decrease in heart rate* or negative chronotropic effect.
- *Decrease in force contraction* or negative inotropic effect.

2. Medullary Parasympathetic Centre

Medullary parasympathetic centre or *cardiac vagal centre* (earlier also called cardioinhibitory centre) is now called by its specific name, i.e. the *nucleus ambiguus.* The neurons located in this centre are not tonically active. Nucleus ambiguus receives afferents via NTS and, in turn, sends inhibitory pathway in the form of vagal fibres to: *heart* to decrease the heart rate and force of cardiac contraction.

3. Medullary Relay Station for Cardiorespiratory Afferents

NTS of the vagus nerve forms the so-called medullary relay station for the cardiorespiratory afferents. It receives afferents from most of the baroreceptors and chemoreceptors. Cells of the NTS, in turn, relay the information to VMC and cardiac vagal centre (nucleus ambiguus) that control sympathetic and parasympathetic outputs, respectively.

Autonomic Nerve Supply to Heart and Blood Vessels

Autonomic Nerve Supply to Heart

Sympathetic Supply

Spinal sympathetic centre is formed by the neurons located in the intermediolateral horns of the spinal cord extending from T_1 to L_2 spinal segments.

- ***Preganglionic sympathetic fibres*** (small, myelinated) supplying the heart arise from the neurons lying in the intermediolateral horns of the T_1–T_5 *spinal segments* and pass into the sympathetic trunk to superior, middle and inferior cervical ganglia, and upper thoracic ganglia where they synapse (Fig. 4.5-2).
- ***Postganglionic fibres*** (long, unmyelinated) leave the ganglia and pass via superior, middle and inferior *cardiac sympathetic nerves,* and supply to the nodal tissues (sinoatrial [SA] node and atrioventricular [AV] node) and the cardiac muscles of atria and ventricles (Fig. 4.5-2). It is important to note that:
  - Sympathetics from the right side are primarily distributed to the SA node.

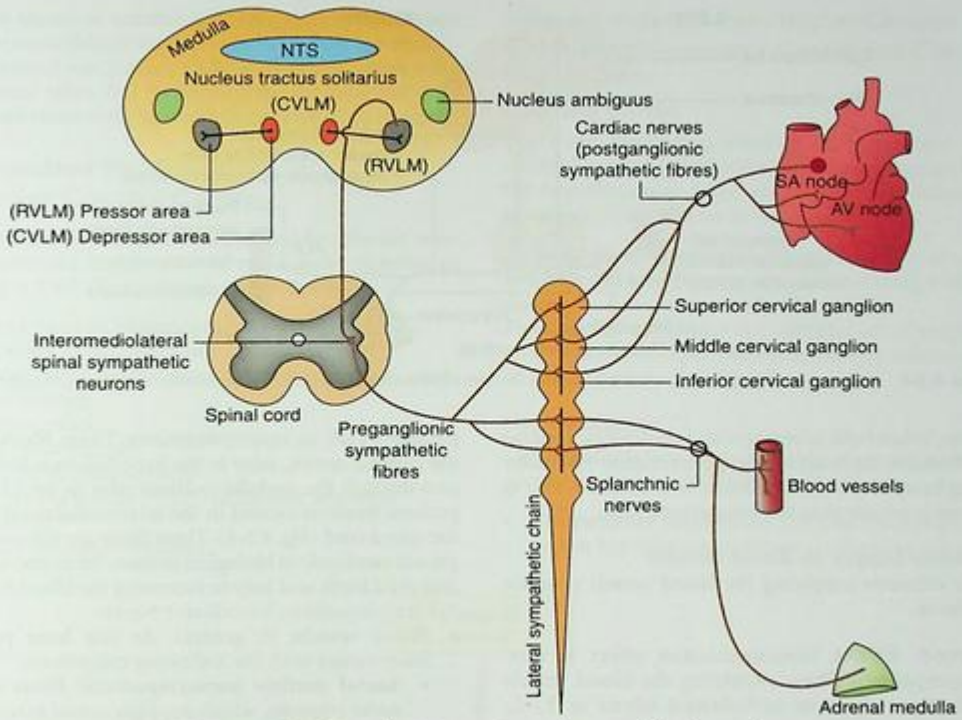


Figure 4.5-2 Sympathetic innervation to heart and blood vessels.

- Sympathetics from the left side are primarily distributed to the AV node.

Stimulation of Cardiac Sympathetic Nerves Causes:

- *Increased heart rate* (positive chronotropic effect)
  Increase in the conduction of impulse through heart (positive dromotropic action)
- *Increase in the excitability* of myocardium (positive bathmotropic effect)
- *Increase in the force of contraction* of myocardium (positive inotropic effect)

Parasympathetic Supply Parasympathetic fibres to the heart are carried through two vagii (Fig. 4.5-3).

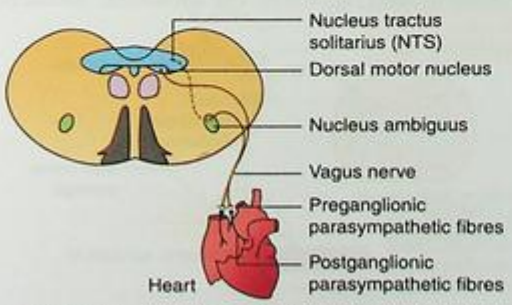


Figure 4.5-3 Parasympathetic innervation of the heart.

Preganglionic fibres (long, myelinated) arise from the *nucleus ambiguus* located in the medulla and travel along the vagii to reach the heart through their cardiac branches to synapse in the *ganglia* located within the superficial and deep cardiac plexuses and also in the walls of atria.
Postganglionic fibres (small, unmyelinated) are distributed to the atria, SA node, AV node and AV bundle. It is important to note that:

- The right vagus is distributed mainly to SA node,
- The left vagus is distributed mainly to AV node,
- No vagal motor fibres are distributed to the ventricles and
- Parasympathetic fibres to the heart are *endocardiac.*

Stimulation of parasympathetic fibres to heart causes:

- *Decrease in heart rate* (negative chronotropic effect).
- *Decrease in conduction of impulse* through the conduction tissue (negative dromotropic effect).
- *Decrease in the excitability of atria* only (negative bathmotropic effect).
- *Decrease in the force of contraction* of atria only (negative inotropic effect). There is no effect on the force of contraction of ventricles.

Vagal Tone. There is a good deal of tonic vagal discharge, called the vagal tone, in humans and other large animals. Therefore, when vagii are cut in the experimental animals, the heart rate rises. Similarly, in adult humans, the resting heart rate which is about 72 beats/min rises to 150–180 beats/min after the administration of vagolytic drugs, such as atropine, because of the unopposed

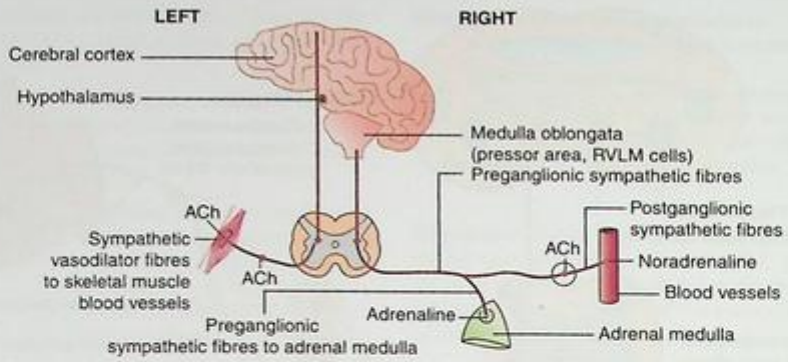


Figure 4.5-4 Pathway of sympathetic vasodilator fibres (on left side) and sympathetic vasoconstrictor system (on right side).

sympathetic tone. When both adrenergic and cholinergic systems are blocked in humans, the heart rate is approximately 100 beats/min. The resting heart rate is about 72/min, so it confirms that at rest the vagal tone is greater than the sympathetic tone.

Autonomic Nerve Supply to Blood Vessels

The autonomic efferents supplying the blood vessels produce two types of effects.

Vasoconstriction Effect Vasoconstriction effect is produced by the sympathetic fibres supplying the blood vessels which originate from the intermediolateral horns in T_1–L_2 spinal segments.

Vasoconstrictor fibres have norepinephrine and sometimes neuropeptide Y as neurotransmitter, and are called *noradrenergic fibres.*

Sympathetic vasoconstrictor fibres show tonic (i.e. continuous) discharge at the rate of about 1 impulse/s. Therefore, when the sympathetic nerves are cut *(sympathectomy)* there occurs:

- ***Vasodilation*** which leads decreased peripheral resistance → decreased diastolic blood pressure.
- ***Venodilatation*** causes increased venous capacity → decreased venous return → decreased end-diastolic volume → decreased stroke volume → decreased cardiac output → decreased systolic blood pressure.

  Stimulation of sympathetic fibres produces:
  - *Constriction of arterioles* leads to increased peripheral resistance → increased diastolic blood pressure.
  - *Venoconstriction* leads to decreased venous capacity → increased venous return → increased end-diastolic volume → increased stroke volume → increased cardiac output → increased systolic blood pressure.

Both these mechanisms are responsible for the regional redistribution of blood and at the time of need the blood is diverted from the skin, skeletal muscles and splanchnic area to the heart and brain.

Vasodilation Effect Neural vasodilation effect on the blood vessels is produced by the following mechanisms.

1. Decrease in Discharge of Noradrenergic Vasoconstrictor Nerves.

2. Sympathetic Cholinergic Vasodilator Nerves. Some of the organs of the body, such as skeletal muscles, heart, lungs, liver, kidney and uterus in addition to adrenergic vasoconstrictor sympathetic fibres also receive innervation by *cholinergic vasodilator sympathetic* fibres having acetylcholine and vasoinhibitory peptide (VIP) as neurotransmitter. These fibres originate from the cerebral cortex, relay in the hypothalamus and midbrain, and pass through the medulla (without relay in the VMC) to the sympathetic neurons located in the intermediolateral grey column of the spinal cord (Fig. 4.5-4). These fibres are not *tonically active* and get activated only in biological stresses, for example during exercise and child birth, and help in increasing the blood flow.

3. Parasympathetic Vasodilator Nerves

- Blood vessels, in general, do not have parasympathetic innervation with the following exceptions:
  - ***Sacral outflow parasympathetic fibres*** represented by *nervi erigentes,* which supplies sexual erectile tissue and is responsible for vasodilation in external genitalia during sexual excitement.
  - ***Cranial outflow of parasympathetic fibres*** along chorda tympani branch of facial nerve to salivary glands.
  - The postganglionic cholinergic neurons on the blood vessels contain acetylcholine, VIP and PHM-27 as neurotransmitters.

IMPORTANT NOTE

It is important to note that parasympathetic vasodilator fibres play little role in the control of general circulation. Activation of such nerves only contributes to pleasure and fulfilling important biological functions.

4. Vasodilation by Axon Reflex. Conduction of normal sensory afferent impulses from the skin to spinal cord is called *orthodromic conduction.* However, in certain situations, for example, when a firm stroke is applied across the skin the afferent impulses in the sensory nerves from the skin are relayed *antidromically* down branches of the sensory nerves that innervate blood vessels (Fig. 4.5-5). The antidromic conduction of

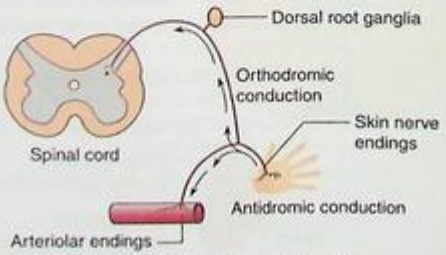


Figure 4.5-5 Pathway of axon reflex.

impulses causes release of substance P from the nerve endings, which produces vasodilation and increases capillary permeability. This local neural mechanism (which does not involve the CNS) is called *axon reflex*. It is responsible for the local vasodilation and does not contribute in systemic control of circulation.

Afferent Impulses to Medullary Cardiovascular Control Centres

The medullary control centres are influenced by afferent control impulses from the higher centres and a large number of other areas (Fig. 4.5-6). These include the following:

- Afferent impulses from higher centres controlling VMC.
- Afferent impulses from respiratory centres.
- Cardiovascular reflex mechanisms operating through medullary control centres.
  - Baroreceptor reflex
  - Chemoreceptor reflexes
- Direct effects on vasomotor area.
  - Central nervous system (CNS) ischaemic response
  - Cushing reflex
- Afferents from nociceptive stimuli.

Afferent Impulses from Higher Centres Controlling Vasomotor Centre and Cardiac Vagal Centre

Cerebral Cortex

There are descending tracts to the vasomotor area from the cerebral cortex (particularly the limbic cortex) that relay in the hypothalamus. Some examples of the influence of limbic system on the VMC are as follows:

Tachycardia and hypertension produced by emotions.
Bradycardia and fainting occurring during sudden emotional shock.
Fight or flight response is a complex set of response which increases cardiac output and raises blood pressure in anticipation of flight or physical defence.

Hypothalamus

The hypothalamus serves to integrate many somatic and autonomic responses. Examples are as follows:

- ***Temperature regulation.*** The effect of temperature changes on the hypothalamic centres is relayed to the medulla, which

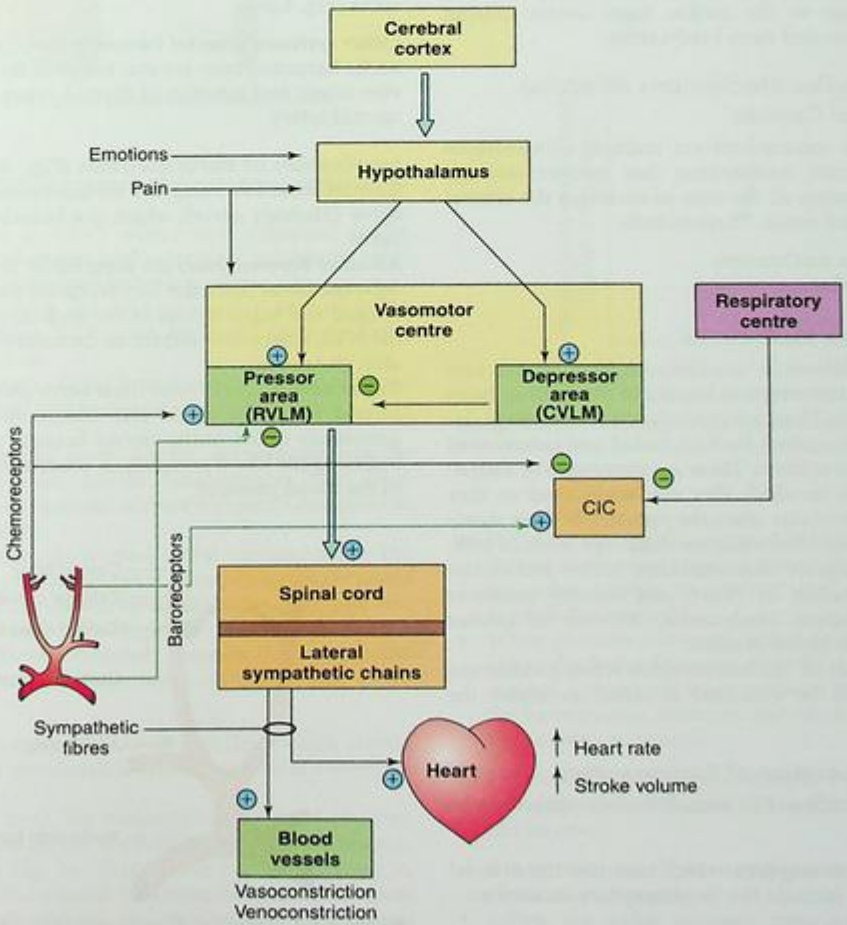


Figure 4.5-6 Scheme to show afferent impulses affecting medullary cardiovascular control centres.

causes the vessels of skin to constrict (heat conservation) or to dilate (heat dissipation).
- ***Emotional stresses*** influence heart rate and blood pressure by impulses relayed from the hypothalamus to stimulate or inhibit the medullary centres.

Reticular Formation

Reticular formation of pons, mesencephalon and diencephalon also influences the vasomotor area, for example:

- *Pain* usually causes rise in the blood pressure via afferent impulses in the reticular formation converging on the vasomotor area. However, prolonged severe pain may cause vasodilation and fainting.

Afferent Impulses from Respiratory Centres

Impulses arising from the respiratory centres affect the heart rate by changing the vagal tone, and the alterations produced are known as *sinus arrhythmia* which occurs during forced breathing.

- *During inspiration,* the impulses arising from the respiratory centres during inspiration inhibit the cardiac vagal centre causing reduced vagal tone and *sinus tachycardia.*
- *During expiration,* the respiratory centres stop sending inhibitory impulses to the cardiac vagal centre causing increased vagal tone and sinus bradycardia.

Cardiovascular Reflex Mechanisms Affecting Medullary Control Centres

Cardiovascular reflex mechanisms are multiple subconscious special nervous control mechanisms that operate through medullary control centres all the time to maintain the arterial pressure within normal range. These include:

- Baroreceptor reflex mechanisms
- Chemoreceptor reflex mechanism

Baroreceptor Reflex Mechanisms

Baroreceptors, also known as mechanoreceptors or pressure receptors, are the stretch receptors located in the walls of heart and large blood vessels. These are spray-type nerve endings, i.e. they are extensively branched, knobby, coiled and intertwined ends of myelinated nerve fibres. These are stimulated by distension of the structures in which they are located and so they discharge at an increased rate when the pressure in these structures rises. The increased baroreceptor discharge leads to *inhibition* of tonic discharge of vasoconstrictor nerves and *excitation* of vagal innervation of heart, and thereby produces vasodilation, venodilation, bradycardia, decrease in cardiac output and decrease in blood pressure.

With this definition of the baroreceptor reflex mechanism the baroreceptors will be discussed in detail as under the following headings.

Classification and Location of Baroreceptors

Functional Classification Functionally baroreceptors can be grouped as follows.

1. ***High-pressure baroreceptors,*** which monitor the arterial circulation. These include the baroreceptors located at:
   - Carotid sinus
   - Aortic arch
   - Wall of left ventricle
   - Root of right subclavian artery
   - Junction of the thyroid artery with common carotid artery
2. ***Low-pressure baroreceptors*** are located in the low-pressure area of circulation and are collectively referred to as *cardiopulmonary receptors.* These include:
   - *Atrial receptors* scattered in the wall of right and left atrium.
   - *Baroreceptors* located in the right atrium at the entrance of the superior and inferior vena cavae and in the left atrium at the entrance of pulmonary veins.
   - *Pulmonary receptors* located in the wall of pulmonary trunk and its divisions into the right and left pulmonary artery.

Carotid and Aortic Arch Baroreceptors

Location of Carotid and Aortic Arch Baroreceptors

Carotid baroreceptors are located in the carotid sinus, which is a small dilatation of the internal carotid artery just above the bifurcation of the common carotid artery into external and internal carotid branches (Fig. 4.5-7).

Aortic arch baroreceptors are located in the wall of arch of aorta (Fig. 4.5-7).

Other systemic arterial baroreceptors (similar to carotid and aortic baroreceptors) are also found at the root of right subclavian artery and junction of thyroid artery, and in the common carotid artery.

Innervation of Baroreceptors (Fig. 4.5-8)

Carotid sinus baroreceptors are innervated by the carotid sinus nerve (Hering's nerve), which is a branch of glossopharyngeal nerve.

All other baroreceptors are supplied by the vagus nerve.

Afferent fibres from the baroreceptors pass via the glossopharyngeal and vagus nerves to the medulla. Most of them end in the NTS, where they secrete an excitatory transmitter, presumably, glutamate.

Buffer nerves. The carotid sinus nerve and vagal fibres from the carotid sinus and aortic arch baroreceptors, respectively, are commonly called buffer nerves because these are involved in buffering the blood pressure, i.e. preventing sudden rise and fall in the blood pressure.

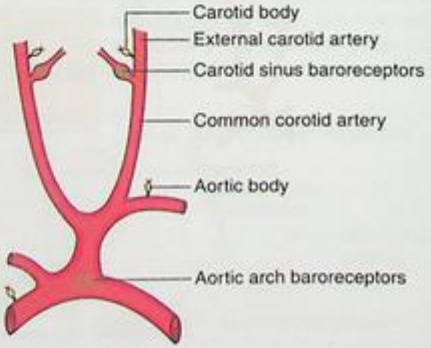


Figure 4.5-7 Location of baroreceptors (carotid sinus and aortic arch) and chemoreceptors (carotid bodies and aortic bodies).

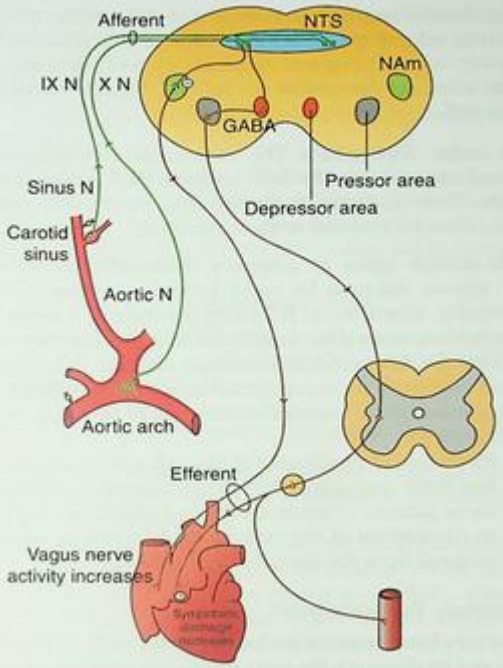


Figure 4.5-8 Neural pathway of baroreceptor reflex.

Projections from NTS (excitatory glutaminergic projections) terminate on to the:

- *Depressor area of VMC,* where they stimulate GABA (gamma-aminobutyric acid)-secreting inhibitory neurons which decrease sympathetic activity.
- *Cardiac vagal centre* (nucleus ambiguus), after receiving the impulses from NTS, *sends inhibitory* pathway along the vagus nerve to:
  - *Heart* (through cardiac branches of the vagus nerve to decrease heart rate and force of contraction).

Response of Carotid and Aortic Baroreceptors to Pressure Response from carotid baroreceptors have been studied in detail. Salient features of these receptor's responses to pressure are given below.

Baroreceptor Response. At normal blood pressure levels the fibres of the buffer nerves discharge at a low rate which increases when the pressure in the carotid sinus and aortic arch rises, and declines when the pressure falls (Figs 4.5-9 and 4.5-10).

The Effect of Different Arterial Pressure Levels on the Discharge Rate in carotid sinus nerve shown in Fig. 4.5-10 depicts that:

- The minimum pressure of about 60 mm Hg at which carotid baroreceptors are stimulated is called *threshold of baroreceptor reflex.*
- Above threshold level, the baroreceptors respond progressively more rapidly till the discharge rate reaches *a plateau,* at 150–160 mm Hg, i.e. there is no further increase in response. Thus, the carotid baroreceptors exhibit a great sensitivity as they respond to pressure that varies from approximately 50–160 mm Hg.

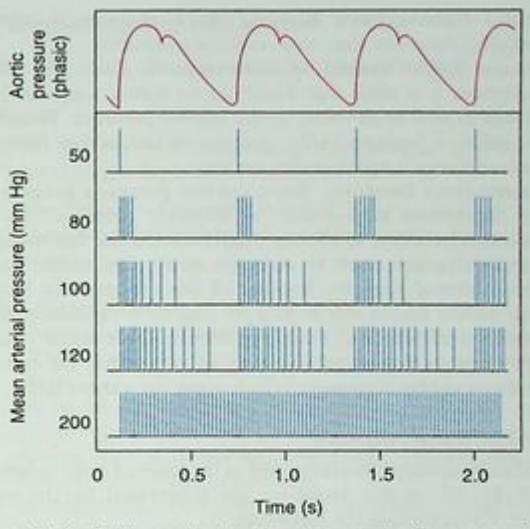


Figure 4.5-9 Discharges (vertical lines) in a single afferent nerve fibre from carotid sinus at various levels of mean arterial pressure, plotted against changes in aortic pressure with time.

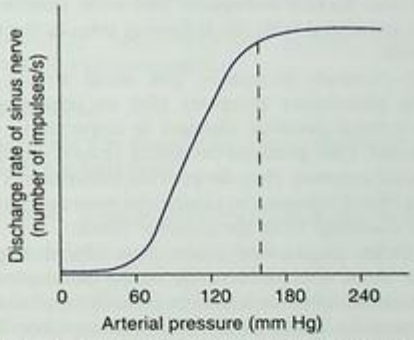


Figure 4.5-10 Response of carotid baroreceptors at different levels of arterial pressure.

- In the normal operating rate at 95–100 mm Hg, even a slight change in pressure causes a strong change in the baroreceptor reflex signals to readjust the arterial pressure back towards the normal.
- When pressure decreases below normal levels, the baroreceptor discharge decreases and reflexly brings the pressure to normal. Conversely, when pressure increases above normal, the baroreceptor discharge also increases and reflexly brings the pressure to normal.

The Carotid Baroreceptors Respond Both to the Mean Pressure and the Pulse Pressure. Thus, the baroreceptor discharge would increase:

- When the mean pressure rises and the pulse pressure remains unchanged
- When the pulse pressure rises and the mean pressure remains unchanged

Carotid Baroreceptors Respond much more to a Rapidly Changing Pressure than to a stationary pressure.

Pressure–Buffer System of Baroreceptors. From the above description it is clear that baroreceptor system opposes both increase as well as decrease in the arterial pressure. Therefore, it is called *a pressure–buffer system* and the nerves from the baroreceptors are called buffer nerves.

Baroreceptors Resetting. Baroreceptors possess a property to reset themselves in 1–2 days to whatever pressure they are exposed. Therefore, in chronic hypertension the baroreceptor reflex mechanism resets to maintain an elevated rather than a normal arterial pressure. Because of this property the *baroreceptor system has no role to play for long-term regulation of the mean arterial pressure.* Thus, the baroreceptor reflex mechanism plays an important role only in preventing the extreme variations in blood pressure which occur for a short term.

Cardiac Baroreceptors

Cardiac baroreceptors are located in the walls of heart subendocardially. All cardiac receptors are innervated by the vagus nerve. These include the following.

Atrial Stretch Receptors Atrial stretch receptors present in the walls of atria are also called *low-pressure receptors.*

Atrial stretch receptors have been studied in detail by Prof. A.S. Paintal (an Indian scientist) in 1953.

Role of Atrial Stretch Receptors The atrial stretch receptors have been associated with the following roles in the cardiovascular control.

1. As Low-pressure Receptors. The atrial stretch receptors along with pulmonary receptors play an important role to minimize arterial pressure changes in response to change in blood volume. Low-pressure receptors cannot detect the systemic arterial pressure, they do provide information about the circulating blood volume, i.e. greater the venous return, greater will be the discharge from the receptor fibres.
2. Atrial Reflex Control of Heart Rate (Bainbridge Reflex). Bainbridge noted that sudden rise in the atrial pressure after rapid infusion of saline or blood in anaesthetised animals produced tachycardia, if the initial heart rate was low. This effect is known as Bainbridge reflex. Atrial stretch receptors may be responsible for this reflex. The afferent signals from these receptors pass through the vagus nerves to the medulla of brain. The efferent signals are transmitted back through both the vagal and the sympathetic nerves to increase the heart rate and force of contraction. Thus, this reflex helps to prevent damming of blood in the veins, atria and pulmonary circulation.
3. Atrial Reflex Control of Blood Volume (Volume Reflex). When there is volume overload the atrial stretch receptors help to return the blood volume back towards normal by the following mechanisms, which collectively are called volume reflex:

(i) Stretch of the atria causes very significant reflex dilatation of the afferent arterioles in the kidney leading to rise in glomerular capillary pressure with resultant increase in filtration of fluid into the kidney tubules.

(ii) *Stretch of the atria also transmits signals to the hypothalamus* to decrease the secretion of antidiuretic hormone (ADH), which diminishes the reabsorption of water from tubules.

(iii) Stretch of the atria also causes release of a chemical *called atrial natriuretic peptide* (ANP), which causes powerful diuresis and thus brings blood volume back to normal.

The above-described mechanisms (i–iii), which collectively constitute volume reflex, act as a volume controller and thus indirectly act *as a pressure controller* as well. Because excess volume increases the cardiac output and thus the arterial pressure as well.

Ventricular Receptors The ventricular baroreceptors are scattered throughout the left ventricle and interventricular septum. They discharge irregularly and no physiological significance can be attached to these receptors.

Bezold–Jarisch reflex or coronary chemoreflex refers to the reflex apnoea followed by rapid breathing, hypotension and bradycardia, which occur following injection of certain drugs like serotonin, veratridine or nicotine into the coronary arteries supplying the left ventricle (injection into the right coronary artery is ineffective) in experimental animals. This reflex is probably produced by the chemical stimulation of the left ventricular stretch receptors.

- *Physiological significance of* this reflex is uncertain, but it has been speculated that the persistent hypotension in some patients of acute myocardial infarction may be due to stimulation of the ventricular receptors by substances released from the necrotic cardiac tissue.

Pulmonary Baroreceptors

Pulmonary baroreceptors are located in the walls of pulmonary trunk and its divisions, the right and left pulmonary artery. The pulmonary receptors along with the atrial receptors constitute the so-called *low-pressure receptors or cardiopulmonary receptors,* and play an important role to minimize arterial pressure changes in response to change in blood volume as discussed above.

Role of Chemoreceptor Reflexes in Cardiovascular Control

Chemoreceptors are chemosensitive cells that respond to the following changes in blood:

- Oxygen lack (decreased PO_2)
- Carbon dioxide excess (increased PCO_2)
- Hydrogen ion excess (decreased pH)

Location of Chemoreceptor. The chemoreceptors are present in (Fig. 4.5-7):

1. ***Carotid bodies.*** These are 1–2 mm in size and are located in the bifurcation of each common carotid artery. These are innervated by carotid sinus nerve, which is a branch of glossopharyngeal nerve.
2. ***Aortic bodies*** are one to three in number, located adjacent to arch of aorta. These are innervated by aortic nerve (branch of vagus nerve).

Functions of Chemoreceptors

1. Respiratory Control. Chemoreceptors are primarily concerned with the regulation of pulmonary ventilation and are discussed in much more detail in Chapter 5.6, page 205.

2. Cardiovascular Control. The chemoreceptors exert their role in cardiovascular regulation in the following conditions:

- ***In hypoxia,*** there occurs increased chemoreceptor discharge, which not only produces hyperventilation but also excites the VMC leading to peripheral vasoconstriction and

increase in the arterial blood pressure. Thus, unlike the inhibitory action of arterial baroreceptors, the chemoreceptors have an excitatory effect on the VMC.
- ***In hypotension*** *due to severe haemorrhage,* the increased chemoreceptor discharge may help to raise the arterial blood pressure.

Note. It is important to note that the chemoreceptors are not stimulated strongly until the arterial pressure falls below 60 mm Hg. Therefore, it is at lower pressures that this reflex becomes important and helps to prevent still further fall in pressure.

Direct Effects on Vasomotor Area

The VMC is directly affected by locally produced hypoxia and hypercapnia. Examples of direct effects are CNS ischaemic response and Cushing reflex.

1. Central Nervous System Ischaemic Response

- When blood pressure falls below 60 mm Hg, the blood flow to the vasomotor area in the brainstem is decreased enough to cause CNS ischaemia.
- As a result of CNS ischaemia, the CO_2/lactic acid are accumulated locally near the VMC and excite the neurons of VMC strongly.
- Excitation of VMC causes strong sympathetic stimulation leading to vasoconstriction. There occurs immediate increase in the blood pressure. This most powerful response that activates sympathetic vasoconstrictor system strongly is called *CNS ischaemic response.* This acts as an emergency arterial pressure control system.

2. Cushing Reflex When intracranial pressure is increased and becomes equal to the arterial pressure, it compresses the arteries in the brain, and blood supply to the vasomotor area is compromised. The hypoxia and hypercapnia produced locally increase the discharge from VMC. The resultant rise in the systemic pressure tends to restore the blood supply to medulla. This effect is called *Cushing reflex.* The resultant increase in blood pressure also causes reflex bradycardia via baroreceptor response. Thus, bradycardia is an important feature of raised intracranial pressure.

Afferents from Nociceptive Stimuli Afferents carrying pain sensations also affect VMC and evoke either pressor or depressor reflex effect as:

Pressor effect in the form of an increase in the blood pressure and tachycardia is caused due to the sympathetic activity by *somatic pain afferents,* i.e. unmyelinated C-fibres which stimulate the pressor area of VMC.

Depressor effect in the form of hypotension and bradycardia is produced by *visceral pain afferents,* i.e. thin myelinated fibres which synapse with depressor area of VMC and cause inhibition of sympathetic activity.

HUMORAL CONTROL MECHANISMS

Humoral regulation of circulation refers to the regulation by substances secreted into or absorbed into body fluids, e.g. hormones and ions. Most important humoral factors affecting circulation are as follows:

- Circulating vasodilators
- Circulating vasoconstrictors
- Ions and other chemical factors

Circulating Vasodilators

The circulating vasodilators include the following.

Kinins

Kinins are peptides which cause vasodilation. Two forms of kinins with similar action found are as follows:

- ***Bradykinin*** is nonapeptide found in the plasma
- ***Lysyl-bradykinin*** or kallidin is a decapeptide found in body tissues

Functions of Kinins
- They cause *vasodilation* by relaxing vascular smooth muscle (VSM) via nitric oxide (NO) and increase *capillary permeability.*
- Kinins play role in regulating blood flow especially to skin, salivary glands and GIT glands. Therefore, they are formed during active secretion in sweat glands, salivary glands and in exocrine portion of pancreas.
- By regulating blood flow to skin the kinins probably play a role in thermoregulatory vascular adjustments.

Atrial Natriuretic Peptide

See page 345.

Circulating Vasoconstrictors

The circulating vasoconstrictors include catecholamines, angiotensin II and vasopressin.

Catecholamines

Catecholamines are released on the sympathetic stimulation and include the following.

Epinephrine. It stimulates both α and β adrenergic receptors:

- *Stimulation of α-receptors* results in vasoconstriction in skin and splanchnic areas.
- *Stimulation of β-receptors* results in dilation of the vessels in the skeletal muscles, liver and coronary arteries.
- The β-receptor-induced vasodilation is more dominant than α-receptors-induced vasoconstriction. So, the net effect is slight lowering of peripheral resistance producing slight fall in diastolic blood pressure.

Norepinephrine. It has a generalized vasoconstrictor action as it has much greater effect on α- than on β-receptors. Therefore, it increases peripheral resistance and raises the diastolic blood pressure.

Renin–Angiotensin System

The renin–angiotensin system has important roles in the regulation of blood pressure and extracellular fluid volume.

Renin Secretion and Angiotensin Formation
- *Renin,* a protease enzyme is secreted *by juxtaglomerular cells* of the kidney into the blood. Its secretion is stimulated by a decrease in the blood pressure.
- Renin catalyses the conversion of *angiotensinogen* (α_2-globulin substrate present in the plasma) to angiotensin I.
- *Angiotensin I* is converted into angiotensin II by the action of *angiotensin-converting enzyme* (ACE) present in the

endothelium of blood vessels throughout the body, especially in the lungs and kidneys.

$$\text{Angiotensinogen} \xrightarrow{\text{Renin}} \text{Angiotensin I}$$

$$\text{Angiotensin I} \xrightarrow{\text{ACE}} \text{Angiotensin II}$$

Effects of Angiotensin II Angiotensin II has three principal effects by which it can elevate the arterial pressure.

1. Vasoconstriction. Angiotensin II is the most potent pressor substance being 4–8 times more potent than norepinephrine. This effect of angiotensin II is important in the intermediate blood pressure control during circumstances, such as acute haemorrhage.
2. Decrease in Salt and Water Excretion by Kidney. Angiotensin II causes salt and water retention by the kidney. This action slowly increases extracellular fluid volume, which increases arterial pressure over a period of hours and days. Thus, this effect of angiotensin II plays an important role in the long-term control of arterial pressure.
3. Stimulation of Thirst. Angiotensin II is a powerful stimulator of thirst. It leads to consumption of large volumes of water, leading to a rise in blood volume. This mechanism also plays some role in long-term control of blood pressure.

Vasopressin

Vasopressin or ADH is secreted in minute quantities and therefore mainly affects water reabsorption in renal tubules. However, after a severe haemorrhage its concentration rises to a high level and then it has vasoconstrictor effect.

Ions and Other Chemical Factors

The increased concentration of many different ions and chemical factors can also alter local blood flow by causing vasodilation or vasoconstriction.

- Calcium ions cause vasoconstriction.
- Potassium ions cause vasodilation.
- Hydrogen ions (decreased pH) cause vasodilation.
- Carbon dioxide causes vasodilation in most tissues and marked vasodilation in the brain.
- Glucose or other vasoactive substances, when increased in quantities, raise the osmolarity of blood and cause vasodilation.

LOCAL CONTROL MECHANISMS

Local cardiovascular control mechanisms are primarily concerned with the control of blood flow to the tissues locally.

The mechanisms that are present in most tissues of the body are as follows:

1. Autoregulation, i.e. control of flow during changes in the arterial pressure
2. Role of local vasodilator metabolites and factors
3. Role of local vasoconstrictors
4. Role of substances secreted by the endothelial cells

1. Autoregulation (Control of Flow during Changes in Arterial Pressure) Autoregulation is the ability of an organ or tissue to adjust its vascular resistance and maintain a relatively constant blood flow over a wide range of arterial pressure. For details see page 140.

2. Role of Local Vasodilator Metabolites The accumulation of local vasodilator metabolites increases local blood flow. The greater the rate of metabolism in the tissue, the greater is the rate of production of tissue metabolites. These include:

- *Decrease in O_2 tension and pH*
- *Increase in pCO_2 and osmolality*
- *Rise in temperature*
- *Potassium (K^+) and lactate ions*
- *Histamine*
- *Adenosine*

Local vasodilator metabolites increase blood flow during the following conditions.

Active Hyperaemia refers to the vasodilation which occurs when the tissue metabolic rate increases. The dilation of local blood vessels helps the tissues to receive the additional nutrients required to sustain its new level.

Metabolic Theory of Autoregulation states that any vasodilator metabolites which accumulate in the tissues during active metabolism will produce autoregulation. When blood flow decreases, they accumulate and the vessels dilate; when blood flow increases, they are washed away.

Reactive Hyperaemia is a phenomenon by which the local blood flow to the organ is controlled after a period of ischaemia.

3. Role of Localized Vasoconstrictors

Serotonin released from platelets in the injured tissue is responsible in part for the vasoconstriction, which occurs in haemostasis.

Decrease in tissue temperature causes vasoconstriction and this local response to cold plays a part in temperature regulation.

4. Role of Substances Released by Endothelium Vascular endothelial cells make up a large and important organ. These cells secrete many growth factors and vasoactive substances, which play an important role in the local control of blood flow. The vasoactive substances include:

- Prostaglandins and thromboxane A_2
- Endothelium-derived relaxing factor (EDRF)
- Endothelins

(i) Prostaglandins and Thromboxane A_2

- ***Prostacyclin*** is prostaglandin produced by the endothelial cells from arachidonic acid via cyclooxygenase pathway. It inhibits platelet aggregation and promotes vasodilation.
- ***Thromboxane A_2*** is produced by platelets and also from arachidonic acid. It promotes platelet aggregation and vasoconstriction.

(ii) Endothelium-derived Relaxing Factor EDRF is the name given to a substance which is released by vascular endothelial cells and produces vasodilation. Later on, it was identified to be *nitric oxide (NO)* in chemical structure.

Mechanism of Vasodilation by NO. The NO that is synthesized in the endothelium diffuses to smooth muscle cells, where it activates soluble guanylyl cyclase, producing cyclic GMP, which, in turn, mediates the relaxation of VSM by decreasing intracellular Ca^{2+} concentration.

(iii) Endothelins (ET) Endothelins are family of three similar polypeptides: ET-1, ET-2 and ET-3. Endothelin-1 produced by the endothelial cells is the most potent vasoconstrictor agents.

SELF-ASSESSMENT

1. Discuss briefly the rapidly acting mechanisms for regulation of cardiac output and blood pressure.
2. Discuss the role of renin angiotensin mechanism in regulation of blood pressure.
3. Describe the role of kidney in regulation of BP.
4. Describe the components of neural control mechanism of cardiovascular regulation.
5. Differentiate between
   - Baroreceptor and chemoreceptor reflex
   - Stress and reverse stress relaxation mechanism
   - Effect of exercise in trained and untrained individual
6. Write notes on:
   - Sympathetic cholinergic vasodilator nerves and their significance
   - Axon reflex
   - Baroreceptors resetting
   - Buffer nerves
   - Arterial stretch receptors
   - Bezold–Jarisch reflex
   - CNS ischemic response
   - Cushing reflex
   - Circulating vasodilators
   - Circulating vasoconstrictors

4.6 Regional Circulation

CHAPTER OUTLINE

Introduction

Coronary Circulation
Coronary Blood Vessels
Coronary Blood Flow: Characteristic Features
Regulation of Coronary Blood Flow
Coronary Artery Disease

Cerebral Circulation
Cerebral Blood Vessels
Cerebral Blood Flow: Characteristic Features
Regulation of Cerebral Blood Flow

Cutaneous Circulation
Cutaneous Blood Vessels
Cutaneous Blood Flow: Characteristic Features
Regulation of Cutaneous Blood Flow
Cutaneous Vascular Responses

Skeletal Muscle Circulation
Skeletal Muscle Blood Flow: Characteristic Features
Regulation of Muscle Blood Flow

Splanchnic Circulation

INTRODUCTION

After discussing the 'dynamics of circulation' and 'cardiovascular regulation mechanisms', it will be worthwhile to know how these basic principles apply to circulation in various regions of the body. This chapter includes the following:

- Coronary circulation
- Cerebral circulation
- Cutaneous circulation
- Skeletal muscle circulation
- Splanchnic circulation

Circulation to other regions, such as pulmonary circulation and renal circulation, has been described in the concerned sections.

CORONARY CIRCULATION

Coronary Blood Vessels

Coronary Arteries

Two Coronary Arteries (right and left) arise from the root of ascending aorta and supply blood to the myocardium (Fig. 4.6-1).

Right coronary artery supplies blood to the right ventricle, the right atrium, the posterior part of left ventricle, the posterior part of interventricular septum and major portion of the conducting system of heart including SA node.

Left coronary artery supplies blood mainly to the anterior part of left ventricle, left atrium, anterior part of the interventricular septum and a part of the left branch of bundle of His.

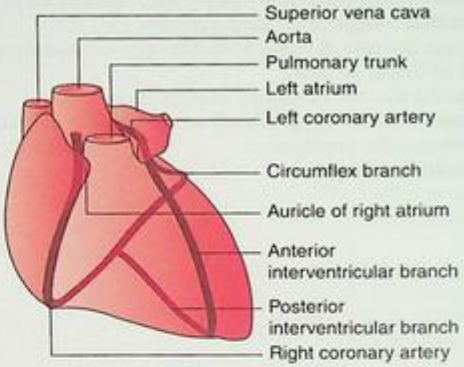


Figure 4.6-1 Major coronary arteries and their branches.

Coronary Veins

Coronary Sinus is a wide vein about 2 cm long, which drains most of the venous blood from the myocardium (mainly left ventricle) into the right atrium. Its tributaries are the *great cardiac vein*, the *small cardiac vein*, *the posterior vein of left ventricle* and the *oblique vein of left ventricle* (Fig. 4.6-2).

Anterior Cardiac Vein draining venous blood mainly from the right ventricle opens directly into the right atrium.

Thebsian Veins and *coronary luminal vessels* (connections between the coronary vessels and the lumen of heart) constitute the deep venous system. These vessels drain only less than 10% of the venous blood from the myocardium directly into the various cardiac chambers, contributing to an *anatomic shunt effect*. The coronary luminal connections carry a larger proportion of the flow in the right ventricle than in the left ventricle.

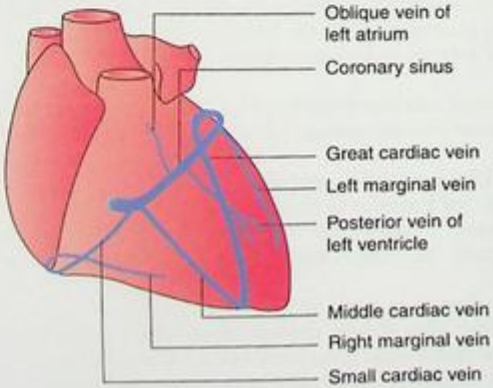


Figure 4.6-2 Coronary sinus and its tributaries.

Coronary Blood Flow: Characteristic Features

Normal Coronary Blood Flow and Oxygen Demand

A continuous flow of blood to the heart is essential to maintain an adequate supply of O_2 and nutrients.

Normal coronary blood flow at rest is about 250 mL (70 mL/100 g tissue/min), i.e. about 5% of the resting cardiac output (5 L). Threefold to sixfold increase in the coronary blood flow may occur during exercise.

Oxygen consumption by the myocardium is very high (8 mL/min/100 g at rest). Because of this, even at rest 70%–80% of the oxygen is extracted from each unit of the coronary blood as compared to the whole body (average of 25%) oxygen extraction at rest. The increased oxygen demand of the myocardium during exercise is met with by almost total (nearly 100%) extraction of oxygen and by manifold increase in the coronary blood flow.

Phasic Changes in Coronary Blood Flow

The coronary blood flow shows changes during phases of the cardiac cycle. The blood flow is determined by the balance between *pressure head* (i.e. aortic pressure) and the resistance (i.e. extravascular pressure exerted by the myocardium on the coronary vessels) offered to the blood flow during various phases of cardiac cycle is shown in Table 4.6-1 and Fig. 4.6-3, and is described here.

Blood Flow to Left Ventricle

During Systole the tension developed in the left ventricle is so high that it has throttling effect on the branches of the coronary arteries penetrating through them. As a result, the average blood flow through the capillaries of left ventricles falls to the extent that during isometric contraction phase the blood flow to the left ventricle practically ceases, i.e. becomes zero.

During Diastole the cardiac muscles relax and blood flow increases. Thus, most of the coronary blood flow (over 70%) occurs during diastole (Fig. 4.6-3). In severe tachycardia the duration of diastole is drastically reduced. This tends to reduce the coronary blood flow during diastole as well, but due to local metabolic regulation the blood flow to the myocardium is not seriously affected.

Blood Flow to Right Ventricle and Atria Blood passing through coronary capillaries of right ventricle also shows phasic changes similar to the left ventricle. However, the changes in the right ventricular flow are far less because force of contraction of the right ventricle is much less (Table 4.6-1). Thus, the blood flow to the right ventricle and atria occurs both during systole and diastole.

Blood Flow through Coronary Sinus As shown in Fig. 4.6-3, in the coronary sinus the inflow of blood gradually rises from the *isovolumic ventricular contraction phase*, reaches its peak during *protodiastole phase* and then gradually falls.

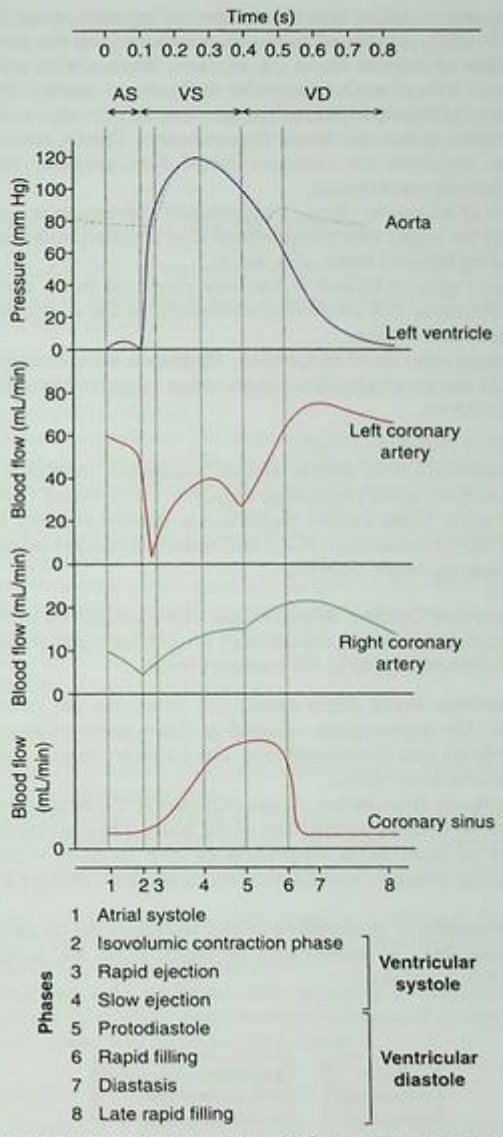


Figure 4.6-3 Blood flow in right and left coronary arteries and coronary sinus during different phases of cardiac cycle.

TABLE 4.6-1 Pressure Gradients between Ventricles and Aorta During Systole and Diastole

Phase of Cardiac Cycle	PRESSURE (mm Hg)			PRESSURE GRADIENT (mm Hg) BETWEEN AORTA AND VENTRICLE	
	Right Ventricle	Left Ventricle	Aorta	Right Ventricle	Left Ventricle
Systole	25	121	120	95	−1
Diastole	0	0	80	80	80

Regulation of Coronary Blood Flow

I. Local Control Mechanism

1. Autoregulation. Like other vital organs of the body coronary circulation shows well-developed phenomenon of autoregulation, as described in detail on page 140. However, this phenomenon of autoregulation of coronary blood flow fails when blood pressure falls below 70 mm Hg and coronary perfusion is seriously compromised.

2. Role of Local Metabolites. Metabolic local factors are the most important factors which regulate the coronary blood flow.

- It is important to note that under resting state about 50%–70% of O_2 is released to the myocardium from the haemoglobin of arterial blood (in contrast, haemoglobin releases about 25% of its O_2 content for the body as a whole). Therefore, not much additional oxygen can be provided to myocardium unless the blood flow increases. The O_2 consumption regulates the coronary blood flow probably by the following mechanisms.
- *Role of adenosine* (Berne's hypothesis). Adenosine is considered the major factor in production of coronary vasodilation during hypoxic states (Fig. 4.6-4).
- *Direct effect of O_2 lack.* It has been proposed that a decrease in the tissue PO_2 could also act directly on the arterioles and cause vasodilation.
- *Role of other local metabolites.* Hydrogen ions, bradykinin, CO_2 and prostaglandins are the other suggested vasodilator substances.

3. Role of Endothelial Cells

- Endothelial cells release several *vasodilator* autacoids that contribute to the physiologic regulation of coronary vasomotor tone. These include endothelium-derived relaxing factor (EDRF), prostacyclin (PGI_2) and endothelium-derived hyperpolarizing factor (EDHF).

II. Nervous Control Mechanism Nervous control on coronary circulation is exerted through sympathetic and parasympathetic nerve supply to the coronary vessels.

Sympathetic nerve fibres extensively innervate the coronary vessels. The transmitters released at their nerve endings are epinephrine and norepinephrine. The coronary vessels contain both α-and β-receptors.

Sympathetic stimulation causes increase in the heart rate and increase of force of contraction of the heart. Thus, an increased activity of heart helps conversion of ATP to ADP, which by producing coronary vasodilation increases the coronary blood flow.

Parasympathetic stimulation causes decreased heart rate and decreased force of contraction of heart. Thus, the coronary blood flow is reduced.

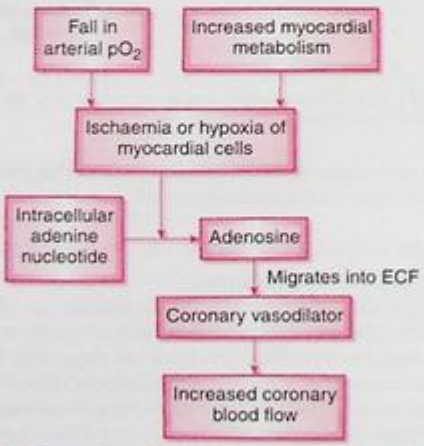


Figure 4.6-4 Berne hypothesis (adenosine mechanism) of increase in coronary blood flow.

Neurohumoral Control Factors Several nonadrenergic noncholinergic neurotransmitters also play a modulatory role, which include the following:

- ATP (purine)
- *Neuropeptide-Y* (NPY)
- *Calcitonin gene-related peptide (CGRP)* and substance P

Coronary Artery Disease

Coronary artery disease (CAD) also known as ischaemic heart disease (IHD) results due to the insufficient coronary blood flow.

Causes of CAD include the following:

- Atherosclerosis of coronary arteries
- Thrombus formation
- Embolus coming from other areas
- Spasm of coronary vessels

Atheromatous coronary artery stenosis is the commonest cause, so it has become synonymous with CAD.

CEREBRAL CIRCULATION

Cerebral Blood Vessels

Arteries of the Brain

- The arteries which supply blood to the brain are derived from two internal carotid arteries and the basilar artery (formed by union of the right and left vertebral arteries). Branches of the internal carotid arteries and basilar artery anastomose on the inferior surface of the brain to form the circulus arteriosus (circle of Willis).
- The *circle of Willis* (Fig. 4.6-5) is thus basically a free anastomoses between the two internal carotid arteries and the two vertebral arteries which equalize pressure on the arteries of the two sides. In this way the circulus arteriosus allows blood that enters by either internal carotid or vertebral artery to be distributed to any part of both cerebral hemispheres.
- *Six large arteries* taking part in the formation of circle of Willis supply by their central and cortical branches to the brain substance.

Venous Drainage of the Brain The cerebral hemisphere has two sets of veins: the superficial and deep. The veins draining the brain open into the various dural venous sinuses. Ultimately, the blood from all these sinuses reaches the sigmoid sinuses, which become continuous with the two internal jugular veins. The venous drainage of individual part of the brain is as follows.

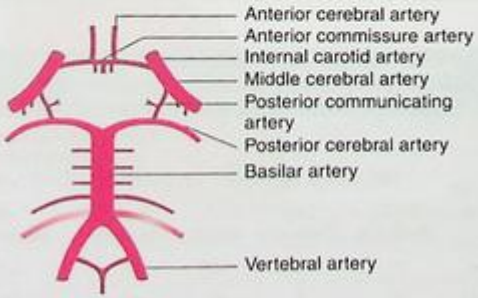


Figure 4.6-5 The circle of Willis.

Cerebral Blood Flow: Characteristic Features

Normal Blood Flow

- Brain relies on a continuous blood flow for adequate function. It is most susceptible to ischaemia. Interruption of blood flow only for 5–10 seconds causes a loss of consciousness and circulatory arrest for only 3–4 minutes results in irreversible brain damage. The vegetative structures in brainstem are more resistant to hypoxia than cerebral cortex.
- Brain has a very rich blood supply. Normal blood flow to brain (which forms less than 2% of the body weight) represents approximately 15% of the resting cardiac output (75 mL/min) or about 50–55 mL blood/100 g tissue/min.
- When cerebral blood flow falls below 18 mL/100 g tissue/min *(critical flow level)*, there occurs unconsciousness.

Normal O_2 Consumption

- Total O_2 consumption of the brain is approximately 50 mL/min (3.3 mL/100 g tissue/min), i.e. 20% of the whole body at rest.

Regulation of Cerebral Blood Flow

The cerebral blood flow is regulated by the following mechanisms.

1. Metabolic Regulation The important metabolic factors which play important role are given below.

(i) Carbon Dioxide. Physiologically, pCO_2 is the most potent vasodilator of cerebral blood vessels. A rise in pCO_2 is associated with a rise in H^+ concentration. Carbon dioxide easily diffuses through the blood–brain barrier and reaches the cerebrospinal fluid (CSF). In the CSF, CO_2 combines with water to form carbonic acid, which partially dissociates to form H^+ ions. The H^+ ions induce cerebral vasodilation in proportion to their concentration.

(ii) pO_2. Slight fall in pO_2 causes vasodilation and produces increase in cerebral blood flow due to rapid formation of *adenosine*, which is potent dilator of pial arterioles.

(iii) K^+ ions. An increase in K^+ concentration in the CSF following hypoxia causes rapid increase in cerebral blood flow.

2. Autoregulation of Cerebral Blood Flow Like other vital organs of the body cerebral circulation also shows phenomenon of autoregulation. Due to autoregulation cerebral blood flow remains nearly constant between 60 and 140 mm Hg blood pressure; when blood pressure falls below 60 mm Hg, the cerebral blood flow becomes extremely compromised and syncope may result. When blood pressure rises above 140 mm Hg, there may occur disruption of blood–brain barrier due to stretching and cerebral oedema or cerebral haemorrhage may result.

3. Role of Intracranial Pressure in Regulation of Cerebral Blood Flow The intracranial pressure level regulates cerebral blood flow by the following two mechanisms.

(i) Monro–Kellie Doctrine. According to this doctrine the brain, CSF and blood in the cerebral vessels are three elements enclosed in a rigid cranial cavity; and when any of them increases, it is at the expense of other two. This relationship helps to maintain the cerebral blood flow when changes in the arterial blood pressure occur at the level of head.

(ii) Cushing Reflex. When intracranial pressure is increased and becomes equal to the arterial pressure, it compresses the arteries in the brain and blood supply to vasomotor area is compromised. The hypoxia and hypercapnia produced locally increases the discharge from vasomotor centre. The resultant rise in a systemic pressure tends to restore the cerebral blood flow (see page 157).

CUTANEOUS CIRCULATION

Cutaneous Blood Vessels (Fig. 4.6-6)

Cutaneous Arterioles form a dense network just under the dermis layer of the skin.

- *Meta-arterioles* which arise from the arterioles are relatively high-resistance conduits present between the arterioles and capillaries.
- *Cutaneous capillaries.* The meta-arterioles subdivide into capillary loops, which provide a large surface area for heat exchange.
- *Venules* form an extensive subpapillary venous plexus, which holds large quantity of blood and lie parallel to the surface of skin, and play an important role in maintaining the body temperature.
- *Arteriovenous anastomoses* are located in the distal parts of the extremities (hands and feet), nose, lips and ear lobules. These vessels serve as shunts and allow blood to bypass the superficial capillary loops and play a major role during control of body temperature.

Cutaneous Blood Flow: Characteristic Features

Principal function of cutaneous circulation is to aid in the regulation of body temperature.

Resting cutaneous blood flow, i.e. the flow when a person is at thermal equilibrium with the environment (at approximately 27°C atmospheric temperature) is about 10–15 mL/min/100 g of skin tissue.

During exposure to cold, when sweating is minimal, the cutaneous blood flow falls to about one-tenth of resting blood flow, i.e. about 1 mL/min/100 g tissue.

During exposure to heat, when sweating is maximum, the cutaneous blood flow may increase 10 times of resting blood flow, i.e. about 150 mL/min/100 g tissue.

Regulation of Cutaneous Blood Flow

The cutaneous blood flow is predominantly regulated by the nervous control instead of metabolic control.

Nerve Supply of Cutaneous Vessels

Sympathetic vasoconstrictor nerves supplying the cutaneous vessels exhibit a sympathetic constrictor discharge under resting

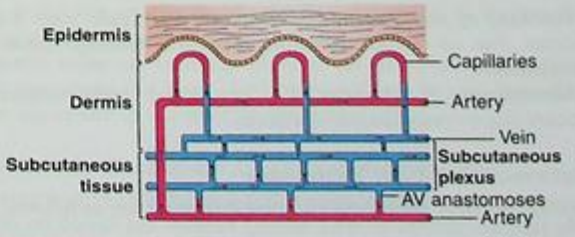


Figure 4.6-6 Arrangement of blood vessels in subcutaneous region.

condition. The sympathetic tonic discharge is more marked on A–V anastomoses vessels than the other vessels.

Parasympathetic vasodilator nerves do not supply the cutaneous blood vessels. Vasodilation of cutaneous vessels results due to:

- Reduction of sympathetic vasoconstrictor effect
- Local production of bradykinin (a potent vasodilator polypeptide) in sweat glands
- Production of other local vasodilator substances

Neural Control Mechanisms The cutaneous blood flow is regulated by the following neural control mechanisms.

1. Hypothalamic Control Mechanism The reflex increase or decrease in the sympathetic discharge to cutaneous vessels during thermoregulation is mediated through the temperature regulation centres of the hypothalamus as:

Under resting conditions, i.e. when the person is at thermal equilibrium with the environment (at about 27°C atmospheric temperature), the sympathetic vasoconstrictor fibres have a mild tonic discharge. The tonic sympathetic discharge normally keeps the A–V anastomoses closed.

During exposure to heat stress, the tonic sympathetic discharge is reflexly abolished by a hypothalamic mechanism. Thus the blood flow to skin is increased by the following responses in a chronological sequence:

- First of all, A–V anastomoses of hands, feet and ear lobules dilate due to reduction in the sympathetic tonic discharge.
- Secondly, rest of the cutaneous vessels dilate due to progressive withdrawal of sympathetic vasoconstrictor activity.
- Thirdly, sweat glands get activated due to the cholinergic sympathetic discharge. The *bradykinin* produced by the secretory activity of the sweat glands acts locally as a powerful vasodilator and increases blood flow to skin.

All the above mechanisms collectively may increase the cutaneous blood flow to as high as 150 mL/min/100 g tissue. The increased blood flow carries heat to the surface of the body, where it is dissipated by *radiation, evaporation* and *conduction* to the environment.

During exposure to cold stress, via hypothalamic mechanism, there occurs widespread cutaneous vasoconstriction due to increased sympathetic discharge. Consequently, cutaneous blood flow is markedly decreased to as low as 1 mL/min/100 g. In this way *heat conservation* is accomplished by markedly diminishing the rate of blood flow to skin.

2. Baroreceptor-Mediated Reflex Cutaneous blood vessels participate in the baroreceptor-mediated reflexes during conditions of circulatory stress, such as exercise and haemorrhage.

3. Cortical Control Mechanism The *emotions* affect the cutaneous circulation through the corticohypothalamic pathway. The effects of emotions on cutaneous circulation manifest in the following forms:

Blanching of skin during situations of fear (pale with fear) occurs due to vasoconstriction mediated through cortical mechanism.

Phenomenon of blushing, i.e. emotional embarrassment occurs due to vasodilation of vessels.

Cutaneous Vascular Responses

Certain peculiar cutaneous vascular responses are as follows:

- White reaction
- Triple response
- Reactive hyperaemia
- Cold vasodilatation
- Cold vasoconstriction

White Reaction White reaction refers to an appearance of a pale stroke line when a pointed object is drawn lightly over the skin. This occurs due to the fact that the mechanical stimulus initiates contraction of the precapillary sphincter and blood drains out of the capillaries and small veins. This response appears in about 15 seconds.

Triple Response Triple response is a three-part response consisting of the red reaction, wheal and flare; when the skin is stroked more firmly with a pointed instrument, instead of white reaction, there occurs triple response.

The Red Reaction refers to the red line which appears at the site of injury in about 10 seconds. It occurs due to dilatation of the precapillary sphincters in the injured area. The dilatation of the precapillary sphincters is produced by histamine and/or some polypeptides such as bradykinin released from the damaged skin.

The Flare refers to the diffusely spreading and irregularly outlined redness of the skin surrounding the red line.

- It occurs after a few minutes of the appearance of red line.
- It occurs due to the dilatation of the arteriole and precapillary sphincters.
- The dilatation of arteriole is mediated by nerves, because it is abolished by the local anaesthetic agents.
- The flare is mediated by the *axon reflex* in the cutaneous fibres, which does not involve the central nervous system like a typical reflex.

Wheal refers to the swelling or localized oedema that develops within the area of flare.

- It occurs due to increased capillary permeability with consequent extravasation of fluid.
- The increase in capillary permeability responsible for the wheal formation is produced by histamine or histamine-like substance (released from local mast cells) and by P substance (the transmitter released at the central termination of the sensory fibre neurons).

Reactive Hyperaemia Reactive hyperaemia is a phenomenon by which the vessels control blood flow to the organ after a period of *ischaemia* following occlusion of the artery to an organ or tissue. This response of the blood vessels occurs in many organs but is visible in the skin as fiery red skin.

Cold Vasodilatation As discussed above, normally during exposure to cold stress, there occurs widespread cutaneous vasoconstriction via hypothalamic mechanism. However, prolonged and severe vasoconstriction may lead to tissue damage known as *frostbite*. This usually occurs when skin temperature falls below 10°C. The tissue injury so produced is painful and associated with release of histamine and/or some other polypeptide, which excites the sensory terminals and produces *vasodilatation* due to *axon reflex* operating particularly on A–V anastomoses. Cold vasodilatation is the cause of ruddy cheeks seen in fair complexioned individuals on a cold day.

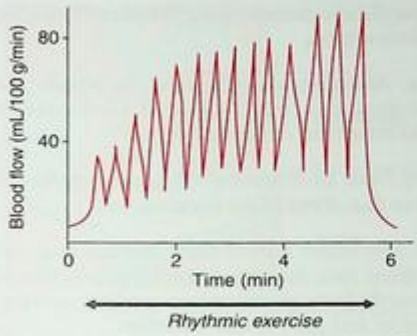


Figure 4.6-7 Blood flow through skeletal muscles.

Cold Vasoconstriction Exposure to cold causes vasoconstriction via hypothalamic mechanism. Prolonged cold-induced vasoconstriction, especially in damp conditions, results in cutaneous ischaemia producing lesions such as *trench foot.*

SKELETAL MUSCLE CIRCULATION

Skeletal Muscle Blood Flow: Characteristic Features

At Rest the blood flow to the skeletal muscle is about 2–4 mL/min/100 g of the muscle tissue.

- The whole body skeletal muscles weight is approximately 30 kg in adults, so the total blood flow to the body muscle mass is about 750–800 mL/min.
- At rest only 20%–25% of muscle capillaries have flowing blood.

During Exercise. During strenuous exercise muscle blood flow can increase up to 20 times, i.e. about 50–80 mL/min/100 g muscle tissue or over 20 L/min to the whole body skeletal mass. This is called exercise hyperaemia.

- The tremendous increase in the muscle blood flow mainly occurs due to local metabolite-induced vasodilatation.
- During exercise the blood flow to the muscle is intermittent because during each contraction muscle fibres squeeze the blood vessels passing through them and thus the blood flow decreases or even stops (Fig. 4.6-7). During relaxation period, muscle blood flow increases and myoglobin acts as an O_2 acceptor and it yields its O_2 to the myofibrils during the subsequent muscle contraction.
- Sustained and severe contractions lasting more than 10 seconds lead to cessation of blood flow, myoglobin supply of O_2 is exhausted and anaerobic metabolites accumulate causing fatigue and ischaemic pain.
- Following heavy phasic exercise the blood flow does not subside immediately, but falls exponentially from its high level during the exercise to resting values. This is due to the *oxygen debt of exercise.*

Regulation of Muscle Blood Flow

The blood flow to the skeletal muscles is regulated by an autoregulation mechanism, metabolic control mechanism and nervous control mechanism.

1. Autoregulation Mechanism Mechanism of autoregulation is well developed in the skeletal muscles like that of kidney, heart and brain.

2. Metabolic Control Mechanism Local metabolic control mechanism is chiefly responsible for the tremendous increase in the skeletal muscle blood flow during exercise (exercise hyperaemia). The decreased tissue pO_2 leads on to vasodilatation. In addition, the exercising skeletal muscle levels of adenosine, potassium ions, hydrogen ions, lactic acid and carbon dioxide. Furthermore, rise of *tissue temperature* due to muscular activity may also contribute to the dilatation of arterioles and precapillary sphincter. As a result there is 10–100-fold increase in the number of open capillaries in the skeletal muscles.

3. Nervous Control Mechanisms Vessels of the skeletal muscles are supplied by both sympathetic vasoconstrictor and sympathetic vasodilator fibres.

Sympathetic Vasoconstrictor Control

During circulatory shock and other type of circulatory stress the sympathetic vasoconstrictor mechanism assumes a great physiological importance. Sympathetic vasoconstriction reduces muscle blood flow profoundly. Thus help in diverting substantial amount of blood from the muscles towards the heart and other vital organs.

Sympathetic Vasodilator Fibres

- Skeletal blood vessels are also supplied by the sympathetic vasodilator fibres which have acetylcholine as neurotransmitter.
- These fibres are activated by *corticohypothalamic reticulospinal* pathways (see page 152).
- Sympathetic vasodilator fibres play no significant role in increasing the muscle blood flow either during or before exercise.
- These fibres play an important role in preventing the sudden rise in the systemic blood pressure at the beginning of exercise, i.e. these provide a *safety valve mechanism as* just before the start of exercise there occurs a considerable increase in the sympathetic activity.

SPLANCHNIC CIRCULATION

Splanchnic Vessels

Splanchnic circulation includes the combined vascular beds of the intestines, pancreas, spleen and liver. The main vessels which constitute the splanchnic circulation are:

Arteries supplying the blood to intestines, pancreas, spleen and liver (Fig. 4.6-8) include:

- *Coeliac trunk* is about 1 cm long and after arising from the abdominal aorta it divides into three main branches the *left gastric artery, hepatic artery and splenicartery,*
- *Superior mesenteric artery* and
- *Inferior mesenteric artery.*

Hepatic portal system is formed by the veins draining blood from the abdominal part of the GIT. The veins comprising the hepatic portal system are shown in Fig. 4.6-9. All these veins end in the *portal vein.* The portal vein supplies the blood collected from GIT to the liver by its right and left branches.

Hepatic veins are terminal parts of an elaborate venous tree that permeates the liver. The hepatic veins emerging from the liver tissue end in the inferior vena cava.

Splanchnic Circulation: Characteristic Features

During rest, the abdominal GIT, viscera and liver receive about 1500 ml blood per minute (about 30% of cardiac output) via coeliac, superior mesenteric and inferior mesenteric arteries (Fig. 4.6-8).

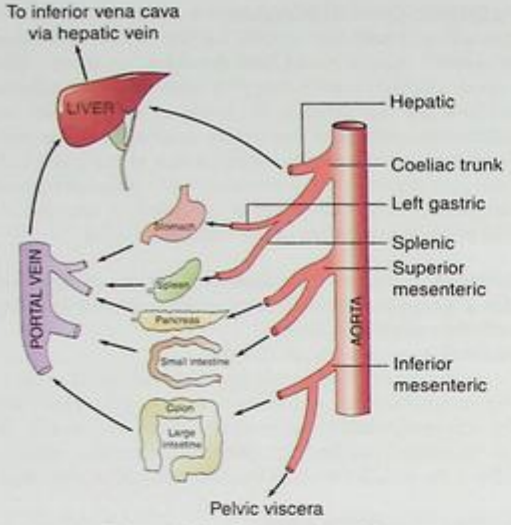


Figure 4.6-8 Splanchnic circulation.

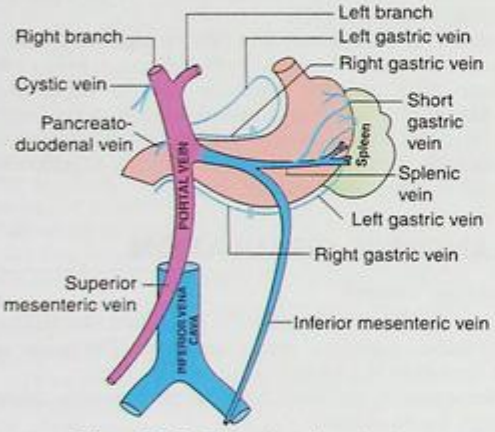


Figure 4.6-9 Tributaries of portal vein.

If the entire GIT becomes simultaneously active, the splanchnic blood flow would have increased to about 4.0 L/min. However, since during digestion and absorption, the GIT is sequentially activated, the maximum circulation is about 3.0 L/min.

The unique feature of the splanchnic circulation is that the venous blood from GIT viscera is not directly carried to the heart through systemic veins, but is carried to the liver forming hepatic portal system.

For the purpose of discussion the splanchnic circulation is considered to consist of three parts:

- Intestinal (mesenteric) circulation,
- Splenic circulation and
- Hepatic circulation.

Intestinal Circulation

Intestinal or Mesenteric Circulation is constituted by the blood supplied to the intestines and pancreas (about 100 ml/min) by a series of parallel circulations via the branches of superior and inferior mesenteric arteries.

Extensive Anastomoses between the vessels constituting mesenteric circulation, but blockage of a large intestinal artery still leads to infarction of the below.

The Blood Flow to Intestinal Mucosa is much more (about 5 times) than that of rest of the intestinal wall.

Capillary Filtration Coefficient for mucosal capillaries is about 10 times than that for skeletal muscles, that is why the mucosal vessels have an enormous capillary surface available for absorption and pore bound secretion.

During Metabolic Activity the blood flow to GIT increases due to vagal activity (in the stomach), humoral activity, the local release of bradykinin from the mucosal glands and metabolites in the intestinal tract itself.

Countercurrent system exists in the capillaries and venules in a villus, i.e. the direction of blood flow in the capillaries and venules in a villus is opposite to that in the main arteriole (Fig. 4.6-10).

This system permits diffusion of O_2 from the ascending arterial limb of villi into the descending venous limb (Fig. 4.6-10B). In this way, at low flow rates substantial amount of O_2 from the arterioles is shifted to venules near the base of villi resulting in decrease in O_2 supply to the mucosal cells at the tips of villi. When intestinal blood flow is very low, the transfer of O_2 from arterioles to venules is exaggerated and may cause extensive necrosis of intestinal villi.

Splenic Circulation

Splenic Artery, which is branch of coeliac trunk, supplies about 200 ml of blood/min to the spleen during rest via its splenic branches, which enter the hilum of the spleen.

Spleen Serves as Reservoir of Blood. In spleen, two structures are involved in storage of blood, namely splenic venous sinuses and splenic pulp. The small arteries and arterioles open directly into the splenic venous sinuses (Fig. 4.6-11). Due to dilation of venous sinuses, a large amount of blood is stored in spleen and the spleen distends. The capillaries of the splenic pulp are

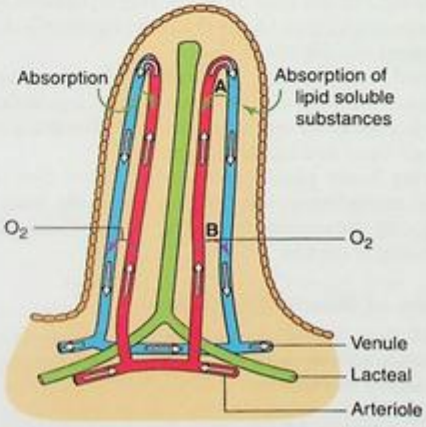


Figure 4.6-10 Countercurrent system of villus blood vessels depicting transfer of lipid-soluble substances from venous limb to arterial limb **(A)** and that of O_2 from arterial to venous limb **(B)**.

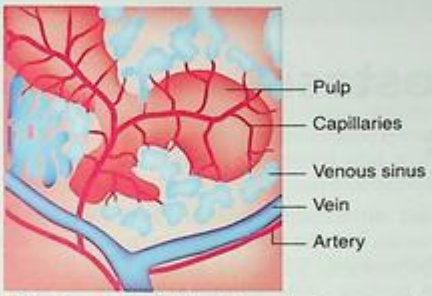


Figure 4.6-11 Storage of blood in splenic venous sinuses and splenic pulp.

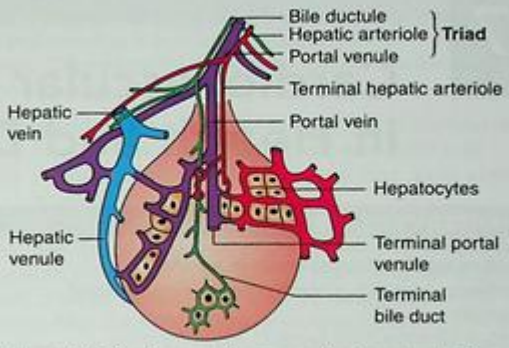


Figure 4.6-12 Concept of acinus as functional unit of liver.

highly permeable. So, lot of blood cells pass through the capillary membrane and are stored in the pulp.

The constriction of Splenic Venous Sinuses by sympathetic stimulation causes release of blood into the circulation.

Hepatic Circulation

Characteristic Features of Hepatic Circulation

Source of Blood. Liver receives about 1500 ml blood/min from two sources:

Hepatic Artery which is a branch of coeliac trunk supplies about 20–25% (300–400 ml) of the total blood which caters to the metabolic requirements of the liver tissue.

Portal Vein which collects blood from the mesenteric and splenic vascular bed supplies about 75–80% (1100–1200 ml/min) of the total blood.

The hepatic and portal blood streams meet in the sinusoids.

Functional Unit of Liver The functional unit of liver is *acinus*. The acini have been likened to grapes or berries, each on a vascular stem. There are about 10000 acini in human liver. Thus, each acinus is at the end of vascular stalk containing terminal branches of portal vein, hepatic arteries and bile ducts (Fig. 4.6-12). Blood flows from these terminal vessels into the sinusoids, which represent the capillary network of the liver. The sinusoids radiate toward the periphery of acinus, where they drain into the terminal branches of hepatic veins. Blood from these terminal hepatic venules drains into progressively larger branches of the hepatic veins, which are tributaries of the inferior vena cava.

SELF-ASSESSMENT

1. Describe briefly:
   - Characteristic features of coronary blood flow
   - Regulation of coronary blood flow
   - Factors affecting coronary blood flow
2. Draw a labelled diagram to show changes in coronary blood flow with different phases of cardiac cycle.
3. Write briefly:
   - Monro–Kellie doctrine
   - Autoregulation of cerebral blood flow
   - Regulation of cerebral circulation
   - Significance of blood–brain barrier
4. Write notes on:
   - Axon reflex
   - Triple response
   - Reactive hyperaemia
   - Hepatic circulation
5. Explain why:
   - Blood flow to left ventricle decreases during systole
   - Coronary supplying the left ventricle has greater flow
   - The A-VO_2 difference is more in myocardium as compared to other body tissues.

4.7 Cardiovascular Homeostasis in Health and Disease

CHAPTER OUTLINE

Cardiovascular Homeostasis in Health
Cardiovascular Adjustments during Gravitational Changes
Posture Change from Lying to Standing
Prolonged Quiet Standing
Postural Hypotension
Cardiovascular Adjustments during Muscular Exercise

Cardiovascular Homeostasis in Diseases
Circulatory Shock
Types and Causes
Stages and Clinical Features
Nonprogressive Shock
Progressive Shock
Refractory Shock

CARDIOVASCULAR HOMEOSTASIS IN HEALTH

Cardiovascular homeostasis in health refers to the compensatory adjustments of the cardiovascular system to challenges faced by the circulation in everyday life. The common situations during which cardiovascular adjustments are required in day-to-day life include the following:

- Gravitational changes
- Exercise

Cardiovascular Adjustments During Gravitational Changes

Gravitational changes occur under the following conditions in life:

- Posture change from lying to standing
- Prolonged quiet standing

Adjustments During Posture Change from Lying to Standing

When posture is changed from lying (recumbent) to standing (erect) the haemodynamic changes occur as a result of the effect of gravity on the blood column, which tends to reduce the cardiac output and blood pressure. However, in humans, the compensatory mechanisms are so well developed that in normal persons no effect is felt on the posture changes in day-to-day life. The sequences of events which occur during change in posture from lying to standing are discussed below.

In standing position, due to hydrostatic (gravitational) effect of blood column, in normal adults, the blood pressure at the level of feet in both the arteries and veins is increased approximately by 80 mm Hg.

Increased intraluminal pressure has no effect on thick-walled arteries, but the thin-walled veins distend and accommodate more blood.

Venous pooling (300–500 mL) results in decreased venous return and so decreased cardiac output; and hence the blood pressure is also reduced.

A drop in the blood pressure in carotid sinus and aortic arch within seconds triggers the baroreceptor-mediated compensatory mechanism which causes the following changes:

- **Heart rate** is increased by 5–10 beats/min.
- **Force of cardiac contraction** is increased leading to an increase in the stroke volume and cardiac output.
- **Peripheral resistance** is increased due to arteriolar constriction in the cutaneous, renal and splanchnic circulation. An increase in peripheral resistance increases the diastolic pressure.
- **Venoconstriction** in the body transfers blood from the capacitance vessels towards the heart increasing the venous return.
- **Increased secretion of renin** and aldosterone, which also helps in normalization of blood pressure.

In spite of the above-mentioned compensatory changes, the stroke volume and cardiac output in standing posture are about 25% less than in supine position.

However, due to a 25% increase in the total peripheral resistance the blood pressure becomes almost normal.

The above events are summarized in Fig. 4.4-15 (at page 146).

Changes During Prolonged Quiet Standing

The prolonged quiet standing (a situation particularly met with military or police personnel, i.e. standing in attention for long periods) along with the venous pooling the fluid begins to accumulate in the interstitial spaces because of the increased hydrostatic pressure in the capillaries. The cardiac output is decreased due to decreased venous return. A stage may come when cerebral blood flow decreases to less than about 60% and symptoms of cerebral ischaemia develop. The individual may faint and fall down.

The fainting, in a sense, is also a homeostatic mechanism because falling to horizontal position promptly restores venous return, cardiac output and cerebral blood flow to adequate levels.

Postural Hypotension

Postural hypotension or orthostatic hypotension in which there occurs a sudden fall in blood pressure on changing posture from lying to erect. The individual experiences transient blurring of vision, dizziness or even fainting.

Pathophysiology Postural hypotension develops in individuals in whom the cardiovascular compensatory mechanism (described above), which maintain normal blood pressure and adequate cerebral blood flow are very slow to develop.

Cardiovascular Adjustments During Muscular Exercise

Severe muscular exercise is the most stressful physiological condition that the cardiovascular homeostasis mechanisms face in everyday life. In addition to cardiovascular system adjustments, respiratory and other adjustments also occur in the body, so they are comprehensively discussed in the Chapter 5.8 'Physiology of Exercise' (see page 217).

CARDIOVASCULAR HOMEOSTASIS IN DISEASES

Cardiovascular homeostasis mechanism operates in almost all cardiorespiratory and many other multiorgan diseases. The most important condition which needs special description is circulatory shock.

Circulatory Shock

Circulatory shock or simply called shock is a syndrome (collection of different entities that share certain common features) characterized by *serious reduction of tissue perfusion* with a relatively or absolutely inadequate cardiac output. In other words, the shock is a condition characterized by an inadequate delivery of oxygen and nutrients to critical organs, such as heart, brain, liver, kidneys and gastrointestinal tract (GIT).

Types and Causes of Shock

Depending on the cause of inadequacy of cardiac output (relative or absolute) the circulatory shock may be of the following types:

I. Hypovolaemic shock
II. Low-resistance or distributive or vasogenic shock
III. Cardiogenic shock
IV. Obstructive shock

I. Hypovolaemic Shock Hypovolaemic shock, also known as cold shock, is caused by a low blood volume resulting in decreased cardiac output.
Causes. Depending on the causes, the hypovolaemic shock may be of the following types.

Haemorrhagic shock occurs as a result of external or internal blood loss caused by the ruptured vessels.
Dehydration shock. It is the fluid loss when insufficient amount can dehydrate the body and reduce the circulating blood volume. Fluid loss can occur from:

- GIT in diarrhoea or vomiting
- *Kidney* in diabetes mellitus, diabetes insipidus or excessive use of diuretics
- *Skin* in burns

Traumatic shock is a special type of hypovolaemic shock in which there is associated neurogenic shock caused by severe pain which inhibits the vasomotor centre (VMC).

II. Low-Resistance or Distributive or Vasogenic Shock Low-resistance or distributive or vasogenic shock occurs when neural reflexes or toxic substances cause excessive vasodilation within the vascular system. Due to vasodilation the size of capacitance vessels is increased and thus the cardiac output is decreased in spite of normal blood volume. Low-resistance shock is also called *warm shock* because skin is warm, and not cold and moist as it is in hypovolaemic shock.
Causes. Depending on the causes the low-resistance shock is of the following types.

1. ***Neurogenic shock*** occurs due to two types of nervous effects:
   (i) *Marked reduction in sympathetic vasomotor tone*
   (ii) *Pronounced increased in the vagal tone*, as in vasovagal syncope or emotional fainting
2. ***Anaphylactic shock.*** Anaphylaxis refers to an acute allergic reaction. Large quantities of histamine and histamine-like substances released in the allergic reaction cause widespread and marked *vasodilation*, thus reducing peripheral resistance. Also, there is marked *increase in capillary permeability* leading to a fluid loss and adding hypovolaemic element to the low-resistance shock.
3. ***Septicaemic shock.*** Septicaemia is a condition in which bacteria circulate, multiply in the blood, form toxic products and cause high fever and marked vasodilation due to peripheral arteriolar paralysis.

III. Cardiogenic Shock Cardiogenic shock occurs due to the decreased pumping ability of the heart because of some cardiac abnormality.
Causes of cardiogenic shock are as follows:

- Myocardial infarction
- Cardiac arrhythmias
- Congestive heart failure
- Severe valvular dysfunctions

IV. Obstructive Shock Obstructive shock or to be more precise the extracardiac obstructive shock occurs due to the impairment of ventricular filling during diastole due to some external pressure on the heart. Due to decreased ventricular filling the stroke volume and hence the cardiac output is decreased causing circulatory shock.
Causes of obstructive effusion shock are as follows:

- Pericardial cardiac tamponade, i.e. bleeding into the pericardium with external pressure on the heart
- Tension pneumothorax
- Constrictive pericarditis
- Pulmonary embolism

Stages and Clinical Features of Shock

Stages and clinical features of all types of shock are similar with minor differences. However, the haemorrhagic shock is of more common occurrence, so the discussion in this section will be centred on it. Depending on the severity the circulatory shock can be divided into three stages:

- First stage or nonprogressive shock
- Second stage or progressive shock
- Third stage or refractory shock

I. First Stage of Shock or NonProgressive Shock Nonprogressive shock, also known as *compensated shock* or initial stage of shock, occurs when there is a moderate reduction in cardiac output.

Hypovolaemic shock due to acute blood loss, in other words the *haemorrhagic shock*, occurs when at least 10%–15% of total blood volume is lost. Thus, about 10% of the total blood volume may be lost without any significant effect.

Compensatory mechanisms of rapid onset (short-term mechanisms) immediately set into motion following the acute loss of blood and try to maintain the blood flow to vital organs in spite of reduced cardiac output. The compensatory mechanisms are discussed below.

A. Rapid compensatory mechanisms (neural mechanism) Rapid or the so-called short-term control mechanisms primarily include the following three nervous reflexes.

1. ***Baroreceptor reflex.*** When the blood pressure is decreased, there occurs decrease in the impulse discharge from the arterial baroreceptors (for details, see page 154). As a result there is a generalized increase in the sympathetic vasomotor discharge to heart, arterioles and veins. There occurs generalized vasoconstriction (sparing vessels of brain and heart). This causes shifting of greater amount of blood in circulation. All these mechanisms maintain blood pressure at such a level that the blood flow to the vital organs like heart and brain is not affected.
2. ***Chemoreceptor reflex.*** An acute haemorrhage causes loss of red blood cells leading to reduced O_2-carrying capacity. The resultant anaemia and stagnant hypoxia as well as acidosis stimulate chemoreceptors, which also excite VMC to cause the same effects as caused by the baroreceptor reflex. Fall in blood pressure below 60 mm Hg usually initiates the chemoreceptor reflex.
3. ***Central nervous system ischaemic response.*** When blood pressure falls below 50 mm Hg, this response is initiated (for details see page 157). It causes more powerful sympathetic stimulation.

The rapid compensatory mechanisms discussed above account for the following.

Symptoms and Signs observed in patients with shock:

- ***Pale, cold and moist skin*** occurs due to decreased blood flow to skin and increased sweating (due to increased sympathetic discharge).
- ***Cyanotic tinge of skin*** may sometimes occur because of increased O_2 extraction from the blood.
- ***Tachycardia and fall*** *in pulse pressure* produce *thin and thready pulse,* the characteristic feature of hypovolaemic shock.
- ***Increased rate and force of respiration*** is due to greater sinoaortic chemoreceptors discharge.
- ***Oliguria,*** another important feature of the hypovolaemic shock, is due to the renal arteriolar constriction.
- ***Restlessness and apprehension*** may occur due to the stimulation of brainstem reticular formation by circulating catecholamines, because haemorrhage is a potent stimulator of secretion of these hormones from the adrenal medulla.

B. Intermediate Compensatory Mechanisms

- Renin–angiotensin vasoconstrictor mechanism (see page 157)
- Reverse stress relaxation (see page 147)
- Capillary fluid shift mechanism (see page 147)

C. Long-Term Compensatory Mechanisms

1. ***Restoration of plasma volume and proteins.*** After a moderate haemorrhage, the plasma volume is restored to normal in 12–72 hours. There is rapid entry of preformed albumin from the extravascular stores.
2. ***Restoration of red cell mass.*** In the meantime, there is excess release of erythropoietin, which increases the rate of cell production in the bone marrow within 10 days. Normal cell mass is restored in 4–8 weeks.

Note. Under normal circumstances, the circulatory compensatory mechanisms described above eventually cause full recovery without help of outside therapy during the stage of nonprogressive shock. However, a timely outside therapy may hasten the recovery.

II. Second Stage of Shock or Progressive Shock Second stage of the circulatory shock is progressive stage which occurs after 15%–25% loss of total blood volume. In this stage the compensatory mechanisms are not able to stop the progression of the shock. In progressive shock the structures of circulatory system begin to deteriorate and various types of *positive feedback mechanisms* develop. Therefore, timely therapeutic interventions are essential in this stage; otherwise, the vicious cycle of positive feedback mechanisms will cause progressive decrease in the cardiac output and ultimately patient will go into the stage of refractory shock.

Positive Feedback Cycles Positive feedback cycles responsible for the continuous progression of shock, if not interrupted by therapeutic intervention, which lead into refractory stage are as follows (Figs 4.7-1 and 4.7-2):

1. ***Cardiac failure.*** Due to severe decrease in arterial pressure, particularly diastolic pressure, the coronary blood flow also decreases and coronary ischaemia occurs. This positive feedback causes progressive cardiac deterioration and may ultimately cause complete heart failure.
2. ***Vasomotor failure.*** It is very severe fall in blood pressure; there may occur cerebral ischaemia and failure of medullary VMC. Failure of VMC results in marked vascular dilatation causing venous pooling and decreased venous return. The cardiac output and blood pressure are further decreased.
3. ***Peripheral circulatory failure.*** Due to prolonged and intense vasoconstriction, there occurs hypoxia and accumulation of metabolites in the body tissues.
4. ***Septicaemia and toxicaemia.*** Due to prolonged vasoconstriction of splanchnic vessels, there occurs hypoxia of GIT. The hypoxic damage causes a breakdown of normal protective mucosal barrier in the gut, leading to entry of the intestinal bacteria into the portal circulation. Simultaneous deterioration of hepatic functions permits bacteria and bacterial endotoxins to reach into the systemic circulation leading to the widespread failure of arteriolar and precapillary sphincter functions and cardiac depression. There occurs extensive vasodilatation. At this stage, no amount of treatment can restore the circulatory functions to normal.

Effect on Body Tissues in Progressive Shock In progressive shock there occurs *widespread cellular degeneration* in the body tissues. Generalized cellular damage usually occurs first in highly metabolic tissues, such as liver, lung and heart. Liver cells are usually the first to be affected because hepatic cells have very high rate of metabolism and also is the first organ exposed to toxins from the intestine through the portal vein.

III. Refractory Shock As mentioned above, when the shock is in the progressive stage and is not treated adequately a vicious cycle of various positive feedback mechanisms (Fig. 4.7-2) set in and patient passes into the third stage of shock, the *refractory shock* (previously known as *irreversible shock). In this stage, all therapeutic* interventions are usually ineffective and eventually the patient dies.

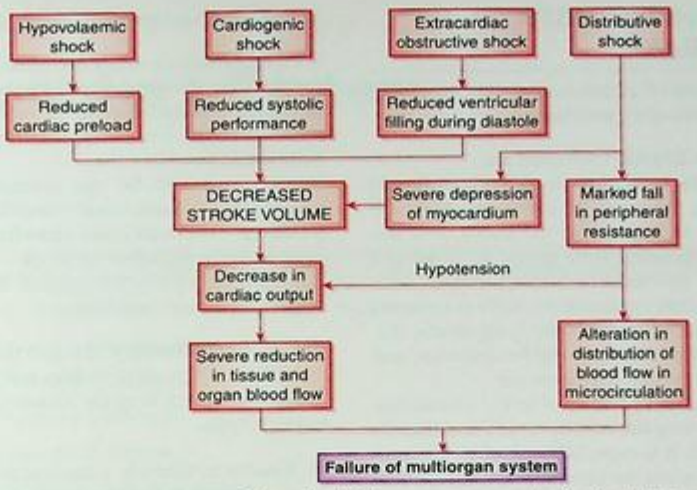


Figure 4.7-1 Chain of events that ultimately cause failure of multiple organ system and refractive shock in different types of shocks.

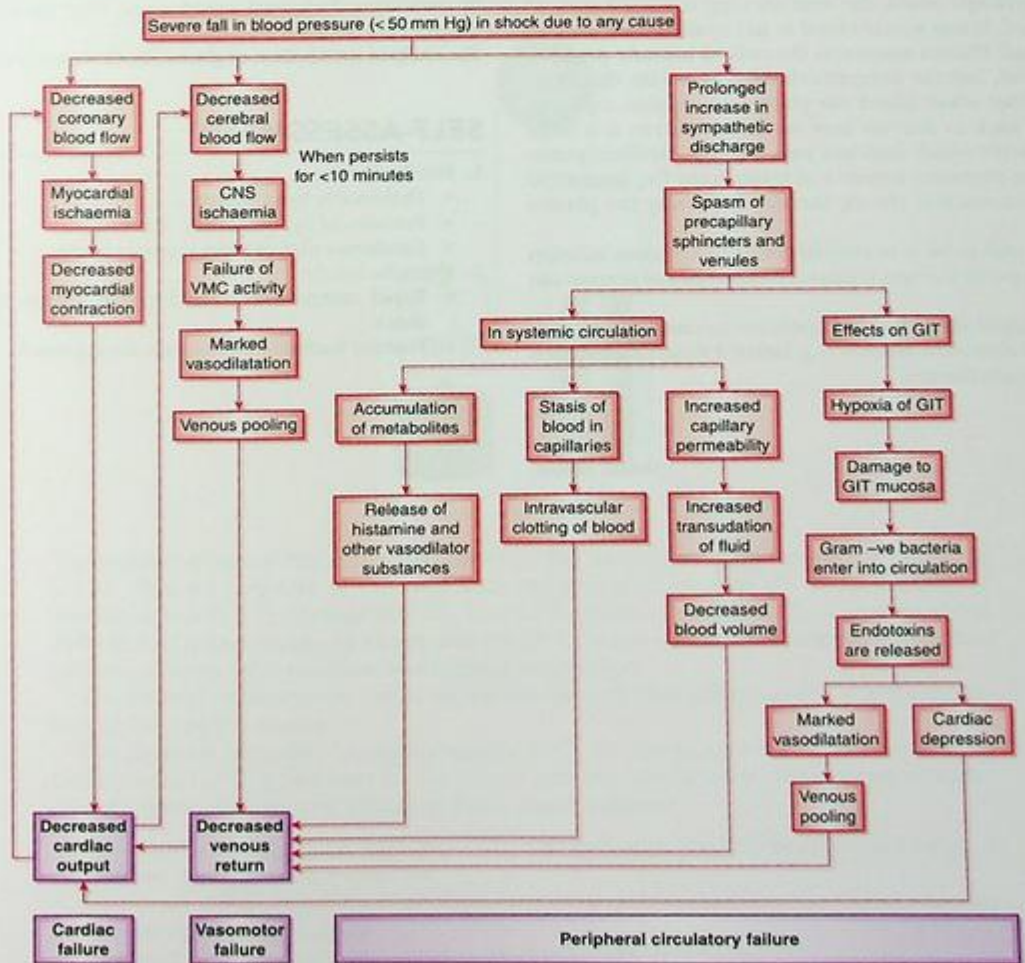


Figure 4.7-2 Chain of events of various positive feedback cycles which cause progression of shock to refractory stage. Note. In severe haemorrhage (blood loss > 40% of blood volume), the refractory shock develops due to these chain of events.

TREATMENT OF SHOCK WITH PHYSIOLOGICAL BASIS

The treatment of shock is aimed at correcting the causes and helping physiological compensatory mechanisms.

1. General Measures for Shock treatment are

Room temperature. Where the patients of shock are kept should be cold. If exposed to warm, there will be sweating which will cause further hypovolaemia and aggravate the shock. It is important to note that most patients with shock are cold and therefore reflex warming of the body of a shock patient with water bottles or providing warm environment such as covering the patient with blankets, etc. will abolish the sympathetic discharge. So, the compensatory mechanism will be disturbed and shock will be aggravated and patient may even die.

Raising the foot end of the patient's bed by 6" to 12" (*Trendelenburg position*) helps in promoting the venous return and thereby increasing the cardiac output. It is especially useful in haemorrhagic and neurogenic shock when the blood pressure is too low.

2. Replacement Therapy is very useful in hypovolaemic shock.

In haemorrhagic shock the best therapy is transfusion of whole *blood*. When whole blood is not available the *plasma* may be used. Plasma maintains the colloid osmotic pressure of the blood, but the haematocrit decreases with this therapy. If neither whole blood nor plasma is available, a plasma substitute such as *dextran* may be used. Dextran is a large polysaccharide which does not pass through capillary pores. It therefore promotes osmosis of water from the interstitial fluid to intravascular spaces, thereby increasing the plasma volume.

In patients with burns or interstitial obstruction, plasma infusion is the appropriate therapy. If plasma is not available *dextran* can be used.

In hypovolaemic shock due to dehydration intravenous infusion of *balanced electrolytic solution* (e.g. lactated Ringer's solution is the appropriate therapy.

3. Sympathomimetic Drugs are useful as:

Sympathomimetic drugs are usually not useful in haemorrhagic shock where the sympathetic system is already very active.

These are especially useful in *neurogenic shock* and *anaphylactic shock* where the cause of shock is marked vasodilation due to lost neurogenic vascular tone.

Dopamine should be the sympathomimetic drug of choice, because it produces renal vasodilation and at the same time, produces vasoconstriction elsewhere in the body. It also has a positive inotropic effect on heart.

Epinephrine or norepinephrine drug may also be used when dopamine is not available.

4. Oxygen Therapy Oxygen therapy may have some beneficial effects. In general, it does not have marked effect since the hypoxia of shock is of the anaemic or stagnant type and not of hypoxic type.

5. Glucocorticoids Glucocorticoids are useful in shock because of their below-mentioned effects. They are particularly useful in anaphylactic shock:

They increase the strength of heart in the last stages of shock,

By stabilizing lysosomal membranes, they prevent release of enzymes of cells and

They help in metabolism of glucose by the severely damaged cells.

SELF-ASSESSMENT

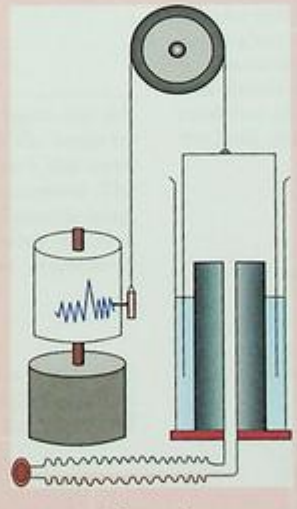
1. Briefly discuss:
   - Orthostatic hypotension
   - Features of hypovolaemic shock
   - Cardiovascular changes during exercise
2. Describe briefly:
   - Rapid compensatory mechanisms during hypovolaemic shock
   - Positive feedback mechanism during shock

SECTION 5

Respiratory System

SECTION OUTLINE

5.1 Respiratory Tract: Structure and Functions
5.2 Pulmonary Ventilation
5.3 Pulmonary Circulation
5.4 Pulmonary Diffusion
5.5 Transport of Gases
5.6 Regulation of Respiration
5.7 Respiration: Applied Aspects
5.8 Physiology of Exercise



The word respiration has been derived from the Latin word *respirae*, which means to breath. The primary role of the respiratory system is to provide O_2 to the tissues for metabolic needs and remove the CO_2 formed by them. An adult body consumes about 250 mL of O_2 and produces about 200 mL of CO_2 per minute. Respiration entails two processes: external respiration and internal respiration.

The *internal respiration* or tissue respiration refers to the utilization of O_2 and production of CO_2 by the tissues.

The *external respiration* includes supply of O_2 to the tissues from the environment and excretion of CO_2 released by the tissues into the atmosphere. The process of external respiration involves the following three major events:

- *Pulmonary ventilation*, i.e. exchange of gases between the environment and lungs. It includes mechanics of respiration
- *Pulmonary diffusion*, i.e. transfer of gases from alveoli to the blood by diffusion across the respiratory membrane
- *Transport of gases* from the blood to the body cells and back

The *respiratory adjustments in health and diseases* are essential for life, and to understand these, knowledge about *regulation of respiration* is must.

5.1 Respiratory Tract: Structure and Functions

CHAPTER OUTLINE

Functional Anatomy
Respiratory Passages
Respiratory Parenchyma
Blood Supply
Innervation

Functions of Respiratory System
Respiratory Functions
Nonrespiratory Functions
Functions Subserved by Lung Defence Mechanisms
Functions Subserved by Pulmonary Circulation
Metabolic Functions of Lungs

FUNCTIONAL ANATOMY

The chief organs of the respiratory system are right and left *lungs*. The oxygen in the atmospheric air reaches the lungs by passing through a series of *respiratory passages*, which also serve for the removal of CO_2 from the alveoli to the atmosphere. The respiratory system also includes a pump that ventilates the lung. This pump consists of the chest wall and respiratory muscles. Salient points about the functional anatomy of respiratory passages and lungs are discussed here.

Respiratory Passages

Respiratory passages include the following structures (Fig. 5.1-1):

1. Nasal Cavities The air enters the body through right and left anterior (external) nares, which open into the right and left nasal cavities. Through the posterior (internal) nares, the nasal cavities open into the pharynx. The nasal cavities warm up the air to the body temperature and humidify the air to 100% saturation, and clean and filter the air of its particulate contents by channelling the air through a tortuous path between the turbinates. The particles are deposited at the bends where they adhere to the mucus layering the nasal cavity.
2. Pharynx From above downwards, the pharynx is divided into nasopharynx, oropharynx and laryngopharynx. Air from nasal cavities enters the nasopharynx and passes down through the oropharynx and laryngopharynx to larynx. From the mouth, the air can directly pass to oropharynx.
3. Larynx It is continuous above with laryngopharynx and below with trachea. The air passes through the glottis (the triangular space between vocal cords) into the trachea. Apart from being a respiratory passage, the larynx also acts as a voice box.
4. Tracheobronchial Tree The air passages between trachea and alveoli divide 23 times to form the extensive tracheobronchial tree (Fig. 5.1-2). These multiple divisions greatly increase the total cross-sectional area of the airway from 2.5 cm^2 in the

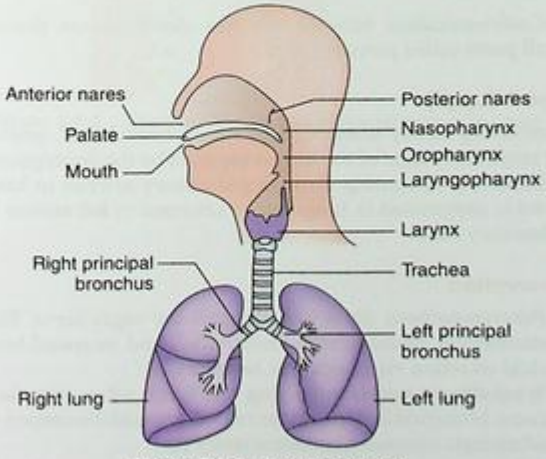


Figure 5.1-1 The air passages.

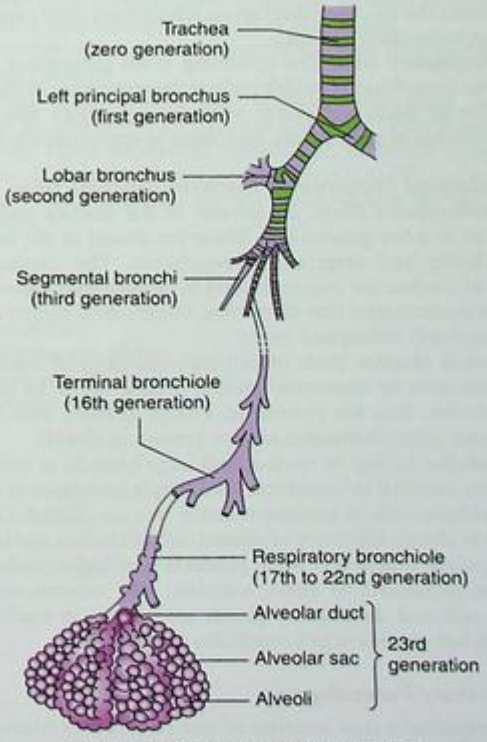


Figure 5.1-2 The tracheobronchial tree.

trachea to 11,800 cm^2 in the alveoli. Consequently, the velocity of air flow in the small airway declines to very low values. The 23-generation divisions of tracheobronchial tree have been numbered by E.R. Wieble (a Swiss anatomist) as follows:

The trachea is designated as generation zero.

The ***principal bronchi*** (right and left), which are two major divisions of trachea, constitute the first generation:

- *Lobar bronchi*, which are a division of the principal bronchus, form the second generation.
- *Segmental bronchi*, which are further division of each lobar bronchus, form the third generation. Each segmental bronchus divides into several generations of branches that ultimately end in very small tubes called *bronchioles*.
- *Terminal bronchioles* is the name given to the 16th generation of the divisions. Up to this generation of division, no exchange of gases is possible.
- *Respiratory bronchiole* is the name given to the 17th–22nd generations of divisions. These are labelled respiratory bronchioles because some exchange of gases is possible in these tubes.
- *Alveolar ducts* end in the alveoli or the alveolar sacs to form the 23rd generation division. It is here that most of the O_2 and CO_2 exchange occurs.

Thus, from the functional point of view, the tracheobronchial tree can be divided into two major zones:

(i) ***Conducting zone:*** This zone of the air passages is formed by the first 16 generations of passages, and it transports gases only from and to the exterior. Thus, the conducting zone starts from the trachea and extends up to the terminal bronchioles. No exchange of gases is possible here, so starting from the nose to the terminal bronchioles this zone forms the so-called *dead space*, which has a total capacity of approximately 150 mL.

(ii) ***Respiratory zone:*** The remaining seven generations of tracheobronchial tree, which include the respiratory bronchioles, alveolar ducts and alveoli, form the respiratory zone where exchange of gases occurs. Its volume is approximately 4 L.

Histological Features of Tracheobronchial Tree

1. Cartilaginous Rings are present in the trachea and initial bronchi of a few generations. These are absent in the terminal bronchioles and respiratory bronchioles. The cartilaginous rings of trachea are incomplete on their posterior aspect. This allows some contraction of trachea, but tracheal lumen cannot be completely obliterated easily.

2. Smooth Muscles Ends of cartilaginous rings of trachea are approximated by transverse smooth muscle fibres. In terminal bronchioles, they are present in a large amount and form a sphincter. Smooth muscles are not present in alveoli.

3. Epithelial Lining in trachea and large bronchi is columnar, becomes cuboidal in bronchioles and simple squamous in alveoli. The epithelial cells of tracheobronchial tree are ciliated. Cilia are absent in alveoli. Efficiency of ciliated cells of trachea and bronchi in propelling mucus and waste products is of higher order. Cilia are not influenced by nerve impulses. The mucous-secreting goblet cells and deep serous glands are present in trachea and bronchi but are absent in bronchioles and alveoli.

Respiratory Parenchyma

Each respiratory unit consists of one respiratory bronchiole, which opens into a number of alveolar ducts, and each alveolar duct, in turn, opens into a number of alveoli. The two lungs contain about 300 million alveoli. Each alveolus has a diameter of about 0.2 μm. The alveoli are surrounded by the pulmonary capillaries. The total area of the alveolar walls in contact with capillaries in both the lungs is about 70 m^2.

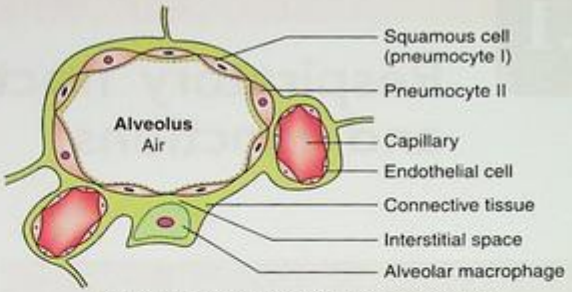


Figure 5.1-3 Microscopic structure of alveolus.

Microscopic Structure of Alveolus (Fig. 5.1-3) Each alveolus is lined by two types of epithelial cells:

- ***Type I cells*** are flat cells with large cytoplasmic extensions, and are the primary lining cells.
- ***Type II cells*** (granular pneumocytes) are thicker and contain numerous lamellar inclusion bodies. These cells secrete *surfactant*.

The alveolar wall also contains the following:

- Other *special type of epithelial cells*
- *Pulmonary alveolar macrophages* (PAM), which are active phagocytic cells
- *Lymphocytes*
- *Plasma cells*, which form and secrete immunoglobulins
- *Amine precursor uptake and decarboxylation (APUD) cells*, which store and secrete many biologically active peptides, e.g. vasoactive intestinal peptide (VIP) and substance P
- *Mast cells*, which contain heparin, various lipids, histamine and various proteases that participate in the allergic reactions

Communication between the two alveoli occurs through small pores called *pores of Kohn*.

Blood Supply

Conducting airway is supplied by the systemic blood, whereas the respiratory zone of the lung is supplied by the deoxygenated (venous) blood coming through pulmonary arteries to lungs. Blood is oxygenated in lungs and is returned to left atrium via pulmonary veins.

Innervation

- ***Parasympathetic*** fibres pass through the vagus nerve. Their stimulation causes bronchoconstriction and increased bronchial secretion via muscarinic receptors.
- ***Sympathetic nerves*** supplying the lungs when stimulated cause bronchodilation and decreased bronchial secretion via adrenergic receptors, predominantly β_2.
- ***Afferents*** from the lungs pass through vagii.

FUNCTIONS OF RESPIRATORY SYSTEM

Respiratory Functions

The main function of the respiratory system, in general, and lung, in particular, is exchange of gases between atmosphere and blood.

Nonrespiratory Functions

Functions Subserved by Lung Defence Mechanisms

1. Immunoglobulin-A (IgA) is secreted in the bronchial secretion and protects against respiratory infections. *Ciliary escalator action* is an important defence system against the air-borne infection. The dust particles in the inhaled air are often laden with bacteria. While passing through the repeatedly branched bronchial tree, the dust particles and the bacteria are caught in the mucous layer present at the mucosal surface of respiratory passages and are moved up towards pharynx by the rhythmic upward beating action of cilia (Fig. 5.1-4) and swallowed. Cigarette smoke disturbs the ciliary function.

2. Pulmonary Alveolar Macrophages (PAM) Being actively phagocytic cells, they ingest the inhaled bacteria and small particles. Thus, they play an important role in the defence system.

3. Cough Reflex The laryngeal, tracheal and bronchial mucous membranes contain vagal afferent terminals, which act as *irritant receptors*. Stimulation of these receptors by chemical or mechanical stimuli (excessive mucus, inadvertently inhaled foodstuff, etc.) produces a bout of coughing, which helps in expulsion of foreign material.

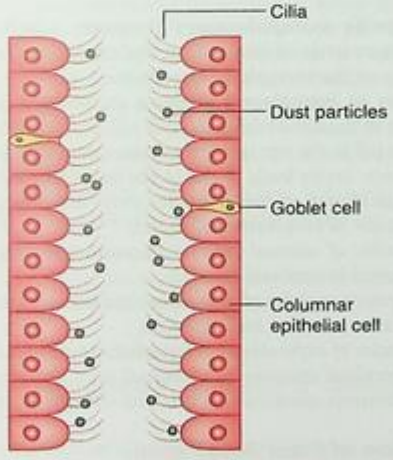


Figure 5.1-4 Ciliary escalator action of the respiratory mucosa.

Functions Subserved by Pulmonary Circulation

1. Reservoir for Left Ventricle When the left ventricle output becomes transiently greater than the systemic venous return, the blood stored in the pulmonary circulation helps in maintaining the left ventricular output for a few strokes.

2. Pulmonary Circulation Acts as a Filter and filters *out* particles from the blood, which may include small fibrin or blood clots, detached cancer cells, fat cells, gas bubbles, agglutinated red blood cells, masses of platelets and debris from the stored blood.

3. Removal of Fluid from Alveoli Because of low pulmonary hydrostatic pressure, the fluid entering the alveoli is absorbed by the capillaries. *This* protects the gas exchange function of lungs and opposes transudation of fluid from capillaries to the alveoli.

4. Role in Absorption of Drugs Certain drugs that rapidly pass through the alveolar capillary barrier by diffusion are administered by *inhalation*, e.g. anaesthetic gases, aerosol and other bronchodilators.

Metabolic Functions of Lungs

1. Surfactant produced in the lungs plays an *important* role in respiration (for details, see page 183).

2. Protein Synthesis maintains the structural framework.

3. Conversion of Angiotensin I into II is performed by the angiotensin converting enzyme (ACE) present in the pulmonary capillary endothelium.

4. Inactivation (Partly or Completely) of many vasoactive substances present in the blood is done by capillary endothelial cells as they pass through pulmonary circulation.

5. Fibrinolytic Mechanism present in the lung lyses clot in the pulmonary vessels.

6. Storage of Hormones and Certain Biologically Active Peptides is done in the APUD cells and nerve fibres present in the alveoli. These substances include VIP, substance P, opioid peptides, cholecystokinin-pancreozymin (CCK-PZ) and somatostatin. These substances are later released into the systemic circulation.

SELF-ASSESSMENT

Write notes on:

- Tracheobronchial tree
- Nonrespiratory functions of lungs
- Functions of nasal cavity

5.2 Pulmonary Ventilation

CHAPTER OUTLINE

Introduction

Mechanics of Pulmonary Ventilation
Mechanism of Breathing
Mechanism of Tidal Respiration
Mechanism of Forced Respiration
Pressure and Volume Changes during Respiratory Cycle
Intrapulmonary Pressure Changes
Intrapleural Pressure Changes
Lung Volume Changes

Lung Volumes and Capacities
Static Lung Volumes and Capacities
Dynamic Lung Volumes and Capacities

Pulmonary Elastance and Compliance
Pulmonary Elastance
Elastance of Thoracic Cage
Elastance of Lungs
Alveolar Surface Tension
Pulmonary Surfactant
Compliance
Definition and Normal Value
Static Versus Specific Lung Compliance
Factors Affecting Lung Compliance
Changes in the Lung Compliance

Work of Breathing
Resistance to Breathing
Components of Work of Breathing

INTRODUCTION

As we know, respiration, to be more precise, the *external respiration* (supply of O_2 from atmosphere to body tissues and removal of CO_2 from the body to atmosphere) involves three major processes:

- *Pulmonary ventilation*, i.e. exchange of gases between the environment and lungs
- *Pulmonary diffusion*, i.e. transfer of gases from the alveoli to capillary blood across the respiratory membrane
- *Transport of gases* from the blood to tissue cells and back

In this chapter, the following aspects and concepts related to pulmonary ventilation are discussed:

- Mechanics of pulmonary ventilation
- Lung volumes and capacities
- Pulmonary elastance and compliance
- Work of breathing

MECHANICS OF PULMONARY VENTILATION

Mechanism of Breathing

Pulmonary ventilation is accomplished by the following two processes:

- ***Inspiration*** refers to the inflow of atmospheric air into the lungs. This obviously occurs when the intrapulmonary pressure falls below the atmospheric air pressure.
- ***Expiration*** refers to the outflow of air from the lungs into the atmosphere. This obviously occurs when the intrapulmonary pressure rises above the atmospheric air pressure.
- ***Changes in intrapulmonary pressure***, which govern the respiratory cycle of inspiration and expiration, are related to changes in the intrapleural pressure.
- ***Changes in intrapleural pressure*** are brought about by the changes in the size of thoracic cavity. Expansion of thoracic cage leads to fall in the intrapleural pressure, and decrease in the size of thoracic cavity leads to rise in the intrapleural pressure.
- ***Changes in size of the thoracic cavity*** are brought about by the actions of respiratory muscles:
  - *Muscles of normal tidal inspiration* are diaphragm and external intercostal muscles.
  - *Accessory muscles of inspiration* are scaleni, sternomastoid, serratus anterior and alae nasi.
  - *Muscles of expiration* are internal intercostal muscles and abdominal muscles (abdominal recti muscles, transverse abdominis muscles and internal oblique muscles).

Mechanism of Tidal Respiration

Inspiration *Inspiration* is an active process normally produced by contraction of the *inspiratory muscles* (*negative-pressure breathing*). During tidal inspiration (quiet breathing), the diaphragm and external intercostal muscles contract and cause increase in all the three dimensions of thoracic cavity.

Role of Diaphragm The diaphragm is a dome-shaped, musculotendinous partition between thorax and abdomen. The convexity of this dome is directed towards the thorax. When the diaphragm contracts, the following changes occur:

- The dome becomes flattened and the level of diaphragm is lowered, thereby *increasing the vertical diameter* of the thoracic cavity (Fig. 5.2-1A). During quiet breathing, the descent of diaphragm is about 1.5 cm, and during forced inspiration, it increases to 7 cm.

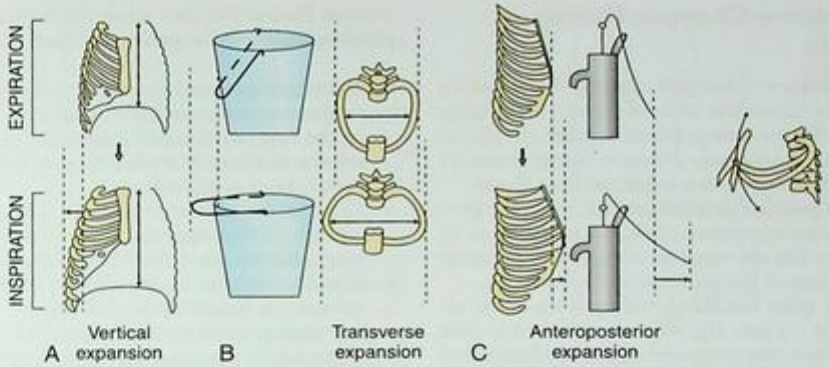


Figure 5.2-1 Mechanism of increase in diameter of thoracic cavity: (A) increase in vertical diameter (descent of diaphragm); (B) increase in transverse diameter (bucket handle effect); and (C) increase in anteroposterior diameter (pump handle effect).

- Contraction of diaphragm also lifts the lower ribs, causing thoracic expansion laterally and anteriorly (the bucket handle and pump handle effects, respectively) (Fig. 5.2-1B and C). In tidal inspiration (quiet breathing), 70%–75% of expansion of chest is caused due to contraction of diaphragm.

Role of External Intercostal Muscles The fibres of external intercostal muscles slope downwards and forwards. They are attached close to the vertebral ends of the upper ribs than the lower ribs (Fig. 5.2-2). From a pivot-like joint with the vertebrae, the ribs slope obliquely downwards and forwards. So, when the external intercostal muscles contract (because of the lever effect), the ribs are elevated, causing lateral and anteroposterior enlargement of thoracic cavity due to the so-called bucket handle and pump handle effects, respectively (Fig. 5.2-1B and C).

Role of Laryngeal Muscles The abductor muscles of the larynx contract during inspiration, pulling the vocal cords apart.

Expiration Expiration in quiet breathing is largely a passive phenomenon and is brought about by the following:

- Elastic recoil of the lungs
- Decrease in size of the thoracic cavity due to relaxation of diaphragm and external intercostal muscles

Mechanism of Forced Respiration

Forced Inspiration Forced inspiration is characterized by the following:

1. ***Forceful contraction of diaphragm*** leading to a descent of diaphragm by 7–10 cm as compared to 1–1.5 cm during quiet inspiration.
2. ***Forceful contraction of external intercostal muscles*** causing more elevation of ribs, leading to more increase in transverse and anteroposterior diameters of thoracic cavity.
3. ***Contraction of accessory muscles of inspiration***, which causes the following effects:
   - Sternomastoid muscles contract and lift the sternum upwards.
   - Anterior serrati muscles contract and lift most of the ribs upwards.
   - Scaleni muscles contract and lift the first two ribs.

Forced Expiration Forced expiration is required when respiration is increased during exercise or in the presence of severe respiratory disease. It is an active process caused by the following:

1. ***Contraction of abdominal muscles causes the following:***
   - Downward pull on the lower ribs, thus decreasing the anteroposterior diameter of the thoracic cavity
   - Fixation of the lower ribs so that internal intercostal muscles act more effectively
2. ***Contraction of the internal intercostal muscles*** causes the effect which is just opposite to that of the external intercostal muscles. This is because of the leverage mechanism of the direction of the muscle fibres, which slope downwards and backwards (Fig. 5.2-3). Hence, their contraction tends to pull all the ribs downwards, thereby reducing the anteroposterior diameter (because of falling of the pump handle effect) as well as the transverse diameter (because of action of ribs like the falling of the bucket handle) of the thoracic cavity.

Note. Besides their role in deep breathing, the expiratory muscles are also involved in other forced expiratory efforts, e.g. in coughing, vomiting and defecation and the Valsalva manoeuvre.

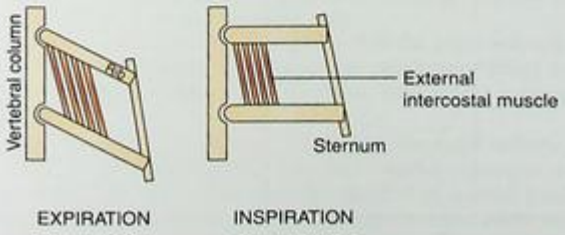


Figure 5.2-2 Contraction of external intercostal muscle favours elevation of ribs due to the mechanical leverage effect of the attachments of its fibres close to the pivot on the upper ribs as compared to the lower ribs.

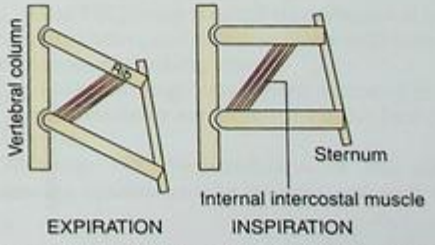


Figure 5.2-3 Contraction of internal intercostal muscle pulls the ribs down due to the mechanical leverage effect of its fibres close to the pivot on the lower ribs as compared to upper ribs.

Pressure and Volume Changes During Respiratory Cycle

Intrapulmonary Pressure Changes during Respiratory Cycle *(Fig. 5.2-4)* The movement of air in and out of the lungs depends primarily on the pressure gradient between the alveoli and the atmosphere (i.e. *transairway pressure*). Intrapulmonary or alveolar pressure is the air pressure inside the lung alveoli.

At the End Expiration and End Inspiration, i.e. when the glottis is open and there is no movement of air, the pressures in all parts of the respiratory tree are equal to atmospheric pressure; the intrapulmonary pressure is considered to be 0 mm Hg.

During inspiration in quiet breathing, the pressure in the alveoli decreases to about −1 mm Hg, which is sufficient to suck in about 500 mL of air into the lungs within 2-second period of inspiration. At the end inspiration, the intrapulmonary pressure again becomes zero.

During forced inspiration against a closed glottis (Muller's manoeuvre), the intrapulmonary pressure may be as low as −80 mm Hg below the atmospheric pressure.

During expiration in quiet breathing, the elastic recoil of the lungs causes the intrapulmonary pressure to swing slightly to the positive side (+1 mm Hg), which forces the 500 mL of inspired air out of the lungs during 2–3 seconds of expiration. At the end expiration, once again the alveolar pressure regains the atmospheric pressure (0 mm Hg).

Forceful expiration against the closed glottis (Valsalva's manoeuvre) may produce intrapulmonary pressure of as much as 100 mm Hg.

Intrapleural (Pleural) Pressure Changes during Respiratory Cycle *(Fig. 5.2-4)* Pleural pressure is the pressure of fluid in the space between the visceral pleura and parietal pleura.

Normal Pleural Pressure when the respiratory muscles are completely relaxed and the airways are open is about −2.5 mm Hg.

- The negative pleural pressure (−2.5 mm Hg) is the amount of suction required to hold the lungs at their equilibrium volume or the functional residual capacity (FRC). FRC is the lung volume at the end of normal (eupnoeic), relaxed expiration, and is about 2–2.5 L of gas.
- The negative pleural pressure (−2.5 mm Hg) is the result of balance of two opposite forces: the recoil tendency of the lungs and the recoil tendency of thoracic cage.
- Recoil tendency of the lungs (continuous tendency to collapse) is caused by the following:
  - Presence of many elastic fibres in the alveolar walls, which are under constant stretch in the inflated lungs
  - Surface tension of the fluid lining the alveoli due to which the alveoli tend to become progressively smaller and collapse
- Recoil tendency of the thoracic cage, i.e. a constant tendency to expand (to pop outwards) is because of the fact that the chest wall is an elastic structure which is normally partially pulled inwards. The elastic property of the thoracic cage is because of the elastic nature of ribs, muscles and tendons.

During inspiration, due to expansion of the chest wall, the pleural pressure becomes still more negative (−6 mm Hg) and pulls the surface of lungs with a greater force, creating negative intrapulmonary pressure.

During expiration: At the end of inspiration, the inspiratory muscles relax, and the recoiling force of lungs begins to pull the chest wall back to expiratory position. At the end-expiratory position, where the recoil force of the lungs and recoil force of thoracic cage balance, the pleural pressure returns back to −2.5 mm Hg.

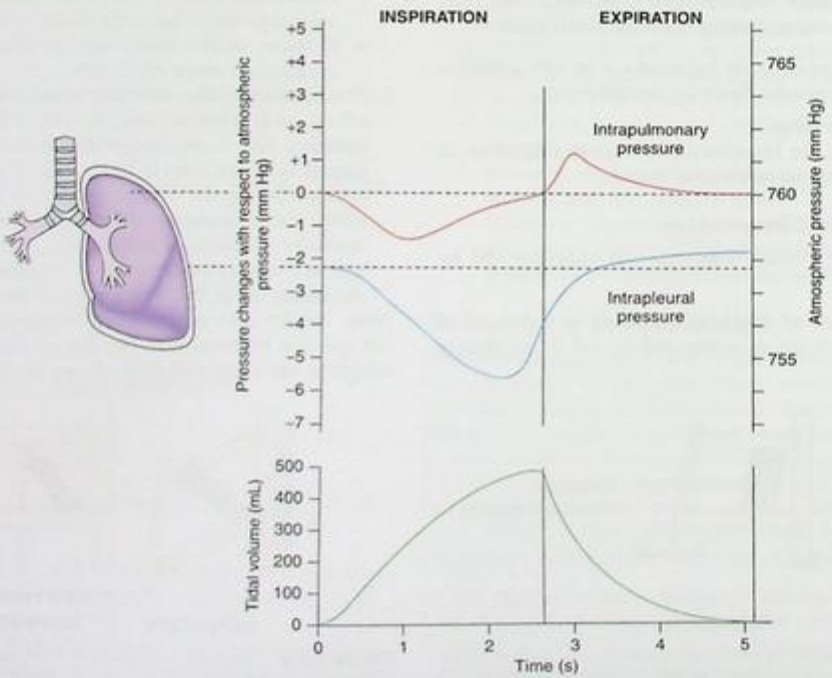


Figure 5.2-4 Pressure and volume changes during the respiratory cycle.

Factors Affecting Pleural Pressure

1. ***Deep inspirations:*** The pleural pressure may become as low as –30 mm Hg during deep inspiration.
2. ***Valsalva manoeuvre*** or when expiratory muscles are working against closed glottis, there occurs a marked decrease in the thoracic volume, causing deflation of lungs. Under such circumstances, the intrapleural pressure can become positive by 60–70 mm Hg (greater than atmospheric pressure), e.g. during defecation and coughing.
3. ***Gravity:*** The pleural pressure in the standing position is more negative (–7 mm Hg) at the apices of the lungs as compared to the bases (–2 mm Hg). Because of this, lungs are less expanded at the base, and even the airway at the base may become closed at the end of expiration. This is why during the first part of inspiration most of the inspired gas goes to the apices than bases of lungs.
4. ***Injury to the chest wall*** causing exposure of pleural cavity to the exterior causes air to enter the pleural cavity (pneumothorax), and the pleural pressure rises from a subatmospheric level to the atmospheric level. Since there is no opposing force to elastic recoil of the lung, in the pneumothorax the lung is collapsed.
5. ***Emphysema*** is a disease of the lungs in which lung elasticity is decreased or lost. Due to decrease in the recoiling force of lungs, the intrapleural pressure becomes less negative (i.e. increases). Because of this, in this disease the lung alveoli expand, and chest also expands and becomes barrel shaped.

Lung Volume Changes during Respiratory Cycle

- ***During tidal inspiration***, the volume of air in the lungs increases by 500 mL (tidal volume).
- ***During tidal expiration***, the elastic forces compress the gas in the lungs, which starts flowing out, and at the end of expiration, the volume of air in the lungs decreases by 500 mL (Fig. 5.2-4).

LUNG VOLUMES AND CAPACITIES

Static Lung Volumes and Capacities

Static lung volumes and capacities are not dependent on time factors, hence expressed either in mL or L.

Lung Volumes

The maximum volume to which a lung can be expanded has been divided into the four nonoverlapping volumes (Fig. 5.2-5):

1. Tidal Volume (TV) It is the volume of air inspired or expired with each breath during normal quiet breathing. It is approximately 500 mL in a normal adult male.
2. Inspiratory Reserve Volume (IRV) It is the extra volume of air that can be inhaled by a maximum inspiratory effort over and beyond the normal TV. It is about 3000 mL in a normal adult male.
3. Expiratory Reserve Volume (ERV) It is the extra volume of air that can be exhaled by the maximum forceful expiration over and beyond the normal TV (i.e. after the end of normal passive expiration). It is approximately 1100 mL in a normal adult male.
4. Residual Volume (RV) It is the volume of air that still remains in the lungs after the most forceful expiration. It is about 1200 mL in a normal adult male.

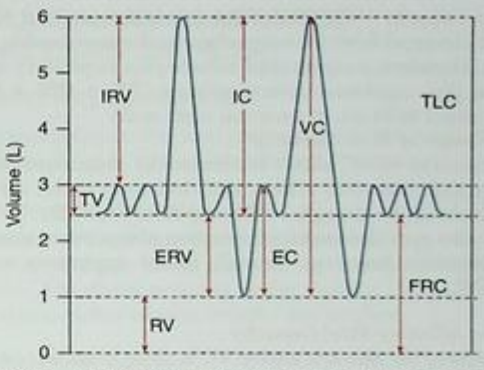


Figure 5.2-5 A spirogram showing various lung volumes and capacities. RV, residual volume; TV, tidal volume; IRV, inspiratory reserve volume; ERV, expiratory reserve volume; FRC, functional residual capacity; TLC, total lung capacity; IC, inspiratory capacity; VC, vital capacity; and EC, expiratory capacity.

Lung Capacities

Lung capacities are a combination of two or more pulmonary volumes and also include the following (Fig. 5.2-5):

1. Inspiratory Capacity (IC) This is the maximum volume of air that can be inspired after normal tidal expiration. Therefore, it equals the tidal volume plus inspiratory reserve volume (TV + IRV), and is approximately 3500 mL in a normal adult male.
2. Expiratory Capacity It is the maximum volume of air that can be expired after normal tidal inspiration. It equals tidal volume plus expiratory reserve volume (TV + ERV), and is approximately about 1600 mL in a normal adult male.
3. Functional Residual Capacity It is the volume of air remaining in the lungs after normal tidal expiration. Therefore, it equals the expiratory reserve volume plus the residual volume (ERV + RV), and is about 2300 mL in a normal adult male.

Significance of FRC The FRC (RV + ERV) of about 2300 mL represents the air that remains in the lungs most of the times. Even after the most forceful expiration, about 1200 mL (RV) of air is always present in the lungs. This has several advantages:

(i) ***Continuous exchange of gases*** is possible due to the presence of some air always present in the lungs, and thereby concentrations of O_2 and CO_2 in blood are kept constant.
(ii) ***Breath holding*** is made possible due to the FRC.
(iii) ***Dilution of toxic inhaled gases*** occurs due to the reserve of 2300 mL of air in the lungs (FRC) most of the times.
(iv) ***Load on respiratory mechanism and left ventricle*** would have been much more if there was no FRC because:
- Without FRC, lungs would have collapsed at the end of each expiration, and re-expansion would have required tremendous breathing effort.
- The collapsed lungs would have increased pulmonary vascular resistance and imposed a heavy load on the left ventricle.

Factors Affecting FRC Hyperinflation of the lungs seen in the following conditions may be associated with increased FRC:

- Old age due to loss of elasticity of lungs
- Emphysema
- Bronchial asthma

4. Vital Capacity (VC) This is the maximum amount of air a person can expel from the lungs after the deepest possible inspiration. Therefore, it equals tidal volume plus inspiratory reserve volume plus expiratory reserve volume (TV + IRV + ERV), and is about 4600 mL in a normal adult male.

Significance of Vital Capacity

- Estimation of VC allows assessment of maximum inspiratory and expiratory efforts, and thus gives useful information about the strength of the respiratory muscles.
- VC also provides useful information about other aspects of pulmonary functions through forced expiratory volume (FEV).

Factors Affecting Vital Capacity

(i) ***Size of the thoracic cavity***: VC is more in males (2.6 L/m^2 body surface area) because of the larger chest size and more muscle power than females.

(ii) ***Age***: In the old age, VC is decreased due to decrease in elasticity of the lungs.

(iii) ***Strength of respiratory muscles***: In swimmers and divers, VC is more because of the increased strength of the respiratory muscles.

(iv) ***Gravity***: In the standing position, VC is more than in the sitting and lying positions because of the following:
- Increased size of thoracic cavity in the standing position (diaphragm moves down)
- Reduced pulmonary blood flow due to decreased venous return

(v) ***In pregnancy***, VC is reduced due to the pushing up of diaphragm and reduced capacity of the thoracic cavity.

(vi) ***In ascites*** (accumulation of fluid in the abdominal cavity), VC is reduced due to the same reason as in pregnancy.

(vii) ***Pulmonary diseases*** like pulmonary fibrosis, emphysema, respiratory obstruction, pulmonary oedema, pleural effusion and pneumothorax are associated with decreased VC.

5. Total Lung Capacity (TLC) It is the volume of air present in the lungs after the maximal inspiration. It equals the vital capacity plus the residual volume (VC + RV), and is about 5800 mL in a normal adult male.

All volumes and capacities except RV, FRC and TLC are recorded by a *spirometer*. FRC is determined by the nitrogen washout method or helium dilution method, and then residual volume and total lung capacity are calculated.

Dynamic Lung Volumes and Capacities

Dynamic lung volume and capacities are dependent on time factor and so expressed in units of mL/min and L/min, respectively.

Timed Vital Capacity (TVC) or Forced Vital Capacities (FVC)

Forced VC is the volume of air that can be expired rapidly with a maximum force following a maximum inspiration. The volume of air expired can be timed by recording the VC on a spirograph moving at the known speed.

Components of TVC or FVC (Fig. 5.2-6)

(i) Forced Expiratory Volume in 1 second (FEV_1) It represents the volume expired in the first second of an FVC.

- Estimation of FEV_1 is the most commonly used screening test for airway diseases.

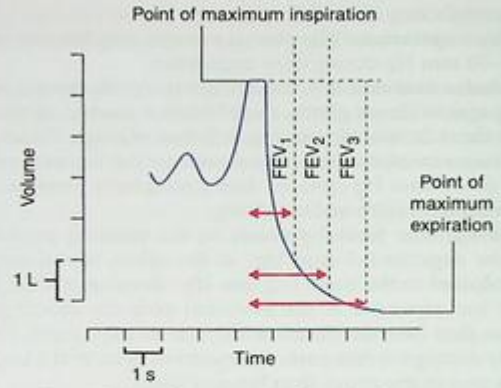


Figure 5.2-6 Components of timed vital capacity.

- The FEV_1 is actually a flow rate; its units are L/s.
- FEV_1% is the percent of FVC expired in 1 second (i.e. $FEV_1\% = FEV_1/FVC \times 100$); normally, FEV_1% is about 80% of the FVC (Fig. 5.2-7A).

Clinical application: It is useful in distinguishing between restrictive and obstructive lung diseases.

- Patients with *restrictive lung disease* (e.g. kyphoscoliosis and ankylosing spondylitis) have a reduced FVC but are able to achieve relatively high flow rates; therefore, their FEV_1% exceeds 80% (Fig. 5.2-7B).
- Patients with *obstructive lung disease* (e.g. bronchial asthma) have low flow rates as a result of high airway resistance; therefore, their FEV_1% is abnormally low (Fig. 5.2-7C).

(ii) Forced Expiratory Volume in 2 seconds (FEV_2) It represents the volume of air expired in the first 2 seconds of FVC; FEV_2% is about 90% of FVC under normal conditions.

(iii) Forced Expiratory Volume in 3 seconds (FEV_3) It represents the volume of air expired in the first 3 seconds. Normally, FEV_3% is 98%–100% of FVC.

Minute Ventilation (MV) or Pulmonary Ventilation (PV)

It is the volume of air inspired or expired per minute. It equals the tidal volume multiplied by respiratory rate (TV × RR). The TV at rest averages 500 mL (0.5 L) and the normal respiratory rate is 12–15 breaths/min; therefore, normal minute volume is 6–7.5 L/min.

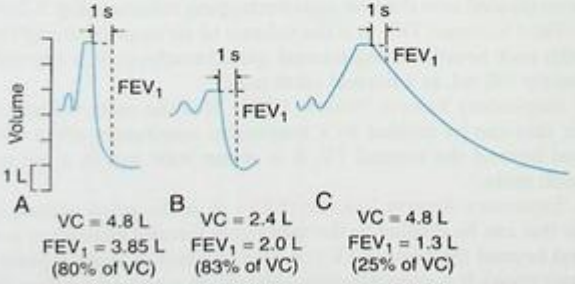


Figure 5.2-7 Forced expiratory volume in the first second (FEV_1) component of timed vital capacity: (A) in normal subject; (B) in a patient with restrictive lung disease (RLD); and (C) in a patient with obstructive lung disease (OLD).

Maximum Breathing Capacity (MBC) or Maximum Voluntary Ventilation or Maximum Ventilation Volume (MVV)

It is the maximum volume of air that can be ventilated on command during a given interval.

This index of ventilatory function depends upon the complete cooperation of the subject, who is asked to breathe as rapidly and deeply as he/she can for a 15-second interval. The volume of air moved is either recorded by a spirometer fitted with a writing point or is collected in a Douglas bag; the result is expressed in L/min.

Normal adult male can attain a MVV of 80–170 L/min (average 120 L/min).

MVV is profoundly reduced in patients with emphysema, airway obstruction and very poor respiratory muscle strength.

Measurement of Static Lung Volumes and Capacities

Spirometry Spirometry refers to recording of volume changes during various clearly defined breathing manoeuvres. It can be performed using a simple spirometer, a modified spirometer called respirometer or computerized spirometer.

Simple spirometer (Fig. 5.2-8) is made of metal. It consists of the following parts:

- *Outer chamber* or container, which is filled with water.
- *Floating drum* or a gas bell with 6 L capacity floats in the water in an inverted manner. It is attached to a chain which passes over a pulley bearing a balancing weight and a writing needle (pen). The needle (pen) moves with the movement of the floating drum. The floating drum is thus counterpoised and has very little inertia and friction.
- *Inner chamber* is open at the top end, which lies above the water level in the outer chamber and is connected to a tube at the bottom end. At the end of the tube, a mouth piece is attached through which the subject is made to respire.
- *Kymograph is* a recording drum on which the movements of the needle are recorded.

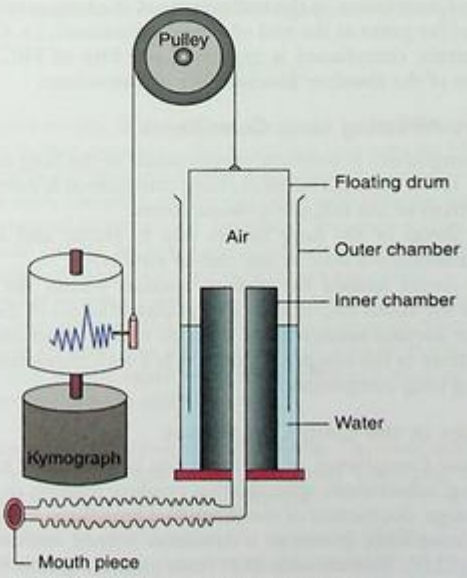


Figure 5.2-8 Simple spirometer.

PULMONARY ELASTANCE AND COMPLIANCE

Pulmonary Elastance

Elastance refers to the *recoil* (retractive) tendency of a structure. Both the thoracic cage and lungs have elastance.

Elastance of Thoracic Cage

Elastance or recoil tendency of the thoracic cage refers to the constant tendency of the thoracic cage to expand (to pop outwards). The elastic property of the thoracic cage is because of the elastic nature of ribs, muscles and tendons.

Elastance of Lungs

Elastance or recoil tendency of the lungs refers to the constant tendency of the lungs to collapse. The recoil forces in the lungs are generated by tissue and surface forces:

1. Tissue Forces These are due to the presence of many elastic tissues such as smooth muscle, elastic and collagen in the lung parenchyma, which are kept under constant stretch in the inflated lungs.
2. Surface Forces These are generated at the alveolar surface lined by fluid (*alveolar surface tension*) due to which the alveoli tend to become progressively smaller and tend to collapse.

Alveolar Surface Tension

Alveolar surface tension is generated because of the unbalanced attraction of the liquid molecules at the surface of alveolar membrane. A phase change occurs between the alveolar gas and the surface of the alveolar membrane. Alveolar surface tension increases the tendency of the lungs to deflate. An increased transmural pressure is necessary to counteract the effects of surface tension. According to the *law of Laplace*, in a spherical structure like alveoli, the transmural pressure generated equals two times the (surface) tension divided by radius, i.e. $P = 2T/r$. Therefore, small alveoli tend to become still smaller, whereas large alveoli tend to become still larger (Fig. 5.2-9). Thus, surface tension tends to produce collapse of the alveoli.

Pulmonary Surfactant

Pulmonary alveolar surface tension opposes the expansion of the lungs during inspiration. However, the presence of pulmonary surfactant in the fluid lining the alveoli reduces the surface tension markedly.

Source Pulmonary surfactant is secreted by type II alveolar epithelial cells (granular pneumocytes).

Composition Pulmonary surfactant is a complex mixture of several phospholipids, proteins and ions. Dipalmitoylphosphatidylcholine (DPPC) along with several other phospholipids is responsible for reducing surface tension.

Surface tension with normal alveolar fluid lining without a surfactant is about 50 dynes/cm^2, and with a surfactant, it varies between 5 and 30 dynes/cm^2, depending upon the concentration of surfactant.

Functions of Pulmonary Surfactant

1. Reduces the Tendency of Alveoli to Collapse The surface tension in a thin-walled sphere like alveolus tends to make the sphere smaller to collapse. Surfactant, by reducing surface tension, decreases the tendency to collapse.

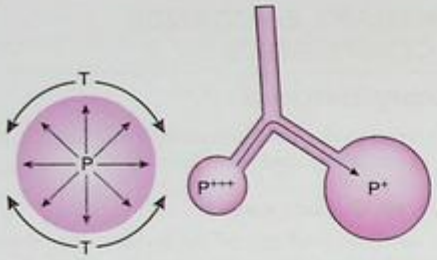


Figure 5.2-9 Pressure in the alveoli (P) is directly proportional to the surface tension (T) and inversely proportional to the radius (r). Therefore, small alveoli tend to become still smaller and large alveoli tend to become still larger.

2. Reduces Work of Breathing According to Laplace's law, due to reduction in the surface tension, the mean alveolar radius is increased. This reduces the transmural pressure required for expanding the alveoli. As alveoli are easily expanded, so work of breathing is reduced. The low surface tension also facilitates the reopening of collapsed airway and alveoli.

3. Prevents Pulmonary Oedema Surface tension is retracting force which not only pulls the alveolar wall to the centre of alveolus but also pulls fluid from the capillaries into the interstitial space surrounding the alveoli and into the alveoli leading to pulmonary oedema. Surfactant prevents this phenomenon by lowering the surface tension.

4. Alveolar Stabilization Surfactant causes stability of alveoli, i.e. it maintains an almost uniform size of alveoli.

Pulmonary surfactant causes alveolar stabilization by the following mechanisms:

- In the presence of a surfactant, the surface tension developed in the alveoli is inversely proportional to the concentration of surfactant per unit area.
- In the smaller alveolus, the surfactant molecules form a thick layer, while in a larger alveolus, the surfactant molecules are scattered on the larger surface (as the number of molecules is limited) (Fig. 5.2-10).
- Thus, in a smaller alveolus, the tendency to develop more pressure due to a smaller radius will be neutralized by the tendency to develop less pressure due to a higher concentration of surfactant per unit area, and the reverse will occur in a larger alveolus. In this way, there will not be much pressure gradient between the two alveoli helping to keep the size of alveolar sac constant. Thus, due to the presence of surfactant, the stability of alveoli is maintained.

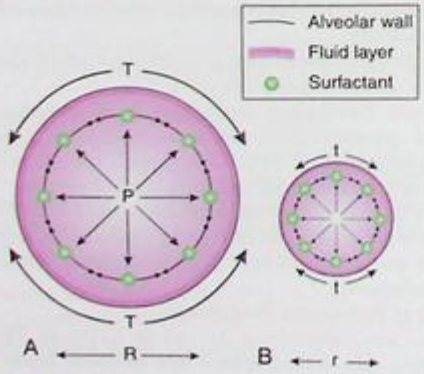


Figure 5.2-10 Distribution of surfactant in a large (A) and a small (B) alveolus.

APPLIED ASPECTS

Clinical Significance of Pulmonary Surfactant

Respiratory distress syndrome (RDS) of newborn or the *hyaline membrane disease* occurs in the newborn babies (especially premature) due to inadequate formation of surfactant, resulting in an elevated alveolar surface tension. In this condition, it is extremely difficult to expand the lungs. Respiratory work is greatly increased, and there is inadequate exchange of gases due to alveolar instability, pulmonary oedema and collapse of alveoli (atelectasis) in many areas. This results in severe respiratory insufficiency and the infant may die.

Compliance

Definition and Normal Value

- Compliance (C) refers to change in lung volume (ΔV) per unit change in transpulmonary pressure (ΔP), i.e.

$$C = \frac{\Delta V}{\Delta P}$$

Transpulmonary pressure is the difference between the alveolar pressure and the pleural pressure.

- Compliance expresses the distensibility (expansibility) of the lung and chest wall.
- Normal value of compliance for the lungs and chest wall combined is 0.13 L/cm of H_2O and for the lung alone it is 0.22 L/cm of H_2O.

Static Versus Specific Lung Compliance

Static Compliance The static compliance of any system is dependent on its size. Thus, the lung compliance depends on the amount of functional lung tissue. Thus, static compliance is not a good measure of absolute distensibility.

Specific Compliance is the compliance of the lung at relaxation volume (the point at the end of a tidal expiration), i.e. the FRC. The specific compliance is expressed per litre of FRC. It is a measure of the absolute distensibility of a structure.

Factors Affecting Lung Compliance

Lung compliance is inversely proportional to the lung elastance (elastic recoil force). Therefore, lung compliance is determined on the basis of the following elastic forces:

Elastic forces of the lung tissues due to elastic and collagen fibres contribute a smaller amount of elasticity.

Elastic forces caused by surface tension within the alveoli account for about two-thirds of total elastic forces in the lungs.

Alveolar surface tension plays a major role in generating elastance forces in the lungs, and, thus, it is a very important factor affecting lung compliance.

Changes in the Lung Compliance

Decreased Compliance of the lungs can be caused by lung diseases (e.g. tuberculosis, silicosis) that produce scarring or fibrosis of the lungs, destruction of the functional lung tissue or both. Reduced compliance produces a condition termed *restrictive lung disease* (RLD). Patients with RLD must generate greater than the normal forces to expand the lungs.

Increased Compliance is produced by the pathologic processes that occur in emphysema as well as from the ageing process. Alveolar septa, which provide some of the retractive forces in lungs, are destroyed in both conditions, but emphysema causes a much more extensive loss of septa than the normal ageing process.

WORK OF BREATHING

The contraction of respiratory muscles causes the expansion of thoracic cage, thereby causing expansion of lungs and fall in intra-alveolar pressure and allowing atmospheric pressure to push air into the lungs during inspiration. Thus, to move the air into the lungs, the respiratory muscles have to do work to overcome the following *resistances.*

Resistance to Breathing

Tissue Resistance It is the resistance offered by the tissues as they expand or contract. Tissue resistance comprises the following:

1. ***Elastic resistance:*** It is the sum of forces of elastic recoil exerted by the lung and chest wall. The elastic recoil of the lungs is due to the presence of elastic fibres in the lungs and due to the alveolar surface tension.
2. ***Viscous resistance:*** It is the resistance offered by the nonelastic tissues in the lungs.

Airway Resistance It is the resistance caused by the friction of gas molecules between themselves and the walls of the airways. Factors affecting airway resistance are given below:

1. ***Rate of gas flow:*** The greater the rate of gas flow, the greater is the resistance. Rate of gas flow is highest in the intermediate-sized bronchi as they have the highest cross-sectional area, so the highest resistance to flow occurs in this part of tracheobronchial tree.
2. ***Airway radius:*** It is the most powerful determinant of resistance. The smaller the radius of airway, the greater is the resistance. According to the *Poiseuille–Hagen formula* (see page 136):

$$\text{Resistance} \propto \frac{1}{r^4}$$

   In other words, if the radius decreases by half (keeping the other factors constant), the resistance increases by 16 times. Airway radius increases during inspiration and decreases during expiration. Therefore, airway resistance is high during expiration as compared to inspiration. Because of this, in bronchial asthma patients (where bronchoconstriction develops), inspiration is possible but there is extreme difficulty in expiration.
3. ***Length of airway:*** It does not change much during respiration or in lung diseases and, therefore, is not an important factor.
4. ***Type of air flow:*** The airway resistance is more in a turbulent flow (e.g. during rapid respiration) than in a laminar flow or streamline flow in quiet breathing.

Components of Work of Breathing The total work done by the respiratory muscles during quiet breathing may be divided into the following components:

- Work done to overcome elastic resistance (65%)
- Work done to overcome viscous resistance (7%)
- Work done to overcome airway resistance (28%)

The work done during normal inspiration can be divided into the following three fractions:

Compliance work refers to the work done by respiratory muscles to inflate the lungs against the *elastic resistance* of the chest wall and lungs. Thus, most of the work done (65%) is used to overcome elastic resistance.

Nonelastic resistance work is done to overcome the nonelastic resistance. It includes the work done to overcome the following:

- Viscous resistance of lungs (7%)
- Airway resistance (28%)

Thus, only a small amount (7%) of the work done is used to overcome the viscosity of the lungs, and 28% of the work done is utilized to overcome the resistance of air flow through the respiratory passages.

Work Done During Expiration Since in quiet breathing expiration is a passive process, so no work is done during expiration. This stored energy can compress the alveolar gas and create an expiratory flow. When the lungs are recoiling back, some energy is required to overcome *nonelastic resistance*, i.e. the airway resistance plus viscous tissue resistance. In normal quiet expiration, stored energy is utilized to overcome this resistance; thus, no extra work is done.

Factors Affecting Total Work of Breathing Total work of breathing during quiet respiration under normal circumstances ranges from 0.3 to 0.8 kg m/min. Normally, the work of breathing represents 2%–3% of the resting O_2 consumption.

- If either the respiratory resistance increases or the compliance decreases, the respiratory work will increase and therefore the respiratory muscles will use more O_2 to overcome the added load.
- The work of breathing is also increased markedly during muscular exercise (physiological).

SELF-ASSESSMENT

1. Describe briefly:
   - Mechanism of tidal respiration
   - Pressure and volume changes during respiratory cycle
   - Factors affecting vital capacity
2. Differentiate between:
   - Intrapulmonary and intrapleural pressure
   - Functions of external intercostal and internal intercostal muscles
   - Vital capacity and timed vital capacity
   - Pulmonary and alveolar ventilation
3. Write notes on:
   - Pulmonary surfactant
   - Compliance
   - Respiratory distress syndrome
   - Functional residual capacity
4. Define briefly:
   - Tidal volume
   - Vital capacity
   - Residual volume
   - Maximum breathing capacity
   - Laplace's law
   - Minute ventilation

5.3 Pulmonary Circulation

CHAPTER OUTLINE

Functional Anatomy
Pulmonary Circulation
Bronchial Circulation
Lymphatic Circulation

Characteristic Features of Pulmonary Circulation
Introduction
Pressures in the Pulmonary System
Pulmonary Blood Volume

Regulation of Pulmonary Blood Flow
Neural Control
Chemical Control

FUNCTIONAL ANATOMY

The lungs have three circulations: pulmonary, bronchial and lymphatic.

Pulmonary Circulation

Pulmonary trunk arises from the right ventricle, and divides into the right and left pulmonary arteries, which convey the deoxygenated blood to the right and left lungs, respectively. The blood circulates through a capillary plexus intimately related to the walls of alveoli and receives oxygen from the alveolar air. This blood, which is now oxygenated, is returned to the heart (left atrium) through four pulmonary veins.

Bronchial Circulation

The lungs also receive oxygenated blood like other tissues in the body through *bronchial arteries* (two left and one right), which are branches of the descending thoracic aorta. Bronchial blood flow amounts to about 1%–2% of total cardiac output. The oxygenated blood in the bronchial arteries supplies the connective tissues, septa, and large and small bronchi of the lungs. Because the bronchial blood empties into the pulmonary veins and bypasses the right heart, the bronchial circulation, therefore, constitutes a *physiological shunt*, i.e. a channel that bypasses oxygenation in the lungs.

Lymphatic Circulation

Lungs are richly supplied by lymphatics. Lymphatics are present in the walls of the terminal bronchioles and in all the supportive tissues of the lungs. Particulate matter entering the alveoli during inspiration is removed by way of lymphatic channels. Lymphatics also remove the plasma proteins leaking from the lung capillaries and thus help to prevent the pulmonary oedema. The deep lymphatic vessels follow the bronchi, and first drain into the *pulmonary nodes* (in the substance of the lungs) and then into the *bronchopulmonary nodes*. The superficial lymph vessels lie near the surface of lungs and converge on to bronchopulmonary nodes. From the bronchopulmonary node, lymph drains into the *tracheobronchial nodes* and from there into the *bronchomediastinal trunk*.

CHARACTERISTIC FEATURES OF PULMONARY CIRCULATION

Introduction

- The pulmonary arteries and their branches are thin walled and distensible, giving the pulmonary arterial tree a large compliance. The distensibility of pulmonary vessels makes the pulmonary circulation a *low-pressure*, *low-resistance* and *high-capacitance system*.
- The pulmonary capillaries surround the alveoli and are sandwiched between their walls; as a result, each alveolus seems to be enclosed in a basket of capillaries (Fig. 5.3-1).

Pressures in the Pulmonary System (Fig. 5.3-2)

Right Ventricular Pressure during each cardiac cycle reaches a peak value of 25 mm Hg in systole (if 120 mm Hg in the left ventricle) and falls to 0–1 mm Hg in diastole (if 5 mm Hg in the left ventricle).

Pulmonary Artery Pressures vis-á-vis aorta, respectively, are as follows:

- Systolic pressure: 25 mm Hg and 120 mm Hg
- Diastolic pressure: 8 mm Hg and 80 mm Hg
- Mean arterial pressure: 15 mm Hg and 100 mm Hg
- Pulse pressure: 17 mm Hg and 40 mm Hg

Left Atrial Pressure in major pulmonary veins averages about 5 mm Hg in the recumbent human being. Therefore, the pressure gradient in the pulmonary system (mean pulmonary artery pressure – mean pulmonary vein pressure) is 15 − 5 = 10 mm Hg (if 120 mm Hg in the systemic circulation).

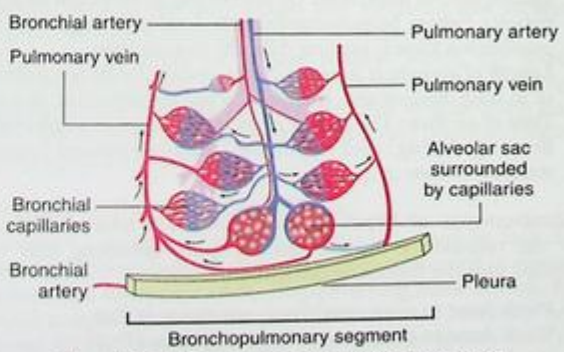


Figure 5.3-1 Organization of pulmonary circulation.

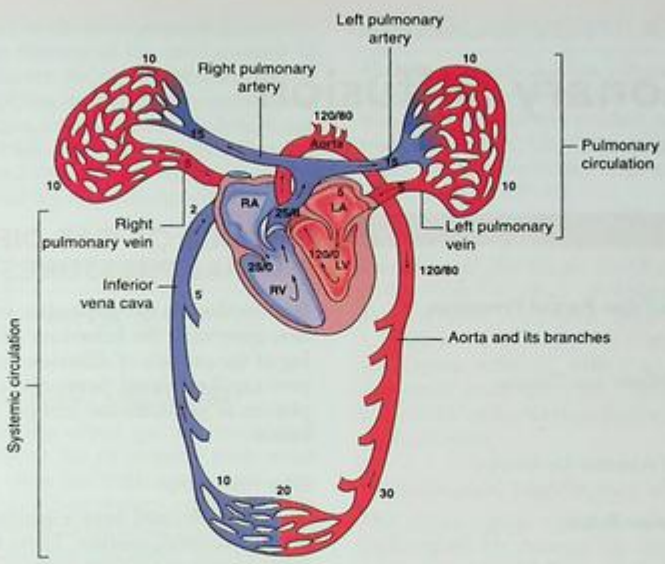


Figure 5.3-2 Blood pressure (mm Hg) in pulmonary and systemic circulation.

Pulmonary Capillary Pressure is about 10 mm Hg. This pressure is far below the colloid osmotic pressure (25 mm Hg), so a net suction force of 15 mm Hg tends to draw fluid from the alveolar interstitial space into the pulmonary capillaries, *which keeps the alveoli dry.* However, if the pulmonary capillary hydrostatic pressure rises above 25 mm Hg, fluid can escape into the interstitial space, leading to *pulmonary oedema.* This reduces the rate of gas exchange in the lungs. The resultant hypoxia may be fatal.

Pulmonary Blood Volume

Pulmonary vessels contain about 600 mL of blood at rest. The pulmonary vessels act as capacitance vessels, so their blood content can vary from 200 to 900 mL. In pathological conditions, like haemorrhage, transfer of blood from pulmonary vessels to systemic circulation can partly compensate for the blood loss. Thus, the pulmonary vessels act as a reservoir of blood.

REGULATION OF PULMONARY BLOOD FLOW

Neural Control

Efferent Sympathetic Vasoconstrictor Nerves richly innervate the pulmonary blood vessels. However, these nerves have *no resting discharge and tone*, which means they can show an increase in activity only when stimulated. These participate in the vasomotor reflexes, e.g.:

- *Baroreceptor stimulation* produces reflex dilatation of pulmonary vessels.
- *Chemoreceptor stimulation* causes pulmonary vasoconstriction.

However, the effect of vasodilatation and vasoconstriction is more on the capacity rather than the resistance of pulmonary vessels. The vasoconstriction produced in the lungs due to sympathetic discharge is considerable and results in transfer of pulmonary blood in the systemic circulation, e.g. during acute haemorrhage.

Afferent Control Through Vagus is Mediated Through Following Receptors

- ***Pulmonary baroreceptors*** are present in tunica adventitia of pulmonary trunk and its two major branches. These are mechanoreceptors which detect rise in pressure in pulmonary artery and produce reflex bradycardia and hypotension.
- ***Pulmonary volume receptors*** are the vagal mechanoreceptors present at the junction of pulmonary vein with left atrium. Stimulation of these receptors produces tachycardia and diuresis, which help in regulating blood volume. These vagal receptors could be an afferent limb of the Bainbridge reflex.
- ***J receptors*** (juxtapulmonary receptors) are present adjacent to pulmonary capillaries in the alveolar interstitial space. Stimulation of J receptors leads to *reflex tachypnoea* (increase in rate of breathing) and reduction of skeletal muscle tone.

Chemical Control

1. Local Hypoxia is responsible for most significant alterations in pulmonary blood flow by producing *vasoconstriction.*

2. Hypercapnia and Acidosis also produce vasoconstriction. The effects of pCO_2 and acidosis on pulmonary vessels are just opposite to those in the systemic vessels, where these stimuli produce vasodilation. The functional significance of this response is the same as in the case of local hypoxia.

3. Chronic Hypoxia, which occurs in high-altitude dwellers, is associated with a marked increase in pulmonary arterial pressure (*pulmonary hypertension*).

SELF-ASSESSMENT

1. Describe briefly:
   - Pressures in pulmonary circulation
   - Functions of pulmonary circulation
   - Regulation of pulmonary circulation

5.4 Pulmonary Diffusion

CHAPTER OUTLINE

Introduction

Physics of Gas Diffusion and Gas Partial Pressures
Gas Pressure
Partial Pressure
Partial Pressure of Gases in Water and Tissues
Water Vapour Pressure

Alveolar Ventilation
Physiological Significance of Alveolar Ventilation
Dead Space Air

Alveolar Ventilation–Perfusion Ratio
Effect of Gravity on VA/Q
Effects of Alterations in VA/Q Ratio

Alveolar Air
Composition of Alveolar Air
Composition of Expired Air

Diffusion of Gases through Respiratory Membrane
Respiratory Unit and Respiratory Membrane
Factors Affecting Diffusion across Respiratory Membrane
Diffusion Capacity of Lung

INTRODUCTION

Pulmonary diffusion is transfer of gases from alveoli to capillary blood across the respiratory membrane.

To understand the *intricacies* of diffusion of gases across the respiratory membrane, it is essential to have knowledge about the following related aspects and concepts, most of which form the contents of this chapter:

- *Pulmonary perfusion*, i.e. *pulmonary blood flow*, has been discussed in Chapter 5.3.
- *Physics of gas diffusion and gas partial pressures*: The rate at which the respiratory gases diffuse across the respiratory membrane requires an understanding of the physics of diffusion and gas exchange.
- *Alveolar ventilation*, i.e. the rate at which new air reaches the gas exchange area of the lungs. Alveolar ventilation governs the process of pulmonary diffusion in its own way.
- *Alveolar ventilation–perfusion ratio*: It is the ratio of alveolar ventilation and pulmonary blood flow. This is a highly quantitative concept, which was developed to help in understanding respiratory exchange when there is imbalance between alveolar ventilation and alveolar blood flow.
- *Diffusion of gases through the respiratory membrane* is the main process which transfers gases from the alveoli into the capillaries. Various important aspects of this process have also been discussed in this chapter.

PHYSICS OF GAS DIFFUSION AND GAS PARTIAL PRESSURES

It is worthwhile to recapitulate some of the basic principles and laws governing the behaviour of gases for a better understanding of the process of diffusion between alveolar air and pulmonary capillary blood. Some of the important aspects concerning physics of gas diffusion and gas partial pressures are discussed below.

Gas Pressure

The gas molecules have a kinetic energy so they are in a continuous random motion. These molecules bounce against each other and/or against the walls of container and exert a pressure. The gas pressure (P) exerted depends on the following factors:

Concentration of Molecules (n) The pressure of a gas is directly proportional to its concentration, i.e.

$$P \propto n \qquad \text{(i)}$$

Volume (V) Unlike liquids, gases expand to fill the volume available to them. Therefore, at a constant temperature, the pressure (P) of a given mass of gas is inversely proportional to its volume (V), i.e.

$$P \propto \frac{1}{V} \qquad \text{(ii)}$$

This is called *Boyle's law* of gases.

Absolute Temperature (T) According to *Charles' law*, at a constant pressure the volume of gas is directly proportional to its absolute temperature, i.e. $V \propto T$, and as mentioned above, according to Boyle's law

$$P \propto \frac{1}{V} \qquad \text{(iii)}$$

Therefore, it can be derived that

$$P \propto T$$

From equations (i), (ii) and (iii), it can be derived that

$$P = \frac{nRT}{V},$$

where

P = pressure of gas
n = number of molecules of gas
T = absolute temperature
V = volume of gas
R = gas constant

Partial Pressure

According to *Dalton's law* of partial pressure, the total pressure exerted by a mixture of gases is equal to the sum of the partial pressures of all gases present in the mixture. Thus, the partial pressure (p) refers to the pressure exerted by any one gas present

in a mixture of gases. It is equal to the total pressure exerted by the mixture of gases times the fraction of the total amount of mixture of gases it represents. Hence, the partial pressure (p) of a gas can be calculated by multiplying its fractional concentration by the total pressure. For example, environmental air (which has atmospheric pressure [at sea level] of about 760 mm Hg) is a mixture of 21% oxygen (O_2) and 79% nitrogen (N_2). Therefore, the partial pressure (p) of O_2 and N_2, respectively, will be:

$$pO_2 = 760 \times \frac{21}{100} = 160 \text{ mm Hg},$$

$$pN_2 = 760 \times \frac{79}{100} = 600 \text{ mm Hg}.$$

Partial Pressure of Gases in Water and Tissues

It is important to have knowledge about partial pressure of gases in water and tissues because the respiratory gases must first dissolve in the tissues to cross the respiratory membrane and then diffuse into the plasma of pulmonary capillaries. The pressure (p) of a gas in a solution is determined not only by its concentration but also by its solubility coefficient. According to *Henry's law*, when temperature is kept constant, the content of gas (n) dissolved in any solution is directly proportional to the partial pressure of a gas, i.e.

$$n = p \times c.$$

where
n = concentration (amount) of a gas in a solution
p = partial pressure of gas
c = solubility coefficient of the gas

Solubility Coefficient is a constant for each gas that equates gas content and partial pressure. Solubility coefficient of gases (important to respiratory physiology) is given in Table 5.4-1. Increasing the temperature reduces the solubility coefficient of gases (Table 5.4-1). It is important to note that the *solubility coefficient of carbon dioxide (CO_2) is about 24 times more and that of nitrogen (N_2) and one-half that of oxygen (O_2).*

Water Vapour Pressure

The atmospheric air entering the respiratory passages during inspiration is humidified by the water vapours from the conducting passages. By the time the atmospheric air reaches the alveoli, it is saturated with water vapours. Thus, in the alveolar air, besides O_2 and N_2, water vapours also exert its partial pressure. Vapour pressure of water is dependent on its temperature. At body temperature (37°C), the vapour pressure of water in alveolar air is 47 mm Hg.

TABLE 5.4-1 Solubility Coefficient of Important Gases to Respiratory Physiology

Temperature (°C)	SOLUBILITY COEFFICIENT (mL GAS/mL SALINE/mm Hg GAS TENSION)			
	O_2	N_2	CO_2	CO
0	0.049	0.024	1.71	0.035
20	0.032	0.016	0.90	0.023
37	0.024	0.012	0.58	0.019

ALVEOLAR VENTILATION

Alveolar ventilation is the volume of the fresh air which reaches the gas exchange area of the lung each minute. During inspiration, some of the air inhaled never reaches the gas exchange areas but instead fills the non–gas exchange areas (conducting zone) of the respiratory tract called the *dead space*, which is equal to about 150 mL.

During expiration, out of 500 mL of tidal volume, 150 mL of the alveolar expired air remains in the conducting passages. Therefore, of 500 mL air entering the lungs, only 350 mL/breath is the fresh air, which contributes to the alveolar ventilation. Thus, alveolar ventilation can be calculated as follows:

Alveolar ventilation (VA) = respiratory rate × (tidal volume – dead space volume), with a normal tidal volume of 500 mL, a normal dead space of 150 mL and a respiratory rate of 12 breaths/min; alveolar ventilation equals 12 × (500 − 350) or 4200 mL/min.

Physiological Significance of Alveolar Ventilation

The physiological significance of alveolar ventilation can be understood by comparing the alveolar ventilation of two subjects with the following parameters:

Subject A, having normal breathing with a tidal volume (TV) of 500 mL and respiratory rate (RR) of 12 breaths/min will have the following:

- Pulmonary ventilation = 12 × 500 = 6 L/min.
- Alveolar ventilation = 12 × (500 − 150) = 4.2 L/min.

Subject B, having rapid shallow breathing with tidal volume of 200 mL and respiratory rate 30/min will have the following:

- Pulmonary ventilation = 30 × 200 = 6 L/min.
- Alveolar ventilation = 30 × (200 − 150) = 1.5 L/min.

On Comparison, we see that both the subjects A and B have similar amounts of pulmonary ventilation (6 L/min), but the subject B has the alveolar ventilation (1.5 L/min) much less than that of the subject A (4.2 L/min). Consequently, the subject B is likely to suffer from hypoxia and hypercapnia.

Dead Space Air

Dead space air is the portion of minute ventilation that does not take part in the exchange of gases. There are three types of dead spaces (Fig. 5.4-1):

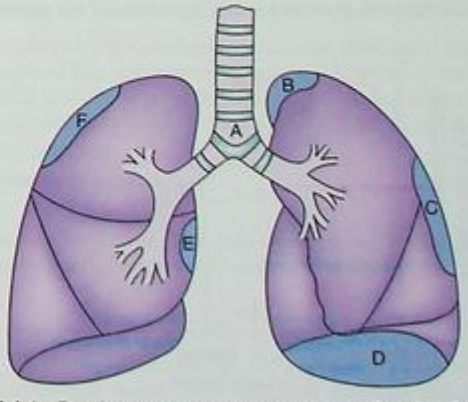


Figure 5.4-1 Dead space: anatomical (A), alveolar (B + C + D + E + F) and physiological (A + B + C + D + E + F).

1. Anatomical Dead Space refers to the volume of air present in the conducting zone of the respiratory passage, i.e. from nose to terminal bronchioles. As mentioned earlier, the anatomical dead space contains approximately 150 mL of air.

2. Alveolar Dead Space Air refers to the volume of air present in those alveoli which do not take part in gas exchange. Normally, all the alveoli take part in the gas exchange, but in some lung diseases, some alveoli do not take part in the gas exchange because of the following reasons:

- ***When alveoli have zero blood flow***, the volume of air ventilating such alveoli does not take part in gas exchange.
- ***When alveoli are overventilated***, some of the air which is in excess of the volume required to equilibrate with the blood is not able to take part in gas exchange.

3. Physiological Dead Space refers to the total dead space, which includes both the anatomical and alveolar dead spaces. In a normal healthy person, the physiological dead space nearly equals the anatomical dead space.

ALVEOLAR VENTILATION–PERFUSION RATIO

Alveolar ventilation–perfusion ratio (VA/Q) is the ratio of alveolar ventilation per minute to quantity of blood flow to alveoli per minute. Normally, alveolar ventilation (VA) is 4.2–5.0 L/min and the pulmonary blood flow (equal to cardiac output) is approximately 5 L/min. So, the normal VA/Q is about 0.84–0.9. At this ratio, maximum oxygenation occurs.

Effect of Gravity on VA/Q

- Because of the effect of gravity, the basal alveoli are overperfused and apical alveoli are underperfused. There is almost a linear reduction in the blood flow from the base to apex (Fig. 5.4-2).
- The alveolar ventilation also reduces linearly from the base to apex (Fig. 5.4-2), and thus the basal alveoli are overventilated and apical alveoli are underventilated.

Effects of Alterations in VA/Q Ratio

1. Normal VA/Q Ratio implies that there is both normal alveolar ventilation and normal alveolar perfusion. The exchange of gases is optimal and the alveolar pO_2 is about 104 mm Hg and pCO_2 is about 40 mm Hg.

2. Increased VA/Q Ratio means that the alveolar ventilation is more than the perfusion. As a result, the whole of the alveolar air is not utilized for gaseous exchange. The extra air in the alveoli which goes waste forms the so-called alveolar dead space air. There will also be change in the composition of alveolar air (Fig. 5.4-3).

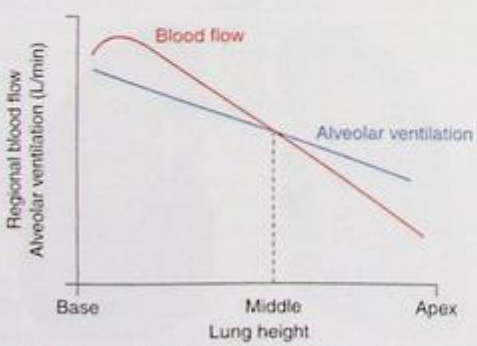


Figure 5.4-2 Distribution of alveolar ventilation and pulmonary blood flow in different regions of lung during standing.

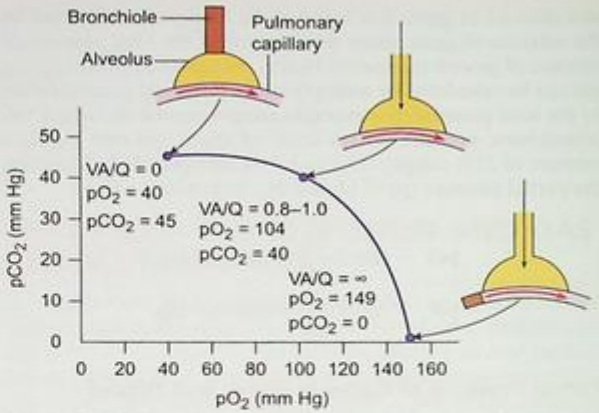


Figure 5.4-3 Relationship of alveolar ventilation–perfusion ratio (VA/Q) with alveolar air pO_2 and pCO_2.

3. Decreased VA/Q Ratio occurs when the rate of blood *flow is more than the rate* of alveolar ventilation. The alveolar ventilation is not enough to provide oxygen, so a fraction of venous blood passes through the pulmonary capillaries without becoming oxygenated. This fraction is called *shunted blood*. This shunted blood along with the additional deoxygenated blood from the bronchial veins to the pulmonary vein (about 2% of cardiac output) forms the so-called *physiological shunt*. The greater the physiological shunt, the greater is the amount of blood that fails to be oxygenated as it passes through the lungs.

ALVEOLAR AIR

Volume of air which is available for the exchange of gases in the alveoli per breath is called alveolar air, which is equivalent to tidal volume minus dead space, i.e. (500 – 150) or 350 mL.

Composition of Alveolar Air

Composition of alveolar air can be studied by *alveolar air sampling* that involves analysis of the last few millilitres of air that issues from the lungs during expiration. Alveolar air composition is considerably different from that of atmospheric air (Table 5.4-2) because of the following reasons:

1. Water vapours dilute the other gases in the inspired air.
2. Alveolar air is renewed very slowly by the atmospheric air.
3. Oxygen is constantly being absorbed from the alveolar air.
4. Carbon dioxide is constantly diffusing from the pulmonary blood to the alveoli.

Composition of Expired Air

As shown in Table 5.4-2, the composition of expired air is different than that of the alveolar air. This is because of the fact that the expired air is a combination of dead space air and alveolar air. The expired air can be split into the following three portions:

- ***First portion*** of the expired air represents the dead space air, and its composition is similar to typical humidified air.

TABLE 5.4-2 Composition and Partial Pressure of Gases in Atmospheric Air, Humidified Air, Alveolar and Expired Air

Gas	PARTIAL PRESSURE (mm Hg) AND CONCENTRATION (PERCENTAGE) OF VARIOUS GASES			
	Atmospheric Air	Humidified Air	Alveolar Air	Expired Air
N_2	597 (78.62%)	563.4 (74.09%)	569 (74.9%)	566 (74.5%)
O_2	159 (20.84%)	149.3 (19.67%)	104 (13.6%)	120 (15.7%)
CO_2	0.3 (0.04%)	0.3 (0.04%)	40 (5.3%)	27 (3.6%)
H_2O	3.7 (0.5%)	47 (6.20%)	47 (6.2%)	47 (6.2%)
Total	760 100%	760 100%	760 100%	760 100%

- ***Middle portion*** of the expired air is a mixture of more and more alveolar air with the dead space air until the dead space air is washed out.
- ***Last portion*** of the expired air represents the alveolar air and so is used to study the alveolar air composition (*alveolar air sampling*).

DIFFUSION OF GASES THROUGH RESPIRATORY MEMBRANE

Respiratory Unit and Respiratory Membrane

Each Respiratory Unit is composed of a respiratory bronchiole, alveolar ducts, atria and alveoli. There are about 300 million respiratory units in the two lungs. Gas exchange occurs through the membranes of all the structures forming a respiratory unit, not merely in the alveoli themselves.

Respiratory Membrane or pulmonary membrane or the alveolocapillary membrane is the name given to the tissues which separate the capillary blood from the alveolar air. The exchange of gases between the capillary blood and alveolar air requires diffusion through this membrane.

Structure of respiratory membrane: It consists of the following layers (Fig. 5.4-4):

- Layer of pulmonary surfactant and fluid lining the alveolus (I)
- Layer of alveolar epithelial cells (II)
- Basal lamina of the alveolar epithelial cells (III)
- A very thin interstitial space (IV) between the epithelial and endothelial cells
- Basement membrane of capillary endothelial cells (V)
- Layer of capillary endothelial cells (VI)
- Plasma (VII)
- Membrane of red blood cells (VIII)

Characteristic Features of respiratory membrane which optimize for the gas exchange are as follows:

- *Thickness* of the respiratory membrane, despite the large number of layers forming it, averages about 0.6 μm.
- *Surface area* of the total respiratory membrane is about 70 m^2 in a normal adult.

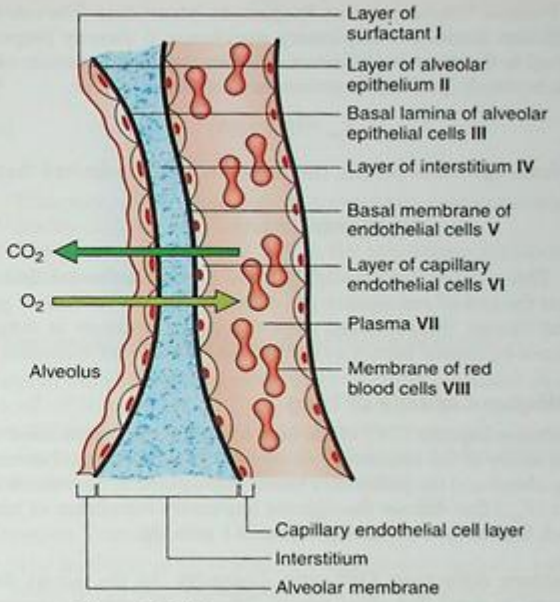


Figure 5.4-4 Layers of respiratory membrane.

Factors Affecting Diffusion across Respiratory Membrane

The diffusion of gases across the respiratory membrane is affected by the following factors:

1. Thickness of Respiratory Membrane The rate of diffusion through the membrane is inversely proportional to the membrane thickness (diffusion distance, denoted by d), i.e.

$$V_{gas}(\text{volume of gas diffused}) \propto \frac{1}{d} \qquad \text{(i)}$$

Any factor which increases the thickness will therefore significantly decrease the gaseous exchange. Examples include the following:

- Pulmonary oedema, i.e. a collection of fluid in the interstitial space and alveoli
- Pulmonary fibrosis occurring in certain lung diseases, increasing the thickness of the respiratory membrane

2. Surface Area of Respiratory Membrane Normally, the total surface area of the respiratory membrane is about 70 m^2. Rate of diffusion is directly proportional to the surface area (A), i.e. with the decrease in total surface area, the rate of diffusion of gases decreases, i.e.

$$V_{gas} \propto A \qquad \text{(ii)}$$

3. Diffusion Coefficient The rate of diffusion is directly proportional to the diffusion coefficient (D) of the gas, i.e.

$$V_{gas} \propto D \qquad \text{(iii)}$$

- The diffusion coefficient of CO_2 is about 20 times that of O_2 through water (and therefore through the fluid of respiratory membrane). Therefore, CO_2 diffuses much more easily through the respiratory membrane.

4. Pressure Gradient Across Respiratory Membrane The rate of diffusion across the respiratory membrane is directly proportional to the pressure difference between the partial pressure of a gas in alveoli (pA) and in pulmonary capillary (pC), i.e.

$$V_{gas} \propto (pC - pA) \quad \text{(iv)}$$

From equations (i), (ii), (iii) and (iv), it can be derived that

$$V_{gas} = (pC - pA)\ \frac{D.A.}{d} \quad \text{(v)}$$

This is called *Fick's law of diffusion*. Thus, it can be concluded that the rate of pulmonary gas diffusion, i.e. the volume of gas that crosses the respiratory membrane per minute is determined by several factors as defined by Fick's law of diffusion.

Diffusion Capacity of Lung

Diffusion capacity (DL) of the lung is a quantitative expression of the ability of the respiratory membrane to exchange gas between the alveoli and the pulmonary blood. It is defined as the volume of gas (V_{gas}) that diffuses through the respiratory membrane of lung each minute for a pressure gradient of 1 mm Hg.

Factors Affecting Diffusion Capacity All the factors discussed in detail that affect rate of diffusion through the respiratory membrane (see page 191) will obviously affect the diffusing capacity of lung.

Diffusion Capacity of Lung for Different Gases Depending on the above factors, the diffusion of lungs is bound to be different for different gases. Diffusion capacity of the lungs for common gases is discussed below.

Diffusion Capacity of Lungs for O_2

- ***At rest***, the diffusing capacity of lungs for O_2 is about 20–25 mL/min/mm Hg. As the mean oxygen pressure gradient across the respiratory membrane is about 11 mm Hg, so at rest about 250 mL of O_2 diffuses through the lungs per minute.
- ***During exercise***, the diffusing capacity of lungs for O_2 is increased. It may reach up to 65 mL/min/mm Hg during strenuous exercise (three times of diffusing capacity for O_2 at rest). It occurs due to the following:
  - *Increase in surface area* of respiratory membrane caused by opening up of closed pulmonary capillaries and dilation of open capillaries
  - *Improvement in ventilation–perfusion* ratio

Diffusion Capacity of Lungs for CO_2

- *At rest*, the diffusing capacity of lungs for CO_2 is about 20 times that for O_2, i.e. about 400–500 mL/min/mm Hg.
- *During strenuous exercise*, the diffusing capacity for CO_2 is increased to 1200–1300 mL/min/mm Hg.

Clinical significance of higher diffusion capacity of CO_2: When the diffusing capacity of respiratory membrane is markedly decreased due to certain diseases, one expects retention of CO_2 and lack of O_2. However, due to a vast difference in the diffusing capacities for O_2 and CO_2, a serious impairment of diffusion of O_2 causes a significant lack of O_2 with little signs of CO_2 retention.

SELF-ASSESSMENT

1. Describe briefly:
   - Alveolar ventilation–perfusion ratio
   - Physiological significance of alveolar ventilation
   - Factors affecting diffusion across alveolar membrane
2. Differentiate between:
   - Alveolar air and expired air
   - Partial pressure and gas pressure
   - Anatomical and physiological dead space

5.5 Transport of Gases

CHAPTER OUTLINE

Transport of Oxygen
Uptake of Oxygen by Pulmonary Blood
Transport of Oxygen in Arterial Blood
Oxygen Transport in Dissolved Form
Oxygen Transport in Combination with Haemoglobin
Oxygenation of Haemoglobin
Oxygen Carrying Capacity of Haemoglobin
Oxygen–Haemoglobin Dissociation Curve
Shifts in O_2–Hb Dissociation Curve
Concept of p_{50} and its Significance
O_2–Hb Dissociation Curve of Fetal Haemoglobin
Effect of Carbon Monoxide on O_2 Transport
Oxygen Dissociation Curve for Myoglobin
Release of Oxygen in Tissues

Transport of Carbon Dioxide
Diffusion of CO_2 in the Blood
Transport of CO_2 in the Blood
In Dissolved Form
In Bicarbonate Form
In Carbamino Form
Carbon Dioxide Dissociation Curve
Release of CO_2 in the Lungs
Other Facts about CO_2 Transport
Rate of Total CO_2 Transport
Changes in Blood pH During Transport of CO_2
Respiratory Quotient

TRANSPORT OF OXYGEN

Transport of oxygen from the lungs to the tissues occurs due to constant *circulation of blood* and *diffusion* of O_2 that occurs in the direction of concentration gradient, which is represented by O_2 tension (pO_2) differences given below:

- Alveolar air pO_2: 104 mm Hg
- Arterial blood pO_2: 95 mm Hg
- Venous blood pO_2: 40 mm Hg
- Tissue interstitial fluid pO_2: 40 mm Hg

Transport of oxygen from the lungs to the tissues can be described as follows:

A. Uptake of oxygen in the lungs by pulmonary blood
B. Transport of oxygen in arterial blood
C. Release (diffusion) of oxygen from blood to the interstitial fluid in tissues

Uptake of Oxygen by Pulmonary Blood

- As mentioned above, pO_2 of pulmonary arterial blood is about 40 mm Hg and that of alveolar air is 104 mm Hg. Therefore, due to this high concentration gradient, oxygen readily diffuses from the alveoli into the blood.
- The process of diffusion across the respiratory membrane has been described in Chapter 5.4.

Transport of Oxygen in Arterial Blood

Arterial blood contains about 20 mL and venous blood about 15 mL of O_2 per 100 mL. Thus, about 5 mL of O_2 is transported per 100 mL of blood from the lungs to the tissue cells.

Oxygen is transported in the blood in two forms: dissolved form and in combination with haemoglobin.

Oxygen Transport in Dissolved Form

- The solubility of O_2 in water (plasma) is so little that at a pO_2 value of 100 mm Hg, out of the 20 mL of O_2 present in 100 mL of blood, only 0.3 mL is in dissolved form and the rest is in combination with haemoglobin (as oxyhaemoglobin).
- The dissolved oxygen obeys Henry's law, i.e. the amount dissolved is proportional to pO_2. Thus, there is no limit to the amount of O_2 that can be carried in dissolved form, provided the pO_2 is sufficiently high. This is a distinct advantage over O_2 transport as oxyhaemoglobin, which cannot exceed a certain limit.
- Therefore, dissolved O_2 at high pO_2 (hyperbaric oxygen) is utilized in clinical practice for the oxygenation of tissues when the haemoglobin gets denatured in certain types of poisoning, e.g. carbon monoxide poisoning.

Oxygen Transport in Combination with Haemoglobin

Oxygenation of Haemoglobin After entering the blood from the alveolar air, most of the oxygen combines with haemoglobin to form a *loose and reversible* combination. This process is called *oxygenation* (not oxidation) and converts deoxyhaemoglobin into oxyhaemoglobin. The reaction is very rapid requiring <0.01 second. The *driving force* for this reaction is O_2 tension in the pulmonary capillaries.

One molecule of oxygen combines with one iron ion of the haem molecule. The O_2 molecule occupies the sixth *coordination* position of the iron atom. Haemoglobin contains four molecules of haem, so each molecule of haemoglobin can combine with as many *as four* O_2 molecules. The reaction proceeds in the following four steps:

$$Hb_4 + O_2 \rightarrow Hb_4O_2$$
$$Hb_4O_2 + O_2 \rightarrow Hb_4O_4$$
$$Hb_4O_4 + O_2 \rightarrow Hb_4O_6$$
$$Hb_4O_6 + O_2 \rightarrow Hb_4O_8$$

After the first step, the affinity of haemoglobin for O_2 increases with each next step. This happens so because the insertion of an O_2 molecule ruptures all the salt links and changes the quaternary structure of haemoglobin from the

tense or *T-state* to relaxed or *R-state*, which favours O_2 binding. This is the reason for the sigmoid nature of oxygen haemoglobin association or dissociation curve.

Oxygen-Carrying Capacity of Haemoglobin One gram of haemoglobin can bind with a maximum of 1.34 mL of O_2. Thus, 100 mL of blood with a haemoglobin level of 15 g/dL can carry 1.34×15 or 20.1 mL of oxygen. However, due to the presence of various physiological shunts (venous admixture), only 95% of the haemoglobin is available for carrying the oxygen. Therefore, practically 100 mL of the arterial blood carries about 19.8 mL of oxygen, out of which about 19.5 mL is present as oxyhaemoglobin and 0.3 mL is present as dissolved form in the plasma.

Thus, under normal circumstances, the haemoglobin carries most of the bulk of oxygen present in the blood. The only *disadvantage* is that the amount of oxygen that can be carried by the haemoglobin depends on the concentration of haemoglobin in the blood.

Haemoglobin saturation is the percentage of haemoglobin that is combined with oxygen. When all the four sites on haemoglobin are occupied by O_2, then that molecule of haemoglobin is 100% saturated. The *percentage saturation* is the average saturation of the all haemoglobin molecules in the blood and is calculated as follows:

$$\% \text{ Saturation} = \frac{O_2 \text{ content of blood/100 mL}}{O_2 \text{ carrying capacity of blood}} \times 100$$

Oxygen–Haemoglobin Dissociation Curve

Oxygen–Haemoglobin Dissociation Curve refers to the curve obtained when the relation between the pO_2 and the percentage of haemoglobin saturation is plotted (Fig. 5.5-1). The O_2–Hb dissociation curve shows that the percentage saturation of haemoglobin increases with increase in pO_2 of the arterial blood. However, the relation is not linear but *sigmoid or S-shaped* (because of the reason explained above), but it has several physiological advantages (vide infra).

Two distinct zones of the O_2–Hb dissociation curve are recognized.

Loading (Association) Zone refers to the upper flat part (plateau) of the curve, which is related to the process of O_2 *uptake in the lungs*. The curve shows that at pO_2 values of 100 mm Hg or above the haemoglobin is 100% saturated. More important to note is the fact that even if pO_2 falls to 60 mm Hg, the Hb saturation is still 90%. Thus, the loading zone provides a *margin of safety* because it ensures a fairly high uptake of O_2 by pulmonary blood even when alveolar pO_2 is moderately decreased in situations such as those given below:

- Climbing mountains to moderate altitude
- Pulmonary diseases

Unloading (Dissociation) Zone of the O_2–Hb dissociation curve refers to the *steep portion* of the curve that occurs at pO_2 below 60 mm Hg. The steep part of the curve is concerned with O_2 delivery in the tissues and shows that large amounts of oxygen can be liberated from the blood with a relatively minor fall of O_2 tension. This property keeps the O_2 tension in the capillary blood relatively high so that the diffusion gradient for O_2 is maintained. At a pO_2 value of 40 mm Hg, Hb is 75% saturated with O_2 (Fig. 5.5-1). Thus, each 100 mL of blood can hold only 15 mL of O_2 as compared to 20 mL at pO_2 of 100 mm Hg (Fig. 5.5-2). Thus, 5 mL of O_2 is extracted by the tissues at rest. At values of pO_2 lower than 40 mm Hg, still a larger volume of O_2 would be offloaded and become available to the tissue (e.g. during exercise). The greater release of O_2 with a slight decrease in tissue pO_2 (due to increased O_2 consumption) minimizes decrease of tissue pO_2 that would otherwise take place. Thus, it will regulate tissue pO_2 (buffering effect).

Physiological Advantages of S-shaped O_2–Hb Dissociation Curve, which can be summarized from the above discussion, are as follows:

- It allows a higher uptake of O_2 at lungs despite a high variation in the alveolar air pO_2.
- Tissues are supplied with O_2 according to their needs.
- Haemoglobin acts as a buffer and maintains tissue pO_2 at about 40 mm Hg.

Shifts in O_2–Hb Dissociation Curve Several factors affect the affinity of haemoglobin for O_2 and thus shift the O_2–Hb dissociation curve to either right or left.

Shift to Right Shift to right of the O_2–Hb dissociation curve signifies decreased affinity of haemoglobin for O_2 (Fig. 5.5-3).

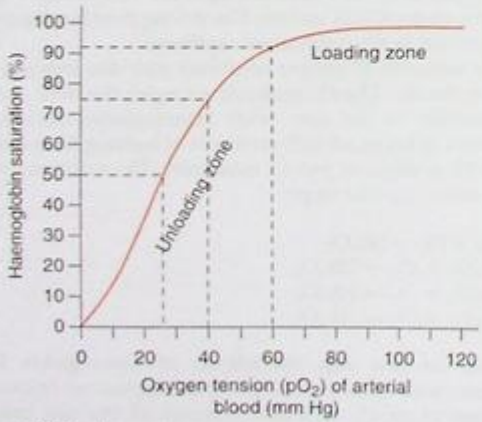


Figure 5.5-1 Normal oxygen–haemoglobin dissociation curve.

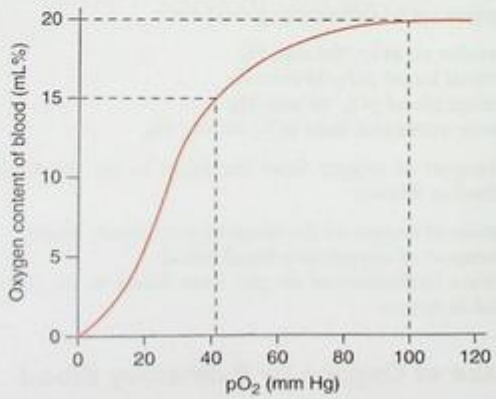


Figure 5.5-2 The relationship between pO_2 and oxygen contents of the blood.

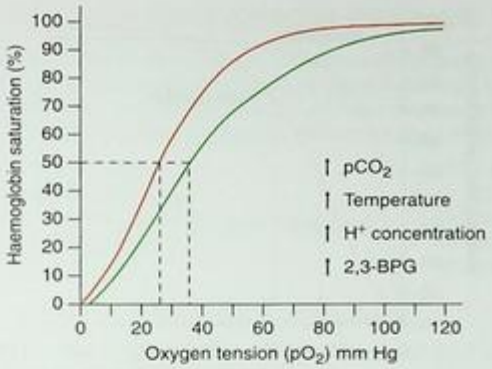


Figure 5.5-3 Right shift of oxygen–haemoglobin dissociation curve, which occurs due to increase in pCO_2, H^+ concentration, temperature and 2,3-BPG. Note: p_{50} is increased.

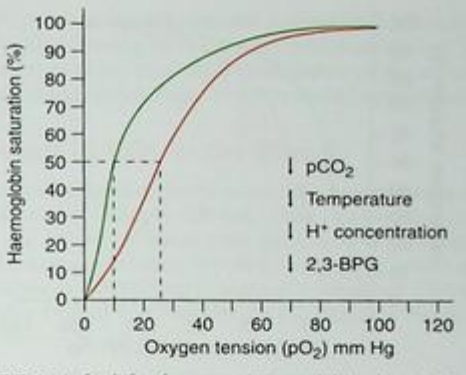


Figure 5.5-4 Left shift of oxygen–haemoglobin dissociation curve, which occurs due to decrease in pCO_2, H^+ concentration, temperature and 2,3-BPG. Note: p_{50} is decreased.

Thus, at every level of pO_2, the oxygen saturation of haemoglobin is somewhat lower than the normal curve, leading to more offloading of O_2.

Causes The factors causing the shift to right are as follows:

- ***An increase in pCO_2*** shifts the curve to the right; this phenomenon is known as *Bohr's effect* (Fig. 5.5-3). When the arterial blood reaches the tissues, it is exposed to not only low tissue pO_2 (40 mm Hg) but also higher pCO_2 (45 mm Hg). So, normally in tissues the curve shifts to the right, and due to Bohr's effect, for a given decrease in pO_2, a larger volume of O_2 is shed off (about 2% more).
- ***A decrease in pH of blood,*** as occurs in the tissues, also shifts the O_2–Hb dissociation curve to the right.
- ***Effect of temperature:*** An increase in the temperature of blood shifts the curve to right. During exercise, the demand of O_2 is increased in skeletal muscles. The factors which facilitate the delivery of the required larger amounts of O_2 (by causing right shift in the curve) are as follows:
  - Increased temperature in skeletal muscles due to more heat production
  - Increased pCO_2 due to accumulation of CO_2 resulting from rapid metabolism
  - Decreased pO_2 due to rapid consumption
  - Decreased pH due to accumulation of lactic acid produced in muscular exercise
- ***Effect of biphosphoglycerate:*** The red blood cells (RBCs) are rich in 2,3-biphosphoglycerate (2,3-BPG), which is formed from 3-phosphoglyceraldehyde produced during glycolysis via the *Embden–Meyerhof pathway*. The 2,3-BPG is a highly charged anion that binds to the β-chain of deoxygenated adult haemoglobin.

$$HbO_2 + 2,3\text{-BPG} \rightarrow Hb\ 2,3\text{-BPG} + O_2$$

Thus, an increase in the concentration of 2,3-BPG decreases the affinity of Hb for O_2 and shifts the normal O_2–Hb dissociation curve to the right. Causes of increased levels of 2,3-BPG are anaemia, exposure to chronic hypoxia at high altitude and certain pulmonary diseases.

Advantages versus disadvantages of right shift

- Right shift is advantageous in the tissues where more O_2 is released from the haemoglobin (at the same pO_2).
- However, right shift is disadvantageous in the lungs because (at the same pO_2) blood takes up less oxygen.

Shift to Left Shift to left of the O_2–Hb dissociation curve signifies increased affinity of haemoglobin for O_2 (Fig. 5.5-4). Thus, at every pO_2 level, the oxygen saturation of haemoglobin is somewhat greater than the normal curve.

Causes for the left shift of the curve are as follows:

- Decreased pCO_2 of blood
- Increased pH of blood
- Decreased temperature
- Fetal haemoglobin

Advantages versus disadvantages of left shift: Left shift of the curve has a limited advantage because though it allows a higher uptake of O_2 at lungs (at the same pO_2), it decreases release of O_2 to the tissues (at the same pO_2).

Concept of p_{50} and Its Significance

p_{50} refers to the partial pressure of O_2 that produces a 50% saturation of the haemoglobin with O_2. Normal p_{50} for the arterial blood in an adult at 37°C body temperature and at pCO_2 of blood 40 mm Hg is 25–27 mm Hg (Fig. 5.5-1).

Haemoglobin affinity for O_2 is inversely related to the p_{50} value; therefore, we have the following:

- *Decreased p_{50}* (Hb gets 50% saturated at lower pO_2) indicates increased affinity of haemoglobin for O_2. Thus, decreased p_{50} is equivalent to the shift of HbO_2 dissociation curve to the left (Fig. 5.5-4). Fetal haemoglobin and myoglobin have a lower p_{50} value than the adult haemoglobin.
- *Increased p_{50}* (Hb gets 50% saturated at higher pO_2) indicates decreased affinity of haemoglobin for O_2. Thus, increased p_{50} is equivalent to the right shift of the O_2–Hb dissociation curve (Fig. 5.5-3).

O_2–Hb Dissociation Curve of Fetal Haemoglobin

- As shown in Fig. 5.5-5, the O_2–Hb dissociation curve of fetal haemoglobin (HbF) is shifted to the left in comparison with the O_2–Hb dissociation curve of adult haemoglobin (HbA).
- The O_2–Hb dissociation curve of HbF is shifted to left because its affinity for 2,3-BPG is considerably less than that of HbA. This is because two gamma (γ) chains present in HbF

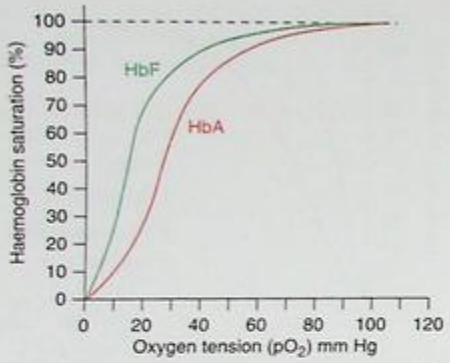


Figure 5.5-5 Oxygen–haemoglobin dissociation curves of adult haemoglobin (HbA) and fetal haemoglobin (HbF).

have very little affinity for 2,3-BPG as compared to the beta (β) chains of HbA.

- Thus, affinity of HbF to combine with O_2 is more than that of HbA. This property of HbF helps it to take up normal volumes of O_2 in spite of the fact that the fetal blood is exposed to rather low pO_2 values of the maternal blood in placenta. As shown in Fig. 5.5-5, at a pO_2 of 20 mm Hg, where HbA is only 35% saturated, the HbF is 70% saturated, due to which HbF can store more O_2.

Effect of Carbon Monoxide on O_2 Transport

- Carbon monoxide (CO) interferes with O_2 transport because it has about 200 times the affinity (of oxygen) for haemoglobin.
- CO combines with Hb at the same site on its molecule as O_2 and forms the *carboxyhaemoglobin*, and thus decreases the functional haemoglobin concentration.
- Because of the extreme affinity of CO for haemoglobin, the carboxyhaemoglobin curve lies along the Y-axis and p_{50} for CO is only 0.5 mm Hg (Fig. 5.5-6).
- CO lowers the tissue O_2 tension by decreasing the O_2 content and the p_{50} for O_2.

Oxygen Dissociation Curve for Myoglobin Myoglobin is present in higher quantities in the muscles specialized for

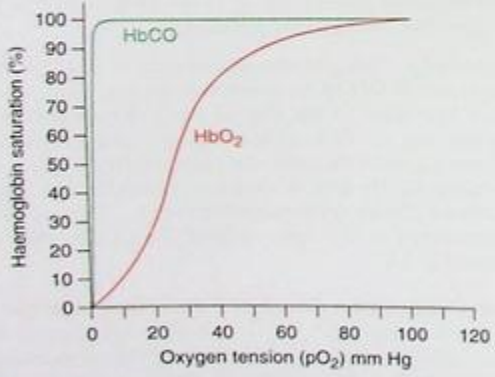


Figure 5.5-6 Haemoglobin saturation curves for both O_2 (HbO_2) and carbon monoxide (HbCO). Note that the HbCO curve lies along the Y-axis, which indicates extreme high affinity of haemoglobin for carbon monoxide. Note: The p_{50} for CO is only 0.5 mm Hg.

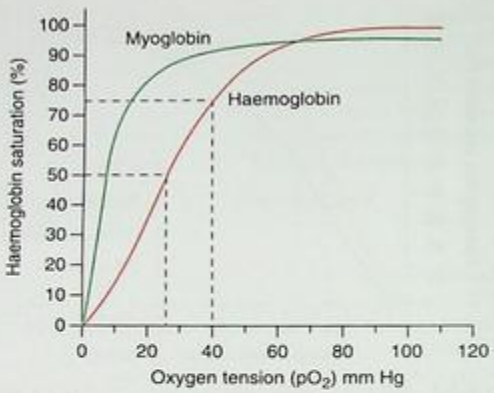


Figure 5.5-7 Oxygen dissociation curve of myoglobin versus haemoglobin.

sustained contraction, e.g. muscles of legs and heart. The characteristic features of the O_2 dissociation curve of myoglobin vis-á-vis haemoglobin are (Fig. 5.5-7) as follows:

- Dissociation curve of myoglobin is a *rectangular hyperbola* rather than sigmoid in shape because it takes up O_2 at low pressure much readily, i.e. the rate of association of myoglobin with O_2 is very fast.
- Myoglobin does not show Bohr's effect.
- At a pO_2 of 40 mm Hg, the myoglobin is 95% saturated, whereas haemoglobin is 75% saturated. Even at a pO_2 of 5 mm Hg, myoglobin is saturated by slightly less than 60%. Thus, it acts as a temporary storehouse for O_2 in the muscles.

Release of Oxygen in Tissues

Oxygen Release at Rest

Oxygen Delivery represents the amount of O_2 that is presented to body cells per minute, and is equal to the arterial O_2 content multiplied by a cardiac output. 100 mL of arterial blood at pO_2 of about 100 mm Hg contains about 20 mL of oxygen; thus, with a cardiac output of about 5 L/min, the normal oxygen delivery to the entire body is about 1 L/min. The oxygen delivery to the tissues decreases with either decrease in the arterial O_2 content or decrease in the cardiac output.

Oxygen Consumption When the arterial blood with an approximate pO_2 of 100 mm Hg reaches the tissues with tissue fluid pO_2 of 40 mm Hg because of pressure gradient, about 5 mL of O_2 diffuses from the tissue capillaries to the interstitial fluid out of 100 mL of blood (containing ~ 19 mL O_2) every minute. Thus, oxygen consumption of the whole body at rest with a cardiac output of 5 L/min $= \frac{5 \times 5000}{100}$ or 250 mL of O_2 per minute.

Utilization Coefficient Utilization coefficient refers to the percentage of oxygen consumed out of oxygen delivered to the tissue, i.e.

$$\text{Coefficient of utilization} = \frac{\text{Oxygen consumed/min}}{\text{Oxygen delivered/min}} \times 100$$

$$\text{So, at rest coefficient of utilization of whole body} = \frac{250 \text{ mL/min}}{1000 \text{ mL/min}} \times 100$$

$$= 25\%$$

TRANSPORT OF CARBON DIOXIDE

Transport of carbon dioxide from the tissue cells to the lungs occurs due to *constant circulation* of blood and diffusion of CO_2 that occurs at various sites in the direction of concentration gradient, which is represented by CO_2 tension differences given as follows:

- Intracellular pCO_2 : 46 mm Hg
- Interstitial fluid pCO_2 : 45 mm Hg
- Arterial blood pCO_2 (in tissue capillaries) : 40 mm Hg
- Venous blood pCO_2 : 45 mm Hg
- Alveolar air pCO_2 : 40 mm Hg

From the above pCO_2 levels, it is clear that:

- CO_2 from the cells diffuses into the interstitial fluid along a tension gradient of 1 mm Hg.
- From the interstitial fluid, the CO_2 diffuses into the capillaries at a tension gradient of 5 mm Hg.
- From the venous blood that is supplied to the pulmonary capillaries, the CO_2 diffuses across the respiratory membrane into the alveoli along a tension gradient of 5 mm Hg.

Transport of carbon dioxide from the tissue cells to the lungs can be described as follows:

A. Diffusion of CO_2 in the blood
B. Transport of CO_2 in the blood
C. Release of CO_2 in the lungs

Diffusion of CO_2 in the Blood

Tissue cells constantly form CO_2 inside the cells due to metabolism. As mentioned above, intracellular pCO_2 is 46 mm Hg and that of interstitial fluid surrounding the cells is 45 mm Hg. Although the cells are continuously forming CO_2, the CO_2 tension gradient between the inside and outside of the cells is still only 1 mm Hg. This is owing to the rapid diffusion of CO_2 (20 times that of O_2) out of the cells into the interstitial fluid. pCO_2 of the arterial blood flowing in the tissue capillaries is lower (40 mm Hg) than that of the interstitial fluid, so CO_2 diffuses inside the capillary blood, which flows in the systemic venous system.

Transport of CO_2 in the Blood

Venous blood contains about 52 mL and the arterial blood contains about 48 mL of CO_2 per 100 mL. Thus, 4 mL of CO_2 is transported per 100 mL of blood from tissue cells to the lungs. Thus, total CO_2 transported from the whole body tissue cells at rest with a cardiac output of 5 L/min is about $4 \times 5000/1$ or 2 dL/min.

Carbon dioxide is transported in the blood in the following three forms (Fig. 5.5-8):

- In dissolved state (7%)
- In bicarbonate form (70%)
- In carbamino compound form (23%)

Carbon Dioxide Transport in Dissolved Form

- The venous blood with pCO_2 of 45 mm Hg contains about 2.7 mL/dL of CO_2 in dissolved state.
- The arterial blood with pCO_2 of 40 mm Hg contains about 2.4 mL/dL of CO_2 in dissolved state.
- Thus, only 0.3 mL of CO_2 is transported in a dissolved state per dL of blood from tissues to the lungs. This represents about 7% of all CO_2 that is transported.

Carbon Dioxide Transport in Bicarbonate Form

Approximately 70% of the carbon dioxide is transported in the form of *plasma bicarbonate ions.* However, these bicarbonate ions are formed in the RBCs and then diffuse into the plasma as explained below:

- After entering the blood, most of the CO_2 enters the RBCs, whereas in the presence of *carbonic anhydrase*, it rapidly reacts with water to form carbonic acid (H_2CO_3).

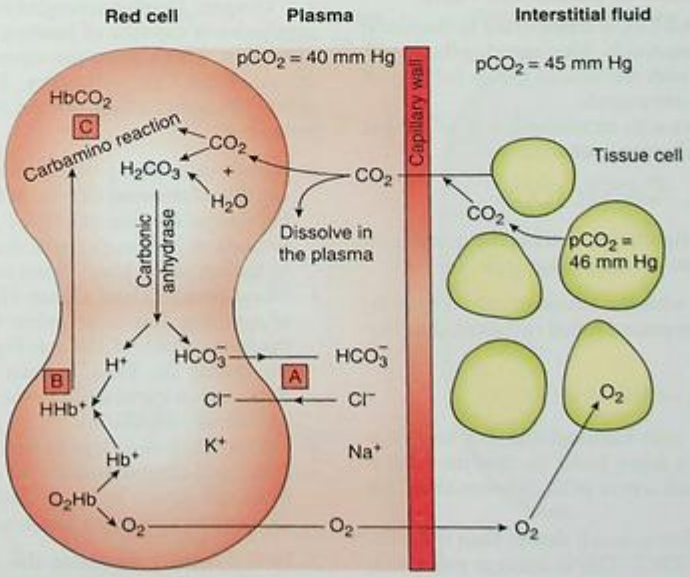


Figure 5.5-8 (A) Transport of carbon dioxide (CO_2) in blood demonstrating formation of HCO_3^- and chloride shift phenomenon; (B) H^+ buffering by haemoglobin; and (C) formation of carbaminohaemoglobin.

- Carbonic acid (H_2CO_3) dissociates into bicarbonate ions (HCO_3^-) and hydrogen ions (H^+).
- *The bicarbonate ions diffuse* out of the RBCs into plasma and are transported as sodium bicarbonate (alkali reserve of blood). Thus, although HCO_3^- is formed within the RBCs, most of the CO_2 is carried in the plasma as HCO_3^- and some in the RBCs as well.
- *The H^+ ions are buffered* by deoxygenated haemoglobin, which is a weaker acid than oxyhaemoglobin. This enables the reaction to proceed unabated in the forward direction.
- *Chloride shift* (Hamburger phenomenon): As the HCO_3^- diffuses out of the RBCs into the plasma, the inside of the cells becomes less negatively charged. Because the RBC membrane is relatively impermeable to cations, so in order to neutralize this effect negatively charged chloride ions (Cl^-) diffuse from the plasma into the RBCs to replace the HCO_3^-. The movement of chloride ions into the RBCs is called *chloride shift* or the Hamburger phenomenon. This process is mediated by Band 3, a major ion exchange membrane protein. The chloride shift occurs very rapidly and essentially completed within 1 second.
- As a result of chloride shift, the total number of ions inside the RBCs increases, so the osmotic pressure inside the RBCs becomes higher than that of plasma. This causes osmotic absorption of fluid into the RBCs. Thus, venous RBCs contain a higher quantity of fluid as compared to the arterial blood RBCs.

IMPORTANT NOTES

- Packed cell volume (PCV) of venous blood is slightly higher (~3%) than that of arterial blood.
- Venous RBCs are more fragile than the arterial RBCs.

Transport of Carbon Dioxide in Carbamino Form

Approximately 23% of the total CO_2 is transported in the blood in the form of carbamino compounds. After entering the blood, some of the CO_2 combines with the amino group ($-NH_2$) of proteins to form carbamino compounds.

In the Plasma, CO_2 combines with an amino group of plasma proteins ($PrNH_2$) to form carbamino proteins:

$$CO_2 + PrNH_2 \rightarrow Pr.NH.COOH$$

- This reaction is much less significant because the quantity of these proteins is one-fourth of that of haemoglobin.

In the RBCs, CO_2 combines with the amino group of haemoglobin ($HbNH_2$) to form a compound called carbaminohaemoglobin.

$$CO_2 + HbNH_2 \rightarrow Hb.NH.COOH$$

- This combination of CO_2 with haemoglobin is a reversible reaction that occurs with a loose bond so that the CO_2 is easily released into the alveoli where pCO_2 is lower than that in the tissue capillaries.
- This reaction of CO_2 with Hb is much slower than the reaction of CO_2 with water in RBCs. This is because more CO_2 (70%) is transported as bicarbonates and less as carbamino compounds (23%).

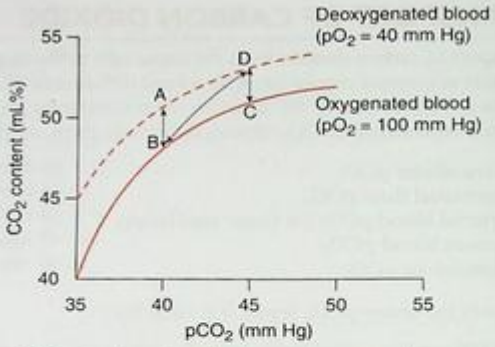


Figure 5.5-9 Carbon dioxide dissociation curve for oxygenated (solid line) and for deoxygenated blood (dotted line) to demonstrate Haldane's effect.

- This reaction of CO_2 with Hb is further decreased to a great extent when the concentration of 2,3-BPG is more because both 2,3-BPG and CO_2 compete for the same sites on Hb.

Carbon Dioxide Dissociation Curve

- Carbon dioxide dissociation curve is obtained by plotting the relationship between pCO_2 and total CO_2 content of the blood (Fig. 5.5-9).
- The graph shows that the relationship between the two is nearly linear over a wider range of pCO_2 (if compared with the O_2–Hb dissociation curve, which is sigmoid shaped).
- It is important to note that, practically, in the body the pCO_2 value of arterial and venous blood varies within a narrow range of 40–45 mm Hg (in contrast, the corresponding values of pO_2 vary from 100 to 40 mm Hg). Physiologically, the curve operates only within the A–V range (Fig. 5.5-9).

Factors Affecting CO_2 Dissociation Curve

1. Oxygen Deoxyhaemoglobin present in the tissue capillaries is capable of loading more CO_2 than the oxyhaemoglobin. Also, the oxygenation of haemoglobin in the lungs increases the CO_2 unloading. This effect is called *Haldane's effect.* Haldane's effect on the transport of CO_2 depicts the following:

- Blood with pCO_2 of 40 mm Hg reaching the tissues is capable of drawing CO_2 from the tissues more at pO_2 40 mm Hg (point A) than at pO_2 of 100 mm Hg (point B). Thus, because of Haldane's effect, the CO_2 dissociation curve shifts to the left when blood flows to the tissues.
- Blood with pCO_2 of 45 mm Hg reaching the lungs is capable of retaining less or, in other words, releasing more CO_2 in the lungs at pO_2 of 100 mm Hg (point C) than at pO_2 40 mm Hg (point D). Thus, because of Haldane's effect, the CO_2 dissociation curve shifts to the right when blood flows in the pulmonary capillaries.
- Figure 5.5-9 also depicts that Haldane's effect is beneficial because it almost doubles the quantity of CO_2 to be carried from the tissues to lungs and also doubles the amount of CO_2 to be excreted by the lungs.

2. BPG 2,3-BPG decreases the formation of carbaminohaemoglobin because it competes with CO_2 for the same sites on Hb, especially in the case of reduced blood. Thus, 2,3-BPG shifts

the CO_2 dissociation curve to the right, meaning thereby that the CO_2-carrying capacity is decreased.
3. Increase in Body Temperature causes release of O_2 from blood, which causes left shift of the CO_2 dissociation curve, i.e. a larger amount of CO_2 can be taken of at given pCO_2.

Release of CO_2 in the Lungs

When the venous blood with pCO_2 of 45 mm Hg, CO_2 content of 52 mL/dL and pO_2 of 40 mm Hg reaches the pulmonary capillaries, it is separated from the alveolar air having pCO_2 40 mm Hg, CO_2 content of 48 mL/dL and pO_2 104 mm Hg by the respiratory membrane. The following changes occur, which lead to diffusion of 4 mL of CO_2 in 100 mL of blood/min in the alveoli (Fig. 5.5-10).

Release of CO_2 from Carbaminohaemoglobin into Plasma (Fig. 5.5-10A)

- O_2 diffuses into the capillary blood with a concentration gradient of 104–40 mm Hg or 64 mm Hg.
- The O_2 enters the RBCs and converts the deoxyhaemoglobin into oxyhaemoglobin, which has very low affinity for CO_2. Therefore, CO_2 is released from the carbaminohaemoglobin, which diffuses into the plasma.

Release of CO_2 from Bicarbonate into Plasma (Fig. 5.5-10B)

- The oxyhaemoglobin so formed is a strong acid. Increased acidity of the blood results in increased H^+ concentration. To neutralize it, the bicarbonate (HCO_3^-) ions diffuse into the RBCs, where H^+ and HCO_3^- react to form H_2CO_3 (carbonic acid), which dissociates to form H_2O and CO_2. This whole reaction occurs in the presence of enzyme carbonic anhydrase. CO_2 so released diffuses into the plasma.
- With the movement of HCO_3^- inside the RBCs, inside of the cell becomes more negative. To neutralize them, either the positively charged cations should move in or negatively charged anions should flow out of the cell. RBC membrane is relatively impermeable to cations, so the Cl^- anions return in the plasma from the RBC. This whole reaction catalysed by carbonic anhydrase inhibitor is called *reversal of chloride shift*.

Diffusion of CO_2 from Plasma to Alveoli The CO_2 dissolved in plasma plus that released from the carbaminohaemoglobin and bicarbonates collectively exerts pCO_2 of 45 mm Hg. The pCO_2 of alveolar air is 40 mm Hg, so because of pressure gradient CO_2 diffuses from the blood to the alveoli. Due to constant ventilation, CO_2 from alveoli is transported to atmosphere.

Other Facts about CO_2 Transport

Rate of Total CO_2 Transport

In Resting Conditions, each 100 mL of blood transports about 4 mL of CO_2 from the tissues to the lungs. Thus, with an average cardiac output of 5 L/min, a total of $(4 \times 5000)/100$ or 200 mL of CO_2 is transported/min.

During Exercise, the amount of CO_2 transported increases depending on the severity of exercise. In severe exercise, as much as 4 L of CO_2 may be transported per minute. Because of greater solubility and transport in different forms, the transport of such large amounts of CO_2 occurs without any difficulty. The conversion of most of CO_2 into bicarbonate ions prevents any significant change in the pH of blood even when such a large volume of CO_2 enters the circulation.

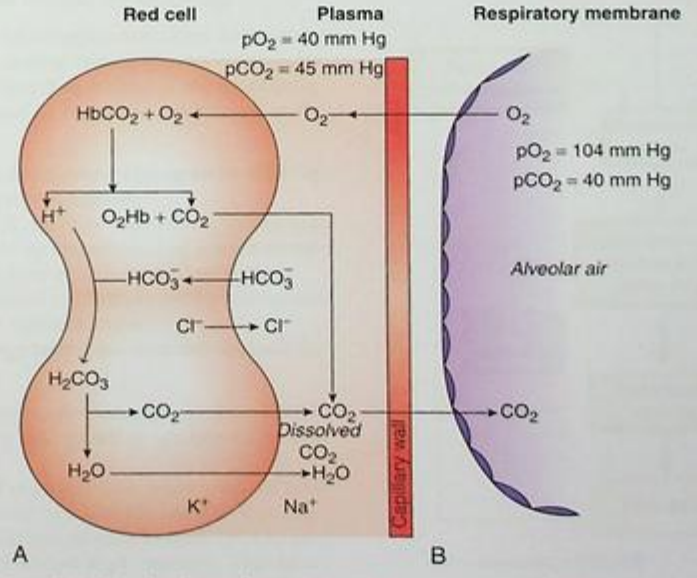


Figure 5.5-10 (A) Release of carbon dioxide in the plasma from carbaminohaemoglobin and from bicarbonate ions and (B) diffusion of CO_2 from the plasma into the alveoli through respiratory membrane.

Changes in Blood pH during Transport of CO_2

Normally, the pH of arterial blood is 7.4. As it passes through the tissues, it acquires CO_2 and the pH of blood falls due to formation of carbonic acid (H_2CO_3) in the venous blood. The pH may fall by about 0.4. However, during exercise, the fall in pH may become to the tune of 0.5 and even more. Nevertheless, most of it is neutralized by the blood buffers.

Respiratory Quotient

Definition Respiratory quotient (RQ) refers to the ratio of the rate of CO_2 excretion and rate of O_2 consumption per minute. It is also called the *respiratory exchange ratio.*

Normal Value Normally, the rate of CO_2 excretion is 4 mL/dL/min and rate of O_2 consumption is 5 mL/dL/min. So, RQ = 4/5 or 0.8.

SELF-ASSESSMENT

1. Describe briefly the transport of O_2 from lungs to tissue.
2. Describe briefly the transport of CO_2 from tissue to blood.
3. Write notes on:
   - Bohr's effect
   - Haldane effect
   - Hamburger phenomenon
   - Haemoglobin–oxygen dissociation curve
4. Explain the following:
   - Oxyhaemoglobin binds less H^+ than reduced.
   - p_{50} value of myoglobin is higher than haemoglobin A.
   - PCV of venous blood is more than that of arterial blood.

5.6 Regulation of Respiration

CHAPTER OUTLINE

Introduction

Neural Regulation of Respiration
Automatic Control System
Medullary Respiratory Centres
Dorsal Respiratory Group Neurons
Ventral Respiratory Group Neurons
Pontine Respiratory Centres
Apneustic Centre
Pneumotaxic Centre
Reticular Activating System

Afferent Impulses to Respiratory Centres
Afferent Impulses from Higher Centres
Voluntary Control System
Limbic Control System
Afferent Impulses from Nonchemical Receptors
Afferent Impulses from Pulmonary Stretch Receptors
Afferent Impulses from J-receptors
Afferent Impulses from Irritant Receptors
Afferent Impulses from Proprioceptors
Afferent Impulses from Chest Wall Stretch Receptors
Afferent Impulses from Baroreceptors
Afferent Impulses from Thermoreceptors

Chemical Regulation of Respiration
Chemoreceptors
Peripheral
Central
Effect of pO_2, pCO_2 and H^+ Concentration on Respiration
Effect of Hypoxia
Effect of Hypercapnia
Effect of Arterial pH
Interaction of pO_2, pCO_2 and pH in Regulation of Respiration
Some Other Aspects Related to Chemical Regulation
Effects of Hyperventilation
Effect of Sleep on Respiration

INTRODUCTION

Respiration is regulated by a complex integration of neural control mechanisms which are modified by certain respiratory reflexes and chemical control mechanisms.

Neural control mechanisms include the following:

- *A system for automatic control* of respiration as an involuntary function: The involuntary control system of respiration is located in the medullary and pontine centres of the brainstem.
- *A system for voluntary control* of respiration is located in the cerebral cortex.

Thus, respiration enjoys the distinction of being an involuntary function which can be influenced voluntarily.

Respiratory reflexes which modify the effects of neural mechanisms are those initiated by stimulation of stretch receptors, irritant receptors, J-receptors and chest wall receptors.

Chemical control mechanisms are influenced by alterations in arterial pO_2, pCO_2 and H^+ concentration.

Functions of respiratory regulatory mechanisms include the following:

- *Genesis of normal respiratory spontaneous rhythm*: This is the function of medullary and pontine centres of neural mechanism.
- *Control of rate and depth of respiration*, i.e. adjustment of total ventilation to match metabolic needs of the body so that arterial oxygen tension (pO_2), carbon dioxide tension (pCO_2) and H^+ concentration (pH) are almost kept constant. This function is accomplished by all the respiratory control mechanisms acting in unison (Fig. 5.6-1).

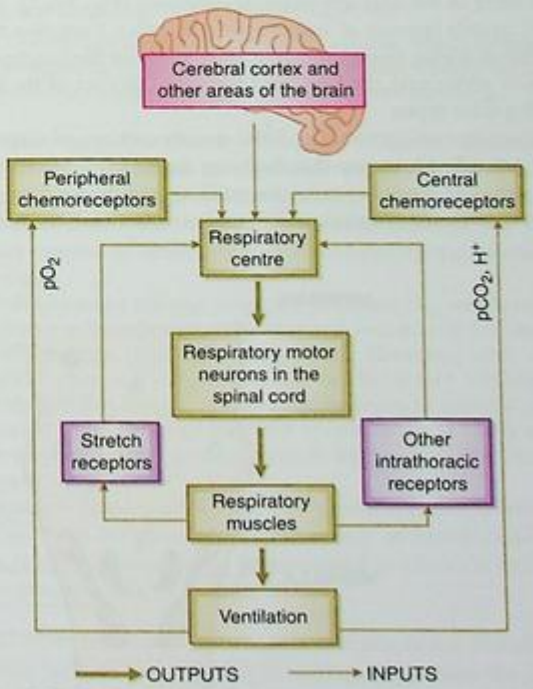


Figure 5.6-1 Diagrammatic representation of the inputs to the respiratory centre that generate the output to the respiratory muscles.

NEURAL REGULATION OF RESPIRATION

The neural mechanisms regulating respiration can be described under the following two headings:

- Automatic control system
- Afferent impulses to respiratory centres

Automatic Control System

Neural Genesis of Respiratory Rhythm

The involuntary neural control system regulates respiration by several groups of neurons situated bilaterally in medulla and pons, which include medullary respiratory centres, pontine respiratory centres and the reticular activating system (RAS).

The respiratory control pattern generator is responsible for automatic respiration, and is located in the medulla. A group of neurons called pacemaker cells from the pre-Botizinger complex (BOTC) are situated between nucleus ambiguus and lateral reticular nucleus. The rhythmic activity is initiated by these synaptically coupled neurons. These neurons discharge rhythmically and generate rhythmic motor activity in the phrenic nerve, hypoglossal nerve and intercostal nerves.

I. Medullary Respiratory Centres

The medullary respiratory centres include two groups of neurons: dorsal respiratory group (DRG) and ventral respiratory group (VRG) apparently projected to pre-BOTC.

1. *Dorsal Respiratory Group Neurons* Most of the neurons are located within the nucleus of tractus solitarius (NTS) and some in the adjacent reticular substance (Fig. 5.6-2). The DRG mainly consists of inspiratory cells called *I-neurons* that discharge during inspiration only. Depending on the functional activity performed, the I-neurons forming DRG are of the following three types:

(i) Inspiratory Neurons The DRG mainly consists of inspiratory cells called *I-neurons* that discharge during inspiration only. The axons of *I-neurons* cross the midline and descend on the contralateral side of spinal cord to make contact with the spinal motor neurons of the inspiratory muscles: the diaphragm (supplied by the phrenic nerve arising from C3–C5) and the external intercostal muscles (supplied by intercostal nerves). In other words, the I-neurons in the DRG are the upper motor neurons of respiratory muscles. These cells are thought to be responsible for generating basic respiratory rhythm activity.

(ii) Inspiratory Off-switch (IOS) Neurons Inspiratory off-switch neurons refer to a groups of neurons that are responsible for terminating the activity of I-neurons and causes turning off of excitation of muscles of inspiration (diaphragm and external intercostal muscles). These muscles therefore relax, allowing elastic recoil of the chest wall and the lungs to cause expiration. After expiration again there is signal for starting another cycle.

(iii) Integrator Neurons Integrator neurons are another type of DRG neurons. They subserve the following integrating functions:

- The integrator neurons when depolarize to a critical level lead to firing of the so-called *IOS* neurons, which are responsible for terminating the inspiratory ramp. The I-neurons trigger the IOS neurons indirectly through integrators and thereby bring about the termination of their own discharge. This forms the basic circuitry of the generation respiratory rhythm (Fig. 5.6-3). In this way, the cycle of inspiration/expiration goes on continuously to cause tidal respiration.
- The *integrator neurons receive both excitatory and inhibitory inputs* (Fig. 5.6-3) and thus integrate the activity of I-neurons and IOS neurons accordingly.
- *The excitatory inputs* to integrator neurons come from the following:
  - Cerebral cortex
  - Pneumotaxic centre (PNC)
  - Vagal afferents from stretch receptors
- *The inhibitory inputs* to integrator neurons come from the pontine inhibitory neurons, which form the so-called *apneustic centre* (APN).

2. *Ventral Respiratory Group Neurons* Ventral respiratory group neurons contain both inspiratory cells called I-neurons and expiratory cells called E-neurons (cf DRG, which contains only I-neurons). Their axons cross the midline and

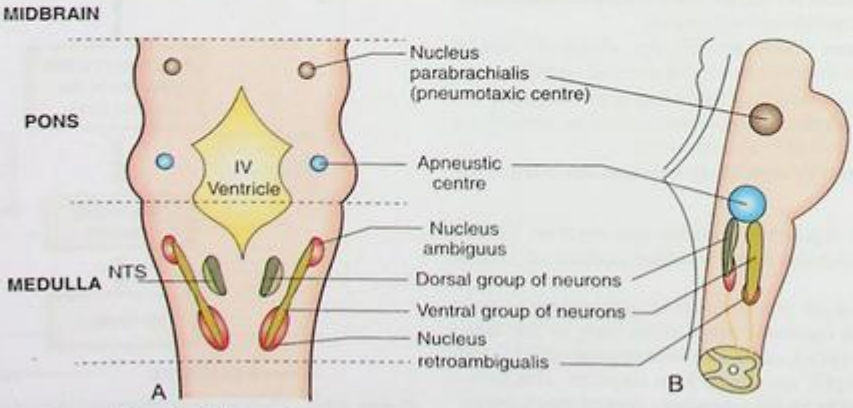


Figure 5.6-2 Medullary and pontine respiratory centres: (A) front view and (B) lateral view.

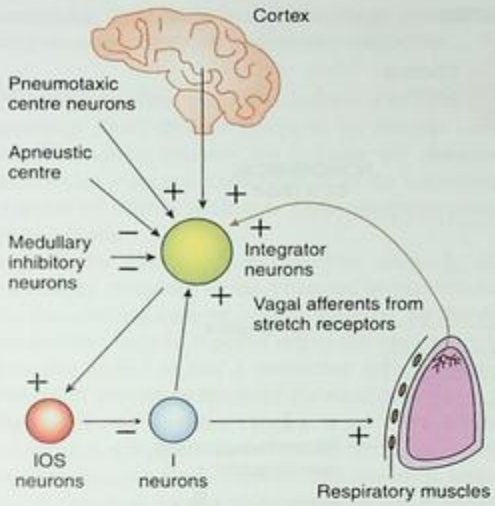


Figure 5.6-3 Basic circuitry for generation of respiratory rhythm.

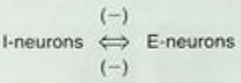


Figure 5.6-4 Reciprocal innervation of I- and E-neurons.

descend on the contralateral side to make contact with the motor neuron pool for the muscles of expiration, i.e. internal intercostal muscles and abdominal muscles.

Interaction of I- and E-Neurons The I- and E-neurons have inhibitory connections to each other, i.e. there exists *reciprocal innervation* between the two. Therefore, the motor neurons to the expiratory muscles are inhibited when those supplying the inspiratory muscles are active and vice versa (Fig. 5.6-4).

Role of VRG Neurons The VRG neurons normally remain totally inactive during quiet breathing. The VRG neurons become active during inspiration (role of I-neurons) as well as expiration (role of E-neurons) during forceful respiration, for example, during exercise.

II. Pontine Respiratory Centres

The pontine centres include APN and PNC, both of which modify the activity of medullary respiratory centres.

1. Apneustic Centre APN refers to a group of inhibitory neurons located bilaterally in the lower part of pons (Fig. 5.6-2). It sends signals to the integrator neurons of DRG that affect the IOS neurons and prevent the switch-off of the inspiratory ramp signals from the I-neurons (Fig. 5.6-3). This increases the tidal volume and duration of inspiration, resulting in a deeper and more prolonged inspiratory effort termed *apneusis*. However, normally the APN is inhibited by impulses carried by the vagus nerves and also by the activity of the PNC.

2. Pneumotaxic Centre The PNCs are located bilaterally in the upper pons.

Functions: The PNC inhibits the APN. Therefore, stimulation of PNC shortens inspiration, leading to a shallow and more rapid respiratory pattern.

Thus, though the rhythm of respiration resides in the DRG neurons in medulla, PNC and APN control these neurons to regulate the depth and rate of respiration.

III. Reticular Activating System

The RAS stimulates the respiratory centres to increase respiratory drive. During sleep, RAS activity diminishes, thereby decreasing respiratory drive, which diminishes alveolar ventilation and results in a slight elevation of arterial CO_2 tension.

AFFERENT IMPULSES TO RESPIRATORY CENTRES

The respiratory centres generate the respiratory rhythm and execute their effects through the efferent nerves supplying the respiratory muscles. The activity of respiratory centres, in turn, is influenced by the afferent impulses from the lungs and other parts of the body.

Various afferent impulses to the respiratory centres can be grouped as (Fig. 5.6-5) follows:

- Afferent impulses from higher centres
- Afferent impulses from nonchemical receptors, which may constitute *nonchemical regulation of respiration*
- Afferent impulses from the chemical receptors, which constitute the 'chemical regulation of respiration'

Afferent Impulses from Higher Centres

The afferent impulses from the higher centres, which influence the involuntary activity of respiratory centres, mainly include the voluntary control system and limbic control system.

1. Voluntary Control System The voluntary control of respiration is mediated by a pathway which originates from the neocortex and bypasses the medullary respiratory centres to project directly on the spinal respiratory neurons. The voluntary control of breathing is exercised during the following activities:

Activities like talking, singing and swimming, and breath-holding, i.e. breathing can be stopped voluntarily for about 50–60 seconds (breath-holding time). However, after this time the chemical drive overrides the voluntary inhibition and the person has an uncontrollable desire to breathe, and ultimately breathing is resumed involuntarily. That is why it is impossible to commit suicide by holding the breath voluntarily.

Voluntary Hyperventilation, i.e. voluntary overbreathing can be done for some time similar only to breath-holding. Effects of hyperventilation are discussed in chemical control of respiration (see page 208).

2. Limbic Control System Pain and emotional stimuli influence the rate and depth of breathing. It indicates the presence of afferents from the limbic system to the pontomedullary respiratory neurons.

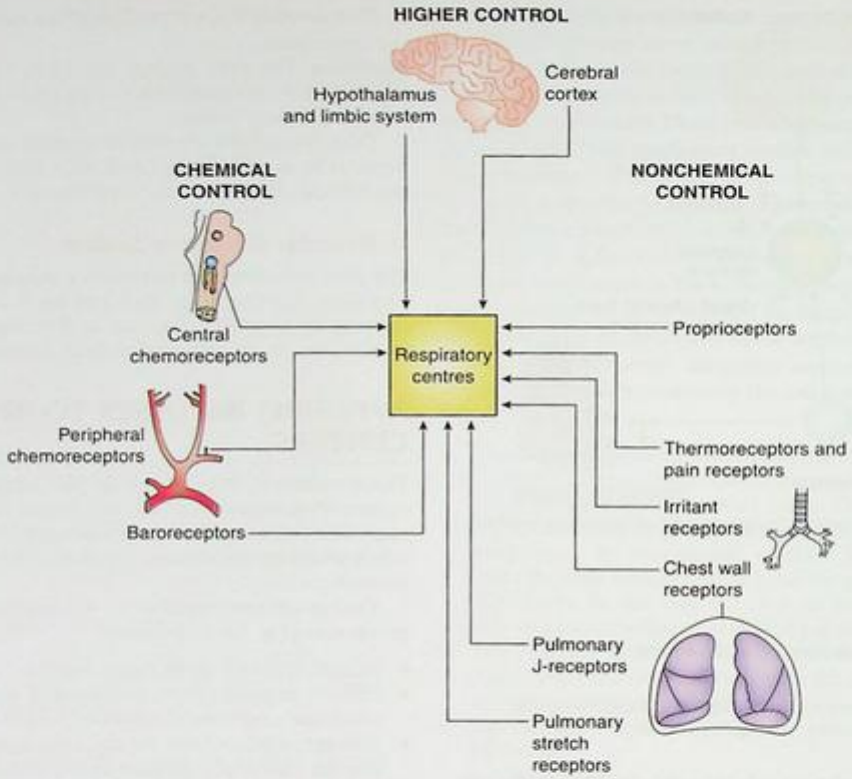


Figure 5.6-5 Afferent impulses to respiratory centres.

Afferent Impulses from Nonchemical Receptors

Afferent impulses from the receptors other than the chemoreceptors, i.e. from nonchemical receptors include the following:

1. Afferent Impulses from Pulmonary Stretch Receptors (Hering–Breuer Reflex) The Hering–Breuer inspiratory inhibitory reflex is initiated when the stretch receptors located in the smooth muscles of the bronchi and bronchioles are stimulated by inflation of the lungs. The impulses are then sent through *vagii nerves* to pontomedullary respiratory centres to inhibit respiration. This reflex is weakest in humans. It does not play any regulatory role in tidal respiration. This reflex is initiated only when the tidal volume is more than 1–1.5 L. Thus, the reflex tends to limit the tidal volume.

2. Afferent Impulses from J-receptors Afferent impulses from J-receptors constitute the J-reflex. The J-receptors were discovered by an Indian physiologist A.S. Paintal in 1954. The name J-receptors (juxtapulmonary capillary receptors) was given to them because of their location very close to the pulmonary capillaries (Fig. 5.6-6).

- The J-reflex response is characterized by apnoea followed by hyperventilation, bradycardia, hypotension and weakness of skeletal muscles.

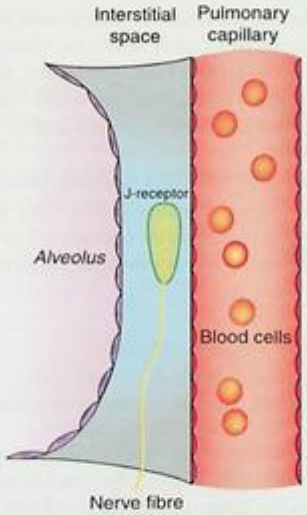


Figure 5.6-6 Location of J-receptors.

- Physiological role of J-receptors has been postulated during exercise, especially at high altitude when some fluid is entrapped in the alveolar interstitial space, which stimulates the J-receptors producing dyspnoea and reduction of the skeletal

muscle tone. This effect would discourage exercise, thereby taking away the trigger for pulmonary congestion.

3. Afferent Impulses from the Irritant Receptors in the Respiratory Tract Irritant receptors are located below the mucosa of whole respiratory tract. These are stimulated by smoke, noxious gases, particulate matter in the inspired air and in a number of other conditions. These receptors initiate the following reflexes:

(i) Cough Reflex This is a protective reflex caused by stimulation of irritant receptors in the pharynx, larynx, trachea and bronchi (conducting zone of respiratory tract). By this endeavour, the irritants may be expelled out of the respiratory tract.

(ii) Sneezing Reflex is also a protective reflex produced on stimulation of irritant receptors of the nasal mucosa.

(iii) Hering–Breuer Deflation Reflex is produced on stimulation of irritant receptors located in the bronchial epithelium due to distortion of bronchial epithelium caused by large deflations of the lungs as seen in pneumothorax and lung collapses (atelectasis). This reflex may also be responsible for the *sighs* or *yawning*. The reflex helps in opening up the collapsed alveoli again.

(iv) Deglutition Reflex refers to temporary apnoea produced during the pharyngeal phase of swallowing of food. It is a protective reflex which prevents the entry of food particles into the respiratory tract.

4. Afferent Impulses from Proprioceptors Proprioceptors are the receptors present in the muscles, tendons and joints, and are stimulated during change in the position of different parts of the body. This reflex helps in increasing ventilation during exercise.

IMPORTANT NOTE

The paediatricians employ this reflex for initiating first breath in the newborn by slapping it.

5. Afferent Impulses from Chest Wall Stretch Receptors Chest wall stretch receptors are nothing but the *muscle spindles* present in the intercostal muscles. Stretching of the intercostal muscles produces a stretch reflex due to the stimulation of muscle spindles that is characterized by contraction of intercostal muscles. The muscle spindles present in the respiratory muscles help to coordinate breathing during change in posture or during speech.

6. Afferent Impulses from Baroreceptors Baroreceptors or pressure receptors located in the carotid sinus and aortic arch (see details on page 154) are stimulated by increase in the arterial blood pressure. Though they play a primary role in regulation of blood pressure, but the impulses do travel to respiratory centres and cause inhibition of respiration; in physiological conditions, the baroreceptors play an insignificant role in regulation of respiration. The *adrenaline apnoea* observed on injection of high doses of adrenaline causes a large rise in the arterial pressure, which, in turn, inhibits respiration by afferent impulses from the baroreceptors to the respiratory centres.

7. Afferent Impulses from Thermoreceptors Thermoreceptors are those receptors which are stimulated by a change in the body temperature. When warm receptors are stimulated, the impulses are conveyed to cerebral cortex via somatic afferent nerves. Cerebral cortex, in turn, stimulates the respiratory centres to produce hyperventilation.

Respiration helps to maintain body temperature, as some amount of heat is lost in the expired air. In dogs, panting is one of the major mechanisms of thermoregulation.

CHEMICAL REGULATION OF RESPIRATION

The chemical factors regulating respiration are pCO_2, pO_2 and pH of blood. These factors influence respiration in such a way that their own blood levels are kept constant. The chemical mechanism of regulation operates through the chemoreceptors.

Chemoreceptors

Chemoreceptors are the sensory nerve endings which are highly sensitive to changes in pCO_2, pO_2 and pH of blood. These are of the following three types:

- Peripheral chemoreceptors
- Central chemoreceptors

Peripheral Chemoreceptors

Location Peripheral chemoreceptors include the carotid and aortic bodies (Fig. 5.6-7).

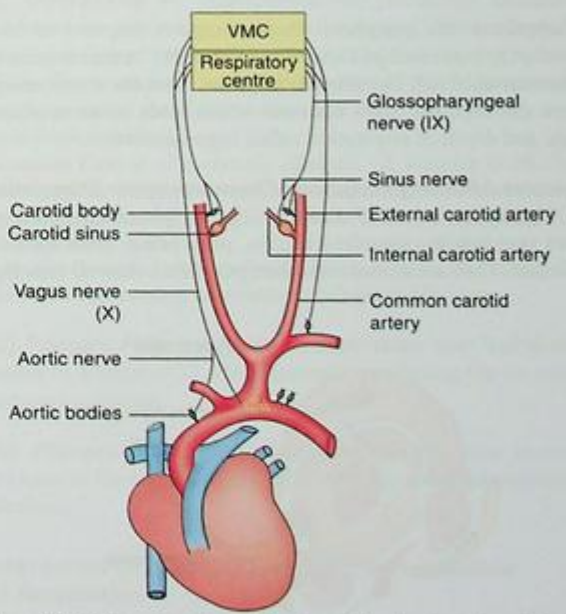


Figure 5.6-7 Location of carotid and aortic bodies (peripheral chemoreceptors).

- *Carotid body* is located on either side near the bifurcation of common carotid artery.
- *Aortic bodies*, two or more in number, are located near the arch of aorta.

Structure Each carotid and aortic body consists of the following:

Capsule surrounding each carotid and aortic body is very thin.

Sinusoidal large capillaries present below the capsule surround the main mass of each body.

Epithelial Cells The main mass of the body consists of islands of epithelial cells which are of two types: type I and type II (Fig. 5.6-8).

Type I or Glomus Cells: These cells have dense-core granules containing catecholamines (probably dopamine). Unmyelinated nerve endings are closely applied to these cells; these nerve endings are cup shaped and have dopamine receptors (D_2) on them. When exposed to hypoxia, the type I cells release catecholamine, which stimulates the D_2 receptors.

Type II Cells, are probably glial cells which are closely applied to the type I cells.

Nerve Fibres: Afferent fibres from the carotid body join the sinus nerve, a branch of glossopharyngeal (IX) nerve, and ultimately ascend to the medulla. Those from the aortic body join the aortic nerve branch of vagus (Xth cranial) nerve and ascend to the medulla.

Blood Flow to each carotid and aortic body is highest in the body (2000 mL/100 g/min). Therefore, the O_2 needs of these cells can be met largely by dissolved O_2 only.

Functions The peripheral chemoreceptors respond to lowered pO_2, increased pCO_2 and increased H^+ concentration in the arterial blood. The afferent impulses from the chemoreceptors stimulate the DRG neurons, which leads to an increased rate and depth of respiration called *hyperventilation.*

Factors Affecting Peripheral Chemoreceptor Stimulation

(i) O_2 Tension Versus O_2 Content The peripheral chemoreceptors monitor the dissolved O_2, i.e. pO_2, rather than its total content. They are stimulated when pO_2 falls below 60 mm Hg.

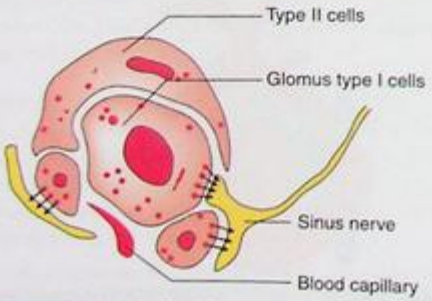


Figure 5.6-8 Histological structure of carotid body.

(ii) Elevated pCO_2 Elevated pCO_2 (by 10 mm Hg) also stimulates the peripheral chemoreceptors, but the major effect of CO_2 is on the central chemoreceptors.

(iii) H^+ Concentration when increased in the blood (decreased pH by 0.1 unit) stimulates the peripheral chemoreceptors.

(iv) Increase in Plasma K^+ Levels may stimulate the peripheral chemoreceptors even in the absence of hypoxia. Increase in plasma K^+ levels during exercise contributes to exercise-induced hyperventilation.

(v) Asphyxia, i.e. combination of O_2 lack plus CO_2 excess in the blood stimulates the peripheral chemoreceptors.

Effects of Stimulation of Peripheral Chemoreceptors

- They regulate the respiration from breath to breath and their stimulation increases the rate and depth of respiration.
- They also cause increase in the blood pressure and tachycardia.
- About 15%–20% of resting respiratory drive is due to the stimulatory effect of CO_2 on the peripheral chemoreceptors.

Central Chemoreceptors

Location Central chemoreceptors are the cells (neurons) that lie just beneath the ventral surface of the medulla oblongata and are therefore also called medullary receptors (Fig. 5.6-9).

The neurons forming central chemoreceptors project directly over to the respiratory centres, which are located slightly deeper to the central chemoreceptors.

Stimulation Characteristics of central chemoreceptors are as follows:

- They respond to H^+ concentration in the surrounding interstitial fluid and cerebrospinal fluid (CSF).

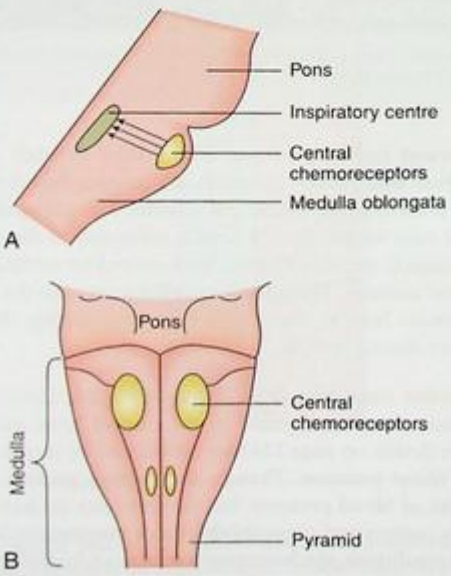


Figure 5.6-9 Location of central chemoreceptors in medulla: (A) lateral view and (B) front view.

- The magnitude of stimulation is directly proportional to the local H^+ concentration, which, in turn, parallels arterial pCO_2.
- *Mechanism by which an increase in CO_2 concentration affects central chemoreceptors:* CO_2 readily crosses the blood–brain barrier because it is a small, very soluble, uncharged molecule. In the CSF, CO_2 combines with water to form H_2CO_3, which dissociates into H^+ and HCO_3^- ions. The increase in H^+ concentration of CSF and interstitial fluid stimulates the central chemoreceptors, whereas a decrease in the H^+ concentration inhibits respiration. It is important to note that the blood–brain barrier does not allow the charged ions (e.g. H^+, HCO_3^-) to cross through readily. Because of this, if the arterial pCO_2 is kept constant experimentally, a decrease in the arterial pH (raised H^+ concentration) fails to stimulate central chemoreceptors.
- Central chemoreceptors are not stimulated by hypoxia; rather, like any other cell, they are depressed by hypoxia.
- Central chemoreceptors are also inhibited by anaesthesia, cyanide and during sleep.

Effects of Stimulation of central chemoreceptors are to regulate the respiration from minute-to-minute. Their stimulation leads to an increase in rate and depth of respiration.

IMPORTANT NOTE

It is important to note that about 80%–85% of the resting respiratory drive is due to the stimulatory effect of CO_2 on the central chemoreceptors, whereas peripheral chemoreceptors provide only 15%–20% of initial drive to increase respiration.

Effect of pO_2, pCO_2 and H^+ Concentration on Respiration

Effect of Hypoxia on Respiration

The Normal Arterial pO_2 is 100 mm Hg, which may fall in many conditions (see page 212), producing the so-called hypoxic hypoxia.

When the Arterial pO_2 Levels Fall to between 100 and 60 mm Hg, not much effect is produced on ventilation. However, a marked increase in the pulmonary ventilation occurs when the pO_2 falls below 60 mm Hg (Fig. 5.6-10).

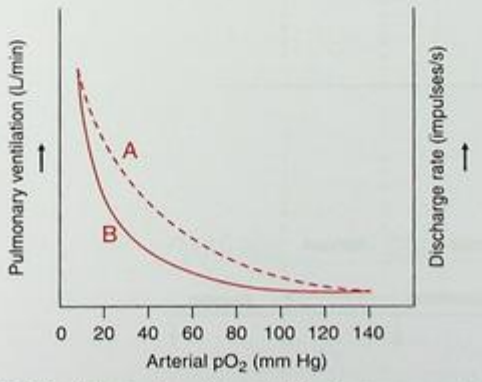


Figure 5.6-10 Relationship of arterial pO_2 with sinus nerve discharge rate (A) and pulmonary ventilation (B).

Effect of Hypercapnia on Respiration

Normal Arterial pCO_2 is 40 mm Hg, which is kept constant by chemical regulation of respiration.

Hypercapnia, i.e. rise in pCO_2, rarely occurs due to an increase in CO_2 production. Clinically, it may occur in restrictive lung disorders (see page 213).

- *An increase in arterial pCO_2* causes a prompt increase in the pulmonary ventilation mainly by stimulating the central chemoreceptors, resulting in CO_2 washout and a near restoration of arterial pCO_2 to a normal level (40 mm Hg). There exists a linear relation between increase in arterial pCO_2 and increase in pulmonary ventilation.
- When central chemoreceptors are depressed by anaesthesia, then CO_2 increases respiration through stimulation of peripheral chemoreceptors. Thus, CO_2 acts as a main regulator of respiration.

Carbon Dioxide Narcosis It develops when arterial pCO_2 increases above 50 mm Hg. Accumulation of such a large amount of CO_2 (hypercapnia) in the body depresses the central nervous system, including respiratory centres, producing headache, confusion, convulsions, and finally coma and death may occur.

Effect of Arterial pH on Respiration

(i) Increased H^+ Concentration (metabolic acidosis) produces prolonged respiratory centre stimulation via peripheral chemoreceptors, leading to a decrease in the arterial pCO_2 by elimination of larger amounts of CO_2, thus producing compensatory fall in the blood H^+ concentration. The related aspects of renal correction of acid–base balance are discussed in Chapter 6.3, page 244.

(ii) Decreased H^+ Concentration (metabolic alkalosis) depresses the respiratory centre via peripheral chemoreceptors, leading to retention of CO_2 and an increase in the arterial pCO_2. The secondary changes in the arterial pCO_2 compensate for the primary metabolic defects and help to restore H^+ concentration of blood.

Common Causes of metabolic alkalosis, i.e. increase in HCO_3^- concentration in blood secondary to decreased H^+ concentration in blood: excessive vomiting with loss of HCl from the body.

Respiratory acidosis and alkalosis: It may be added here that primary changes in the pulmonary ventilation also affect the pH of blood, causing respiratory acidosis or alkalosis.

(iii) Primary Pulmonary Hypoventilation may lead to elevation of arterial pCO_2 (hypercapnia), producing the so-called *respiratory acidosis.*

(iv) Primary Pulmonary Hyperventilation may cause a decrease in the arterial pCO_2, producing the so-called *respiratory alkalosis.*

Interaction of pO_2, pCO_2 and pH in Regulation of Respiration

In many physiological or clinical situations, more than one factor may be present. Their interaction is summarized below.

1. *Interaction of pCO_2 and pO_2* ***Hypoxia*** sensitizes the respiratory mechanism to excess of CO_2 or H^+ concentration; therefore, increased pCO_2 and H^+ concentration produce a much greater effect.

2. *Interaction of pH and CO_2 Response* The stimulatory effect of H^+ concentration and CO_2 on respiration is *additive*.

3. *Interaction of CO_2 and Body Temperature* The effect of CO_2 on respiration increases with increase in body temperature.

Some other Aspects Related to Chemical Regulation of Respiration

Effects of Hyperventilation

Effect of Short-Lasting Severe Hyperventilation The voluntary hyperventilation may show the following effects (Fig. 5.6-11):

(i) Effects on Respiration After a period of hyperventilation, any of the following patterns of respiration may be seen for a small period before normal respiration is restored:

- ***Hypoventilation*** for a prolonged period is seen in most of the individuals.
- ***Apnoea***, i.e. complete cessation of breathing for 1–2 minutes, may occur in some individuals.
- ***Periodic breathing (Cheyne–Stokes breathing)***, i.e. alternate phases of apnoea and breathing may occur for sometime in a few individuals.

(ii) Effects on Arterial pCO_2 and pO_2, and Their Correlation with Effect on Respiration (Fig. 5.6-11) are as follows:

- Arterial pO_2 may go as high as 150 mm Hg and pCO_2 as low as 15 mm Hg after a period of voluntary hyperventilation.
- Apnoea occurring in some individuals at the end of hyperventilation seems to be related to lack of CO_2.
- During the phase of apnoea, due to metabolism of body, there occurs a decline in the arterial pO_2 and an increase in pCO_2. Depending on the interaction between levels of pO_2 and pCO_2 attained, the following are the effects on respiration:
  - If the arterial pCO_2 is reached at the threshold level (40 mm Hg), then a normal breathing is resumed.
  - If the hypoxic stimulus (decreased pO_2) becomes strong before the pCO_2 reaches a threshold level, then *periodic breathing* (Cheyne–Stokes breathing) may result, i.e. a few breaths eliminate hypoxic drive, then breathing stops and restarts when again hypoxic drive stimulates it. Such cycles are repeated till pCO_2 reaches the threshold level to normalize breathing.

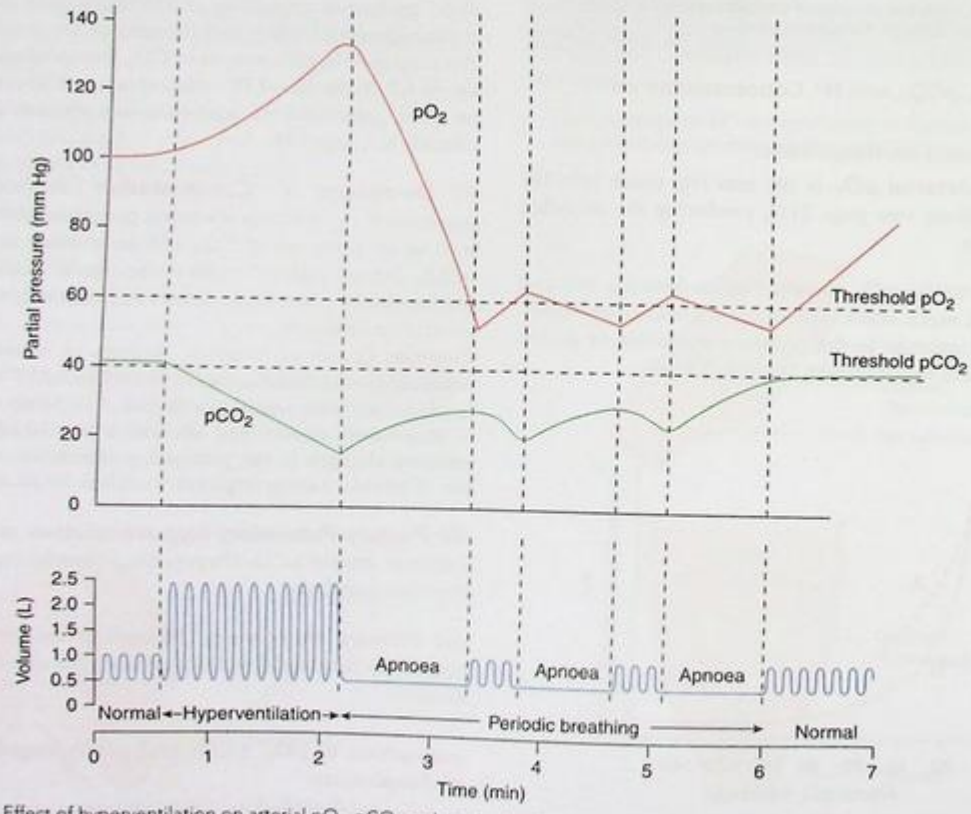


Figure 5.6-11 Effect of hyperventilation on arterial pO_2, pCO_2 and respiration. Note the correlation between pCO_2, pO_2 and periods of hyperventilation, apnoea, and periodic breathing and normal breathing.

Effects of Prolonged Moderate Hyperventilation Prolonged moderate hyperventilation, i.e. twofold to fivefold increase in the pulmonary ventilation, may occur under the following circumstances:

- In residents of high altitude
- In clinically hypoxic patients due to some pulmonary disease
- May also be maintained even voluntarily

The prolonged moderate hyperventilation is associated with a decrease in alveolar and arterial pCO_2. The low arterial pCO_2, which lasts for many days, may result in the following complication in the body:

Neurological changes include *tetany*, dizziness and light headache. The consciousness may be dulled or even lost.

Effect of Sleep on Respiration

It has been reported that due to inhibition of central chemoreceptors during sleep, the sensitivity of respiratory centre neurons to arterial pCO_2 is decreased. It may cause the following effects:

- *Apnoea for brief period (10-second duration)* is of common occurrence during sleep in normal individuals.
- *Sleep apnoea syndrome* is a serious clinical problem, which may occur in some individuals.

SELF-ASSESSMENT

1. Describe briefly:
   - Neural control of respiration
   - Chemical control of respiration
   - Role of pontine centres on breathing
2. Write notes on:
   - Hering–Breuer's reflex
   - Significance of J receptors
   - Cough reflex
   - Pulmonary chemoreflex
   - Asphyxia
3. Differentiate between:
   - Peripheral and central chemoreceptors
   - Carotid and aortic bodies
   - Apneustic and pneumotaxic centres

5.7 Respiration: Applied Aspects

CHAPTER OUTLINE

Introduction

Respiratory Adjustments to Stresses in Health
Exercise
High Altitude
High Atmospheric Pressure

Disturbances of Respiration
Abnormal Respiratory Patterns
Apnoea
Hypoventilation
Hyperventilation
Dyspnoea
Periodic Breathing
Disturbances Related to Respiratory Gases
Hypoxia
Hypercapnia
Hypocapnia
Asphyxia
Carbon Monoxide Poisoning

High-Altitude Physiology
Hypoxia at High Altitude

Physiology of High Atmospheric Pressure
Introduction
Physiological Problems Due to the Effect of High Pressure on Respiratory Gases
Physiological Problems of Ascent
Decompression Sickness
Air Embolism
Prevention of Physiological Problems Occurring at Depth and on Ascent

Artificial Respiration and Cardiopulmonary Resuscitation
Artificial Respiration
Cardiopulmonary Resuscitation

INTRODUCTION

Applied respiratory physiology forms a link between the basics of respiration and clinical manifestations of respiratory diseases. This chapter is concerned with some of the important applied aspects of respiration, which include the following:

- Respiratory adjustments to stresses in health
- Disturbances of respiration
- Artificial respiration
- Cardiopulmonary resuscitation

RESPIRATORY ADJUSTMENTS TO STRESSES IN HEALTH

Respiratory adjustments to stresses in health illustrate the integrated operation of the respiratory regulatory mechanisms. The stresses faced by respiration requiring adjustments in day-to-day life include the following:

1. Respiratory Adjustments during Exercise Exercise is the most frequently faced stress in day-to-day life. During exercise, many complex adjustments of muscular blood flow, metabolism, respiration, circulation and temperature are required, so they have been discussed on page 220.

2. Respiratory Adjustments at High Altitude When a person is exposed to high altitude, particularly by a rapid ascent, the different systems of the body cannot cope with the lowered O_2 tension and the effects of hypoxia start. Respiratory adjustments are thus a part of changes in the body at high attitude, so these have been discussed on page 213.

3. Respiratory Adjustments to High Atmospheric Pressure form a part of the physiological problems faced by the body while going under the sea, and they have been discussed on page 214.

DISTURBANCES OF RESPIRATION

From the physiological viewpoint, disturbances of respiration can be discussed under the following headings:

- Abnormal respiratory patterns
- Disturbances related to respiratory gases

Abnormal Respiratory Patterns

Eupnoea refers to the normal respiratory pattern, which implies a normal rate, rhythm and depth of respiration. Various abnormal respiratory patterns (Fig. 5.7-1) can be produced by the changes in the environment or diseases affecting the respiratory system, cardiovascular system or brain. The terms used for the altered pattern of respiration are as follows:

- ***Tachypnoea*** refers to an increase in the rate of respiration.
- ***Bradypnoea*** means decrease in the rate of respiration.
- ***Polypnoea*** is used to denote the rapid but shallow breathing, resembling panting in dogs. In this, the rate of respiration is increased, but the force does not change significantly.
- ***Apnoea*** refers to the temporary cessation of breathing.
- ***Hypoventilation*** is used to describe a decrease in the rate and force of respiration.

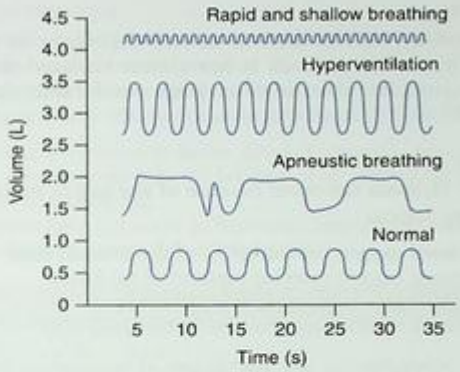


Figure 5.7-1 Various abnormal respiratory patterns.

- ***Hyperventilation*** refers to an increase in the rate as well as force of respiration.
- ***Hyperpnoea*** signifies a marked increase in the pulmonary ventilation due to an increase in rate and/or force of respiration.
- ***Dyspnoea:*** When hyperpnoea involves fourfold to fivefold increase in the pulmonary ventilation, an unpleasant sensation or discomfort is felt. This type of respiration is called dyspnoea.
- ***Periodic breathing*** refers to a respiratory pattern characterized by alternate periods of respiratory activity and apnoea. Some of the abnormal respiratory patterns are discussed in detail.

Apnoea

Apnoea refers to a temporary cessation of breathing. Depending on the cause, apnoea may be of the following types:

1. Voluntary Apnoea refers to a temporary arrest of breathing due to the voluntary control of respiration. It is also called breath holding. The breath-holding time or apnoea time during which breathing can be withheld voluntarily is about 40–60 seconds in a normal person after a deep inspiration (for details, see page 203).

2. Apnoea after Hyperventilation occurs due to the reduced stimulation of respiratory centre owing to CO_2 wash caused by hyperventilation (for details, see page 208).

3. Deglutition Apnoea occurs reflexively during swallowing (about 0.5 second). During the pharyngeal stage of swallowing, the fluid or food stimulates the sensory nerve endings (5th, 9th and 10th cranial nerves) around the pharynx. Nerve impulses from these irritant receptors via the swallowing centres specifically inhibit the respiratory centre, stopping the breathing at any point of the cycle (deglutition apnoea). Simultaneously, there is closure of glottis (the opening between vocal cords). Both these effects prevent aspiration of fluid or food into the lungs (also see page 205).

Hypoventilation

Hypoventilation is used to describe a decrease in the rate and force of respiration. Thus, in hypoventilation, the amount of air moving in and out of lungs is reduced.

Causes of hypoventilation are as follows:

- Depression of respiratory centres by some drugs
- Partial paralysis of respiratory muscles

Effects: Hypoventilation leads to hypoxia and hypercapnia (respiratory acidosis), which results in an increase in rate and force of respiration, and the patient may develop dyspnoea.

Hyperventilation

Hyperventilation refers to an increase in the rate and force of respiration. Thus, in hyperventilation, the amount of air moving in and out of lungs is increased.

Causes of hyperventilation are as follows:

- During exercise due to stimulation of respiratory centres by increased pCO_2
- Voluntary hyperventilation
- Secondary to hypoxia

Effects of hyperventilation on respiration are described on page 208.

Dyspnoea

Dyspnoea literally means distressed breathing. Increased respiration without discomfort is called *hyperpnoea*. One is not aware of one's respiration till resting pulmonary ventilation becomes more than double. When hyperpnoea involves fourfold to fivefold increase in pulmonary ventilation, an unpleasant sensation or discomfort is felt. This type of respiration is called dyspnoea. The word 'air hunger' is used as a synonym for dyspnoea in common language.

Pulmonary Reserve (PR) or Breathing Reserve

PR refers to the maximum amount of the air above the pulmonary ventilation that can be inspired or expired in 1 minute.

It equals maximum voluntary ventilation (MVV) minus pulmonary ventilation (PV), i.e.

$$PR = MVV - PV/min$$

PR is usually expressed as percentage of MVV and is known as percentage pulmonary reserve (%PR) or *dyspnoeic index* (DI), i.e.

$$DI = \frac{MVV - PV}{MVV} \times 100$$

Normal values of DI or %PR range from 70% to 95% with an average of 75%.

Dyspnoea is usually present when the value of DI becomes less than 60%.

Dyspnoea point refers to the height of hyperpnoea at which dyspnoea appears.

Causes of dyspnoea are as follows:

- *Physiologically, dyspnoea occurs* in severe muscular exercise.
- *Pathological causes* include respiratory disorders such as bronchial asthma, emphysema, pneumonia, pulmonary oedema and pneumothorax.

Periodic Breathing

Periodic breathing is characterized by the alternate periods of respiratory activity and apnoea.

Cheyne–Stokes Respiration The Cheyne–Stokes respiration is a periodic type of breathing in which the alternate periods of

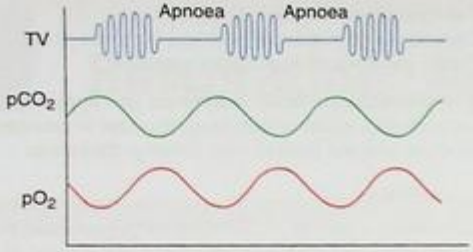


Figure 5.7-2 Periodic breathing (Cheyne–Stokes breathing).

respiratory activity and apnoea occur at regular intervals, and during the period of respiratory activity, there is waxing and waning of tidal volume. The duration of one cycle is about 1 minute. The arterial pO_2 and pCO_2 fluctuate during each cycle. The pO_2 is lowest and the pCO_2 is highest at the end of apnoea (Fig. 5.7-2).

Disturbances Related to Respiratory Gases

Respiratory disturbances related to respiratory gases include the following:

- Hypoxia
- Hypercapnia
- Hypocapnia
- Asphyxia
- Carbon monoxide poisoning

Hypoxia

The term hypoxia is used to denote deficiency of oxygen supply at the tissue level. It has almost replaced the term anoxia (complete absence of oxygen), which rarely occurs in practice.

Causes and Types

Causes: Hypoxia can occur because of any one or more of the following defects:

- Decreased oxygen tension (pO_2) of the arterial blood
- Decreased oxygen carrying capacity of the blood
- Decreased rate of blood flow to the tissue
- Decreased utilization of oxygen by the tissue cells

Types: Depending on the mechanism of occurrence, there are four types of hypoxia:

- Hypoxic hypoxia
- Anaemic hypoxia
- Stagnant hypoxia
- Histotoxic hypoxia

Characteristic features of four types of hypoxia are summarized in Table 5.7-1.

Signs and Symptoms of Hypoxia Symptoms of hypoxia depend on the following:

- Rapidity of development of hypoxia
- Severity of hypoxia
- Effectiveness of the body's compensatory mechanisms

TABLE 5.7-1 Characteristic Features of Different Types of Hypoxia

Features	Hypoxic Hypoxia	Anaemic Hypoxia	Stagnant Hypoxia	Histotoxic Hypoxia
Pathophysiology	Occurs due to decreased O_2 tension (decreased arterial pO_2)	Occurs due to low O_2 carrying capacity of blood	Occurs due to decreased blood flow to tissue	Occurs due to decreased ability of the tissue to utilize O_2
Causes	• Low O_2 tension (low pO_2 in inspired air) • Hypoventilation • ↓ Diffusion of O_2 across respiratory membrane • Physiological shunt • Anatomical shunt	• ↓ RBC count • ↓ Hb content of blood • Altered Hb	• Shock • Circulatory failure	• Cyanide poisoning
Arterial pO_2	Decreased	Normal	Normal	Normal
Arterial O_2 contents	Decreased	Markedly decreased	Normal	Normal
Arterial Hb contents	Normal	Reduced	Normal	Normal
% O_2 saturation (in arterial blood)	Decreased	Decreased	Normal	Normal
O_2 carrying capacity of arterial blood	Normal	Decreased	Normal	Normal
A–V (arterial–venous) pO_2 difference	Decreased	Normal	More than normal	Less than normal (nil)
Cyanosis	Present	Absent	Present	Absent
Peripheral chemoreceptor stimulation	Present (because dissolved oxygen in plasma is reduced)	Absent (because dissolved oxygen in plasma is sufficient)	Present (because arterial pCO_2 increases and pO_2 decreases)	Present (cyanide decreases oxygen utilization at tissue level)
Tachypnoea	Present	Absent	Absent	Absent

Signs of Hypoxia

1. Cyanosis is the bluish discolouration of skin and mucous membrane caused by the presence of more than 5 g of deoxyhaemoglobin/dL of the capillary blood.

Cyanosis is not a reliable sign of hypoxia because of the following:

- Anaemic patients may never develop cyanosis, even though they are extremely hypoxic because of an inadequate haemoglobin concentration.
- Cyanosis does not occur in histotoxic hypoxia because the O_2 saturation of haemoglobin is normal.

IMPORTANT NOTES

There are two types of cyanosis:

Peripheral cyanosis is seen in the nail beds and is suggestive of *stagnant hypoxia*. This is because perfusion in these distally located areas is worst affected in hypotensive states. A large amount of O_2 is extracted from the haemoglobin, and the concentration of deoxyhaemoglobin rises to produce cyanosis.

Central cyanosis is seen in the earlobes where skin is thin and in the mucous membrane of lips and tongue. These areas receive good blood supply and become cyanotic only if the O_2 saturation of blood is low, as occurs in the *hypoxic hypoxia*.

2. Tachycardia It occurs as a peripheral chemoreceptor reflex response to the low arterial oxygen tension.

3. Tachypnoea presents in the hypoxic hypoxia where arterial pO_2 is low, but absent in both anaemic hypoxia and stagnant hypoxia in which the arterial pO_2 is normal.

Physiological Compensatory Responses to Chronic Hypoxia Two types of physiologic compensatory responses known to occur in hypoxia are *accommodation* and *acclimatization*.

I. Accommodation refers to immediate reflex adjustments of the respiratory and cardiovascular systems to hypoxia. These include the following:

- Hyperventilation
- Tachycardia
- Increase in concentration of 2,3-biphosphoglycerate (2,3-BPG) in red blood cells (RBCs), occurring in response to hypoxia and alkalosis

II. Acclimatization refers to the changes in body tissues in response to long-term exposure to hypoxia, such as when a person living at sea level goes and stays at high altitude for a long time. With longer stay, the person gradually gets acclimatized to low pO_2 by the following changes in the body tissues:

1. ***Increase in RBC count*** or the polycythaemia secondary to tissue hypoxia. For details see page 61.
2. ***Increase in pulmonary ventilation:*** There is gradual increase in ventilation to an average of about five times the normal.
3. ***Cardiovascular changes*** in the form of increased heart rate, force of contraction and increased cardiac output, which occur in the initial accommodation period, and later on decrease back to normal once the O_2 supply to tissues becomes normal due to changes in blood.
4. ***Pulmonary hypertension:*** It occurs secondary to the generalized hypoxic pulmonary vasoconstriction.
5. ***Increase in total lung capacity and diffusing capacity of the lung*** occurs in high-altitude natives as compared to their sea-level counterparts. The increase in total lung capacity is evidenced by the enlarged chest that high-altitude natives develop.
6. ***Cellular and tissue acclimatization*** occurs after a long stay at high altitude. These include the following:
   - *Increase in oxidative enzyme concentrations* within the mitochondria of many tissues
   - *Increase in mitochondrial density* within the cells
   - *Increase in capillary density* in skeletal and cardiac muscles

Treatment of Hypoxia

Treatment of hypoxia basically includes the following:

- Treatment of underlying cause
- Oxygen therapy

Physiological Basis of Oxygen Therapy in Hypoxia Oxygen therapy is of great value in certain types of hypoxia, and at the same time of almost no value in other types.

In general, simple O_2 therapy is not of much help in treatment of hypoxia because diffusion across the respiratory membrane depends on the partial pressure of gases; therefore, alveolar pO_2 can be increased by the following:

- Inhalation of 100% pure oxygen
- Inhalation of 100% pure oxygen at high barometric pressure called hyperbaric oxygen therapy

Oxygen Therapy with 100% Pure Oxygen at Atmospheric Pressure, i.e. at 760 mm Hg

1. Oxygen Therapy is Useful in most types of the hypoxic hypoxia. It is useful in different causes of hypoxic hypoxia, including the following:

- In atmospheric hypoxia
- In hypoventilation hypoxia
- In hypoxia due to an impaired respiratory membrane diffusion

2. Oxygen Therapy is of Limited Value in an anaemic hypoxia, stagnant hypoxia and hypoxic hypoxia caused by the physiological or anatomical shunts because in all these conditions oxygen is already available in the alveoli. However, in these conditions, hyperbaric O_2 therapy is more useful than O_2 therapy at atmospheric pressure.

3. Oxygen Therapy is of No Use in the histotoxic hypoxia.

Hypercapnia

Hypercapnia refers to an increase in the arterial pCO_2 (normal value 40 mm Hg). When hypercapnia is the primary problem, it is associated with the respiratory acidosis (see page 207) because an increase in CO_2 promptly generates excess H^+.

Causes of Hypercapnia Hypercapnia occurs due to the following:

1. ***Defective elimination of CO_2*** as occurs in the following cases:
   - Reduced pulmonary ventilation
   - Reduced effective alveolar ventilation

2. ***Accidental inhalation of CO_2*** in persons working in breweries and refrigeration plants. For more details, see page 207.

Hypocapnia

Hypocapnia, i.e. reduced pCO_2, is usually associated with *respiratory alkalosis*. Hypocapnia occurs due to hyperventilation.

Asphyxia

Asphyxia refers to a condition in which hypoxia (decreased pO_2) is associated with hypercapnia (increased pCO_2).

Causes

- Strangulation
- Drowning
- Acute tracheal obstruction (due to entry of food or due to choking)
- Paralysis of diaphragm as in acute poliomyelitis

Carbon Monoxide Poisoning

Carbon monoxide (CO) is a dangerous gas present in exhaust of gasoline engines, coal mines, gases from deep wells and underground drainage systems.

Toxic Effects CO produces anaemic hypoxia and derangement of the cellular metabolic system.

Anaemic Hypoxia: When CO is inhaled accidentally from the above-mentioned sources, CO having 200 times more affinity than O_2 for haemoglobin combines with it to form *carboxyhaemoglobin*. The carboxyhaemoglobin produces severe anaemic hypoxia.

Derangement of Cellular Metabolic System CO causes toxic effects on the cytochrome system of the cells, causing derangement of the cellular metabolic system.

Treatment of CO Poisoning When diagnosed timely, the following measures should be taken promptly:

- Immediate termination of exposure to CO
- Immediate hyperbaric 100% O_2 therapy
- Administration of air with a few percent of CO_2 to stimulate the respiratory centres

HIGH-ALTITUDE PHYSIOLOGY

Composition of air and effect of altitude on it: Composition of air does not change with altitude, i.e. the composition of atmosphere (percentage of gases) remains constant from sea level to about 30,000 feet.

Barometric pressure and partial pressure of gases: Barometric pressure at sea level is 760 mm Hg, and it falls progressively with increasing height. With decrease in total pressure of air at increasing altitude, the partial pressure of gases will change.

- According to Dalton's law, the total pressure of air (P) is equal to the sum of partial pressures of the gases contained, i.e. $P = pO_2 + pCO_2 + pN_2 + pH_2O$.
- *Changes in the body at high altitude* are produced mainly by hypoxic *hypoxia* produced by falling pO_2. *Other factors* which produce changes in the body at high altitude are effects of expansion of gases, fall in atmospheric temperature, light rays and gravity.

Hypoxia at High Altitude

The effects of hypoxic hypoxia produced by decreasing pO_2 at high altitude depend on the following:

- Level of altitude
- Rate at which hypoxia develops, i.e. hypoxia occurring due to a rapid ascent (acute hypoxia) or slow ascent (subacute hypoxia)
- Duration of exposure to hypoxia, i.e. whether short-term stay or long-term stay (chronic hypoxia)

For more details on hypoxic hypoxia, see page 212.

PHYSIOLOGY OF HIGH ATMOSPHERIC PRESSURE

Introduction

Atmospheric pressure of 760 mm Hg at sea level is considered 1 atmospheric pressure (atm).

Pressure increases by 1 atm for a depth of every 10 m (33 feet) as one descends beneath the sea. As the depth under sea increases, the pressure also increases proportionately (Table 5.7-2).

Decrease in volume of gases occurs due to compression as the pressure increases under sea. According to Boyle's law, the volume to which a given quantity of gas is compressed is inversely proportional to the pressure. With increase in the pressure, the volume is decreased proportionately (Table 5.7-2).

High atmospheric pressure is met under the following conditions:

- Deep sea diving
- Going under the sea in submarines
- Caisson's workers, i.e. the men who dig an underwater tunnel, work in a chamber (Caisson's chamber) in which atmospheric pressure is high to prevent entry of water

Physiological problems associated with life under high pressure may be divided into the following categories:

- Physiological problems at depth (due to the compression effect of high atmospheric pressure)
- Physiological problems of ascent (due to the decompression phenomenon)

TABLE 5.7-2 Effect of Depth on Pressure and Volume of Gas

Depth (m [feet])	Pressure (atm)	Volume (L)
Sea level	1	1
10 (33)	2	1/2 (0.5)
20 (66)	3	1/3 (0.33)
30 (100)	4	1/4 (0.25)
40 (133)	5	1/5 (0.2)
50 (166)	6	1/6 (0.167)
60 (200)	7	1/7 (0.143)
90 (300)	10	1/10 (0.1)
120 (400)	13	1/13 (0.077)
10 (500)	16	1/16 (0.062)

Physiological Problems Due to Effect of High Pressure on Respiratory Gases

Air under high atmospheric pressure is breathed under the sea. At high atmospheric pressure of air, the partial pressure of oxygen (pO_2), nitrogen (pN_2) and carbon dioxide (pCO_2) is also increased, producing the following physiological problems:

1. Effects of increased pO_2 (oxygen toxicity)

Acute oxygen toxicity occurs on exposures to 4 atm pressure of oxygen (pO_2 in lungs is about 3000 mm Hg).

- At high tissue pO_2, the molecular oxygen is converted into active oxygen, i.e. superoxide anion (O^-_2), which is a free radical.
- *Nervous complications of acute oxygen poisoning* include disorientation, dizziness, convulsions and even coma.

2. Effects of increased pN_2 (nitrogen narcosis)

Due to increased pN_2, the nitrogen dissolves *gradually* into the body fluids and more easily into fats. The cell membrane of neurons contains a high lipid content, so more nitrogen is dissolved in the neurons of brain, producing nitrogen toxicity known as nitrogen narcosis. Nitrogen narcosis is characterized by the following:

Euphoric symptoms: The individual becomes jovial and carefree. These are followed by the impairment of mental functions and intelligence, and the individual becomes drowsy and has poor muscular coordination.

Physiological Problems of Ascent

The two physiological problems which occur when an individual ascends back to sea level after sufficient exposure to high atmospheric pressure in the deep sea are as follows:

- Decompression sickness
- Air embolism

Decompression Sickness

Decompression sickness is also known as Caisson disease, dysbarism, compressed air sickness, and the bends and diver's palsy. When the individual ascends rapidly to the sea level after sufficient exposure to a high atmospheric pressure deep in the sea, nitrogen is decompressed and escapes from the tissues at a faster rate. Being gas, it forms bubbles while escaping rapidly from the tissues. The gas bubbles block the blood vessels, producing tissue ischaemia and sometimes the tissue death.

Symptoms of decompression sickness are as follows:

- ***Pain in joints and muscles*** of legs or arms: The joint pain accounts for the term *'bends'* that is often used to describe the decompression sickness.
- ***Sensation of numbness.***
- ***The chokes***: The chokes refer to the serious shortness of breath, which is often followed by severe pulmonary oedema and occasionally death.
- ***Paralysis of muscles*** may occur temporarily due to escape of nitrogen bubbles from the myelin sheath of motor nerves. This is called *diver's palsy* (one of the names of this disease).
- ***Coronary ischaemia*** or myocardial infarction may occur due to the blockage of coronary capillaries by the nitrogen bubbles.
- ***Neurological symptoms*** like dizziness, paralysis of muscles, or collapse and unconsciousness may occur due to the blockage of blood vessels of brain and spinal cord.

Treatment of decompression disease: Tank decompression is used for the treatment of the decompression disease.

Air Embolism

Air embolism is another physiological problem which may occur during the rapid ascent from a depth below the sea level. In severe cases, air emboli may travel to the systemic circulation, block the blood flow to some vital organs and may even result in death.

Prevention of Physiological Problems Occurring at Depth and on Ascent

Deeper and longer dives can be made safe by taking the following preventive measures:

1. Use of breathing apparatus Use of breathing apparatus delivers gas to breath and either absorbs carbon dioxide (closed circuit apparatus) or releases carbon dioxide as bubbles into the surrounding (open circuit apparatus). An example of such an apparatus is SCUBA diving.

2. Use of breathing mixture containing helium and low oxygen concentration Use of breathing mixture containing helium and low oxygen concentration is less harmful than natural air because of the following:

Low oxygen concentration prevents occurrence of oxygen toxicity.

Helium when replaced with nitrogen provides the following advantages:

- Because of its smaller molecule and lower density than nitrogen, it is easier to breathe, it diffuses faster and it is easier to eliminate its bubbles from the body.

3. Slow ascent or use of decompression tank

Slow ascent with short stay at regular intervals, i.e. slow and stepwise ascent, ensures that only a small amount of bubbles are formed at a time.

Decompression tank is based on the principle of slow ascent. After a rapid ascent, the individual is put into a pressurized tank whose pressure is lowered gradually up to a normal atmospheric pressure.

ARTIFICIAL RESPIRATION AND CARDIOPULMONARY RESUSCITATION

Artificial Respiration

Artificial respiration (AR) alone is required as an emergency life-saving procedure.

I. ***When there is sudden stoppage of breathing*** as seen in the following cases:
   - Drowning
   - Electrocution
   - Anaesthetic accidents
   - Carbon monoxide poisoning
   - Strangulation
   - Accidents

Figure 5.7-3 Mouth-to-mouth breathing: (A) the neck is extended by placing one hand under the neck and pressing the forehead with the other hand; (B) nostrils are closed with the thumb and index finger, and resuscitator exhales into the patient's airway by tightly placing his or her mouth over the patient's mouth; and (C) it allows the patient to exhale passively by unsealing the nose and mouth.

II. ***Artificial respiration may also be needed when breathing is expected to stop gradually*** as in paralysis of muscles in the following cases:
- Poliomyelitis
- Diphtheria
- Ascending paralysis

IMPORTANT NOTE

It is important to note that the tissues of brain, particularly cerebral cortex, develop irreversible damage if oxygen supply is stopped for 5 minutes. So, the resuscitation must be started quickly without any delay before the development of cardiac failure.

Methods of Artificial Respiration

Mouth-to-Mouth Breathing Method Various manual methods of AR have been described in the past and have become obsolete as well. Presently, the only manual method employed is mouth-to-mouth breathing (exhaled air ventilation) (Fig. 5.7-3) because of the following advantages:

- It can be applied quickly without waiting for the availability of any aid.
- It is a simple and effective measure of resuscitation.
- It can be applied to all age groups.
- It is the only technique capable of producing adequate ventilation.
- It also works by expanding the lungs.
- It is important to remember that the following:
  - Mouth-to-mouth method is the most effective manual method because the CO_2 present in the air expired by the resuscitator can also directly stimulate the respiratory centres and facilitate the onset of respiration.

Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) is required in some patients when both heart and respiration stop. Breathing usually stops before the heart stops, so AR should be started immediately.

Figure 5.7-4 Procedure showing external cardiac massage.

Emergency Plan of Cardiopulmonary Resuscitation

The following plan called the ABC of CPR has proven useful in reviving such patients:

A. Airway Care is required in the unconscious patients. In this, the head is immediately tilted back with a hand under the neck to maintain an open airway (Fig. 5.7-3).

B. Breathing by the AR method is required when the patient is not breathing. Mouth-to-mouth respiration should be immediately started. Carotid pulse is felt, and if present, only AR is continued.

C. Cardiac Massage is required when carotid pulse cannot be felt. During external cardiac massage, sternum should be depressed by 4–5 cm at a rate of 80–90 times/min. The cardiac compression should be alternated with mouth-to-mouth respiration at a rate of one ventilation to five chest compression (Fig. 5.7-4).

SELF-ASSESSMENT

1. Discuss briefly the effect of exercise on respiration.
2. Describe briefly:
   - Dyspnoea
   - Cyanosis
   - Acclimatization at high altitude
   - Carbon monoxide poisoning
   - Nitrogen narcosis
   - Decompression sickness
3. Differentiate between voluntary and involuntary hyperventilation.

5.8 Physiology of Exercise

CHAPTER OUTLINE

Introduction
Exercise: Types and Grading
Adjustments to Exercise

Responses to Exercise
Oxygen Consumption during Exercise
Oxygen Deficit and O_2 debt
Cardiovascular Responses to Exercise
Skeletal Muscle Blood Flow
Redistribution of Blood Flow
Increase in Cardiac Output
Blood Pressure Changes during Exercise
Changes in Blood Volume during Exercise
Summary of Cardiovascular Responses to Exercise
Respiratory Responses to Exercise
Increase in Pulmonary Ventilation
Increase in Oxygen Uptake in the Lungs
Changes at the Tissue Level
Endocrinal Responses to Exercise

Effects of Training
On Cardiovascular System
On Respiratory System
On Skeletal Muscles
Psychological Effects

INTRODUCTION

Physiology of exercise has generated significant interest and has gained importance because of the following:

- Current concern with physical conditioning and improvement in performance of athletes, sportspersons, military and paramilitary personnel all over the world.
- Role of exercise in prevention of cardiovascular diseases and physical fitness among population groups.
- Role of exercise (stress tests) in evaluation of the cardiovascular and respiratory systems.
- Role of exercise in rehabilitation of the cardiac invalids.

Exercise: Types and Grading

Types of Exercise Exercise may be dynamic or isotonic and static or isometric.

Dynamic exercise involves isotonic muscle contractions. External work is involved in this type of exercise.

Static exercise involves isometric muscle contractions.

Grading of Exercise WHO (1978) has classified muscular exercise into four grades depending on the heart rate and oxygen consumption. Oxygen consumption can be expressed as litres per minute or as relative load index (RLI), i.e. percentage of maximum O_2 utilization. The oxygen utilization can also be expressed as the metabolic energy expenditure (MET) test. One MET is equivalent to resting O_2 uptake of 250 mL/min for an average adult man and 200 mL/min for an average adult woman. The four grades of exercise are discussed in Table 5.8-1.

Adjustments to Exercise

Adjustments to physical (muscular) exercise depend on the type of exercise, grade of exercise, cardiac reserve (i.e. efficiency of the heart), muscle power, training, motivation and the state of nutrition.

RESPONSES TO EXERCISE

Exercise, basically, is a period of enhanced energy expenditure. The energy for muscular exercise is provided by the increased fuel consumption, which is reflected as *greater O_2 consumption and CO_2 production*. The increased O_2 delivery to the tissues and removal of CO_2 from the tissues is achieved by the following:

- Cardiovascular responses to exercise,
- Respiratory responses to exercise, and
- Changes at tissue levels during exercise.

In addition, endocrine responses to exercise occur and play a regulatory role by regulating the water loss and availability of fuel during exercise.

TABLE 5.8-1 Grades of Exercise

Grade	Level	Heart Rate (beats/min)	O_2 Consumption (L/min)	Relative Load Index (% of Max. O_2 Consumption)	METs
I	Light (mild)	<100	0.4–0.8	<25	<3
II	Moderate	100–125	0.8–1.6	25–50	3.1–4.5
III	Heavy	125–150	1.6–2.4	51–75	4.6–7
IV	Severe	>150	>2.4	>75	>7

Oxygen Consumption During Exercise

Oxygen consumption during exercise: The energy for muscular work during exercise is provided by the increased fuel consumption, which is reflected in greater O_2 consumption and CO_2 production.

Oxygen consumption (VO_2) during rest is about 250 mL/min, which increases linearly with severity of exercise up to a certain limit, beyond which a plateau is reached (Fig. 5.8-1).

Maximal oxygen consumption (VO_2 max) is the term used to define the level of oxygen consumption beyond which no further increase in O_2 consumption occurs with further increase in the severity of exercise.

- Average VO_2 max in an adult is 3 L/min and in a trained athlete it may be as high as 5 L/min.
- VO_2 max represents the highest attainable rate of aerobic metabolism during the performance of rhythmic muscular work that exhausts the subject within 5–10 minutes.

Oxygen Deficit and O_2 Debt

The period of muscular exercise can be divided into the following three phases (Fig. 5.8-2):

1. Adaptation Phase refers to the beginning of muscular exercise (first 2–4 minutes) during which oxygen consumption increases linearly and reaches the VO_2 max. The VO_2 max at this stage is much less than the oxygen demand; thus, an *oxygen deficit* is established. So, the energy requirement over and above the limits of O_2 consumption is met with by the anaerobic pathway.

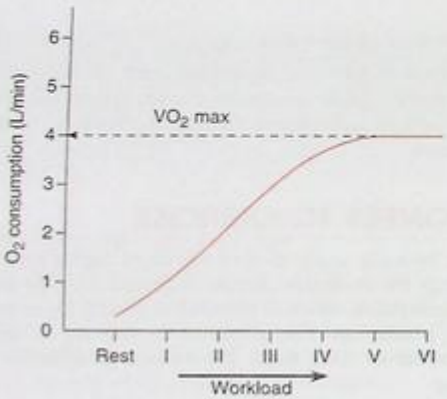


Figure 5.8-1 Oxygen consumption during exercise.

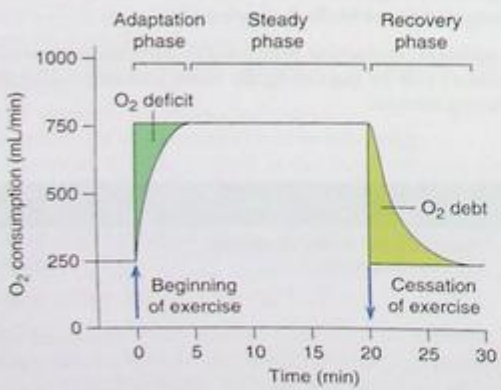


Figure 5.8-2 Oxygen deficit and oxygen debt.

2. Steady Phase of exercise is characterized by a VO_2 max throughout, i.e. a plateau phase of O_2 consumption and work done relationship. During this phase also, as mentioned above, the excess energy requirement is met with by the anaerobic pathway, i.e. by breakdown of creatine phosphate and muscle glycogen. As a result of anaerobic release of energy in the muscles, the blood levels of lactic acid begin to rise steeply.

3. Recovery Phase refers to the period after the cessation of exercise during which an extra amount of O_2 is consumed. The amount of extra O_2 consumed during the recovery phase is called O_2 debt and is proportional to the extent to which *oxygen deficit* occurred during exercise. In other words, the O_2 deficit which occurs during exercise is repaid during the recovery phase, in the form of O_2 debt. The extra amount of O_2 consumed during the recovery phase (O_2 debt) is used to carry out the following:

- To remove the excess lactate collected due to anaerobic glucose breakdown,
- To replenish the ATP and phosphorylcreatine store,
- To replace the small amounts of O_2 that have come from the myoglobin,
- To resupply dissolved O_2 in the tissue fluids and blood.

Cardiovascular Responses to Exercise

To meet the increased energy demand of muscles during exercise, the primary cardiovascular response is in the form of the following:

- Increase in the skeletal muscle blood flow
- Redistribution of blood flow in the body
- Increase in the cardiac output
- Blood pressure changes
- Changes in the blood volume

Skeletal Muscle Blood Flow

At rest, the blood flow to the skeletal muscle is about 2–4 mL/100 g/min of muscle tissue. During strenuous exercise, muscle blood flow can increase up to 20 times, i.e. about 50–80 mL/100 g/min muscle tissue. This is called *exercise hyperaemia.* This tremendous increase in the muscle blood flow during exercise is made possible by the following:

- Arteriolar dilatation
- Opening up of the closed capillaries, which greatly increase the surface area and the rate of blood flow (page 165)

Redistribution of Blood Flow

As mentioned earlier, the tremendous increase in the skeletal muscle blood flow is possible due to increased cardiac output (discussed later in detail) and redistribution of cardiac output in the following manner (Table 5.8-2):

Coronary Blood Flow During exercise, coronary blood flow is increased by four to five times with 100% O_2 utilization (page 161).

TABLE 5.8-2 Redistribution of Cardiac Output in Standing Posture During Exercise

	At Rest	During Heavy Exercise	Change
Cardiac output	5 L/min	24 L/min	Increased by 5–6 times
Blood flow to:			
• Skeletal muscles	750–800 mL/min	20 L/min	25 times
• Heart	250 mL/min	1 L/min	4 times
• Brain	750 mL/min	750 mL/min	No change
• Visceral	2600 mL/min	500 mL/min	Decreased by 80%
• Cutaneous	500 mL/min	400 mL/min 1000 mL/min	Initially decreased Later increased

Visceral Blood Flow is temporarily curtailed in coordination with increase in muscle blood flow. It is brought about by the increased sympathoadrenal discharge.

Splanchnic Blood Flow is decreased by 80% in severe exercise.

Renal Blood Flow is also decreased by 50%–80% in severe exercise.

Cutaneous Blood Flow at rest is about 500 mL/min.

- *Decrease* in cutaneous blood flow occurs initially in the beginning of exercise due to reflex vasoconstriction.
- *Increase* in cutaneous blood flow is noted in sustained exercise when body temperature rises to dissipate the heat generated during exercise, as the blood flow through the skin is controlled predominantly by the requirements of temperature regulation.

Cerebral Blood Flow at rest is about 750 mL/min and remains unchanged during any grade of muscular exercise.

Adipose Tissue Blood Flow is increased by four times during exercise. This helps to deliver fatty acids mobilized from triglyceride stores to the working muscles.

Increase in Cardiac Output

Normal cardiac output is about 5–6 L/min. During exercise, the cardiac output is increased depending on the severity of exercise. During maximum exercise, it may increase by five to six times. Cardiac output is the product of heart rate and stroke volume, so an increase in both contributes to the increase in cardiac output during exercise (Fig. 5.8-3).

Increase in Heart Rate Heart rate increases linearly with the severity of exercise. The increase in heart rate occurs as soon as the exercise begins or may be seen even before the exercise begins (anticipatory tachycardia).

Factors Contributing to Tachycardia during exercise are as follows:

- *Increased sympathetic discharge.*
- *Peripheral reflexes* originate from the exercising muscles (muscle spindles, muscle–tendon receptors and organ of Corti) and joints.

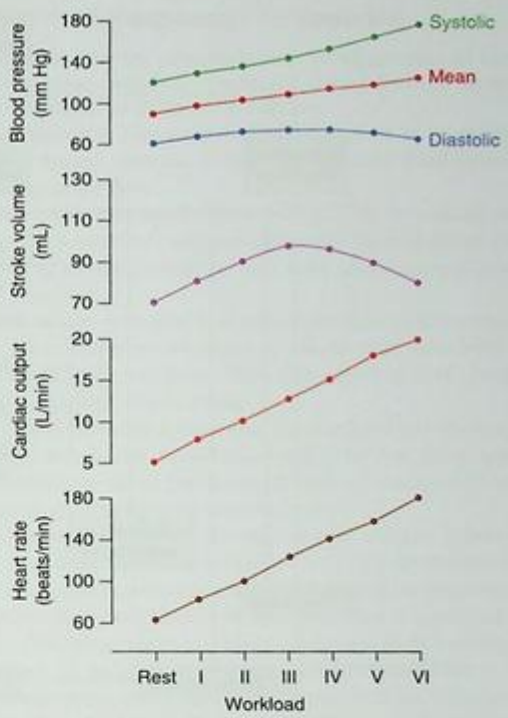


Figure 5.8-3 Effect of severity of muscular exercise on cardiovascular functions.

- *Local metabolic factors*: Muscle tissue has free nerve endings, which are stimulated by the lactic acid, potassium ions and other metabolites, which collect in exercising muscles, possibly contributing to the sustained increase in heart rate during prolonged exercise.
- *Humoral factors*: Adrenaline and noradrenaline and possibly thyroid hormones are released during exercise.
- *Intrinsic factors*: Stimulation of sinoatrial node (SA) in the right atrium due to increased venous return increases the heart rate during exercise. This is known as the *Bainbridge reflex.*
- *Increased temperature* in the myocardium due to increased activity of the heart during exercise may directly increase the rhythmicity of the pacemaker.

Increase in Stroke Volume Under normal conditions, the average stroke volume is about 80 mL/beat and may increase up to twice the normal value during exercise (Fig. 5.8-3).

Mechanisms Responsible for Increase in Stroke Volume It has been stated that an increase in the stroke volume during exercise occurs due to gearing up of both the control mechanisms, i.e.

- Intrinsic autoregulation or Frank–Starling mechanism, i.e. increase in venous return (for details, see page 131)
- Extrinsic regulation or autonomic and neural mechanism (for details, see page 132) as explained

Blood Pressure Changes during Exercise (Fig. 5.8-3)

In Systemic Circulation Systolic blood pressure is always raised by exercise because it depends on the cardiac output,

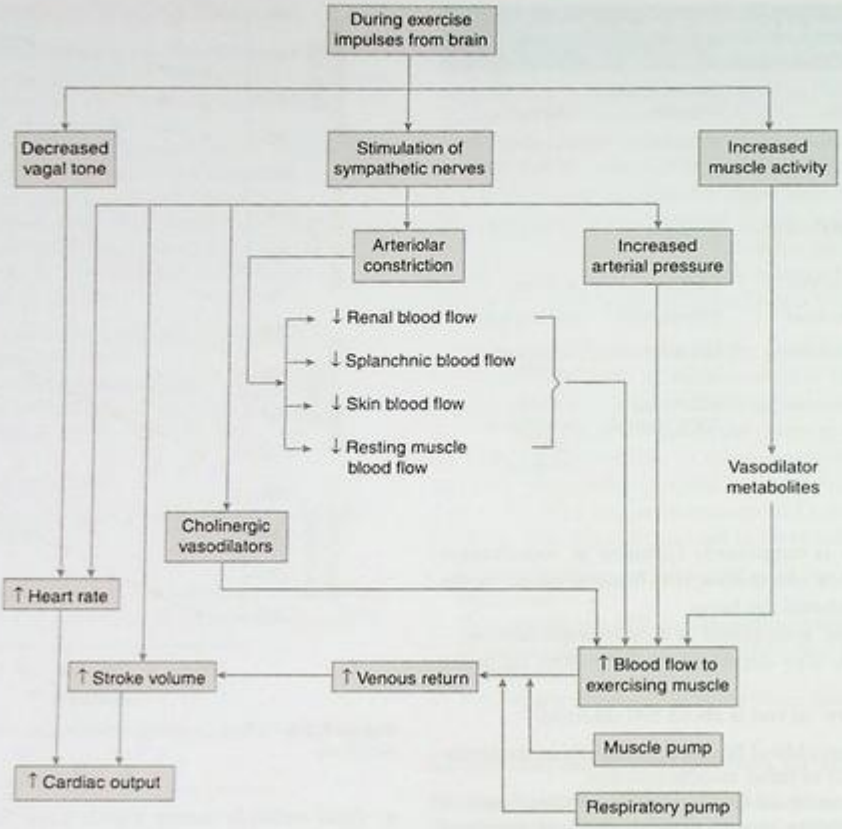


Figure 5.8-4 Summary of cardiovascular responses to exercise.

which is increased in exercise. The blood pressure remains elevated during exercise and is not reflexively corrected by baroreceptor reflex. This has been explained by the fact that the neurons descending from the hypothalamic defence centre inhibit the baroreceptor afferents.

Diastolic blood pressure, which primarily depends on the peripheral resistance, may mildly increase or decrease or remain unchanged depending on the change in total peripheral resistance. Mostly, the vasodilatation in the skeletal muscles balances the vasoconstriction in other tissues, so diastolic blood pressure is usually not changed much.

Mean blood pressure is usually increased. It helps to increase the skeletal muscle blood flow by providing a higher pressure head in the face of dilated resistance vessels.

In Pulmonary Circulation

- ***Systolic blood pressure*** in the pulmonary artery may rise during heavy exercise to 25–30 mm Hg from 15–20 mm Hg at rest.
- ***Diastolic blood pressure*** may rise from 5–8 mm Hg at rest to 8–10 mm Hg.
- ***Mean blood pressure*** may reach to 15 mm Hg from 8–12 mm Hg at rest.

Changes in Blood Volume during Exercise

Blood volume during exercise is decreased by 15%, resulting in haemoconcentration. Blood volume is decreased due to more plasma loss at the capillary level due to the following reasons:

- Increased hydrostatic pressure in capillaries,
- Increased tissue fluid osmotic pressure due to accumulation of osmotically active metabolites in tissue spaces such as potassium, phosphate and lactic acid.

Summary of Cardiovascular Responses to Exercise

The cardiovascular responses to exercise are summarized in Fig. 5.8-4.

Respiratory Responses to Exercise

I. Increase in Pulmonary Ventilation

The pulmonary ventilation increases linearly with increase in intensity of exercise (O_2 consumption) until the anaerobic threshold is reached. The anaerobic threshold occurs at approximately 60% of the maximal exercise level, regardless of the

level of physical fitness. Above the anaerobic threshold, the pulmonary ventilation increases out of proportion to increase in O_2 consumption because lactic acid that is generated imposes an additional respiratory drive.

Mechanism of Increased Pulmonary Ventilation There are several factors which can account for the marked increase in the pulmonary ventilation occurring in severe exercise. Some of the probable factors are as follows:

1. Neural Control Mechanisms Neural control mechanisms which have been suggested to make a contribution to exercise hyperpnoea are as follows:

- ***Cerebral cortex***, the seat of conscious thought and voluntary activity may be responsible for the anticipatory hyperpnoea, which may occur due to psychic stimuli just before the beginning of exercise.
- ***Afferent impulses from proprioceptors*** in the muscles and joints are at least partly responsible for exercise hyperpnoea.
- ***Increase in body temperature*** during sustained exercise may also make some contribution to the exercise hyperpnoea through the neural mechanism.

2. Chemical Mechanism does not play the main role in exercise hyperpnoea, as the alveolar and arterial pO_2 and pCO_2 are well maintained during exercise; however:

- ***Acidosis produced due to accumulation of lactic acid*** during severe exercise (above the aerobic threshold level) is responsible for the increase in pulmonary ventilation.

II. Increase in Oxygen Uptake in the Lungs

The oxygen uptake by the blood in the lungs increases from 250 mL/min at rest to about 4 L/min during heavy exercise. This is made possible by the following:

1. Increased pulmonary perfusion
2. Increased alveolar capillary pO_2 gradient
3. Increased pulmonary diffusion capacity

Changes at the Tissue Level

The changes at the tissue level which facilitate transfer of a large amount of O_2 from the blood to the exercising muscles and that of CO_2 from the tissues to the blood are as follows:

Blood Flow to the skeletal muscles is increased during strenuous exercise, which brings more O_2 to the tissue per minute.

Capillary bed of the contracting muscles is dilated, and many previously closed capillaries are open. Because of these changes, the mean distance from the blood to the tissues cells is greatly decreased; this facilitates movement of O_2 from the blood to the cells.

Gradient of pO_2 between capillary blood and tissue fluid is increased. Due to the increased gradient of pO_2 between capillaries and tissue fluid, more O_2 is removed from the capillary blood into the tissue fluid.

O_2–Hb Dissociation Curve shifts to the right due to accumulation of CO_2, rise in temperature and rise in red blood cell 2,3-biphosphoglycerate (2,3-BPG). This results in a threefold increase in O_2 extraction from each unit of blood.

Endocrinal Responses to Exercise

Endocrines play an important role in adjustment to exercise. The hormones which are increased during exercise along with the role played by them are as follows:

1. Antidiuretic Hormone (ADH) secretion is markedly increased during exercise. It helps to maintain fluid balance by reducing urine flow.

2. Adrenocorticotrophic Hormone (ACTH) is released during the endurance events and probably helps by mobilizing fats for providing energy directly as well as by stimulating glucocorticoid secretion.

3. Endorphin secretion is significantly increased during exercise. They improve tolerance to discomfort associated with exercise by relieving pain. They also relieve mental stress and induce a feeling of well-being.

4. Cortisol secreted during exercise is helpful in reducing exercising stress. It also mobilizes protein and fats. Fatty acids are particularly useful as fuel during exercise. Consequently, carbohydrates are spared to be used by brain.

5. Aldosterone secreted during exercise reduces urinary loss of water and sodium like ADH. This helps to maintain fluid balance in the presence of excessive sweating during exercise.

6. Adrenaline and Noradrenaline secretion is significantly increased in intense exercise. These hormones mobilize fatty acids and glucose, and thus improve the availability of fuel.

7. Insulin secretion is decreased during exercise. However, due to training, tissue sensitivity to insulin improves at rest. The improved sensitivity at rest accounts for the improvement in glucose tolerance test seen as a result of regular exercise. Because of this effect, exercise is considered one of the most useful components of treatment of diabetes.

8. Glucagon Prolonged exercise stimulates secretion of glucagon. It mobilizes glucose from glycogen and fatty acids from the adipose tissue, thereby improving fuel availability during prolonged exercise.

EFFECTS OF TRAINING

Training to the body tissues is provided by different sets of exercise regimes. Endurance training (aerobic) produces different effects in the skeletal muscles. Only aerobic exercises produce cardiovascular conditioning.

Usefulness of training to the body systems is as follows:

- Training is most essential for the performance by athletes and sportspersons, and forms the main aspect of sports physiology.
- Training by regular physical exercise is likely to slow the ageing process, which helps to prevent several degenerative and metabolic diseases, thereby making life healthier and longer.
- Patients who exercise regularly 'feel better'. Such effects may also be attributed to the release of endorphins during exercise, which are reported to relieve mental stress and induce a sense of well-being.
- Regular exercise is one of the most useful components of treatment of diabetes because it reduces the insulin requirement by virtue of improvement in the glucose tolerance.
- There is some evidence that regular exercise decreases the incidence and severity of myocardial infarctions.

Effects of training on the body tissues can be described as follows:

- Effects of training on cardiovascular system,
- Effects of training on respiratory system,
- Effects of training on skeletal muscles,
- Psychological effects of training.

Effects of Training on Cardiovascular System

Athletic training has the following effects on cardiovascular system:

1. Low Resting Heart Rate Consequently, trained athletes have a low resting heart rate (50–60/min) due to increase in the vagal tone. This is useful during exercise because it increases the range through which the heart rate can increase.

2. Higher Resting Stroke Volume The aerobic athletic training leads to a cardiac hypertrophy and an increase in end-diastolic volume, which increases the resting stroke volume to about 105 mL as compared to about 75 mL in an untrained individual.

3. Much larger Cardiac Output During Exercise Because of the low resting heart rate and higher resting stroke volume, a trained athlete can achieve much larger cardiac output during exercise than an untrained individual.

Effects of Training on Respiratory System

1. Increase in Maximal Oxygen Consumption VO_2 max increases by 5%–20% by conditioning (athletic training).

2. Increase in Maximal Minute Ventilation

- Endurance (aerobic) training increases maximal minute ventilation that is achieved during exercise.
- Specific respiratory muscle training allows one to increase the duration and intensity of exercise.

3. Increase in Pulmonary Oxygen Diffusing Capacity Athletic training increases the diffusion capacity of lungs for oxygen because by training the pulmonary capillary density increases.

Effects of Training on Skeletal Muscles

Increased Muscle Strength due to training results from:

- *Increase in muscle mass*, which is due to an increase in the size of muscle fibres *(hypertrophy)* and not due to increase in the number of muscle fibres (hyperplasia).

Changes in the Muscle Fibres, which enhance the capacity of the muscles to extract more O_2 and improve the ability of the muscle fibres to provide energy during prolonged exercise, are as follows:

- Increase in the capillary network,
- Increase in the number of mitochondria in the muscle fibres,
- Increase in the mitochondrial enzymes involved during oxidative metabolism,
- Increase in the muscle glycogen stores,
- Increase in the stored triglycerides.

Psychological Effects of Training

Regular training improves the psychology of the individual, and, thus, the psychic stimuli to the vasomotor centre and respiratory centres are reduced. Consequently, during exercise, the following takes place:

- Less increase in the sympathetic activity
- Less decrease in the parasympathetic activity

SELF-ASSESSMENT

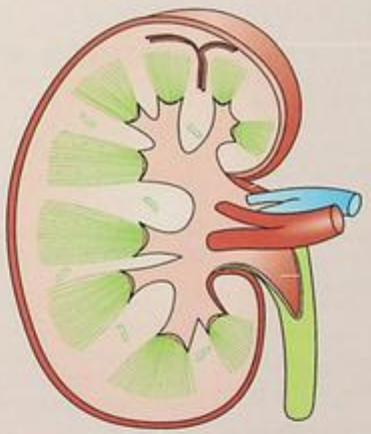
1. Discuss briefly:
   - Cardiovascular adjustments during exercise
   - Respiratory responses during exercise
   - Effect of training on exercise
2. Write notes on:
   - Oxygen debt
   - Endocrine changes during exercise
   - Grading of exercise

SECTION 6

Excretory System

SECTION OUTLINE

6.1 Kidneys: Functional Anatomy and Blood Flow
6.2 Physiology of Excretory System
6.3 Physiology of Acid–Base Balance
6.4 Applied Renal Physiology Including Renal Function Tests
6.5 Physiology of Micturition



Concept of excretory system: *Excretion*: Literally, the word excretion means elimination of any matter from the body of an organism. The organs which are involved in the process of excretion include the following:

- *Kidneys*, which excrete water and water-soluble waste products
- *Lungs*, which excrete carbon dioxide, water vapours and other volatile substances such as acetone
- *Skin*, which excretes water and salts, mainly in the form of sweat
- *Gastrointestinal tract*, which excretes faeces (excreta)

However, *sensu stricto*, the term excretion refers to elimination of principal products of metabolism except carbon dioxide. The principal products of metabolism, other than carbon dioxide, are ammonia, urea, uric acid, creatinine, various pigments and inorganic salts.

Excretory organs: In the strictest sense, kidneys are the excretory organs. Together with a pair of ureters and a urinary bladder, kidneys constitute the excretory system.

Functions of Excretory Kidney

The Kidneys Serve Several Major Functions:

1. *Excretory function*: As mentioned above, the kidneys excrete a number of end products of metabolism in urine. Thus, the formation of urine is the major function of kidneys. The kidneys eliminate these substances from the body at a rate that matches their production. In addition to the metabolic wastes, the kidneys also excrete foreign substances from the body, such as drugs, pesticides and other chemicals ingested in food.
2. *Regulation of water and inorganic ion balance*: Control of volume of body fluids and their inorganic ion balance is an important homeostatic role of kidneys.
3. *Regulation of acid–base balance*: Kidneys, in coordination with lungs, liver and buffers in the body, play a role in regulation of acid–base balance.
4. *Hormonal function*: As an endocrine gland, kidneys produce and secrete renin, calcitriol and erythropoietin.

6.1 Kidneys: Functional Anatomy and Blood Flow

CHAPTER OUTLINE

Functional Anatomy of Kidneys
Gross Anatomy of Kidney
Microscopic Structure of Kidney
Structure of the Nephron
Types of Nephrons
Juxtaglomerular Apparatus

Renal Blood Flow
Renal Blood Vessels
Arrangement of Arterial Vessels
Arrangement of Venous Vessels
Characteristics of Renal Blood Flow
Regulation of Renal Blood Flow

FUNCTIONAL ANATOMY OF KIDNEYS

Gross Anatomy of Kidney

Location The kidneys are bean-shaped reddish-brown organs that lie retroperitoneally on the posterior abdominal wall, one on each side of the vertebral column at the level of T_{12}–L_1 vertebrae.

Each kidney in an adult human weighs about 150 g and measures approximately 10 cm in length, 5 cm in width and 2.5 cm in thickness.

Renal Hilum and Sinus is a vertical cleft present on the concave medial margin. It is the entrance to the space within the kidney – the renal sinus. Through renal hilum the renal artery enters, and the renal vein and renal pelvis leave the renal sinus. The *renal sinus* is thus occupied by the renal pelvis, calyces, vessels, nerves and a variable amount of fat.

Renal Pelvis is the flattened, funnel-shaped expansion of the superior end of ureter. Within the renal sinus, the pelvis divides into two (or three) parts called *major calyces*. Each major calyx divides into a number of *minor calyces*. The end of each minor calyx is shaped like a cup into which fits a projection of kidney tissue called renal papilla (the apex of renal pyramid).

Internal Structure: The kidney, as seen in the coronal section through the organ, exhibits that kidney tissue consists of an outer region called the cortex and an inner region called the medulla (Fig. 6.1-1B).

Cortex: The renal cortex can be divided into the following two parts, which are continuous with each other:

- ***Cortical arches*** or cortical lobules refer to the tissue lying between the bases of pyramids and surface of the kidney.
- ***Renal columns*** refer to the cortical tissue that lies in between the pyramids.
- ***Lobe of kidney***: Each pyramid, surrounded by a shell of cortex, constitutes a lobe of the kidney.

Medulla It is made up of triangular areas of renal tissue that are called the renal pyramids. Pyramids are 4–14 in number and separated from each other by cortical columns of Bertin. Each pyramid has a base directed towards the cortex and an apex (or renal papilla) which is directed towards the renal pelvis and fits into the minor calyx. The medulla can be subdivided into the following two parts:

- ***Outer medulla*** that is further subdivided into the outer stripe and the inner stripe
- ***Inner medulla***, also called the papillary zone

Microscopic Structure of Kidney

Microscopically, the cortex and medulla of the kidney are composed of nephrons, blood vessels, lymphatics and nerves.

Nephron is a structural and functional unit of the kidney. Each kidney contains approximately 1.2 million nephrons. Each nephron is capable of forming urine.

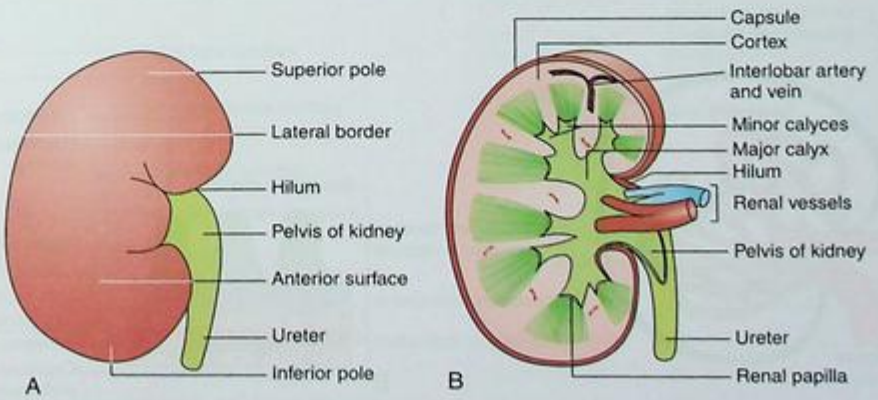


Figure 6.1-1 (A) Gross anatomical features and (B) coronal section through human kidney.

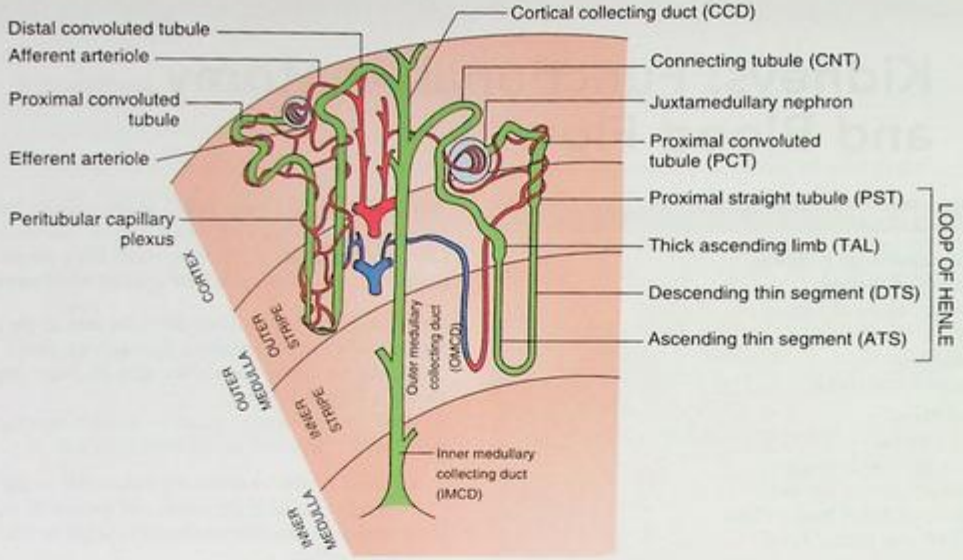


Figure 6.1-2 Parts of a typical nephron. Organization of cortical and juxtamedullary nephrons showing different parts. Note differences between two types of nephrons.

Structure of the Nephron Each nephron consists of the following two major parts (Fig. 6.1-2):

- Renal corpuscle
- Renal tubule

Renal Corpuscle Renal corpuscle or Malpighian corpuscle is a rounded structure comprising glomerulus surrounded by a glomerular capsule (Fig. 6.1-3A).

Glomerulus Glomerulus refers to a rounded tuft of anastomosing capillaries. Blood enters the glomerulus through an *afferent arteriole* and leaves it through an *efferent arteriole* (note that the efferent vessel is an arteriole and not a venule).

Glomerular Capsule Glomerular capsule, also known as Bowman's capsule, encloses the glomerulus and is composed of two layers: inner layer covering the glomerular capillaries, called the *visceral layer*, and outer layer, called the *parietal layer*. In fact, Bowman's capsule represents the cup-shaped blind beginning of the renal tubule. The space between the visceral and parietal layers of the capsule (called Bowman's space or urinary space) is continuous with the lumen of the renal tubule.

Ultrastructure of Glomerular Membrane Glomerular membrane refers to the membrane that separates the blood of the glomerular capillaries from the fluid present in Bowman's space. It is also called the filtration barrier and consists of the following three major layers (Fig. 6.1-3B):

1. ***Capillary endothelium:*** It is fenestrated (i.e. it contains pores of diameter 70–90 nm) and is freely permeable to water, small solutes and even to small proteins.

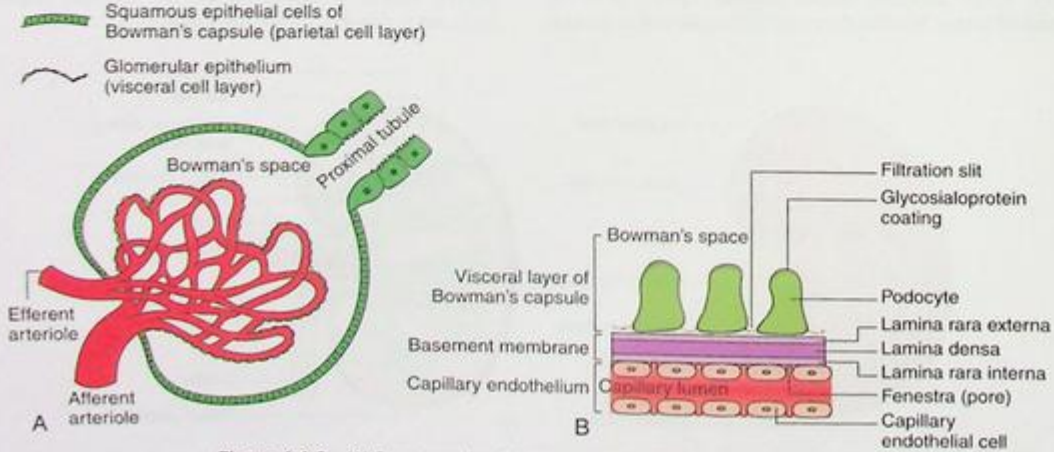


Figure 6.1-3 (A) Structure of a glomerulus and (B) glomerular membrane.

2. ***Basement membrane:*** It consists of a matrix of glycoproteins and mucopolysaccharides. No pores have been demonstrated in the basement membrane; however, its permeability corresponds to the pore size (of about 8 nm).
3. ***Bowman's visceral epithelium*** or the inner layer of Bowman's capsule is formed by special cells called *podocytes*. The podocytes have finger-like processes that interdigitate to cover the basement membrane and are separated by gaps called the *filtration slits* (of diameter approximately 25 nm).

Mesangium is an important component of the renal corpuscle; it consists of mesangium cells that are present between the capillary endothelial cells and the basement membrane. These cells provide a structural support for the glomerular capillaries, secrete the extracellular matrix and exhibit phagocytic activity.

Renal Tubule Renal tubule is a long complicated tubule that is divisible into the following main parts (Fig. 6.1-2):

1. ***Proximal tubule:*** The proximal tubule initially forms several coils, a proximal convoluted tubule, followed by a straight segment, a proximal straight tubule or *pars recta* that descend towards the medulla.
2. ***Loop of Henle*** that consists of the following:
   - Descending thin segment (DTS)
   - Ascending thin segment (ATS)
   - Thick ascending limb (TAL)

   Near the end of the TAL, the nephron passes between its afferent and efferent arterioles. This short segment of the TAL is called the *macula densa*.
3. ***Distal convoluted tubule:*** It begins at a short distance beyond the macula densa and extends to a point in the cortex when the connecting tubules of two or more nephrons join to form the cortical collecting ducts.
4. ***Collecting duct:*** The collecting duct is divisible into the following three parts:
   - *Cortical collecting duct* is the portion present in the cortex.
   - *Outer medullary collecting duct* is the portion present in the outer medulla.
   - *Inner medullary collecting duct* (IMCD) is the portion present in the inner medulla. Several IMCDs coalesce together before finally opening at the tip of the renal papilla.

Characteristics of Epithelium Lining the Renal Tubule The epithelium lining the different segments of renal tubule has some special characteristic features which are suited to perform specific transport functions (Figs 6.1-2 and 6.1-4).

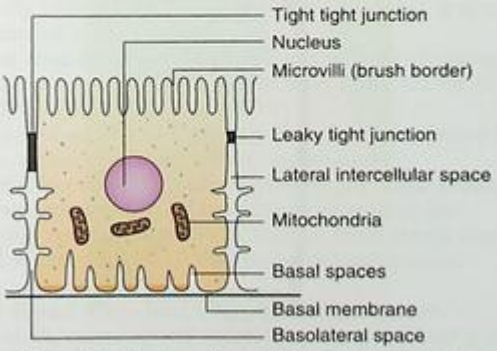


Figure 6.1-4 Ultrastructure of an epithelial cell lining the proximal convoluted tubule.

Type of cells: The cells lining the renal tubule are mostly cuboidal, except in the thin segment where these are flat or squamous type.

Apical surface of cuboidal cells bears a few microvilli in general, which are numerous, dense and amplified in proximal tubule cells to form the so-called brush border.

Basolateral membrane of the proximal convoluted tubule cells, thick ascending segment cells and distal convoluted tubule cells is highly invaginated and contains many mitochondria. These infoldings create basal spaces.

Lateral surfaces of the cells of renal tubules bear the lateral cell processes, which interdigitate with lateral processes of the adjacent cells. *Lateral intercellular* spaces are present in between the interdigitations. Lateral intercellular spaces do not communicate with the basal spaces. The lateral surfaces of cells form tight junctions.

Cortical collecting duct is composed of the following two cell types:

- ***Principal cells*** have a moderately invaginated basolateral membrane and contain few mitochondria.
- ***Intercalated cells*** have a high density of mitochondria.

Inner medullary collecting duct is composed of a single layer of cells that have poorly developed apical and basolateral surfaces and a few mitochondria.

Types of Nephrons There are two types of nephrons: cortical (superficial) and juxtamedullary. Differences between the cortical and juxtamedullary nephrons are depicted in Fig. 6.1-2 and Table 6.1-1.

Juxtaglomerular Apparatus Juxtaglomerular (JG) apparatus, as the name indicates ('juxta' meaning 'near'), refers to the

TABLE 6.1-1 Differences between Cortical and Juxtamedullary Nephrons

Feature	Cortical Nephron	Juxtamedullary Nephron
Location of glomerulus	Upper region of cortex	Near the junction of cortex and medulla
Percentage of total nephron	85%	15%
Size of glomeruli	Small	Larger
Size of loop of Henle	Small, extend up to the outer layer of medulla	Large, extend deep into the medulla
Descending limb of loop of Henle comprises:	Thin segment	Thin segment
Ascending limb of loop of Henle comprises:	Thick segment	Thin segment
Efferent arterioles	Have a large diameter and break up into peritubular capillaries	Have a small diameter and continue as vasa recta
Rate of filtration	Slow	High
Major function	Excretion of waste products in urine	Concentration of urine by the counter current system

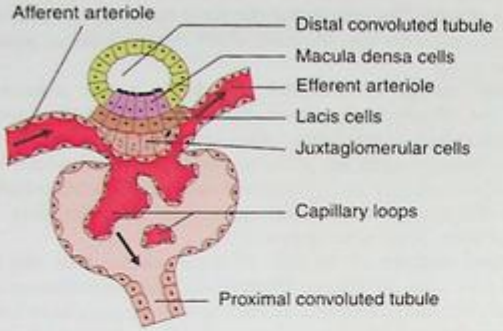


Figure 6.1-5 Juxtaglomerular apparatus.

collection of specialized cells located very near to the glomerulus. It forms the major component of the renin–angiotensin–aldosterone system. The JG apparatus comprises the following three types of cells (Fig. 6.1-5):

- Juxtaglomerular cells
- Macula densa cells
- Mesangial cells

1. Juxtaglomerular Cells JG cells are specialized *myoepithelial* (modified vascular smooth muscle) cells located in the media of the *afferent arteriole* in the region of JG apparatus.
Characteristic features of JG cells are as follows:

- They synthesize, store and release an enzyme called *renin*. Renin is stored in the secretory granules of JG cells.
- They are densely innervated by the *sympathetic nerve* fibres and release their renin content in response to the sympathetic discharge.
- They act as *baroreceptors* (tension receptors) and respond to changes in the transmural pressure gradient between the afferent arterioles and the interstitium.
- As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypovolaemia or decreased renal perfusion pressure.

2. Macula Densa Cells Macula densa cells refer to the specialized renal tubular epithelial cells of a short segment of the thick ascending limb of loop of Henle, which passes between the afferent and efferent arterioles supplying its glomerulus of origin.
Characteristic Features of macula densa cells are as follows:

- These cells are in direct contact with the mesangial cells and in close contact with the JG cells.
- They act as *chemoreceptors* and are stimulated by decreased NaCl concentration, thereby causing increased renin release.

3. Mesangial Cells Mesangial cells or *lacis* cells are the interstitial cells of the JG apparatus.
Characteristic features of these cells are as follows:

- They are in contact with both the macula densa cells (on one side) and JG cells (on the other side).
- Functionally, these cells possibly relay the signals from macula densa to the granular cells after modulating the signals. In this way, a decreased intraluminal Na^+ load, Cl^- load or both in the region of macula densa stimulate the JG cells to secrete renin.

RENAL BLOOD FLOW

Renal Blood Vessels

Arrangement of Arterial Vessels (Renal Artery and Its Branches) in the Kidney (Fig. 6.1-6)

Renal artery (one for each kidney), a major branch from the aorta, divides into a number of lobular arteries at the hilum of kidney.
Lobular artery (one for each pyramid) divides into two or more interlobar arteries.
Interlobar arteries enter the tissue of the renal columns and run towards the surface of kidney. Reaching the level of the bases of the pyramids, the interlobar arteries divide into arcuate arteries.
Arcuate arteries run at right angles to the parent interlobar arteries. They lie parallel to the renal surface at the junction of pyramid and cortex. They give a series of interlobular arteries.
Interlobular arteries run through the cortex at right angles to the renal surface to end in a subcapsular plexus. Each interlobular artery gives off a series of afferent arterioles.
Afferent arterioles: Each afferent arteriole enters Bowman's capsule and divides into a rounded tuft of anastomosing capillaries called *glomerulus*. The glomerular capillaries join to form the efferent arteriole.
Efferent arterioles leaving the glomeruli of two types of nephrons exhibit the following behaviours:

- *Efferent arterioles* arising from the cortical nephrons divide into the *peritubular capillaries* that surround the proximal and distal convoluted tubules forming a rich meshwork of microvessels. These capillaries drain into the interlobular veins.

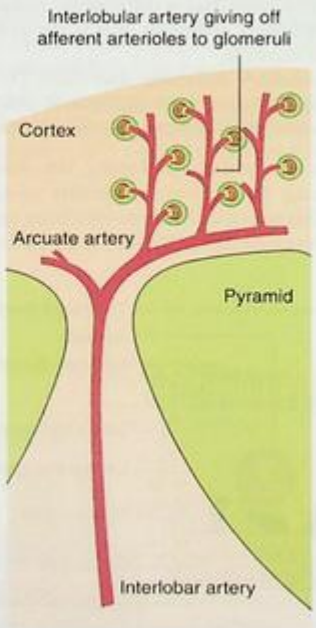


Figure 6.1-6 Scheme to show arrangement of arteries within the kidney.

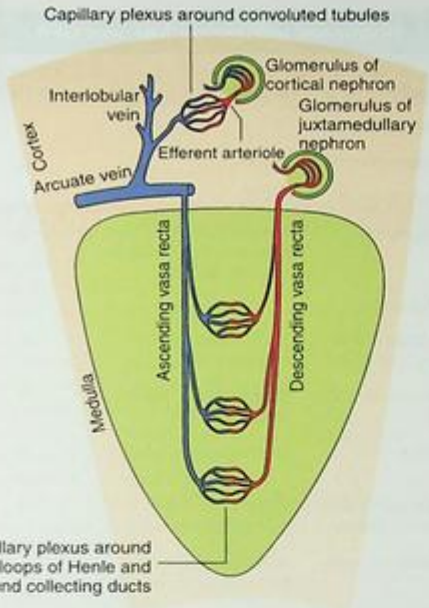


Figure 6.1-7 Scheme to show the behaviour of efferent arterioles arising from the glomeruli of cortical and juxtamedullary nephrons.

- *Efferent arterioles arising from the juxtamedullary nephrons* give rise to *vasa recta*. The *vasa recta* descend with the long loops of Henle into renal medulla, return to the area of the glomerulus and drain into the interlobular or arcuate vein.

Side branches arising from the vasa recti form a capillary network at different levels along the loop of Henle (Fig. 6.1-7).

Arrangement of Venous Vessels (Renal Veins) The corresponding veins which run parallel to the arterial vessels are the interlobular veins, the arcuate veins, the interlobar veins and the renal veins which exit the kidney at hilus.

Characteristics of Renal Blood Flow

Amount and Rate of Blood Flow

- *Rate of renal blood flow* under basal conditions, approximately 1200 mL/min (400 mL/100 g tissue/min), is very high compared to other tissues.
- *Total renal blood flow* is approximately 20% of resting cardiac output, whereas the two kidneys make <0.5% of total body weight.
- *Higher blood flow* to kidneys is related to its excretory function, rather than its metabolic requirement.
- *In the face of blood pressure changes*, the renal blood flow shows remarkable constancy due to autoregulation.
- *During exercise*, sympathetic tone to renal vessels increases and shunts renal blood flow to the skeletal muscles.

Renal Blood Flow and Oxygen Consumption

- *Renal* O_2 consumption (approximately 6 mL/100 g tissue/min) is very high, being only second to heart (i.e. 8 mL/100 g tissue/min) in the body.

Hydrostatic Pressure in Renal Vessels and Their Physiological Significance

- ***Glomerular capillaries*** have a relatively high hydrostatic pressure (45 mm Hg), which is an important factor in the formation of glomerular filtrate.
- ***Peritubular capillaries*** have very low hydrostatic pressure (8 mm Hg only) due to drop in the pressure in efferent arterioles. This low hydrostatic pressure in the peritubular capillaries facilitates the reabsorptive function of the proximal and distal *convoluted* tubules.
- ***Renal veins*** have a hydrostatic pressure of only 4 mm Hg.

Regulation of Renal Blood Flow

The regulatory mechanisms affect the renal blood flow (RBF) and glomerular filtration rate (GFR) by changing the arteriolar resistance. The *relationship between selective changes in the resistance of afferent and/or efferent arterioles and RBF and GFR* (Fig. 6.1-8) is as follows:

- *Constriction of afferent arteriole* decreases both RBF and GFR without any change in the filtration fraction (FF) (Fig. 6.1-8A).
- *Dilatation of the afferent arteriole* increases both RBF and GFR without change in FF (Fig. 6.1-8B).
- *Constriction of the efferent arteriole* decreases the RBF and increases GFR and FF (Fig. 6.1-8C).
- *Dilatation of the efferent arteriole* increases the RBF and decreases GFR and FF (Fig. 6.1-8D).

Regulatory mechanisms of RBF include the following:

- Autoregulation
- Hormonal regulation
- Nervous regulation

Autoregulation of Renal Blood Flow The RBF and thus the GFR remain constant over a wide range of renal arterial

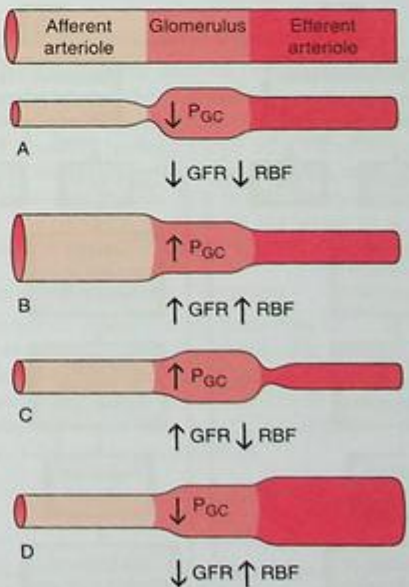


Figure 6.1-8 Relationship between selective changes in arteriolar resistance and of either afferent or efferent arteriole and renal blood flow (RBF) and glomerular filtration rate (GFR). P_{GC}, hydrostatic pressure in glomerular capillaries.

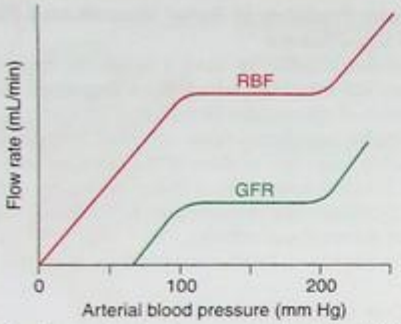


Figure 6.1-9 Autoregulation keeps renal blood flow (RBF) and glomerular filtration rate (GFR) constant over a wide range of arterial pressures (80–200 mm Hg).

pressures (80–200 mm Hg) (Fig. 6.1-9). This occurs due to an intrarenal mechanism known as autoregulation.

Mechanisms of Autoregulation The following two mechanisms are considered responsible for the autoregulation of RBF and GFR:

1. ***Myogenic mechanism:*** It is related to an intrinsic property of vascular smooth muscle: the tendency to contract when it is stretched. Thus, when renal arterial pressure is raised, the afferent arterioles are stretched, which contract and increase the vascular resistance. The increased vascular resistance offsets the effect of increased arterial pressure, thereby maintaining a constant RBF and GFR (Fig. 6.1-9).
2. ***Tubuloglomerular feedback mechanism:*** Tubuloglomerular feedback (TGF) mechanism is based on the NaCl concentration of tubular fluid. It involves a feedback loop, which operates as shown in Fig. 6.1-10.

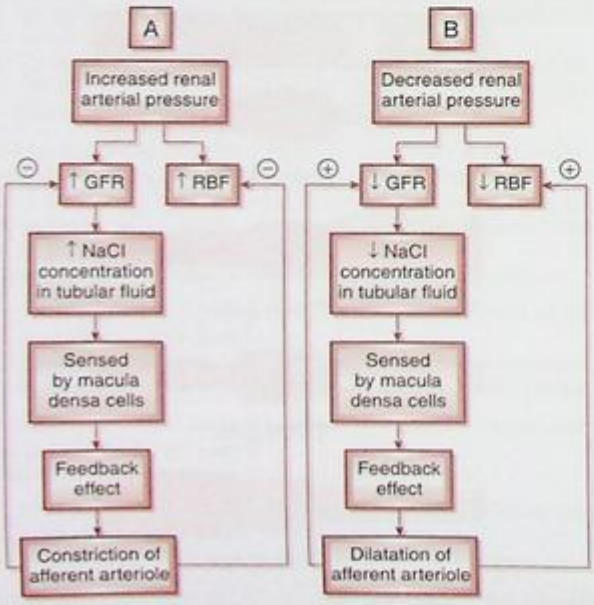


Figure 6.1-10 Tubuloglomerular feedback mechanism, which maintains a constant RBF and GFR (A) when renal arterial pressure increases; and (B) when renal arterial pressure decreases.

TABLE 6.1-2 Hormones Influencing RBF and GFR

Hormone	Stimulus	Effect on GFR	Effect on RBF
Vasoconstrictors			
• Norepinephrine	↓ECV	↓	↓
• Angiotensin II	↓ECV	↓	↓
• Endothelin	↑Stretch, ↓ECV, angiotensin II, bradykinin, epinephrine	↓	↓
Vasodilators			
• Prostaglandins (PGI_2 and PGE_2)	↓ECV, stretch, angiotensin II	NC	↑
• Nitric oxide (NO)	↑Stretch, ACh, histamine, bradykinin, ATP	↑	↑
• Bradykinin	Prostaglandin, ↓ACE	↑	↑
• Atrial natriuretic peptide (ANP)	↑ECV	↑	↑
• Glucocorticoids	Administration in therapeutic dose	↑	↑
• Dopamine	–	NC	↑
• Histamine	Inflammation, injury	NC	↑

Note: ACE, angiotensin-converting enzyme; ECV, effective circulatory volume; NC, no change.

Hormonal Regulation As mentioned above, despite autoregulation, several hormones and other factors have a major effect on RBF and GFR by affecting afferent and/or efferent arteriolar resistance (Table 6.1-2).

Nervous Regulation The afferent and efferent arterioles are innervated by sympathetic nerve fibres from T_1 to L_2 intermediolateral grey segments of spinal cord through the splanchnic nerves. The sympathetic cell bodies are located in the superior mesenteric ganglion.

- *Under normal circulatory conditions,* sympathetic tone is minimum.
- *Strong acute stimulation* of sympathetic nerves may produce a marked fall in RBF (even to 10%–30% of normal) temporarily due to constriction of both afferent and efferent arterioles. This effect is mediated mainly by α_1-adrenergic receptors, and to a lesser extent by postsynaptic α_2-adrenergic receptors.

SELF-ASSESSMENT

1. Describe briefly the renal blood flow and its regulation.
2. Write notes on:
   - Nephron
   - Juxtaglomerular apparatus
   - Endocrine functions of kidney
   - Tubuloglomerular feedback mechanism

6.2 Physiology of Excretory System

CHAPTER OUTLINE

Urine Formation
Glomerular Filtration
Composition of Glomerular Filtrate
Dynamics of Glomerular Filtration
Normal Glomerular Filtration Rate
Factors Affecting Glomerular Filtration Rate
Tubular Reabsorption and Secretion
Transport Across Different Segments of Renal Tubule
Transport Across Proximal Tubule
Transport Across Loop of Henle
Transport Across Distal Tubules and Collecting Duct
Renal Handling of Common Solutes and Water
Renal Handling of Sodium and Water
Renal Handling of Potassium
Renal Handling of Glucose
Renal Handling of Proteins, Peptides and Amino Acids
Renal Handling of Urea
Renal Handling of Uric Acid
Renal Handling of Para-amino Hippuric Acid
Concentration and Dilution of Urine
Purpose of Concentration and Dilution of Urine
Principal Factors
Medullary Hyperosmolality and Medullary Gradient
Countercurrent System
Mechanism of Urine Dilution and Concentration
Production of Diluted Urine
Production of Concentrated Urine
Urine Volume and Osmolality Changes in Response to Water Intake and Water Deprivation
Acidification of Urine
Hydrogen Ion Secretion
Reabsorption of Filtered HCO_3^-
Generation of New HCO_3^-
Excretion of H^+ as Titrable Acid
Excretion of H^+ as Ammonium Ion

URINE FORMATION

Processes Concerned with Urine Formation

The main function of the kidneys is to clear waste products from the blood and excrete them in the urine. The kidneys accomplish their excretory function by the formation of urine.

The following three processes are involved in the urine formation (Fig. 6.2-1):

- Glomerular filtration
- Tubular reabsorption
- Tubular secretion

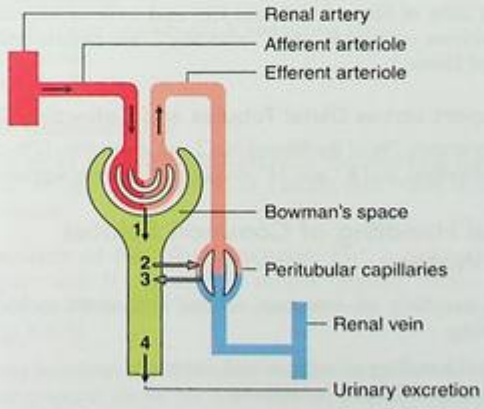


Figure 6.2-1 Steps involved in the formation of urine: 1, filtration; 2, reabsorption; 3, secretion; and 4, excretion.

Glomerular Filtration

Glomerular filtration refers to the process of ultrafiltration of plasma from the glomerular capillaries into Bowman's capsule.

Composition of Glomerular Filtrate

The unique characteristic features of the glomerular filtration membrane determine the composition of the glomerular filtrate; in that sense, it is like that of the plasma except for the absence of proteins (colloids) and cells. Filtration membrane permeability alteration in diseases, however, may alter diffusibility of colloids and cells. As a result, filtration of proteins is increased, and albumin appears in the urine in a significant amount (*albuminuria or proteinuria*).

Dynamics of Glomerular Filtration

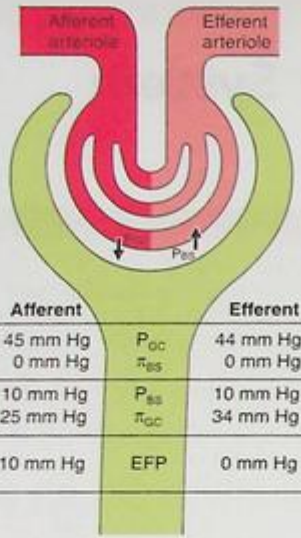
The forces which determine the bulk flow or ultrafiltration of protein-free plasma across the glomerular membrane are the same, which determine the formation of tissue fluid.

The glomerular filtration rate (GFR) will depend on the balance of Starling forces (Fig. 6.2-2). According to the Starling hypothesis, GFR can be expressed as

$$GFR = K_f [(P_{GC} - P_{BS}) - (\pi_{GS} - \pi_{BS})]$$

Where,

GFR is the filtration across the glomerular membrane.
K_f is the filtration coefficient of the glomerular membrane. The filtration coefficient (K_f) normally equals 12.5 m^3/min/mm Hg.
P_{GC} is the glomerular capillary hydrostatic pressure. Its normal value is about 45 mm Hg.



	Afferent		Efferent	
Outward forces	45 mm Hg	P_{GC}	44 mm Hg	Outward forces
	0 mm Hg	π_{BS}	0 mm Hg	
Inward forces	10 mm Hg	P_{BS}	10 mm Hg	Inward forces
	25 mm Hg	π_{GC}	34 mm Hg	
	10 mm Hg	EFP	0 mm Hg	

Figure 6.2-2 Depiction of the Starling forces across the glomerular filtration membrane. P_{GC}, glomerular capillary hydrostatic pressure; P_{BS}, Bowman's space hydrostatic pressure; π_{GC}, glomerular capillary oncotic pressure; π_{BS}, Bowman's space oncotic pressure.

P_{BS} is Bowman's space hydrostatic pressure. Its normal value is about 10 mm Hg.
π_{GC} is the glomerular capillary oncotic pressure. Its normal value is 25 mm Hg.
π_{BS} is Bowman's space oncotic pressure. Its normal value is zero because glomerular filtrate contains no proteins.

Effective filtration pressure is the net outward force and is calculated as the difference between the outwardly (i.e. P_{GC} and π_{BS}) and inwardly (P_{BS} and π_{GC}) directed forces (Fig. 6.2-4). Thus, under normal circumstances, we have

$$GFR = 12.5\,(45 - 10) - (25 - 0) = 125 \text{ mL/min}$$

Normal Glomerular Filtration Rate

The normal GFR in an average-sized man is about 125 mL/min (range 90–140 mL/min). Thus, in 24 hours, 180 L of plasma is filtered. The values in women are 10% lower than those in men.

Factors Affecting Glomerular Filtration Rate

1. **Filtration coefficient (K_f):** Increased K_f raises GFR and decreased K_f reduces GFR. As mentioned earlier, K_f is the product of permeability and filtration area of the glomerular capillary membrane.
2. **Hydrostatic pressure in Bowman's space fluid (P_{BS})** opposes filtration and therefore GFR is inversely related to it. It is increasing in an acute obstruction of urinary tract (e.g. a ureteric obstruction by stone); therefore, GFR decreases.
3. **Glomerular capillary hydrostatic pressure (P_{GC}):** GFR is mainly dependent on arterial pressure, renal blood flow, afferent arteriolar resistance and efferent arteriolar resistance.
4. **Glomerular capillary oncotic pressure (π_{GC}):** GFR is inversely proportional to π_{GC}. In hyperproteinaemia and in haemoconcentration, the π_{GC} is raised, leading to a decrease in GFR. Conversely, in hypoproteinaemia and haemodilution, the π_{GC} is reduced, leading to increased GFR.

Tubular Reabsorption and Secretion

Of the 180 L glomerular filtrate formed per day, about 1.5 L (i.e. less than 1%) per day is excreted as urine. The different segments of the renal tubule, namely proximal tubule, loop of Henle, distal tubule and collecting duct determine the composition and volume of the urine by the process of *selective reabsorption* of solutes and water and *selective secretion* of solutes.

Tubular reabsorption denotes the active transport of solutes and passive movement of water from the tubular lumen into the peritubular capillaries. In other words, reabsorption is the removal of substances of nutritive value, such as glucose, amino acids, electrolytes (Na^+, K^+, Cl^-, HCO_3^-) and vitamins from the glomerular filtrate. Small proteins and peptide hormones are reabsorbed in the proximal tubules by endocytosis.

Tubular secretion refers to the transport of solutes from the peritubular capillaries into the tubular lumen, i.e. it is the addition of a substance to the glomerular filtrate.

Active secretion of substances occurs into the tubular fluid with the help of certain nonselective carriers. The carrier which secretes para-aminohippuric (PAH) acid can also secrete uric acid, bile acids, oxalic acid, penicillin, probenecid, cephalothin and furosemide.

Transport across Different Segments of Renal Tubule

The substances transported across the different segments of renal tubules are described below and are enlisted in Table 6.2-1.

Transport across Proximal Tubule

The proximal tubule reabsorbs the following:

- Approximately 67% of the filtered water, Na^+, Cl^-, K^+ and other solutes
- Almost all the glucose and amino acids filtered by the glomerulus

The proximal tubule does not reabsorb inulin, creatinine, sucrose and mannitol.

The proximal tubule secretes H^+, PAH, urate, penicillin, sulphonamides and creatinine.

Transport across Loop of Henle

About 20% of filtered Na^+ and Cl^- and 15% of filtered water and cations, such as K^+, Ca^{2+} and Mg^{2+}, are reabsorbed in the loop of Henle.

Transport across Distal Tubules and Collecting Duct

Approximately 7% of the filtered NaCl and about 8%–17% of water are reabsorbed, and K^+ and H^+ are secreted in these segments.

Renal Handling of Common Solutes and Water

Renal handling of common solutes and water includes the following:

- Renal handling of sodium and water
- Renal handling of potassium
- Renal handling of glucose
- Renal handling of proteins, peptides and amino acids

TABLE 6.2-1 Transport of Substances Across Different Segments of Renal Tubule

REABSORPTION			
Active	**Passive**	**Nonreabsorption**	**Secretion**
Proximal Tubule			
Na^+	Cl^-	Inulin	H^+
K^+	HCO_3^-	Creatinine	Water
Ca^{2+}	HPO_4^-	Sucrose	Penicillin
Mg^{2+}	Water	Mannitol	Sulphonamide
HPO_4^{2-}	Urea		Creatinine
SO_4^{2-}			Urate
NO_3^-			Water
Glucose			
Amino acids			
Protein			
Urate			
Vitamins			
Acetoacetate			
β-hydroxybutyrate			
Loop of Henle			
Na^+	Cl^-		
K^+	HCO_3^-		
Ca^{2+}	Water		
Distal Tubule and Collecting Duct			
Na^+	Cl^-		K^+
Ca^{2+}	HCO_3^-		H^+
Mg^{2+}	Water		
Water			

Renal Handling of Sodium and Water

Percentage reabsorption of the filtered sodium in different segments of the renal tubule is as follows:

- Proximal tubule: 67%
- Loop of Henle (mainly thick ascending limb): 20%
- Distal tubule: 7%
- Cortical collecting duct: 5%

Sodium Reabsorption

The process of sodium reabsorption in the proximal tubule is *isosmotic*, i.e. the reabsorption of sodium and water is exactly proportional.

Mechanisms of Na^+ Reabsorption Na^+ is reabsorbed by *cotransport with H^+* or organic solutes (*glucose, amino acids, phosphate and lactate*). The Na^+ absorption is a two-step process (Fig. 6.2-3).

Across the basolateral membrane, Na^+ moves against an electrochemical gradient via an Na^+–K^+–ATPase pump, which pumps Na^+ into the paracellular spaces and lowers the intracellular Na^+ concentration.

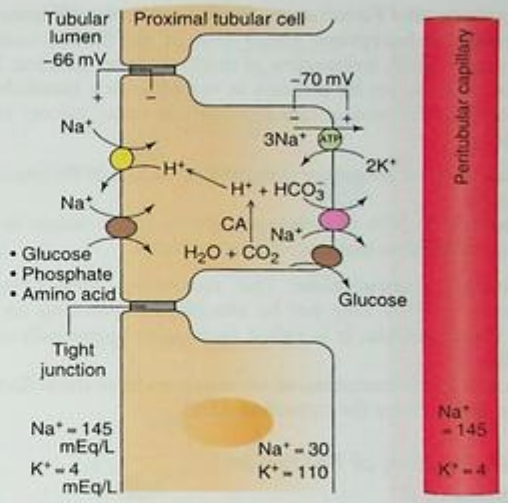


Figure 6.2-3 Mechanism of reabsorption of sodium and other solutes in the proximal tubule.

Across the apical membrane, the sodium moves down an electrochemical gradient as above. The entry of Na^+ is mediated by the specific antiporter and symporter proteins. These include the following:

- *Na^+–H^+* antiporter is the main determinant of Na^+ and H_2O reabsorption in the proximal tubule. Na^+–H^+ exchange is linked directly to the reabsorption of HCO_3^-.
- ***Note.*** Carbonic anhydrase inhibitors (e.g. acetazolamide) are diuretics that act in the early proximal tubule by inhibiting the reabsorption of filtered HCO_3^-.
- *Na^+*–glucose (and other organic solutes) symporter mechanisms are also involved in the entry of Na^+ in the proximal cells. The glucose, amino acids, phosphate and lactate are almost completely absorbed along with Na^+ by the symporter (carrier) proteins, which are different for different molecules.

Water Reabsorption

Site and Mechanism of Reabsorption Water is absorbed passively by osmosis in response to a transtubular osmotic gradient. The reabsorption of Na^+–HCO_3^- and Na^+–organic solutes across the proximal tubule establishes a transtubular osmotic gradient that provides the driving force for the passive absorption of water by osmosis. Rapid diffusion of water across the cell membrane occurs through water channels made up of proteins called *aquaporins*. Different types of aquaporins are aquaporin-1, -2, -5 and -9. Mostly, these aquaporins are present in the kidney. In the collecting ducts, reabsorption of water is controlled by ADH. Renal handling of water by different segments of renal tubule is discussed below.

Proximal tubule: passively reabsorbed (67%).
Loop of Henle

- Descending thin segment (DTS): passively reabsorbed (15%)
- Ascending thin segment (ATS): impermeable
- Thick ascending limb (TAL): impermeable

Distal tubule and collecting duct *(8%–17%)*

- Distal convoluted tubule (DCT): Impermeable

Obligatory and Facultative Reabsorption of Water

Obligatory reabsorption: About 85% of the filtered water is always reabsorbed, irrespective of the body water balance. This reabsorption occurs by osmosis in response to a transtubular osmotic gradient and is called obligatory (must occur) reabsorption.

- About 67% of obligatory reabsorption occurs in the proximal tubules.
- About 15%–18% of obligatory reabsorption occurs in the descending thin segment of loop of Henle.

Facultative reabsorption: The remaining 15%–18% of the water may or may not be absorbed depending on the body water balance. It is called facultative (optional) reabsorption.

Facultative reabsorption of water occurs from the collecting tubule and is under the control of ADH.

Renal Handling of Potassium

Functions of K^+

Potassium (K^+) is one of the most abundant cations in the body. It is the *principal intracellular cation*, and is equally important in the extracellular fluid for specific functions. Potassium is required for the following biochemical functions:

- Maintenance of intracellular osmotic pressure
- Optimal activity of enzyme pyruvate kinase (of glycolysis)
- Proper synthesis of DNA and proteins by ribosomes
- Optimal cell growth
- Transmission of nerve impulse
- Generation of cell membrane potential and muscle contraction
- Extracellular K^+ influences cardiac muscle activity
- Regulation of acid–base balance and water balance in the cells

Transport of Potassium across Major Nephron

Glomerular Filtration Filtration occurs freely across the glomerular capillaries; potassium is not bound to plasma proteins.

Tubular Reabsorption and Secretion As shown in Fig. 6.2-4, 67% of the filtered K^+ is reabsorbed in the proximal tubule, 20% in the loop of Henle and approximately 10% is delivered to the early distal tubule. In contrast to proximal tubule and loop of Henle, which are capable of reabsorbing only K^+, the distal tubule (DT) and collecting duct (CD) are able to either reabsorb or secrete K^+. The role of reabsorption or secretion by DT and CD depends on a variety of hormones and factors.

Reabsorption of K^+ by Proximal Tubule In proximal tubule, approximately 7% of the filtered K^+ is reabsorbed passively in proportion to the H_2O reabsorption (solvent drug) and about 60% of the filtered K^+ is reabsorbed actively by the paracellular transport mechanism.

The K^+ that exits from the basolateral membrane is immediately absorbed in the peritubular capillaries.

Reabsorption of K^+ by Loop of Henle About 20% of the filtered K^+ is reabsorbed in the *TAL* of the loop of Henle along with Na+ reabsorption by the following two mechanisms:

1. Na^+–K^+–$2Cl^-$ active transport mechanism
2. *Paracellular passive reabsorption*, occurring as a function of voltage gradient across TAL

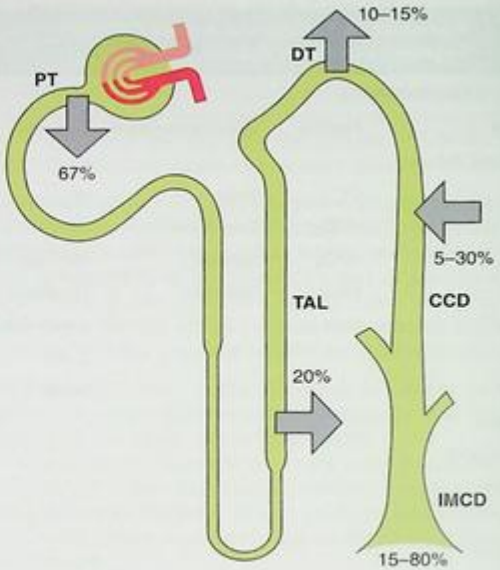


Figure 6.2-4 Potassium transport along the nephron.

Reabsorption and Secretion of K^+ by Distal Tubule and Collecting Duct *(Fig. 6.2-5)* Normally, K^+ is secreted in the distal convoluted tubule. However, when there is a need to conserve body K^+ (e.g. during K^+ depletion), K^+ is reabsorbed. Both secretion and reabsorption occur in the same

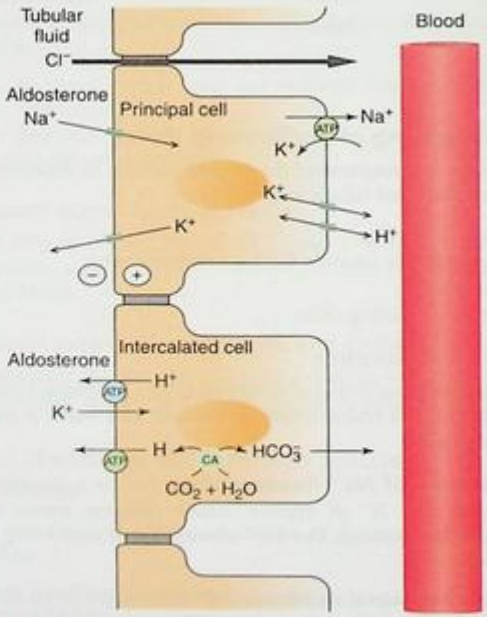


Figure 6.2-5 Mechanism of transport in principal cells and intercalated cells of the late distal tubule and collecting duct. CA, carbonic anhydrase.

cell, i.e. distal tubular cell, depending on the status of K^+ balance in the body.

Reabsorption of K^+ occurs only when the dietary intake is very low (i.e. during K^+ depletion). Under these circumstances, K^+ excretion can be as low as 1% of the filtered load because the kidneys conserve as much K^+ as possible.
Secretion of K^+ is variable and accounts for the wide range of urinary K^+ excretion, depending on the dietary K^+ intake, aldosterone levels, acid–base status and urine flow rate.

Factors that Regulate Urinary K^+ Excretion

Hormones and other factors involved in the regulation of K^+ tubular secretion and thus of urinary K^+ excretion include the following:

1. ***Plasma K^+ level***, which mainly depends on the following:
   Dietary intake of K^+ is an important determinant of K^+ secretion by principal cells (Fig. 6.2-6). Hyperkalaemia, resulting from a high K^+ diet or any other factor (e.g. rhabdomyolysis), stimulates K^+ secretion within minutes.
   Hypokalaemia, resulting from a low K^+ diet or other factors (e.g. diarrhoea), decreases K^+ secretion by mechanisms opposite to those described for hyperkalaemia.
2. ***Aldosterone:*** Aldosterone by its effect on the principal cell increases Na^+ reabsorption and K^+ secretion. About 2% of overall Na^+ absorption is affected by aldosterone (Fig. 6.2-5). *Aldosterone* also increases H^+ secretion by intercalated cells by stimulating the K^+–H^+–ATPase (in addition to its actions on the principal cells).

Renal Handling of Glucose

Glucose Reabsorption

Glucose is freely filtered into the glomerular filtrate. Filtration load of glucose increases in direct proportion to the plasma glucose concentration (P glucose). Filtered load of glucose = GFR × P glucose (P_G).
Mechanism of Tubular Reabsorption All the filtered glucose is completely reabsorbed into the proximal tubule by an active transport mechanism (Fig. 6.2-7).

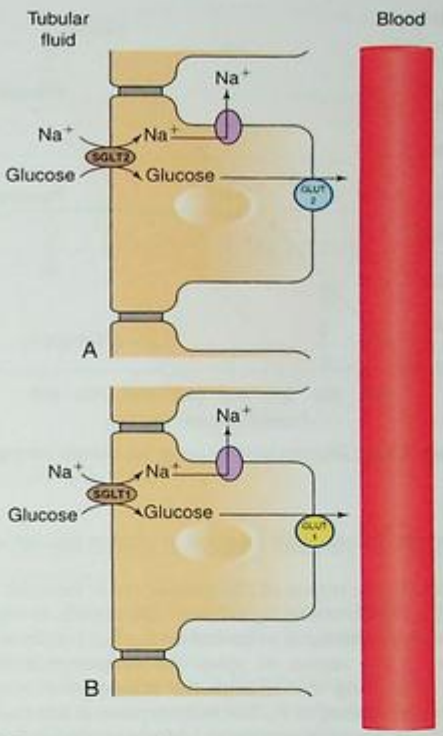


Figure 6.2-7 Mechanism of glucose reabsorption in the proximal tubule.

Carrier-mediated Na^+–glucose cotransport: Carrier protein located at the apical membrane in the proximal tubule reabsorbs glucose from tubular fluid into the blood.

- The carrier protein for glucose in early and late proximal tubules is called SGLT-2 and SGLT-1, respectively (SGLT = sodium-dependent glucose transporter).

Facilitated diffusion moves the glucose out of the cell through the basolateral membrane. The carrier for facilitated diffusion across the basolateral membrane in early and late proximal tubules is called GLUT-2 and GLUT-1, respectively (GLUT = glucose transporter).
Characteristics of Glucose Transport and Glucose Excretion Glucose is reabsorbed by a transport maximum process, i.e. there are a limited number of Na^+–glucose carriers. The characteristics of glucose transport and glucose excretion can be elicited from the glucose titration curve.

Glucose titration curve (Fig. 6.2-8) depicts the following:

Filtered load increases with the plasma glucose concentration (P_G).
Renal threshold, i.e. the plasma glucose concentration at which glucose first appears in the urine (glycosuria), is about 180–200 mg/dL. At plasma levels below the renal threshold, the reabsorption of glucose is complete (100%).
Transport maximum: As shown in Fig. 6.2-8, beyond a plasma glucose concentration of 350 mg/dL (T_{mG}), the reabsorption rate does not increase, i.e. remains constant and is independent of P_G. Therefore, as the T_{mG} is reached, the urinary excretion

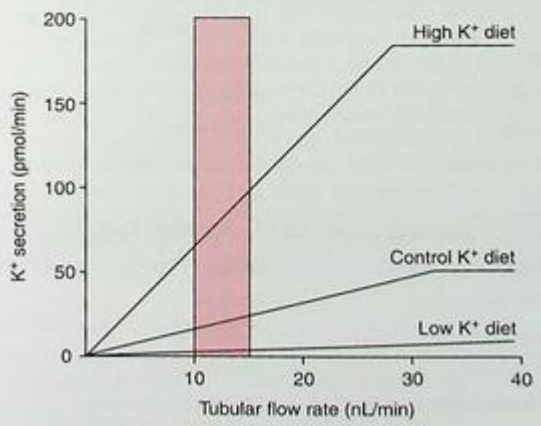


Figure 6.2-6 Effect of dietary intake of K^+ on the relationship between tubular flow rate and K^+ secretion by the distal tubule and collecting duct.

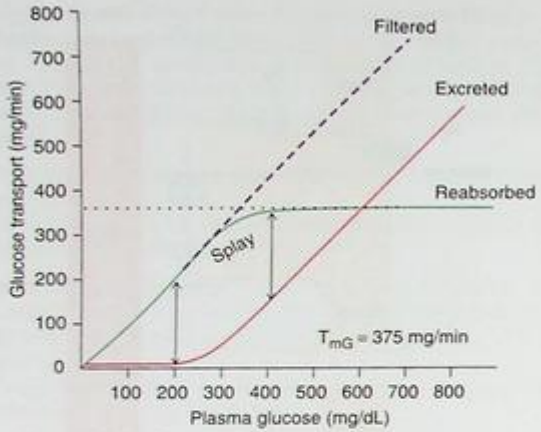


Figure 6.2-8 Glucose titration curve (for details, see text).

rate increases linearly with increase in plasma glucose concentration.

Splay refers to the region of the glucose curve between threshold and T_{mG}, i.e. between P_G 180 and 350 mg/dL. It represents the excretion of glucose in urine before the T_{mG} is fully achieved. Note that in the region of splay, the reabsorption curve is rounded, indicating that though the reabsorption rate is increasing with increase in P_G, but reabsorption is less than filtration. Similarly, the excretion curve is also rounded in the region of splay, indicating that though the urinary excretion is increasing with increase in P_G, but there is no linear relation.

Causes of splay are as follows:

- *Heterogenicity in glomerular size*, proximal tubular length and number of carrier proteins for glucose reabsorption
- *Variability in* T_{mG} of the nephron

Renal Handling of Proteins, Peptides and Amino Acids

Protein Reabsorption

Normally, only a small amount of proteins is filtered by the glomerulus (40 mg/L). However, because of high GFR (180 L/day), the total amount of protein filtered per day is significant (180 L/day × 40 mg/L = 7.2 g/day). Normally, the proteins are completely taken into the cells of proximal tubules by the process of *endocytosis*. Once inside the cells, enzymes digest the proteins and peptides into their constituent amino acids, which exit across the basolateral membrane and return to the blood in the peritubular capillaries.

When the amount of filtered proteins increases (due to disruption of the glomerular filtration barrier in kidney diseases), the reabsorbing mechanisms saturate and the proteins may appear in the urine (*proteinuria*).

Renal Handling of Urea

Glomerular Filtration

Urea is freely filtered into the glomerular filtrate. The amount of urea filtered by the glomerular capillaries varies with the protein intake.

Tubular Transport

Proximal tubules reabsorb 5% of the filtered urea passively.

Proximal straight tubule (PST) *Descending thin segment (DTS)* and *ascending thin segment (ATS)* of loop of Henle receive urea by diffusion (*tubular secretion*) from the interstitium of renal medulla, in which urea is present in high concentration.

Thick ascending limb, DCT, CNT, CCD and OMCD are all impermeable to urea.

Inner medullary collecting duct (IMCD) reabsorbs a large amount of urea employing a specialized *urea transport protein* (UT-A). This protein is stimulated by ADH, which consequently increases urea permeability of IMCD.

Renal Handling of Uric Acid

Glomerular Filtration

Urate is freely filtered by the glomerular capillaries.

Tubular Transport

Early proximal tubule reabsorbs 95% of the filtered uric acid.

Mechanism of Uric Acid Reabsorption The uric acid is reabsorbed by the following two mechanisms:

Passive reabsorption occurs through a *paracellular* pathway.

Secondary active transport occurs through transcellular pathways. The carrier protein involved is called *urate transport protein*. Across the basolateral membrane, the urate moves out using another anion exchanger. The same anion exchangers are employed for the urate secretion also.

Renal Handling of Para-Amino Hippuric Acid

The cells of proximal tubule, in addition to reabsorbing solutes and water, also secrete organic anions and organic cations, which include some end products of metabolism circulating in plasma, exogenous organic compounds and certain drugs (Table 6.2-2).

TABLE 6.2-2 Some Organic Anions and Cations Secreted by Proximal Tubule Cells

ANIONS SECRETED BY PROXIMAL TUBULE	
Endogenous Anion	**Drugs**
PAH	Acetazolamide
cAMP	Furosemide
Bile salts	Penicillin
Oxalate	Probenecid
Prostaglandins	Salicylate (Aspirin)
Water	NSAIDs
CATIONS SECRETED BY PROXIMAL TUBULE	
Endogenous Cation	**Drugs**
Creatinine	Atropine
Dopamine	Cimetidine
Epinephrine	Morphine
Norepinephrine	Quinine
	Procainamide
	Verapamil

Mechanism of secretion of organic anions can be considered an example of PAH secretion. Para-amino hippuric acid is an exogenous weak organic acid that is neither stored nor metabolized and is excreted virtually unchanged in the urine. Because 10% of PAH is bound to plasma proteins, so it is cleared from the plasma both by glomerular filtration and by tubular secretion through the kidney. As with glucose, the filtered load of PAH increases in direct proportion to the plasma PAH concentration.

Secretion of PAH occurs from the peritubular capillary blood into the tubular fluid via carriers in the proximal tubule by a transport maximum T_m limited process.

Note: PAH clearance can be used to measure renal plasma flow.

Concentration and Dilution of Urine

The kidneys possess a unique property of regulating the volume and osmolality of the urine by concentrating and diluting it as per the need of the body.

Purpose of concentration and dilution of urine: The main purpose is to maintain the osmolality and volume of the body fluids within a narrow range, which is accomplished by kidneys, in concert with other systems, by regulating the excretion of water and NaCl, respectively.

The kidney can produce urine with osmolality as low as 30 mOsm/kg H_2O to as high as 1400 mOsm/kg H_2O by changing the water excretion as high as 23.3 L/day to as low as 0.5 L/day, respectively.

Principal factors: Principal factors responsible for the mechanism of concentration and dilution of urine are as follows:

- Antidiuretic hormones (see page 309)
- Hyperosmolality and osmolality gradient in medullary interstitium of kidneys

Medullary Hyperosmolality and Medullary Gradient

The interstitial fluid of the medulla is critically important in concentrating the urine because the osmotic pressure of this fluid provides the driving force for reabsorbing water from both the descending thin segment (DTS) and the collecting duct.

Normal osmolality of plasma and other body fluids is about 300 mOsm/kg H_2O. The interstitial fluid of the renal cortex has the same osmolality as that of plasma, and virtually all osmoles are attributable to NaCl. The osmolality of the renal medulla is higher than the plasma (i.e. *hyperosmolar)* and that it goes on increasing progressively from about 300 mOsm/kg H_2O at the corticomedullary junction to about 1200 mOsm/kg H_2O at papilla (medullary gradient), where a maximally concentrated urine is excreted (Fig. 6.2-9). This hyperosmolality and medullary gradient are generated and maintained by the so-called countercurrent system.

Countercurrent System

A countercurrent system refers to a system in which the inflow runs parallel to, counter to and in close proximity to the outflow for some distance. The countercurrent flow system is formed by U-shaped tubules.

In the kidney, the structures which form the countercurrent system are the loop of Henle and the vasa recta. The countercurrent system of kidney consists of the following two components:

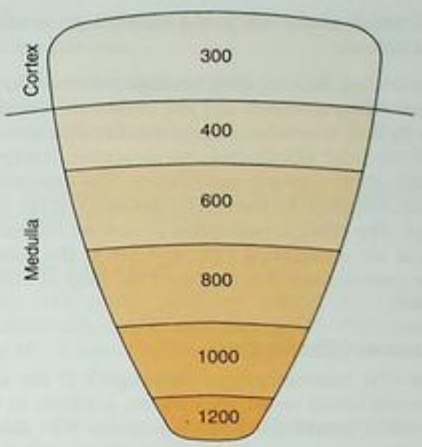


Figure 6.2-9 Osmolality gradient of renal medullary interstitium (values are in mOsm/kg H_2O).

- *Countercurrent multiplier*, which is formed by the operation of the loop of Henle, is responsible for hyperosmolality and a gradient in renal medulla.
- *Countercurrent exchanger*, which is formed by the operation of the vasa recta, is responsible for the maintenance of the medullary gradient and hyperosmolality.

Countercurrent Multipliers

The working of a countercurrent multiplier, which operates in the loop of Henle and generates hyperosmolarity and medullary gradient, can be best understood by the following two processes:

- Origin of the single effect
- Multiplication of the single effect

Origin of Single Effect in Inner Medulla The origin of single effect for the development of medullary gradient and hyperosmolality occurs in the inner medullary interstitium due to the following:

- Passive transport of sodium ions from the ascending thin segment into the interstitium
- Active transport of sodium from the inner medullary collecting duct
- Diffusion of urea from the collecting duct into the medullary interstitium

Role of urea: Urea plays an important role in the development of medullary osmotic gradient, especially when the concentration of ADH is high in the blood. Under such circumstances, the inner medullary collecting duct absorbs a large amount of urea, which plays an important role in the countercurrent system.

Multiplication of the Single Effect The hyperosmolality and medullary gradient are in fact generated by the multiplication of the single effect by the countercurrent multiplier. The main characteristics of the components of countercurrent

multiplier, which play a role in the multiplication of single effect, are as follows:

- The descending thin segment has high permeability to water.
- Impermeability to water and the ability to actively absorb solutes by TAL is another important characteristic.
- In renal medulla, all other tubular structures (except ascending limb) are in osmotic equilibrium. The descending limb, therefore, acquires the increased osmolality of the surrounding fluid. The effect is multiplied as new iso-osmolar filtrate arrives at the descending limb and forces the concentrated tubular contents towards the tip of the loop of Henle (hair-pin band).

Countercurrent Exchanger

Vasa recta (the countercurrent exchanger): If the vasa recta were a straight blood vessel, the osmotic gradient in the medullary pyramid would not last long, as the Na^+ and urea in the interstitial spaces would be removed by the circulation (Fig. 6.2-10). However, because of the hair-pin (U-shaped) anatomical arrangement, the vasa recta operates as a countercurrent exchanger and retains these solutes in the medullary interstitium. Thus, the countercurrent exchanger formed by the vasa recta is responsible for the maintenance of the hyperosmolality medullary gradient generated by the countercurrent multiplier.

Mechanism of Urine Dilution and Concentration

Production of Diluted Urine

Conditions in Which Dilute Urine Is Formed

Dilute urine is called *hypoosmotic urine*, in which urine osmolality is less than blood osmolality. It is produced under the following circumstances:

- When circulating levels of ADH are low (e.g. after water drinking; central diabetes insipidus [see page 311])
- When ADH is ineffective (e.g. nephrogenic diabetes insipidus)

Principal Factors Governing Formation of Dilute Urine

As mentioned earlier, the principal factors governing the formation of dilute and concentrated urine are hyperosmolality medullary gradient and the presence or absence of ADH. The renal medullary osmotic gradient is smaller in the absence of ADH. This is because ADH stimulates both countercurrent multiplication and urea cycling.

Production of Concentrated Urine

Conditions in Which Concentrated Urine Is Formed

Concentrated urine is also called *hyperosmotic urine*, in which urine osmolality is more than that of blood. It is produced when circulating ADH levels are high. Examples include the following:

- Water deprivation
- Haemorrhage
- Syndrome of inappropriate antidiuretic hormone, i.e. SIADH (see page 311)

Principal Factors Governing Formation of Concentrated Urine

The high level of ADH is the main factor governing the formation of concentrated urine because of the following:

- It increases the size of the hyperosmolality medullary gradient.
- It augments the urea cycling from the inner medullary collecting ducts into the medullary interstitial fluid.

Urine Volume and Osmolality Changes in Response to Water Intake and Water Deprivation

Water Diuresis versus Osmotic Diuresis

Water Diuresis Water diuresis refers to an increased urinary output following excessive intake of water or hypotonic solution.

Pathophysiology: It occurs due to absence of ADH in the plasma.

Characteristic Features

- Water diuresis begins about 15 minutes after the ingestion of water and reaches its maximum in 40 minutes.

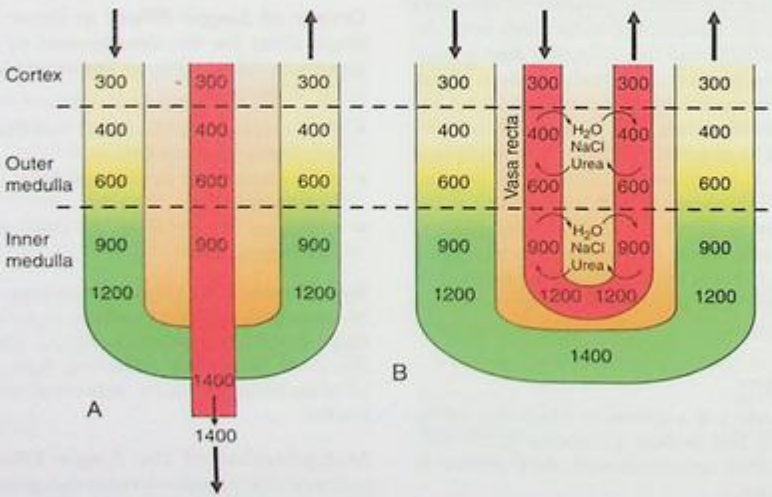


Figure 6.2-10 Operation of vasa recta as countercurrent exchangers in the kidney: (A) effect on medullary osmolality if vasa recta would be a straight vessel without a hair-pin arrangement and (B) as it is a U-shaped vessel.

- Urine output may be increased to 20 L/day.
- Urine formed is diluted, osmolality is always below 30 mOsm/kg H_2O and may be as low as 50 mOsm/kg H_2O.
- Specific gravity of urine always stays below 1.010.

Osmotic Diuresis Osmotic diuresis refers to an increased urine output because of an osmotic effect.

Pathophysiology: Presence of large quantities of unreabsorbed solutes in the proximal tubules exerts an appreciable osmotic effect. Osmotic diuresis may occur under the following circumstances:

- When the filtered load of naturally occurring substances such as Na^+, glucose (e.g. in diabetes mellitus), urea, etc., exceeds the maximum capacity of the tubules to reabsorb (T_m)
- Following administration of compounds such as mannitol and related polysaccharides that are filtered but not reabsorbed
- Following infusion of large amounts of sodium chloride and urea

Characteristic Features

- Urine output may be >20 L/day in spite of maximal ADH secretion.
- Urine osmolality is higher than 300 mOsm/kg H_2O.
- Urine specific gravity is over 1.010.

Water Deprivation

Water deprivation is followed by a sequence of changes, which are opposite to water diuresis. As a consequence, urine volume is decreased but urine osmolality is increased.

Acidification of Urine

The pH of urine is variable, depending on the concentration of H^+ ions. Under normal circumstances, the pH of urine is acidic (~6.0). This clearly indicates that kidneys have contributed to the *acidification of urine* when it is formed from the plasma (pH 7.4). In other words, H^+ ions generated in the body in the normal circumstances are eliminated by the acidified urine. Thus, the role of kidneys in the maintenance of acid–base balance of the body (blood pH) is highly significant.

The kidneys regulate the blood pH through the following three main mechanisms:

- Reabsorption of the filtered HCO_3^-
- Generation of $NaHCO_3^-$ of the alkali reserve of the body
- Excretion of acid in the form of titrable acid and ammonium ions

All these mechanisms are accomplished through the process of H^+ secretion by the nephron.

Hydrogen Ion Secretion

The tubular cells of the proximal tubule, distal tubule and collecting ducts are capable of secreting H^+. The kidney is the only organ which can eliminate the fixed acids by active secretion of H^+.

Mechanism of H^+ Secretion by Proximal Tubule Steps involved are (Fig. 6.2-11) as follows:

- ***Formation of carbonic acid:*** Carbonic acid (H_2CO_3) is first formed in the cells of proximal tubules from CO_2 and H_2O by a reaction that is catalysed by the intracellular *carbonic anhydrase.*
- ***Dissociation of carbonic acid*** (H_2CO_3) then occurs in H^+ and HCO_3^-.
- ***Secretion of H^+ into the lumen*** occurs via an *Na^+–H^+ exchange mechanism* in the luminal membrane by an *Na^+–H^+ antiporter* (Fig. 6.2-11).
- ***The secreted H^+, in the lumen, combines with the filtered HCO_3^-*** and helps its reabsorption (as described below). Therefore, this process does not result in net secretion of H^+.
- ***HCO_3^- formed in the cell*** (from dissociation of H_2CO_3) diffuses into the interstitial fluid. Thus, for each H^+ secreted, one Na^+ ion and one HCO_3^- ion enter the interstitial fluid. The latter adds up to the alkali reserve of the body.

Mechanism of H^+ secretion by distal tubules and collecting ducts In the distal tubule and collecting ducts, H^+ secretion occurs independently of Na^+.

- H^+, K^+–ATPase is also responsible for the secretion of some of the H^+ coupled with reabsorption of K^+ in these parts of renal tubules.

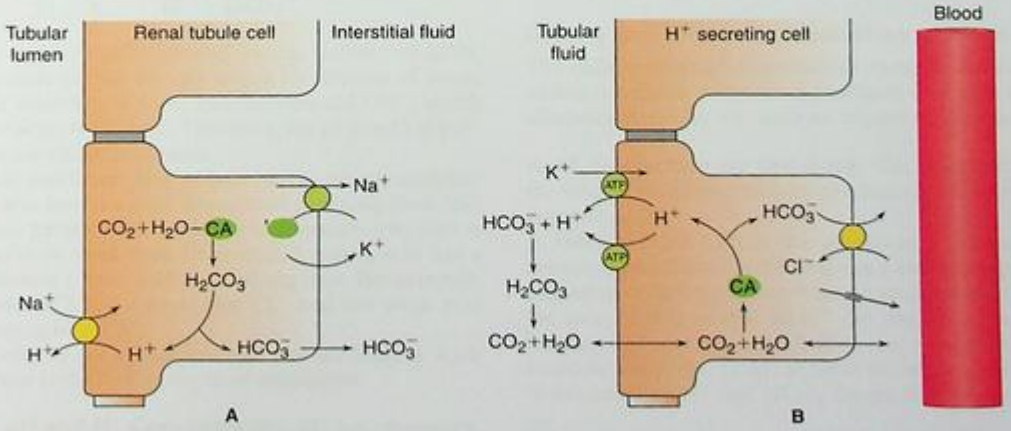


Figure 6.2-11 Cellular mechanism for secretion of H^+ by a proximal tubular cell (A) and intercalated cells of late tubule (B).

Fate of H^+ secreted in the renal tubule: The secretion of H^+ in the renal tubule can continue only if the H^+ is immediately buffered in the luminal fluid.

- In the proximal tubule, the secreted H^+ is buffered by the filtered HCO_3^- (i.e. consumed in reabsorption of filtered HCO_3^-, vide infra).
- In the distal tubule and connecting ducts, the secreted H^+ ions are buffered by Na_2HPO_4 and NH_3, and are excreted as titrable acid and ammonium ion (NH_4^+, vide infra).

Reabsorption of Filtered HCO_3^-

Proximal tubule reabsorbs approximately 80% of the filtered HCO_3^-.

Loop of Henle reabsorbs 15% of the filtered HCO_3^-, mainly in the region of TAL.

Generation of New HCO_3^-

As discussed above, the kidneys play an important role in the maintenance of acid–base balance of the body by completely reabsorbing the filtered HCO_3^-. However, in reality, HCO_3^- reabsorption alone does not replenish the HCO_3^- lost during the titration of nonvolatile acids, which are daily added to the plasma from the diet and produced by metabolism. Therefore, to maintain acid–base balance, the kidneys replace this lost HCO_3^- with new HCO_3^- by the following processes:

- Excretion of H^+ as titrable acid
- Excretion of H^+ as NH_4

Excretion of H^+ as Titrable Acid

Excretion of H^+ as titrable acid refers to the excretion of secreted H^+ along with the primary urinary buffer – the dibasic phosphate (HPO_4^{2-}). This reaction occurs in the distal tubules and collecting ducts (Fig. 6.2-12).

As a result of H^+ excretion in the form of a titrable acid, the pH of urine is progressively decreased (from 7.4 – that of blood). The *acidification of the urine* may lower its pH to a minimum of 4.5.

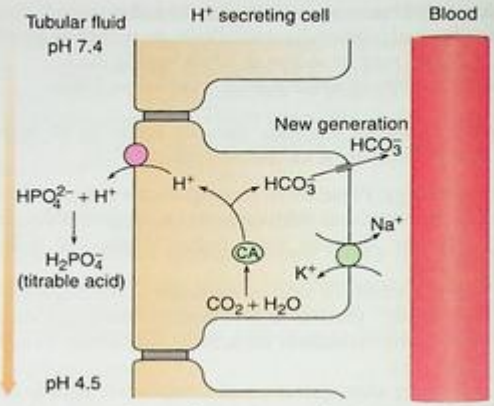


Figure 6.2-12 Mechanism for excretion of H^+ as titrable acid and synthesis of new HCO_3^-.

Excretion of H^+ as Ammonium Ion

Excretion of H^+ as NH_4^+ is another mechanism of excretion of secreted H^+ and formation of new HCO_3^-. The amount of H^+ excreted as NH_4^+ depends on both the amount of NH_3^- synthesized by renal cells and the urine pH. *NH_4^+ is a major urine acid.* It is estimated that about half to two-thirds of body acid load is eliminated in the form of NH_4^+ ions. The process by which the kidneys excrete NH_4 is complex.

SELF-ASSESSMENT

1. Write briefly:
   - Mechanism of urine formation
   - Dynamics of glomerular filtration
   - Factor affecting glomerular filtration
   - Concentration and dilution of urine by renal tubules
2. Write notes on:
   - Countercurrent system
   - Acidification of urine
   - Vasa recta

6.3 Physiology of Acid–Base Balance

CHAPTER OUTLINE

General Considerations
Acids and Bases
Concept of pH and H^+ Concentration
H^+ Concentration and pH of Biologic Fluids

Maintenance of Blood pH
General Considerations
Defences against Changes in H^+ Concentration
Buffer System: Primary Defence
Bicarbonate Buffer System
Phosphate Buffer System
Protein Buffer System
Respiratory Mechanism for pH Regulation
Renal Mechanism for pH Regulation

Acid–Base Disorders
Metabolic Acidosis
Metabolic Alkalosis
Respiratory Acidosis
Respiratory Alkalosis

GENERAL CONSIDERATIONS

Acids and Bases

Acids and bases: Acid refers to a substance that acts as a proton (H^+) donor, whereas base refers to a substance that accepts proton (H^+). Examples of a few acids and their corresponding base are as follows:

Acid	*Base*
HCl	$H^+ + Cl^-$
H_2CO_3	$H^+ + HCO_3^-$

Alkalies refer to the metallic hydroxides, e.g. NaOH and KOH. These compounds do not directly satisfy the criteria of bases. However, they dissociate to form metallic ions and OH^-, which being the base accepts H^+ ions. Therefore, for all practical purposes, alkalies are considered bases.

Strong acids and bases: Acid or base having strong tendency to dissociate into ions is called strong acid or strong base, and the acid or base having weak tendency to dissociate into ions is called weak acid or weak base. In general, a strong acid has a weak base, whereas a weak acid has a strong base. For example, the strong acid HCl has a weak base Cl^- and the weak acid HCN has a strong base CN^-.

Ampholytes refer to the substances that can act both as acids and bases. Water is the best example of ampholyte.

Concept of pH and H^+ Concentration **H^+ ion concentration:** The acidic or basic nature of a solution is measured by H^+ ion concentration. The concentration of H^+ ions in the biological fluids is exceedingly low, so the conventional units such as mEq/L or moles/L are not commonly used to express H^+ concentration. Therefore, ***pH*** is the term suggested to express H^+ ion concentration. pH is defined as the negative logarithm of H^+ concentration.

$$pH = -\log [H^+]$$

It is important to note that pH and H^+ are inversely related. For example, pH of plasma with an H^+ ion concentration of 0.00004 mEq/L is 7.4, whereas pH of HCl with an H^+ ion concentration of 150 mEq/L is 0.8.

Neutral pH, acidic pH and alkaline pH: Pure water has an equal concentration of H^+ and OH^- ions, i.e. 10^{-7} M each. Thus, pure water has pH of 7, which is neutral. Therefore, solutions with pH less than 7 are considered acidic and those with more than 7 are considered alkaline.

H^+ Concentration and pH of Biological Fluids

The H^+ concentration and pH of some biological fluids are depicted in Table 6.3-1.

MAINTENANCE OF BLOOD pH

General Considerations

Blood and Plasma pH

- The term blood pH always refers to the plasma pH.
- Normal plasma pH is 7.4 (H^+ concentration −40 mEq/L), which is higher than the intracellular pH of the erythrocyte (7.2).
- Plasma pH compatible with life varies from 7.7 to 6.9 (H^+ concentration is from 20 to 120 nEq/L).
- Normally, the pH of extracellular fluid (ECF) is maintained in a narrow range of 7.35–7.45.

Dietary and Metabolic Production of Acids and Bases

The daily consumed diet contains many acids and alkalies. In addition, cellular metabolism produces a number of acidic and alkaline substances that have an impact on the body pH.

Acid Production by the Body The metabolic activities of the body are accompanied by production of the following two types of acids:

1. Volatile Acids CO_2 is the volatile acid produced from the aerobic metabolism of cells. It is also a major end product in the oxidation of carbohydrates, fats and amino acids. CO_2 accounts for over 12,000 mEq/L of H^+ per day. It is considered acid because CO_2 combines with H_2O (by a reaction catalysed by carbonic anhydrase [CA]) to form the weak acid H_2CO_3, which dissociates into H^+ and HCO_3^- by the following reaction:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

TABLE 6.3-1 H^+ Concentration and pH of Biological Fluids

Fluid	H^+ CONCENTRATION nEq/L	mol/L	pH
1. Pure water	100	1×10^{-7}	7.0
2. Blood			
Normal mean	40	3.98×10^{-8}	7.4
Normal range	44–36	4.36×10^{-8} to 3.6×10^{-7}	7.36–7.44
Acidosis (severe)	126	1.26×10^{-7}	6.9
Alkalosis (severe)	20	2.00×10^{-8}	7.7
3. Cerebrospinal fluid CSF (normal range)	44–36	4.36×10^{-8} to 3.6×10^{-7}	7.36–7.44
4. Gastric juice (pure)	100,000,000	1×10^{-1}	1.0
5. Pancreatic juice	10	1×10^{-8}	8.0
6. Urine			
Normal average	1000	1×10^{-6}	6.0
Maximum acidity	31,600	3.16×10^{-5}	4.5
Maximum alkalinity	10	1×10^{-8}	8.0
7. Intracellular fluid (ICF)	158	1.58×10^{-7}	6.8

It is called volatile because it is a gas, and under normal circumstances, almost all the CO_2 is excreted by lungs.

2. Nonvolatile Acids, also called fixed acids, contribute about 50–100 mEq H^+ per day, depending on the diet. These include the following:

- Sulphuric acid
- Phosphoric acid
- Hydrochloric acid
- Organic acids like lactic acid, acetic acid and β-hydroxybutyric acid
- Uric acid produced in the metabolism of nucleoproteins

Production of Bases by the Body In a normal circumstance, a negligible amount of bases is formed in the body because of the following:

- HCO_3^- produced by the metabolism of organic anions (e.g. citrate) offsets nonvolatile acid production to some degree.
- *Ammonia* produced in the amino acid metabolism is converted into urea; hence, its contribution as a base in the body is insignificant.

Defences Against Changes in H^+ Concentration

There are three lines of defence to regulate the body's acid–base balance and maintain the blood pH (around 7.4).

I. **Buffer systems of body fluid**
- Form the first line of defence
- Act instantaneously in ECF
- Immediately combine with H^+ to prevent changes in H^+ concentration and form a temporary measure to control changes in the H^+ concentration

II. **Respiratory mechanism to regulate acid–base balance**
- Forms the second line of defence
- Acts within a few minutes
- Acts via the respiratory centre to regulate removal of CO_2 (and therefore H_2CO_3)
- Forms a short-term measure to regulate changes in the H^+ concentration

III. **Renal mechanism to regulate acid–base balance**
- Forms the third line of defence
- Takes days or weeks
- Slow, but most powerful and effective in regulating pH
- Acts by reabsorbing filtered HCO_3^-, generating new HCO_3^- and excreting H^+ as titrable acid and ammonium ion
- Provides a permanent solution to acid–base balance

Buffer System: Primary Defence

Buffers: A buffer is a solution consisting of a weak acid and its salt with a strong base that prevents a change in pH when H^+ ions are added to or removed from a solution. It must be borne in mind that a buffer cannot remove H^+ ions from the body. It temporarily acts as a shock absorbent to reduce the free H^+ ions. The H^+ ions have to be ultimately eliminated by the renal mechanism.

When acid is added to a buffer solution, its H^+ ion concentration is increased, and the reaction is forced towards right, leading to an increase in undissociated molecules; therefore, increase in H^+ concentration is less.

When a base is added to a buffer, the reaction shifts towards left; more H^+ ions are released from the buffer to combine with the base, thereby limiting the decrease in H^+ concentration.

The *Henderson–Hasselbalch equation,* which is used to calculate the pH in a buffer system, can be derived as shown below. The general equation for a buffer is

$$HA \rightleftharpoons H^+ + A^-,$$

where A^- represents any anion from a buffer (i.e. H^+ acceptor) and HA is the undissociated acid from a buffer (i.e. H^+ donor). By the law of mass action, at equilibrium

$$K = \frac{[H^+][A^-]}{[HA]} \quad \text{(i)}$$

(K = dissociation constant of the acid HA).

The equation to represent a free H^+ ion in a solution can be rewritten as

$$[H^+] = K \times \frac{[HA]}{[A^-]}. \quad \text{(ii)}$$

We know that $pH = \log \frac{1}{H^+}$

By taking the reciprocals and logarithms (for log, multiplication becomes addition), we have

$$\log \frac{1}{[H^+]} = \log \frac{1}{K} + \log \frac{A^-}{[HA]}. \quad \text{(iii)}$$

$$\text{As } \log \frac{1}{K} = pk,$$

Equation (iii) may be rewritten as

$$pH = pK + \log \frac{[A^-]}{HA}.$$

From this equation, it is evident that the buffering capacity of a buffer system is greatest when the amount of anions $[A^-]$ and undissociated acid [HA] is the same, i.e.

$$\frac{[A^-]}{[HA]} = 1, \text{ or } \left[\log \frac{[A^-]}{[HA]}\right]$$

Thus, pH = pK. Therefore, the most effective buffers in the body are those with pK close to the pH in which they operate.

Classification of the Buffer Systems

Buffer systems in the body can be classified as follows.

Bicarbonate Versus Nonbicarbonate Buffers

1. ***Bicarbonate buffer*** forms 53% of the buffering in the whole body with a contribution from the following:
   - Plasma HCO_3^- contributes 35%.
   - Erythrocyte HCO_3^- contributes 18%.
2. ***Nonbicarbonate buffers*** form the remaining 47% of the buffering in the whole body with a contribution from the following:
   - Haemoglobin and oxyhaemoglobin: 35%
   - Plasma proteins: 7%
   - Organic phosphate: 3%
   - Inorganic phosphate: 2%

Major Buffer Systems of the Body

The major buffer systems involved in the maintenance of body pH are as follows:

- Bicarbonate buffer
- Phosphate buffer
- Protein buffer

1. Bicarbonate Buffer System The carbonic acid–sodium bicarbonate (H_2CO_3–$NaHCO_3$) is the most predominant buffer system of ECF; particularly, the plasma H_2CO_3 in the body is formed from CO_2 and H_2O as follows:

$$CO_2 + H_2O \xrightarrow[\text{anhydrase}]{\text{carbonic}} H_2CO_3$$

This reaction is catalysed by the enzyme carbonic anhydrase, which is present in the RBCs, walls of the lungs, alveoli and epithelial cells of renal tubules.

Dynamics of Bicarbonate Buffer System Carbonic acid dissociates into hydrogen and bicarbonate ions as shown below:

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

According to the Henderson–Hasselbalch equation for this system, we have

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]} \quad \text{(iv)}$$

The pK^1 of this system (6.1) is still low relative to the pH of the blood (7.4), but the system is one of the most effective buffer systems in the body because the amount of dissolved CO_2 is controlled by respiration, and the plasma concentration of HCO_3^- is regulated by the kidney. Therefore, the pH of ECF can be precisely controlled.

2. Phosphate Buffer System

Inorganic Orthophosphate Buffer System Inorganic orthophosphate buffer system is formed by sodium dihydrogen phosphate and disodium hydrogen phosphate ($NaH_2PO_4 \sim Na_2HPO_4$), which exist at a plasma pH of 7.4 in a concentration ratio of 1:4.

Sites of Operation of NaH_2PO_4–Na_2HPO_4 Buffer

A. ***In ECF (plasma and interstitial fluid),*** the HPO_4^{2-}–$H_2PO_4^-$ buffer exists in a small concentration (0.66 mmol/L) and thus contributes little to the buffering capacity of plasma.
B. ***In intracellular fluid (ICF),*** HPO_4^{2-}–$H_2PO_4^-$ forms an important buffer pair because of the following:
   - Its concentration in ICF is high (6 mmol/L).
   - Its pK (6.8) is much closer to pH of ICF (6.9).
C. ***In renal tubules,*** HPO_4^{2-}–$H_2PO_4^-$ forms an effective extracellular buffer because of the following:
   - Phosphate becomes greatly concentrated in the tubular fluid due to reabsorption of H_2O.
   - pH of tubular fluid and urine is more acidic than the pH of ECF, i.e. close to the pK of phosphate buffer.

The HPO_4^{2-}–$H_2PO_4^-$ system is a major elimination route for H^+ via the urine.

Organic Phosphate Buffer System Organic phosphates (such as AMP, ADP, ATP and 2,3-biphosphoglycerate [2,3-BPG]) exist in a quantitatively significant amount in the ICF (8.4 mmol/L), giving this compartment the capacity to effectively buffer both noncarbonic and carbonic acids, as well as alkali.

3. Protein Buffer System The protein buffer system of the blood is constituted by the plasma proteins and haemoglobin combinedly.

Plasma Proteins Buffer System Plasma proteins buffer system accounts for 15% of the buffering capacity of the whole blood. Plasma proteins are effective buffers because both their free carboxyl and free amino groups dissociate as shown below:

$$RCOOH \rightleftharpoons RCOO^- + H^+;$$

$$pH = pK^1 RCOOH + \log \frac{[RCOO^-]}{[RCOOH]}$$

$$RNH_3^+ \rightleftharpoons RNH_2^+ + H^+;$$

$$pH = pK^1 RNH_3 + \log[(RNH_2)/(RNH_3)]$$

Because of their amphoteric nature, plasma proteins can combine with acids and bases in the following ways:

- *In acidic pH*, the NH_2 group of the proteins acts as a base, accepts a proton and is converted into NH_3.
- *In alkaline pH*, the –COOH group of the proteins acts as an acid, can donate a proton and thus becomes COO^-.
- *At normal pH* of blood, proteins act as acids and combine with cations (mainly sodium).

Haemoglobin Buffer System Haemoglobin buffer system (Hb/HHb and HbO_2^-/$HHbO_2$) accounts for 35% of the total buffering capacity of the whole blood. It mainly buffers the fixed acids, besides being involved in the transport of gases (O_2 and CO_2).

***Deoxyhaemoglobin* (Hb) *is a better buffer than oxyhaemoglobin* (HbO_2)** because the imidazole groups of Hb dissociate less than those of HbO_2, making Hb a weaker acid.

Respiratory Mechanism for pH Regulation

Second line of defence against acid–base disorders is formed by the respiratory mechanism, which provides a short-term but rapid control. It acts via a respiratory centre located in the medulla to regulate removal of CO_2 and therefore carbonic acid (H_2CO_3) concentration in the blood.

Role of Respiratory Centres Respiratory centres are influenced by both CO_2 and H^+ concentrations through central and peripheral chemoreceptors.

Respiratory response occurs only in response to metabolic acid–base disorders and consists of the following:

1. ***Hyperventilation***: It occurs in response to the metabolic acidosis and results in lowering of pCO_2 to match the decreased (HCO_3^-).
2. ***Hypoventilation***: It occurs in response to metabolic alkalosis and results in raising the pCO_2 to match the increased (HCO_3^-).

Renal Mechanism for pH Regulation

The kidneys regulate pH through three main processes (see page 239.

ACID–BASE DISORDERS

Acidosis refers to a decline in blood pH, whereas *alkalosis* refers to a rise in blood pH. As described above, our body has been provided with an efficient system for the maintenance of acid–base equilibrium with a result that the pH of blood remains almost constant (7.4). The blood pH compatible to life is 6.8–7.8, beyond which life cannot exist.

Simple Acid–Base Disorders

The physiological aspects of single acid–base disorders are summarized in Table 6.3-2 and are described as follows.

Metabolic Acidosis

Physiological Disturbance that produces metabolic acidosis is either increased net nonvolatile acid load or loss of base (HCO_3^-).

Primary Disturbance in metabolic acidosis is *decreased plasma* (*HCO_3^-*) producing a *low plasma pH*.

Causes of metabolic acidosis include the following:

- Diabetic ketoacidosis
- Lactic acidosis in hypoxia
- Diarrhoea (GI loss of HCO_3^-)
- Chronic renal failure (failure to excrete H^+ as titrable acid and NH_4)

Compensatory Mechanisms When metabolic acidosis is produced by the nonrenal factors, the respiratory and renal compensatory mechanisms tend to minimize the change in pH of blood. In renal failure, only respiratory compensation is possible.

1. ***Respiratory compensation:*** Increased H^+ stimulates the respiratory centre through peripheral chemoreceptors and produces *hyperventilation* (Kussmaul *breathing*), which, in turn, decreases the arterial pCO_2 value and minimizes the degree of acidosis.
2. ***Renal compensation*** is slow but an effective mechanism to control metabolic acidosis. It includes the following:
   - Increased excretion of fixed H^+ as titrable acid and NH_4

TABLE 6.3-2 Summary of Characteristics of Simple Acid–Base Disorders

		ARTERIAL PLASMA (APPROXIMATE VALUES)			DEFENCE MECHANISM		
Disorder	Primary Disturbance	pH (Normal 7.4)	HCO_3^- (mEq/L) (Normal 24)	pCO_2 (mm Hg) (Normal 40)	Buffering	Respiratory Compensation	Renal Compensation
Metabolic acidosis	↓ Plasma HCO_3^-	↓ (7.28)	↓ (18)	→ (40)	ECF and ICF	Hyperventilation (↓ pCO_2)	↑ H^+ excretion ↑ New HCO_3^- reabsorption
Metabolic alkalosis	↑ Plasma HCO_3^-	↑ (7.5)	↑ (30)	→ (40)	ECF and ICF	Hypoventilation (↑ pCO_2)	↓ H^+ excretion ↓ New HCO_3^- reabsorption
Respiratory acidosis	↑ pCO_2	↓ (7.34)	↑ (25)	↑ (48)	ICF	None	↑ H^+ excretion ↑ New HCO_3^- reabsorption
Respiratory alkalosis	↓ pCO_2	↑ (7.53)	↓ (22)	↓ (27)	ICF	None	↓ H^+ excretion ↓ New HCO_3^- reabsorption

Note: ECF, extracellular fluid; ICF, intracellular fluid; ↑, increased; ↓, decreased; →, normal.

- Increased reabsorption of new HCO_3^-, which replenishes the HCO_3^- used in buffering the added fixed H^+
- Adaptive increase in NH_3 synthesis in chronic metabolic acidosis, helping in the excretion of excess H^+

Metabolic Alkalosis

Physiological Disturbance that produces metabolic alkalosis is either addition of nonvolatile alkali or loss of H^+ from the body.
Primary Disturbance in metabolic alkalosis is *increased plasma* HCO_3^-, producing a high plasma pH.
Causes of metabolic alkalosis include the following:

- Haemorrhage
- Vomiting (H^+ is lost from the stomach)
- Hyperaldosteronism (increased H^+ secretion by distal tubule)

Compensatory Mechanisms

1. ***Respiratory compensation:*** Increased pH (or decreased H^+) inhibits the respiratory centre through peripheral chemoreceptors and produces *hypoventilation*, which, in turn, elevates pCO_2 and thus normalizes plasma pH.

Note: It is important to note that the magnitude of respiratory compensation is limited by the fact that hypoventilation results in decreased arterial pO_2, which stimulates the respiratory centres via peripheral chemoreceptors.

2. ***Renal compensation*** for metabolic alkalosis includes the following:
   - There is decreased H^+ secretion by the renal tubules.
   - There is increased HCO_3^- excretion as the filtered load of HCO_3^- exceeds the ability of renal tubule to reabsorb it. The urinary loss of HCO_3^- decreases the plasma level of HCO_3^-, thereby restoring the pH of blood to near normal.

Respiratory Acidosis

Primary Disturbance in respiratory acidosis is *increased* pCO_2, which by mass action causes an increase in H^+ and thus lowers the blood pH.

Causes The pCO_2 is increased due to decreased gas exchange across the alveoli because of the following causes:

- *Inadequate ventilation* (airway obstruction)
- *Impaired gas diffusion*

Compensatory Mechanisms Note: There is no respiratory compensation for respiratory acidosis; only renal composition is there.

Respiratory Alkalosis

Primary Disturbance in the respiratory alkalosis is decreased pCO_2 associated with low (H^+) and thus an elevated plasma pH.
Causes The pCO_2 is decreased due to increased gas exchange in the lungs because of increased ventilation.
Compensatory Mechanisms There is no respiratory compensation for respiratory alkalosis.
Renal compensation: Decreased pCO_2 causes a deficit of H^+ in the renal cells for secretion, which leads to the following:

- Decreased excretion of H^+ as titrable acid and NH_4^+
- Decreased reabsorption of new HCO_3^-
- Decreased reabsorption of the filtered HCO_3^-

The resulting decrease in serum (HCO_3^-) helps to normalize the pH. In this way, the alkalosis is mostly but not completely compensated by the renal mechanism.

SELF-ASSESSMENT

1. Describe the renal mechanism of pH regulation.
2. Discuss in brief the body buffer system.
3. Write notes on:
   - Metabolic acidosis
   - Metabolic alkalosis

6.4 Applied Renal Physiology Including Renal Function Tests

CHAPTER OUTLINE

Pathophysiology of Common Renal Disorders
Common Urinary Symptoms
Renal Failure

Renal Function Tests
Analysis of Urine
Analysis of Blood
Renal Clearance Tests
Radiology and Renal Imaging
Renal Biopsy

PATHOPHYSIOLOGY OF COMMON RENAL DISORDERS

The applied aspects of common renal disorders which need some elaboration are as follows:

- Common urinary symptoms
- Renal failure

Common Urinary Symptoms

Polyuria, Nocturia and Urinary Frequency Normal urine output per day is 800–2500 mL. Therefore, a reasonable criterion to satisfy the definition of polyuria is excretion of 3.0 L of urine daily, provided the patient is not on high-fluid diet.

Nocturia means an excessive amount of urine passed at night.

Urinary frequency means the increase in the number of times the patient goes for urination. Polyuria is differentiated from increased frequency by measuring the 24-hour urine output.

Dysuria and Urgency of Micturition *Dysuria* refers to pain or burning during micturition. *Urgency of micturition* is the exaggerated sense or urge to micturate. It is due to either irritative or inflammatory disorders of the urinary bladder. This is often associated with an increased frequency of urination.

Incontinence This refers to inability to retain urine in the bladder. It results from the neurological or mechanical disorders of the complicated system that controls normal micturition.

Enuresis refers to the involuntary passage of urine at night or during sleep. It is also called night bed-wetting or nocturnal enuresis. It is normal in children up to 2–3 years of age. In some children, it continues for long.

Oliguria refers to the urine output less than 500 mL/day in an average adult. It invariably occurs in acute or chronic renal failure or acute renal failure.

Anuria is said to occur when the patient does not pass any urine or passes less than 50 mL of urine/day. In physiological sense, the term anuria means less formation or absence of formation of urine by the kidney.

Renal Failure

Renal failure refers to the deterioration of renal functions, resulting in a decline in the glomerular filtration rate (GFR) and rise in urea and non-nitrogenous substances in the blood.

It is of the following two types:

- Acute renal failure
- Chronic renal failure

Acute Renal Failure Acute renal failure refers to a sudden decrease in GFR, associated with the rapid rise in blood urea.

Common causes of acute renal failure are as follows:

- Severe haemorrhage
- Shock
- Acute glomerulonephritis
- Urinary tract obstruction

Chronic Renal Failure Chronic renal failure refers to a slow, insidious deterioration of kidney functions, resulting in uraemia.

Common causes of chronic renal failure are mainly due to kidney diseases: polycystic kidney, pyelonephritis.

RENAL FUNCTION TESTS

Renal function tests are carried out to assess the functional capacity of the kidneys. Renal function tests can be divided into the following groups:

- Analysis of urine
- Analysis of blood
- Renal clearance tests
- Radiology and renal imaging
- Renal biopsy

Analysis of Urine

Analysis of urine helps, of course, to a limited degree, to assess kidney functioning. In patients with suspected renal disorder, the urine analysis should be performed for volume, specific gravity, osmolality, pH, abnormal constituents, microscopic examination and bacteriological finding.

1. Volume Normal urine output per day is 800–2500 mL. Abnormalities of urine volume include polyuria, oliguria and anuria.

2. Colour The normal light-yellow colour of the urine is due to the presence of urochrome pigment (a compound of urobilin and urobilinogen with peptide). On standing, the colour deepens due to oxidation of urobilinogen into urobilin. Abnormalities of urine colour include the following:

- *Brownish yellow* colour is due to the presence of conjugated bilirubin in patients with hepatic and posthepatic jaundice.
- *Cloudy appearance* is seen in strongly alkaline urine due to precipitation of calcium phosphate and due to precipitation of urates.
- *Frothy appearance* is an indicative of proteinuria.
- *Red-dark brown* tinge of urine is seen in porphyria.

3. Osmolality and Specific Gravity Normal urinary osmolality varies from 50 to 1200 mOsm/kg and specific gravity from 1.003 to 1.030, depending on the state of hydration of the body. If the early morning urine sample after an overnight fast has an osmolality of <600 mOsm/kg H_2O (and specific gravity > 1.018), then the patient has a normal urine concentrating ability. A few abnormalities are as follows:

- Fixed urinary osmolality of 300 mOsm/kg H_2O (specific gravity 1.010) is evidence of fairly advanced urinary failure.
- Persistently low urinary osmolality (less than 100 mOsm/kg H_2O) even after 8 hours of fluid deprivation is a diagnostic feature of diabetes insipidus.

4. Urine pH Normal pH of urine varies from 4.5 to 8.0. Urine is normally slightly acidic, except for a short postprandial alkaline tide. Intake of a high-protein, nonvegetarian diet shifts the urinary pH towards the acidic side, while a vegetarian diet shifts it towards alkaline side.

5. Chemical Analysis for Abnormal Urinary Constituents includes the following:

(i) Proteinuria Normally, up to 150 mg of proteins is excreted daily in urine. Excretion of >150 mg/day of protein is called proteinuria. It occurs in the following conditions:

- In congestive heart failure
- After prolonged standing
- Renal diseases and in toxaemia of pregnancy

(ii) Glycosuria refers to the presence of glucose in the urine. Glycosuria may be due to diabetes mellitus, renal disorders (renal glycosuria) and GIT disorder (alimentary glycosuria).

(iii) Ketonuria refers to the presence of ketone bodies (acetoacetic acid, β-hydroxybutyric acid and acetone) in the urine. Ketonuria occurs in the patients suffering from ketosis due to severe diabetes mellitus or prolonged starvation.

(iv) Bilirubinuria refers to the appearance of bilirubin in the urine of patients with elevated conjugated bilirubin levels in hepatic or posthepatic jaundice. Normally, 1–3.5 mg of urobilinogen is excreted daily in the urine. Its excessive excretion in the urine is one of the characteristic features of haemolytic jaundice.

(v) Haemoglobinuria, i.e. presence of haemoglobin in the urine, indicates intravascular haemolysis, as seen in the blackwater fever due to falciparum malarial infection.

(vi) Haematuria, i.e. presence of blood in the urine, is seen in acute glomerulonephritis and renal stone disease.

6. Microscopic Examination Examination of a centrifuged sediment of urine may show casts, cells and crystals.

(i) Casts are proteinaceous plugs formed by the coagulation of Tamm–Horsfall protein within the renal tubules and washed out by the flow of tubular fluid. They have a cylindrical shape, broken ends and various shapes corresponding to the tubule in which formed casts may be cellular or noncellular.

(ii) Crystals are usually present in normal urine and thus have no pathological significance. Commonly seen are crystals of calcium oxalate, calcium phosphate, calcium ammonium–magnesium phosphate (triple phosphate) or uric acid.

(iii) Cells found on microscopic examination may be red blood cells, leucocytes, tubular epithelial cells and squamous epithelial cells.

7. Bacteriological Examination of Urine The midstream sample of urine is examined for pus cells and bacteria. Bacteriuria and pyuria indicate urinary tract infection.

Analysis of Blood

Estimation of blood levels of the substances that are excreted by the kidneys sheds some light on the functional status of kidney, although these tests are less sensitive than the clearance tests.

1. Blood Urea level (normal 20–40 mg/dL) is an index of glomerular function. The blood urea levels begin to rise after about 50% glomerular damage has occurred.

2. Plasma Creatinine Concentration (normal 0.6–1.5 mg/dL) is more reliable than blood urea, as the latter is subjected to variations by dietary proteins, hydration and tissue breakdown.

3. Serum Proteins Levels (normal: total protein, 6.7–8 g/dL; albumin, 3–5 g/dL; globulins, 2–3 g/dL and A/G ratio, 1.7:1) are reduced if there is significant proteinuria with renal failure. In nephrotic syndrome, the albumin levels decrease and globulin levels increase, leading to reversal of A/G ratio.

4. Serum Cholesterol Levels (normal, 150–200 mg/dL) are increased in the nephrotic syndrome.

Renal Clearance Tests

The renal clearance can be defined as the volume of plasma that is cleared of a substance in 1 minute by excretion of the substance in the urine. It is a 'virtual volume'. The unit of renal clearance (C) is mL/min and is calculated by the following formula:

$$C = \frac{UV}{P},$$

where

C = renal clearance,
U = urine concentration of the substance,
V = rate of flow of urine,
P = plasma concentration of the substance.

Renal Clearance as Kidney Function Test Renal clearance of a substance is correlated more directly with the status of kidney function. It shows a deviation from normal (earlier) in the course of renal damage.

Renal clearance tests, therefore, can be employed to assess the different functions of a nephron, e.g.:

- To assess glomerular filtration
- To assess tubular secretory capacity
- To assess renal plasma flow and renal blood flow

Radiology and Renal Imaging

Though not strictly speaking, kidney function tests are quite useful investigations in present-day clinical practice to assess anatomical and physiological abnormalities of the kidneys.

Renal Biopsy

Renal biopsy is performed percutaneously with the help of a needle. The biopsy specimen is subjected to light, electron and immunofluorescence microscopic studies. This technique leads to enhancement in knowledge and a better understanding of glomerular and tubular diseases.

SELF-ASSESSMENT

1. Describe various renal function tests.
2. Write notes on:
   - Glycosuria
   - Renal failure
   - Artificial kidney

6.5 Physiology of Micturition

CHAPTER OUTLINE

Urinary Bladder and Urethra
Functional Anatomy
Structure of the Bladder
Urethra and its Sphincters
Innervation of the Urinary Bladder

Physiology of Micturition
Filling of Urinary Bladder
Transport of Urine from Ureters to Bladder
Capacity of the Bladder
Emptying of the Bladder
Micturition Reflex
Voluntary Control of Micturition

URINARY BLADDER AND URETHRA

Functional Anatomy The urinary bladder, a hollow muscular viscus, is a temporary reservoir for urine. The main body of empty bladder is pyramidal, having an apex and a base. The lowest part of the bladder is called neck, which continues as urethra.

Interior of the Bladder In an empty bladder, the greater part of the mucosa shows irregular folds due to its loose attachments to the muscular coat. The interior of the base (posterior surface) of the bladder presents a triangular area, the trigone where the mucosa is smooth due to its firm attachment.

Internal urethral orifice is located at the apex (inferior angle) of the trigone. The ureters open into the bladder at superior angles of the trigone (Fig. 6.5-1). The ureters pierce the bladder wall obliquely, and this provides a valve-like action, which prevents a reverse flow of urine towards the kidneys as the bladder fills.

Structure of the Bladder The wall of the urinary bladder consists of three layers: inner mucous membrane, thick coat of smooth muscle and outer serous layer.

Mucous membrane is lined by the transitional epithelium.

Muscular layer is formed by smooth muscle fibres, which constitute the detrusor muscle. Contraction of this muscle coat is responsible for emptying of the bladder.

Serous coat is a reflection of peritoneum and covers only the superior surface.

Urethra and Its Sphincters

Male urethra is about 20 cm in length and is divided into three parts: prostatic urethra (3 cm), membranous urethra (1.25 cm) and penile urethra (15.75 cm). Membranous urethra is surrounded by the external sphincter.

Female urethra is about 3.8 cm long. It extends from the neck of the bladder to the external meatus. It traverses the external sphincter and lies immediately in front of the vagina.

Sphincters of the Urethra

1. Internal Sphincter The circular smooth muscle fibres in the area of the neck of bladder are thickened to form the internal sphincter (sphincter vesicae). The natural tone of the internal sphincter prevents emptying of the bladder until the pressure in the body of bladder rises above a threshold level.
2. External Sphincter Beyond the bladder neck, it is encircled by a ring of voluntary (skeletal type) muscles known as the external sphincter of the bladder. The external sphincter provides voluntary control over micturition.

Innervation of the Urinary Bladder (Fig. 6.5-2)

Motor Innervation

Parasympathetic Innervation The parasympathetic efferent fibres (nervi erigentes) are derived from the second, third and fourth sacral segments (mainly S_2 and S_3). These fibres carry motor impulses to the urinary bladder, causing contraction of detrusor muscle and emptying of the bladder. These fibres are inhibitory to the internal sphincter.

Sympathetic Innervation These nerves arise in the 11th thoracic to the second lumbar segments (T_{11}–L_2). These fibres are said to be inhibitory to detrusor muscle and motor to the sphincter vesicae.

Somatic Motor Innervation The somatic pudendal nerve (S_2, S_3 and S_4) supplies the external sphincter, which is voluntary.

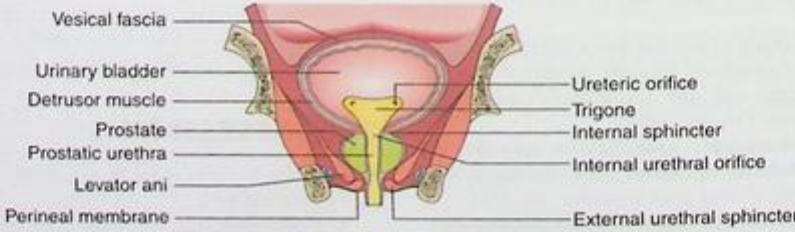


Figure 6.5-1 Coronal section through the bladder and prostate to show the interior of the bladder, internal urethral sphincter and external urethral sphincter.

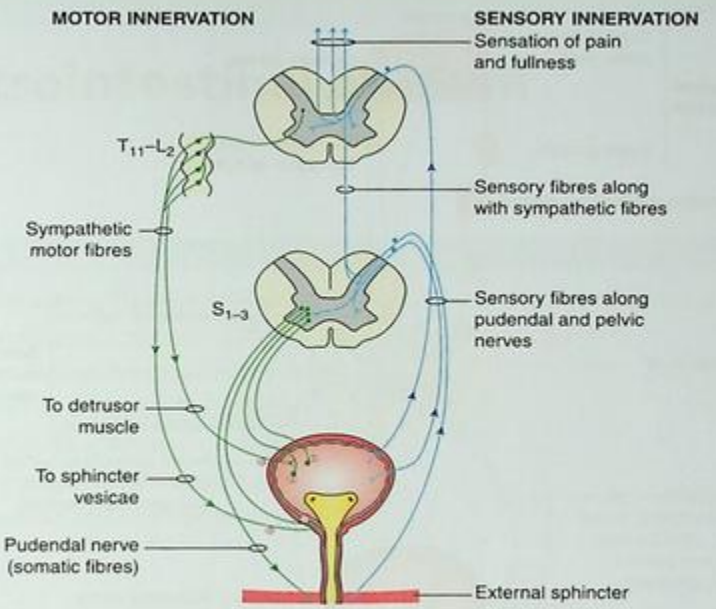


Figure 6.5-2 Innervation of urinary bladder.

Sensory Innervation

Sensation of Bladder Distension Afferents from the detrusor stretch receptors travel to the spinal cord via the pelvic splanchnic nerve (nervi erigentes). From the region of the bladder neck and trigone, the afferents travel via the hypogastric plexus to spinal cord segments T_{11}–L_2.

In the spinal cord, the fibres of awareness of bladder distension run in the posterior column (fasciculus gracilis) to reach the spinal, pontine and suprapontine micturition centres.

Sensation of Bladder Pain The pain fibres are stimulated by excessive distension or spasm of the bladder wall, or by stone, inflammation or malignant disease irritating the bladder. The pain fibres run predominantly in the hypogastric plexus but are also present in the nervi erigentes.

In the spinal cord, the fibres carrying pain sensation run in the lateral spinothalamic tract.

Urethral Sensations include sensation of imminent voiding associated with maximal bladder filling, and reach the spinal cord via the pudendal nerve.

In the spinal cord, fibres carrying urethral sensations travel in the dorsal column.

PHYSIOLOGY OF MICTURITION

Micturition is the process by which urinary bladder empties when filled. The main physiological events in the process of micturition are as follows:

- Filling of urinary bladder
- Emptying of urinary bladder

Filling of Urinary Bladder

Transport of Urine into Urinary Bladder Through Ureters

As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter to force urine towards the bladder.

Capacity of the Bladder

Physiological capacity of the bladder varies with age, being 20–50 mL at birth, about 200 mL at 1 year and can be as high as 600 mL in young adult males. In all cases, the physiological capacity is about twice that at which the first desire to void is felt.

Emptying of the Bladder

Emptying of the bladder is basically a reflex action called the micturition reflex, which is controlled by supraspinal centres and is assisted by contraction of perineal and abdominal muscles.

Micturition Reflex

Initiation Micturition reflex is initiated by the stimulation of the stretch receptors located in the wall of urinary bladder.

Stimulus Filling of bladder by 300–400 mL of urine in adults constitutes the adequate stimulus for the micturition reflex to occur.

Afferents The afferents from the stretch receptors in the detrusor muscle and urethra travel along the pelvic splanchnic nerves and enter the spinal cord through dorsal roots to S_2, S_3 and S_4 segments to reach the sacral micturition centre (Fig. 6.5-3).

Sacral Micturition Centre is formed by the sacral detrusor nucleus and sacral pudendal nucleus.

Efferents Efferents arising from the sacral detrusor nucleus are the preganglionic parasympathetic fibres, which relay in the ganglia near or within the bladder and urethra (Fig. 6.5-3). The postganglionic parasympathetic fibres are excitatory to the detrusor muscle and inhibitory to the internal sphincter.

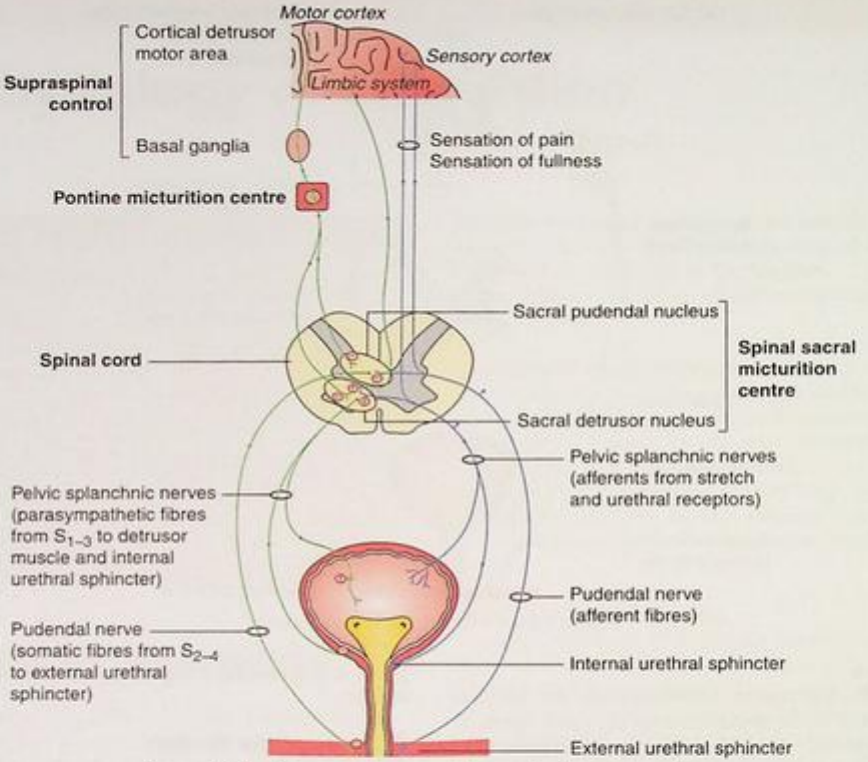


Figure 6.5-3 Pathway and supraspinal control of micturition reflex.

Response Once micturition reflex is initiated, it is self-regenerative, i.e. initial contraction of the bladder wall further activates the receptors to increase the sensory impulses (afferents) from the bladder and urethra, which cause further increase in the reflex contraction of detrusor muscle of the bladder. The cycle thus keeps on repeating itself again and again until the bladder has reached a strong degree of contraction.

Voluntary Control of Micturition

Role of Supraspinal Centres The micturition reflex is fundamentally a *spinal reflex* facilitated and inhibited by higher brain centres *(supraspinal centres)* and, like defecation, is subjected to voluntary facilitation and inhibition. In infants and young children, micturition is purely a reflex action. *Voluntary control* is gradually acquired as a learned ability of toilet training.

Supraspinal control centres, which control the micturition reflex (a completely automatic cord reflex), include the pontine micturition centre (PMC) and suprapontine centres.

Role of Perineal and Abdominal Muscles in Micturition

Certain muscular movements, which aid the emptying of bladder, but are not the essential component of micturition process are as follows:

- At the onset of micturition, the levator ani and perineal muscles are relaxed, thereby shortening the posturethra and decreasing the urethral resistance.
- The diaphragm descends.
- The abdominal muscles contract, accelerating the flow of urine by raising intra-abdominal pressure, which, in turn, secondarily increases the intravesical pressure, thereby increasing the flow of urine.

SELF-ASSESSMENT

1. Describe briefly:
   - Physiology of micturition
   - Micturition reflex

SECTION 7

Gastrointestinal System

SECTION OUTLINE

7.1 Organization, General Principles and Functions of Gastrointestinal System
7.2 Physiological Activities in Mouth, Pharynx and Esophagus
7.3 Physiological Activities in Stomach
7.4 Pancreas, Liver and Gall Bladder
7.5 Physiological Activities in Small Intestine
7.6 Physiological Activities in Large Intestine
7.7 Digestion and Absorption

To sustain life, body needs a continual supply of water, electrolytes and nutrients. This function is served by the gastrointestinal or the so-called digestive system.

Gastrointestinal system is composed of alimentary canal and other associated organs, such as liver, gall bladder and pancreas. Alimentary canal is a long tube starting at the mouth, passing through pharynx, esophagus, stomach, small intestine, large intestine, rectum and ending at anus.

Functions of Gastrointestinal System

I. **Digestive functions.** The major function of the gastrointestinal system is to transfer nutrients, minerals and water from external environment to the circulating body fluids for distribution to all the body tissues. This function is accomplished by the following processes.

1. ***Ingestion of food.*** It involves:
   - Placing the food into the mouth. Most of the foodstuffs are taken into mouth as large particles mainly made of carbohydrates, proteins and fats.
   - Chewing the food into smaller pieces is carried out with the help of teeth and jaw muscles. This process is called mastication.
   - Lubrication and moistening of the food is done by the saliva.
   - Swallowing the food (deglutition). It refers to pushing the bolus of food from mouth into the stomach. It is accomplished in three phases: oral phase, pharyngeal phase and esophageal phase.
2. ***Digestion of food.*** It refers to the conversion of complex insoluble large organic molecules (food) into soluble, smaller and simpler molecules which can be easily absorbed. Digestion of food is accomplished with the help of hydrochloric acid and digestive juices containing various enzymes.
3. ***Absorption of digested food.*** Absorption of food refers to the movement of digested molecules from the lumen of alimentary canal across its epithelial lining to the blood or lymph. The absorbed water, electrolytes and nutrients are carried away to the various tissues by the circulating blood.
4. ***Egestion,*** i.e. excretion of unwanted undigested food by the alimentary canal in the form of faeces is called defecation.

To understand the digestive function of gastrointestinal system it is imperative to have knowledge about:

- Functional anatomy and organization of the gastrointestinal system
- Gastrointestinal motility
- Gastrointestinal blood flow
- Role of salivary glands, liver, gall bladder and pancreas
- Neural and hormonal control of gastrointestinal functions

II. **Nondigestive functions.** The principal nondigestive function of the gastrointestinal system is its role as an immune system. The lymphoid tissue in the tonsils, adenoids and Peyer's patches constitute an important part of body's immune system. These provide both the humoural and cellular immunity, which is especially effective against the microorganisms trying to enter the body from the alimentary canal.

7.1 Organization, General Principles and Functions of Gastrointestinal System

CHAPTER OUTLINE

Functional Anatomy
Functional Organization
Mouth
Pharynx
Eesophagus
Stomach
Small Intestine
Large Intestine
Structural Characteristics of GIT Wall
Innervation of the GIT
Intrinsic Innervation
Extrinsic Innervation
Gastrointestinal Blood Flow

FUNCTIONAL ANATOMY

Functional Organization

The digestive system is composed of gastrointestinal tract (GIT) and accessory organs of digestion like teeth, tongue, salivary glands, liver and exocrine part of pancreas.

Gastrointestinal Tract, also known as alimentary canal, is basically a muscular tube extending from the mouth to the anus (Fig. 7.1-1). At either end, the lumen is continuous with external environment. It measures about 10 m (30 feet) and is composed of the following parts.

Mouth The mouth is loosely used term to denote the external opening and for the cavity it leads to. The cavity containing anterior two-thirds of tongue and teeth is the *mouth cavity* or *oral cavity* or *buccal cavity*.

Tongue, in the digestive system, plays two important roles:

- Tells the taste of food
- Helps in chewing and swallowing of the food

Teeth are accessory organs of digestion which help in chewing of food.

Pharynx The pharynx is a median passage that is common to the gastrointestinal and respiratory systems. It is divisible, from above downwards, into three parts:

- *Nasal part* or *nasopharynx* into which nasal cavities open.
- *Oral part* or *oropharynx* which is continuous with posterior end of oral cavity.
- *Laryngeal part* or *laryngopharynx* which is continuous in front with larynx and below with esophagus.

Esophagus It is a fibromuscular tube about 25 cm long. At its junction to the pharynx upper esophageal sphincter is present and at its junction with the stomach lower esophageal sphincter is present.

Stomach It is a hollow muscular bag connected to the esophagus at its upper end and to the duodenum at the lower end. It serves the following motor functions:

- Storage of food
- Mixing of food with gastric secretions to form a semiliquid mixture called chyme

Small Intestine It is a long tubular structure which can be divided into three parts:

- *Duodenum* is the first part of the small intestine. It is C-shaped and measures about 25 cm in length.
- *Jejunum,* the middle part of the small intestine is about 25-m long.
- *Ileum,* the last part of the small intestine, is about 3.5-m long.

Large Intestine It arches around and encloses the coils of the small intestine, and tends to be more fixed than the small intestine. It is divided into the following parts (Fig. 7.1-1).

- ***Caecum*** is a blind ended sac into which opens the lower end of ileum.
- ***Appendix*** is worm-shaped tube that arises from the medial side of caecum, which in human being is a vestigial organ.
- ***Colon*** consists of the following parts:
  - *Ascending colon* extends upward from the caecum along the right side of the abdomen up to the liver.
  - *Transverse colon* extends from the right hepatic flexure to the *left splenic flexure*. It forms a wide U-shaped curve.
  - *Descending colon* extends from the left splenic flexure to the pelvic inlet below.

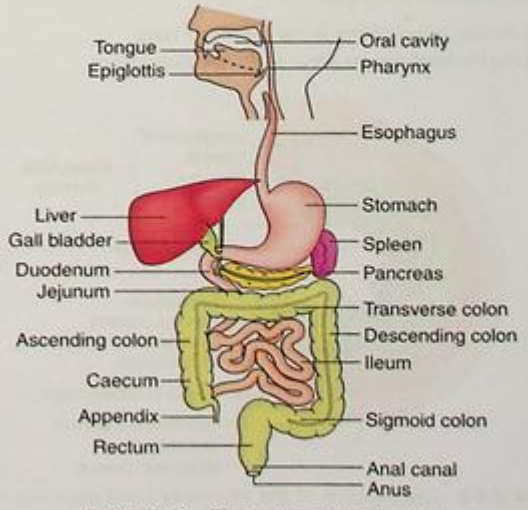


Figure 7.1-1 The gastrointestinal system.

- ***Sigmoid colon*** begins at the pelvic inlet as continuation down of the descending colon and joins the rectum in front of the sacrum.
- ***Rectum*** descends in front of the sacrum to leave the pelvis by piercing the pelvic floor. Here it becomes continuous with anal canal in the perineum.
- ***Anal canal*** opens to the exterior through the anus, the opening which is guarded by two sphincters.

In large intestine, there occurs absorption of water and electrolytes from the intestinal contents. The remaining material is called *faecal matter*. The mucus secreted from the wall of large intestine lubricates the faecal matter. The faecal matter is stored in the sigmoid colon (pelvic colon) till expelled by the process of defecation, which is assisted by the movements of large intestine, activity of anal canal and anal sphincters.

Structural Characteristics of GIT Wall

Different parts of the GIT are specialized for carrying out different functions particularly digestion and absorption, but the basic structural characteristics of the wall of whole GIT are similar. The intestinal wall from inside to outwards consists of the following layers (Fig. 7.1-2).

1. Mucosa (mucous layer) It is innermost coat consisting of three layers:

- ***Surface epithelium*** lining the luminal surface consists of epithelial cells which vary in type from simple squamous to tall columnar depending on the function of the part of GIT.
- ***Lamina propria*** is composed of loose connective tissue, which contains numerous glands, small blood vessels, lymphatics and nerve fibres.
- ***Muscularis mucosa*** is composed of two thin layers of smooth muscle fibres, which help in localised movements of the mucosa.

2. Submucosa This refers to the layer of connective tissue present outside the mucosa. It contains blood vessels, lymphatics and a network of nerve fibres and nerve cells called submucosal nerve plexus (Meissner's plexus).

3. Muscle Coat It is formed by a thick layer of smooth muscle fibres surrounding the submucosa. The smooth muscle fibres are arranged in two layers:

- *Circular muscle fibres* form the inner layer
- *Longitudinal muscle fibres* form the outer layer

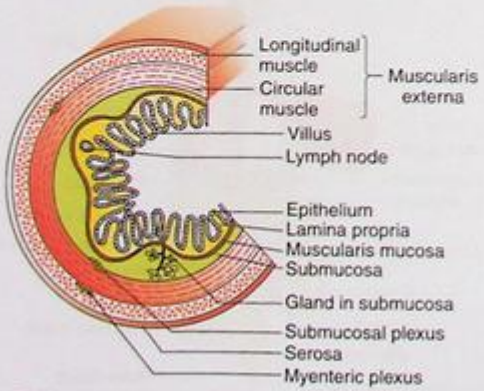


Figure 7.1-2 Cross-section of the alimentary canal depicting structural characteristics of its wall.

In between the circular and longitudinal muscle fibres is present an extensive network of nerve cells and fibres named *Auerbach's plexus* (myenteric plexus).

4. Serosa (serous layer) This is the outermost layer consisting of a layer of connective tissue. This layer helps in the attachment of gut to the surrounding structures.

Innervation of the GIT

The innervation of the GIT includes intrinsic and extrinsic system (Fig. 7.1-3).

1. Intrinsic Innervation The intrinsic nervous system, also called *enteric nervous system*, consists of nerve cells and fibres which originate and are located in the intestinal wall itself. This system supplies the smooth muscles of GIT (i.e. musculature of GIT except upper esophagus and external anal sphincter which contain striated muscle). This system controls most of the gastrointestinal functions like secretion and motility. The enteric nervous system is composed mainly of two plexuses.

Myenteric Plexus or Auerbach's plexus is present in between the circular and longitudinal muscle fibres of muscular coat of the GIT. Stimulation of myenteric plexus causes increase in tone of the gut wall, intensity of rhythmical contractions of gut wall, rate of contraction and velocity of contraction.

Meissner's Plexus or submucosal plexus is present in the submucosal layer. It *controls the secretory activity* and blood flow to the gut.

The Auerbach's and Meissner's plexuses are interconnected with each other and are under the control of parasympathetic and sympathetic components of extrinsic nervous system. In both the plexuses, the axons branch profusely, so that stimulation of one region produces a widespread response in the GIT.

2. Extrinsic Innervation The extrinsic system of nerves supplying the gut consists of the parasympathetic and sympathetic components of autonomic nervous system.

Parasympathetic Innervation The parasympathetic supply to the gut is made up of cranial and sacral divisions:

- ***Cranial parasympathetic fibres*** originate in medulla, come through vagus and supply the esophagus, stomach, small intestine, pancreas and first half of the large intestine. They also make synaptic connections with intramural plexuses.
- ***Sacral parasympathetic fibres*** originate in sacral spinal cord, pass through pelvic nerves to hypogastric (pelvic) ganglion as a postganglionic fibre, and supply to the distal half of large intestine and rectum.

Functions of parasympathetics. Parasympathetic stimulation causes an increase in the gastrointestinal motility and secretory activity.

Sympathetic Innervation The sympathetic fibres to gut arise from eighth thoracic (T_8) to second lumbar (L_2) spinal segments. The sympathetics innervate all portions of the GIT.

Functions of sympathetic innervation. Sympathetic stimulation causes:

- Vasoconstriction
- Excitation of ileocaecal and internal anal sphincters, and smooth muscles of muscularis mucosa throughout (to increase number of folds)
- Inhibition of motility in the gut

Thus most of the effects of sympathetic stimulation are opposite to that of the parasympathetic stimulation.

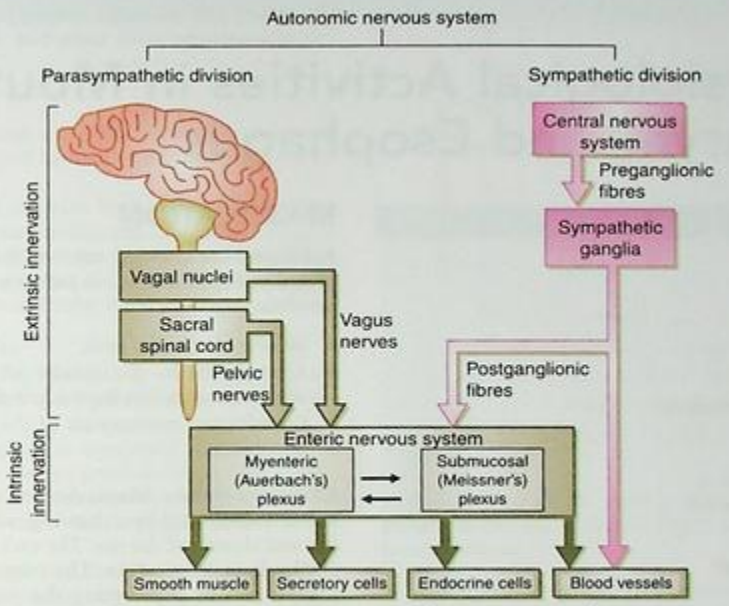


Figure 7.1-3 Schematic illustration of the innervation of gut.

Gastrointestinal Blood Flow

The blood supply of the GIT forms part of splanchnic circulation. The principal characteristic feature of the gastrointestinal blood flow is that it is *usually proportional to the level of local activity*. For details see page 165.

SELF-ASSESSMENT

Give a brief account on structural characteristics and innervation of gut.

7.2 Physiological Activities in Mouth, Pharynx and Esophagus

CHAPTER OUTLINE

Introduction
Ingestion

Mastication
Chewing Reflex
Muscles of Mastication

Lubrication of Food by Saliva
Salivary Glands
Saliva
Secretion and Composition
Control of Salivary Secretion
Functions of Saliva

Deglutition (Swallowing)
Phases of Swallowing
Oral Phase
Pharyngeal Phase
Esophageal Phase
Disorders of Swallowing
Abolition of Deglutition Reflex
Aerophagia
Dysphagia
Cardiac Achalasia
Gastro-esophageal Reflux Disease

INTRODUCTION

The functioning of digestive system starts from the mouth (oral cavity) and ends at the anus.

Ingestion of food involves the following processes:

- Placing of food into the mouth
- Mastication, i.e. chewing the food into smaller pieces
- Lubrication of the food with saliva
- Swallowing, i.e. deglutition

The above-mentioned physiological activities which take place in the mouth, pharynx and esophagus are discussed in this chapter.

MASTICATION

Mastication or chewing refers to the process by which the food placed in the mouth is cut and grounded into smaller pieces. It involves:

- Movements of the jaws,
- Action of teeth – the incisors provide a strong cutting action, whereas the molars have a grinding action and
- Coordinated movements of the tongue and muscles of the oral cavity.

Chewing Reflex Mastication or chewing, though a voluntary act, is coordinated by a chewing reflex that facilitates the opening and closing of the jaw. The cycle of opening and closing the jaw leads to mastication. The tongue contributes to the grinding process by positioning the food between the upper and lower teeth.

Muscles of Mastication Muscles of mastication include masseter, temporalis, and internal and external pterygoids. Buccinator is an accessory muscle of mastication which prevents accumulation of food between the cheek and teeth.

Net Effect of Mastication The bolus of food becomes a homogenized mixture of small food particles, saliva and mucus, which is easy to swallow and digest.

LUBRICATION OF FOOD BY SALIVA

Salivary Glands

In addition to the chewing, another important physiological activity which takes place in the mouth is lubrication of food by saliva. The saliva is secreted by three pairs of major salivary glands.

1. Parotid Glands

Location Parotid glands are the largest salivary glands (each weighing 20–30 g) located near the angles of jaw.

Acini The parotid glands are purely serous glands (Fig. 7.2-1) which secrete watery saliva containing more than 90% water. Parotid glands secrete 25% of the total salivary secretion (which is about 1500 mL/day).

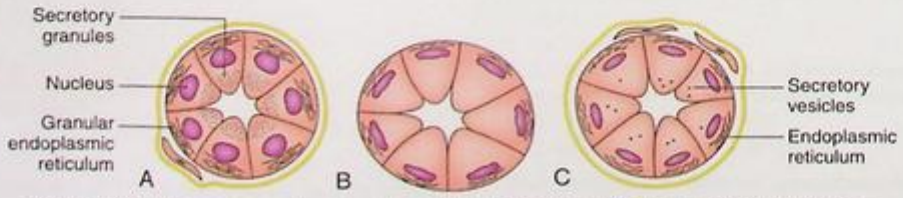


Figure 7.2-1 Different types of acini in salivary glands: (A) serous; (B) mucous; and (C) seromucous.

Ducts Ducts of the parotid glands open on the inner side of the right and left cheek, and pour their secretions in the vestibule.

2. Sublingual Glands

Location The sublingual gland is the smallest of the three principal salivary glands. It lies just below the mucosa on the floor of mouth.

Acini The sublingual gland contains both serous and mucous acini (Fig. 7.2-1), the latter predominating.

Ducts Ducts of sublingual gland are 8–20 in number. Most open into the mouth on the summit of the sublingual fold but a few may open into the submandibular duct.

3. Submandibular Glands

Location The submandibular glands are the large salivary glands which lie (one on each side) partly under cover of the body of the mandible.

Acini The submandibular gland is composed of a mixture of serous and mucous acini, the former predominating (Fig. 7.2-1).

Ducts S-shaped duct of each submandibular gland opens on the sublingual papilla located just lateral to the frenulum lingua.

Note. The sublingual and the submandibular glands secrete a fluid that contains a higher concentration of proteins and so is more viscus as compared to the watery secretion of parotid glands.

Smaller Salivary Glands In addition to the three pairs of salivary glands described above, several smaller glands are located throughout the oral cavity. Those in the tongue secrete lingual lipase.

Saliva

Secretion and Composition

Amount Under normal circumstances the salivary glands secrete about 500–1500 mL of saliva every day. pH of saliva varies from 6 to 7.4.

Composition Saliva is composed of 99% *water* and 1% *solids*, which include:

- *Organic substances*, such as L-amylase (ptyalin), lingual lipase, kallikrein, lysozyme, small amounts of urea, uric acid, cholesterol and mucin.
- *Inorganic substances* are Na^+, Cl^-, K^+ and HCO_3^-.

Note. Composition of saliva varies with the salivary flow rate.

Effects of Flow Rate on the Composition of Saliva

1. At High Flow Rates, there is less time for reabsorption and secretion, and therefore the saliva is most like the initial secretion by the acinar cells. Thus, with the increase in flow rate the concentration of ions changes (Fig. 7.2-2):

- Sodium ion (Na^+) concentration increases progressively to a plateau value of 80–90 mEq/L.
- Chloride ions (Cl^-) concentration increase to about 50 mEq/L.

Note. Na^+ and Cl^- concentrations of saliva are always lower than that in the plasma.

- Potassium ion (K^+) concentration decreases to 15–20 mEq/L.
- Bicarbonate ion (HCO_3^-) concentration increases when salivary flow rate increases (up to 50–70 mEq/L).

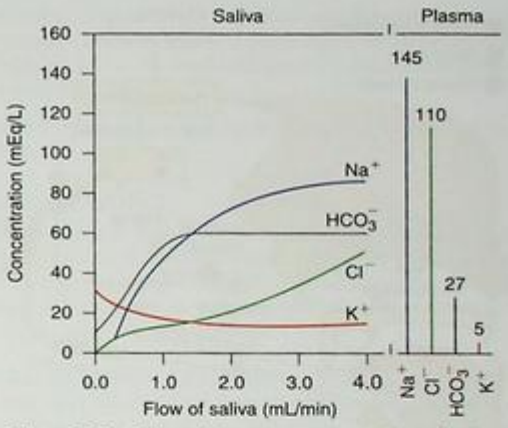


Figure 7.2-2 Effect of flow rate on composition of saliva.

2. At Low Flow Rates, there is more time for reabsorption and secretion, therefore, the modified saliva under resting conditions contains:

- Low concentration of Na^+ (about 15–20 mEq/L)
- Low concentration of Cl^- (15–20 mEq/L)
- Low concentration of HCO_3^- (10–15 mEq/L)
- High concentration of K^+ (25–30 mEq/L)

Control of Salivary Secretion

- Salivary secretion is controlled entirely by the autonomic nervous system (ANS) reflexes.
- Salivary secretion production is increased by both parasympathetic and sympathetic activity; however the activity of former is more important.

I. Parasympathetic Control

Parasympathetic Nerve Supply *(Fig. 7.2-3)*

Parotid glands are supplied by the parasympathetic fibres (preganglionic), which arise from the inferior salivary nucleus (dorsal nucleus of IXth nerve) of medulla.

Submandibular and sublingual glands are supplied by the parasympathetic fibres originating from superior salivary nucleus (dorsal nucleus of VIIth nerve).

Parasympathetic Reflexes Parasympathetic nerves are secretomotor to the salivary glands and control their secretion via the following reflexes.

1. Conditioned Reflexes Sight, smell or even thought of palatable food increases the salivary secretion by the conditioned reflexes. In conditioned reflexes, the parasympathetics supplying the salivary glands are stimulated by impulses coming from higher centres of brain.

2. Unconditioned Reflexes are initiated by the stimulation of receptors in the buccal cavity. Receptors and afferents, and efferents of unconditioned reflexes are discussed as follows:

- ***Receptors and afferents***
  - *Mechanoreceptors* which are excited by tactile stimulation from the tongue, mouth and pharynx.
  - *Afferent path of tactile stimulation reflexes* run in trigeminal nerve branches (such as lingual, buccal and palatine nerves), pharyngeal branches of vagus and glossopharyngeal nerve.

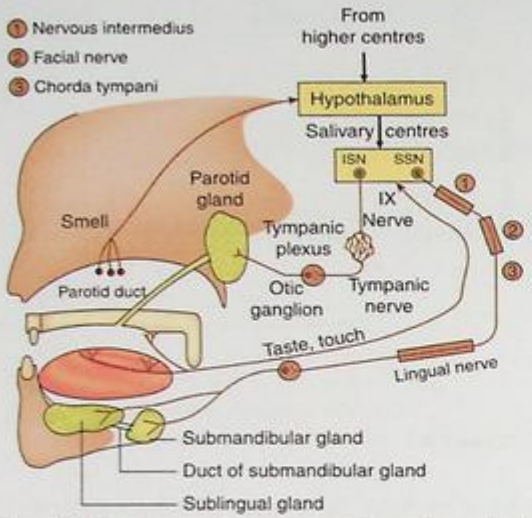


Figure 7.2-3 Parasympathetic nerve supply to salivary glands.

- *Chemoreceptors*, i.e. taste buds are stimulated by the sensation of taste and chemicals in the food. Afferents for taste sensation from:
- Posterior one-third of tongue passes via glossopharyngeal nerve to end in inferior salivary nucleus (dorsal nucleus of IXth nerve).
- Anterior two-thirds of tongue pass via nervous intermedius (branch of VIIth nerve) to end in superior salivary nucleus (dorsal nucleus of VIIth nerve).
- *Salivary centre* is thus constituted by superior and inferior salivary nuclei.
- *Efferents* from superior salivary nucleus stimulate the submandibular and sublingual salivary glands, whereas those from the inferior salivary nucleus stimulate the parotid glands.

Effects of Parasympathetic Stimulation Parasympathetic nerve stimulation causes the salivary gland cells to secrete a large volume of watery fluid that is high in electrolytes but low in proteins.

Stimulation of parasympathetic nerves liberates a proteolytic enzyme kallikrein from the gland cells, which acts on $\alpha 2$-globulin in interstitial fluid to form bradykinin. It also causes local release of VIP (vasoactive intestinal peptide). These increase the saliva production by causing vasodilatation of blood vessels of salivary gland.

IMPORTANT NOTE

It is important to note that:

- Cholinergic receptors on acinar and ductal cells are muscarinic.
- Anticholinergic drugs (e.g. atropine) inhibit the production of saliva and cause dry mouth.

II. Sympathetic Control

Sympathetic Nerve Supply

- *Preganglionic fibres* originate from the lateral horn cells of T_1 and T_2 segments of spinal cord and enter paravertebral sympathetic chain via ventral roots to synapse with the cells in *superior cervical ganglion*.
- *Postganglionic fibres* run along the carotid artery branches and are supplied to the three pairs of salivary glands along with their blood supply.

Effects of Sympathetic Stimulation Stimulation of sympathetic fibres causes vasoconstriction in the salivary glands and transient secretion of a very small amount of thick viscid saliva, rich in mucus and other organic constituents.

Functions of Saliva

1. Protective Function

Dilutes hot and irritant food substances, thus preventing injury to buccal mucosa.

Washes away food particles that remain in the oral cavity at the end of meal and thus cleans the oral cavity, i.e. helps in maintaining oral hygiene. In this way, growth of several harmful bacteria in the oral cavity is prevented.

Destroys harmful bacteria in the mouth and thus minimizes the risk of buccal infection and dental caries because of its following constituents:

- *Lysozymes*, which have bactericidal action.
- *IgA*, which provides immunological defence against bacteria and viruses.
- *Lactoferrin*, which has bacteriostatic action, i.e. prevents multiplication of bacteria.

Dilutes any hydrochloric acid (HCl) and bile, which regurgitate into esophagus and mouth.

2. Role in Mastication and Deglutition

- Salivary mucus lubricates the food and buccal mucosa, and thus aids in mastication and swallowing.
- Helps bolus formation by acting as a glue.

3. Digestive Functions

- *Initial starch digestion* starts by α-amylase (ptyalin) present in the saliva. Salivary amylase acts on α-1,4 linkage (but not on α-1,6 linkage) and digests starch to maltose.
- *Initial triglyceride digestion* is caused by the lingual lipase present in the saliva.

4. Role in Taste Sensation

Saliva acts as a solvent for various foodstuffs. As taste is a chemical sense, the taste receptors respond only to the dissolved substances.

5. Role in Speech

Salivary mucus lubricates the oral mucosa and thus aids speech by the facilitating movements of lips and tongue.

6. Excretory Function

Saliva acts as a vehicle for excretion of certain heavy metals, thiocyanate ions, alcohol and morphine.

7. Role in Temperature Regulation

- During state of dehydration, the salivary secretion is reduced which induces thirst.
- Panting mechanism. In dogs, saliva is evaporated from the surface of tongue to cause evaporative heat loss.

DEGLUTITION (SWALLOWING)

Phases of Swallowing

Deglutition or swallowing refers to the passage of food from the oral cavity into the stomach. It comprises three phases:

- Oral phase (voluntary)
- Pharyngeal phase (reflex or involuntary)
- Esophageal phase (reflex or involuntary)

Oral Phase

- Oral phase or the first stage of swallowing is a voluntary phase.
- During this phase the bolus of food formed after mastication is put over the dorsum of tongue. The tongue forces the bolus into the oropharynx by pushing up and back against the hard palate (Fig. 7.2-4A).

Pharyngeal Phase

Pharyngeal phase or second stage of swallowing is an involuntary phase caused by a swallowing reflex.

Deglutition centre coordinating the reflex activity is located in the medulla oblongata and lower pons, i.e. in the nucleus of the tractus solitarius (NTS) and the nucleus ambigus (Fig. 7.2-5).

Events during Pharyngeal Phase Events which take place during movement of bolus from the pharynx into the esophagus occur in the following sequence (Fig. 7.2-4B–D):

- *Oral cavity is shut off* from the pharynx by the approximation of posterior pillars of the fauces.
- *Nasopharynx* is *closed* by the upward movement of soft palate, preventing regurgitation of food into the nasal cavities.
- *Palatopharyngeal folds are pulled medially* to make a slit-like opening for food, allowing only properly masticated food to pass through (selective action).
- *Vocal cords* strongly approximate stopping the breathing temporarily *(deglutition apnoea). Larynx* is pulled upward and anteriorly by neck muscles enlarging the opening of esophagus, which is normally a slit and *epiglottis* swings backwards to close laryngeal opening. All this guides the food towards the esophagus and prevent its entry into the trachea.
- *Upper esophageal sphincter (UES)* which normally remains contracted tonically opens up and allows the bolus of food to be pushed into the upper part of esophagus by the rapid peristaltic contraction wave of pharynx, which also continues in the esophagus.
- Once the bolus of food has passed into the esophagus, cricopharyngeus contracts, vocal cords open up allowing normal breathing to be resumed and the UES once again goes into tonic contraction.

The entire process of pharyngeal phase is completed in 1–2 seconds.

Esophageal Phase

During esophageal phase, the food bolus is propelled from the upper part of esophagus to the stomach by the esophageal peristalsis and aided by gravity. Before describing the features of esophageal peristalsis, it will be worthwhile to discuss briefly the applied anatomy of esophagus.

Applied Anatomy of Esophagus The esophagus is a fibromuscular tube about 25 cm long. It is separated from the pharynx by the upper esophagus sphincter (UES) and from the stomach by the lower esophageal sphincter (LES).

Upper Esophageal Sphincter UES is a true sphincter that is normally contracted tonically, and serves to prevent the entry of air into the esophagus during normal respiration. Its tone is maintained by the continual firing of vagal fibres.

The UES opens during swallowing when a rapid peristaltic wave starting in the pharyngeal muscles passes on to esophagus.

Lower Esophageal Sphincter LES also known as cardiac sphincter refers to distal 2 cm of esophagus.

The principal function of LES is to prevent regurgitation of gastric contents (food, gastric juice and air) into the esophagus. The local hormone, gastrin, increases the tone of LES and helps to keep the sphincter more tightly closed during digestion.

Esophageal Peristalsis

- The esophageal phase of deglutition (Fig. 7.2-5E) is completed by two types of esophageal peristalsis, primary and secondary.

Primary Esophageal Peristalsis propels the food downwards.

- The LES (which normally remains tonically contracted) relaxes as the peristaltic wave approaches the sphincter and allows the bolus of food to enter the stomach without causing any resistance.

Secondary Esophageal Peristalsis

- When the primary esophageal peristalsis is not able to push a bolus of solid food all the way down the esophagus, the food remaining in the esophagus stretches mechanical

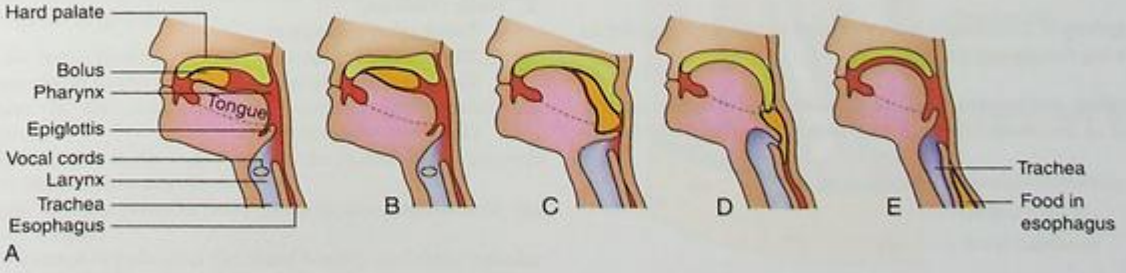


Figure 7.2-4 Phases of swallowing: (A) oral phase; (B–D) early, middle and late pharyngeal phase; and (E) esophageal phase.

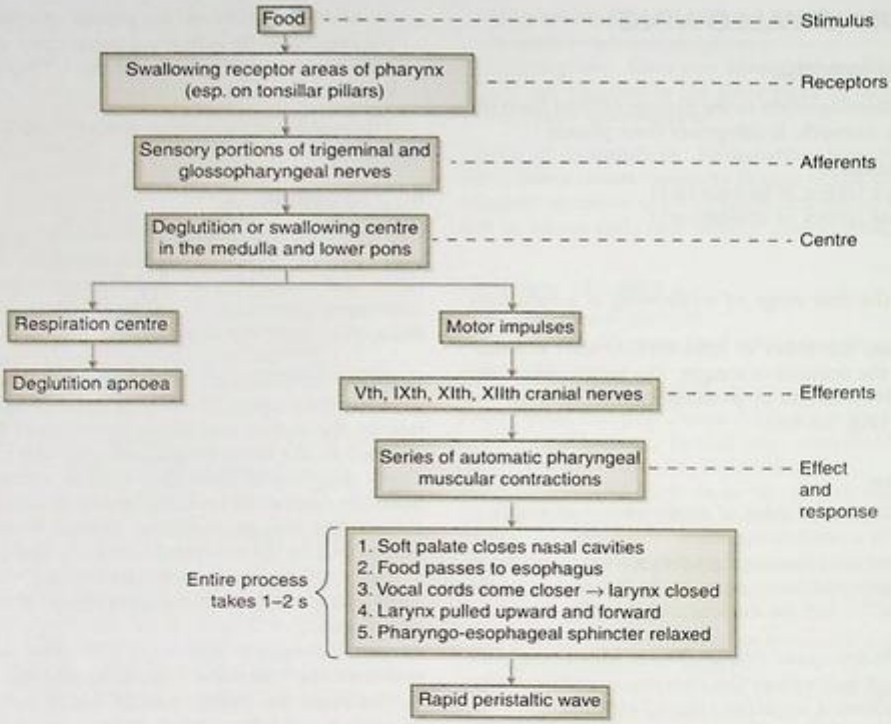


Figure 7.2-5 Summary of swallowing reflex.

receptors and initiates another peristaltic wave called the secondary esophageal peristalsis.

Note. After the food enters the stomach, the LES contracts to prevent regurgitation of food into the esophagus. With this the esophageal phase of deglutition is completed.

Disorders of Swallowing

1. Abolition of Deglutition Reflex Abolition of deglutition reflex causes regurgitation of food into the nose or aspiration into the larynx and trachea. It may occur: when IXth or Xth nerve is paralysed in lesions of medulla.

2. Aerophagia Aerophagia refers to the unavoidable swallowing of air along with the swallowing of food bolus and liquids.

3. Dysphagia Dysphagia is a term used to denote difficulty in swallowing due to any cause.

4. Cardiac Achalasia Cardiac achalasia is a neuromuscular disorder of the lower two-thirds of esophagus, characterized by absence of esophageal peristalsis and failure of the LES to relax during swallowing.

5. Gastro-esophageal Reflux Disease Gastro-esophageal reflux disease refers to a condition in which incompetence of the LES causes reflux of acidic gastric contents into the esophagus. Reflux of stomach acid causes esophageal pain (heartburn) and may lead to irritation of esophagus or bronchioles (due to aspiration).

SELF-ASSESSMENT

1. Describe briefly:
   - Composition and functions of salivary secretion
   - Mechanism and regulation of salivary secretion
   - Phases of salivary secretion
   - Mechanism and phases of deglutition
2. Write notes on:
   - Esophageal sphincters
   - Deglutition reflex
   - Cardia achlasia
   - Aerophagia
   - Gastro-esophageal reflux

7.3 Physiological Activities in Stomach

CHAPTER OUTLINE

Functional Anatomy
Gross Anatomy
Structural Characteristics

Physiology of Gastric Secretion
Gastric Juice
Composition
Secretion
Regulation of Gastric Secretions
Neural Control
Chemical Control
Phases and Regulation of Gastric Secretion

Physiology of Gastric Motility
General Considerations
Initiation of Gastric Motility
Types of Gastric Motility
Motility of Empty Stomach
Migratory Motor Complexes
Hunger Contractions
Gastric Motility Related to Meals
Receptive Relaxation
Mixing Peristaltic Waves
Gastric Emptying

Functions of Stomach

Applied Aspects
Gastric Mucosal Barrier and Pathophysiology of Peptic Ulcer
Physiology of Vomiting

FUNCTIONAL ANATOMY

Gross Anatomy

Stomach is a J-shaped, hollow, muscular bag connected to the esophagus at its upper end and to the duodenum at the lower end.

Parts of Stomach The stomach can be divided into five anatomic regions (Fig. 7.3-1):

- *Cardia* is the narrow conical portion of the stomach immediately distal to the gastro-esophageal junction.
- *Fundus* is the dome-shaped proximal portion of the stomach.
- *Body or corpus* is the main part of the stomach that extends up to the incisura angularis.
- *Pyloric antrum* extends from the incisura angularis to the pyloric canal.
- *Pyloric canal or pylorus* is the distal most 1-inch long tubular part of stomach.

Note. Anatomically, the antrum and pylorus are continuous and respond to nervous control as a unit. Functionally, first part of duodenum is associated with the pyloric part of stomach.

Structural Characteristics

The gastric wall consists of mucosa, submucosa, muscular coat and serosa (serous layer).

Gastric Mucosa

- The inner surface of the stomach exhibits coarse *rugae*. These infoldings of mucosa and submucosa are most prominent in the proximal stomach.
- The delicate texture of the mucosa is punctured by millions of gastric foveolae or pits, leading to the mucosal glands.

Histological Features Gastric mucosa comprises (Fig. 7.3-2) the following:

Surface foveolar cells are tall columnar mucin-secreting cells, which line the entire gastric mucosa as well as the gastric pits.

Mucous neck cells are present deeper in the gastric pits. These cells are thought to be the progenitors of both, the surface epithelium and the cells of gastric glands.

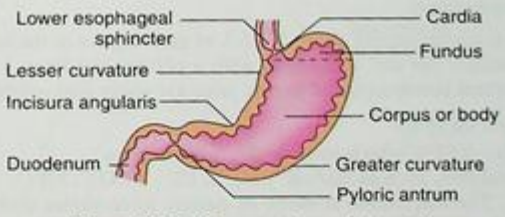


Figure 7.3-1 Gross anatomy of stomach.

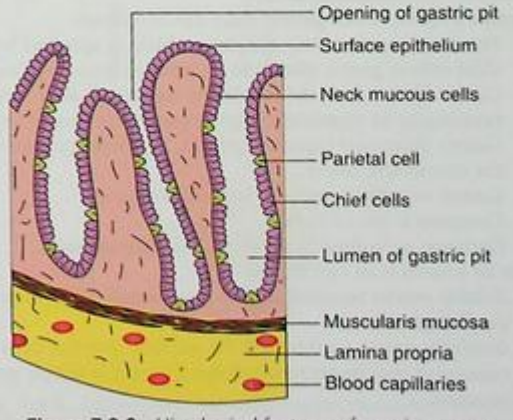


Figure 7.3-2 Histological features of gastric mucosa.

Glandular cells form the gastric glands. There are three types of gastric glands.

1. **Main gastric glands** are found in the body and fundus of stomach. These are simple tubular glands (Fig. 7.3-2). The alveoli of main gastric glands contain two types of cells:
   - *Chief cells*, also known as peptic or zymogen cells, are basophilic. These cells are concentrated at the base of main gastric glands and secrete proteolytic proenzymes, pepsinogen I and II.
   - *Parietal cells* (oxyntic cells) are acidophilic. These cells line predominantly the upper half of glands and have an extensive intracellular canalicular system. These secrete *hydrochloric acid* (HCl) and the *intrinsic factor*.
2. **Cardiac tubular glands** are found in the mucosa of cardia. These secrete *soluble mucus*.
3. **Pyloric (antral) glands** are found in the antrum and pylorus region of the stomach. These glands contain two types of cells:
   - *Mucus cells*, which secrete *soluble mucus*
   - *G-cells*, which are responsible for the release of the hormone gastrin

Musculature of Stomach Characteristic features of gastric musculature are as follows:

- The muscle coat of stomach has three layers: an outer longitudinal, middle circular and an inner oblique.
- The stomach and duodenum are divided by a thickened circular smooth muscle layer called *pyloric sphincter*.

PHYSIOLOGY OF GASTRIC SECRETION

Gastric Juice

Composition

Gastric glands secrete about 2–2.5 L of gastric juice in the lumen of stomach per day. It is acidic with a pH varying from 1 to 2. Important constituents of gastric juice are water and solids.

Water – 99.45%
Solids – 0.55%, which include the following.
Electrolytes, such as Na^+, K^+, Mg^{2+}, Cl^-, HCO_3^-, HPO_4^- and SO_4^-. The electrolyte content of gastric juice varies with the rate of secretions. At low secretory rates, Na^+ concentration is high and H^+ concentration is low, but as acid secretion increases Na^+ concentration falls.
Enzymes present in the gastric juice are as follows:
- *Pepsin* is a proteolytic enzyme, which is secreted by the chief cells of gastric glands in an inactive form pepsinogen.
- *Gastric lipase* is a weak fat-splitting enzyme. It is of little importance in fat digestion except in pancreatic insufficiency.
- *Gastric gelatinase* liquefies gelatin, a protein contained in the connective tissue.
- *Gastric amylase* is present in small amounts.
- *Lysozyme* is bactericidal.
- *Carbonic anhydrase* is present in small amounts.

Mucin or mucus is of two types:
- *Soluble mucus* secreted by the mucus cells of pyloric and cardiac glands
- *Insoluble mucus* secreted by the surface foveolar cells (tall columnar mucin-secreting cells) lining the entire gastric mucosa

Intrinsic factor is secreted by the parietal cells of gastric glands.

Secretion of Gastric Juice

Secretion of HCl

General Consideration HCl is secreted by the *parietal cells* (also called oxyntic cells).
Mechanism of HCl Secretion Various theories have been put forward to explain the origin of H^+ of HCl. The hypothesis more widely accepted is shown in Fig. 7.3-3. HCl is composed of hydrogen (H^+) and chloride ions (Cl^-); therefore, its secretion can be described in two steps: secretion of H^+ and secretion of Cl^-.

Secretion of H^+

- The H^+ ions are believed to be generated inside the parietal cell from metabolic CO_2 and H_2O present in the cell. The enzyme carbonic anhydrase present in abundance in the parietal cells is essential for the secretion. It accelerates the formation of $H_2CO_3^-$, which dissociates to release H^+ and HCO_3^- as

$$CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3 \rightarrow H^+ + HCO_3^-$$

- The H^+ ions generated by the above reaction are then secreted into the lumen of the canaliculi in exchange for K^+ by a primary active transport mediated by a H^+–K^+–ATPase pump (Fig. 7.3-3).

Note. The drug omeprazole used to decrease HCl formation inhibits the H^+–K^+–ATPase and blocks H^+ secretion.

- The HCO_3^- ions produced in the parietal cell are transported by an antiport in the serosal (basolateral) membrane into the blood in exchange of Cl^- by an active transport.

IMPORTANT NOTE

The HCO_3^- released into the blood is responsible for the postprandial alkaline tide associated with an increased gastric acid secretion after meals, which is characterized by alkaline urine, slightly depressed breathing and raised alveolar pCO_2.

Secretion of Cl^- Because of the high intracellular negativity, the Cl^- present in the parietal cell is forced out into the lumen

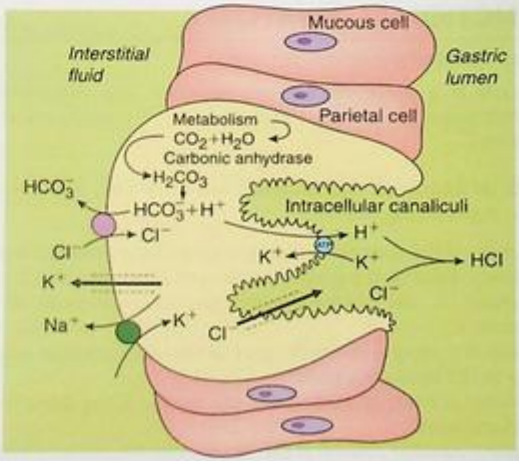


Figure 7.3-3 Mechanism of HCl secretion in the parietal cells of stomach.

of gland through the Cl^- channels located on the apical membrane of the cell.

Factors Affecting HCl Secretion

Factors stimulating HCl secretion are as follows:

- Vagal stimulation
- Gastrin
- Histamine

Factors that inhibit HCl secretion are as follows:

- Low pH in stomach (<3) by negative feedback mechanism
- Intestinal influences
- Somatostatin
- Prostaglandins (PGE and PGI), epidermal growth factor (EGF) and transforming growth factor (TGF)

Functions of HCl

- HCl participates in the breakdown of protein.
- It provides an optimal pH for the action of pepsin.
- It hinders the growth of pathogenic bacteria.

Pepsinogen Secretion

Pepsinogen is an inactive precursor (proenzyme) of pepsin. It is mainly secreted by the *chief cells* of the main gastric glands. A small amount of pepsinogen is also secreted by the pyloric glands. The pepsinogen secreted by the chief cells is called *pepsinogen I* and that secreted by the pyloric glands is called *pepsinogen II*.

Pepsinogen is converted to pepsin (the active form) by the action of HCl or preformed pepsin.

$$\text{Pepsinogen} \xrightarrow{\text{HCl}} \text{Pepsin}$$
$$\text{Pepsinogen} \xrightarrow{\text{Pepsin}} \text{Pepsin}$$

Function of Pepsinogen Pepsin, the active form of pepsinogen, is a proteolytic enzyme that helps in the process of protein digestion.

Secretion of Mucus Mucus is of two types: insoluble and soluble.

Insoluble mucus is secreted by the mucous-secreting cells lining the entire gastric mucosa. The insoluble mucus is such a viscid that it forms a gel-like coat over the mucosa.

Soluble mucus is secreted by the mucus cells of pylorus and cardiac glands.

Secretion of Intrinsic Factor Intrinsic factor (IF), a glycoprotein, is secreted by the parietal cells of gastric mucosa, chiefly by those in the fundus.

Functions The IF is essential for the absorption of Vitamin B_{12}. It forms a complex with B_{12}, which is carried to the terminal ileum where the vitamin is absorbed.

IMPORTANT NOTE

Deficiency of intrinsic factor in some patients with idiopathic atrophy of gastric mucosa may cause a serious disorder called pernicious anaemia (see page 73).

Regulation of Gastric Secretion

Mechanisms regulating the gastric secretion include neural control and chemical control.

Neural Control

Neural control over the gastric glands is exerted by a local enteric plexus involving cholinergic neurons and impulses from the central nervous system via vagal (extrinsic) innervation.

Vagal Stimulation increases the secretion of HCl by the parietal cells and pepsin by the chief cells. Vagal stimulation increases H^+ secretion by a direct and an indirect path (Fig. 7.3-4):

- In the *direct path*, the vagus nerve fibres innervating the parietal cells stimulate H^+ secretion by releasing neurotransmitter acetylcholine (ACh), which acts on the *muscarinic* receptors on the parietal cells. In addition, ACh also potentiates the effects of histamine on H_2 receptors of parietal cells.
- In the *indirect path*, the vagus nerve innervates G-cells and stimulates the release of gastrin into circulation through gastrin-releasing peptide (GRP). The gastrin, in turn, stimulates H^+ secretion.
- Furthermore, vagal stimulation also inhibits the release of *somatostatin*, and thus indirectly stimulates H^+ secretion by removing the inhibitory effect of somatostatin on the parietal cells.
- ACh released on the vagal stimulation also acts on the enterochromaffin-like (ECL) cells, which release histamine. Histamine increases H^+ secretion by acting on H_2 receptors on the parietal cells.

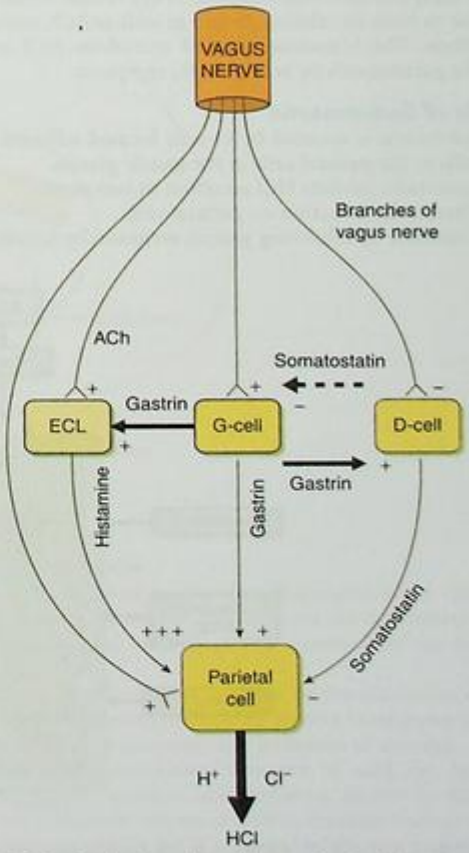


Figure 7.3-4 Mechanisms by which vagal stimulation increase H^+ secretion in the parietal cell.

Chemical Control

Chemical control on the gastric glands is exerted mainly through:

- *Gastrin*, a hormone secreted by G-cells
- *Histamine*, a paracrine agent released from the mast cells of gastric mucosa
- *Somatostatin*, secreted by D-cells
- *Low pH* (3.0) in stomach acts in a negative feedback mechanism
- *Local hormones* released in the duodenum inhibit the gastric secretion in addition to promoting the secretion of pancreatic juice and bile

1. Role of Gastrin Gastrin, a hormone, is secreted by the G-cells into the blood circulation (and not into gastric juice). It reaches the stomach through the arterial circulation and stimulates secretory activity of the parietal cells and chief cells.

Functions of Gastrin

- The main function of gastrin is to stimulate HCl secretion by increasing the transport of H^+ into the gastric lumen by H^+–K^+–ATPase (Fig. 7.3-5).
- Gastrin also increases the HCl secretion by stimulating secretion of histamine from the ECL cells present in the body of the stomach.

2. Role of Histamine Histamine is released from the ECL cells found in the base of the gastric gland. ECL cells bear both gastrin receptors and ACh receptors. They release histamine in response to both circulating gastrin as well as ACh released by vagal fibres. The histamine released stimulates *HCl secretion* from the parietal cells by acting on H_2 receptors.

3. Role of Somatostatin

- Somatostatin is secreted by D-cells located adjacent to the G-cells or the parietal cells in the gastric glands.
- Somatostatin inhibits HCl secretion in two ways:
  - Directly by its action on parietal cells.
  - Indirectly by inhibiting gastrin secretion by G-cells.
- Somatostatin, prostaglandins, epidermal growth factor (EGF) and transforming growth factor (TGF) act on the parietal cells to inhibit HCl secretion by inhibiting adenylyl cyclase (Fig. 7.3-5).

4. Role of Low pH (<3) in Stomach Low pH (<3) in the stomach inhibits the secretion of H^+ by the parietal cells by a negative feedback mechanism.

5. Intestinal Influences Chyme containing acid, fats and products of protein digestion when reaches the duodenum causes the release of several intestinal hormones like secretin, CCK and GIP.

Phases of Gastric Secretion and Their Regulation

Meal-related gastric secretion can be divided into three phases:

- Cephalic phase
- Gastric phase
- Intestinal phase

1. Cephalic Phase

- Cephalic phase of the gastric secretion occurs before the entry of food into the stomach.
- The secretion is *initiated* by the thought, sight, smell or taste of food. Neurogenic signals originate in the cerebral cortex and hypothalamus. The impulses are transmitted to dorsal vagal nuclei and from there through vagii to the stomach (Fig. 7.3-6).
- Emotions also influence this vagally mediated gastric secretion. *Anger and hostility* are associated with an increased gastric secretion. *Fear and depression* decrease the gastric secretion and motility.

2. Gastric Phase

- Gastric phase of the gastric secretion occurs when food enters the stomach.

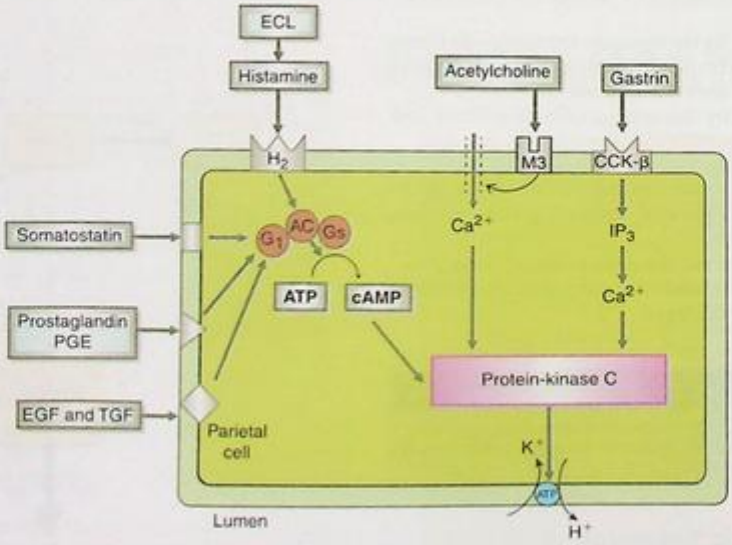


Figure 7.3-5 Control of HCl secretion at the parietal cell level. Acetylcholine (ACh), histamine and gastrin act agonists of HCl secretion by distinct mechanism (for details, see text). Somatostatin, prostaglandins (PGE), epidermal growth factor (EGF) and transforming growth factor (TGF) act as endogenous antagonists of HCl secretion by inhibiting adenylyl cylase.

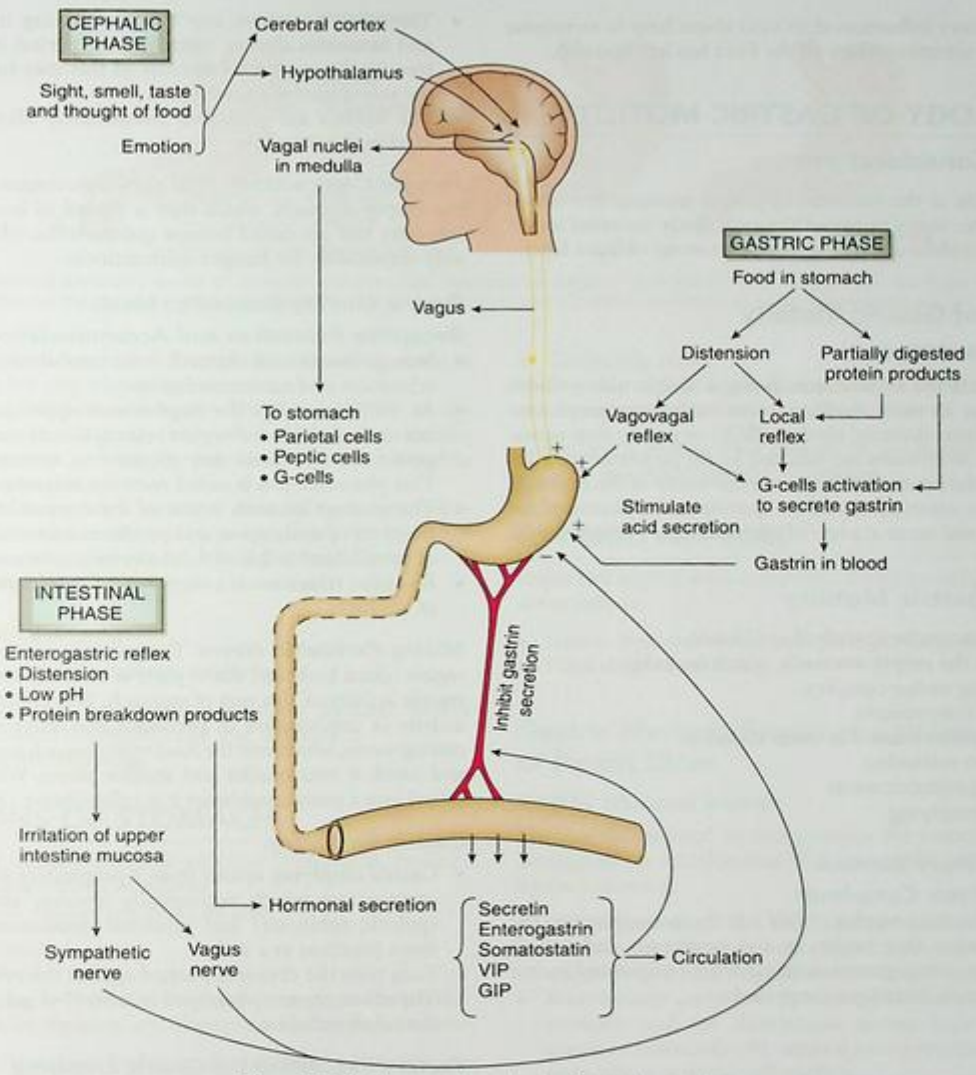


Figure 7.3-6 Phases and regulation of gastric secretion.

- The presence of food in the stomach induces gastric secretion by the following *mechanisms:*
  - *Distension of the body of stomach acting* through local myenteric and vagovagal reflexes results in an increase in HCl secretion.
  - *Distension of the antrum* initiates vagally mediated and local reflexes that result in gastrin release from the antral G-cells. Gastrin release is inhibited when pH becomes low (<3).
  - *Products of partial protein digestion* also stimulate gastrin secretion, and this increases mainly secretion of gastric acid.
- *Low pH* causes increased pepsinogen secretion through local reflexes.

3. Intestinal Phase

- Intestinal phase of gastric secretion begins as the chyme begins to empty from the stomach into the duodenum.
- Intestinal factor inhibits gastric secretion by the following mechanisms:
  - *Enterogastric reflex* is initiated by the distension of small intestine, presence of acid or protein breakdown products in the upper intestine, and irritation of mucosa.
  - *Hormonal mechanism.* Presence of acid, fat, hyper- or hypotonic solution and irritating factors in the upper small intestine release several hormones, such as secretin, cholecystokinin (CCK), gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP) and somatostatin, which inhibit gastric secretion.

- The inhibitory influences discussed above help to terminate the gastric secretion when all the food has left stomach.

PHYSIOLOGY OF GASTRIC MOTILITY

General Considerations

Gastric motility is the function of gastric musculature which consists of three layers of smooth muscle fibres: an outer longitudinal layer, middle circular layer and an inner oblique layer.

Initiation of Gastric Motility

Basal Electrical Rhythm

- The musculature of stomach, being a single unit smooth muscle, has its only rhythmic contractile myogenic tone called the *basic electrical rhythm* (BER) or *gastric slow waves.*
- The gastric slow waves are initiated *by the pacemaker cells* located near the fundus on the greater curvature of the stomach.
- Gastric slow waves consist of an *upstroke* and a *plateau* phase (Fig. 7.3-7) and occur at a rate of approximately 3–4 waves/min.

Types of Gastric Motility

Gastric motility can be described as follows:

- **Motility of the empty stomach,** which includes:
  - Migrating motor complex
  - Hunger contractions
- **Gastric motility related to meal** includes:
  - Receptive relaxation
  - Mixing peristaltic waves
  - Gastric emptying

Motility of Empty Stomach

Migrating Motor Complexes

- Migrating motor complex (MMC) is the name given to the peristaltic wave that begins in the esophagus and travels through the entire gastrointestinal tract (migratory motor activity) during interdigestive period.

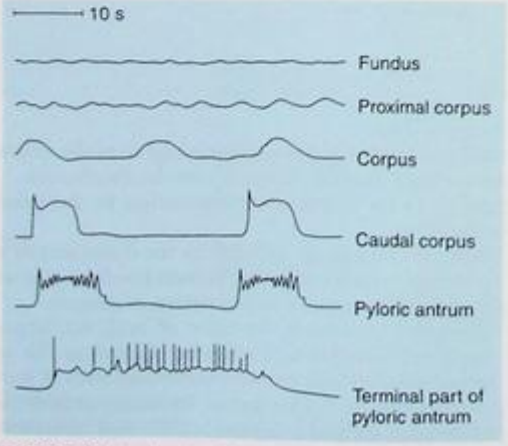


Figure 7.3-7 Basic electrical rhythm (BER) recorded from different parts of the stomach.

- The MMCs remove any food remaining in the stomach and intestines during interdigestive period in the preparation for the next meal because of this they have been called the *interdigestive housekeepers.*
- The MMCs are abolished immediately after the entry of food in the stomach.

Hunger Contractions Mild peristaltic contractions occur in the empty stomach, which over a period of hours increase in intensity and are called hunger contractions. MMCs are probably responsible for hunger contractions.

Gastric Motility Related to Meals

Receptive Relaxation and Accommodation

- Storage function of stomach is accomplished by the receptive relaxation and accommodation.
- As the food enters the fundus and upper part of body of stomach, i.e. the *oral region* relaxes to accommodate the ingested food without any increase in intramural pressure. This phenomenon is called *receptive relaxation*
- The passage of each bolus of food stimulates the stretch *receptors of oral region* and produces relaxation. By the end of meal about 1–2 L of food can be accommodated.
- Receptive relaxation is a *vagovagal reflex* initiated by distension of stomach.

Mixing Peristaltic Waves The presence of food in the caudal region (distal body and antral part) of stomach increases the contractile activity of this part of stomach. This enhanced contractile activity (a combination of peristalsis and retropulsion) is called mixing waves, which mix the food with stomach acid and enzymes, and break it into smaller and smaller pieces. When the food is mixed into a pasty consistency it is called *chyme.* (Fig. 7.3-8)

Gastric Emptying

- Gastric emptying results from a progressive wave of forceful contraction, which sequentially involves antrum, pylorus (pyloric sphincter) and proximal duodenum; thus all the three function as a unit.
- Each time the chyme is pushed against the pyloric sphincter. Therefore, chyme is pumped in a bit (2–7 mL) at a time into the small intestine.

Factors Regulating the Gastric Emptying After a normal meal, the emptying time is 2–3 hours. The gastric emptying is regulated by various factors.

1. Fluidity of the Chyme The rate of gastric emptying of liquids is much faster than solids.

2. Gastric Factors, which affect emptying, are as follows:

- ***Volume of food in the stomach.*** Greater the volume of food in the stomach, greater is the stretching of stomach wall leading to increased rate of gastric emptying.
- ***Gastrin hormone.*** Gastrin promotes gastric emptying.
- ***Type of food ingested*** (present in the stomach) affects the gastric emptying as:
  - Carbohydrate-rich food causes rapid gastric emptying.
  - Protein-rich food causes slow gastric emptying.
  - Fat-rich food causes slowest gastric emptying.

3. Duodenal Factors, which inhibit gastric emptying, are the following:

- ***Enterogastric reflex.*** The enterogastric reflex is initiated in the duodenum and passes to the stomach through the

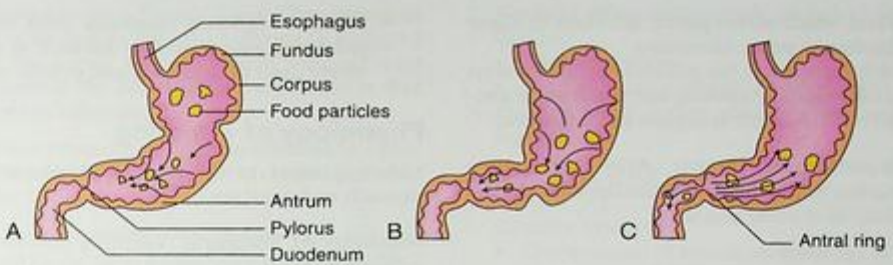


Figure 7.3-8 Mixing peristaltic waves of stomach: (A) peristaltic contractions begin in the mid stomach and pushes the food towards pylorus; (B) when food reaches the pylorus it strikes against closed pyloric sphincter; and (C) antral contents forced back (retropulsion).

myenteric plexus and also through the extrinsic nerves to inhibit or even stop emptying.

- ***Size of duodenal osmoreceptors.*** High osmolality of the chyme causes shrinkage and low osmolality increases the size of osmoreceptors. In both the conditions the rate of gastric emptying decreases.
- ***Enterogastric hormones.*** A variety of intestinal hormones, collectively called enterogastrones, inhibit gastric contractions. Some of the hormones which have been identified are as follows:
  - *Cholecystokinin*
  - *Secretin*
  - *Gastric inhibitory peptide*

4. Other factors affecting gastric emptying

- *Emotions* such as anger and aggression increase gastric motility, whereas depression and fear decrease it.
- *Vagotomy* slows emptying.

FUNCTIONS OF STOMACH

After studying the physiological activities of stomach, its functions can be summarized as follows.

1. Mechanical or Motor Functions include:

- Storage of food
- Mixing of food
- Slow emptying of food into the duodenum occurs to provide proper time for digestion and absorption by the small intestine

2. Digestive Functions Only small amounts of foods are digested in stomach as:

- *Carbohydrate digestion* in the stomach depends on the action of salivary amylase, which remains active until halted by the low pH of stomach.
- *Protein digestion.* About 10% of ingested protein is broken down completely in the stomach. *Gastric pepsin* facilitates later digestion of protein by breaking protein into peptone.
- *Fat digestion* in stomach is minimal due to the restriction of gastric lipase activity to triglycerides containing short-chain (<10 carbon) fatty acids.

3. Absorptive Function Stomach contributes little in absorptive function:

- *Ethanol* is absorbed rapidly in proportion to its concentration.

4. Reflex Functions Various reflexes initiated from the stomach are as follows:

- Gastrosalivary reflex
- Gastroileal reflex
- Gastrocolic reflex
- Presence of food in the stomach reflexly stimulates secretion of pancreatic juice and expulsion of bile

5. Antiseptic Action HCl present in the gastric juice kills the bacteria and other harmful substances.

APPLIED ASPECTS

Important applied aspects of stomach which need special attention are as follows:

- Gastric mucosal barrier and pathophysiology of peptic ulcer
- Physiology of vomiting

Gastric Mucosal Barrier and Pathophysiology of Peptic Ulcer

Gastric Mucosal Barrier

The gastric mucosal barrier protects the gastric mucosa from damage by the intraluminal HCl, i.e. autodigestion. It is created by the following:

- ***Mucin secretion.*** The thin layer of surface mucus in the stomach and duodenum prevents the direct contact of acid- and pepsin-containing fluid with surface epithelial cells.
- ***Bicarbonate secretion.*** Surface epithelial cells in both the stomach and the duodenum secrete bicarbonate, which create an essentially pH-neutral microenvironment immediately adjacent to the cell surface.
- ***Epithelial barrier.*** Intercellular tight junctions provide a barrier to the back-diffusion of H^+.
- ***High mucosal blood flow.*** It rapidly carries away any acid that penetrates the cellular lining, and also provides oxygen, bicarbonate and nutrients to the epithelial cells.
- ***Prostaglandins*** are responsible for maintaining the gastric mucosal barrier.

Pathophysiology of Peptic Ulcer

Peptic ulcer refers to an excavation of mucosa of duodenum or pyloric part of stomach caused by the digestive action of gastric juice. Peptic ulcer can be caused by either of two ways.

1. Diminished Ability of the Gastroduodenal Mucosal Barrier to protect against the digestive properties of the acid–pepsin complex. Factors that disturb mucosal barrier include:

Bacterial Infection by Helicobacter Pylori At least 75% patients with peptic ulcer have recently been found to have chronic infection by *H. pylori*. The bacterium releases digestive enzymes

that liquefy the barrier, which allows gastric secretion to digest the epithelial cells leading to peptic ulceration.
Other Factors, which can disrupt the mucosal barrier are ethyl alcohol, vinegar, bile salts, cigarette smoking and nonsteroidal anti-inflammatory drugs (NSAIDs), such as Aspirin and ibuprofen.

2. Excessive Secretion of Gastric Acid Hyperacidity leads to ulcer formation in the duodenum and pyloric part of stomach. Hyperacidity may occur due to:

- Increased parietal cell mass
- Increased sensitivity for secretory stimuli
- Excess gastrin secretion, as seen in the *Zollinger–Ellison syndrome* in which patients are having *gastrinomas* (tumours that secrete gastrin)

Physiologic Basis of Management of Peptic Ulcer Commonly employed measures for treatment of peptic ulcer are the following.

Antacids. These form a gel that coats the mucosa and neutralizes the acid.
Drugs such as:

- *H_2-receptor–blocking drugs,* such as cimetidine.
- *M_1-muscarinic receptor–blocking drugs,* such as atropine.
- *Gastric H^+–K^+–ATPase inhibiting drugs,* such as omeprazole.
- *H Pylori eradication.* In proven cases of acute and chronic gastric ulcer with *H Pylori.*
- *Bilateral vagotomy combined with resection of gastrin-producing pyloric part of stomach* is performed in very severe cases of duodenal and pyloric ulcers.

Physiology of Vomiting

Vomiting refers to the forceful expulsion of contents from stomach and intestine.

Initiation of Vomiting Vomiting may be initiated by either activation of vomiting centre or by an activation of the chemoreceptor-trigger zone.
1. Activation of Vomiting Centre Vomiting centre is situated in the reticular formation of medulla oblongata near the vagal nucleus. It may be activated directly or through afferents.

(i) ***Direct activation of the vomiting centre*** occurs due to an injury to the area or by raised intracranial pressure.
(ii) ***Afferent impulses*** activating vomiting centre includes (Fig. 7.3-9):

- *Visceral afferent pathway* in the sympathetic and vagi relay impulses arising due to the irritation of mucosa of upper GIT.
- *Afferent impulses from the vestibular nuclei* mediate nausea and vomiting of motion sickness.
- *Afferents from higher centres* (diencephalon and limbic system) mediate emetic response to stimuli, such as nauseating smell, sickening sights and memory.

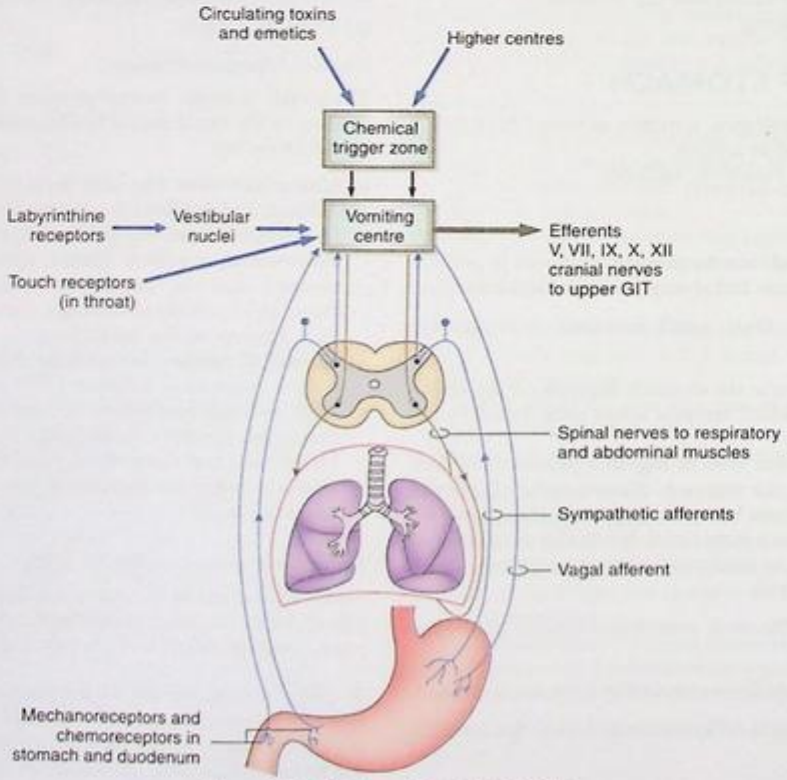


Figure 7.3-9 Pathway for vomiting reflex.

2. Activation of Chemoreceptor Trigger Zone Chemoreceptor trigger zone (CTZ) is located in the area *postrema*, a V-shaped band of tissue on the lateral walls of fourth ventricle near the obex, which is outside the blood–brain barrier and is thus more permeable to many substances.

- The chemoreceptors present in CTZ are stimulated by circulating emetic substances in patients with ureamia and radiation sickness (Fig. 7.3-9).

Efferent Impulses from Vomiting Centre and CTZ Efferent impulses from the vomiting centre and CTZ, which give effect to act of vomiting, are transmitted via V, VII, IX, X and XII cranial nerves to upper GIT, and through spinal nerves to the muscles of respiration.

Sequence of Mechanical Events of Vomiting Vomiting is a complex process and consists of the following phases.

1. ***Pre-ejection phase.*** It is characterized by the feeling of nausea, excessive salivation and also deep, rapid and irregular breathing.
2. ***Retching phase*** may precede in many cases. It is characterized by:
   - *Closure of glottis*
   - *Rhythmic action of respiratory muscles*
3. ***Ejection phase*** during which the GIT contents are actually expelled out.

SELF-ASSESSMENT

1. Describe briefly:
   - Composition of gastric secretion
   - Mechanism of HCl secretion and factors affecting
   - Functions of gastric secretion and its regulation
   - Phases of gastric secretion
2. Write notes on:
   - Basal electrical rhythm
   - Gastric emptying
   - Gastrin
   - Migrating motor complexes
   - Gastric mucosal barrier
   - Physiology of vomiting

7.4 Pancreas, Liver and Gall Bladder

CHAPTER OUTLINE

Pancreas
Functional Anatomy
General Considerations
Structural Characteristics of Exocrine Part of Pancreas
Pancreatic Juice
Properties
Composition
Functions of Pancreatic Juice
Regulation of Pancreatic Secretion

Liver and Gall Bladder
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Structural Characteristics
Hepatic Circulation
Hepatic Biliary System
Intrahepatic Biliary System
Extrahepatic Biliary Apparatus
Functions of Liver
Gall Bladder
Bile
General Considerations
Composition of Bile
Regulation of Bile
Applied Aspects
Disorders of Liver and Gall Bladder
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PANCREAS

Functional Anatomy

General Considerations

The pancreas – an elongated, accessory digestive gland – lies posterior to the stomach between the duodenum on the right and spleen on the left (Fig. 7.4-1). It is divided into four parts: head, neck, body and tail.

Physiologically, on the basis of functions performed, the pancreas consists of two parts:

- ***Exocrine part,*** which produces a secretion called pancreatic juice.
- ***Endocrine part*** of the pancreas, the islets of Langerhans, produces the hormones insulin and glucagon. The endocrine part is discussed in Section VIII (see page 338).

Structural Characteristics of Exocrine Part of Pancreas

The exocrine part of the pancreas consists of serous, compound tubuloalveolar glands, very similar to the parotid gland in general structure (Fig. 7.4-2).

Acinar cells lining the alveoli produce thick secretion containing numerous enzymes (listed in composition of pancreatic juice).

Centroacinar cells that are so called because they appear to be located near the centre of the acinus (alveolus). These cells

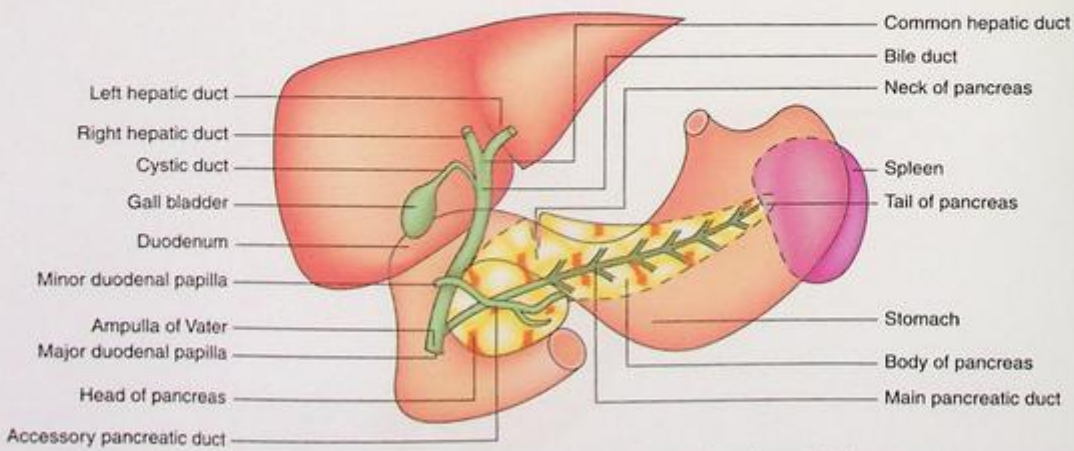


Figure 7.4-1 Anatomical relations of pancreas, pancreatic duct and extrahepatic biliary system.

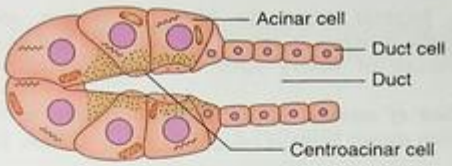


Figure 7.4-2 Histology of functional unit of pancreas.

really belong to the intercalated ducts, which are invaginated into the acinus (Fig. 7.4-2).

Pancreatic Ducts

The intercalated ducts, which receive secretions produced by the acini, pass the secretions on to the interlobular ducts. Ultimately, the pancreatic secretion passes into the duodenum through the principal pancreatic duct and accessory pancreatic duct.

Principal pancreatic duct, also known as a duct of *Wirsung*, begins in the tail and runs the length of the gland, receiving numerous tributaries on the way. It joins the common bile duct (CBD) to form the ampulla of Vater, which opens into the second part of the duodenum at about its middle on the major duodenal papilla (Fig. 7.4-1). Ampulla of Vater is guarded by the sphincter of Oddi.

Accessory pancreatic duct, also called a duct of Santorini, when present, drains the upper part of the head and then opens into the duodenum about 2 mm above the principal duct on the minor duodenal papilla.

Innervation of Pancreas Nerve supply comes from both sympathetic and parasympathetic (vagi) nerves. Preganglionic vagal fibres synapse with the ganglionic cells embedded in the pancreatic tissue; the postganglionic fibres innervate both the acinar cells and the smooth muscles of the ducts. Vagal stimulation increases pancreatic juice secretion.

Pancreatic Juice

Properties

- Pancreatic juice is a transparent colourless fluid isotonic with plasma.
- About 1200–1500 mL of pancreatic juice is secreted per day.
- Its specific gravity varies from 1.010 to 1.018.
- Pancreatic juice is markedly alkaline (pH 7.8–8.4) due to very high concentration of HCO_3^- (about 4–5 times that of plasma).

Composition

Pancreatic juice is composed of 99.5% water and 0.5% solids, which include organic and inorganic substances.

Organic Constituents of pancreatic juice are certain enzymes amylase, lipase, protease and trypsin inhibitor, and other organic substances present in traces are albumin and globulin.

Inorganic Substances present in the pancreatic juice are cations like Na^+, K^+, Ca^{2+}, Mg^{2+} and Zn^{2+}; and anions such as HCO_3^-, Cl^-, and traces of SO_4^{2-} and HPO_4^{2-}. Electrolyte composition varies with rate of secretion.

Pancreatic Enzymes Pancreatic acini secrete four major types of enzymes.

1. Pancreatic α-Amylase It is secreted in its active form. Its action on the carbohydrates is like that of the salivary amylase. It hydrolyses glycogen, starch and most other complex carbohydrates except cellulose to form disaccharides.

2. Pancreatic Lipases or lipolytic enzymes include pancreatic lipase, cholesterol ester hydrolase and phospholipase A_2.

3. Pancreatic Proteases or proteolytic enzymes include three endopeptidases (trypsin, chymotrypsin and elastase) and two exopeptidases (carboxypeptidase A and B).

Trypsin. It is the most powerful proteolytic enzyme secreted in an inactive form of trypsinogen, which is activated by the enzyme enterokinase (enteropeptidase) secreted by duodenal mucosa. Once formed, trypsin also activates trypsinogen – an autocatalytic reaction.

$$\text{Trypsinogen} \xrightarrow{\text{Enterokinase}} \text{Trypsin}$$

$$\text{Trypsinogen} \xrightarrow{\text{Trypsin}} \text{Trypsin}$$

- Trypsin hydrolyses proteins into proteoses and to polypeptides.
- It activates trypsinogen and other pancreatic enzymes.

Chymotrypsin. It is also secreted in an inactive form chymotrypsinogen and is activated by trypsin. It hydrolyses the proteins into small polypeptides.

Elastase. It is secreted as proelastase, which is activated by trypsin. It digests elastin.

Carboxypeptidase A and B. These are secreted as procarboxypeptidase A and B, and are activated by enterokinase and trypsin.

Nucleases (ribonuclease and deoxyribonuclease). They split nucleic acids of ribose and deoxyribose type into nucleotides.

Collagenase. It is also activated by trypsin and digests collagen.

4. Trypsin Inhibitor If even a small amount of trypsin is released into the pancreas, the resulting chain reaction would produce active enzymes that could digest the pancreas. It is therefore, not surprising that the pancreas normally contains a trypsin inhibitor which is secreted by the same cells and at the same time as the pancreatic proenzymes. Trypsin inhibitor protects the pancreas from autodigestion.

Functions of Pancreatic Juice

1. Digestive Functions The pancreatic juice is the major source of digestive enzymes that digest all components of the food – proteins, carbohydrates, fats and nucleic acids.

2. Neutralizing Function Pancreatic juice is highly alkaline due to high concentration of HCO_3^- and neutralizes the gastric HCl in the chyme that enters the duodenum.

Regulation of Pancreatic Secretion

Both, neural and hormonal mechanisms are involved in the regulation of pancreatic secretion, with the later playing the predominant role. *Neural regulation* is through vagal efferents supplying the exocrine gland of pancreas and hormonal regulation is through secretin, cholecystokinin (CCK), gastrin and somatostatin. The exact role of these regulatory mechanisms in regulation of different phases of pancreatic secretion, such as

TABLE 7.4-1 Summary of Regulation of Cephalic, Gastric and Intestinal Phases of Pancreatic Secretion

Phase	Stimulus	Mediator	Pancreatic Response
Cephalic	Conditioned reflex initiated by: • Taste • Smell • Thought of food Unconditioned reflex initiated by taste of food in mouth	Vagus	Little secretion of pancreatic enzymes and HCO_3^-
Gastric	• Distension of stomach by food • Amino acids and peptides • Low pH of chyme in duodenum	Vagus Gastric Secretin	Low volume of pancreatic HCO_3^- and enzymes Low-volume high-enzyme secretion Large amount of aqueous secretion with high HCO_3^- concentration
Intestinal	• Amino acids and peptides in chyme in duodenum • Food in small intestine	CCK Vagus through – Secretin – CCK	Pancreatic juice rich in enzymes Pancreatic juice rich in enzymes and HCO_3^-

cephalic phase, gastric phase and intestinal phase is summarized in Table 7.4-1.

1. Regulation of Cephalic Phase *Cephalic phase* of pancreatic secretion, like that of gastric secretion, occurs before the entry of food into the stomach.

Regulation of this phase is mainly through the *reflex vagal stimulation* which occurs:

- *By conditioned reflexes* initiated by sight, smell and thought of food
- *Unconditioned reflexes* initiated by stimulation of taste buds by the food in the mouth cavity, the act of chewing and swallowing

2. Regulation of Gastric Phase Gastric phase of pancreatic secretion occurs when stomach is distended by the food. This phase is regulated by *neural control* exerted through vagus and *hormonal control* executed through the hormone gastrin.

3. Regulation of Intestinal Phase The intestinal phase of pancreatic secretion begins when the chyme enters the duodenum and jejunum. It is characterized by a marked increase in the secretion of both enzymes and aqueous component of the pancreatic juice. This phase is regulated by the hormones secretin and CCK.

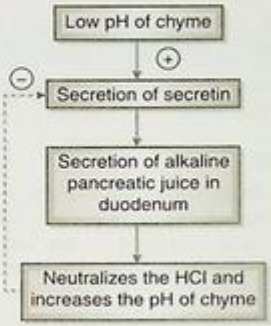
(i) Role of Secretin Secretin was the first hormone ever discovered by Bayliss and Starling in 1902. It is a polypeptide with 27 amino acids.

Source of secretin is endocrinal S-cells located among the epithelial cells of mucous membrane of the duodenum and jejunum.

Stimulant for the release of secretin is *low pH* (<4.5) of chyme caused by the presence of gastric HCl.

Actions. Secretin enters the blood circulation, and after reaching the pancreas it *acts on the duct* cells and produces a large amount of watery juice with high concentration of HCO_3^-.

Regulation of secretin occurs through a negative feedback mechanism shown below:



(ii) Role of Cholecystokinin *CCK* is polypeptide containing 33 amino acids.

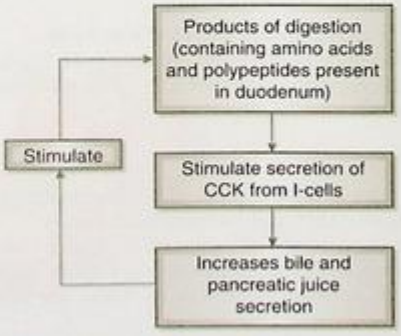
Source of secretion of CCK is endocrinal I-cells located among the epithelial cells of mucosa of the duodenum and jejunum.

Actions. CCK passes via blood to the pancreas and causes *secretion of pancreatic juice rich in* enzymes.

Other actions of CCK are as follows:

- Contraction of gall bladder to release bile.
- Potentiates the effect of secretin to produce more alkaline pancreatic juice.
- Increases the secretion of enterokinase (enteropeptidase) from the duodenum.
- Inhibits the gastric motility.
- Increases the motility of the small and large gut.
- Increases the pancreatic growth (trophic effect).
- It is also found in the neurons in the brain (especially in the cerebral cortex), where it is involved in the regulation of food intake and is related to the production of anxiety and analgesia.

Regulation of CCK secretion occurs through a positive feedback mechanism shown below:



Interaction of nervous and humoral regulation A vagovagal reflex is initiated during the intestinal phase of digestion, which greatly potentiates the effects of secretin and CCK through the

acetylcholine. Thus, vagus stimulation is much more potent in stimulating pancreatic secretions when CCK and secretin are present in the plasma.

LIVER AND GALL BLADDER

Liver: Physiological Anatomy

General Considerations

- Liver, the largest gland in the body, weighs approximately 1500 g.
- Anatomically, the liver has been divided into *right and left lobes.* Right lobe is much larger and includes caudate lobe and quadrate lobe. Left lobe is much smaller (Fig. 7.4-3).
- Liver has got considerable physiological reserve. Even after removal of 80% of liver tissues, all *physiological* functions of liver can be accomplished normally.
- The liver possesses considerable *regeneration power.* Original liver mass is restored within 6–8 weeks of removal of up to three-fourth of liver. This occurs due to an active mitotic division of the cells.

Structural Characteristics

The liver tissue comprises about one lakh hexagonal areas that constitute the *hepatic lobules* (Fig. 7.4-4A).

- Each hepatic lobule is made of ramifying columns of hepatic cells *(hepatocytes)* that are arranged in the form of one-cell thick plates. In between the cells are present bile canaliculi. These hepatic cell plates are tunnelled by a communicating system of lacunae called *blood sinusoids.* The sinusoids open into a central vein present in the centre of each lobule (Fig. 7.4-4B).
- Blood sinusoids are lined by the endothelial cells. Few tissue macrophages called *Kupffer* cells are found at regular intervals in between the endothelial cells.
- Along the periphery of each lobule are present *portal triads* consisting of a branch of portal vein, branch of hepatic artery and an interlobular bile duct. Blood from the branch of portal vein and hepatic artery enters the sinusoids, which drain into central vein.
- *Concept of portal lobule,* instead of hepatic lobule, has been suggested by some workers. It has been described to consist of adjoining part of three hepatic lobules centred on a portal triad.

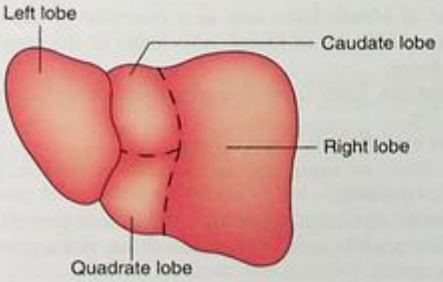


Figure 7.4-3 Gross anatomy of the liver viewed from the back.

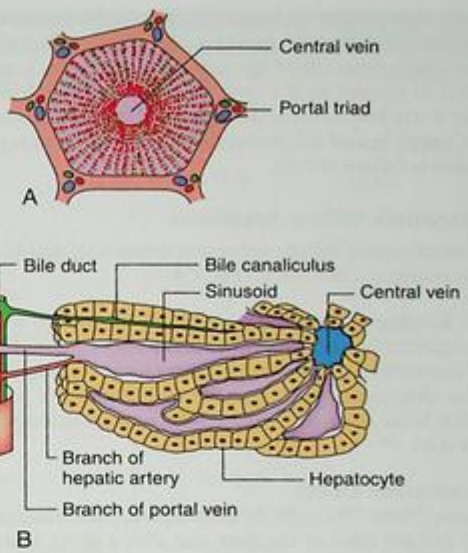


Figure 7.4-4 Histological characteristics of the liver: (A) hexagonal lobule with portal triad and (B) hepatocyte, sinusoid and biliary canaliculi seen under high magnification.

- Presently, acinus is considered the functional unit of liver. Each acinus has been considered to have three zones: 1, 2 and 3.
  Zone 1 refers to the central portion of the acinus immediately surrounding the terminal hepatic arteriole and terminal portal venule. This zone is well oxygenated.
  Zone 2, i.e. the intermediate zone, which is present in between zone 1 and 3 is moderately well oxygenated.
  Zone 3 refers to the peripheral most part of the acinus. It is least oxygenated and most susceptible to an anoxic injury.

Hepatic Circulation

Liver receives about 1500 mL blood/min from two sources.

Hepatic Artery, which is a branch of coeliac trunk, supplies about 20%–25% (300–400 mL/min) of total blood which caters to metabolic requirement of the liver tissue.

Portal vein, which collects blood from the mesenteric and splenic vascular bed, supplies about 75%–80% (1100–1200 mL/min) of the total blood.

Hepatic vein The hepatic and portal streams of blood meet in the sinusoids. The various substances produced by the liver cells, the waste products and CO_2 are discharged into the sinusoids. The sinusoids drain into the central vein of the lobule. The central veins from different lobules unite to form bigger veins. These veins ultimately form the right and left hepatic veins, which open into the inferior vena cava.

Hepatic Biliary System

Intrahepatic Biliary System

The bile is secreted by the liver cells into bile canaliculi. At the periphery of a lobule, the canaliculi become continuous with

delicate *intralobular ductules*, which, in turn, become continuous with larger interlobular ductules of portal triads. The *interlobular ductules* are lined by cuboidal epithelium. Some smooth muscle is present in the wall of larger ducts. Ultimately, the larger ducts join to form the *right and left hepatic ducts*, which leave the right and left parts of the liver and form a part of extrahepatic biliary system.

Extrahepatic Biliary Apparatus

The extrahepatic biliary apparatus consists of gall bladder and the extrahepatic bile ducts (Fig. 7.4-1).

Gall Bladder The gall bladder is a pear-shaped sac lying on the undersurface of liver. It has a capacity of about 30–50 mL and stores bile, which it concentrates by absorbing water.

For descriptive purposes, the gall bladder is divided into fundus, body and neck. The neck becomes continuous with the *cystic duct*.

Extrahepatic Ducts

Hepatic Ducts The right and left hepatic ducts emerge from the right and left lobes of the liver, and after a short course, join to form *common hepatic duct* which is about 4 cm long.

Cystic Duct It is also about 4 cm long and connects the neck of gall bladder to the common hepatic duct to form the common bile duct (CBD).

Common bile duct It is about 8 cm long. It joins the pancreatic duct to form the common hepatopancreatic duct, which is otherwise called the ampulla of Vater. *Ampulla of Vater* opens into the duodenum at major duodenal papilla. The terminal parts of bile ducts and ampulla of Vater are surrounded by circular muscle fibres known as *sphincter of Oddi*, which plays an important role in the storage and release of bile from the gall bladder.

Functions of Liver

The fact that mitochondria are maximally present in the liver emphasizes that liver is involved in many biochemical functions. Although details of the various functions performed by liver are discussed under their respective places, they are summarized here briefly.

I. Secretory Functions Liver cells act as an exocrine gland and continuously secrete bile, which is important for digestion and absorption of fats.

II. Metabolic Functions Liver is the key organ and the principal site where the metabolism of carbohydrates, lipids and proteins takes place. Liver is also involved in the metabolism of vitamins and minerals to certain extent.

1. Role in Carbohydrate Metabolism

(i) Liver acts as a glucostat in three ways:
- *Glycogenesis*, i.e. glycogen is formed from glucose and stored in liver.
- *Glycogenolysis*, i.e. breaking down of liver glycogen to glucose.
- *Glucogenesis*, i.e. formation of glucose from noncarbohydrate sources, such as non-nitrogenous residues of amino acids.

(ii) Liver is the principal site of alcohol metabolism for which liver cells contain the enzyme *alcohol dehydrogenase*.

(iii) The interconversion of three monosaccharides, as glucose, galactose and fructose, also occurs in liver.

2. Role in Fat Metabolism Both degradation and synthesis of fats take place in the liver.

Degradation of fat. Liver contains enzyme lipoprotein lipase which hydrolyses triglycerides, cholesterol and phospholipids into fatty acids.
- β-oxidation, i.e. a process which oxidises the fatty acids into acetoacetic acid.

Synthesis of fat also takes place in liver.
- Liver synthesizes triglycerides, cholesterol, phospholipids and lipoproteins, such as HDL, LDL, VLDL and chylomicrons.

3. Role in Protein Metabolism
- Liver brings about *deamination* of amino acids, and this is essential for energy production and their conversion into carbohydrates or fats.
- Liver is the principal site for formation of all nonessential amino acids by the transamination of ketoacids.

III. Detoxicating and Protective Functions
- Kupffer cells efficiently remove bacteria and other foreign bodies from the portal circulation. This is the blood-cleansing action of liver.
- Liver detoxifies certain drugs by either oxidation or hydrolysis, or reduction or conjugation, and excretes out through bile.

IV. Storage Functions Liver stores glucose (in the form of glycogen), vitamin B_{12} and vitamin A.

V. Excretory Functions Certain exogenous dyes like bromsulphthalein (BSP) and rose bengal dye are exclusively excreted through the liver cells.

VI. Synthesis Functions Liver is the site for synthesis of:

Plasma proteins, especially albumin and to some extent α- and β-globulins.

Blood coagulation factors. Liver cells are responsible for the conversion of preprothrombin (inactive) to active prothrombin in the presence of vitamin K. It also produces other clotting factors, such as fibrinogen (I), factors V, VII, IX and X.

Enzymes, such as alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum isocitrate dehydrogenase.

Urea. Liver removes ammonia from the body to synthesize urea.

Cholesterol. It is synthesized from the active acetate.

VII. Miscellaneous Functions

Reservoir of blood. Liver acts as a reservoir of blood and it stores about 650 mL of blood. Also helps in the regulation of blood volume.

Erythropoiesis. Liver is an important site of erythropoiesis in the fetal life.

Hormone metabolism. Liver causes:
- *Inactivation* of some hormones, such as insulin, glucagon and vasopressin.
- *Reduction and conjugation* of adrenal and gonadal steroid hormones, such as cortisol, aldosterone, oestrogen and testosterone.

Destruction of RBCs also occurs in the liver.

Gall Bladder Gall bladder is a pear-shaped sac about 7–10 cm long, 2.5 cm wide and has a capacity to store about 30–50 mL of bile.

Functions of Gall Bladder

Gall bladder subserves the following functions:

Storage of Bile The bile secreted during interdigestive period is stored in the gall bladder. The gall bladder typically stores 30–50 mL of bile. During meals, the gall bladder contracts and releases its contents into the duodenum.

Concentration of Bile The mucosa of gall bladder is extensively folded and can actively absorb fluid and electrolytes. In this way, the gall bladder bile, in comparison to liver bile, becomes thicker, viscous and darker in colour.

Effect on the pH of Bile In the gall bladder, due to rapid absorption of HCO_3^- (mainly), Na^+ and Cl^-, the pH of bile is decreased from 8–8.6 to 7–7.6.

Secretion of Mucus Gall bladder secretes mucin, which is added to the bile stored in it. The mucin acts as a lubricant in the intestine for the chyme.

Bile

General Considerations

- Bile is a digestive juice, formed continuously in the liver.
- During the interdigestive period when the sphincter of Oddi is closed, the bile is directed via cystic duct to the gall bladder, where it is stored and concentrated.
- During meals the sphincter of Oddi is relaxed and when food reaches the duodenum there occurs release of CCK, which causes contraction of the gall bladder. Then the bile is released into the duodenum along with the pancreatic juice through the common opening of ampulla of Vater.

Composition of Bile

The bile is an alkaline juice composed of:

- Water and solids
- Solids include organic and inorganic substances
- Organic substances are bile salts, bile pigments, cholesterol, lecithin, fatty acids and enzyme alkaline phosphatase
- Inorganic substances are Na^+, K^+, Ca^{2+}, HCO_3^- and Cl^-

Bile is concentrated in the gall bladder, so the concentration of its ingredients in the liver bile and gall bladder bile is bound to differ as shown in Table 7.4-2.

Salient features of the some of the ingredients of bile are described here.

TABLE 7.4-2 Liver Bile Versus Gall Bladder Bile

Properties and Composition	Liver Bile	Gall Bladder Bile
• pH	7.8–8.6	7–7.6
• Specific gravity	1010–1011	1026–1032
• Water	97.5%	87.5%
• Solids	2.5%	12.5%
Organic substances		
• Bile salts	1.10 g/dL	8.0 g/dL
• Bile pigments	0.20 g/dL	1.0 g/dL
• Cholesterol	0.10 g/dL	0.5 g/dL
• Fatty acid	0.15 g/dL	0.5 g/dL
• Fat	0.10 g/dL	0 g/dL
• Lecithin	0.1 g/dL	0.8 g/dL
• Mucin	Absent	Present
Inorganic substances	0.75 g/dL	8.7 g/dL

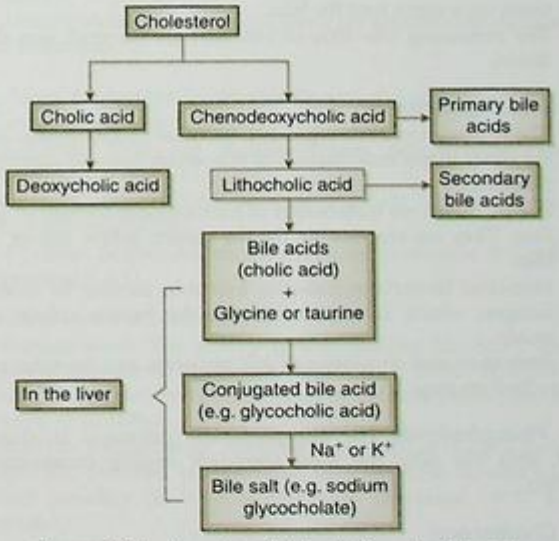


Figure 7.4-5 Formation of bile salts from the bile acids.

1. Bile Salts

Formation of Bile Salts Bile salts are sodium and potassium salts of bile acids conjugated with either taurine or glycine. Bile acids are of two types: primary and secondary. Steps in the formation of bile salts are shown in Fig. 7.4-5.

- ***Primary bile acids*** are cholic acid and chenodeoxycholic acid. These are synthesized by the hepatocytes from cholesterol.
- ***Secondary bile acids*** are deoxycholic acid and lithocholic acid. These are formed from the primary bile acids in the colon by the action of intestinal bacteria.
- *The conjugation of bile acids.* In the liver, the bile acids are conjugated with either glycine (an amino acid) or taurine forming the conjugated bile acids.
- The conjugated bile acids, namely glycocholic acid and taurocholic acid, form bile salts in combination with sodium or potassium.

Functions of Bile Salts Bile salts help in digestion as well as absorption of fat by their following actions:

Emulsification of fat, i.e. breaking of large fat drops into smaller droplets.

Acceleration of action of pancreatic lipase occurs in the presence of bile salts.
Micelle formation. The bile salts combine with the products of hydrolysis of triglycerides to form *small water-soluble, cylindrical, disc-shaped particles called* micelle, which are transported to the brush border of the epithelial cells for absorption.
Absorption of fat-soluble vitamins (A, D, E and K) is aided by the bile salts by forming complexes more soluble in water (hydrotrophic action).
Choleretic action, i.e. they stimulate liver to secrete bile and then make more bile salts available for fat digestion.
Cholesterol is kept in soluble form in the gall bladder bile by the bile salts. This property of bile salts prevents formation of gallstone.
Intestinal motility is stimulated by the bile salts. This action of bile salts help in defecation (laxative action).
Enterohepatic Circulation of Bile Salts Enterohepatic circulation is the re-circulation of bile salts from the liver to small intestine and then back again.
Path of Circulation Bile salts travel from the liver to duodenum via the CBD.

- When the bile salts reach *terminal ileum,* 90%–95% of bile salts are reabsorbed into the portal circulation. The liver then extracts the bile salts from the portal blood and secretes them once again into the bile.
- The remaining 5%–10% of bile salts are excreted into the faeces.

2. Bile Pigments

- The two principal bile pigments, *bilirubin* and *biliverdin,* are the other major constituents of bile which have no digestive function.
- Bile pigments are metabolites of haemoglobin formed in the liver. They are responsible for the golden yellow colour of bile.
- Intestinal bacteria metabolize bilirubin further to urobilinogen, which is responsible for the brown colour of stools.

Formation and circulation of bile pigments and *jaundice* are described on page 70.

3. Phospholipids

The phospholipids (primarily lecithins) are, after bile salts, the most abundant organic compounds in bile.

4. Cholesterol

- Cholesterol is another important constituent of bile that does not have digestive function. Normal biliary content of cholesterol is about 100 mg/dL (60–170 mg/dL) as compared to 150–240 mg/dL in the blood.
- Biliary secretion of cholesterol is important because it is one of the few ways in which cholesterol stores can be regulated.

5. Electrolytes

- Biliary content of inorganic substances is about 0.75 g%.
- The cations Na^+, K^+ and Ca^{2+} are all present in concentration of about 20% greater than in the plasma.
- Two major anions are Cl^- and HCO_3^-, Cl^- is present far less in concentration than in plasma, while HCO_3^- concentration is far greater which needs the bile juice alkaline.

Regulation of Bile

The regulation of bile juice released into the duodenum after the meals is performed at two levels:

- Regulation of biliary secretion
- Regulation of release of bile from the gall bladder

A. Regulation of Biliary Secretion

The secretion of aqueous component (water and electrolytes) and the bile (containing bile salts and other organic substances) though occur together but is controlled separately by the following mechanisms:

Regulation of bile-independent fraction of biliary secretion is controlled by secretin and vaso-vagal reflex.

- *Secretin* acts on ductal cells of hepatic duct and produces large amount of watery fluid with high concentration of HCO_3^-.
- *Vago vagal reflex* is initiated during intestinal phase of digestion acts through to release of Ach on ductal cells.

Regulation of bile-dependent fraction of biliary secretion depends on the amount of bile salts secreted by the liver.

B. Regulation of Release of Bile from the Gall Bladder

Filling of gall bladder. Occurs during interdigestive phase when sphincter of Oddi remain closed and is controlled by pressure gradient.
Emptying of gall bladder. When the chyme enters the duodenum, the gall bladder is contracted along with relaxation of sphincter of Oddi, raising the pressure to about 20 cm of water. Because of the increase in pressure, the bile from the gall bladder enters the duodenum. The contraction of gall bladder and relaxation of sphincter of Oddi are regulated by the following factors.
Hormonal Control The hormone CCK is the major stimulus for the gall bladder contraction and sphincter of Oddi relaxation. When chyme enters the small intestine, *fat and protein digestion products* directly stimulate the secretion of CCK (for details about CCK, see page 272).
Neural Control Vagal stimulation also causes contraction of the gall bladder and relaxation of sphincter of Oddi. Vagal stimulation occurs directly during the cephalic phase of digestion and indirectly via a vagovagal reflex during the gastric phase of digestion.
Note. Substances that cause contraction of gall bladder are called *cholagogues.* Thus, CCK is well-known cholagogue and acetylcholine released on the vagal stimulation also acts as a cholagogue.

Applied Aspects

Disorders of Liver and Gall Bladder

Jaundice or Icterus Jaundice or icterus refers to the yellow discolouration of skin and mucous membrane due to raised levels of bilirubin in the blood.

- *Normal values* of serum bilirubin range between 0.3 and 1 mg/dL
- *Jaundice* manifests when serum bilirubin becomes more than 2 mg/dL

Types of Jaundice Jaundice is of three types:

- *Haemolytic jaundice* prehepatic jaundice.
- *Hepatocellular jaundice* occurs due to damage to hepatocytes, as seen in viral hepatitis, cirrhosis and drug-induced hepatitis.
- *Obstructive jaundice,* also called posthepatic jaundice, occurs due to blockage in bile duct either due to stone or any growth (e.g. in carcinoma of head of pancreas).
  For further details, see page 71.

Cirrhosis of Liver Cirrhosis of liver refers to an irreversible chronic damage to liver with extensive fibrosis and regenerative nodule formation.

Viral Hepatitis Viral hepatitis (inflammation of liver) is caused by hepatitis virus A, B, C, D, E, F or G.

Hepatitis A is caused by hepatitis A virus and spread by faecal-oral route.

Hepatitis B is more common and is caused by hepatitis B virus. The sources of hepatitis B infections are by horizontal transmission, i.e.

- injection of unscreened blood products,
- tattoo/accupuncture, and
- unprotected sex.

Cholecystitis Cholecystitis refers to the inflammation of gall bladder.

Gallstones

Gallstone formation (cholelithiasis) is not an uncommon problem.

These are formed due to precipitation of cholesterol. Normally, cholesterol is present in soluble form due to a proper ratio of cholesterol and bile salts (1:20–1:30). When, this ratio falls below 1:13, the cholesterol is precipitated forming many small crystals. This stimulates further formation of crystals, so that the crystals grow larger and larger. In these crystals, bile pigments and calcium also get inspirated forming gallstones.

Liver Function Tests

The liver function tests (LFTs) are the investigations to assess the capacity of the liver to carry any of the functions it performs. Thus, LFTs help in:

- Assessing the extent of functional damage to the liver
- Diagnosing the cause of hepatic insufficiency
- Assessing the progress/regress of the disease

I. Tests to Assess Secretory Functions of Liver

1. Serum Bilirubin The *normal values* are as follows:

- Total serum bilirubin: 0.3–1.0 mg/dL
- Conjugated bilirubin: 0.1–0.3 mg/dL
- Unconjugated bilirubin: 0.2–0.7 mg/dL

Van den Bergh test is specific to identify the increase in serum bilirubin (above reference level). For procedure, see page 71. The results of test are interpreted as:

- Normal serum: Negative reaction
- Haemolytic jaundice: Indirect positive reaction
- Obstructive jaundice: Direct positive reaction
- Hepatic jaundice: Biphasic reaction

2. Urine Bilirubin and Bile Salts Normally, urine does not contain bilirubin and bile salts. In liver insufficiency, when the serum bilirubin levels increase above 2 mg/dL, the bilirubin is excreted in the urine *(bilirubinuria)*.

3. Urine Urobilinogen In normal individuals with urine flow of about 1 mL/min, less than 4 mg of urobilinogen is excreted in the urine. In liver insufficiency, initially there occurs mild increase in the daily excretion of urine urobilinogen. However, in later stages urobilinogen is absent in the urine. This occurs because of the fact that the swollen liver cells block bile canaliculi and prevent excretion of the conjugated bilirubin in the bile.

4. Faecal Stercobilinogen

- Normal levels are 20–25 mg/dL.
- Increased initially in liver insufficiency producing dark brown stools.
- Decreased in later stages of liver insufficiency producing pale coloured stool.

5. Faecal Fat Levels

- Normally 5%–6% of total fat intake per day is excreted in the faeces.
- In liver insufficiency, fat excretion in faeces increases up to 40%–50% of total intake (steatorrhoea).

II. Tests to Assess Metabolic Functions of Liver

1. Galactose Tolerance Test This test is based on the principle that galactose after absorption from the gut gets converted into glycogen in the liver. Therefore, in liver insufficiency its level in the blood rises.

2. Blood Glucose Level The normal fasting blood glucose level is 70–90 mg/dL. In hepatic insufficiency its level decreases.

3. Blood and Urine Amino Acids Levels Blood and urine amino acids levels are estimated to assess protein metabolism. In liver damage blood amino acid levels (normal 30–65 mg/dL) and urine amino acid levels are increased.

4. Lipid Profile In hepatic insufficiency lipid profile is affected as follows:

Abnormalities of serum lipid levels are sensitive but nonspecific indicators.

III. Tests to Assess Synthesis Functions of Liver

1. Estimation of Plasma Proteins

- *Albumin.* Liver cell damage causes hypoalbuminaemia (normal 6.4–8.3 g/dL).
- *Globulins.* Hyperglobulinaemia is usually associated with hypoalbuminaemia.
- *A:G ratio.* In liver disorder, there occurs reversal of A:G ratio (normal 1.7:1).

2. Serum Levels of Liver Enzymes

- *Transaminases.* The activity of transaminase like SGPT and SGOT increases in the hepatic insufficiency. Serum SGPT levels are increased by 10–1000 times in an acute phase (normal value < 40 IU%).
- *Alkaline phosphatase.* Alkaline phosphatase is not a liver-specific enzyme, but secreted into the bile. In obstructive jaundice its level is markedly increased (<30 KA units).

3. Blood Urea Liver is the principal site for urea formation from ammonia. Decreased level of blood urea (normal 20–40 mg/dL) and raised blood ammonia level (normal 20–80 mg/dL) occur in the liver insufficiency.

4. Coagulation Factors Factors II, V VII, IX and X and vitamin K needed to activate these factors are synthesized by the liver. The integrity and activity of these factors is determined by prothrombin time test (PTT). Prolonged prothrombin time (PT) (normal 10–16 seconds) indicates severe liver disease.

IV. Tests to Assess Detoxification Functions of Liver

1. Bromsulphthalein (BSP) Excretion Test BSP is taken up by the liver cells from the blood, and detoxified and excreted in the bile. The rate of removal of BSP from the blood depends on the functional efficiency of liver and rate of hepatic blood flow.

V. Tests to Assess Hepatic Cellular Integrity

1. Ultrasonography is done to detect diffuse disease of parenchyma of the liver (cirrhosis liver, fatty liver), abscess, cysts, tumours, gallstones and dilatation of biliary system proximal to site of obstruction.
2. Computed Tomography (CT) CT scan has the same diagnostic significance as the ultrasonography except that it can also detect even smaller lesions.
3. Radionucleotide Imaging Technetium (^{99m}Tc) is a sulphur colloid, which is easily taken up by the liver cells, monocyte–macrophage system (Kupffer's cells) and emits γ-rays. Gamma camera picks up these rays and is used to find out the size and lesions of the liver (such as filling defect, diffuse liver disease and portal hypertension).
4. Liver Biopsy This is performed by a special needle passed through intercostal space under local anaesthesia to obtain tissue for histopathological examination.
5. Fine-needle Aspiration (FNA) Very fine needle is usually guided by an ultrasound and material is aspirated for cytological, histopathological and bacteriological examination.
6. Serology To detect hepatitis virus antigens and antibodies.

SELF-ASSESSMENT

1. Describe briefly:
   - Composition, functions and regulation of pancreatic juice
   - Composition, functions and regulation of bile secretion
   - Functions of liver
2. Write notes on:
   - Bile salts
   - Enterohepatic circulation of bile salts
   - Functions of gall bladder
   - Cholecystokinin
   - Secretin

7.5 Physiological Activities in Small Intestine

CHAPTER OUTLINE

Functional Anatomy
Gross Anatomical Considerations
Structural Characteristics of Small Intestine

Small Intestinal Secretions
Composition
Regulation

Motility of Small Intestine
Interdigestive Period
Digestive Period
Motility Reflexes

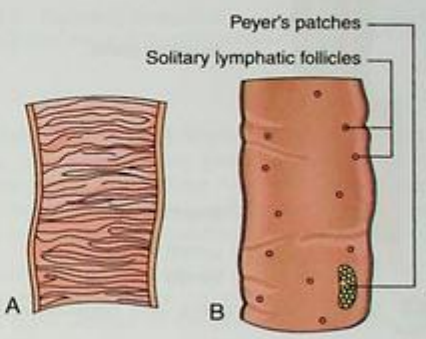


Figure 7.5-1 The mucosal surface of jejunum (A) and ileum (B).

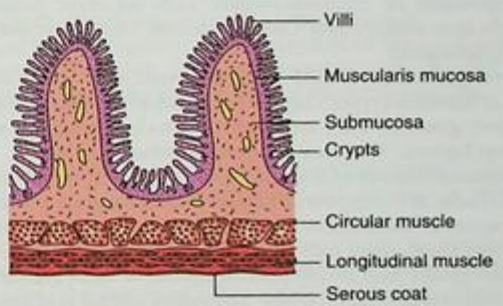


Figure 7.5-2 Longitudinal section of small intestine showing plica circulares and villi.

FUNCTIONAL ANATOMY

Gross Anatomical Considerations

The small intestine is convoluted tube which extends from the pylorus to the ileocaecal valve, where it joins with caecum – the first part of large intestine. It is divided into three parts: the duodenum, the jejunum and the ileum (see Fig. 7.5-1).

Duodenum The first and *shortest* part (25 cm long) of the small intestine. It is C-shaped and the superior part of duodenum is also called *duodenal cap* or bulb. It is the region which is struck by the acidic gastric contents when they pass through pylorus and is a *common site for* peptic ulcer. The bile and pancreatic ducts open by a common hepatopancreatic ampulla of Vater on the posteromedial wall of descending (2nd) part of duodenum.

Jejunum and ileum The jejunum and ileum form, respectively, the proximal two-fifth and distal three-fifth of the remaining part of small intestine.

Structural Characteristics of Small Intestine

Histologically, the wall of small intestine is composed of four layers, which from within to outwards consist of mucosa, submucosa, muscle coat and serosa (for details, see page 254)

Characteristic Features of Mucous Membrane of Small Intestine Although the small intestine is about 6-m long, it has an absorptive area of over 250 mm^2. This larger surface area is created by the following.

Plica Circulares The mucosal surface shows numerous circular folds (*plicae circulares* or valvulae conniventes) which increase surface area for absorption and also slow down the passage of contents through small intestine, which facilitate absorption (Fig. 7.5-1).

Villi Villi are finger-like projections of mucous membrane seen throughout the length of small intestine (Fig. 7.5-2). Each villus is about 0.5–1 mm long.

Structure. Each villus is covered by a single layer of columnar epithelial cells called enterocytes. The core of each villus contains an arteriole and venule with their communicating capillary plexus (Fig. 7.5-3) and blind-ended lymphatic vessel called lacteal.

The Crypts of Lieberkuhn The crypts of Lieberkuhn are tubular intestinal glands which invaginate deep into the lamina propria, present between the villi throughout the length of small intestine (Fig. 7.5-3). These glands are lined by undifferentiated columnar cells and also contain goblet cells, argentaffin cells and Paneth cells.

Epithelial Cells of the Mucous Membrane of the Small Intestine and Intestinal Glands The mucous membrane of small intestine is composed of the following types of epithelial cells.

1. Columnar Cells are called enterocytes. These cells are specialized for the absorptive function. The luminal surface of each enterocyte shows small multiple projections of the cell membrane called the *microvilli* or the *brush border* (Fig. 7.5-3), which increase the surface area to about 600 times.

2. Goblet Cells are mucous-secreting cells that can be seen among the epithelial cells of the mucous membrane.

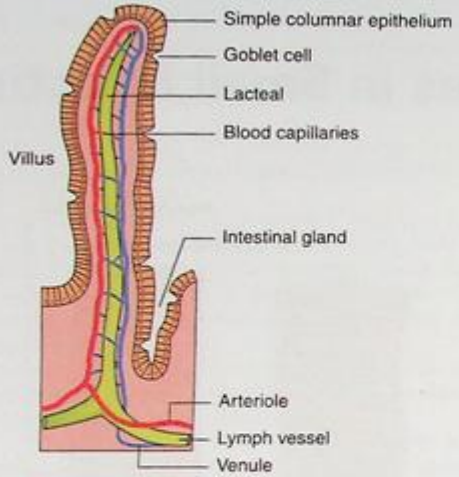


Figure 7.5-3 Structure of an intestinal villus, crypts of Lieberkuhn and an enterocyte.

3. Argentaffin or Enterochromaffin Cells are most numerous near the *lower ends of crypts*. These cells secrete 5-hydroxytryptamine (5-HT, serotonin).

4. Zymogen cells or Paneth Cells are found only in the deeper parts of intestinal crypts. They are large acidophilic cells containing secretory granules. They are known to produce lysozyme which destroys bacteria. They may also produce other enzymes.

5. Duodenal Glands of Brunner are limited only to the duodenum. These are compound tubulo-alveolar glands present in submucosa of duodenum. Their ducts pass through the muscularis mucosa to open into the crypts of Lieberkuhn. They are situated mostly near the pylorus. Secretion of these glands contains *mucus and* HCO_3^-, which neutralizes gastric acid entering the duodenum and thus protects its mucosa.

SMALL INTESTINAL SECRETIONS

Composition

The intestinal juice also called succus entericus comprises the intestinal secretions which include the following:

- Aqueous component (water and electrolytes)
- Intestinal enzymes
- Mucus

About 2 L of secretion is produced per day, which is alkaline (pH 7.5–8.6).

Intestinal Enzymes

- The enzymes which have been identified in the brush border are as follows:

1. Peptidases (proteolytic enzymes)
2. Disaccharidases, such as sucrase, maltase and lactase
3. Intestinal Lipases
4. Enterokinase or enteropeptidase

- Mucus in the small intestine is secreted by *Brunner's glands* and goblet cells. It is thick alkaline secretion that serves a protective role, preventing HCl and chyme from damaging the duodenal mucosa and lubricates the chyme.

Regulation of Small Intestinal Secretions

1. Local Stimuli Local mechanical and chemical stimuli to the intestinal mucosa form the most important means of regulation of intestinal secretions. Mechanical distension of intestinal mucosa by the food or irritation by chemicals, via local myenteric reflexes, increase the volume and total enzyme output of the small intestine; that is why, the greater is the chyme, greater is the secretion of intestinal secretion.

2. Role of Vasoactive Intestinal Polypeptide (VIP) Although the secretion of the crypts of Lieberkuhn is mainly regulated by the local stimuli, the local hormone VIP is also reported to increase its secretion.

3. Secretion of Brunner's Gland is increased by:

- Vagus stimulation
- Direct tactile stimulation or irritation of the duodenal mucosa
- Secretin

MOTILITY OF SMALL INTESTINE

Motility of small intestine can be described as follows.

A. *Motility of the small intestine during interdigestive period,* which includes:
   - Migrating motor complexes (MMC)

B. *Motility of the small intestine during digestive period* (related to meals), which includes:
   - Mixing movements, such as segmentation contractions and pendular movements
   - Propulsive movements, such as peristaltic contractions and peristaltic rush
   - Movements of villi

C. *Motility reflexes*, which include the following:
   - Peristaltic reflex
   - Gastroileal reflex
   - Intestinointestinal reflex

Motility of Small Intestine during Interdigestive Period

Migrating Motor Complexes

- The MMCs sweep out the chyme remaining in the small intestine.
- The MMCs occur every 60–90 minutes and last for about 10 minutes.

Motility of Small Intestine during Digestive Period

1. Mixing Movements The mixing movements of small intestine are responsible for the proper mixing of chyme with digestive juices like pancreatic juice, bile juice and intestinal juice. The mixing movements of small intestine include the following:

- Segmentation contractions
- Pendular movements

(i) Segmentation Contractions

Features

- Segmentation is the most common type of intestinal contractions which occurs throughout the digestive period in a rhythmic fashion, and hence also called *rhythmic segmentation contractions.*

- During segmentation contraction, a section of the small intestine (about 2–5 cm) contracts, sending the intestinal contents (chyme) in both oral and caudal directions. That section of the small intestine then relaxes and the contents move back into the segment. At the same time, the adjoining segment which was relaxed now contracts (Fig. 7.5-4A).
- The alternate contracted and relaxed segments give a ring-like appearance resembling the chain of sausages (Fig. 7.5-4B).

Function This back-and-forth movement of chyme produced by the segmentation contractions causes thorough mixing without any net forward movement of chyme (Fig. 7.5-4A).

(ii) Pendular Movements These are small constrictive waves which sweep forward and backward or upward and downward in a pendular fashion. These mixing movements can be noticed only by close observation.

2. Propulsive Movements

The propulsive movements of small intestine are involved in pushing the chyme towards the aboral end of intestine. These include the following:

- Peristaltic contractions
- Peristaltic rush

(i) Peristaltic Contractions

Characteristic Features

- The peristaltic contractions are highly coordinated and typically a peristaltic contraction involves contraction of a segment behind the bolus and simultaneous relaxation of the segment in front of the bolus, causing the chyme to be propelled caudally (Fig. 7.5-5).
- Each contraction travels for a variable but short distance, and then dies out. A new contraction is then initiated from a site

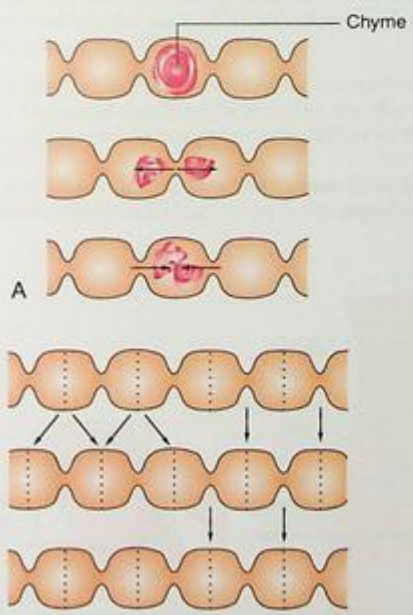


Figure 7.5-4 Segmentation contraction of small intestine: (A) steps of segmentation are shown to reveal back and forth movements of chyme and (B) the alternate contracted and relaxed segments give a ring-like appearance resembling the chain of sausages.

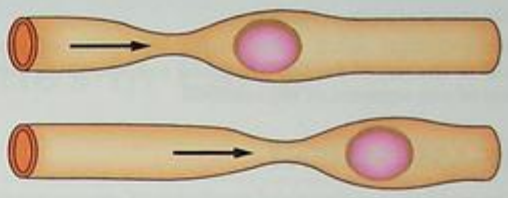


Figure 7.5-5 Peristaltic contraction moves the food through intestine by pushing bolus ahead of muscle contraction.

little distal to the site of origin of the previous contraction. In this way, a continuous peristaltic wave is set up in the intestine. Several of these wave-like contractions occur simultaneously along the length of the intestine, resulting in vermiform movements (worm-like movements).

Law of Intestine The peristaltic waves always travel from the oral end towards the aboral end of the intestine. This phenomenon has been labelled as the *law of the intestine* by Starling in 1901.

Functions subserved by the peristaltic waves are as follows:

- Help to propel the intestinal contents aborally.
- Also help in digestion and absorption of the food particles because different types of nutrients are digested and absorbed in different segments of the small intestine.

(ii) Peristaltic Rush

- Peristaltic rush refers to a very powerful peristaltic contraction, which occurs when intestinal mucosa is irritated intensely as in some infectious processes.
- This type of powerful contraction begins in duodenum, passes through entire length of small intestine and finally reaches the ileocaecal valve within few minutes. Thus, they sweep the contents of intestine into the colon, thereby relieving the small intestine of irritant or excessive distension, as it occurs in cases of diarrhoea.

3. Movements of Villi

Features Movements of villi consist of alternate shortening, and elongation of the villi is caused by contraction and relaxation of the muscle.

Functions Movements of villi help in emptying lymph from the central lacteal into the lymphatic system.

Villikinin, a hormone secreted from small intestinal mucosa is also believed to play an important role in increasing the movements of villi.

Motility Reflexes

1. Gastroileal Reflex

- Gastroileal reflex refers to a marked increase in the peristaltic contractions of ileum associated with relaxation of ileocaecal sphincter, which occurs immediately after the meals. As a result, the intestinal contents are delivered to the large intestine.
- This reflex is initiated by the distension of stomach by the food.
- The peristaltic contractions are caused by reflex stimulation of vagus, and the relaxation of ileocaecal sphincter seems to be produced by the hormone gastrin.

2. Intestinointestinal Reflex

Intestinointestinal reflex refers to the relaxation of smooth muscles of the rest of the small intestine in response to overdistension of one segment of the intestine.

SELF-ASSESSMENT

1. Composition, functions and regulation of succus entericus
2. Motility of small intestines
3. Write notes on:
   - Crypt of Lieberkuhn
   - Mixing movements of small gut
   - Gastroileal reflex
   - Peristaltic rush

7.6 Physiological Activities in Large Intestine

CHAPTER OUTLINE

Functional Anatomy
Gross Anatomical Considerations
Structural Characteristics

Large Intestinal Secretions and Bacterial Activity
Large Intestinal Secretions
Intestinal Bacterial Activity

Motility of Large Intestine
Movements of Large Intestine
Haustral Shuttling
Peristalsis
Mass Movements
Gastrocolic Reflex
Faeces

Applied Aspects
Role of Dietary Fibres
Hirschsprung Disease

FUNCTIONAL ANATOMY

Gross Anatomical Considerations

Functional Organization The large intestine is a tube about 6 cm in diameter and 100 cm in length. It normally arches around and encloses the coils of small intestine. It is divided into the following parts (Fig. 7.6-1):

Caecum is a blind-ended sac into which opens the lower end of ileum. The ileocaecal junction is guarded by the ileocaecal valve, which allows inflow but prevents backflow of the intestinal contents.

Appendix is a worm-shaped tube that arises from the medial side of caecum, which in human being is a vestigial organ.

Ascending colon extends upward from the caecum along the right side of abdomen up to the liver. On reaching the liver it bends to the left, forming the right hepatic flexure.

Transverse colon extends from the right hepatic flexure to the left splenic flexure.

Descending colon extends from the left splenic flexure to the pelvic inlet below.

Sigmoid colon begins at the pelvic inlet as a continuation of the descending colon and joins the rectum in front of the sacrum.

Rectum descends in front of the sacrum to leave the pelvis by piercing the pelvic floor. Here it becomes continuous with anal canal in the perineum.

Anal canal opens to the exterior through the anus, the opening which is guarded by two sphincters.

Structural Characteristics

Histological structure of large intestines is similar to that described in general (see page 254) with the following special characteristics.

Mucosa of large intestine is characterized by:

- Absence of plica circulares and villi (seen in small intestine).
- A large number of simple tubular glands (crypts of Lieberkuhn) are lined by simple columnar epithelial cells with large number of goblet cells, which secrete mucus (Fig. 7.6-2). Epithelial cells contain no enzyme.

Longitudinal Layer of Muscle Coat of Colon is Unusual

- Most of the fibres in it are collected to form three thick bands, the taenia coli, which can be seen through the serous layer (Fig. 7.6-1). A thin layer of longitudinal fibres is present in the intestines between the taenia.
- The taenia coli are shorter in length than other layers of the wall of colon. This results in the production of *sacculations* (also called *haustrations*) on the wall of colon.

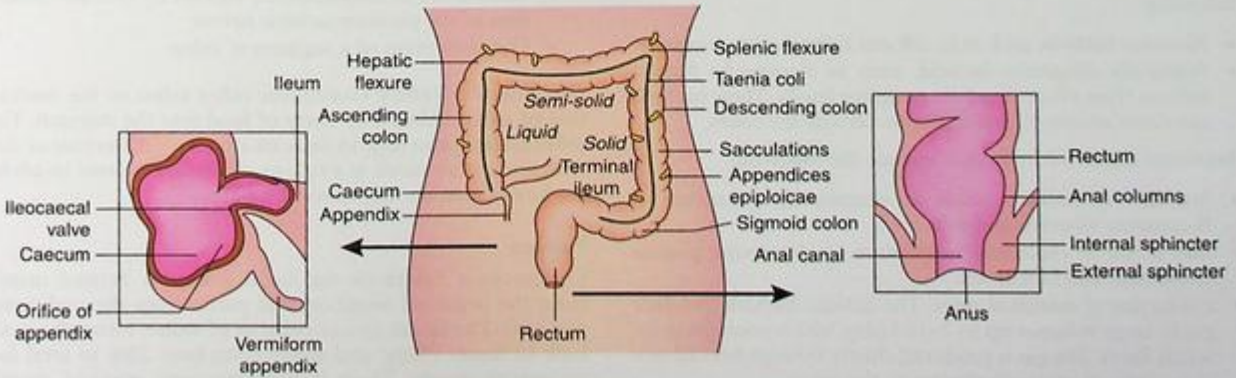


Figure 7.6-1 Functional organization of the large intestine.

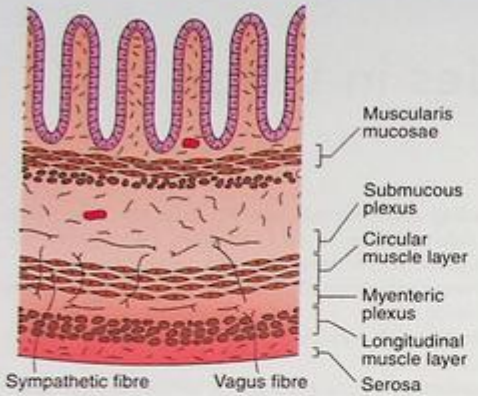


Figure 7.6-2 Histological structure of the colon.

Serous layer is missing over the posterior aspect of the ascending and descending colon. At places small peritoneal bags of fat called appendices epiploicae project from the colonic serosa.

LARGE INTESTINAL SECRETIONS AND BACTERIAL ACTIVITY

Large Intestinal Secretions

- The large intestinal secretions mainly composed of mucus secreted by the goblet cells; and some water and lot of HCO_3^- are secreted by the *glands of Lieberkuhn.*
- The mucus lubricates the faecal matter and also protects the mucous membrane of the large intestine by preventing the damage caused by the mechanical injury or chemical substances.
- The alkaline nature (pH 8.0) of the mucoid secretions of the large intestine is due to the presence of HCO_3^-. It serves to neutralize the acids formed by the bacterial action on the faecal matter.

Intestinal Bacterial Activity

Bacterial Flora At birth, the colon is sterile, but the colonic bacterial flora becomes established early in life and includes the following:

- *Harmless bacteria, such as E. coli and Enterobacter aerogenes.*
- *Potentially dangerous bacteria,* such as *Bacteroides fragilis,* various types of cocci and gas gangrene bacilli. These bacteria can cause serious disease in tissues outside the colon.

Intestinal Bacterial Activities include the following:

- *Synthesis of vitamins,* such as vitamin C, a number of B-complex vitamins and folic acid.
- *Play a role in cholesterol metabolism* by decreasing plasma cholesterol and LDL levels.
- *Production of intestinal gases.* The colonic bacteria produce gas in large volumes up to 7–10 L/day, which contribute towards flatus. The gas is produced chiefly through breakdown of undigested nutrients that reach the colon.
- *Organic acids* formed by the colonic bacteria from the carbohydrates are responsible for the slight acidic reaction of the stools (pH 5–7).
- *Pigments formed* by the colonic bacteria from the bile pigments are responsible for the known colour of stools.
- *Production of ammonia.* Colonic *bacteria* also produce ammonia, which is absorbed by blood and is normally detoxified quickly by the liver.

MOTILITY OF LARGE INTESTINE

Movements of Large Intestine

Types of Movements The different types of movements (most accepted nomenclature) of colon are as follows.

1. Haustral Shuttling The haustral shuttling or haustral contractions are similar to the segmentation contractions of small intestine.

Functions. The haustral contractions perform two main functions:

- *Mixing,* i.e. all the faecal material is gradually exposed to the surface of the large intestine, and fluid and dissolved substances are progressively absorbed.
- *Propulsion.* Haustral contractions at times move slowly towards the anus during the period of contraction and thereby provide forward propulsion of the colonic contents.

2. Peristalsis Peristalsis is a progressive contractile wave preceded by a wave of relaxation.

Function. They propel the contents towards rectum very slowly (5 cm/h). It can take up to 48 hours for the chyme to traverse the colon.

3. Mass Movements

- The mass movements are special type of peristaltic contractions which are observed in the colon only.
- These occur 3–4 times a day generally after meals and each contraction lasts for about 3 minutes.
- The mass movements force the faecal material rapidly in mass down the colon. They also move material into the rectum and rectal distension initiates the defecation reflex.
- A mass movement can be initiated by:
  - Gastrocolic or duodenocolic reflexes by intense stimulation of the parasympathetic nerves
  - Overdistension of a segment of colon

Gastrocolic Reflex Gastrocolic reflex refers to the contraction of colon induced by entry of food into the stomach. This reflex results in an urge to defecate after a meal. Because of this, defecation after meals is a rule in children. However in adults, the bowel training suppresses this reflex.

Faeces

Composition Faeces or the faecal matter is derived mainly from the intestinal secretion and partly from the undigested material. The faecal matter consists of *water,* forms the main bulk of faeces (75%) and *solids,* contribute 25% to total faecal matter weight. These include inorganic material, mostly

calcium and phosphate, undigested plant fibres, epithelial cells, dead bacteria, constituents of intestinal secretions including bile pigments, fats and proteins.

pH of Stools is slightly acidic (5–7) due to the organic acids formed from the carbohydrates by colonic bacteria.

Brown Colour of stools is due to the pigment *urobilin*, which is formed from oxidation of urobilinogen which is colourless.

Odour of Stools is due to the presence of substances like indole, skatole, mercaptans and hydrogen sulphide. These substances are formed by the action of colonic bacteria on the food.

APPLIED ASPECTS

Role of Dietary Fibres

Physiological Role of Dietary Fibres on Intestinal Food Transit Dietary fibres are constituted by the cellulose, hemicellulose and lignin components of the vegetable products in diet.

- In human beings, there is no appreciable digestion of the dietary fibres, at all. The ingested dietary fibres reach the large intestine in an essentially unchanged state and thus add bulk to the faeces, and thus play a role in defecation reflex by distending the rectum.

Role of Dietary Fibres on Prevention of Diseases The dietary fibres might be playing role by their following effects:

- *Reduction in absorption of digested foodstuffs.*
- *Reduction in blood cholesterol level* by dietary fibres is caused by increasing excretion of bile salts in faeces.

Therefore, dietary fibres are especially useful in the patients with atherosclerosis, obesity, hypercholesterolaemia and diabetes mellitus.

Hirschsprung Disease Hirschsprung disease (megacolon) occurs due to congenital absence of ganglionic cells in the myenteric as well as in Meissner's plexuses. This disease leads to blockage of both peristaltic as well as mass movements at the aganglionic segment of colon leading to difficulty in passage of faecal matter. Therefore, due to accumulation of faecal matter aganglionic segment gets dilated.

SELF-ASSESSMENT

1. Describe briefly functions of large intestine.
2. Write notes on:
   - Intestinal bacterial activity
   - Gastrocolic reflex
   - Dietary fibres
   - Hirschsprung disease

7.7 Digestion and Absorption

CHAPTER OUTLINE

Digestion and Absorption of Carbohydrates
Dietary Carbohydrates
Digestion of Carbohydrates
Absorption of Carbohydrates
Fate of Glucose in the Body

Digestion and Absorption of Proteins
Sources of Proteins
Digestion of Proteins
Absorption of Proteins

Digestion and Absorption of Fats
Dietary Fats
Digestion of Fats
Absorption of Fats

Absorption of Water, Electrolytes, Minerals and Vitamins
Absorption of Water
Absorption of Sodium
Absorption of Chloride
Absorption of Potassium
Absorption of Calcium
Absorption of Iron
Absorption of Vitamins

DIGESTION AND ABSORPTION OF CARBOHYDRATES

Dietary Carbohydrates

Dietary intake of carbohydrates is 250–850 g/day, which represents 50%–60% of the diet. Major carbohydrates in the human diet are as follows:

1. Polysaccharides These may be present in the following forms:

- *Starch*
- *Glycogen*
- *Cellulose* (plant polysaccharide)

2. Oligosaccharides On the basis of number of monosaccharide units present, oligosaccharides are further subdivided into di-, tri-, tetra- and pentasaccharide.

Disaccharides include the following:

- Sucrose (glucose + fructose) is also known as table sugar (cane or beet sugar).
- Lactose (glucose + galactose) is also called milk sugar.
- Maltose (glucose + glucose). It is a product of starch hydrolysis. It is present in germinating seeds.

3. Monosaccharides Monosaccharides consumed mostly in human diet are the following.

Hexoses such as:

- Glucose (in fruits, vegetables and honey)
- Fructose in fruits

Pentoses do not occur in free form, but are found in nucleic acid and in certain polysaccharides, such as pentosans of fruits and gums.

Digestion of Carbohydrates

The digestion of carbohydrates begins in mouth, continues in stomach, but occurs mainly (almost all) in the small intestine.

Digestion of Carbohydrates in the Mouth Initial starch digestion starts in the mouth by the enzyme α-amylase (ptyalin) present in the saliva. It acts on the 1–4 linkages (but not on 1–6 linkages). It digests cooked starch to maltose.

Digestion of Carbohydrates in the Stomach In the stomach, there occurs minimal carbohydrate digestive activity.

α-Amylase (which enters the stomach with food) activity continues in the stomach for 20–30 minutes till the highly acidic gastric juice mixes with the food and makes it inactive.

The HCl of the gastric juice may hydrolyse some sucrose.

Digestion of Carbohydrates in the Small Intestine In the small intestine the carbohydrates are digested by the following enzymes.

Pancreatic α-amylase is present in the pancreatic juice which is poured into the duodenum. Its actions on the carbohydrates are much powerful, and so it acts on boiled as well as unboiled starch and variety of other carbohydrates except cellulose.

Brush Border Enzymes of Small Intestine The carbohydrate-splitting brush border enzymes of small intestine include *dextrinase*, *maltase*, *sucrase* and *lactase*. These brush border enzymes digest the oligosaccharides into monosaccharides on the surface of epithelial cells of villi as below.

α-Limiting dextrinase. It is the only enzyme in GIT which attacks 1,6 α-glycoside linkage at the branching points of α-limit dextrins.

$$\text{Dextrin} \xrightarrow{\alpha\text{-limiting dextrinase}} \text{Glucose}$$

Maltase, sucrase and lactase hydrolyse the corresponding disaccharides into monosaccharides as follows:

$$\text{Maltose} \xrightarrow{\text{Maltase}} \text{Glucose}$$

$$\text{Sucrose} \xrightarrow{\text{Sucrose}} \text{Glucose} + \text{Fructose}$$

$$\text{Lactose} \xrightarrow{\text{Lactase}} \text{Glucose} + \text{Galactose}$$

End Products of Carbohydrate Digestion

- The end products of carbohydrates are monosaccharides such as glucose, fructose and galactose.
- A little amount of pentoses are the end products of digestion of nucleic acids and partial digestion of pentosans.

Absorption of Carbohydrates

Carbohydrates are absorbed from the GIT in the form of monosaccharides.

Site of Absorption Most of the monosaccharides are absorbed from the mucosal surface of jejunum and upper ileum.

Mechanism of Absorption Various monosaccharides are absorbed by the following mechanisms:

- *Glucose and galactose* are absorbed by a common Na^+ dependent active transport system.
- *Fructose* is absorbed by *facilitated diffusion*.
- *Pentoses* are absorbed by simple diffusion.

Absorption of Glucose and Galactose Glucose and galactose are absorbed into the epithelial cells (enterocytes) lining the mucous membrane of the small intestine from their brush border surface (luminal surface) by an *active* transport mechanism – the *sodium cotransport* mechanism. Salient points of glucose absorption are (Fig. 7.7-1).

Binding of Glucose and Na^+ to Carrier Protein The carrier protein (present in the cell membrane) has two binding sites, one for sodium and another for glucose. It is called *sodium-dependent glucose transporter-1(SGLT-1)*. The conformational change in the carrier protein occurs only when the binding sites are occupied by the sodium and glucose present in the gut lumen forming the sodium–glucose-carrier complex.

Creation of Electrochemical Gradient across the Epithelial Cell The active transport of sodium by Na^+–K^+–ATPase pump through the basolateral membrane into the paracellular spaces lowers the intracellular Na^+ concentration. This creates an electrochemical gradient.

Movement of Sodium and Glucose Inside the Cell Because of the electrochemical gradient created, the sodium moves into the cell (downhill transport). The flow of sodium ions down the gradient is so forceful that glucose (or galactose) molecule attached to the carrier protein also enters the cell, even against concentration gradient for glucose (uphill movement). The energy is required for Na^+–K^+ pump activity to maintain the sodium gradient.

Transport of Glucose into Blood Capillaries From the epithelial cell, the glucose is transported into the interstitial space and thence to blood capillaries of portal system through *facilitated diffusion* by *glucose transporter-2(GLUT-2)*.

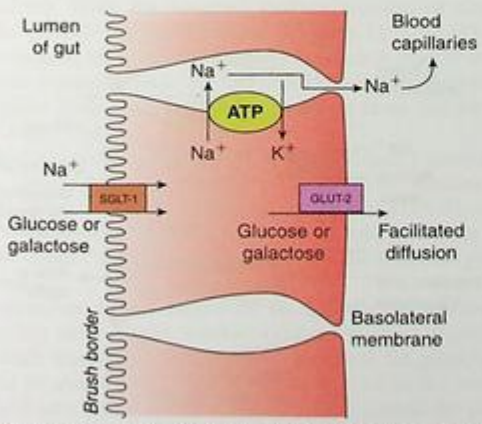


Figure 7.7-1 Mechanism of glucose absorption across intestinal epithelial cell.

Rate of absorption of monosaccharides is variable, being:

- Fastest with glucose and galactose
- Intermediate with fructose
- Slowest with mannose or pentoses

Fate of Glucose in the Body

1. Storage as Glycogen About 5% of the total glucose absorbed is stored as glycogen in the liver and muscles.
2. Catabolism to Produce Energy About 50%–60% of the glucose absorbed is catabolised in the body tissues to produce energy.
3. Conversion into Fat About 30%–40% of glucose is converted into fat and is stored in the fat depot.

DIGESTION AND ABSORPTION OF PROTEINS

Sources of Proteins

The proteins that are digested and absorbed in the GIT come from two sources: exogenous and endogenous.

1. Exogenous (Dietary) Proteins

Daily requirement of dietary proteins for adults is 0.5–0.7 g/kg body weight and for children (1–3 years) it is 4 g/kg.

Sources of dietary proteins with high biological value are meat, fish, eggs, cheese and other milk products. Soya beans, wheat and various types of pulses are also rich sources of proteins.

2. Endogenous Proteins Endogenous proteins, totalling 30–50 g/day, are the proteins which reach the intestine through various gastrointestinal secretions, and those which are present in the desquamated epithelial cells of the gut.

Digestion of Proteins

Proteins are digested by the proteolytic enzymes to amino acids and small polypeptides before they are absorbed. Digestion of proteins does not occur in the mouth, as there are no proteolytic enzymes in the saliva. Digestion of proteins thus begins in the stomach and is completed in the small intestine.

Digestion of Proteins in the Stomach

Pepsin, secreted by chief cells of the main gastric glands in an inactive form (pepsinogen), is responsible for digesting about 10%–15% proteins entering the GIT.

- Pepsinogen is converted into pepsin (active form) by the action of HCl or preformed pepsin.
- Pepsin splits proteins into proteoses, peptones and polypeptides (Fig. 7.7-2).
- It is important to note that the optimum pH for the action of pepsin is 2.0; therefore, HCl secretion by the stomach is as essential as pepsinogen secretion for the digestion of proteins.

Digestion of Proteins in the Small Intestine In the small intestine the proteins are digested by the pancreatic proteases, brush border peptidases and intracellular peptidases.

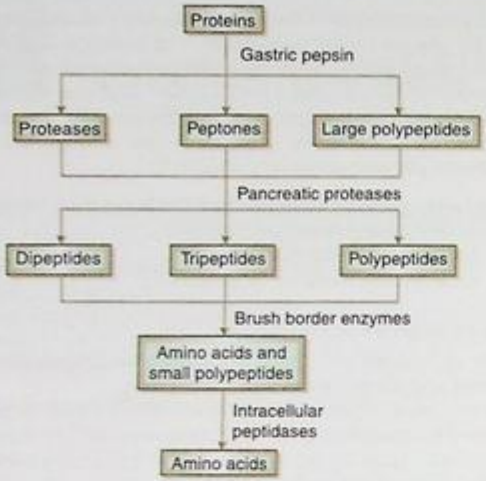


Figure 7.7-2 Digestion of proteins.

Pancreatic Proteases or proteolytic enzymes of pancreas play a major role in protein digestion.

- *Pancreatic proteases* digest the proteins and split them into dipeptides, tripeptides and small polypeptides, which are further digested by brush border peptidases (Fig. 7.7-2).
- Some of the dipeptides and tripeptides are absorbed directly into the epithelial cells of mucosa of small intestine, and are further digested by the intracellular enzymes into the amino acids.

Brush Border Peptidases include aminopeptidases, dipeptidases, tripeptidases, nuclease and related enzymes. These enzymes eventually convert the proteins to small polypeptides and amino acids (Fig. 7.7-2).
Intracellular Peptidases are the proteolytic enzymes present in the cytosol of epithelial cells of small intestine. These peptidases are specific for linkages between the various amino acids. Within minutes, these digest the last dipeptides and tripeptides into amino acids, which then enter the blood.

Digestion of Nucleic Acid and Nucleoproteins

Sources

Nucleic acid and nucleoproteins are found in abundance in the foodstuffs which are rich in nuclei such as liver, kidney, pancreas and yeast.

In the Stomach, HCl hydrolyses the nucleoproteins, removing proteins which are digested together with other proteins as described above.

$$\text{Nucleoproteins} \xrightarrow{\text{HCl}} \text{Proteins} + \text{Free nucleic acid}$$

In the small intestine, the free nucleic acids are digested by the pancreatic enzymes and brush border enzymes.

- *Pancreatic enzymes* such as ribonuclease and deoxyribonuclease in the duodenum digest free nucleic acids into nucleotides and nucleosides.

$$\text{Free nucleic acids (RNA + DNA)} \xrightarrow[\text{Deoxyribonuclease}]{\text{Ribonuclease}} \text{Nucleotides} + \text{nucleosides}$$

- *Brush border enzymes* such as nucleases, nucleotidases and nucleosidases convert nucleotides and nucleosides into pentoses (purine and pyrimidine).

$$\text{Nucleotides + Nucleosides} \xrightarrow[\text{Nucleosidases}]{\text{Nucleases, Nucleotidase}} \text{Pentoses (purine + pyrimidine)}$$

End Products of Protein Digestion The protein digestion which starts in the stomach is completed in the enterocyte of the small intestine.

The end products of protein digestion are amino acids.

Absorption of Proteins

Mechanisms of Absorption into the Intestinal Epithelial Cells The end products of protein digestion (amino acids, dipeptides and tripeptides) are absorbed through the luminal membrane of the epithelial cells of small intestine. The following mechanisms of absorption are known.

1. Na^+ dependent active transport mechanism The levo amino acids, dipeptides and tripeptides are absorbed by a Na^+ dependent active transport mechanism.

- Separate transporters (carriers) are present for the absorption of basic, acidic and neutral amino acids.
- Steps of active transport mechanism are similar to those described for glucose absorption (see page 254). These include (Fig. 7.7-3) the following:
  - Binding of amino acid and Na^+ to carrier protein.
  - Creation of electrochemical gradient across the epithelial cells.
  - Movement of Na^+ and amino acids inside the cell.

2. Simple Diffusion The dextro amino acids are absorbed solely by the passive diffusion.

3. Endocytosis Small amounts of larger polypeptides are absorbed by endocytosis. Proteins absorbed by endocytosis usually excite immunological/allergic reaction.

Note: In newborn infants, immunoglobulins present in the colostrum are absorbed in the intestinal mucosa by endocytosis and impart passive immunity to child.

Further Digestion in the Epithelial Cells Once amino acids and polypeptides are absorbed into the intestinal epithelial cells, the intracellular peptidases break the remaining linkages of tripeptides and dipeptides causing release of amino acids.

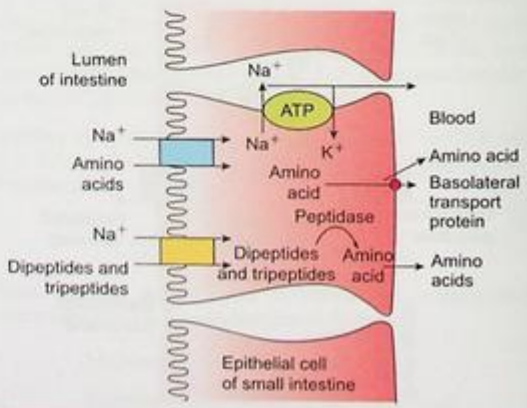


Figure 7.7-3 Mechanism of absorption of amino acids, dipeptides and tripeptides by intestinal epithelial cells.

Transport of Amino Acids into Blood Capillaries From inside of the epithelial cells the amino acids are transported into the interstitial space across the basolateral membrane of the cells by facilitated or simple diffusion. From the interstitium, the amino acids enter the capillaries of villus by simple diffusion, and then via portal vein, they reach the liver and general circulation.

DIGESTION AND ABSORPTION OF FATS

Dietary Fats

Types of Fats Fats are of three types:

- *Simple fats or neutral fats*, e.g. triglycerides and cholesterol
- *Compound fats*, e.g. phospholipids
- *Associated fats*, e.g. steroids and fat-soluble vitamins

Dietary fat is of both vegetable and animal origin. Mostly, it is in the form of neutral fat (triglycerides). It also includes small amounts of phospholipids, cholesterol, some free fatty acids, lecithin and cholesterol esters.

Daily intake of fats in the diet varies widely, from about 25–160 g.

Digestion of Fats

Site of Digestion Although lipolytic enzymes are secreted in the mouth *(lingual lipase)* and stomach *(gastric lipase)*, their action is so insignificant that practically digestion of all the dietary fats occurs in the small intestine. Under normal conditions gastric lipase is soon inactivated by gastric juice at acidic pH (pH 2.5).

Mechanism of Digestion of Fats The digestion of fat includes three steps:

- Emulsification of fat by bile salts
- Hydrolysis of fat by pancreatic and intestinal lipolytic enzymes
- Acceleration of fat digestion by micelle formation

1. Emulsification of Fat by Bile Salts Emulsification, i.e. breaking of large fat drops into smaller droplets is a prerequisite for the action of pancreatic lipase. It is so because the pancreatic lipase being water-soluble acts only on the oil–water interface of fat.

Emulsification of fat is caused by the bile salts because of their property of lowering the surface tension (detergent-like action). With the lowered surface tension of the fats, large fat globules break into fine droplets (1 μm). The bile salts surround the fine fat droplets in such a way that their lipophilic nonpolar ends are towards the fat and their hydrophilic polar ends separate the fat droplets from the aqueous phase (Fig. 7.7-4).

2. Hydrolysis of Fat Droplets by Pancreatic and Intestinal Lipolytic Enzymes Pancreatic juice is markedly alkaline (pH 7.8–8.4). When it mixes with the acidic chyme (pH 6.0) coming from the stomach into the duodenum, the pH of chyme is adjusted to about 7 (which is optimal pH for the action of pancreatic lipases).

3. Acceleration of Fat Digestion by Micelle Formation The micelles are small, water-soluble, cylindrical, disc-shaped particles. Each micelle is composed of a central fat globule surrounded by about 30 molecules of bile salts in such a way that their lipid-soluble nonpolar ends are in the central fat globule and water-soluble polar ends fan out to form the outer covering of micelle. The monoglycerides and free fatty acids released from the digestion of fat are quickly incorporated into the central fatty portion of the micelles forming, what are known as the *mixed micelles* (Fig. 7.7-5). In this way, bile salts accelerate the fat digestion by allowing the lipolytic action to continue.

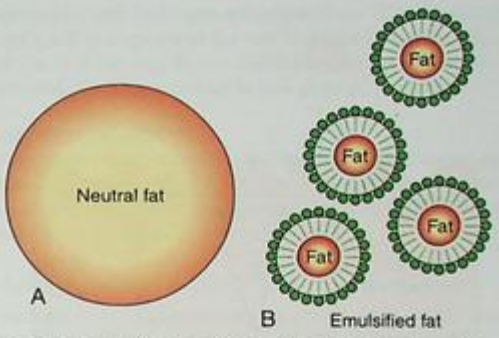


Figure 7.7-4 Emulsification of fats by bile salts: (A) a large fat particle and (B) small fat particles surrounded by the bile salts.

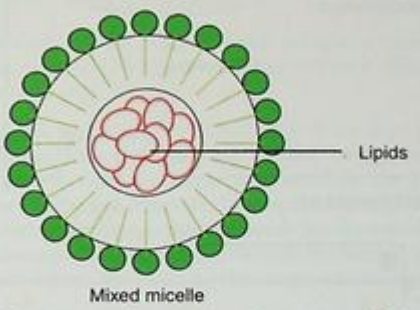


Figure 7.7-5 Structure of a mixed micelle composed of lipids (monoglycerides, fatty acids, cholesterol) in the centre surrounded by bile salts.

Absorption of Fats

Most of the fat absorption occurs in the duodenum. Absorption of fats is accomplished by the following steps (Fig. 7.7-6):

1. Transportation as Micelles to the Brush Border Membrane The bile salt micelle acts as a transport vehicle for the products of fat digestion.

2. Diffusion of Lipids across the Enterocyte Cell Membrane Once the micelle comes in contact with the cell membrane, the monoglycerides, free fatty acids, cholesterol and fat-soluble vitamins (being soluble in the cell membrane) *diffuse passively* at a rapid speed through the enterocyte cell membrane to the interior of the cell, leaving bile salts in the intestinal lumen.

The bile salts released from the micelle after diffusion of their associated lipids are absorbed in the terminal ileum by a Na^+-dependent active transport process.

3. Transport of Lipids from Inside the Enterocytes to the Interstitial Space Once inside the cell, the end products of fat digestion enter the interstitium by two mechanisms.

(i) ***Diffusion across the basal border of enterocyte.*** The small-chain fatty acids with less than 12–14 carbon atoms are able to diffuse across the basal border of enterocytes to enter the interstitium.

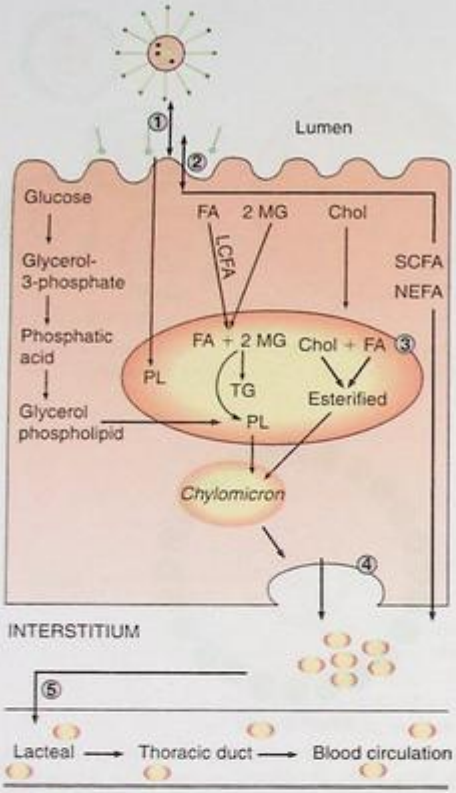


Figure 7.7-6 Steps of fat absorption: 1, transportation of micelle to enterocytes brush border; 2, diffusion of lipids across the enterocyte membrane leaving bile salt in the lumen; 3, formation of chylomicron in the endoplasmic reticulum; 4, release of lipids into interstitium by exocytosis; and 5, diffusion of lipids from interstitium into lacteal (from where lipids enter into lymphatic circulation) and through thoracic duct into circulation. FA, fatty acid; MG, monoglycerides; chol, cholesterol; TG, triglycerides; LCFA, long-chain fatty acid; SCFA, short-chain fatty acids; NEFA, nonesterified fatty acids; PL, phospholipid.

(ii) ***Formation and excretion of chylomicrons from the enterocytes by exocytosis.*** The large-chain fatty acids, cholesterol and lysophosphatides enter the smooth endoplasmic reticulum, where they are reconstituted:
- 2-Monoglycerides are combined with fatty acids to produce triglycerides.
- Lysophosphatides are combined with fatty acids to form phospholipids.
- Cholesterol is re-esterified.

The reformed lipids coalesce to form a small lipid droplet called chylomicrons, which are then excreted into the interstitium by *exocytosis* from the basolateral membrane of enterocyte. Covering of β-lipoproteins is essential for the exocytosis to occur.

4. Transport of Lipids into Circulation From the interstitium, the lipids diffuse into the *lacteals*, from which they enter the lymphatic circulation and via thoracic duct gain access into the blood circulation.

Serum Lipid Profile

Lipids are present as lipoprotein complexes. Depending up the density the lipoproteins are of the following types:
(i) Very low-density lipoproteins (VLDL): Density is <1.060.
(ii) Low-density lipoproteins (LDL)
(iii) High-density lipoproteins (HDL): Density is 1.060– 1.200.

Normal Values
- Serum triglycerides: 30–150 mg/dL
- Serum cholesterol: 150–240 mg/dL
- Serum phospholipids: 150–300 mg/dL
- Serum-free fatty acids (FFA or NEFA = 10–30 mg/dL).

ABSORPTION OF WATER, ELECTROLYTES, MINERALS AND VITAMINS

Absorption of Water

Water Balance in the GIT
- The GIT receives about 9 L of water per day, which includes about 2 L of ingested water and about 7 L contained in salivary, gastric, biliary, pancreatic and intestinal secretions (Table 7.7-1).
- The GIT absorbs about 8.8 L of water (about 95% of total water received) per day. About 60% of absorption occurs in jejunum, 20%–25% in ileum and 10%–15% in colon (Table 7.7-1).
- The GIT excretes about 0.2 L of water in the faeces per day.

Mechanism of Water Absorption In general, water is absorbed passively and iso-osmotically across the gastrointestinal mucosa following the osmotic gradient created by the active absorption of electrolytes and nutrients.

Absorption of Sodium

Sodium Balance in GIT GIT receives about 40 g of sodium per day, out of which about 10 g is ingested with food and about 30 g is contained in the gastrointestinal secretions. All of it is reabsorbed.

Site of Absorption Although sodium can be reabsorbed in the entire length of the intestine, but maximum absorption occurs in the jejunum.

TABLE 7.7-1 Daily Water Balance in GIT

Input (L)		Absorption (L)		Faecal Excretion (L)
Water ingested	2	Jejunum (60%)	5.5	0.2
Water in GIT	7	Ileum (25%)	2.0	
Secretions • Saliva: *1.50* • Gastric juice: *2.50* • Bile: *0.75* • Pancreatic juice: *0.75* • Intestinal juice: *1.50*		Colon (10%–15%)	1.3	
Total	9		8.8	0.2

Mechanism of Absorption Absorption of sodium is two-step process.

1. ***Transport of sodium from the lumen into the enterocyte occurs by the following mechanisms:***
   - Na^+ glucose, Na^+–amino acid and Na^+–di- or tripeptide cotransport system accounts for 30% of Na^+ transport into the cell.
   - Neutral Na^+–Cl^- cotransport system also transports about 30% of Na^+.
   - Na^+–H^+ exchange.
   - Passive diffusion (through Na^+ channels) down an electrochemical gradient is responsible for transport of remainder 40% of Na^+.

In the Small Intestine, Na^+–glucose cotransport, Na^+–amino acid cotransport and Na^+–H^+ exchange mechanisms are most important.
In the Colon, passive diffusion via Na^+ channels is most important.

2. ***Transport of Na^+ out of the enterocytes into interstitium*** occurs against its electrochemical gradient across the basolateral membrane by Na^+–K^+–ATPase active transport system.

Absorption of Chloride

In the jejunum and proximal ileum most of the Cl^- is absorbed passively through the enterocytes down the electrochemical gradient established by the active transport of Na^+.
In the distal ileum and large intestine, the Cl^- is absorbed by an active Cl^-–HCO_3^- exchange mechanism. In this mechanism Cl^- is absorbed from the lumen in exchange of HCO_3^-, which is secreted into the lumen. Bicarbonate (HCO_3^-) secreted into the lumen helps to neutralize the acidity produced by the action of colonic bacteria on the food.

Absorption of Potassium

Passive diffusion via paracellular route down its electrochemical gradient is the mechanism involved in absorption of dietary K^+ from the small intestine.

Absorption of Calcium

Dietary Calcium Best sources of dietary calcium are milk and milk products. Good sources of calcium are beans, leafy vegetables, fish, cabbage and egg yolk.

Dietary requirements of calcium are as follows:
- Infants (<1 year): 300–500 mg/day
- Children (1–18 years): 800–1200 mg/day
- Adult men and women: 800 mg/day
- Women during pregnancy, lactation and postmenopause: 1500 mg/day

Site of absorption. Most of the ingested calcium is absorbed in the upper small intestine (duodenum and jejunum). Most of the calcium is absorbed by an active transport mechanism.

Regulation of Calcium Absorption Calcium absorption from the small intestine is well regulated to maintain the plasma calcium *(homeostasis of calcium)* levels within a narrow range (9–11 mg/dL). Vitamin D and parathyroid hormone play main role in the regulation of calcium absorption.

Importance of calcium–phosphorus (Ca:P) Ratio The ratio of Ca:P is important for calcification of bones. The product of Ca × P (in mg/dL) in children is about 50 and in adults it is around 40. This product is less than 30 in rickets.

Absorption of Iron

- Absorption occurs mainly in the duodenum and upper jejunum.
- Normally about 10% of the 15–20 mg iron ingested each day is actually absorbed in healthy adult male. This absorption is more in menstruating women.

Mechanism of Iron Absorption

Mechanism of iron absorption for the purpose of understanding can be described under three headings:

A. Transport of iron across the brush border of enterocyte
B. Fate of iron in the enterocyte
C. Transport of iron in the plasma

A. Transport of iron across brush border of enterocyte

In the diet, iron may be present as haem (derived from meat) or nonhaem iron (Fig. 7.7-7).

1. ***Absorption of haem iron*** Haem iron is the iron present in myoglobin, haemoglobin and related compounds. From these compounds, the haem is released by the proteolytic enzymes in the gut. From the lumen, the haem is transported inside the enterocyte across the brush border membrane by a *haem transport* protein. Inside the cell, the ferrous iron (Fe^{2+}) is released from the haem by the enzyme haemoxygenase.

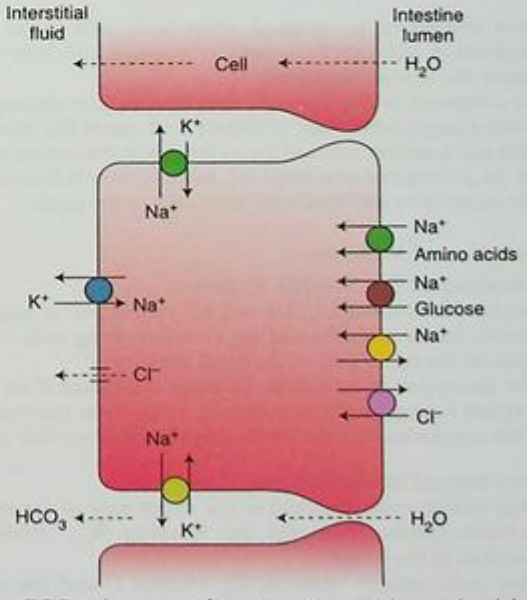


Figure 7.7-7 Absorption of iron. Haem is carried across brush border of enterocyte by a haem transport protein (HT) and Fe^{2+} of nonhaem iron by iron transport protein (IT), inside the enterocyte some iron binds to ferritin and some crosses the basolateral membrane by active transport process (AT). In the blood, iron binds to the transport protein transferrin (TF).

2. *Absorption of nonhaem iron* Most of the dietary nonhaem iron is present in ferric form (Fe^{3+}), whereas iron can be absorbed more efficiently in ferrous form (Fe^{2+}).
   - Iron has got tendency to form insoluble complexes with dietary phytates, phosphates and dietary fibres. Gastric HCl tends to break insoluble iron complex apart and thus facilitates iron absorption.
   - Ferrous iron (Fe^{2+}) is transported across the brush border by the *iron transport protein* or *receptors* present on the cell membrane (Fig. 7.7-7). Once inside the enterocyte, the fate of nonhaem ferrous iron is same as that of the haem iron.

B. Fate of iron in the enterocyte As shown in Fig. 7.7-7, in the cytosol of enterocyte the free ferrous iron (Fe^{2+}) has two fates:

- A part of Fe^{2+}, depending up the body's requirement, is actively transported across the basolateral membranes of the enterocytes into the interstitium, from where it enters the blood.
- Rest of the ferrous iron is oxidized to ferric form and bound to apoferritin forming ferritin. It is difficult to release iron from this storage form, and in general the ferritin stays in the enterocyte until the cell is sloughed off at the tip of villus.

C. Transport of iron in the blood Normally, the iron absorbed into the blood binds with a β-globulin (apotransferrin) to form the *transferrin*, and is transported in this form in the plasma. Iron combines loosely in the globulin apotransferrin and can be released easily to enter any of the tissue cells of any point in the body.

Mucosal Block Theory of Absorption This theory states that:

- Iron absorption is increased when body iron stores are depleted or when erythropoiesis is increased and decreased under the reverse conditions.
- As compared to the normal conditions, in iron deficiency states a larger percentage of dietary iron enters the circulation and a smaller amount forms ferritin in the enterocytes.
- In the presence of iron overload, more ferritin is formed in the enterocytes and shed with these cells in the stools.

Absorption of Vitamins

Absorption of Fat-Soluble Vitamins

- Fat-soluble vitamins (A, D, E and K) become part of micelle formed by the bile salts and are absorbed along with other lipids in the upper part of the small intestine.
- The absorption of fat-soluble vitamins is deficient if fat absorption is depressed because of lack of pancreatic enzymes or if bile is excluded from the intestine by obstruction of bile duct.

Absorption of Water-Soluble Vitamins

- Most vitamins are absorbed in the upper part of the small intestine (jejunum) except the vitamins B_{12}, which is absorbed in the ileum.
- Most water-soluble vitamins, e.g. vitamin C and the vitamins B (biotin, folic acid, nicotinic acid B_6, i.e. pyridoxine, B_2, i.e. riboflavin, and B_1, i.e. thiamine) are absorbed by facilitated transport or by a Na^+-dependent active transport system in the proximal small intestine.
- Vitamin B_{12} absorption is most complex than that of other water-soluble vitamins and needs separate description.

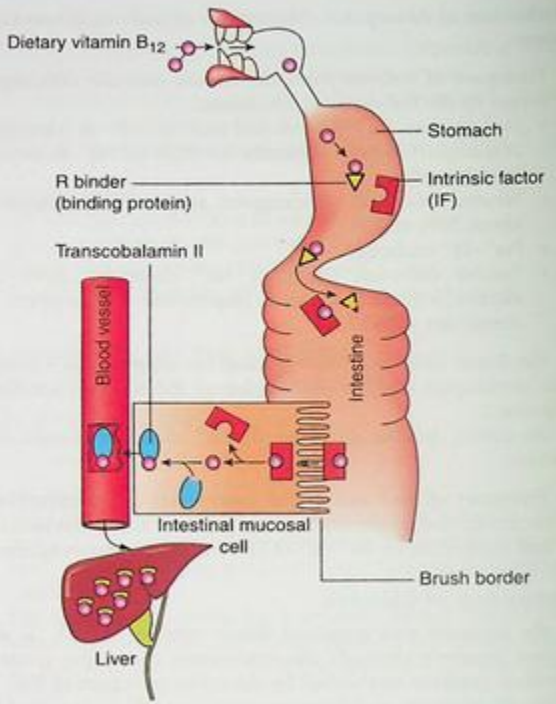


Figure 7.7-8 Schematic diagram showing absorption and transport of vitamin B_{12}.

Absorption of Vitamin B_{12} involves the following steps (Fig. 7.7-8).

- ***In the stomach,*** vitamin B_{12} is exposed to specific binding protein R and vitamin B_{12} binding protein called intrinsic factor (IF). As the affinity of R protein for vitamin B_{12} is much more than that of IF, so most of the vitamin B_{12} gets bound to R protein in the stomach.
- ***In the lumen of intestine,*** the pancreatic proteases cleave vitamin B_{12} from the R protein. Then, the vitamin B_{12} binds to IF to form a complex (IF–B_{12}).
- ***On the brush border of enterocyte,*** IF–B_{12} complex gets bound to the specific receptors. Following this, the vitamin B_{12} is transported into the cytosol of enterocyte by endocytosis, leaving behind IF at the brush border. It is important to note that absorption of vitamin B_{12} from the IF–B_{12} complex can occur only after the complex binds to the receptors. In the absence of intrinsic factor, vitamin B_{12} absorption is markedly decreased and patient may develop pernicious anaemia (see page 73).
- ***From the basolateral border of enterocyte,*** vitamin B_{12} enters the portal circulation after binding with plasma globulin called transcobalamine-II.
- ***In the liver,*** vitamin B_{12} is stored in large amounts after binding with another globulin called *transcobalamin-1*. The storage of water-soluble vitamin is unique to vitamin B_{12}. Liver may store up to 3 years of supply. Vitamin B_{12} is also stored in muscles for some extent. Whenever required, it is transported from the liver to the bone marrow.

SELF-ASSESSMENT

1. Discuss briefly:
   - Mechanism of digestion and absorption of carbohydrates
   - Mechanism of digestion and absorption of proteins
   - Mechanism of digestion and absorption of fats
2. Write notes on:
   - Pancreatic enzymes
   - Absorption of fat soluble vitamins
   - Iron absorption
   - Regulation of calcium absorption

SECTION 8

Endocrine System

SECTION OUTLINE

8.1 General Principles of Endocrine System
8.2 Endocrinal Functions of Hypothalamus and Pituitary Gland
8.3 Thyroid Gland
8.4 Endocrinal Control of Calcium Metabolism and Bone Physiology
8.5 Adrenal Glands
8.6 Pancreatic Hormones
8.7 Endocrinal Functions of Other Organs and Local Hormones

The biological functions of the multicellular living organisms are very well coordinated. This coordination is achieved by two main control systems: nervous system and endocrine system.

Nervous system is principally related to functions of the body in external and internal environments. The nervous system coordinates the body functions through transmission of impulses via nerve fibres.

Endocrine system is mainly concerned with different metabolic functions of the body, especially the chemical reactions and transport of various substances. The endocrinal functions are accomplished through a wide range of chemical messengers, the hormones.

The nervous system and the endocrine system often respond together to incoming stimuli so as to integrate the organism's response to changes in its external and internal environments.

Organization of Endocrine System

The endocrinal system consists of various endocrine glands and neurosecretory cells located in the hypothalamus. The various endocrine glands present in the body are as follows:

1. *Pituitary gland (hypophysis):* Pituitary gland is also known as hypophysis, which in Greek means undergrowth of the brain. It has two main parts: adenohypophysis and neurohypophysis. *Adenohypophysis* secretes growth hormone (GH) or somatotropins, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyrotropin or

thyroid-stimulating hormone (TSH) and corticotropin or adrenocorticotropic hormone (ACTH). The *neurohypophysis* stores the antidiuretic hormone (ADH) or vasopressin and oxytocin synthesized by the hypothalamus.

2. ***Thyroid gland:*** The thyroid gland is present in the neck in front of the trachea. It secretes thyroxine (T_4) and triiodothyronine (T_3). The C-cells or parafollicular cells secrete calcitonin.
3. ***Parathyroid glands:*** These are four in number, very small glands situated behind the lobes of the thyroid gland and secrete parathormone.
4. ***Adrenal glands:*** These are situated on the upper poles of the two kidneys, hence also called suprarenal glands. The outer cortex region of the adrenal glands secretes cortisol, aldosterone and sex steroids, and the inner medullary region secretes catecholamines (adrenaline and noradrenaline).
5. ***Pancreatic islets (islets of Langerhans):*** These are small groups of cells, which secrete insulin, glucagon and somatostatin.
6. ***Gonads:*** These include ovaries in females and testes in males. The ovaries secrete, oestrogens and progesterone (female sex steroids), and testes secrete male sex hormone (testosterone).
7. ***Pineal gland:*** It is a small gland present in the roof of the third ventricle in the brain. It secretes melatonin and other biogenic amines.
8. ***Placenta:*** During pregnancy, placenta secretes various hormones like human chorionic gonadotropin (HCG), oestrogen, progesterone, somatotropins and relaxin.
9. ***Gastrointestinal mucosa*** also secretes various hormones collectively known as gastrointestinal (GI) hormones, e.g. gastrin, secretin, cholecystokinin–pancreozymin (CCK-PZ), etc.
10. ***Kidneys:*** In addition to their renal functions, the kidneys secrete erythropoietin, prostaglandins and 1,25-dihydroxycholecalciferol, and also help in the activation of angiotensin production.
11. ***Atrial muscle cells:*** These secrete atrial natriuretic peptides (ANP) and many other peptides.
12. ***Skin:*** This is also considered to act as an endocrine structure by producing vitamin D, which is now considered to be a hormone.

8.1 General Principles of Endocrine System

CHAPTER OUTLINE

Hormones: Definition and Classification
Definition
Classification

Hormones: General Considerations
Hormone Transport, Plasma Concentration and Half-life
Functions of Hormones
Hormone Disposal
Regulation of Hormone Secretion

Hormone: Receptors and Mechanism of Action
Hormone Receptors
Mechanism of Action of Hormones
Action through Change in Membrane Permeability
Action through Effect on Gene Expression
Action through Second Messengers
Action Via Tyrosine Kinase Activation

Measurement of Hormones
Bioassay
Immunoassay
Cytochemical Assay
Dynamic Tests

HORMONES: DEFINITION AND CLASSIFICATION

Definition

The word hormone is derived from the Greek word *hormaein*, which means to execute or to arouse. In the classic definition, hormones are secretory products of the ductless glands, which are released in catalytic amounts into the blood stream and transported to specific target cells (or organs), where they elicit physiologic, morphologic and biochemical responses.

Classification of Hormones

A. Depending on the Chemical Nature

1. ***Amines or amino acid derivatives***
   - Catecholamines (epinephrine and norepinephrine)
   - Thyroxine (T_4) and triiodothyronine (T_3)
2. ***Proteins and polypeptides***
   - Posterior pituitary hormones (antidiuretic hormone and oxytocin)
   - Insulin
   - Glucagon
   - Parathormone
   - Other anterior pituitary hormones
3. ***Steroid hormones***
   - Glucocorticoids
   - Mineralocorticoids
   - Sex steroids
   - Vitamin D

B. Depending on the Mechanism of Action

1. ***Group I hormones:*** These act by binding to intracellular receptor and mediate their actions via the formation of a hormone–receptor complex. These include steroid, retinoid and thyroid hormones.
2. ***Group II hormones:*** These involve a second messenger to mediate their effect. Depending on the chemical nature of the second messengers, group II hormones are further divided into four subgroups: A, B, C and D (Table 8.1-1).

HORMONES: GENERAL CONSIDERATIONS

Hormone Transport, Plasma Concentration and Half-life

Hormone Transport After secretion into the blood stream, the hormones may circulate in the following two forms:

Unbound Form Some hormones circulate as free molecules, e.g. catecholamines, and most peptide and protein hormones circulate unbound.

TABLE 8.1-1 Types of Group II Hormones Based on the Chemical Nature of Second Messenger Involved in Their Mechanism of Action

Group	Second Messenger	Hormones
Group II-A	Cyclic AMP (cAMP)	Adrenocorticotropic hormone (ACTH) Antidiuretic hormone (ADH) Angiotensin II Calcitonin Corticotropic hormones (CRH) Catecholamine (α_2 adrenergic) Follicular-stimulating hormone (FSH) Glucagon Luteinizing hormone (LH) Parathormone (PTH) Somatostatin Thyroid-stimulating hormone (TSH)
Group II-B	Cyclic GMP (cGMP)	Atrial natriuretic factor (ANF) and nitric oxide
Group II-C	Calcium/or phosphatidyl inositol/or both	Acetylcholine (ACh), catecholamines (α_1 adrenergic), gastrin, oxytocin, thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), platelet-derived growth factor (PDGF) and substances.
Group II-D	Kinase or phosphatase cascade	Human chorionic somatotropin (HCS), erythropoietin, growth hormone, insulin and insulin-like growth factors (IGF-I and IGF-II), nerve growth factor (NGF), prolactin and other growth factors

Bound Form Some hormones, such as steroids, thyroid hormones and vitamin D, circulate bound to specific globulins that are synthesized in the liver. The binding of hormones to proteins is advantageous on account of the following:

- Protects the hormone against clearance by the kidney
- Slows down the rate of degradation by the liver
- Provides circulating reserve of the hormone

Plasma Concentration Hormones are usually secreted into the circulation in extremely low concentrations as follows:

- *Peptide hormone concentration is between* 10^{-12} and 10^{-10} mol/L.
- *Epinephrine and norepinephrine concentrations are* 2×10^{-10} and 13×10^{-10} mol/L, respectively.
- *Steroid and thyroid hormone concentrations are* 10^{-9} and 10^{-6} mol/L, respectively.

Half-life Most hormones are metabolized rapidly after secretion. The following are the main characteristics:

- Peptide hormones have a short half-life.
- Steroids and thyroid hormones have a significantly longer half-life because they are bound to the plasma proteins. Table 8.1-2 depicts the half-life of some of the hormones.

Functions of Hormones

Hormones regulate existing fundamental processes but do not initiate reactions de novo.

1. Regulation of Biochemical Reactions Hormones regulate the metabolic functions in a variety of ways:

- They stimulate or inhibit the rate and magnitude of biochemical reactions by controlling enzymes, thereby causing morphologic, biochemical and functional changes in target tissues.
- They modulate energy-producing processes and regulate the circulating levels of energy-yielding substances (e.g. glucose, fatty acids). However, they are not used as energy sources in biochemical reactions.

2. Regulation of Bodily Processes Hormones regulate different bodily processes, such as growth, maturation, differentiation, regeneration, reproduction and behaviour. Thus, the main function of the endocrine glands is to maintain homeostasis in an internal environment.

TABLE 8.1-2 Half-life of Some of the Important Hormones

Class of Hormone	Hormone	Half-life
Protein and peptide hormones	ADH	<1 min
	Oxytocin	<1 min
	Insulin	5 min
	Prolactin	12 s
	Growth hormone	<30 min
	ACTH	15–25 s
	LH	15–45 min
	FSH	180 min
Amines	Epinephrine	10 s
	Norepinephrine	15 s
	Thyroxine (T_4)	5–7 days
	Triiodothyronine (T_3)	1–3 days
Steroid hormones	Aldosterone	30 min
	Cortisol	90–100 min
	1,25-Dihydroxycholecalciferol	15 h
	25-Hydroxycholecalciferol	15 days

Hormone Disposal

Mechanisms of Hormone Disposal The circulating hormones are disposed of by the following mechanisms:

- Target cell uptake and intracellular degradation
- Metabolic degradation/inactivation
- Urinary or biliary secretion

Regulation of Hormone Secretion

The quantity of hormones secreted is regulated in accordance with their requirement. General mechanisms that govern the secretion of hormone include the following:

- Feedback control
- Neural control
- Chronotropic control

1. Feedback Control Feedback control is of two types:

- Negative feedback control
- Positive feedback control

Negative Feedback Control Generally, the influence of blood concentration of the hormone concerned or its effect is to inhibit further secretion of the hormone and is called negative feedback control (Fig. 8.1-1A).

Positive Feedback Control It is less common and acts to amplify the initial biological effects of the hormone (Fig. 8.1-1B).

Depending on the product involved, the feedback mechanism may be:

- Hormone–hormone feedback
- Substrate–hormone feedback

(i) Hormone–Hormone Feedback Control The best example of hormone–hormone negative feedback control is the regulation of hormone secretions by the hypothalamus and pituitary, which involves the following three loops (Fig. 8.1-2):

- ***Long-loop feedback*** (Fig. 8.1-2A): The peripheral gland hormone (e.g. thyroid, adrenocortical and gonads) can exert

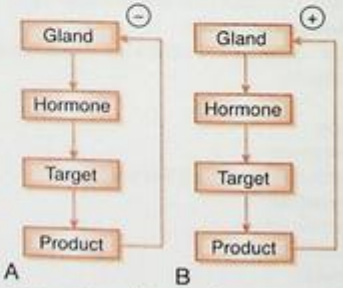


Figure 8.1-1 Hormonal regulation by feedback control mechanisms: (A) negative feedback and (B) positive feedback.

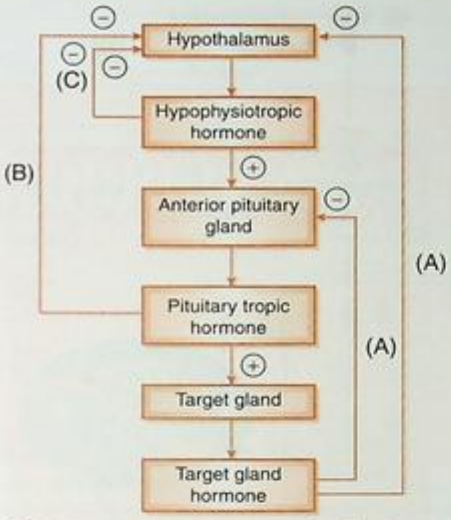


Figure 8.1-2 Hormone–hormone negative feedback control by the hypothalamus and pituitary: (A) long-loop feedback; (B) short-loop feedback; and (C) ultra-short-loop feedback.

long-loop negative feedback control on both the hypothalamus and the anterior lobe of pituitary.

- ***Short-loop feedback*** (Fig. 8.1-2B): The pituitary tropic hormones decrease the secretion of hypophysiotropic hormone e.g. growth hormone releasing hormone (GHRH, growth hormone release inhibiting hormone (GRIH), thyrotropin-releasing hormone [TRH], gonadotropin-releasing hormone [GnRH]) by short-loop feedback.
- ***Ultra-short-loop feedback*** (Fig. 8.1-2C): The hypophysiotropic hormones may inhibit their own synthesis and secretion via an ultra-short-loop feedback mechanism.

(ii) Substrate–Hormone Feedback Control The best example of substrate–hormone feedback control is regulation of insulin secretion from the pancreatic β-cells of the islets of Langerhans and glucagon secretion from the α-cells by blood glucose levels. A rise in blood glucose level promotes the secretion of insulin, whereas a fall in blood glucose promotes secretion of glucagon. These responses keep the blood glucose level within narrow limits in spite of variation in carbohydrate intake in diet.

2. Neural Control Neural control acts to evoke or suppress hormone secretion in response to both external and internal stimuli.

External stimuli, which can modulate hormone release through neural mechanisms, may be visual, auditory, olfactory, gustatory and tactile.

Internal stimuli, which influence hormonal release through neural mechanisms, include pain, emotion, sexual excitement, fright, stress and changes in blood volume.

Examples of neural control of hormones are as follows:

- *Release of oxytocin*, which fills the milk ducts in response to the stimulus of suckling
- *Release of aldosterone*, which augments the circulatory volume in response to upright posture
- *Release of melatonin* in response to darkness

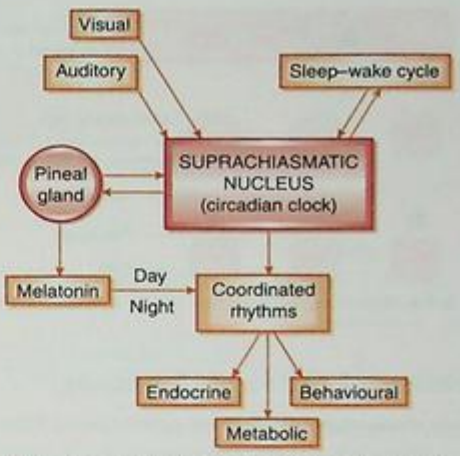


Figure 8.1-3 The origin of circadian rhythms in endocrine gland secretion, metabolic processes and behavioural activity.

3. Chronotropic Control Chronotropic control of hormone secretion accounts for the following:

- Oscillating and pulsatile release of certain hormones
- Diurnal variation in hormonal levels
- Menstrual rhythm
- Seasonal rhythm
- Developmental rhythm

The source of regular oscillatory cycles is a pulse generator(s) located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Fig. 8.1-3).

The intrinsic circadian clock is also located in the SCN, which is responsible for endocrinal, metabolic and behavioural coordinated rhythms.

HORMONE: RECEPTORS AND MECHANISM OF ACTION

Hormone Receptors

All hormones act through specific receptors. Almost all hormone receptors are large proteins present in hormone-sensitive target cells.

Characteristics of Hormone Receptors

Receptor Specificity There are specific receptors for each hormone. This is the reason that all hormones circulate to all parts of the body, yet each hormone has a specific target tissue for its action (Fig. 8.1-4).

Change in Receptor Number The number of receptors of a cell varies depending on the situation. It is regulated by two mechanisms: downregulation and upregulation.

(i) ***Downregulation*** refers to a decrease in the number of active receptors. It happens to regulate the hormone sensitivity when it is present in excess.

(ii) ***Upregulation refers*** to an increase in the number of active receptors on a cell. It happens to regulate the hormone action when its concentration is less. This phenomenon tends to reduce the effect of hormone deficiency.

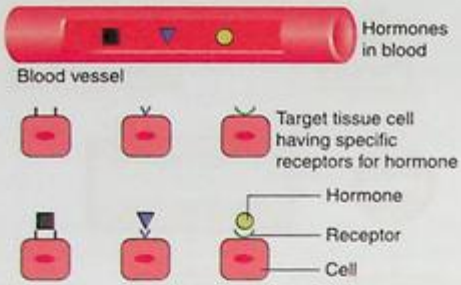


Figure 8.1-4 Specificity of hormone action is because of specific receptors.

Mechanism of Action of Hormones

The main mechanisms of hormone actions are as follows:

- Action through change in the membrane permeability
- Action through effect on gene expression by binding of hormones with intracellular receptors
- Action through secondary messengers, which activate intracellular enzymes when hormones combine with membrane receptors
- Action through tyrosine kinase activation

Action through Change in Membrane Permeability

Certain hormones bind with the receptors present in the cell membrane (external receptors) and cause conformational change in the protein of the receptors, resulting in either opening or closing of the ions channels (such as Na^+ channels, K^+ channels and Ca^{2+} channels). The movement of ions through Ca^{2+} channels causes the subsequent effect, e.g. adrenaline, noradrenaline act by this mechanism.

Action through Effect on Gene Expression by Binding of Hormones with Intracellular Receptors

Group I hormones act by their effect on the gene expression, which include steroid hormones, retinoids and thyroid hormones. These hormones are lipophilic in nature and can easily pass across the cell membrane. They act through intracellular receptors located either in the cytosol or in the nucleus. The sequence of events involved is shown in Fig. 8.1-5: These events include the following:

1. *Transport*: After secretion, the hormone is carried to the target tissue on serum-binding protein.
2. *Internalization*: Being lipophilic, the hormone easily diffuses through the plasma membrane.
3. *Receptor–hormone complex* is formed by binding of a hormone to the specific receptor inside the cell.
4. *Conformational change* occurs in the receptor proteins, leading to activation of receptors.
5. The activated receptor–hormone complex then diffuses into the nucleus and binds on the specific region of the DNA known as the hormone responsive element (HRE), which initiates gene transcription.
6. *Binding of the receptor–hormone complex to DNA* alters the rate of transcription of messenger RNA (mRNA).
7. *The mRNA diffuses in the cytoplasm*, where it promotes the translation process at the ribosomes. In this way, new proteins are formed, which result in specific responses. Some of the new proteins synthesized are enzymes.

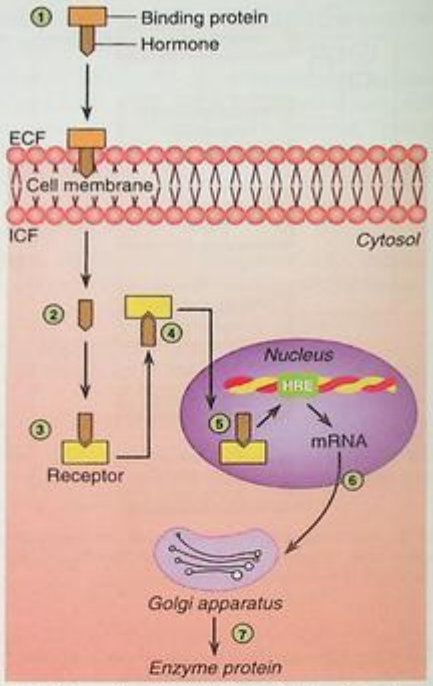


Figure 8.1-5 Action of hormones through their effect of gene expression. Note that (1)–(7) represent the steps involved in the process (for details, see text).

Note. The hormonal action mediated through intracellular receptors is comparatively slower. Therefore, glucocorticoids may take hours to few days to achieve the therapeutic effect.

Action through Second Messengers

Release of second messenger by Group II hormones (Table 8.1-1) is mediated by GTP-binding proteins also called G proteins.

Coupling by G Proteins Events involved in coupling by G protein, which lead to changes in the cellular concentration of the second messengers, are as follows (Fig. 8.1-6):

- Group II hormones are water soluble and bind to the plasma membrane of the target cell via cell surface receptors.
- The hormone-bearing receptor then interacts with a G protein and activates it by binding GTP. There are two classes of G proteins: stimulatory G protein (Gs) and inhibitory G protein (Gi).
- In its activated ('on') state, the G protein interacts with one or more of the effector proteins (most of which are enzymes or ion channels such as adenylyl cyclase; Ca^{2+} or K^+ channels or phospholipase C, A_2 or D) to activate or inhibit them.
- The changed effector molecules, in turn, generate second messenger that mediates the hormone's intracellular action.

Second Messenger Systems The second messenger systems that are activated through coupling of hormone–receptor complexes by G protein include the following:

- Adenylyl cyclase–cAMP system
- Guanyl cyclase–cGMP system
- Membrane phospholipase–phospholipid system
- Calcium–calmodulin system

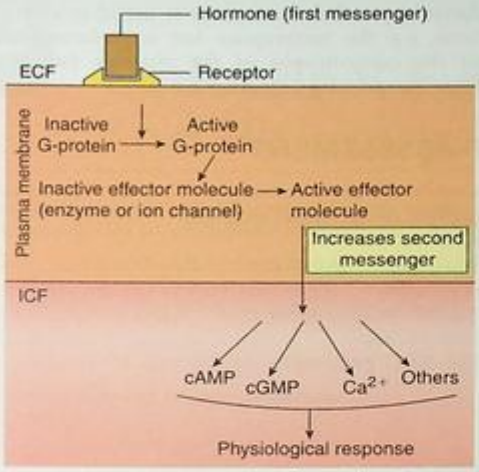


Figure 8.1-6 Schematic mechanism of coupling by G protein, leading to increase in second messenger, which mediates hormone's physiological response.

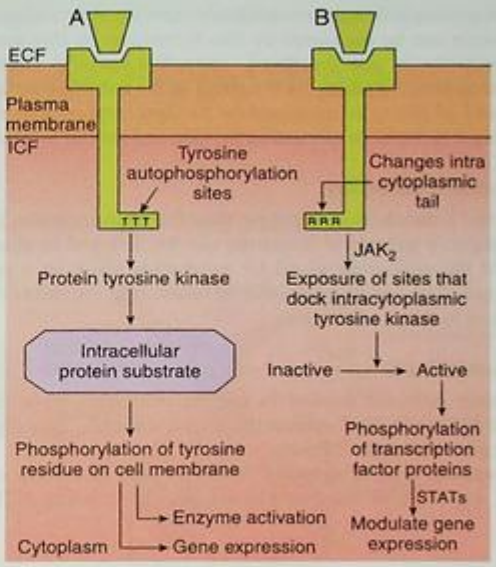


Figure 8.1-7 Mechanism of action of hormone via tyrosine kinase activity: (A) by receptors that possess intrinsic tyrosine activity and (B) by receptors that do not possess intrinsic tyrosine activity.

Mechanism of Action of Hormone via Tyrosine Kinase Activation

Group II D hormones act by activating the tyrosine kinase system (Table 8.1-1).

The activation of tyrosine kinase occurs by the following two mechanisms:

1. ***Hormone receptors possessing intrinsic tyrosine activity***, e.g. those for insulin and epidermal growth factor, involve the following steps (Fig. 8.1-7A):
   - Binding of hormone to the receptor changes its conformation and exposes sites on its intracellular portion that are capable of receptor autophosphorylation at specific tyrosine sites.
   - As a result, the receptor itself becomes a tyrosine kinase that phosphorylates tyrosine residue on the intracellular protein substrates.
   - This latter activity sets into motion a cascade of events leading to enzyme activation and gene transcription.
2. ***Hormone receptors that do not possess intrinsic tyrosine activity***, e.g. those for GH, prolactin-releasing hormones and cytokines, act as follows (Fig. 8.1.7B):
   - Hormone binding to the extracellular portion of the receptor changes its intracytoplasmic tail.
   - The changes produced in the intracytoplasmic tail of receptor expose sites, which attract and dock the intracytoplasmic tyrosine kinases (such as Janus tyrosine kinases [JAK] and signal transducer and activator of transcription [STAT] kinases), and then activate them.
   - The activated intracytoplasmic tyrosine kinases phosphorylate cytoplasmic substrates, such as transcription factor proteins and ultimately modulate gene expression.

MEASUREMENT OF HORMONES

Measurement of the blood level of hormones is essential to confirm the endocrinal disorders associated with either deficiency or excess of a hormone. Hormones exist in the blood in a very low concentration, so the conventional methods of estimation such as colorimetry are not of much use. Therefore, they are measured by hormone assays and some special techniques, which include the following:

- Bioassay
- Immunoassay
- Cytochemical assay
- Dynamic tests

Bioassay

In this method, hormone levels were assessed by injecting the unknown sample of plasma in the experimental animals and observing quantitatively the specific biological effect. The effect chosen was a characteristic action of the hormone for which a clear dose–response relationship existed.

Immunoassay

The immunoassay methods, frequently employed for estimation of hormone levels, include the following:

- Radioimmunoassay (RIA)
- Enzyme-linked immunosorbent assay (ELISA)

1. Radioimmunoassay The radioimmunoassay is performed as follows:

- An unknown sample of plasma in which the concentration of a particular hormone (H) to be estimated is mixed with commercially available purified specific antibody (anti-H), and an appropriate amount of the purified hormone tagged with radioactive isotope (H^*). The mixture is incubated in the cold.
- The antibodies have high affinity for the hormone. There is a competition between the free hormone (H) present in the unknown sample of plasma and the tagged hormone (H^*) for binding to the specific antibody (anti-H).

2. Enzyme-linked Immunosorbent Assay Method The ELISA method is principally similar to RIA, i.e. it is also based

on the principle of antigen–antibody reaction. Any antigen that is protein can be measured by this technique. In this method, radioactivity is not measured, instead a specific antibody–hormone (antigen) complex is stained with a suitable dye, and the intensity of colour is measured by the spectrophotometer. This technique is useful in estimating peptide and steroid hormones.

Cytochemical Assay

This test is much more sensitive than the immunoassay. In this technique, a genesis of hormone can be detected in slices cut out of the endocrine gland by incubating them in a culture medium. This test is very useful in measuring the minute basal levels of hormone secretion.

Dynamic Tests

Dynamic tests are needed in certain situations when simple blood hormone level estimation is not enough. Two types of dynamic tests are as follows:

Suppression type of dynamic tests is useful in certain conditions, e.g. to know whether a lung cancer is secreting ACTH.

Stimulation type of dynamic tests is useful in certain other conditions, e.g. the metyrapone test is performed to know whether the corticotrophs of the pituitary (which secrete ACTH) are functioning normally or not.

SELF-ASSESSMENT

1. Discuss briefly the mechanisms of action of hormones.
2. Regulation of hormonal secretion
3. Write notes on:
   - Feedback control of hormonal secretion
   - G proteins
   - Adenyl cyclase system
   - Immunoassay
   - JAK-STAT pathway

8.2 Endocrinal Functions of Hypothalamus and Pituitary Gland

CHAPTER OUTLINE

Introduction and Functional Anatomy
Functional Anatomy of Pituitary Gland
Histological Structure of Pituitary Gland
Blood Supply of Pituitary Gland
Hypothalamic–Pituitary Relationship

Endocrinal Aspects of Hypothalamus
Functional Anatomy
Endocrinal Functions of Hypothalamus

Anterior Pituitary Hormones
Growth Hormone
Structure and Synthesis
Plasma Levels, Binding and Metabolism
Regulation of GH Secretion
Actions of GH
Human Prolactin
Structure, Secretion and Plasma Concentration
Control of Prolactin Secretion
Physiological Effects of Prolactin
Applied Aspects: Abnormalities of Anterior Pituitary Hormones
Hypopituitarism
Abnormalities of Growth Hormone Secretion

Posterior Pituitary Hormones
Antidiuretic Hormone
Structure, Synthesis, Storage, Release, Transport and Metabolism
Actions of ADH
Vasopressin receptors
Regulation of ADH Secretion
Abnormalities of ADH Secretion
Oxytocin
Structure, Synthesis, Storage and Release of Oxytocin
Actions of Oxytocin
Control of Oxytocin Secretion

INTRODUCTION AND FUNCTIONAL ANATOMY

The hypothalamic–pituitary unit forms a unique component of the entire endocrine system that regulates growth, lactation, fluid homeostasis and the functions of thyroid gland, adrenal glands and gonads.

Functional Anatomy of Pituitary Gland

Pituitary gland, also called hypophysis cerebri, is a small gland, weighs about 0.5 g and is approximately 1 cm in diameter. It is situated in the hypophyseal fossa (sella turcica) of the sphenoid bone.

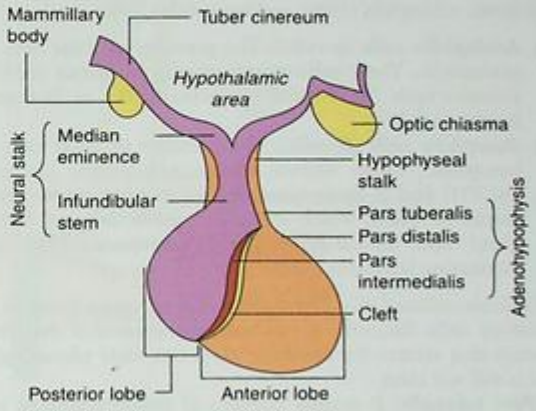


Figure 8.2-1 Anatomical subdivisions of the pituitary gland.

Physiologically, the pituitary gland consists of the following three distinct parts or lobes (Fig. 8.2-1):

- Anterior lobe or adenohypophysis
- Posterior lobe or neurohypophysis
- Intermediate lobe or pars intermedia

Parts of Pituitary Gland

Adenohypophysis The glandular anterior lobe of the pituitary gland is called adenohypophysis. It constitutes about 80% of the pituitary gland. It can be further divided into the following three parts (Fig. 8.2-1):

- *Pars distalis*
- *Pars intermedia*
- *Pars tuberalis*

Neurohypophysis The posterior lobe of the pituitary is a neural structure and hence called neurohypophysis. It consists of the following three parts (Fig. 8.2-1):

- *Pars posterior*: It is also called the infundibular process and forms the main bulk of neurohypophysis.
- *Infundibular stem*: It is the funnel-shaped extension arising from the median eminence at the floor of the third ventricle.
- *Median eminence*: It is a small protrusion from the base of hypothalamus (tuber cinereum). It is situated just beneath the third ventricle and is highly vascular.

Intermediate Lobe of Pituitary Gland is rudimentary in humans as well as in a few other mammalian species. In certain lower animals, this lobe secretes melanocyte-stimulating hormone (MSH) in response to changes in exposure to light and other environmental factors.

Histological Structure of Pituitary Gland

Adenohypophysis Pars distalis consists of cords of cells separated by fenestrated sinusoids. The cells can be divided into two main types: chromophobes and chromophils.

1. Chromophobes These are agranular cells, and it is considered that the chromophils are derived from the chromophobes.
2. Chromophils These are granular cells, constituting 50% of the cells of anterior pituitary. Chromophils are further classified as follows: acidophils (35%) and basophils (15%).

(i) ***Acidophilic cells (α-cells)***: The granules of these cells are acidophilic. These cells secrete growth hormone (GH) or somatotropin (STH), and prolactin (PRL) or lactogenic hormone (LTH).

(ii) ***Basophilic cells (β-cells)***: The granules of these cells are basophilic. These secrete adrenocorticotropic hormone (ACTH) and β-lipotropins, thyrotropic hormone (thyrotropin or TSH), which stimulates the activity of thyroid gland and follicular-stimulating hormone (FSH) and luteinizing hormone (LH).

3. Folliculostellate Cells These cells send processes between the secretory cells. Recently, it has been demonstrated that these contain and secrete the cytokine IL-6, but their physiological role is still not clear.

Pars tuberalis: It mainly consists of undifferentiated cells with a few acidophils and basophils.

Pars intermedia: It contains β-cells, a few secretory cells and chromophobe cells.

Neurohypophysis Histologically, posterior pituitary contains the following structures:

1. Unmyelinated Nerve Fibres These are the axons of the neurons located in the supraoptic and paraventricular nuclei of the hypothalamus. These carry a precursor of posterior pituitary hormones and end as close terminals near the blood capillaries (Fig. 8.2-2).

2. Pituicytes are a special type of supporting cells having long dendritic processes. These are present in between the axons.

3. Glial Cells like astrocytes and oligodendrocytes are also seen.

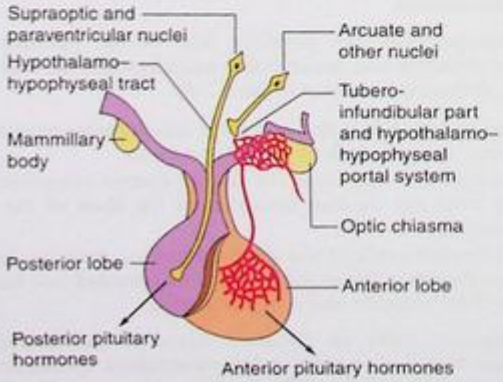


Figure 8.2-2 Anatomical and functional relationship between the hypothalamus and pituitary gland through the hypothalamo–hypophyseal tract and hypothalamo–hypophyseal portal system.

Blood Supply of Pituitary Gland

Arterial Supply The arterial blood to the pituitary gland is supplied by the branches of the following:

- Internal carotid arteries (superior and inferior hypophyseal branches)
- Anterior cerebral artery
- Posterior cerebral artery

Hypothalamo–Hypophyseal Portal System (Figs 8.2-2 and 8.2-3)

- The branches from superior hypophyseal artery form a ring around the upper part of the pituitary stalk and are further branched to form a *capillary network.*
- The blood from this capillary network is drained by *long portal veins* in the infundibulum.
- Then, in the anterior lobe, these long portal veins break up into another set of capillary networks and represented as *sinusoids of pars anterior.* This arrangement is called the *hypothalamo–hypophyseal portal system.*
- The inferior hypophyseal (branch of internal carotid artery) branches to form a capillary network at the lower end of the infundibulum stem.
- The short portal vessels arise from this capillary network and supply blood mainly to the posterior pituitary and some part of the anterior pituitary.
- The short portal vessels provide a link between the anterior and the posterior pituitary.

Venous Drainage The blood from the anterior pituitary is drained to the cavernous sinus and then into the jugular vein.

Note. The anterior pituitary lies outside the blood–brain barrier; hence, it is accessible to influences from general circulation (hormones and neurotransmitter by the brain and hormones secreted in the general circulation).

Hypothalamic–Pituitary Relationship

The influences from the hypothalamus are conveyed to the pituitary gland by the following two different tracts:

1. Hypothalamo–hypophyseal Tract It is composed of axons of the large neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus. These fibres pass to neurohypophysis through the infundibular stem and form a series of dilated terminals known as *Herring bodies* (Fig. 8.2-2). The neurosecretory cells of supraoptic and paraventricular nuclei secrete peptide hormones (vasopressin and oxytocin [OTC]), which travel down their axons in the neurosecretory granules to be stored in the nerve terminals lying in the neurohypophysis. Upon stimulation of the cell bodies, the granules are released from the axonal terminals by exocytosis.

2. Tubero-infundibular Tract and Hypothalamo–hypophyseal Portal System The cell bodies of hypothalamic neurons synthesize certain releasing and inhibiting hormones, which are conveyed by the tubero-infundibular tract to the median eminence region, where they are stored in the nerve terminals. After these hypothalamic neurons are stimulated by nerve impulses, the releasing or inhibiting hormones are discharged into the median eminence and enter the capillary plexus of the superior hypophyseal artery. From here they are transported down the portal vessels (long portal veins) and then exit from the secondary capillary plexus to reach the specific endocrine target cells in the adenohypophysis where they regulate the secretion of tropic hormones of anterior pituitary (Fig. 8.2-3).

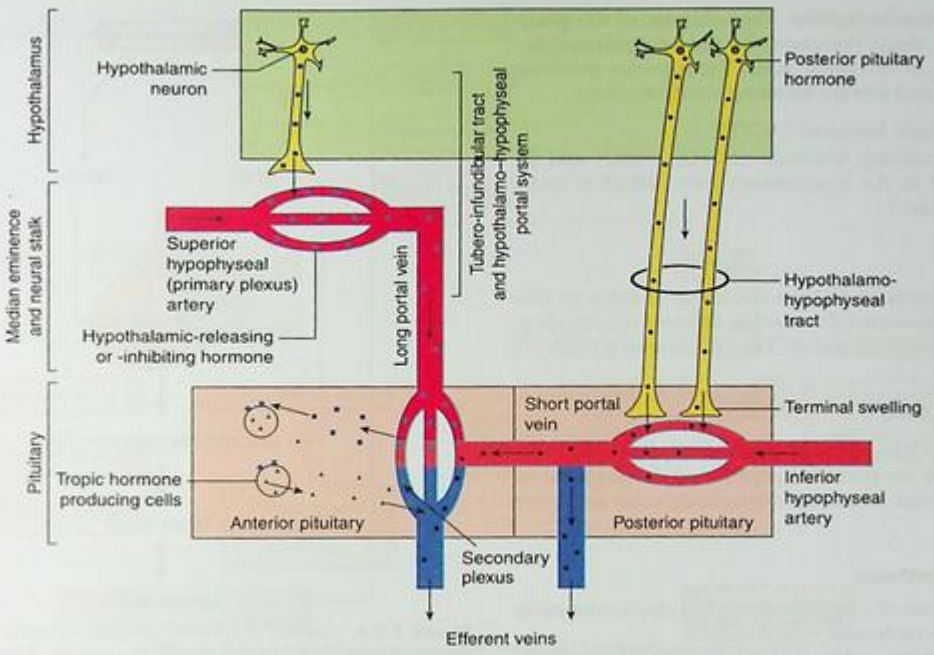


Figure 8.2-3 Schematic diagram to explain the anatomical and functional relationship between the hypothalamus and pituitary gland.

ENDOCRINAL ASPECTS OF HYPOTHALAMUS

Functional Anatomy

Hypothalamus is a specialized centre in the brain that functions as a master coordinator of hormonal action. It is a part of the brain situated below the thalamus and is very closely connected to the pituitary gland, as described above. Thus, hypothalamus provides an important link between the endocrine system and the nervous system. Before proceeding further, see *details of functional anatomy of hypothalamus* at page 396.

Endocrinal Functions of Hypothalamus

The hypothalamus performs its endocrinal functions through the neurosecretory cells, which are arranged in different nuclei of hypothalamus.

The main endocrinal functions of hypothalamus are as follows:

- Control of anterior pituitary function
- Control of posterior pituitary function

1. Control of Anterior Pituitary Function Hypothalamus controls the functioning of anterior pituitary through various hypothalamic–hypophysiotropic hormones, inhibiting hormones, which are released in response to neural stimuli.

Various Hypothalamic-releasing and -Inhibiting Hormones include:

- Growth hormone–releasing hormone (GHRH)
- Growth hormone–inhibiting hormone (GRIH), also called somatostatin
- Corticotropin-releasing hormone (CRH)
- Thyrotropin-releasing hormone (TRH)
- Gonadotropin-releasing hormone (GnRH)
- Prolactin-releasing hormone (PRH)
- Prolactin-inhibiting hormone (PIH)

2. Control of Posterior Pituitary Function The large (magnocellular) neurosecretory cells forming the supraoptic and the paraventricular nuclei of the hypothalamus are responsible for synthesis of the two posterior pituitary peptide hormones; oxytocin (OTC) and antidiuretic hormone (ADH). These hormones reach the posterior pituitary through a hypothalamic–hypophyseal tract, as described above (Figs 8.2-2 and 8.2-3).

ANTERIOR PITUITARY HORMONES

Anterior pituitary is truly the master endocrine organ. The hormones of adenohypophysis are broadly classified into the following three categories:

- Growth hormones (GH) (Prolactin group)
- Glycoprotein hormones
- Pro-opiomelanocortin (POMC) peptides

I. Hormones of Growth Hormone Family GH and PRL are secreted from the anterior pituitary, and human chorionic somatomammotropin (HCS) belonging to this family is secreted from placenta.

II. Glycoprotein Hormone Family The hormones of glycoprotein family secreted by the anterior pituitary include the following:

- Thyroid-stimulating hormone (TSH)
- Luteinizing hormone (LH)
- Follicular-stimulating hormone (FSH)

III. Pro-opiomelanocortin Peptides The hormones of this group are derived from a single precursor, the pro-opiomelanocortin (POMC), consisting of 241 amino acids. The precursor molecule (POMC) is then cleaved into the following three fragments:

- Adrenocorticotropic hormone (ACTH)
- Melanocyte stimulating hormone (MSH), α-MSH and β-MSH, produced in the intermediary lobe (which is rudimentary in humans)
- β-lipotropin
- β-endorphin

Physiological aspects of GH are discussed in detail in this chapter. Other hormones are discussed in different chapters (e.g. TSH with thyroid hormone and ACTH with adrenal gland).

Growth Hormone

Growth hormone (GH), also called *somatotropin*, is the most important hormone for postnatal growth and development to adult size. It also helps to maintain lean body mass and bone mass in adults.

Structure and Synthesis

Structure GH consists of a single unbranched chain containing 191 amino acids. Its molecular weight is 2000.
Synthesis GH is synthesized by acidophilic cells *called somatotrophs* of anterior pituitary.

Plasma Levels, Binding and Metabolism

Plasma Levels

Basal plasma GH level varies from 2 to 4 ng/mL. After every 1- to 2-hour interval, there is a rise in plasma GH level, i.e. GH is released in 10–20 pulses per day. This pulsatility arises from some combination of the pulsatile release of GHRH and of GRIH into the portal blood.

Diurnal variation in plasma levels of GH is noted. The nocturnal peak occurs 1–2 hours after deep sleep. These secretory bursts are greater in children and decrease with age.

Variation in plasma GH levels with age is as indicated below:

- *From birth to early childhood*, plasma GH levels increase progressively.
- *Children versus adults*: In general, children have only slightly higher plasma GH levels than adults.
- *Puberty* is associated with a peak period of plasma GH levels (5–8 ng/mL).
- *Senescence* is associated with a reduction in GH secretion in response to GHRH and other stimuli.

Circulation, Half-life and Metabolism

Circulation Circulating GH is bound to a plasma protein (GH binding protein).
Half-life of circulating GH in humans is 6–20 minutes, and the daily GH output has been calculated to be 0.2–1.0 mg/day in adult.
Metabolism GH is rapidly metabolized, probably at least in part in the liver. Metabolic clearance daily urinary GH excretion correlates well with the integrated 24 hours plasma GH profile.

Regulation of GH Secretion

1. Hypothalamic Control Hypothalamus controls GH secretion by releasing two hormones: growth hormone–releasing hormone and growth hormone release–inhibiting hormone (Fig. 8.2-4).

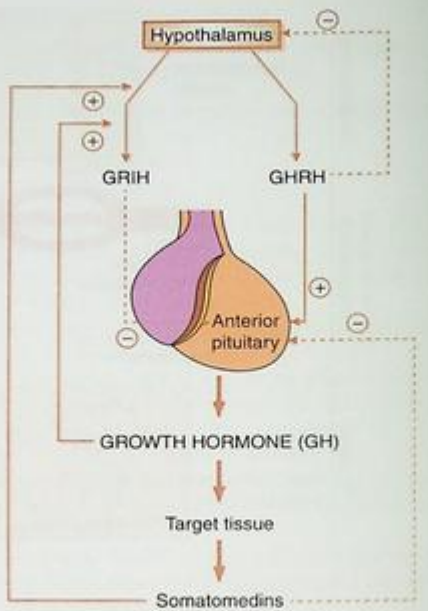


Figure 8.2-4 Control of growth hormone secretion. GHRH, growth hormone–releasing hormone; GRIH, growth hormone release–inhibiting hormone.

Growth Hormone–releasing Hormone (GHRH) It is a polypeptide with 44 amino acids. It stimulates the secretion of GH from the anterior pituitary.
Ghrelin: The main site of synthesis of ghrelin is stomach, but a small amount is also synthesized by hypothalamus. It increases GH secretion in response to various synthetic hexapeptides called growth hormone secretagogues (GHSs).
Growth Hormone Release–inhibiting Hormone (GRIH), also called somatostatin, is a polypeptide with 14 amino acids. It inhibits the release of GH from the anterior pituitary.

2. Negative Feedback Control of GH Secretion The negative feedback control mechanism for GH involves the role of somatomedins: GH and GHRH (Fig. 8.2-4).
(i) Negative Feedback Control by Somatomedins Somatomedins are insulin-like growth factors (IGFs) that are produced when GH acts on the target tissues. Somatomedins inhibit the secretion of GH directly or by stimulating the secretion of somatostatin from the hypothalamus.
(ii) Negative Feedback Control by GH GH also inhibits its own secretion by stimulating the secretion of somatostatin from the hypothalamus.
(iii) Negative Feedback Control by GRIH GRIH inhibits its own secretion from the hypothalamus. This mechanism is called an *ultrashort feedback loop.*

Actions of Growth Hormone

GH promotes growth and also influences the normal metabolism; therefore, besides acting on one specific organ, its actions are generalized (Fig. 8.2-5).

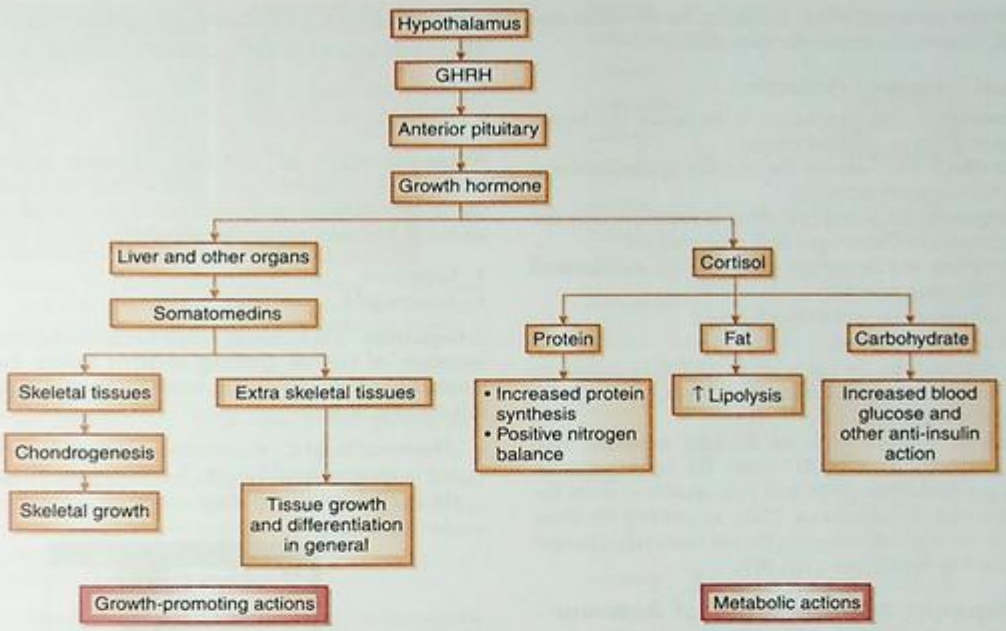


Figure 8.2-5 Growth-promoting and metabolic actions of growth hormone.

1. Growth Promoting Actions of GH GH promotes linear growth of an individual by its effects on the bone, cartilage and other connective tissues.

(i) Effects on Cartilage GH stimulates the proliferation of chondrocytes (cartilage cells) present in the epiphyseal end plates of long bones.

(ii) Effects on Bone GH stimulates the osteoblastic activity, which converts cartilage into bone. This process continues up to adolescence till there is fusion of the epiphyseal end plate with shaft of the bone. The bone mass also increases during this period.

2. Metabolic Actions of GH

(i) Effects on Protein Metabolism GH has an anabolic effect on the protein metabolism. It promotes the protein deposition in the tissues by the following effects:

- Increases the rate of amino acid uptake into the cells
- Increases protein synthesis in the ribosomes
- Stimulates transcription (RNA synthesis from DNA)

The overall effect of GH on the protein metabolism is positive nitrogen balance that leads to an increase in the body weight. In addition, GH also decreases protein breakdown as well as the rate of amino acid degradation for energy purposes.

(ii) Effects on Fat Metabolism GH promotes lipolysis in adipose tissue (catabolic effect) and then increases fat utilization for energy.

(iii) Effects on Carbohydrate Metabolism GH is antagonistic to insulin and produces hyperglycaemia by the following effects on the carbohydrate metabolism:

- It increases gluconeogenesis, i.e. increases hepatic glucose output.
- It decreases the uptake as well as utilization of glucose by the tissues for energy production.
- It inhibits glycolysis and thus glycogen stores tend to increase. This occurs as a consequence of increased mobilization and use of FFA for energy production.

(iv) Effects on Mineral Metabolism GH promotes bone mineralization in growing children.

Human Prolactin

Structure, Secretion and Plasma Concentration

Structure and secretion: Human PRL is a single peptide chain, secreted by acidophilic cells of anterior pituitary gland.

Plasma concentration: The PRL secretion is pulsatile, and shows diurnal variations (secretion increases about one hour after the onset of sleep and continues throughout the sleep period). The normal levels in adults are as follows:

Females – 8 ng/mL
Males – 5 ng/mL

During pregnancy, PRL secretion starts rising from the eighth week onwards, and the peak value (200–400 ng/mL) is reached at term. The sources of PRL during pregnancy are placenta, amniotic fluid and maternal anterior pituitary gland. The PRL secretion during pregnancy and during lactation is affected by *oestrogen*.

Control of Prolactin Secretion

Hypothalamic control: Secretion of PRL from anterior pituitary is controlled by the hypothalamus. A prolactin inhibitory factor (PIF) formed in the arcuate nucleus of the hypothalamus is transported through hypothalamo–hypophyseal portal

system to anterior pituitary, where it checks the synthesis and release of PRL. Dopamine acts as the main PIF.

Physiological Effects of Prolactin

1. **Breast growth:** During pregnancy, it increases the breast growth, particularly of alveolar tissue.
2. **Lactogenic effect:** PRL acts on the alveolar epithelium and stimulates the secretory activity.
   During pregnancy, the lactogenic effect is suppressed by the high concentration of oestrogen and progesterone.
   After parturition, the lactogenic effect of PRL is enhanced because of following reasons:
   - The inhibitory factors are withdrawn.
   - OTC level is increased.

   Note. The women who do not wish to feed their babies or when the baby dies immediately after birth, oestrogen is administered to stop lactation.
3. **Suppression of ovarian cycle in nursing mothers:** PRL inhibits the secretion of GnRH from the hypothalamus. Therefore, gonadotropin (FSH and LH) secretion from the anterior pituitary also decreases. Thus, in nursing mothers, due to low levels of gonadotropins, the ovarian cyclic changes do not occur. For details, see page 369.

Applied Aspects: Abnormalities of Anterior Pituitary Hormones

The abnormalities related to pituitary hormones occur either due to excess or deficiency of the hormones secreted. The most common causes of pituitary hormone disturbances are pituitary tumours, which may cause symptoms of excess of one or more hormones and simultaneous deficiency of other hormones; hence, a mixed picture may evolve. The various hormones of pituitary, their site of action and disease produced by them are given in Table 8.2-1.

Pituitary disorders seen in clinical practice are as follows:

- Hypopituitarism
- Abnormalities of GH
- Cushing syndrome (see page 332)

Hypopituitarism

Hypopituitarism is a clinical condition of hyposecretion of one or more pituitary hormones. Hypopituitarism can be due to hypothalamic causes or pituitary causes. Anterior pituitary has a large reserve, so the endocrine abnormalities are produced only when a large part of pituitary is destroyed.

Abnormalities of Growth Hormone Secretion

The abnormalities of GH secretion include the following:

- Hypersecretion of GH
- Hyposecretion of GH

Hypersecretion of GH Hypersecretion of GH occurs in tumours of acidophilic cells (particularly of somatotrophs) of the anterior pituitary. Depending on the age of an individual, excess of GH may cause the following:

- Gigantism
- Acromegaly

1. Gigantism It is a clinical condition resulting from the hypersecretion of GH in growing children before the closure of epiphysis of long bones. The main features of gigantism are as follows (Fig. 8.2-6):

- ***Abnormal height,*** i.e. excessive growth of long bones, resulting in an abnormal height (7–8 feet) with a huge status, and the person becoming 'giant'

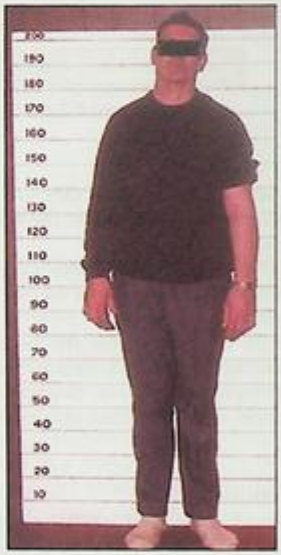


Figure 8.2-6 Photograph showing the tall stature in a patient with gigantism.

TABLE 8.2-1 Pituitary Hormones: Site of Action and Diseases Associated with their Deficiency and Excess

Hormone	Site of Action	DISEASES	
		Excess	Deficiency
Anterior pituitary			
Growth hormone (GH)	All somatic cells	Gigantism (in adolescents) Acromegaly (in adults)	Dwarfism Hypoadrenalism (rare)
Adrenocorticotropic hormone (ACTH)	Adrenal cortex	ACTH-dependent Cushing syndrome	Hypothyroidism
Thyroid-stimulating hormone (TSH)	Thyroid	Hyperthyroidism	–
Prolactin	Breast	Hyperprolactinaemia	Hypogonadism
Gonadotropins	Gonads	Hypergonadism	–
Melanocytic-stimulating hormone (MSH)	Skin	Hyperpigmentation	
Posterior pituitary			
Antidiuretic hormone	Kidneys	–	Diabetes insipidus

Figure 8.2-7 Clinical features of acromegaly: (A) note coarse facial features, broad thick nose, prognathism, prominent eyebrows and thickened skin and (B) large spade-like hand with short, thick wide fingers.

- *Large hands and feet*
- *Coarse facial features*, i.e. thick lips, macroglossia and thickness

2. Acromegaly It is a clinical condition that occurs due to excess of GH in adults (after epiphyseal closure of long bones has occurred) and causes excessive growth in those areas where cartilage persists.

Clinical features are (Fig. 8.2-7) as follows:

- *Acromegalic face* is characterized by thick lips, macroglossia, broad and thick nose, prominent eyebrows, thickened skin and coarse facial features.
- *Prognathism* is protrusion of the lower jaw due to elongation and widening of mandible associated with increased spacing of the teeth.
- *Acral part abnormalities* include large spade-like hands, thick wide fingers, and large feet with an increase in size of the shoes. Height is normal, and build is stout and stocky.
- *Kyphosis* may occur due to improper vertebral growth.
- *Excessive growth of internal organs*, i.e. cardiomegaly, hepatomegaly, splenomegaly and renomegaly, may be associated.
- *Increased sympathetic activity* may cause increased sweating and hypertension.

Hyposecretion of GH

Deficiency of GH in childhood leads to stunted growth or *dwarfism.*

Deficiency of GH in adulthood results in *mild anaemia*, which is refractory to usual treatment with haematinics like iron, with the following features:

- There is reduction in muscle mass.
- Hypoglycaemia may also occur.

Dwarfism Short stature or dwarfism may be due to endocrinal or nonendocrinal causes.

Endocrinal causes of dwarfism are as follows:

- GH deficiency (pituitary dwarf)
- Panhypopituitarism
- Hypothyroid dwarf (see page 318)
- Cushing syndrome (see page 332)

Nonendocrinal causes of dwarfism include the following:

- Familial dwarfism
- Achondroplasia
- Nutritional (malnutrition or malabsorption)
- Chromosomal abnormalities, e.g. Turner syndrome.

Figure 8.2-8 Clinical features of a pituitary dwarf.

Growth Hormone–Related Dwarfism

Pituitary Dwarfism occurs due to deficiency of GH in early childhood.

Characteristic features: Deficiency of GH causes retardation of growth in all parts of the body proportionately. Consequently, a pituitary dwarf with a chronological age of 20 years has the body structure like that of a normal child of 7–10 years of age. Thus, a pituitary dwarf has the following features (Fig. 8.2-8):

- Shortness of stature
- Normal mental activity
- Plumpness (fatness)
- Immature faces
- Delicate extremities
- Sexual immaturity when associated with the gonadotropin deficiency

POSTERIOR PITUITARY HORMONES

The two important hormones released from posterior pituitary are as follows:

- Antidiuretic hormone
- Oxytocin

Antidiuretic Hormone

ADH, as the name indicates, prevents diuresis and is chiefly concerned with the conservation of body water. It also causes vasoconstriction, so it is also called vasopressin or, more precisely, arginine vasopressin (AVP).

Structure, Synthesis, Storage, Release, Transport and Metabolism

Structure, synthesis, storage and release of ADH and OTC being similar are discussed together.

Structures ADH and OTC both are homologous neurohormones, polypeptide in nature, containing nine amino acids each, but the amino acids in positions 3 and 8 differ in the two hormones.

Synthesis ADH as well as OTC is synthesized in the cell bodies of magnocellular neurons of both paraventricular and supraoptic nuclei of the hypothalamus.

Storage The axons of ADH- and OTC-synthesizing neurons end in the posterior pituitary gland as terminal swelling. The secretory granules containing hormone precursors, known as Herring bodies, are transported down the axons by axoplasmic flow to the nerve endings in the posterior pituitary.

Secretion ADH and OTC are released when a nerve impulse is transmitted from the cell body in the hypothalamus down the axon, where it depolarizes the neurosecretory vesicles.

Transport The hormone and other secreted products separately enter the closely adjacent capillary. The hormone then reaches the target cells and also to the anterior pituitary by circulatory interconnections.

Biological half-life of ADH is 16–20 minutes after its release into the circulation.

Metabolism The circulating vasopressin is rapidly inactivated in the liver and kidney.

Actions of ADH

ADH acts through receptors.

Vasopressin Receptors The vasopressin receptors are G protein coupled receptors.

The following three types of vasopressin receptors have been recognized:

- V_1–A *receptors*: These are involved in the vasoconstrictor effect of ADH.
- V_1–B *receptors*: These are involved in the action of ADH on the anterior pituitary.
- V_2 *receptors*: These are involved in the action of ADH on kidney.

1. Action on Kidney The main role of ADH is regulation of water balance in the body by acting on the kidney, where it decreases the excretion of free water (i.e. antidiuretic and concentrating effect on kidney).

Site of Action The ADH-responsive cells line the distal convoluted tubules and collecting ducts of the renal nephron. ADH increases the permeability of these cells to water.

2. Vasoconstrictor Effect ADH in large doses causes vasoconstriction and leads to rise in blood pressure. Haemorrhage is a potent stimulus to ADH secretion, and it has been reported that ADH plays an important role in blood pressure homeostasis by causing constriction of the splanchnic vascular bed. The ADH exerts its vasoconstrictor effect by binding to the V_1–A receptors on the arterial smooth muscles and causing it to constrict.

3. Action on Anterior Pituitary ADH travels to the anterior pituitary via the portal veins, combines with the V_1–B receptors and causes increased ACTH secretion.

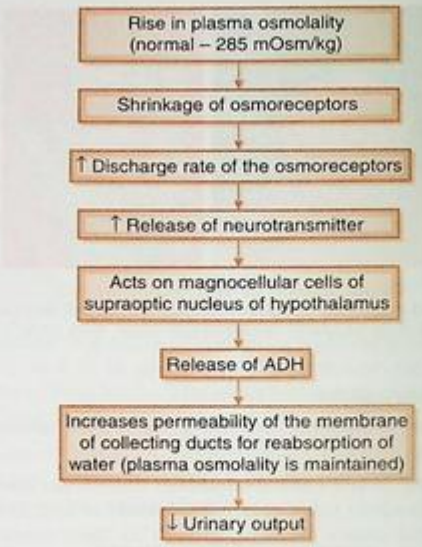


Figure 8.2-9 Mechanism of regulation of ADH by plasma osmolality.

Regulation of ADH Secretion

The main factors which regulate the ADH secretion are as follows:

1. Effective Osmotic Pressure of Plasma or Plasma Osmolality Plasma osmolality in normal individuals is maintained very close to 285 mOsm/kg by ADH. In other words, change in plasma osmolality is a very potent regulator of ADH secretion. Thus, water deprivation (which increases plasma osmolality) stimulates ADH secretion. On the other hand, a water load (which decreases plasma osmolality) decreases ADH secretion.

Mechanism of Action Changes in plasma osmolality affect the osmoreceptors.

- *Osmoreceptors* refer to a group of neurons located in the anterior hypothalamus.
- The rise in plasma osmolality by even 1%–2% results in the shrinkage of osmoreceptors, causing an increased rate of discharge and reflexly increased ADH secretion, thus maintaining plasma osmolality (Fig. 8.2-9).
- The substances like Na^+, mannitol and sucrose are potent stimulators for ADH secretion.

2. Changes in Blood Volume Changes in the circulating blood volume, central blood volume, cardiac output and blood pressure affect the secretion of ADH.

3. Other Factors Affecting ADH Secretion Factors, other than the two major stimuli (i.e. hypovolaemia and plasma osmolality), which affect ADH secretion, are as follows:

- *Stress* of pain, chronic emotional stress and surgical procedures cause increase in ADH secretion, leading to reduction in urine formation under these conditions.
- *Adrenaline* decreases the ADH. Hence, one experiences an increased frequency of micturition during acute emotional stresses such as interviews or examinations.

Summary of factors regulating ADH secretion is shown in Fig. 8.2-10.

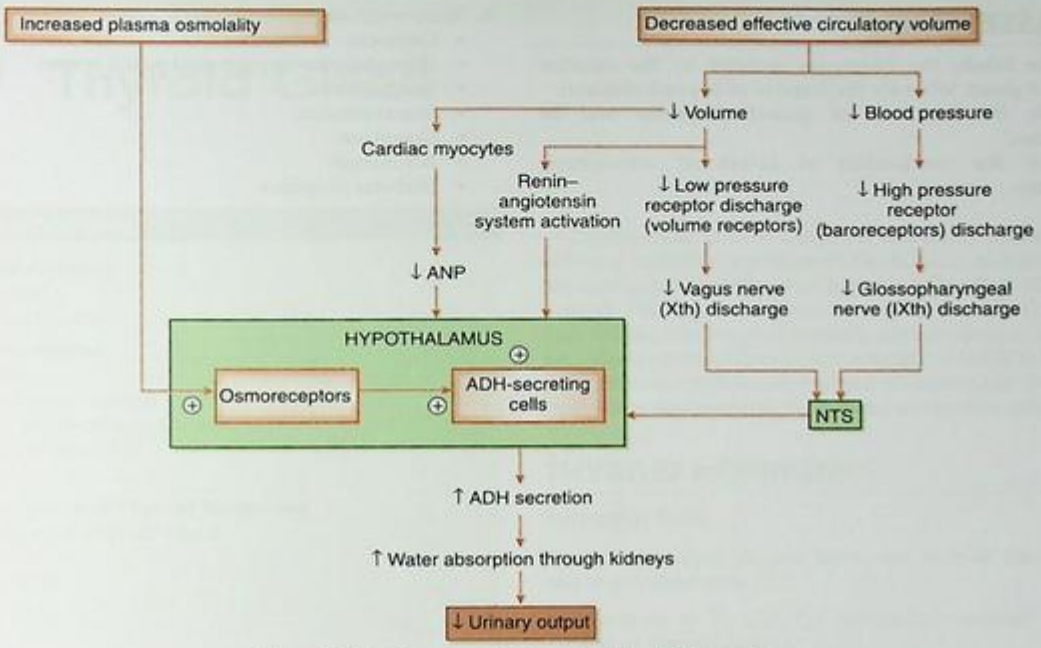


Figure 8.2-10 Summary of factors regulating ADH secretion.

Abnormalities of ADH Secretion

Abnormalities of ADH secretion include the following:

- Syndrome of inappropriate hypersecretion of ADH
- Diabetes insipidus

Syndrome of Inappropriate Hypersecretion of ADH

Syndrome of inappropriate hypersecretion of antidiuretic hormone (SIADH) refers to a condition in which ADH secretion is increased despite the presence of hypoosmolality. Excessive ADH secretion leads to water intoxication, i.e. overhydration, and because of this, SIADH is also called *dilution syndrome.*

Diabetes Insipidus

Diabetes insipidus refers to a clinical condition of polyuria that occurs either due to deficiency of ADH (vasopressin) release or due to failure of renal response to ADH.

Characteristic Features The diabetes insipidus is characterized by decreased renal absorption of water, leading to the following features:

*1. **Polyuria,*** i.e. passage of a large amount of urine, up to 3–20 L, is the most important single feature of diabetes insipidus.

*2. **Polydipsia*** Polyuria is followed by obligatory polydipsia (drinking of a large amount of water). It occurs due to the stimulation of the thirst mechanism.

*3. **Dehydration*** may occur in severe cases. Its signs and symptoms include dry tongue, dry mouth, fall of blood pressure and loss of consciousness.

Oxytocin

Structure, Synthesis, Storage and Release of Oxytocin

Structure, synthesis, storage and release of OTC have been described along with ADH (see page **310**).

Actions of Oxytocin

In humans, OTC acts mainly on the uterus and breasts.

Action on breast: OTC causes contraction of myoepithelial cells and thus plays an important role in milk ejection. For details, see page 379.

Action on uterus: OTC causes contraction of uterine smooth muscles and thus plays an important role during parturition (labour). For details, see page 377. OTC also acts on nonpregnant uterus and facilitates the transport of sperm in the female genital tract.

Control of Oxytocin Secretion

Stimuli which increase oxytocin release are as follows:

- OTC secretion increases on cholinergic stimulation.
- Suckling stimulates OTC release (suckling reflex). For details, see page 379.
- Genital tract simulation during coitus and labour increases OTC release (see page 377).

Factors which decrease oxytocin release are as follows:

- Emotional stress
- Sympathetic stimulation
- Drugs such as ethanol and enkephaline

SELF-ASSESSMENT

1. Describe briefly the hormones secreted by the anterior pituitary gland. What are the features of hypopituitarism?
2. Describe the functions of growth hormone and its regulation.
3. Describe the mechanism of action of antidiuretic hormone.
4. Write notes on:
   - Oxytocin
   - Hypothalamo–hypophyseal portal system
   - Prognathism
   - Somatomedins
   - Gigantism
   - Acromegaly
   - Diabetes insipidus

8.3 Thyroid Gland

CHAPTER OUTLINE

Functional Anatomy
Gross Anatomy
Histological Structure

Thyroid Hormones
Introduction
Biosynthesis and Storage
Secretion, Transport and Metabolism
Regulation of Secretion
Actions

Applied Aspects of Thyroid Hormones
Abnormalities of Thyroid Gland
Hyperthyroidism
Hypothyroidism
Goitre

FUNCTIONAL ANATOMY

Gross Anatomy

Thyroid gland is the largest endocrine gland in the body (weighing about 15–25 g in adults). It consists of two lobes joined together by a narrow isthmus and is located on either side of the trachea just below the larynx. It receives high blood supply (400–600 mL/100 g/min).

Histological Structure (Fig. 8.3-1)

Histologically, each *lobe* of thyroid gland is divided into various *lobules* by fibrous tissue septa. Each lobule is made up of an aggregation of several *follicles*. Each follicle is lined by *follicular cells*.

Follicular Cells These vary in shape with the degree of glandular activity. Normally (at an average level of activity), the cells are *cuboidal* and the colloid in the follicles is moderate in amount. During a high degree of activity, the cells become columnar and flat when inactive (Fig. 8.3-1B). These cells secrete thyroid hormones.

Parafollicular cells or *C-cells* are scattered between follicular cells and basement membrane (Fig. 8.3-1A), and secrete calcitonin, which is described in Chapter 8.4 (see Page 324).

Colloid This is a homogeneous material that fills the cavity of each follicle. The major constituent of the colloid is thyroglobulin, a glycoprotein with a molecular weight of 660,000. During the active state, the follicles are depleted of colloid; and in the resting state, when unstimulated, the follicles accumulate colloid.

THYROID HORMONES

Introduction

The two principal thyroid hormones include thyroxine (T_4) and triiodothyronine (T_3).

- *Thyroxine* or T_4 (3,5,3′,5′-tetraiodothyronine) constitutes 90% of thyroid output.
- *Triiodothyronine* or T_3 (3,5,3′-triiodothyronine) constitutes 10% of thyroid output.
- *Calcitonin* is a hormone secreted by the parafollicular cells of thyroid gland. It is concerned with calcium homeostasis.

Biosynthesis and Storage of Thyroid Hormones

Thyroxine (T_4) and triiodothyronine (T_3) are synthesized from tyrosine and iodide by the enzyme complex peroxidase.

Iodine Metabolism

Dietary Intake Iodine is essential for the synthesis of thyroid hormones. It is ingested in the form of iodides. Sources of iodine are sea fish (richest), bread, milk and vegetables. Iodine is added to the table salt to prevent iodine deficiency.

- Daily average intake of iodine is 500 µg.
- Daily requirement of iodine is 100–200 µg.

Fate of Dietary Iodide Most (80% [i.e. 400 µg/day]) of the iodides absorbed from the gastrointestinal tract (GIT) are selectively removed from circulation by cells of the thyroid gland.

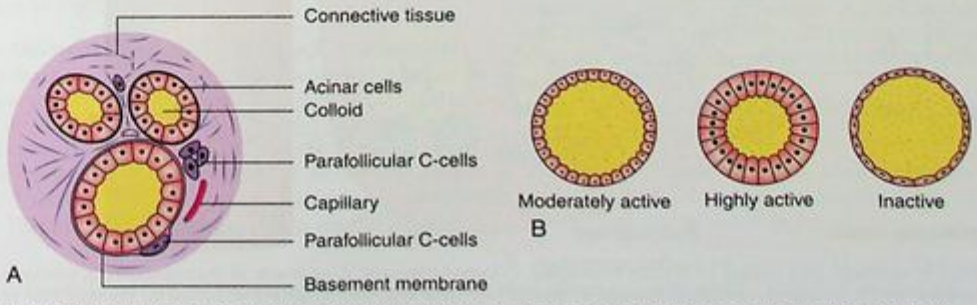


Figure 8.3-1 Histological structure of thyroid gland (A) and variations in the follicular cell size with activity (B).

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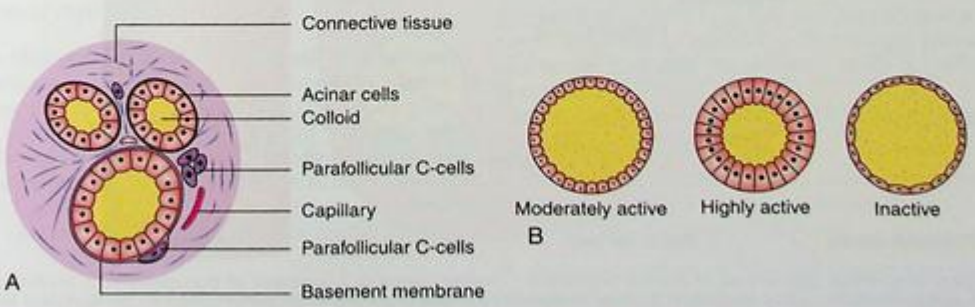

Figure 8.3-1 Histological structure of thyroid gland (A) and variations in the follicular cell size with activity (B).

Plasma iodide level is 0.15–0.3 µg/dL.

Thyroid iodide: Thyroid gland contains 5–8 mg of iodide, i.e. about 95% of total iodine content of the body. Thus, the thyroid serves as a store of iodine. Of the total thyroid iodide, only 5% is present within the cells of the follicular epithelium. The remaining 95% is present in the follicular lumen, stored in the colloid as thyroglobulin.

The steps involved in the synthesis of thyroid hormones are as follows (Fig. 8.3-2):

1. Iodine Trapping The first step in the synthesis of thyroid hormones is *uptake of iodide* by the thyroid gland, which occurs against the chemical (about 30:1) and electrical gradients. It is an energy-requiring process.

2. Synthesis and Secretion of Thyroglobulin Thyroglobulin is a large glycoprotein that is synthesized on the rough endoplasmic reticulum of the thyroid epithelial cells and release into the lumen of follicle (Fig. 8.3-2).

Each molecule of thyroglobulin contains about 140 tyrosine residues.

3. Oxidation of Iodide Once within the gland, iodide rapidly moves to the apical surface of the epithelial cells. From these, it is transported into the lumen of the follicles by a transporter called *pendrin*. The iodide (I^-) is then immediately oxidized to iodine (I^0) by the enzyme *peroxidase* present near the apical border of the epithelial cells.

Thyroid is the only tissue that can oxidize iodide to iodine. Thyroid-stimulating hormone promotes this reaction, whereas antithyroid drugs (thiourea, thiouracil, methimazole) inhibit.

4. Organification of Thyroglobulin refers to the iodination of tyrosine residues present in the thyroglobulin molecule. This reaction occurs at the apical membrane of the cell and requires thyroid peroxidase. Tyrosine (of thyroglobulin) is first iodinated at position 3 to form monoiodotyrosine (MIT) and then at position 5 to form diiodotyrosine (DIT).

5. Coupling Reaction Two molecules of DIT couple to form thyroxine (T_4). When one molecule of MIT is coupled with one molecule of DIT, triiodothyronine (T_3) is produced (Fig. 8.3-3). The enzyme peroxidase is required during coupling.

6. Storage Once thyroglobulin has been iodinated, it is stored in the lumen of the follicle as colloid for several months. It is estimated that the stored thyroid hormones can meet the body requirement for 1–3 months.

Secretion, Transport and Metabolism of Thyroid Hormones

Hormone Secretion Secretion of the thyroid hormone from the colloid stored in the lumen of follicle involves the following steps (Fig. 8.3-2):

Endocytosis The colloid containing iodinated thyroglobulin enters into the epithelial cells from the lumen of the follicle through endocytosis. This process is facilitated by the TG receptor *megalin* located on the apical membrane.

Proteolysis The lysosome vesicles containing proteolytic enzymes digest the thyroglobulin molecule releasing T_4, T_3, DIT, MIT and other amino acid constituents into the cytoplasm of the epithelial cells.

- T_4 and T_3 diffuse through the basal border of epithelial cells into the bloodstream via adjacent rich capillary plexus.

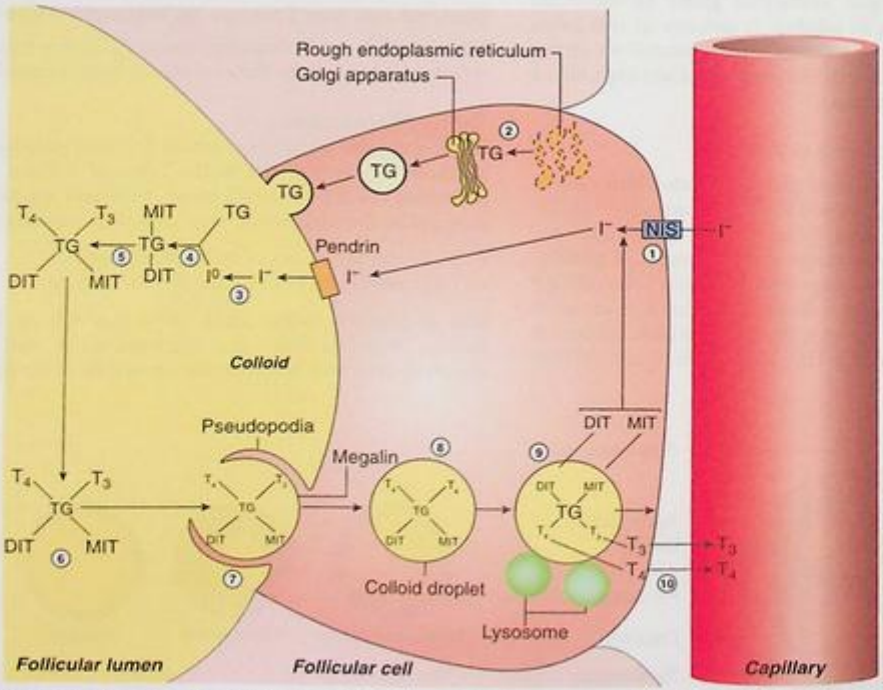

Figure 8.3-2 Steps in synthesis and release of thyroid hormones: 1, iodine trapping; 2, synthesis of thyroglobulin; 3, oxidation of iodine; 4, organification of thyroglobulin; 5, coupling reaction; 6, storage of thyroid hormone in colloid; 7, uptake of colloid by the epithelial cell by endocytosis; 8, colloid vesicle; 9, release of T_3 and T_4 after proteolysis; and 10, diffusion of T_3 and T_4 into the capillary.

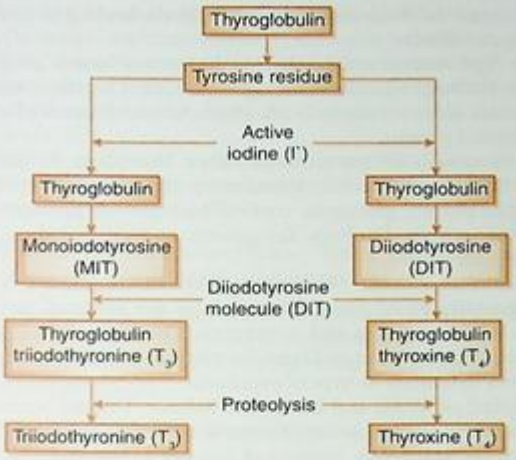

Figure 8.3-3 Coupling reaction to form T_3 and T_4.

- MIT and DIT are rapidly deiodinated within the follicular cells by the enzyme *deiodinase*. In this way, iodide is retrieved for recycling along with the tyrosine into T_4 and T_3 synthesis (Fig. 8.3-2).

Transport of T_4 and T_3 Secreted T_4 and T_3 circulate in the bloodstream in two forms: bound and free.

1. Bound Form Most of the circulating T_4 (99.95%) and T_3 (99.5%) is bound to specific binding proteins, namely thyroid binding globulin (TBG), transthyretin and thyroid binding albumin (TBPA).

2. Free Form Only about 0.05% of T_4 and 0.5% of T_3 circulate unbound (free form) in the plasma. These free, unbound hormones represent the biologically active hormone.

Normal plasma level in an adult is as follows:

T_4 – 8 μg/dL
T_3 – 0.15 μg/dL

Metabolism and Excretion of Thyroid Hormones The major pathways of peripheral metabolism of circulating thyroid hormone include deiodination, deamination (decarboxylation) and conjugation with glucuronic acid.

Regulation of Thyroid Hormone Secretion

The secretion of thyroid hormones is regulated by the following:

- Negative feedback mechanism through the hypothalamus–anterior pituitary–thyroid gland axis
- Autoregulation of thyroid gland

A. Regulation through Negative Feedback Mechanism

The negative feedback mechanism operating through the hypothalamus–anterior pituitary–thyroid gland axis (Fig. 8.3-4) plays an essential role in controlling secretion of thyroid hormones by:

Thyroid-Stimulating Hormone Thyroid-stimulating hormone is a glycoprotein having a molecular weight of 30,000. Average plasma level is 2.3 μIU/mL (range 0.2–0.5 μIU/mL).

Action of TSH: TSH exerts the following effects on the thyroid gland:

1. *It increases the secretion of thyroid hormones* by accelerating all the steps in biosynthesis.

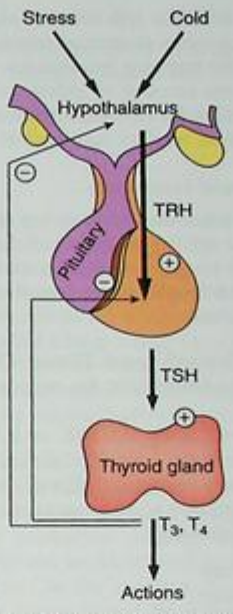

Figure 8.3-4 Regulation of thyroid hormone secretion by the negative feedback control mechanism through the hypothalamus–anterior pituitary–thyroid gland axis.

2. *It increases the number* (hyperplasia) and size (hypertrophy) *of the follicular epithelial cells.*
3. *It increases the vascularity of the thyroid gland.*

Regulation of TSH Production

1. ***Feedback control by plasma T_4 and T_3:*** Day-to-day secretion of TSH depends on the negative feedback control exerted by the plasma levels of free T_4 and T_3 (Fig. 8.3-4):
   - A fall in T_4 and T_3 levels stimulates TSH secretion from the anterior pituitary.
   - A rise in T_4 and T_3 levels inhibits TSH secretion.

   An established inverse relationship exists between the plasma levels of thyroid hormones and TSH; therefore, measurement of the plasma TSH levels is a reliable test for assessing the status of thyroid hormones.
2. ***Hypothalamic control of TSH:*** Hypothalamus exerts its effect by secreting thyrotropin-releasing hormone (TRH).

Thyrotropin-Releasing Hormone (TRH) Thyrotropin-releasing hormone is a tripeptide secreted by the arcuate nucleus of hypothalamus, and is stored in median eminence from where it is released into the hypothalamo–hypophyseal portal vessels to reach the anterior pituitary. Thyrotropin-releasing hormone acts on the basophils (thyrotrophs) in the anterior pituitary and controls the release of TSH.

Control of TRH: Secretion of TRH by the hypothalamus is controlled by the following:

- *Nervous stimuli* like emotion, stress, exposure to cold, etc.
- *Negative feedback control* exerted by plasma T_3 and T_4 levels on the hypothalamus (Fig. 8.3-4)

B. Autoregulation of Thyroid Gland

The secretions of thyroid gland are regulated by food iodine contents. If there is deficiency of iodine content in the diet, then the *iodine-trapping*

mechanism of the follicular cells becomes superefficient, and vice versa is also true, i.e. when there is an excess of iodine content in the food, then iodine trapping becomes less efficient and organification of the excess amount of iodine does not occur. In this way, iodine availability for thyroxine synthesis remains constant, and this phenomenon is called autoregulation of thyroid gland.

Actions of Thyroid Hormone

The thyroid hormones do not have any discrete target organ. They affect cellular activity of almost all the tissues of the body. T_3 acts by its effect on gene expression on the target cell.

The biochemical functions attributed to thyroid hormones are summarized below.

1. Effects on Growth and Tissue Development Thyroid hormones are important for normal body growth and development.

(i) Role in Normal Body Growth and Skeletal Maturation Thyroid hormones exert their effect directly by increasing protein synthesis and enzymes, and indirectly by increasing production of growth hormone and somatomedins. Some important effects are on the following:

- Bone development
- Teeth development
- Normal cycle of growth and maturation
- Subcutaneous tissues

(ii) Role in Tissue Differentiation and Maturation Thyroid hormone plays an important role in tissue differentiation and maturation is evidenced by the absence of metamorphosis in tadpole into baby frog after experimental removal of thyroid gland in the former.

(iii) Role in Development of Nervous Tissue T_3 seems to be necessary for proper axonal and dendritic development as well as normal myelination in the nervous system.

2. Effect on the Metabolic Rate in General The thyroid hormone in general stimulates the metabolic activities and increases the basal rate of oxygen consumption and heat production (calorigenic action) in most tissues of the body except the brain, retina, gonads, lungs and spleen.

3. Effects on Metabolism

(i) Effect on Carbohydrate Metabolism T_4 and T_3 lead on to an overall increase in enzymes, causing the following:

- Increased glucose absorption from the GIT
- Acceleration in almost all aspects of glucose metabolism, i.e. rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, and increased insulin secretion and its effects on the carbohydrate metabolism

(ii) Effect on Fat Metabolism Thyroid hormones cause the following:

- Mobilization of fat from the adipose tissue
- Increase in the levels of fatty acids and enhanced oxidation of free fatty acids by cells
- Decrease in the quantity of cholesterol, phospholipids and triglycerides in plasma; plasma cholesterol level is lowered due to increased excretion in bile

(iii) Effect on Protein Metabolism *In physiological amounts, the thyroid hormones* function as anabolic hormones, i.e. they cause an increase in RNA and protein synthesis, leading to positive nitrogen balance.

In high concentrations, thyroid hormones have a catabolic effect, leading to negative nitrogen balance. Therefore, muscle weakness and creatininuria are characteristic features of a hyperthyroid patient.

(iv) Metabolic Effects through other Hormones T_4 and T_3 potentiate the respective stimulatory effects of epinephrine, norepinephrine, glucagon, cortisol and growth hormone on gluconeogenesis, lipolysis, ketogenesis and proteolysis of the labile protein pool.

(v) Effect on Vitamin Metabolism Thyroid hormones increase the quantity of enzymes. Vitamins are the essential parts of some of the enzymes and coenzymes. Therefore, thyroid hormones cause an increased need for vitamins, leading to relative vitamin deficiency in hyperthyroidism.

(vi) Effect on Water and Electrolyte Balance Thyroid hormones play a role in the regulation of water and electrolyte balance.

4. Respiratory Effects Thyroid hormones could not stimulate O_2 utilization for long without also enhancing oxygen supply, which is accomplished by the following effects of T_4 and T_3:

(i) There is ***increase in the resting respiratory rate, minute ventilation and ventilatory responses*** to hypercapnia and hypoxia. These actions maintain a normal pO_2 when O_2 utilization is increased and a normal pCO_2 when CO_2 production is increased.

(ii) There is ***increase in oxygen-carrying capacity of blood*** by slightly increasing the red blood cell mass.

5. Cardiovascular Effects Thyroid hormone increases cardiac output, ensuring sufficient oxygen delivery in the tissues. In general, the thyroid hormones have the following effects on the cardiovascular system:

(i) ***Vasodilatation and increased blood flow to tissues.***

(ii) ***Blood volume*** in circulation is increased because of the following:
- Effect of vasodilation
- Activation of the renin–angiotensin–aldosterone axis and thereby increasing renal tubular sodium reabsorption

(iii) ***Tachycardia***, i.e. increased heart rate (at rest, even during sleep), is an important physical sign, which is used by clinicians in assessing the function of thyroid gland.

(iv) ***Force of cardiac contraction*** is increased by moderate increase in the thyroid hormone. The cardiac inotropic effects are via adrenergic stimulation. Myocardial calcium uptake and adenylyl cyclase activity are increased, enhancing the contractile force.

(v) ***Cardiac output*** is increased as a result of increased blood volume, increased heart rate and increased force of contraction.

(vi) ***Effect on blood pressure:*** *Systolic blood pressure* is increased due to increased strength and rate of heart beat, whereas *diastolic blood pressure* is decreased due to peripheral vasodilatation. This results into an *increased pulse pressure*, but the mean arterial pressure is usually unchanged.

6. Effects on Nervous System

(a) Effect on Development of Nervous System Thyroid hormones play an essential role in the development of the nervous system. Critical period for the development of nervous system is up to 1 year of life.

(b) Effect on Functioning of Nervous Tissue in Adults

(i) **On central nervous system:** T_4 enhances wakefulness, alertness, responsiveness to various stimuli, auditory sense, awareness of hunger, memory and learning capacity. Normal emotional tone also depends on proper thyroid hormone availability.

(ii) **Effects of thyroid hormones on peripheral nervous system:** Thyroid hormone increases the speed and amplitude of peripheral nerve reflexes.

7. Effects on Gastrointestinal Tract Effects of thyroid hormones on GIT include the following:

- Increase in appetite and therefore increase in food intake
- Increase in rate of secretion of digestive juices
- Increase in motility of GIT, with excess of thyroid hormone causing diarrhoea

8. Effects on Skeletal Muscles

- *Slight increase* in thyroid hormones makes the muscle to react with vigour.
- *Excessive quantities* of thyroid hormones weaken the muscles because of increased protein catabolism.
- *Lack of thyroid hormones* causes sluggishness in muscles.

9. Effects on Reproductive System In both women and men, thyroid hormone plays an important permissive role in the regulation of reproductive functions.

In men, lack of thyroid hormones causes complete loss of libido, and excess of hormones causes impotence.

In women, lack of thyroid hormone has varying effects:

- Menorrhagia and polymenorrhagia
- Irregular periods or even amenorrhoea occurring in some women

10. Effects on other Endocrine Glands Thyroid hormones also have the following significant effects on other parts of the endocrine system:

- ***Pituitary*** production of growth hormone is increased, whereas that of prolactin is decreased.
- ***Adrenocortical*** secretion of cortisol as well as metabolic clearance of this hormone is stimulated, but plasma-free cortisol levels remain normal.
- ***Oestrogens-to-androgens ratio,*** in males, is increased. It accounts for the occurrence of breast engorgement in males in hyperthyroidism.
- ***Parathyroid hormone and 1,25-$(OH)_2$-vitamin D*** are decreased as a compensatory consequence of the effects of thyroid hormone on bone resorption.

11. Effects on Kidney Kidney size, renal tubular epithelium, renal plasma flow, glomerular filtration rate and tubular transport maximum for a number of substances are also increased by thyroid hormone.

APPLIED ASPECTS OF THYROID HORMONES

Abnormalities of Thyroid Gland

- Hyperthyroidism
- Hypothyroidism

Hyperthyroidism

Hyperthyroidism refers to increased secretion of thyroid hormones. Its common causes are as follows:

- *Graves disease* (described below)
- *Toxic nodular goitre*

Graves Disease

Graves disease or toxic goitre or thyrotoxicosis is the most common cause of hyperthyroidism (Fig. 8.3-5).

Aetiology It is an autoimmune disease characterized by the development of thyroid-stimulating antibodies (TSAb) against the TSH receptors, also called a long-acting thyroid stimulator. These antibodies bind to TSH receptors and mimic TSH action on thyroid growth and hormone synthesis. The entire thyroid gland undergoes hyperplasia as a result of autoimmune stimulation.

Symptoms and Signs

1. ***General features*** include the following:
   - Marked increase in basal metabolic rate (BMR)
   - Weight loss, despite an increased intake of food
   - Increased heat production causing discomfort, excessive sweating and a greater intake of water in warm environments
2. ***Goitre:*** Goitre refers to the swelling of the thyroid gland. Graves disease is characterized by diffuse goitre, whereas single or more nodules indicate toxic nodular goitre.
3. ***Cardiovascular features*** are as follows:
   - Increased pulse rate or sinus tachycardia
   - Arrhythmias (atrial fibrillation is commonest)
4. ***Neuromuscular features*** are nervousness, irritability, restlessness, psychosis, tremors of hand, muscular weakness and exaggerated tendon reflexes.
5. ***Gastrointestinal features*** are diarrhoea or steatorrhoea and vomiting.
6. ***Dermatological features*** are perspiration (increased sweating or hyperhidrosis), loss of hair and redness of palm.
7. ***Reproductive features*** are impotence in males, and oligomenorrhoea or amenorrhoea, abortions and infertility in females.
8. ***Ophthalmological signs*** are lid retraction producing a staring look, and lid lag and exophthalmos, i.e. bulging out of eyeball.

Figure 8.3-5 Graves disease.

Hypothyroidism

Hypothyroidism is a clinical syndrome caused by low levels of circulating thyroid hormones.

Aetiology Depending on the aetiology, hypothyroidism can be primary or secondary.

Primary hypothyroidism is caused by the disorder of thyroid gland.

Secondary hypothyroidism is caused by diseases of anterior pituitary and hypothalamus.

Clinical Features Clinical features depend on the age at which deficiency manifests, duration and severity of the disease. Two different clinical entities are as follows:

- Infantile hypothyroidism (cretinism)
- Adult hypothyroidism (myxoedema)

1. ***Infantile hypothyroidism (cretinism):*** It occurs when thyroid deficiency occurs during the first year of life and is characterized by mental retardation (Fig. 8.3-6), marked retardation of growth, delayed milestones of development, pot belly, protruding tongue, flat nose, dry skin and sparse hairs. *Treatment* should be prompt otherwise mental deficiency will persist.
2. ***Adult hypothyroidism*** is also called myxoedema because of characteristic infiltration of skin by myxoedematous tissue (Fig. 8.3-7). Symptoms and signs include the following:
   - *General features*: Tiredness and weight gain without an appreciable increase in caloric intake (due to a lower than normal metabolic rate). Decreased heat production, lower body temperature, causes intolerance to cold and decreased sweating.
   - *Cardiovascular features*: Adrenergic activity is decreased, causing bradycardia. Other features include hypertension, pericardial effusion and precipitation of angina.
   - *Neuromuscular features*: Movement, speech and thought are all slowed down, and lethargy, sleepiness, delayed relaxation of ankle jerks, aches and pain are common. There is pressure palsy of peripheral nerves (e.g. carpal tunnel syndrome) due to entrapment in excess of ground substance.
   - *Dermatological features*: It causes dry thick skin (toad skin), sparse hair and nonpitting oedema due to infiltration by myxoedematous tissue (myxoedema).

Figure 8.3-6 Clinical features of cretinism. Note the short stature, pot belly and idiotic look.

Figure 8.3-7 Photograph of a patient with myxoedema, showing puffy face, thick lips and periorbital oedema.

   - *Reproductive features*: It causes menorrhagia and infertility (common) galactorrhoea and impotence (less common).
   - *Gastrointestinal features*: It causes constipation (common) and adynamic ileus (less common).
   - *Haematological feature* includes anaemia.

Goitre

Goitre refers to any abnormal increase in the size of the thyroid gland. The term goitre does not denote the functional status of thyroid gland because it may be associated with the following:

- *Euthyroid*, i.e. normal thyroid hormone level
- *Hypothyroidism*, i.e. low thyroid hormone level
- *Hyperthyroidism*, i.e. high thyroid hormone levels (as seen in Graves disease and toxic nodular goitre)

Iodine Deficiency Goitre or Endemic Goitre occurs when the daily dietary intake of iodine falls below 10 µg (normal requirement is 100–200 µg/day). It decreases the synthesis and secretion of thyroid hormone, leading to increased TSH levels and proliferation of thyroid gland tissue (goitre). It is mostly found in the geographic regions away from the sea coast where the water and soil are low in iodine content. Consumption of iodized salt is advocated to overcome the problem of endemic goitre. In certain cases, administration of thyroid hormone is also indicated.

SELF-ASSESSMENT

1. Discuss briefly the biosynthesis of thyroid hormone.
2. Briefly discuss the actions and regulation of thyroxin.
3. Write notes on:
   - Graves disease
   - Hypothyroidism
   - Goitre
4. Differentiate between:
   - Pituitary and thyroid dwarf
   - Active and inactive thyroid gland

8.4 Endocrinal Control of Calcium Metabolism and Bone Physiology

CHAPTER OUTLINE

Introduction

Calcium, Phosphorus and Magnesium Metabolism
Calcium Metabolism
Physiological and Biochemical Functions
Calcium Distribution in the Body
Calcium Balance
Hormonal Regulation of Plasma Calcium Level
Phosphorus Metabolism
Physiological and Biochemical Functions
Distribution of Phosphate in the Body
Phosphorus Balance
Regulation of Serum Phosphate Levels
Magnesium Metabolism

Bone Physiology
Functions and Composition

Calcitropic Hormones
Parathyroid Hormone
Vitamin D
Calcitonin
PTH-Related Protein and Other Hormones

Applied Aspects
Hyperparathyroidism and Hypercalcaemia
Hypoparathyroidism and Hypocalcaemia

Metabolic Bone Diseases
Rickets
Osteomalacia
Osteoporosis

INTRODUCTION

Calcium, phosphorus and magnesium belong to a group of principal elements which constitute 60%–80% of the body's inorganic material. The calcium and phosphorus form important structural components of bones and teeth, whereas calcium and magnesium are important determinants of neuromuscular excitability. Various hormones are involved in the regulation of metabolism of these minerals.

CALCIUM, PHOSPHORUS AND MAGNESIUM METABOLISM

Calcium Metabolism

Physiological and Biochemical Functions

Calcium ions regulate a number of important physiologic and biochemical processes. Free, ionized calcium is the biologically active form of calcium. Important physiological and biochemical functions subserved by calcium are as follows:

1. Development of bone and teeth
2. Neuromuscular excitation
3. Blood coagulation
4. Membrane integrity and plasma membrane transport
5. Mediation of intracellular action of hormones
6. Activation of enzymes
7. Release of hormones and neurotransmitters
8. Calmodulin-mediated action of calcium
9. Regulation of secretory processes
10. Contractility of heart

Calcium Distribution in the Body

In the body, the total content of calcium in an adult man is about 1100 g (27.5 mol). As much as 99% of it is present in the bones and teeth as hydroxyapatite. A small fraction (1%) of the calcium found outside the skeletal tissues performs a wide variety of functions.

Calcium in Bones The calcium in bones is present in the following two pools:

1. ***Pool of stable calcium*** is much larger (99% of total bone calcium) and is formed by the calcium present in the stable mature bones.
2. ***Pool (reservoir) of readily exchangeable calcium*** is much smaller (only 1% of the total bony content) and consists of labile (young) newly formed bones.

Calcium in Plasma Most of the blood calcium is present in the plasma.
Normal values of different forms of plasma calcium are as follows:

Total plasma calcium	: 10 mg/dL (2.5 mmol/L) (range 9–11 mg/dL)
• Diffusible calcium	: 6 mg/dL (1.5 mmol/L)
• Ionized calcium	: 5 mg/dL (1.25 mmol/L) (50% of total plasma calcium)
• Complexed to HCO_3^-, citrate, etc.	: 1 mg/dL (0.25 mmol/L) (10% of total plasma calcium)
• Nondiffusible calcium	: 4 mg/dL (1 mmol/L)
• Bound to albumin	: (i.e. 40% of total plasma calcium)

Calcium Balance

The calcium ion is fundamentally important to all the biological systems. Therefore, the concentration of calcium must be maintained within specific limits. The overall calcium homeostasis (calcium balance) or the normal daily calcium

turnover is maintained by interplay of the following processes (Fig. 8.4-1):

- Absorption of ingested calcium
- Exchange of calcium between bone and extracellular fluid (ECF)
- Secretion of calcium from ECF
- Excretion of calcium in the faecal matter and urine

Absorption of Calcium Normally, at a daily intake of 1000 mg of calcium, about 35% (i.e. 350 mg) is absorbed (Fig. 8.4-1). The absorption of calcium mainly occurs in the duodenum and is regulated by 1,25-dihydroxycholecalciferol [$1,25\text{-}(OH)_2D_3$] (for details, see page 291).

Exchange of Calcium between Bone and Extracellular Fluid The ECF contains about 1000 mg of calcium, which is in dynamic equilibrium with the calcium present in the bones.

Two types of exchange occur between the bone and ECF: rapid exchange and slow exchange.

Rapid exchange occurs between the ECF and the smaller (1% of the total bony content) readily exchangeable pool of bone calcium. A large amount of calcium (about 20,000 mg) per day moves into and out of the readily exchangeable pool in the bone.

Slow exchange occurs between the ECF and the larger (99% of total bone content) pool of stable calcium. This exchange is the one concerned with bone remodelling by constant interplay of bone resorption and deposition (about 500 mg/day only).

Excretion of Calcium The same amount of calcium as absorbed from the gut, i.e. about 350 mg, must ultimately be excreted to maintain balance. Excretion of calcium occurs in the faecal matter as well as in the urine (Fig. 8.4-1).

Hormonal Regulation of Plasma Calcium Level

Maintenance of plasma calcium level within a narrow range (9–11 mg/dL) is essential as it is involved in a number of important physiological and biochemical processes. Deviations of the ionized calcium from the normal range cause many disorders and can be life-threatening. The hormones regulating plasma calcium levels include the following:

A. Calcitropic Hormones The three hormones primarily involved in the calcium homeostasis are as follows:

- Parathyroid hormone (PTH)
- Active form of vitamin D [$1,25\text{-}(OH)_2D_3$]
- Calcitonin

The main role of these hormones in calcium metabolism is summarized in Table 8.4-1 and shown in Fig. 8.4-1.

B. Parathyroid Hormone-related Protein (PTHrP) It is a local hormone that acts on the PTH receptors and is important for the skeletal development in utero.

C. Other Hormones which have some effect on calcium metabolism include the following:

- *Growth hormone* has a stimulatory effect on bone deposition.
- *Sex hormones* have an inhibitory effect on bone resorption.
- *Glucocorticoids* have a stimulatory effect on bone resorption.
- *Growth factors* have a stimulatory effect on bone deposition.

Hypocalcaemia is compensated by (Fig. 8.4-2) the following:

- Release of calcium from the bones
- Increased fractional reabsorption in the kidney
- Increased absorption from the intestine

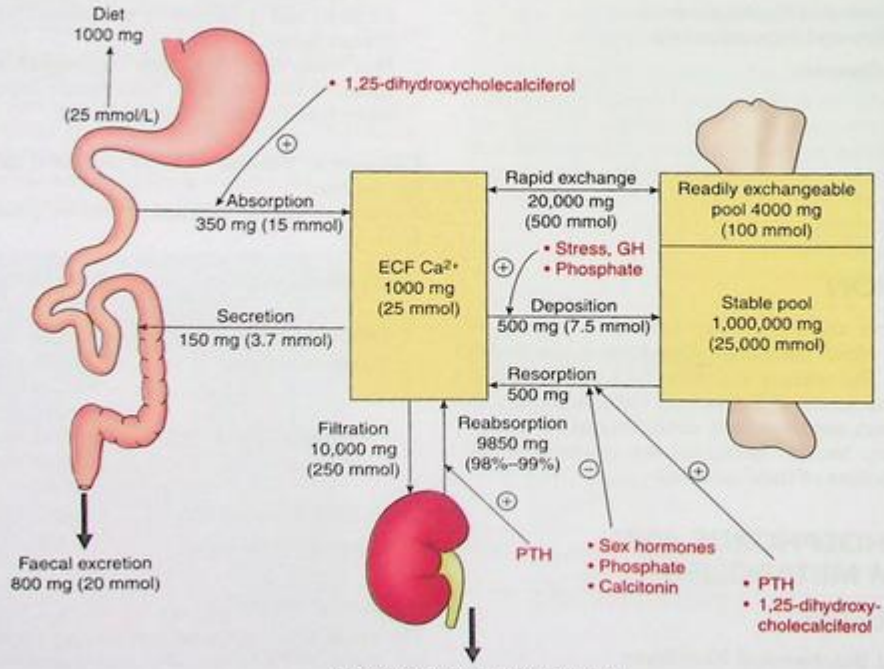

Figure 8.4-1 Hormonal maintenance of calcium balance in an adult human ingesting 1000 mg (25 mmol) of calcium per day.

TABLE 8.4-1 Summary of Calcitropic Hormones that Regulate Calcium Balance

	Parathyroid Hormone	1,25-Dihydroxycholecalciferol	Calcitonin
Stimulus for secretion	↓ Serum Ca^{2+}	↓ Serum Ca^{2+} ↑ PTH ↓ Serum phosphate	↑ Serum Ca^{2+}
Actions on:	↑ Resorption	↑ Resorption	↑ Resorption
• Bone	↓ P reabsorption	↑ P reabsorption	–
• Kidney	↑ Ca^{2+} reabsorption	↑ Ca^{2+} reabsorption	–
• Intestine	↑ Ca^{2+} absorption	↑ Ca^{2+} absorption	–
Overall effect on:	↑	↑	↓
• Serum Ca^{2+}	↓	↑	–
• Serum phosphate			

Note: ↑, increase; ↓, decrease; –, no effect.

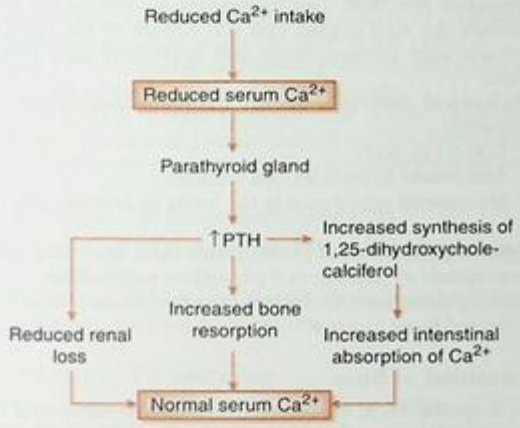

Figure 8.4-2 Mechanism of regulation of serum calcium levels in hypocalcaemia.

Phosphorus Metabolism

Physiological and Biochemical Functions

The phosphate ion is also critically important to all biological systems. Important functions subserved by phosphate are as follows:

1. Development of bone and teeth
2. Forming a structural part of the following:
   - *High energy* transfer and storage compounds, such as ATP, GTP and creatine phosphate
   - *Cofactors*, such as NAD, NADP and thiamine pyrophosphate
   - *Second messengers*, e.g. cAMP and inositol triphosphate
   - *Nucleic acids* (DNA, RNA), phospholipids and phosphoproteins
3. *Activation of enzymes* by phosphorylation
4. *Role in carbohydrate* metabolism
5. *Phosphate buffer system*, which is important for the maintenance of pH in the blood as well as in the cells.
6. *Important intracellular anion* that balances certain cations (K^+ and Mg^{2+}) inside the cells

Distribution of Phosphate in the Body

An adult body contains about 1 kg phosphate (P), which is distributed as follows:

- Bones and teeth : 80% (in combination with Ca^{2+})
- Muscles and blood : 10% (in association with proteins, carbohydrates and lipids)
- Chemical compounds : 10% (widely distributed in the body)

Blood Phosphate

- Plasma levels : 3–5 mg/dL
- Plasma phosphate exists in the following three forms:
- Protein bound :10%
- Free ions :40%
- Complexed with cations (Ca^{2+}, Mg^{2+}, Na^+, K^+) :50%

Phosphorus Balance (Fig. 8.4-3)

1. Intake and Absorption The recommended intake is about 800 mg/day. The recommended ratio of Ca^{2+}:P in adults is 1:1 and in infants 2:1. Sources of P are milk, cereals, leafy vegetables, meat and eggs. Ca^{2+} and P are distributed in the majority of natural foods.

On an average, the dietary intake of P in adults is about 1000 mg/day. P is absorbed actively and maximally in duodenum. About 70%–80% of P as compared to 30%–40% of Ca^{2+} is absorbed from the gut.

Factors affecting phosphorus absorption are as follows:

- Vitamin D, PTH and growth hormone (GH) promote absorption.
- Cortisol and heavy metal ions inhibit absorption.

2. Exchange of Phosphate between ECF and Soft Tissues The soft tissue stores of the phosphate, such as those in the muscle mass, undergo a rapid exchange with the ECF pool of phosphate (Fig. 8.4-3). This process plays an important role in the minute-to-minute regulation of the plasma phosphate concentration.

3. Exchange of Phosphate between ECF and Bone About 250 mg of phosphate enters and leaves the bone from 500 mg of ECF pool in the process of bone remodelling.

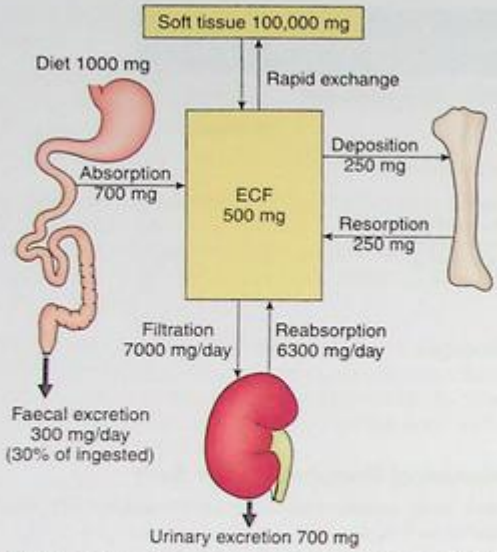

Figure 8.4-3 Maintenance of phosphorus balance in an adult human ingesting 1000 mg of phosphorus.

4. Excretion of Phosphate occurs in the faecal matter and urine.

(i) *Faecal excretion* includes 300 mg (30% of ingested) of phosphate, which is not absorbed (Fig. 8.4-3).
(ii) *Urinary excretion*: About 7000 mg of phosphate is filtered by kidney per day. A larger fraction (90%) of the filtered phosphate is reabsorbed.

Regulation of Serum Phosphate Levels

Hypophosphataemia and hypocalcaemia due to dietary or other causes bring about different adaptive changes to normalize the plasma levels. Responses to hypocalcaemia are more immediate than to hypophosphataemia.

The hypophosphataemia is mainly compensated by reduced urinary loss, and there occurs no change in dietary absorption.

Magnesium Metabolism

The divalent cation, magnesium (Mg^{2+}), is related in some respects to calcium and phosphates.

Functions subserved by magnesium are as follows:

- *Role in the formation of bone and teeth*
- *Serves as a cofactor for several enzymes* requiring ATP, e.g. hexokinase, glucokinase, phosphofructokinase and adenylyl cyclase
- *Required for proper neuromuscular function* (low levels of Mg^{2+} leading to neuromuscular irritability)
- *Required for release of PTH* in response to hypocalcaemia and also for the actions of the hormone on its various target tissues

Distribution of Mg^{2+} in the Body The body contains a total of 25 g of Mg^{2+}, which is distributed as follows:

- 10% in bones, in combination with calcium and phosphate
- 50% in soft tissues and body fluids

Plasma levels range from 1.8 to 2.4 mg/dL.

Magnesium Balance The daily requirement of magnesium is 300–500 mg. Leafy vegetables, nuts and soya bean are rich sources of magnesium. Magnesium is mainly absorbed in the distal part of the small intestine. On an average, 40% (i.e. 120–200 mg) of intake is absorbed daily. Consumption of large amounts of calcium, phosphate and alcohol diminishes Mg^{2+} absorption. PTH increases Mg^{2+} absorption. In a steady state, the same amount is excreted in the urine. Magnesium deficiency is compensated by decreased urinary excretion.

BONE PHYSIOLOGY

Functions and Composition of Bone

Functions of Bone

Bone is a specialized tough connective tissue that forms the skeleton of the body. It subserves the following functions:

1. ***Protective function***: The framework formed by the bones protects the vital organs and soft tissues of the body, e.g. thoracic cage protects lungs and heart, and skull protects brain.
2. ***Mechanical functions*** served by the bones include the following:
   - *Support* to body
   - *Attachment* to muscles and tendons
   - Movements performed at the joints by leverage effects of bones
3. ***Metabolic functions*** of bone include their important role in homeostasis of calcium and phosphate metabolism.
4. Haemopoietic function includes the formation of blood cells in the red bone marrow.

Composition of Bone

Bone, a special form of connective tissue, is composed of a collagenous framework (matrix) impregnated with the bone salts. The dry, fat-free bone consists of one-third organic bone matrix and two-thirds minerals (inorganic).

Bone Matrix Bone matrix, also called osteoid, consists of collagen fibres embedded in the gelatinous ground substance.

Collagen fibres are arranged in lamellae. The fibres of one lamella run parallel to each other, but those of adjoining lamellae run at varying angles to each other. Over 90% of the organic matrix is type I collagen.

Ground substance of a lamella is continuous with that of adjoining lamellae. It is formed by the ECF and proteoglycans (which include chondroitin sulphate and hyaluronic acid). These substances are concerned with the regulation and deposition of bone salts.

Bone Salts The bone salts constitute the inorganic component of bone, which is comprised primarily of calcium and phosphate in the form of hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$]. Each crystal measures about 400 Å units in length, 100 Å units in breadth and 10–30 Å units in thickness. Adsorbed on the surface of hydroxyapatite crystals are present small amounts of other salts such as sodium, potassium, magnesium and carbonate. The bone salts strengthen the bone matrix.

CALCITROPIC HORMONES

Parathyroid Hormone

Functional Anatomy of Parathyroid Glands

The parathyroid glands are two pairs of small endocrine glands closely applied to the back of the thyroid gland. Each gland is about the size of a split pea, measuring 6 × 4 × 2 mm. The total weight of four normal glands is about 140 mg.

Histological Structure The parenchyma of the parathyroid gland is made up of cells that are arranged in cords. The cells of the parathyroid glands are of the following two main types:
Chief cells, also called principal cells, are much more numerous. Chief cells secrete the PTH or parathormone.
Oxyphil cells: These cells first appear at puberty and their function is still not clear.

Structure, Synthesis and Secretion of PTH

Structure PTH is a single-chain polypeptide, containing 84 amino acids and having a molecular weight of 9500.
Synthesis: PTH is synthesized from a precursor molecule called prepro-PTH, which contains 115 amino acids.
Secretion: PTH is released from the chief cells by exocytosis in response to decrease in plasma-ionized calcium concentration that is sensed by the calcium receptors in the parathyroid cells.

Plasma Levels and Degradation of PTH

Plasma Level of PTH is about 130 pg/mL (approximately 3 × 10−12 M).
Degradation of PTH occurs rapidly in the peripheral tissues. PTH is predominantly split in the liver.

Regulation of PTH Secretion

1. Role of Plasma-ionized Calcium The secretion of PTH is mainly regulated by circulating levels of ionized calcium. The secretion of PTH is inversely related to the plasma calcium concentration. Maximum secretion occurs when plasma-ionized calcium levels fall below 3.5 mg/dL.
2. Roles of Serum Magnesium Concentration are as follows:

- *Mild decrease* in serum Mg^{2+} concentration stimulates PTH secretion.
- *Severe decrease* in serum Mg^{2+} concentration inhibits PTH secretion and produces symptoms of hypoparathyroidism (e.g. hypocalcaemia).

3. Role of Plasma Phosphate Concentration A rise in plasma concentration of phosphate causes an immediate fall in ionized calcium concentration, which, in turn, stimulates PTH secretion.
4. Role of Vitamin $1,25\text{-}(OH)_2D_3$ It decreases PTH secretion.

Actions of PTH The primary function of PTH is to elevate the plasma calcium concentration and to decrease the plasma phosphate concentration by acting on three major target organs: directly on bone and kidney, and indirectly on the gastrointestinal tract (Fig. 8.4-4).
1. Actions on the Bone PTH stimulates calcium and phosphate resorption from the bones, i.e. causes decalcification or demineralization of bone by increasing osteoclastic activity.

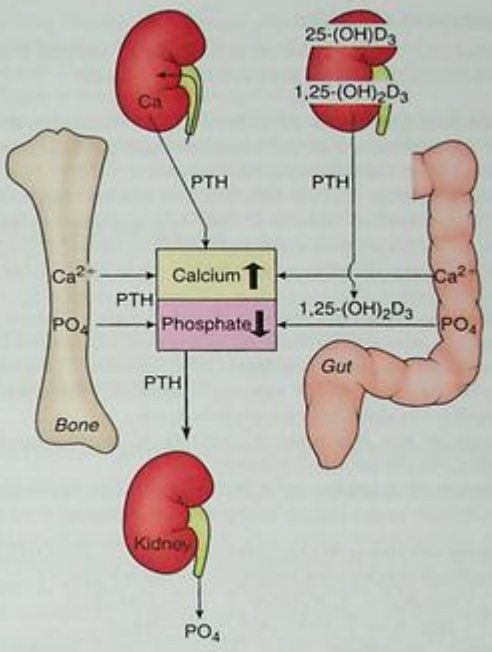

Figure 8.4-4 Actions of PTH on bones (stimulation of calcium and phosphate resorption), kidneys (stimulation of calcium reabsorption but inhibition of phosphate reabsorption) and intestine (increase in absorption of calcium and phosphate both). PTH action leads to direct increase in calcium and decrease in serum phosphate level.

2. Actions on Kidney
(i) ***Increase in calcium reabsorption:*** PTH increases the reabsorption of calcium from the ascending limb of the loop of Henle and the distal tubules of kidney, and helps to prevent hypocalcaemia.
(ii) ***Inhibition of phosphate reabsorption in the proximal tubule*** is the most dramatic effect of PTH on the kidney. This effect produces phosphaturia and hypophosphataemia.
(iii) ***Inhibition of reabsorption of Na$^+$ and HCO_3^- in the proximal tubule and stimulation of Na^+–H^+ exchanger*** by PTH causes acidification, which may prevent the occurrence of metabolic alkalosis.
(iv) ***Stimulation of reabsorption of Mg^{2+} by the renal tubules.***
(v) ***Stimulation of synthesis of $1,25\text{-}(OH)_2D_3$*** is a very important action of PTH in the kidney by increasing renal expression of the enzyme 1α-hydroxylase.

3. Actions on Intestines Parathormone greatly enhances both calcium and phosphate absorption from the intestine indirectly by increasing synthesis of $\mathbf{1,25\text{-}(OH)_2D_3}$ in the kidney.

Vitamin D

The term vitamin D refers to a group of closely related steroids produced by the action of ultraviolet (UV) light on certain provitamins. The active form of vitamin D, i.e. $\mathbf{1,25\text{-}(OH)_2D_3}$, also called calcitriol is now considered a hormone.

Formation of Calcitriol

Calcitriol [1,25-$(OH)_2D_3$] is an active form of vitamin D_3. Steps involved in its formation are summarized below.

Source and Synthesis of Vitamin D_3 Vitamin D_3, the precursor (prohormone) of the hormone **1,25-$(OH)_2D_3$**, reaches the blood from the following two sources:

1. Dietary Sources include fish, fish liver oils and egg yolk. The daily requirement of vitamin D is 400 IU or 10 μg of cholecalciferol. In countries with good sunlight (like India), the recommended dietary allowance for vitamin D is 200 IU (or 5 μg cholecalciferol).

2. Cutaneous Synthesis Besides dietary intake, vitamin D_3 is synthesized primarily in the specialized skin cells called *keratinocytes*, located in the inner layers of epidermis. The synthesis occurs by the action of UV rays on 7-dehydroxycholesterol (an intermediate in the synthesis of cholesterol).

Synthesis of the Hormone 1,25-$(OH)_2D_3$ from vitamin D_3 takes place in the liver and kidney.

Regulation of Synthesis of 1,25-$(OH)_2D_3$ The formation of 1,25-$(OH)_2D_3$ in the kidney is regulated as follows:

1. ***Plasma calcium*** levels regulate synthesis of 1,25-$(OH)_2D_3$ by a feedback mechanism indirectly through PTH:
   - ↓ Calcium → ↑ PTH → ↑ 1,25-$(OH)_2D_3$
   - ↑ Calcium → ↑ PTH → ↑ 1,25-$(OH)_2D_3$
2. ***Plasma phosphate*** level regulates the synthesis of 1,25-$(OH)_2D_3$ by a feedback mechanism that has a direct effect on the enzyme 1,α-hydroxylase:
   - ↓ Phosphate → ↑ 1,α-hydroxylase → ↑ 1,25-$(OH)_2D_3$ activity
   - ↑ Phosphate → ↓ 1,α-hydroxylase → ↓ 1,25-$(OH)_2D_3$ activity
3. ***1,25-$(OH)_2D_3$*** level itself has the following effects:
   - A direct negative feedback effect on its formation
   - A direct action on the parathyroid gland to inhibit the production of mRNA for PTH

↑ 1,25-$(OH)_2D_3$ → ↓ 1,25-$(OH)_2D_3$ formation; ↑ 24,25-$(OH)_2D_3$ formation; ↓ PTH formation

4. ***Other factors*** regarding 1,25-$(OH)_2D_3$ synthesis are as follows:
   - *Prolactin* increases 1,25-$(OH)_2D_3$ synthesis.
   - *Oestrogen* increases total circulatory 1,25-$(OH)_2D_3$, probably due to an increase in the secretion of binding protein (DBP).
   - *Hyperthyroidism* is associated with decreased circulating 1,25-$(OH)_2D_3$ and an increased incidence of osteoporosis.
   - *Metabolic acidosis* depresses the synthesis.
   - *Growth hormone*, human chorionic somatomammotropin (HCS), and calcitonin stimulate the formation of 1,25-$(OH)_2D_3$.

Mechanism of Action and Actions of Calcitriol

Calcitriol [1,25-$(OH)_2D_3$] acts by exerting its effect on the gene expression in the target cells by binding with the intracellular receptors. The vitamin D receptor is found both in the cytoplasm and in the nucleus. This mechanism has been described in detail on page 300.

Actions of Calcitriol The main action of calcitriol is as follows:

Regulation of Plasma Levels of Calcium and Phosphate Calcitriol [1,25-$(OH)_2D_3$] is the biologically active form of vitamin D. It regulates the plasma levels of calcium and phosphate by acting at three different sites: intestine, bone and kidney.

1. ***Action on intestine:*** The major action of calcitriol is to help calcium absorption from the intestine (Fig. 8.4-5).
2. ***Actions on bone:*** Calcitriol increases bone resorption as well as bone mineralization.
3. ***Action on kidneys:*** Calcitriol increases renal reabsorption of calcium and phosphate by increasing the number of calcium pumps.

Calcitonin

Synthesis Calcitonin is synthesized in the C-cells or parafollicular cells of the thyroid gland. These cells are of neural crest origin, which during development migrate to the developing thyroid gland.

Plasma levels of circulating calcitonin range from 10 to 20 pg/mL.

Secretion Calcitonin is secreted in response to rise in the plasma calcium level.

Degradation: Circulating calcitonin is heterogeneous, and it is largely degraded and cleared by the kidney.

Regulation of Secretion

1. ***Increase in plasma calcium concentration*** is the major regulator of calcitonin secretion. It is important to note that calcitonin is not secreted until the plasma Ca^{2+} concentration reaches 9.5 mg/dL, and that above this calcium level, plasma calcitonin is directly proportional to plasma calcium (Fig. 8.4-6).

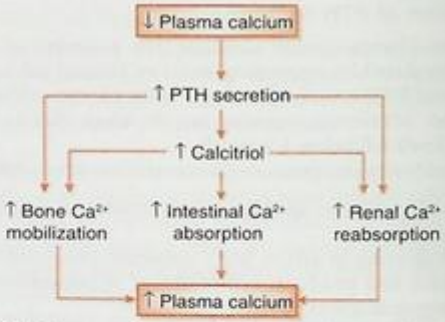

Figure 8.4-5 Summary of actions of calcitriol in elevating plasma calcium.

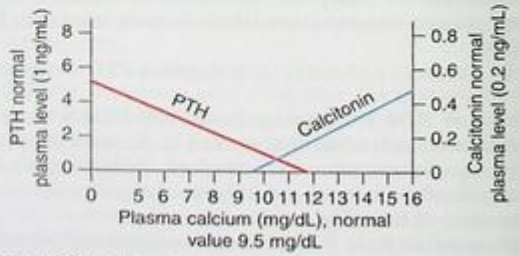

Figure 8.4-6 Relationship of plasma calcium concentration with release of calcitonin and parathyroid hormone.

2. ***Gastrointestinal hormones*** such as gastrin, cholecystokinin (CCK), glucagon and secretin have all been reported to stimulate calcitonin secretion, with gastrin being the most potent stimulus.
3. ***Other factors*** like β-adrenergic agonist, dopamine and oestrogen also stimulate calcitonin secretion.

Actions and Physiological Role of Calcitonin

Actions The major effect of calcitonin is to rapidly lower the plasma calcium level, and it also decreases the plasma phosphate. These effects of calcitonin are due to its following actions:

1. ***Action on the bone:*** The main action of calcitonin on the bone is to oppose the bone resorptive action of PTH.
2. ***Action on kidney:*** Calcitonin increases loss of calcium and phosphate in the urine. This effect also contributes in producing hypocalcaemia and hypophosphataemia.

Physiological Significance of Calcitonin

The Possible Physiological Roles of Calcitonin are as follows:

- *In children and fetus*, the calcitonin may play a role in the skeletal development by promoting calcium storage in bones, but *in adults*, the exact physiological significance of calcitonin is uncertain.
- *It protects the bones of mother from excess calcium loss during pregnancy* and lactation when the demand for calcium to be used elsewhere dramatically increases.

PTH-related Protein and other Hormones Affecting Calcium Metabolism

PTH-related Protein

The PTH-related protein (PTHrP) is produced by many different tissues in the body, such as skin keratinocytes, lactating mammary epithelium, placenta and fetal parathyroid glands.

PTHrP and PTH have marked homology; therefore, PTHrP binds to PTH receptors.

Physiological Roles of PTHrP The PTHrP is found in many tissues and may play a physiological role during intrauterine life and early infancy, and later during the development of different tissues. The physiological roles of PTHrP are as follows:

- Regulation of endochondral bone formation
- Role in the breast development
- Role in tooth development
- Role in skin and hair follicle development
- Protective role in central nervous system

Other Hormones

Certain hormones, other than the calcitropic hormones described above, which also have some effect on calcium metabolism, are as follows:

1. Growth Hormone This not only increases calcium excretion in urine but also increases intestinal absorption of calcium, and this effect seems to be greater than the effect on excretion, with a resultant positive calcium balance. Growth hormone also generates IGF-I, which stimulates protein synthesis in bone.
2. Glucocorticoids These inhibit bone formation and increase bone resorption by several actions, resulting in osteoporosis.
3. Thyroid Hormones Normal plasma levels of thyroxine are essential for the proper skeletal development.
4. Insulin This is required for bone formation, and there is significant bone loss in untreated diabetics.
5. Oestrogens These prevent osteoporosis, probably by direct effects on the osteoblasts. Therefore, incidence of osteoporosis in females increases after menopause.

APPLIED ASPECTS

Some of the important applied aspects with respect to endocrinal control of calcium metabolism and bone physiology are as follows:

- Hyperparathyroidism and hypercalcaemia
- Hypoparathyroidism and hypocalcaemia
- Metabolic bone diseases

Hyperparathyroidism and Hypercalcaemia

Hyperparathyroidism is a clinical condition characterized by excessive secretion of PTH.

Clinicobiochemical Features The main characteristic feature of hyperparathyroidism is involvement of bones, which may present as hypercalcaemia, hypercalciuria and renal calculi (renal stones). Hypercalcaemia may produce muscle weakness, lethargy, constipation and peptic ulcer. Hypercalcaemia is also responsible for hypertension and cardiac arrhythmia.

Hypoparathyroidism and Hypocalcaemia

Hypoparathyroidism refers to a clinical condition characterized by a low level of plasma calcium either due to deficient production of PTH or due to its unresponsiveness.

Characteristic Features of Hypoparathyroidism Characteristic features of hypoparathyroidism are as follows:

Hypocalcaemia Total serum calcium may be decreased to 4–8 mg/dL and the ionized calcium to 3 mg/dL. A 50% fall in the levels of ionized calcium leads to a clinical condition called *tetany* (described below).

Hyperphosphataemia It is an increase in serum inorganic phosphate levels to 6–16 mg/dL.

Tetany

Tetany refers to a clinical condition resulting from increased neuromuscular excitability.

Causes Causes of tetany include the following:

1. ***Hypocalcaemia:*** Hypocalcaemia is the most common cause of increased neuromuscular irritability, leading to tetany.
2. Hypomagnesaemia also causes tetany because magnesium ions are also associated with neuromuscular irritability.
3. ***Alkalosis***, which reduces ionic calcium, can also produce tetany.

Clinical Features The following symptoms may be seen:

- *Carpopedal spasm*: The hands in carpopedal spasm adopt a peculiar posture in which there occurs flexion at metacarpophalangeal joints, extension at interphalangeal and there is apposition of thumb (Fig. 8.4-7). This peculiar posture of

Figure 8.4-7 Carpal spasm in a patient with tetany.

hand is called *obstetric hand*. Pedal spasm is less frequent. In it the toes are plantarflexed and feet are drawn up.

- *Trousseau's sign*: Occluding the blood supply to a limb for about 3 minutes by inflation of a sphygmomanometer cuff (above the systolic blood pressure level) produces characteristic carpal spasm.
- *Laryngeal stridor* (loud sound) results from spasm of laryngeal muscles. It may produce asphyxia.
- *Paraesthesias*, i.e. tingling sensations in the peripheral parts of limbs or around the mouth, is a common feature.
- *Chvostek's sign* refers to the twitching of facial muscles produced by tapping the facial nerve at the angle of jaw. This occurs due to increased excitability of nerves to mechanical stimulation.

Management Management of tetany includes an intravenous injection of 20 mL of 10% calcium gluconate given to correct hypocalcaemia and relieve tetany.

Metabolic Bone Diseases

The term metabolic bone diseases is used for the bone diseases such as rickets, osteomalacia and osteoporosis.

Rickets

Rickets (occurring in children) and osteomalacia (occurring in adults) are metabolic bone diseases produced due to deficiency of vitamin D, in which there is defective calcification of bone matrix.

In rickets, mineralization of organic bone matrix in growing children is defective. It may also involve a cartilaginous matrix of growing end plates of bones.

Clinical Features of Rickets

seen in children are as follows:

- *Craniotabes* refers to the small rounded areas in the membranous bones of skull, which yield under the pressure of finger.
- *Widening of wrist* occurs due to epiphyseal widening of the lower end of radius bone.
- *Collapse of chest wall* occurs due to flattening of sides of thorax with prominent sternum.
- *Rickety rosary* refers to the beading of the costochondral junction of ribs.
- There is *frontal bossing* and posterior flattening of skull.
- *Bowing of legs* or knock knee occurs when the child starts walking.
- Kyphosis and pelvic deformities are also known.

Management Adequate supply of calcium and vitamin D should be ensured.

Osteomalacia

Osteomalacia can be thought of an adult counterpart of rickets. It is characterized by defective mineralization of the adult bones in which epiphyseal growth plates are already closed.

Clinical Features Clinical features of osteomalacia are almost similar to rickets.

1. Skeletal Abnormalities are dominant features and include the following:

- Diffuse skeletal pain and bony tenderness are common complaints. Pain may vary from mild backache to severe pain around hip.
- Muscle weakness is also common. A waddling gait may be present due to proximal muscle weakness.
- Bone becomes soft, especially involved are pelvic girdle, ribs and femurs.

2. Tetany may occur in a few cases with carpopedal spasm.

Treatment Treatment is similar to rickets.

Osteoporosis

Osteoporosis is characterized by a reduction of bone mass per unit volume with a normal ratio of bone matrix and minerals, i.e. there occurs loss of both bone matrix and mineral component. Senile osteoporosis is a common disease and has become a major public health problem of elderly.

Pathogenesis Osteoporosis develops due to a mismatch between bone resorption and bone remodelling process; the bone resorption is in excess.

Characteristic Features of Osteoporosis

Bone Density is reduced. In radiographs, the affected bones show a clear-glass appearance (e.g. ground-glass appearance seen in osteomalacia).

Incidence of Fractures is increased; particularly, fractures of the distal forearm (Colles fracture), vertebral bodies and hips are more common in osteoporosis.

Biochemical Changes Serum calcium and phosphate levels are usually normal. There may be increased urine excretion of calcium and hydroxyproline in a rapidly developing disease.

Treatment Treatment of osteoporosis should include the following:

1. *Calcium intake*, particularly from natural sources such as milk, should be increased.
2. *Moderate exercise* may be useful in preventing or slowing the progress of osteoporosis.
3. *Oestrogen treatment* is effective in arresting the rapidly developing osteoporosis in women after menopause.

SELF-ASSESSMENT

1. Discuss in brief physiological functions of calcium.
2. Discuss in brief hormonal regulation of plasma calcium.
3. Discuss in brief physiological functions and distribution of phosphorus. How is phosphorus balance maintained?
4. Discuss in brief the role of different calciotropic hormones in the maintenance of calcium balance.
5. Write notes on:
   - Bone salts
   - Parathyroid hormone
   - Calcitonin
   - Calcitriol
   - Hyperparathyroidism
   - Hypoparathyroidism
   - Tetany
   - Vitamin D deficiency

8.5 Adrenal Glands

CHAPTER OUTLINE

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Histological Structure

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Glucocorticoids
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Plasma Levels, Transport, Metabolism and Excretion
Mechanism of Action
Actions of Glucocorticoids
Regulation of Glucocorticoid Secretion
Mineralocorticoids
Synthesis
Plasma Levels, Transport, Metabolism and Excretion
Actions of Aldosterone
Regulation of Aldosterone Secretion
Adrenal Sex Steroids
Synthesis
Plasma Levels and Contribution

Applied Aspects
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Hypoactivity of Adrenal Cortex

Hormones of Adrenal Medulla
Synthesis of Catecholamine Hormones
Regulation of Catecholamine Secretion
Circulation, Metabolism and Excretion
Adrenergic Receptors and Actions of Catecholamines
Action of Catecholamines
An Integrated Response to Stress
Diseases of Adrenal Medulla

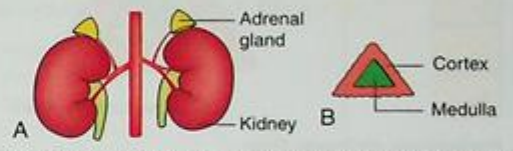


Figure 8.5-1 (A) Location and (B) divisions of adrenal glands.

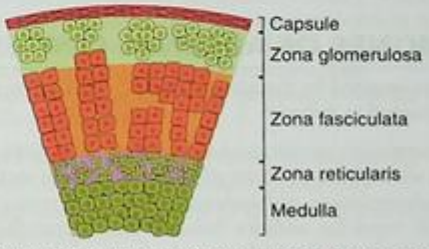


Figure 8.5-2 Histological structure of adrenal gland.

FUNCTIONAL ANATOMY

General Considerations

- There are two adrenal glands, situated one on either side, at the upper pole of kidney, hence also called 'suprarenal gland' (Fig. 8.5-1).
- Normally, each gland weighs about 5 g and consists of the following two parts (Fig. 8.5-1):
  - The cortex (outer zone) makes up to 80%–90% of the gland.
  - The medulla (inner zone) makes up to 10%–20% of the adrenal gland and is a source of catecholamine hormones.

Histological Structure

Adrenal Cortex The adrenal gland is covered by a connective tissue capsule from which septa extend into the gland substance.

The mature human adrenal cortex consists of the following three distinct layers or zones of cells (Fig. 8.5-2):

1. ***Zona glomerulosa,*** constituting the outer one-fifth of cortex, is a small zone present under the capsule. It consists of cells that secrete *aldosterone* and *corticosterone.*
2. ***Zona fasciculata*** is the widest zone forming the middle three-fifths of the cortex. It is made up of cells that are arranged in two cell thick straight columns. Sinusoids intervene between the columns.
3. ***Zona reticularis*** forms the inner one-fifth of the cortex. It is made up of a network of compactly arranged cords of cells (hence the name zona reticularis).

Adrenal Medulla Histologically, it is made up of chromaffin cells innervated by preganglionic sympathetic neurons.
Chromaffin Cells The cells forming adrenal medulla show yellow granules in their cytoplasm (i.e. *chromaffin reaction*) and are hence called chromaffin cells.

- Functionally, these cells are considered to be modified postganglionic neurons which do not have axons.
- Catecholamines are stored in the chromaffin granules. In addition to the catecholamines, the chromaffin granules also contain proteins, lipids and adenine nucleotides (mainly ATP).

Nerve Endings, present in the adrenal medulla, are the *cholinergic preganglionic* sympathetic fibres that synapse directly on the chromaffin cells. These fibres traverse the splanchnic nerve and are myelinated, emanating mainly from the lower thoracic segments (T_5–T_9) of the ipsilateral intermediolateral grey column of the spinal cord (Fig. 8.5-3).

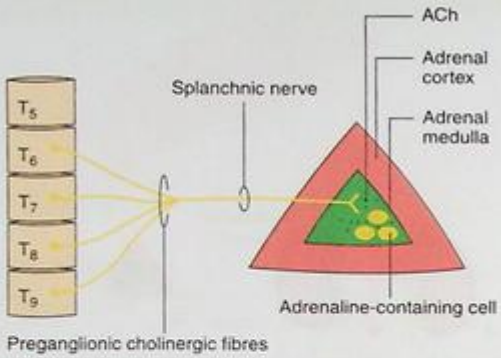


Figure 8.5-3 Preganglionic sympathetic fibres synapsing directly on the chromaffin cells in the adrenal medulla.

HORMONES OF ADRENAL CORTEX

Hormones secreted by the adrenal cortex, called *corticosteroids*, can be grouped as follows:

- *Glucocorticoids*, which include *cortisol* and *corticosterone*, have a widespread effect on glucose and protein metabolism.
- *Mineralocorticoids*: Aldosterone is the chief mineralocorticoid. It regulates sodium balance and extracellular fluid (ECF) volume in the body.
- *Adrenal sex steroids*: These include dehydroepiandrosterone (DHEA) and its sulphate ester.

Glucocorticoids

Synthesis

The glucocorticoids are synthesized largely by the cells forming zona fasciculata with a small contribution by the cells of zona reticularis of adrenal cortex.

Plasma Levels, Transport, Metabolism and Excretion of Glucocorticoids

Plasma Levels Plasma levels of glucocorticoids and other corticosteroids are given in Table 8.5-1. The plasma levels of total cortisol show diurnal fluctuation and range from 10 to 25 µg/dL with an average of 14 µg/dL. The rate of secretion of cortisol, which is about 15 mg/day under normal conditions, may increase to 300–400 mg/day under conditions of severe stress.

TABLE 8.5-1 Average 8 a.m. Plasma Levels and Secretion Rate of Corticosteroids in Adult Humans

Corticosteroid	Plasma Concentration (µg/dL)	Secretion Rate (mg/day)
Cortisol	14.0	15
Corticosterone	1.0	03
Aldosterone	0.009	0.15
Dehydroepiandrosterone (DHEA) sulphate	115	15

Transport

Cortisol In the plasma, cortisol circulates in two forms: bound (90%) and free (10%).

Bound form: Most of the plasma cortisol is bound to specific corticosteroid binding α_2-globulin (CGB), which is a glycoprotein, and is also called *transcortin*. A small amount (15%) is bound to albumin.

Free form of cortisol constitutes only 5%–10% of the total plasma cortisol.

Metabolism and Excretion Corticosteroids are degraded in the liver and conjugated with glucuronic acid. About 70% of the conjugated steroids are excreted in the urine and about 20% in the faeces.

Mechanism of Action of Glucocorticoids

Like other steroid hormones, the glucocorticoids act through an effect on gene expression by binding with specific intracellular receptors called glucocorticoid receptors (GRs). For details on the mechanism of action, see page 300.

Actions of Glucocorticoids

Glucocorticoids are essential for survival.

I. Metabolic Effects of Glucocorticoids Cortisol has major effects on protein glucose and fat metabolism. The different metabolic effects of glucocorticoids are as follows:

1. Effects on Carbohydrate Metabolism Glucocorticoids exert an anti-insulin effect, which leads to hyperglycaemia by the following actions:

(i) ***Increased gluconeogenesis:*** Glucocorticoids increase the rate of glucose production from noncarbohydrate sources by as much as six-fold to ten-fold.

(ii) It results in ***decreased utilization of glucose in peripheral tissues.***

2. Effects on Protein Metabolism exerted by glucocorticoids are as follows:

- ***Catabolic effect:*** Cortisol enhances the release of amino acids by proteolysis in the skeletal muscle and other extrahepatic tissues.
- ***Antianabolic effect:*** It is the ability of the glucocorticoids to inhibit the de novo synthesis of protein, probably at the translational level.

3. Effects on Fat Metabolism are complex and include the following:

(i) ***Lipolytic effects***: Although cortisol itself has only a slight lipolytic activity, its presence is necessary for epinephrine, growth hormone and other lipolytic substances to stimulate hydrolysis of stored triglycerides at maximal rates. Fatty acid synthesis is inhibited in the liver by cortisol – an effect not observed in the adipose tissue.

(ii) ***Lipogenic role:*** Glucocorticoids stimulate lipogenesis by increasing adipocyte lipoprotein lipase and glucose-6-phosphate dehydrogenase activity. The lipogenic effect varies in different regions of the body. Therefore, in the case of cortisol excess, there occurs a selective accumulation of fat in the abdomen, trunk and above (trunked obesity), sparing the extremities which become thin due to loss of muscle mass.

4. Effects on Electrolyte and Water Metabolism lucocorticoids control the distribution of body water and electrolytes by their opposing actions:

(i) It helps in ***retention of sodium and water*** by aldosterone-like activity.
(ii) ***Promotion of diuresis:*** Glucocorticoids promote diuresis by increasing the inactivation of antidiuretic hormone (ADH) by liver.

II. Physiological Actions on Various Organs and Systems In addition to the metabolic effects noted above, the glucocorticoids affect various organs and systems throughout the body (Fig. 8.5-4):

1. Effects on Muscle

(i) ***Contractility and work performance*** of skeletal and cardiac muscles are maintained by the cortisol.
(ii) ***Decrease in muscle mass and strength*** is caused by an excess of cortisol. This occurs due to the decrease in muscle protein synthesis and increase in muscle catabolism.

2. Effects on Bone

(i) ***Increased bone resorption***
(ii) ***Inhibition of bone formation***

Note. Because of the above effects on bone, *osteoporosis* results in skeletal deformity.

3. Effects on Connective Tissue Cortisol decreases collagen synthesis, thereby producing the following:

- Thinning of the skin
- Thinning of walls of capillaries, which leads to their easy rupture and to intracutaneous haemorrhage

4. Effects on Vascular System Cortisol is essential for maintaining normal blood pressure by the following:

- Sustaining myocardial performance
- Enhancing the vasopressure effect (responsiveness of arterioles to constrictive effect) of catecholamines (especially norepinephrine) and angiotensin II, and maintaining normal blood volume

5. Effects on Kidney are as follows:

- Increase in glomerular filtration rate (GFR) by increasing glomerular plasma flow
- Rapid excretion of water load
- Increase in calcium and phosphate excretion by decreasing their reabsorption in the proximal tubules

6. Effects on Central Nervous System Receptors (GRs) are present in various parts of the brain, especially in the limbic system. Through these receptors, the glucocorticoids modulate excitability behaviour and mood.

7. Effects on Gastrointestinal Tract The glucocorticoids increase gastric acid secretion and can lead to peptic ulceration following long-term use of cortisol.

8. Effects on Blood Cells and Lymphatic Organs The excess of glucocorticoids lead to the following:

- Eosinopenia and basopenia
- Lymphopenia
- Neutrophilia
- Polycythaemia
- Thrombocytosis

III. Anti-Inflammatory and Anti-allergic Effects These effects are not produced by the glucocorticoids, which are normally secreted physiologically, but are produced by their large doses when administered therapeutically, and are thus called the pharmacological actions of glucocorticoids.

1. Anti-inflammatory Effects of glucocorticoids are produced by the following actions:

- Cortisol inhibits the activity of phospholipase A_2.
- Cortisol stabilizes the lysosomal membrane.
- Cortisol inhibits migration of circulating leucocytes to the site of inflammation.
- Cortisol inhibits leukotriene.
- Cortisol decreases collagen formation.

2. Anti-immunity Effect Cortisol inhibits both cellular and humoral immunity by decreasing the proliferation of T-cells (involved in cellular immunity) and B-cells (involved in humoral immunity) response.

3. Anti-allergic Effect Cortisol reduces the number of circulating basophils and protects against the release of secretory products of granulocytes, mast cells and macrophages, which have vesicles containing serotonin, histamine and hydrolases.

IV. Role of Glucocorticoids in Fetal Life *Maturation of central nervous system (CNS), retina, skin* and lungs is facilitated by the cortisol in utero.

V. Role of Glucocorticoids in Stress Various stresses, e.g. trauma, cold, illness and starvation, are associated with the activation of the hypothalamic–hypophyseal–adrenal

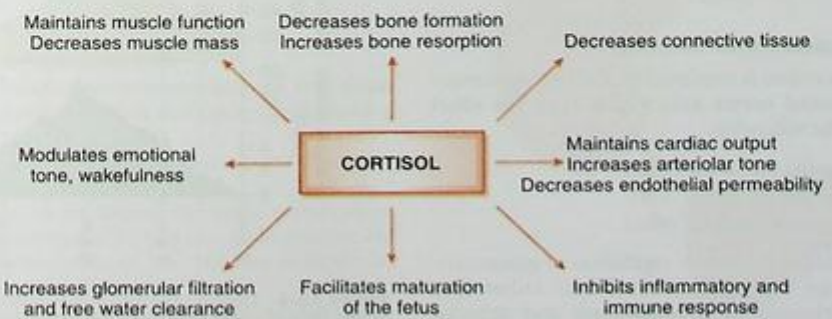


Figure 8.5-4 Effects of glucocorticoids on various tissues, organs and systems of the body.

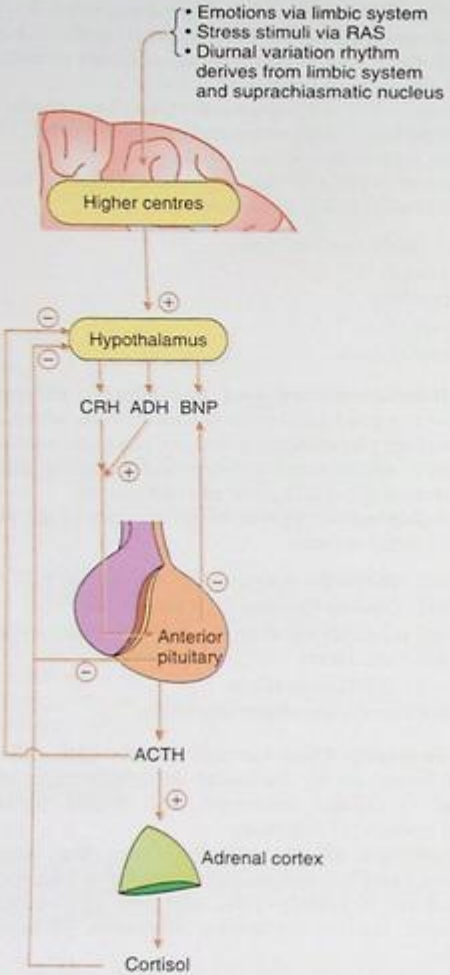


Figure 8.5-5 Hypothalamic–anterior pituitary–adrenal cortex axis and negative feedback mechanism controlling glucocorticoid secretion.

axis. Increased secretion of glucocorticoids is one of the various mechanisms involved in adaptation to various stresses (Fig. 8.5-10).

Regulation of Glucocorticoid Secretion

The glucocorticoid secretion is regulated by the hypothalamic–anterior pituitary–adrenal cortex axis, which exerts its effect through (Fig. 8.5-5) the following:

- Corticotropin-releasing hormone (CRH)
- Adrenocorticotropic hormone (ACTH)
- Glucocorticoids negative feedback effect

Note. CRH and ACTH are related to regulation of glucocorticoid release, so they are described in detail here rather than along with other hormones of hypothalamus and anterior pituitary, respectively.

1. Role of Corticotropin-releasing Hormone CRH is secreted by the small cells of paraventricular nucleus of hypothalamus. CRH is a polypeptide with 41 amino acids.

Actions of CRH

(i) ***Stimulation of synthesis and release of ACTH*** by acting on the *corticotrophs*

(ii) Other actions of CRH related to or independent of ACTH include the following:
- Central arousal
- Increase in blood pressure
- Diminution of reproductive function by decreasing synthesis of gonadotropin-releasing hormone (GnRH) and gonadotropins
- Decrease in feeding activity and growth
- Stimulation of release of cytokines in immune cells

2. Role of Adrenocorticotropic Hormone ACTH is secreted by *corticotrophs.*

Actions of ACTH

(i) ***Actions on adrenal cortex:*** ACTH is primarily concerned with growth and functions of the adrenal cortex.
- It promotes conversion of cholesterol into pregnenolone, which is the precursor of synthesis of all the hormones of adrenal cortex.
- It stimulates the secretion of glucocorticoids and the adrenal androgens.

(ii) ***Extra adrenal actions*** of ACTH occur only with very high levels, which are seen in abnormal conditions.

Regulation of ACTH Secretion

(i) ***Hypothalamic control*** on ACTH secretion is mainly exerted through CRH (see above). The hypothalamic control is responsible for the following characteristics of ACTH secretion:
- *Diurnal variation* in the levels of ACTH (and thus of cortisol) is due to variation in CRH release. As shown in Fig. 8.5-6, a large peak in the levels of ACTH and cortisol occurs in the morning (6–8 a.m.) during awakening (plasma level of ACTH ranges between 20 and 100 pg/mL, with an average of 50 pg/mL). Thereafter, the average level decreases markedly (5 pg/mL), just before or after

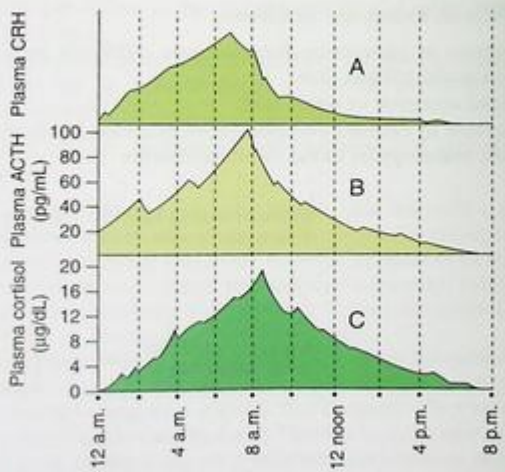


Figure 8.5-6 Diurnal variations and pulsatility in secretion of CRH (A), ACTH (B) and cortisol (C). Note the ACTH peak follows CRH peak, and cortisol peak follows ACTH peak by 10 minutes.

the subject falls asleep. In night workers, the rhythm is reversed. The biological clock responsible for diurnal variation in CRH, ACTH and cortisol levels is located either in the limbic system or the suprachiasmatic nucleus of the hypothalamus.

- *Pulsatile release of ACTH is* also due to pulsatile release of CRH. Up to three pulses per hour occur and each pulse lasts about 20 minutes. Cortisol pulses follow the ACTH pulses.

(ii) ***Negative feedback inhibition of ACTH*** is caused by (Fig. 8.5-5) the following:

- Plasma cortisol levels (long-loop negative feedback)
- Plasma ACTH levels (short-loop negative feedback)

3. Negative Feedback Control of Glucocorticoid Secretion Chronically, elevated plasma levels of free cortisol (and not the total cortisol, i.e. free plus bound form) exert a direct negative feedback action on its own secretion. This effect is exerted at the following two levels (Fig. 8.5-5):

- On hypothalamus to decrease formation of CRH
- On anterior pituitary to decrease formation of ACTH

Mineralocorticoids

The mineralocorticoids include the following:

- Aldosterone – the chief mineralocorticoid
- Deoxycorticosterone (DOC)
- 18-hydroxy-deoxycorticosterone (18-OH-DOC), secreted in a small amount and has some mineralocorticoid activity

Aldosterone is the major mineralocorticoid, so the discussion in this section is limited to it.

Synthesis

Aldosterone, the chief mineralocorticoid, is synthesized exclusively by the *zona glomerulosa cells.*

Plasma Levels, Transport, Metabolism and Excretion

Plasma Levels Depending on the dietary intake of sodium, the aldosterone secretion ranges from 50 µg/day (with dietary sodium intake of 150 mEq) to 250 µg/day (with dietary sodium intake of 10 mEq).

Transport In the plasma, 40% aldosterone circulates in free form and 60% in bound form to the specific aldosterone-binding globulin, transcortin and albumin.

Metabolism and Excretion 90% of aldosterone, like the glucocorticoids, is degraded in the liver and excreted in the urine.

Actions of Aldosterone

A. Primary Actions of Aldosterone

1. Effects on Renal Tubules Aldosterone acts on late distal tubules and collecting ducts of kidney, and causes the following effects:

(i) It causes *sodium reabsorption* from the tubular fluid into the renal tubular epithelial cells.

(ii) *Potassium excretion*: In the kidney, the active reabsorption of Na^+ occurs in exchange of K^+ and H^+. Thus, aldosterone causes not only reabsorption of Na^+ but also excretion of K^+ by renal tubular epithelial cells.

(iii) *H^+ excretion*: Aldosterone also enhances the tubular secretion of H^+ as Na^+ is reabsorbed.

2. Effects on Sweat Glands, Salivary Glands and Colon

Sweat glands and salivary glands produce primary secretions, which contain a large amount of sodium chloride. The sodium chloride is absorbed as the secretion passes through the ducts, and, in turn, K^+ and HCO_3^- are excreted. Thus, aldosterone decreases the loss of Na^+ and Cl^- in sweat and salivary secretion.

Colon: The aldosterone stimulates sodium reabsorption from the colon, while enhancing potassium excretion in the faeces.

B. Secondary Effects of Aldosterone

The secondary effects include the following:

- ***Hypokalaemia***, i.e. decrease in plasma K^+ levels, may occur in aldosterone excess due to increased urinary excretion of K^+.
- ***Hypernatraemia*** may occur in aldosterone excess.

Regulation of Aldosterone Secretion

Aldosterone secretion is controlled by the following factors (Fig. 8.5-7):

1. Renin–Angiotensin System The secretion of aldosterone is influenced by changes in the circulating fluid volume, which are sensed in the kidney. The signals arising from the kidney increase aldosterone secretion when ECF volume is decreased and vice versa.

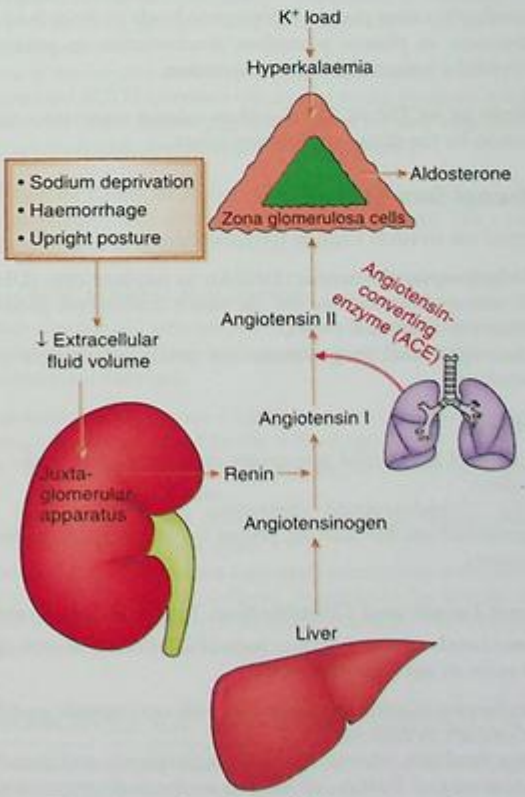


Figure 8.5-7 Regulation of aldosterone secretion.

Conditions Associated with Decreased ECF are as follows:

- Sodium deprivation (e.g. dietary restriction)
- Haemorrhage
- Upright posture for several hours
- Acute diuresis

Steps Involved in the Secretion of Aldosterone by Renin–Angiotensin System are as follows:

- *Decrease in ECF volume* leads to decrease in the renal arterial blood flow and pressure.
- *Decrease in renal perfusion pressure* causes the juxtaglomerular cells of the afferent arterioles to secrete renin.
- *Renin* catalyses the conversion of angiotensinogen (α_2-globulin substrate present in the plasma) into angiotensin I.
- *Angiotensin I* is converted into angiotensin II by the action of angiotensin-converting enzyme present in the endothelium of blood vessels, especially in the lungs.
- *Angiotensin II* binds to specific plasma membrane receptors in adrenal's zona glomerulosa cells and increases the secretion of aldosterone.

Aldosterone Secretion may be increased to four-fold to eight-fold by the renin–angiotensin system.

2. Plasma Potassium Concentration *There exists a vital negative feedback relationship between* plasma potassium concentration and aldosterone secretion as follows:

- *An increase in plasma concentration* by only 0.5 mEq/L immediately raises plasma aldosterone levels to three-fold.
- *Decrease in plasma potassium concentration* in potassium depletion lowers aldosterone secretion.

3. Role of ACTH ACTH also plays roles in mineralocorticoid secretion by the direct stimulating effect.

Adrenal Sex Steroids

Adrenal sex steroids include the following:

- ***Dehydroepiandrosterone* (DHEA):** Its sulphate ester (DHEA-S) and *androstenedione* are the major androgenic precursor products of adrenal cortex.
- ***Oestrogen and progesterone*** are produced in very small amounts.

Synthesis

The adrenal sex steroid precursors are synthesized in the *zona reticularis*.

The 17-hydroxylated derivatives of pregnenolone and progesterone are the starting points for synthesis of androgen precursors.

Plasma Levels and Contribution Towards Sex Steroids

Plasma Levels Normal plasma level of DHEA is 150–200 µg/dL at 25 years of age in both sexes.

Contribution of adrenal glands towards sex steroids and their functions are as follows:

During fetal life, adrenal cortex is hyperplastic and secretes a large amount of DHEA, which acts as the main precursor for synthesis of oestrogen by placenta.

In adult women, the adrenal glands supply 50%–60% of the androgenic hormone requirement. DHEA-S contributes to increased muscle mass, growth of pubic and axillary hair, and libido.

In adult man, testes produce a large quantity of testosterone, so the adrenal androgen precursors are of little biological importance. However, they may be partly responsible for the development of male sex organs in childhood.

APPLIED ASPECTS

The important applied aspects in relation to the adrenal cortex which need mention include the following:

- An integrated response to stress (see page 335)
- Hyperactivity of adrenal cortex
- Hypoactivity of adrenal cortex (see page 333)

Hyperactivity of Adrenal Cortex

Disorders of hyperactivity of adrenal cortex include the following:

- Cushing syndrome (hypercortisol state)
- Conn syndrome (hyperaldosteronism)
- Adrenogenital syndrome (excessive secretion of adrenal androgens)

1. Cushing Syndrome

Cushing syndrome refers to the group of clinical conditions occurring due to prolonged excessive levels of glucocorticoids.

Causes

- *Hyperactivity of pituitary* as seen in tumours of pituitary cells, particularly of basophils, which secrete ACTH
- *Adrenal-origin*-glucocorticoid–secreting tumours, such as adrenal adenoma and adrenal carcinoma
- *Excessive glucocorticoid administration* (i.e. iatrogenic)

Characteristic Features Characteristics features of Cushing syndrome are (Fig. 8.5-8) as follows:

1. ***Truncal or centripetal obesity:*** It occurs due to redistribution of body fat from extremities (which is in the abdominal

Figure 8.5-8 Photograph of a patient with Cushing syndrome showing truncal obesity and purple striae on the abdomen.

wall, back and face), producing the following characteristic features:
- *Buffalo hump is due to the collection of fat at the upper back.*
- *Moon face is due to fat collection on the face.*
- *Purple striae or cutaneous abdominal striae or livid stretch marks: The skin and subcutaneous tissue becomes thin due to protein catabolism. The stretching of abdominal skin due to excessive subcutaneous fat deposition causes rupture of subdermal tissues, producing reddish purple striae.*

2. ***Muscle weakness*** and backache are caused due to protein catabolism.
3. ***Sodium and water retention*** may cause weight gain, oedema and hypertension.
4. ***Hyperglycaemia*** occurs due to gluconeogenesis and inhibition of peripheral utilization of glucose. It may lead to glycosuria and adrenal diabetes.
5. ***Hirsutism and menstrual irregularity*** may occur due to increased adrenal androgens.
6. ***Susceptibility to osteoporosis and bone fracture*** is increased due to protein depletion and bone resorption.
7. ***Susceptibility to infections*** is increased due to immunosuppression.
8. ***Psychological, emotional and personality changes*** may occur due to CNS effects of glucocorticoids.
9. ***Blackening of skin*** may occur due to pigmentation caused by MSH-like effects of excessive ACTH.
10. ***Susceptibility to peptic ulceration*** is increased.

2. Hyperaldosteronism

Hyperaldosteronism refers to overproduction of the hormone aldosterone – a major sodium-retaining hormone.

Characteristic Features of hyperaldosteronism are as follows:

- *Sodium and water retention* leads to hypertension and oedema.
- *Hypokalaemia* may occur due to an increased potassium excretion producing muscle weakness.
- *Metabolic alkalosis* may occur due to secretion of more amount of H^+ into renal tubules. Metabolic alkalosis may produce hypocalcaemia, causing tetany.

IMPORTANT NOTE

It is important to note that marked hypernatraemia and oedema do not occur because Na^+ excretion is soon normalized despite hypersecretion of aldosterone (*escape phenomenon*).

3. Adrenogenital Syndrome

As mentioned earlier, the androgen precursors secreted by the adrenal cortex are of little biological importance under normal circumstances. However, when secreted in large amounts, as in the *tumour of zona reticularis* of adrenal cortex, the following abnormal features may be produced:

- *In prepubertal males,* the excessive androgens produce precocious pseudopuberty.
- *In males,* the oestrogen-producing cells may produce female-like secondary sexual characters, such as enlargement of breasts (gynaecomastia), atrophy of testes, loss of libido and feminine body.
- *In females,* they cause development of male secondary sexual characteristics, such as beard, muscular body, breaking of voice, male-type hair growth, enlargement of clitoris and amenorrhoea.

Note. In virilized children or adult women, a large increase in urinary 17-ketosteroid excretion almost always indicates an adrenal abnormality.

Hypoactivity of Adrenal Cortex

Adrenocortical deficiency occurs due to involvement of adrenal cortex and is associated with high ACTH levels due to the feedback mechanism. The conditions producing adrenocortical deficiency include the following:

- Addison disease
- Congenital adrenal hyperplasia

Addison Disease

Addison disease occurs due to chronic deficiency of hormones secreted by all the three zones of adrenal cortex. Therefore, it concludes the following:

1. ***Glucocorticoid insufficiency*** produces weight loss, malaise, anorexia, nausea, vomiting, weakness and diarrhoea. Glucocorticoids are essential for adaptation to stress; therefore, in Addison disease, exposure to any type of stress, e.g. even mild infection, may be fatal.
2. ***Mineralocorticoid deficiency*** produces hyponatraemia, hyperkalaemia, acidosis and decreased ECF volume with hypotension.
3. ***Loss of androgens*** causes sparse hair in females.
4. ***Increased ACTH secretion*** occurs due to the feedback mechanism and causes diffuse pigmentation of the skin and mucous membranes (because of its MSH-like actions).

Addisonian Crisis or Adrenal Crisis It refers to acute adrenal insufficiency characterized by sudden collapse. The condition becomes fatal if not treated in time.

Congenital Adrenal Hyperplasia

Causes: Congenital adrenal hyperplasia is caused by congenital deficiency of *21-hydroxylase deficiency* and deficiency of *11-hydroxylase enzymes.*

Characteristic features are virilism and excessive body growth.
In boys, it is characterized by the following:
- Precocious body growth, leading to stocky appearance called *infant Hercules*
- Precocious sexual development with an enlarged penis even at the age of 4 years

In female fetus, high plasma androgen levels cause *masculinized pattern* of development (*virilism*). Sometimes the female fetus may be born with male-type external genitalia. This condition is called *pseudohermaphroditism.*

HORMONES OF ADRENAL MEDULLA

The adrenal medulla secretes *catecholamines,* which include epinephrine, norepinephrine and dopamine. About 80% of adrenal medullary catecholamine is epinephrine and the rest is

norepinephrine. Apart from catecholamines, the adrenal medulla also contains small amounts of *dynorphins, neurotensin, encephalin, somatostatin* and *substance P.* The functions of these adrenal peptides are not clear.

Synthesis of Catecholamine Hormones

Synthesis of Catecholamines Epinephrine and norepinephrine are synthesized in different cells. The biosynthetic pathway originates with L-tyrosine. Tyrosine is available from the diet as phenylalanine, which is converted into tyrosine by the enzyme phenylalanine hydroxylase found in the liver. Conversion of tyrosine into epinephrine occurs in the following four steps (Fig. 8.5-9):

1. Conversion of Tyrosine into dihydroxyphenylalanine (DOPA) The conversion of tyrosine into DOPA is catalysed by the enzyme *tyrosine hydroxylase.* This reaction occurs in the chromaffin cell cytoplasm.

2. Conversion of DOPA into Dopamine in the cytosol is catalysed by the enzyme *DOPA decarboxylase.*

3. Conversion of Dopamine into Norepinephrine Dopamine from the cytosol enters the chromaffin granules, where it is converted into epinephrine by the enzyme *dopamine-β-hydroxylase.*

4. Conversion of Norepinephrine into Epinephrine In about 20% of chromaffin cells, the norepinephrine is the end product, and in about 80% of chromaffin cells, norepinephrine diffuses back into the cytoplasm, where it is converted into epinephrine by the enzyme *phenylethanolamine N-methyltransferase* (PNMT).

Regulation of Catecholamine Secretion

Nervous Control of Secretion The catecholamine secretion is entirely controlled by the splanchnic nerves supplying the medulla. These nerves comprise preganglionic sympathetic fibres emerging mainly from lower thoracic segments (T_5–T_9) of the ipsilateral intermediolateral grey column of the spinal cord. These fibres, when stimulated, act by releasing acetylcholine close to the adrenal medullary chromaffin cells.

Physiological and Psychological Stimuli for Release The adrenal medullary activation occurs as part of generalized sympathetic response to any emergency situation. Therefore, this has also been called the *sympathetic alarm* reaction. The sensory stimuli associated with the rapid release of epinephrine (and probably norepinephrine) from adrenal medulla include the following:

- Perception or even anticipation of danger or harm (anxiety)
- Pain, trauma
- Hypovolaemia from haemorrhage or fluid loss
- Hypotension
- Anoxia
- Exposure to extremes of temperature
- Hypoglycaemia
- Severe exercise

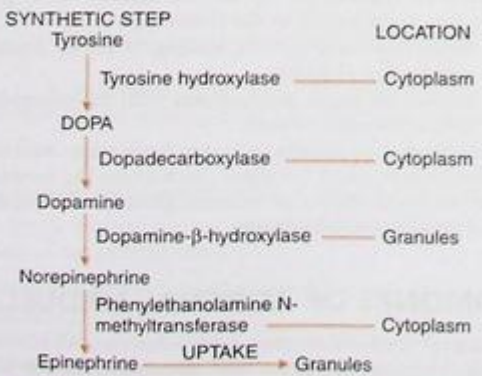


Figure 8.5-9 Steps of catecholamine synthesis in the adrenal medulla.

Circulation, Metabolism and Excretion

Circulation

- *Secreted epinephrine* and norepinephrine from the adrenal medulla is in the ratio of 4:1.
- *Basal plasma levels* (in recumbent humans) of free epinephrine are 30 pg/mL and those of free norepinephrine are 300 pg/mL.
- *Variations in plasma levels* of catecholamines according to physiological or pathological states are quite common.

Metabolism and Inactivation of Circulating Catecholamines Circulating catecholamines (epinephrine and norepinephrine) are metabolized predominantly in the liver and kidney by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). The metabolites are excreted in the urine and bile as vanillylmandelic acid (VMA) and methoxyhydroxyphenyl glycol (MOPG).

Adrenergic Receptors and Actions of Catecholamines

Adrenergic Receptors The adrenergic receptors are of the following two types:

Alpha (α) Receptors These are further divided into two types: α_1 and α_2. The α-adrenergic receptors are sensitive to both epinephrine and norepinephrine. These receptors are associated with most of the excitatory functions of the body but have one major inhibitory function (i.e. inhibition of intestinal motility).

Beta (β) Receptors These are further divided into three types: β_1, β_2 and β_3. β-adrenergic receptors respond to epinephrine and, in general, are relatively insensitive to norepinephrine. These receptors are associated with most of the inhibitory functions of the body but have an important excitatory function (i.e. excitation of myocardium).

Relative potency of two catecholamines varies with each receptor type. In general, epinephrine tends to react more strongly with β receptors and norepinephrine with α receptors, but overlap is considerable.

Actions of Catecholamines

I. Metabolic Actions of Catecholamines Epinephrine affects metabolic functions more than norepinephrine, via α and β receptors, in the following ways:

1. General Metabolic Effects of Epinephrine This includes the following:

- Increased O_2 consumption (by 20%–40%) and increased CO_2 output

- Raised basal metabolic rate (BMR) and respiratory quotient (RQ)
- Increased heat production due to stimulation of cellular oxidative processes

2. Effect on Carbohydrate Metabolism Epinephrine produces hyperglycaemia and makes the glucose available for the brain and other tissues to meet the emergency by the following effects:

- *Glycogenolysis* is stimulated in the liver.
- *Glycogenesis* is reduced in the liver by inhibition of the enzyme glycogen synthase.
- *Gluconeogenesis*, i.e. hepatic production of glucose from lactate, amino acids and glycerol, is increased.
- *Insulin secretion* is inhibited.
- *Glucagon secretion* is stimulated. This amplifies the hyperglycaemic effects of epinephrine.
- *ACTH secretion* is stimulated, which then stimulates cortisol secretion. Cortisol is a potent gluconeogenic hormone.

3. Effects on Fat Metabolism Norepinephrine has more potent action on the lipid metabolism.

- *Catecholamines* cause an increase in lipolysis by stimulating hormone-sensitive lipase in adipose tissue and muscles.

II. Physiological Actions of Catecholamines

1. Effects on Cardiovascular System The net effects of epinephrine and norepinephrine are (Table 8.5-2) discussed below.

2. Effects on Other Systems

On CNS, catecholamines via β receptors activate the reticular activating system (RAS) and thus lead to arousal and alerting responses producing anxiety, apprehension and coarse tremors of extremities.

On GIT, epinephrine via β receptors causes relaxation of smooth muscles of the wall of the gut, decreasing its tone and motility. Via α receptors, epinephrine causes contraction of sphincters of gut; the net result is production of constipation.

On Urinary Bladder Epinephrine produces retention of urine by relaxing the detrusor muscles.

On Skin Catecholamines act on pilomotor muscle, producing piloerection of hair.

On Skeletal Muscle During exercise, epinephrine via β_2 receptors increases blood supply (by causing vasodilation).

TABLE 8.5-2 Cardiovascular Effects of Catecholamine

Parameter	Epinephrine	Norepinephrine
• Heart rate	↑	↓
• Cardiac output	↑	↓
• Peripheral resistance	↓	↑
• Systolic blood pressure	↑	↑
• Diastolic blood pressure	↓	↑
• Mean arterial pressure	↓ or N	↑

Note: ↑, increase; ↓, decrease; N, normal.

On Eyes Epinephrine causes dilation of the pupil (mydriasis) by contracting dilator pupillae (radial) muscle.

On Respiration Epinephrine via β_2 receptors relaxes smooth muscles of bronchioles, producing bronchodilation. It also increases the rate and force of respiration.

On Blood Epinephrine produces the following effects:

- *Reduces blood coagulation time* by increasing activity of factor V.
- *Increases RBC count*, haemoglobin content and packed cell volume (PCV) due to release of RBCs in circulation by causing contraction of spleen.
- *Increases plasma protein concentration* by movement of fluid out of circulation.
- *Neutrophilia* occurs due to release of sequestrated neutrophils into the circulation.

On Secretion of other Hormones Catecholamines regulate secretion of a number of hormones, including the following:

- *Insulin and somatostatin* secretion is decreased via α_2 receptors (by decreasing cAMP).
- *Glucagon and pancreatic peptide* secretion is increased via β_2 receptors.
- *Thyrotropin-releasing hormone (TRH)-induced secretion of TSH* from thyrotrophs is decreased via α_2 receptors.
- *Thyroid hormone* secretion is enhanced by catecholamines under certain circumstances, and peripheral conversion of T_4–T_3 is stimulated via β_2 receptors.

On Renin Secretion and Na^+ and K^+ Movement Catecholamines increase renin secretion by stimulation of β receptors in the kidney. The increase in renin, in turn, increases aldosterone secretion, which, in turn, enhances *sodium retention.*

An Integrated Response to Stress

Stress, may it be emotional, physical or biological, evokes an integrated response of the sympathoadrenal medullary system and hypothalamic–pituitary–adrenal cortex axis.

Steps involved in stress adaptation by an integrated response of the above system are (Fig. 8.5-10) as follows:

Perception of Stress Signals Stress is perceived by many areas of the brain, from the cortex down to brainstem, including the limbic system and reticular activating system (RAS).

Stimulation of Hypothalamus Major stresses activate the CRH and ADH neurons in the paraventricular nucleus and adrenergic neurons.

Activation of Hypothalamic–pituitary–adrenal Axis CRH and ADH release stimulates ACTH release and ultimately elevates plasma cortisol levels.

Activation of Sympathoadrenal Medullary System Sudden exposure to any type of stress initially produces the sympathetic alarm reaction. Stimulation of adrenergic neurons of hypothalamus ultimately leads to a release of epinephrine from the adrenal medulla and norepinephrine from the sympathetic ganglia.

Integrated Role of Hormones Released by the Hypothalamic–pituitary–adrenal Axis and Sympathoadrenal Medullary System in Stress Adaptation Together these hormones help in adaptation to stress by their following actions:

- ***Increase in glucose production:*** Catecholamines rapidly raise plasma glucose by activating glycogenolysis, and

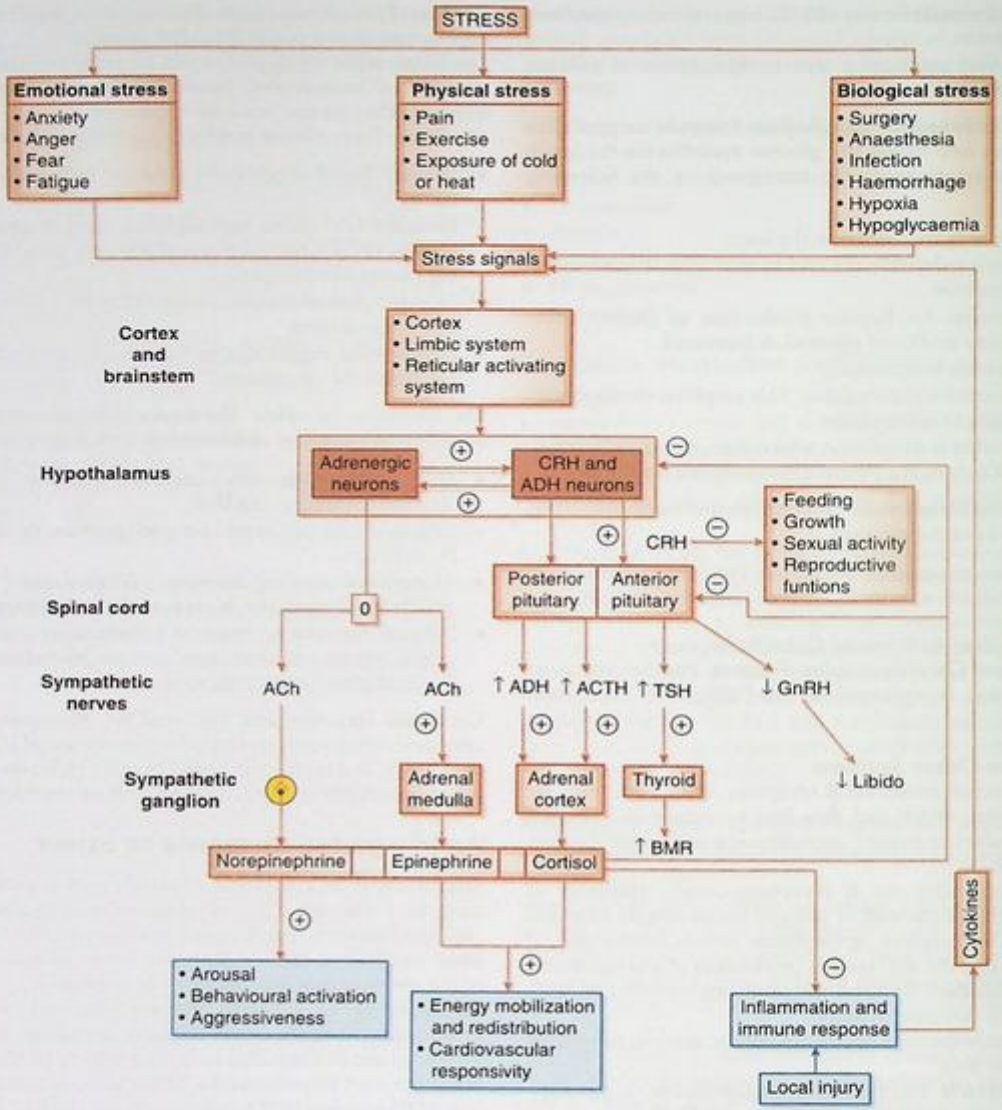


Figure 8.5-10 Steps involved in the adaptation to stress by an integrated response of the hypothalamic–pituitary–adrenal cortex axis and sympathoadrenal medullary system.

cortisol acts more slowly by providing amino acid substrate for gluconeogenesis. Together they shift glucose utilization towards the CNS away from the peripheral tissues.

- ***Free fatty acid supply:*** Epinephrine rapidly augments the supply of free fatty acids to heart and muscles, and cortisol facilitates the lipolytic role.
- ***Cardiovascular adjustments:*** Catecholamines and cortisol raise blood pressure and cardiac output, and they improve the delivery of substrates to tissues that are critical to the immediate defence of the organism.
- ***Inhibition of activities*** that are not useful during stress, and divert individuals and their resources from defensive responses to danger is an important part of adaptation to stress. For example, CRH input to the hypothalamic neurons inhibits its growth hormone, gonadotropin release and sexual activity.
- ***Interaction with immune system:*** The hormones produced during stress interact with the immune system to produce a balance between useful local cytokine production at threatened sites and potentially dangerous systemic effects of these immune system products.

Diseases of Adrenal Medulla

Phaeochromocytoma

Phaeochromocytoma is a rare benign tumour arising from the epinephrine- and norepinephrine-secreting chromaffin cells of adrenal medulla.

Clinical Features are produced by the excess of epinephrine and norepinephrine, and include the following:

- Episodic or nonepisodic hypertension with postural drop
- Attacks of tachycardia, palpitation, sweating, pallor, headache and chest discomfort
- Abdominal pain, vomiting, constipation and glucose intolerance
- Weight loss and weakness

SELF-ASSESSMENT

1. Discuss in brief the hormones secreted by adrenal cortex and why glucocorticoids are essential for survival.
2. Discuss the functions of cortisol and its regulation.
3. Describe briefly:
   - Anti-inflammatory and anti-allergic effects of glucocorticoids
   - ACTH
   - Mineralocorticoids
   - Regulation of aldosterone secretion
   - Cushing syndrome
   - Hyperaldosteronism
   - Addison disease
   - Escape phenomenon
   - Adrenergic receptors
   - Actions of catecholamines
   - Hormonal adaption to stress

8.6 Pancreatic Hormones

CHAPTER OUTLINE

Endocrine Pancreas
Functional Anatomy
Insulin
Structure and Biosynthesis
Regulation of Insulin Secretion
Plasma Insulin Levels, Circulation and Degradation
Actions of Insulin
Glucagon
Structure and Synthesis
Plasma Levels, Circulation and Degradation
Mechanism of Action of Glucagon
Actions of Glucagon
Insulin–Glucagon Ratio
Regulation of Glucagon Secretion
Somatostatin and Pancreatic Polypeptide
Somatostatin
Pancreatic Polypeptide
Hormonal Regulation of Blood Glucose Level

Applied Aspects
Diabetes Mellitus
Hypoglycaemia

ENDOCRINE PANCREAS

Functional Anatomy

The endocrine part of the pancreas comprises numerous rounded collections of cells known as *pancreatic islets* or the *islets of Langerhans*. These are embedded within the exocrine part, and they constitute 1%–1.5% of the human pancreatic mass.

Islets of Langerhans Each islet contains the following four types of cells (Fig. 8.6-1):

- ***Beta cells (β-cells)*** make up 60%–70% of the total cells and constitute the central core of the islet. These cells secrete insulin.
- ***Alpha cells (α-cells)*** form about 20% of the total cells and constitute the outer rim of the islet. These cells secrete glucagon.
- ***Delta cells (δ-cells)***form about 10% of total cells and are intermixed. These are source of somatostatin.
- ***Pancreatic polypeptide (PP) cells:*** These are also peripherally placed and scattered amongst the α-cells. These are sources of PP.

Insulin

Insulin is a polypeptide hormone secreted by the β-cells of islets of Langerhans of pancreas. Historically, insulin is the first hormone to be isolated, purified, crystallized and synthesized.

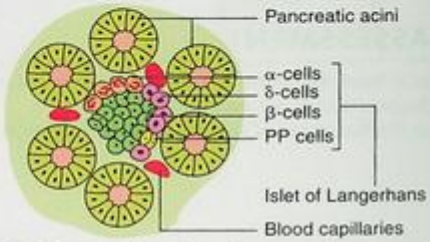


Figure 8.6-1 Schematic histological structure of pancreas showing an islet of Langerhans surrounded by exocrine pancreatic acini.

Structure and Biosynthesis

Structure The human insulin is a protein containing 51 amino acids, arranged in two polypeptide chains: A (having 21 amino acids) and B (having 30 amino acids). These chains are connected to each other by two interchain disulphide linkages (Fig. 8.6-2). Insulin is produced from the cleavage of pre-insulin to pro-insulin and then loss of C chain to insulin. The production of connecting peptide (C-peptide) is therefore used as a marker of endogenous insulin synthesis.

Regulation of Insulin Secretion

I. Role of Exogenous Nutrients Exogenous nutrients (glucose, amino acids, free fatty acids, ketoacids and potassium) control insulin secretion by a feedback mechanism (Fig. 8.6-3).

II. Role of Blood Glucose Insulin secretion is mainly controlled by level of blood glucose by a feedback relationship.

The relationship between plasma glucose and plasma insulin is sigmoidal, as shown in Fig. 8.6-4:

- Below 50 mg/dL levels of plasma glucose, virtually no insulin is secreted.
- Above 100 mg/dL levels of plasma glucose, rate of insulin secretion rises rapidly.
- At about 150 mg/dL levels of plasma glucose, a half-maximal insulin secretory response is obtained.
- At a level of about 300 mg/dL, a maximal insulin response occurs.

The rapidly increased insulin secretion above 100 mg/dL levels of plasma glucose, in turn, reduces blood glucose concentration to the fasting level. Reduction of blood glucose causes rapid turning off of insulin secretion (feedback relationship).

III. Role of Gastrointestinal and other Hormones

Gastrointestinal hormones, like gastrin, secretin, cholecystokinin and gastric-inhibitory polypeptide (GIP; most potent), cause a moderate increase in insulin secretion. These hormones are released immediately after meals, so they cause an anticipatory rise of insulin before actual absorption of glucose and amino acids.

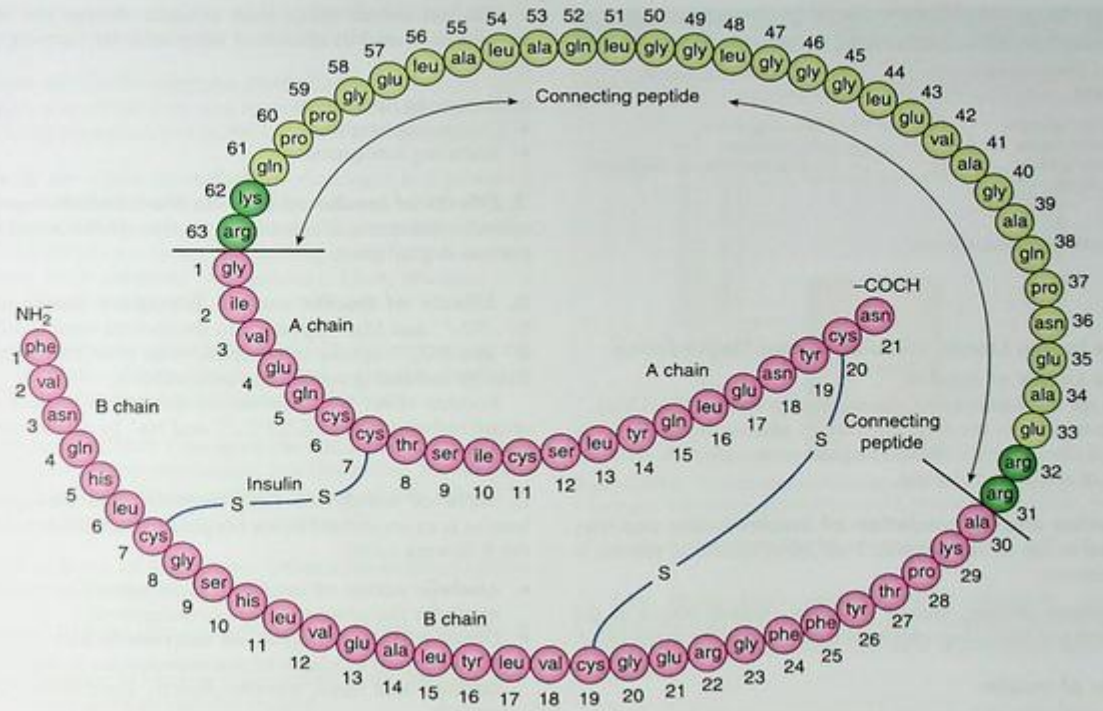


Figure 8.6-2 Structure of an insulin molecule.

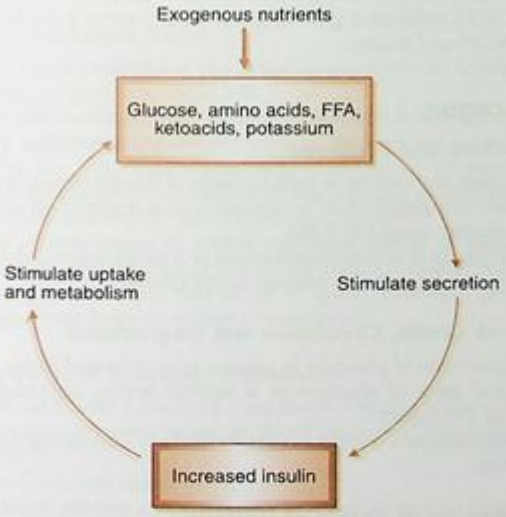


Figure 8.6-3 Feedback control of insulin release by exogenous nutrients.

Other hormones, such as growth hormone, cortisol, glucagon, and to a lesser extent progesterone and oestrogen, also stimulate insulin secretion. Prolonged secretion of any of these hormones can cause burning out of the islets of Langerhans, thereby causing diabetes mellitus.

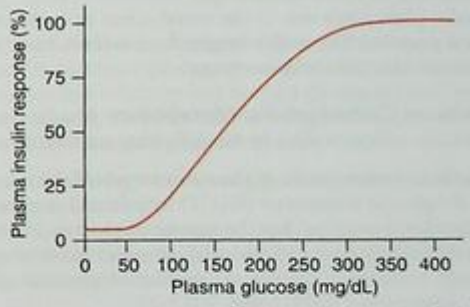


Figure 8.6-4 A sigmoidal relationship between levels of plasma glucose and insulin secretion response.

IV. Role of Sympathetic and Parasympathetic Nervous System

Sympathetic Nerves and Epinephrine Epinephrine is the most predominant inhibitor of insulin release. In emergency situations like stress, epinephrine suppresses insulin release and promotes energy-yielding compounds – glucose from liver and fatty acids from adipose tissue.

Parasympathetic Nerves to Pancreas and Acetylcholine (ACh) increase insulin secretion to the extent which stimulates insulin release. Some of the important factors stimulating and inhibiting insulin secretion are given in Table 8.6-1.

TABLE 8.6-1 Factors Stimulating and Inhibiting Insulin Secretion

Factors Stimulating Insulin Secretion	Factors Inhibiting Insulin Secretion
• ↑ Blood glucose • ↑ Amino acids • ↑ Fatty acids • Glucagon • GIP • ACh • Growth hormones, cortisol	• ↓ Blood glucose • Somatostatin • Norepinephrine, epinephrine

Plasma Insulin Levels, Circulation and Degradation

Plasma Levels of Insulin

- Average basal peripheral plasma insulin level is 10 μU/mL.
- A three-fold to ten-fold increase in plasma insulin level is noted after a typical meal. The peak occurs after 30–60 minutes of initiating the meal.

Circulation and Degradation of Insulin *Insulin circulates* unbound to any carrier protein. *Half-life of insulin* in plasma is 5–18 minutes.

- A protease enzyme, namely *insulinase* (mainly found in the kidneys and liver), degrades insulin and is excreted in the urine.

Actions of Insulin

A. Metabolic effects
B. Effects on ion transport
C. Role in cell growth and development

A. Metabolic Effects of Insulin

The insulin plays a key role in the metabolism of carbohydrate, lipids and proteins. The major targets for insulin actions are the muscle mass, liver and adipose tissue.

1. Effects on Carbohydrate Metabolism Insulin decreases blood glucose concentration by the following mechanisms:

(i) ***Insulin increases uptake of glucose in target cells*** by translocating the glucose transporter (GLUT) into the cell membranes:
- Insulin is required for the uptake of glucose by muscles (skeletal, cardiac and smooth), adipose tissue, leucocytes and mammary glands via sodium-dependent glucose transporters (SGLT-1 and SGLT-2).
- Tissues in which glucose transport is not insulin dependent include nervous tissue, kidney, RBC, retina, blood vessels and intestinal mucosa.

(ii) ***Insulin promotes glucose utilization*** *in the following ways:*
- Glycolysis (oxidation of glucose) is increased in muscle and liver by activating the enzymes photofructokinase and pyruvate kinase insulin.
- Glycogen formation from glucose in muscle and liver is promoted by activating glycogen synthetase insulin.

(iii) ***Insulin decreases glucose production by inhibiting*** *the following:*
- Gluconeogenesis
- Glycogenolysis

2. Effects on Lipid Metabolism The metabolism of both endogenous and exogenous fat is profoundly influenced by insulin.

The net overall effect is to enhance storage and to block mobilization and oxidation of fatty acids by carrying out the following:

- Favouring lipogenesis
- Decreasing lipolysis
- Reducing ketogenesis

3. Effects of Insulin on Protein Metabolism Insulin is an anabolic hormone; it stimulates protein synthesis and inhibits protein degradation.

B. Effects of Insulin on Ion Transport Insulin increases K^+, PO_4^{3-} and Mg^{2+} uptake into the skeletal muscle cell and of K^+ and PO_4^{3-} uptake into hepatic cells from the extracellular fluid by increasing membrane permeability.

Another effect of insulin on the electrolytic balance is to increase reabsorption of K^+, PO_4^{3-} and Na^+ by the tubules of the kidney.

C. Role of Insulin in Cell Growth and Development Insulin is an important factor for growth and development with the following roles:

- ***Anabolic action*** of insulin is as important as growth hormone for the promotion of normal growth.
- ***Direct stimulatory effect on macromolecules:*** Insulin also stimulates the synthesis of macromolecules in tissues such as cartilage and bone, thereby directly contributing to body growth.
- ***Stimulation of other growth factors:*** The genes for insulin and its receptors are related to genes that encode a variety of tissue growth factors. These growth factors include somatomedins (insulin-like growth factors 1 and 2, i.e. IGF-1 and IGF-2), epidermal growth factor (EGF), nerve growth factor (NGF) and relaxin.

Glucagon

Structure and Synthesis

Glucagon secreted by α-cells of islets of Langerhans is a polypeptide composed of 29 amino acids in a single chain and has a molecular weight of 3500.

Glucagon is actually synthesized as a proglucagon, which on sequential degradation releases active glucagon.

Plasma Levels, Circulation and Degradation

- *Circulation of glucagon* in plasma is in unbound form.
- *Basal levels of glucagon* in a normal fasting individual are 100–150 pg/mL.
- *Degradation* – mainly occurs in the liver and excreted in the urine.

Mechanism of Action of Glucagon

Glucagon binds to the specific receptor on the plasma membrane of target cells and acts through the mediation of cyclic AMP as a second messenger.

Actions of Glucagon

The actions of glucagon, in almost all respects, are exactly opposite to those of insulin. It promotes mobilization of stored

nutrients such as glucose, fatty acids and ketoacids, and thus is a hormone of energy release. Its metabolic effects are as follows:

1. Effects on Carbohydrate Metabolism Glucagon predominately acts on the liver and increases the blood sugar level by increasing glycogenolysis in the liver and gluconeogenesis.

2. Effects on Lipid Metabolism Glucagon is a powerful *lipolytic agent*. It activates lipase in adipose tissue, which releases free fatty acid (FFA) and glycerol into the circulation. In the liver, excess of FFAs are oxidized, resulting in energy production and ketone body synthesis (ketogenesis). Thus, glucagon is a ketogenic as well as a hyperglycaemic hormone.

3. Effects on Protein Metabolism Glucagon increases the amino acid uptake of liver, which, in turn, promotes gluconeogenesis. Thus, glucagon *lowers plasma amino acids*.

4. Calorigenic Effect Glucagon also has a calorigenic effect. This is not due to hyperglycaemia, but this action requires the presence of glucocorticoids and T_4. It is probably related to increased hepatic deamination of amino acids.

5. Other Actions of Glucagon Other miscellaneous actions of glucagon include the following:

- Inhibition of renal tubular sodium reabsorption, resulting in natriuresis
- Modest increase in force of contraction of the heart by activation of myocardial adenylyl cyclase
- Stimulation of secretion of growth hormone, insulin and pancreatic somatostatin
- Synthesis of glucagon in the central nervous system (CNS), which may act locally in the regulation of appetite

Insulin–Glucagon Ratio

Under basal conditions, the usual molar ratio of insulin to glucagon in plasma is about 2.0.

Under circumstances that require mobilization and increased use of endogenous substrate, such as fasting and prolonged exercise, the insulin–glucagon ratio drops to 0.5 or less. Low insulin–glucagon ratio is helpful in maintaining glucose supply to the CNS and energy requirements of the body.

Under circumstances in which substrate storage is advantageous, such as after a pure carbohydrate load or a mixed meal, the insulin–glucagon ratio rises to 10 or more. This high insulin–glucagon ratio helps in storage of substrate.

Regulation of Glucagon Secretion

I. Role of Blood Levels of Nutrients There exists a feedback relationship between blood levels of glucagon and nutrients (Fig. 8.6-5).

1. Blood Glucose Level

Low blood glucose concentration is the most potent stimulus for secretion of glucagon. Hypoglycaemia causes twofold to fourfold increase in plasma levels of glucagon (Fig. 8.6-5).

High blood glucose concentration inhibits glucagon secretion (Fig. 8.6-5).

2. Plasma Amino Acids Secretion of glucagon is increased by a protein-rich meal. There exists a feedback relationship, i.e. amino acids stimulate glucagon secretion, and glucagon, in turn, stimulates the conversion of amino acids into glucose (Fig. 8.6-5).

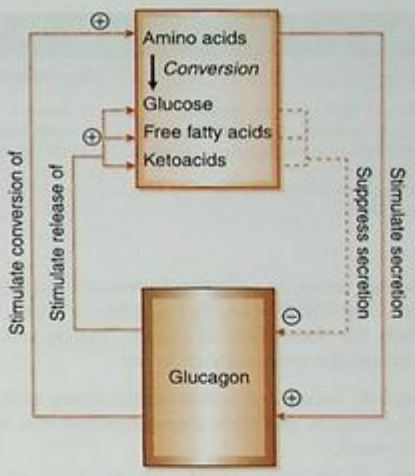


Figure 8.6-5 Feedback relationship between glucagon and nutrients. Glucagon stimulates production and release of glucose, free fatty acids and ketoacids, which, in turn, suppress glucagon secretion, and glucagon, in turn, stimulates the conversion of amino acids into glucose.

3. Free Fatty Acids and Ketoacids Glucagon stimulates production and release of FFA and ketoacids, which, in turn, suppress glucagon secretion, i.e. there is a feedback relationship (Fig. 8.6-5).

II. Role of Gastrointestinal Hormones Gastrointestinal hormones, such as cholecystokinin (CCK), gastrin and GIP, increase glucagon secretion. This accounts for the enhanced glucagon response to orally ingested nutrients, as opposed to the responses to intravenously delivered nutrients.

III. Role of Nervous System *Sympathetic nerve stimulation* to pancreas increases glucagon secretion. Various stresses, fasting, exercise and infection increase the glucagon secretion partly by their stimulatory effect on the sympathetic nervous system and partly by release of glucocorticoids.

- Vagal stimulation and acetylcholine also acutely increase glucagon secretion.
- Neurohormone somatostatin inhibits the secretion of glucagon, probably by paracrine or neurocrine effects made possible by the islet microarchitecture.

Somatostatin and Pancreatic Polypeptide

Somatostatin

Structure and Synthesis Pancreatic somatostatin is a neuropeptide containing 14 amino acids, synthesized by δ-cells. It is also synthesized by the intestinal cells and was originally discovered as a hypothalamic neuropeptide that inhibits growth hormone secretion.

Regulation of Secretion The main factors that affect somatostatin secretion are given in Table 8.6-2.

Actions Somatostatin has the following effects:

- Acts on the islets of Langerhans and inhibits secretion of insulin and glucagon
- Increases the motility of stomach, duodenum and gall bladder

TABLE 8.6-2 Major Stimuli Affecting Somatostatin Secretion

Increased by	Decreased by
1. Ingestion of food, due to increase in blood glucose level, amino acids, fatty acids and GIT hormones 2. Glucogen 3. β-Adrenergic neurotransmitter 4. Acetylcholine	1. Insulin 2. α-Adrenergic neurotransmitter

- Decreases secretion of hydrochloric acid, pepsin, gastrin, secretin, intestinal juices and pancreatic juice
- Inhibits the absorption of glucose, xylose and triglycerides across the mucosal membrane

In a nutshell, actions of somatostatin along with those of insulin and glucagon, probably coordinate nutrient input with substrate disposal.

Pancreatic Polypeptide (PP)

Structure and Synthesis PP has 36 amino acids. It is synthesized by the PP cells of islets of Langerhans.

Regulation of Secretion PP is secreted in response to food ingestion via gastrointestinal secretagogues and cholinergic stimulation. Its secretion is also stimulated by hypoglycaemia and inhibited by glucose administration.

Actions and Physiological Importance Its best-known action is to inhibit exocrine pancreatic secretion. Its true physiological importance is not known.

Hormonal Regulation of Blood Glucose Level

A healthy individual is capable of maintaining the blood glucose level within a narrow range.

- Fasting blood glucose level in a postabsorptive state varies between 70 and 110 mg/dL.
- Postprandial blood glucose level, i.e. after a large carbohydrate meal or following oral administration of glucose in the dose of 1 g/kg body weight, the blood glucose level increases to about 140 mg/dL (less than 150 mg/dL) in a period of less than 1 hour. However, if this response to oral administration of carbohydrate is plotted on a time scale, then it is called the *glucose tolerance curve* (Fig. 8.6-6), and is used clinically as a test to study the maintenance of blood glucose levels.

Role of Hormones in Regulation of Blood Glucose Under normal circumstances, the various hormones play a significant role in maintaining the blood glucose levels within the normal physiological range. This is accomplished by preventing the occurrence of hyperglycaemia and hypoglycaemia.

Prevention of Occurrence of Hyperglycaemia The occurrence of hyperglycaemia after a pure carbohydrate load or a mixed meal in a healthy individual is prevented by a manifold (4–5 times) increase in insulin secretion (for details, see 'Actions of Insulin').

Prevention of Occurrence of Hypoglycaemia Hypoglycaemia, which may occur due to fasting or prolonged exercise, is prevented in a healthy individual by a number of hormones, which include glucagon, epinephrine, growth hormone and glucocorticoids. It is obvious that there is only one hormone, insulin, which prevents hyperglycaemia, whereas at least four hormones are available for the prevention of hypoglycaemia.

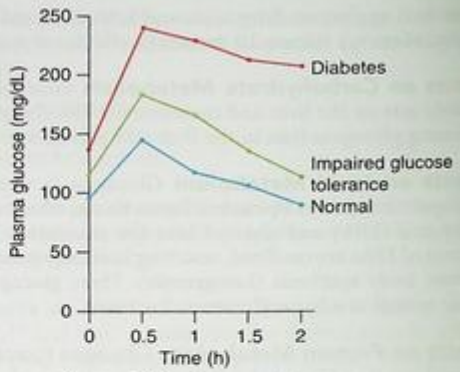


Figure 8.6-6 Glucose tolerance curve.

APPLIED ASPECTS

Important applied aspects of endocrine pancreas which need mention are as follows:

- Diabetes mellitus
- Hypoglycaemia

Diabetes Mellitus

Diabetes mellitus, commonly called diabetes, refers to a clinical syndrome of hyperglycaemia occurring due to deficiency of insulin.

Types and Stages of Diabetes Mellitus

Diabetes mellitus can be classified into the following types:

1. ***Primary diabetes mellitus,*** in which the cause is not known. It is further divided into the following two types:
   - Insulin-dependent diabetes mellitus (IDDM or type I)
   - Noninsulin–dependent diabetes mellitus (NIDDM or type II)
2. ***Secondary diabetes mellitus***: It is associated with certain pathological conditions such as pancreatitis, cystic fibrosis, acromegaly and Cushing syndrome.

Insulin-Dependent Diabetes Mellitus

- IDDM or type I diabetes is considered an autoimmune disorder in which antibodies destroy the β-cells of islets, causing an absolute deficiency of insulin.
- Genetic susceptibility is a major determinant, whereas environmental factors act as a trigger.

Noninsulin–Dependent Diabetes Mellitus NIDDM or type II diabetes is also a genetic disorder. It is supposed to occur due to decrease in insulin receptors on the insulin responsive (target) cells.

IDDM versus NIDDM The comparison between IDDM and NIDDM is given in Table 8.6-3.

Pathophysiology of Diabetes Mellitus

Pathophysiology of diabetes mellitus revolves around the metabolic alterations associated with insulin deficiency. Most important among them are hyperglycaemia, ketoacidosis, hypertriglyceridaemia and protein catabolism (Fig. 8.6-7).

TABLE 8.6-3 IDDM Versus NIDDM

Feature	IDDM (Type I)	NIDDM (Type II)
General features		
Defect	Insulin deficiency due to β-cell destruction	Resistance of target tissues to insulin
Prevalence	10%–20% of diabetic population	80%–90% of diabetic population
Age of onset	<40 years	>40 years
Body weight	Low (thin and lean)	High (obese or normal)
Gene locus	Chromosome 6	Chromosome 1
Family history	Mild or moderate	Very strong
Clinical features		
Duration of symptoms	Weeks (rapid)	Months to year (slow)
Presenting symptoms	Polyuria, polydipsia, polyphagia	Usually patients present with different complications
Complication at the time of diagnosis	Absent	Present (in 10%–20% cases)
Acute complication	Ketoacidosis	Hyperosmolar coma
Biochemical features		
Plasma insulin	Decreased or absent	Normal or increased
Autoantibodies	Frequently found	Rare
Ketonuria	Present	Absent
Treatment		
Treatment of choice	Insulin (oral hypoglycaemics not useful)	Oral hypoglycaemics (insulin usually not required)
Mortality if not treated	High	Low

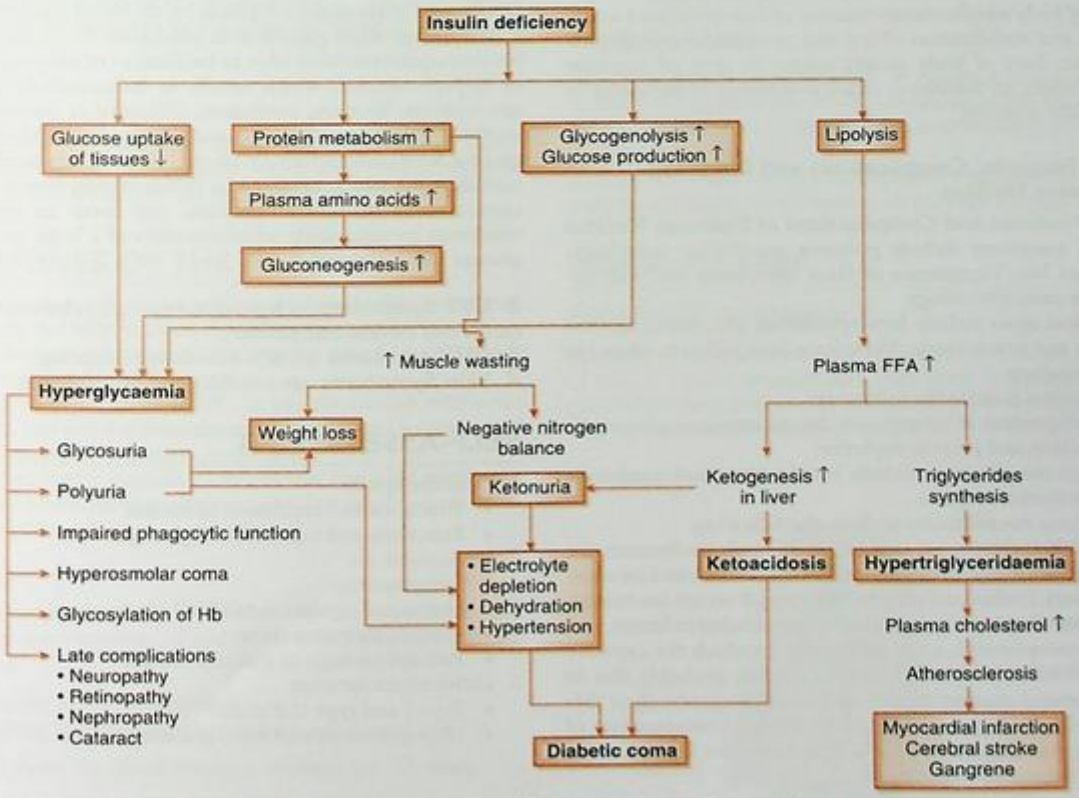


Figure 8.6-7 Pathophysiology of diabetes mellitus and its complication.

Hyperglycaemia and Its Consequences Hyperglycaemia (elevation of blood glucose concentration) is the characteristic feature of uncontrolled diabetes mellitus. It occurs due to lack of insulin. The consequences of hyperglycaemia are as follows:

- ***Glycosuria,*** i.e. excretion of glucose into the urine, occurs when the blood glucose level rises above the renal threshold point, i.e. above 180 mg/dL.
- ***Polyuria,*** i.e. passage of a large amount of urine frequently: It is the result of osmotic diuresis caused by renal excretion of osmotically active glucose molecules.
- ***Loss of electrolytes*** (sodium, potassium and phosphate) in urine also occurs as a side effect of osmotic diuresis.
- ***Cellular dehydration:*** High glucose concentration increases the osmotic pressure of the ECF and osmotic transfer of water from cells to the ECF, leading to dehydration of cells. In addition, osmotic diuresis causes an increased loss of water from the body, thereby reducing the ECF volume, which also causes compensatory dehydration of cells.
- ***Polydipsia,*** i.e. excessive drinking of water, results from the activation of thirst mechanism caused by cellular dehydration.
- ***Increased caloric loss*** is the result of loss of glucose in urine.
- ***Polyphagia,*** i.e. excessive eating, occurs due to stimulation of the satiety centre caused by insufficient utilization of glucose in the hypothalamic ventromedial nuclei. Increased caloric loss also results in compensatory polyphagia.
- ***Loss of body weight*** occurs because of loss of calories in the urine, and mobilization of fats and proteins for energy production. Loss of body weight occurs in spite of excessive food intake, so diabetes is called a *condition of starvation in the midst of plenty.*

Clinical Features, Complications and Diagnosis of Diabetes Mellitus

Clinical Features and Complications of Diabetes Mellitus

Cardinal symptoms include polyuria, polydipsia, polyphagia and weight loss. Occurrence of these symptoms has been explained in pathophysiology.

Biochemical signs include hyperglycaemia, glycosuria, ketosis, ketonuria and ketoacidosis. These have been fully elucidated in pathophysiology.

Complications include the following:

- *Predisposition to infections* is due to impaired phagocytic function and protein depletion
- *Acute complications* include ketotic coma and nonketotic hyperosmolar coma.
- *Chronic complications* include the following:
  - *Atherosclerosis,* i.e. deposition of lipids underneath the tunica intima of blood vessels. The common sites are coronary, cerebral and peripheral arteries. It occurs due to long-standing hyperlipidaemia and hypercholesterolaemia.
- *Microangiopathy,* a vascular lesion in which the capillary basement membrane becomes thicker, probably due to structural changes caused in tissue proteins by their glycosylation. It is responsible for common complications of long-standing diabetes, which includes the following:
  - Diabetic retinopathy
  - Diabetic nephropathy
  - Diabetic neuropathy

Hypoglycaemia

Hypoglycaemia refers to a clinical condition caused by blood glucose levels below 45 mg/dL (2.5 mmol/L). The human body has a well-regulated system for an efficient maintenance of blood glucose concentration. However, still hypoglycaemia (though not common) is observed under some circumstances.

Types and Causes of Hypoglycaemia

Broadly, hypoglycaemia may be divided into the following two types:

- Hypoglycaemia in nondiabetic patients
- Hypoglycaemia in diabetic patients (more common)

Symptoms and Signs of Hypoglycaemia

Symptoms and signs of hypoglycaemia occur due to effects of low levels of glucose per se (mainly on the nervous system, especially the brain) and because of sympathetic stimulation (mainly on the CVS, GIT and skin).

1. CNS symptoms are called *neuroglycopenic symptoms.* Metabolism of brain mainly depends on the blood glucose level, so it is depressed when glucose level falls below 50–70 mg/dL. CNS becomes quite excitable (due to facilitation of neuronal activity by hypoglycaemia), which results in hallucinations, extreme nervousness, tremors, confusion, difficulty in concentration, incoordination, convulsions and drowsiness. When blood glucose levels fall further (<30 mg/dL), hypoglycaemic coma may develop, which needs to be differentiated from hyperglycaemic coma in diabetic patients, and needs an emergency treatment by immediate administration of a large quantity of glucose intravenously.

2. CVS Symptoms in hypoglycaemia are palpitation, tachycardia and cardiac arrhythmias.

3. GIT Symptoms include nausea and vomiting.

4. Skin Symptoms are sweating and hypothermia.

SELF-ASSESSMENT

1. Describe briefly:
   - Functions and regulation of insulin
   - Functions and regulation of glucagon
2. Write notes on:
   - Somatostatin
   - Hormonal regulation of blood glucose level
   - Glucose tolerance curve
   - Pathophysiology of diabetes mellitus
3. Differentiate between
   - Type I and type II diabetes
   - Hypoglycaemic and hyperglycaemic coma

8.7 Endocrine Functions of Other Organs and Local Hormones

CHAPTER OUTLINE

Hormones of the Heart
Actions

Hormones of the Kidney
Renin
1,25-dihydroxycholecalciferol
Erythropoietin

Pineal Gland
Functional Anatomy
Melatonin

Thymus
Functional Anatomy
Functions

Local Hormones
Prostaglandins and Related Substances
Other Local Hormones Synthesized in Tissues

In addition to the main endocrine glands described in the previous chapters, the other organs which have endocrine functions are heart, kidney, pineal gland, thymus and others.

HORMONES OF THE HEART

The heart also acts as an endocrine organ. The hormones secreted by the heart include the following:

Atrial Natriuretic Peptide (ANP) It was the first natriuretic hormone isolated from the heart.

Brain Natriuretic Peptide (BNP) It was the second natriuretic hormone, first isolated from the porcine brain and hence named BNP. In humans, it is present in the heart.

C-type Natriuretic Peptide (CNP) It was the third natriuretic hormone to be isolated in sequence and so named C-type natriuretic peptide.

Actions

1. Increase in Sodium Excretion by Kidneys ANP and BNP increase excretion of sodium ion in urine through the following:

- Increasing glomerular filtration
- Inhibiting Na^+ reabsorption at the level of renal tubules

2. ANP Lowers the Blood Pressure through the following:

- Increasing the capillary permeability, leading to extravasation of fluid and a decline in blood pressure
- Relaxing vascular smooth muscle (VSM) in arterioles and venules

HORMONES OF THE KIDNEY

The kidneys secrete the following three hormones:

- Renin
- 1,25-dihydroxycholecalciferol (see page 323)
- Erythropoietin

Renin

Renin is a glycoprotein with a molecular weight of 37,326 in humans secreted by the granular cells of juxtaglomerular apparatus of the kidneys into the blood stream.

Actions: The only action of active renin is to convert angiotensinogen (renin substrate) into angiotensin-I. For further details about the renin–angiotensin system, see page 157.

Erythropoietin

Erythropoietin is a glycoprotein. In adults, it is mainly (85%) secreted by the juxtaglomerular apparatus of the kidneys with some contribution (15%) from the perivenous hepatocytes in the liver.

Actions The main role of erythropoietin is to stimulate the bone marrow and cause erythropoiesis (for details, see page 65).

PINEAL GLAND

Functional Anatomy

Pineal gland, also known as epiphysis, is a small structure (5 mm × 7 mm) shaped like a pine cone. It is situated in the groove between the two superior colliculi in the diencephalic area of brain above the hypothalamus (Fig. 8.7-1).

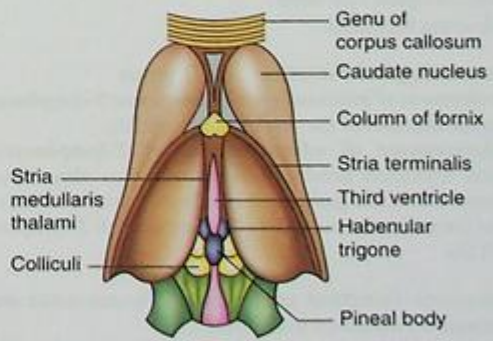


Figure 8.7-1 Location of pineal body in the groove between the two superior colliculi.

Structure The pineal stroma has two types of cells: neuroglial and parenchymal. The *parenchymal cells* are large epithelial cells having secretory function.

- *In infants*, the pineal gland is large and the cells tend to be arranged in alveoli.
- *In adults*, the pineal gland gets calcified, i.e. small concretions of calcium phosphate and carbonate (*pineal sand*) appear in the tissue.

Melatonin

The hormone melatonin is synthesized by the parenchymal cells of the pineal gland.

Functions of Melatonin are as follows:

1. ***Role in circadian rhythm of the body:*** Melatonin secretion shows a diurnal variation. It is secreted more during the dark period of the day than during the day-light hours. This correlates with various internal activities in different periods of the day, i.e. circadian rhythm.
2. ***Effects on the gonads:*** Melatonin exerts both inhibitory and facilitatory effects on the gonads due to the diurnal change in the melatonin secretion. It inhibits onset of puberty.
3. ***Effect on MSH and ACTH secretion:*** An inhibitory effect of melatonin on MSH and ACTH secretion has been reported.
4. ***Sleep.*** Melatonin has a role in induction of sleep.

THYMUS

Functional Anatomy

Thymus is a small lymphoid structure located in the lower part of neck in front of the trachea, below the thyroid gland. At birth, it is small (weighing 10–12 g), gradually enlarges till puberty and then it starts decreasing in size in the old age.

Histologically, thymus consists of the inner medulla and outer cortex.

- *Medulla*: It comprises reticular epithelial cells, a few lymphocytes and concentric corpuscles of Hassall.
- *Cortex*: It includes actively multiplying, closely packed lymphocytes and contains no Hassall's corpuscles.

Functions

Thymus performs the following two functions:

- Immunological functions
- Endocrine functions

1. Immunological Functions of Thymus

(i) Development of immunologically competent T-lymphocytes is an essential function of the thymus (see page 83).

(ii) Maintenance of adequate pool of T-lymphocyte The hormone thymosin produced by the thymus also stimulates lymphopoiesis in the peripheral lymphoid tissue and thus plays a role in the maintenance of an adequate pool of T-lymphocytes in adult life.

2. Endocrine Function of Thymus Thymus tissue secretes two hormones: thymosin and thymin.

(i) Thymosin It is a peptide, which, as described above, promotes proliferation of T-lymphocytes in the thymus and peripheral lymphoid tissue.

(ii) Thymin, also called thymopoietin, inhibits acetylcholine release at motor nerve endings and thus suppresses neuromuscular activity.

LOCAL HORMONES

The local hormones are the substances which are produced in many tissues, and when activated in certain circumstances, execute their actions in the same area or in the immediate neighbourhood. Commonly produced local hormones are discussed below.

Prostaglandins and Related Substances Prostaglandins (PGs) and related substances include thromboxanes, prostacyclin, leukotriene and lipoxin. These substances are called *eicosanoids,* reflecting their origin from *arachidonic acid,* linoleic and linolenic acid.

Prostaglandins were so named by Von Euler in 1937 because they were first isolated from prostatic secretion in semen. However, now they are known to be synthesized in almost all tissues of the body. Presently, a variety of PGs are identified.

Actions of PGs PGs have multitudinous and varied actions on almost all tissues of the body. Many of them are discussed in the chapters on the systems in which they play an important role. Some important actions of PGs are as follows:

1. ***Actions on cardiovascular system:*** They cause peripheral arteriolar dilatation, especially in the splanchnic and muscular beds.
2. ***Actions on kidneys:*** PGA_2 increases renal cortical blood flow and urinary excretion of sodium, potassium and water.
3. ***Actions on the female reproductive system are as follows:***
   - Initiate labour by stimulating contraction of gravid uterus
   - Responsible for painful uterine contractions during menstruation (dysmenorrhoea)
   - Promote secretion of hypothalamic gonadotropin releasing hormone (GnRH)
4. ***Role of PGs in inflammation:*** PGs mediate the following effects of inflammation:
   - Increase vascular permeability and cellular infiltration
   - Pain-producing effect of bradykinin by sensitizing cutaneous nerves
5. ***Action on blood platelets is as follows:***
   - PGE-1 inhibits platelet aggregation.
6. ***Action on bronchial musculature is as follows:***
   - $PGE_{2\alpha}$ causes contraction of bronchial smooth muscles and may precipitate bronchial asthma.
7. ***Actions on GIT are as follows:***
   - Inhibit the secretion of gastric HCl
   - Cause inhibition of sodium and water absorption, producing profuse watery, cholera-like diarrhoea
   - Increase intestinal motility
8. ***Actions on nervous system are as follows:***
   - On the central nervous system (CNS), the PGs function as transmitters or modulators of neuron activity.

Actions of Thromboxane A_2 Thromboxane A_2 is synthesized by platelets. It promotes the following:

- Vasoconstriction
- Platelet aggregation

Actions of Prostacyclin Prostacyclin is produced in vascular endothelium. It produces vasodilatation.

Actions of Leukotrienes Leukotrienes are mediators of allergic responses and inflammation. Their release is provoked when specific allergens combine with IgE antibodies on the surfaces of mast cells.

Actions of Lipoxins Physiological role of lipoxins is uncertain. Their actions include the following:

- Dilatation of microvasculature (by lipoxin A)
- Inhibition of cytotoxic effects of natural killer cells (by lipoxin A and lipoxin B)

Other Local Hormones Synthesized in Tissues In addition to PGs and related substances, the other local hormones synthesized in the tissues are as follows:

- Acetylcholine
- Serotonin
- Histamine
- Substance P
- Heparin
- Gastrointestinal hormones

SELF-ASSESSMENT

Describe briefly:

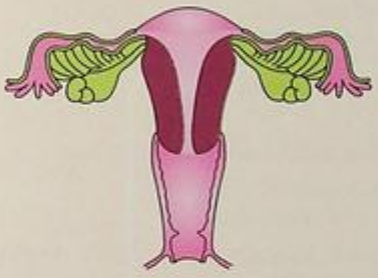
- Hormones of kidney
- Pineal gland
- Thymus
- Prostaglandins

SECTION 9

Reproductive System

SECTION OUTLINE

9.1 Sexual Growth and Development
9.2 Male Reproductive Physiology
9.3 Female Reproductive Physiology
9.4 Physiology of Pregnancy and Parturition
9.5 Physiology of Lactation
9.6 Physiology of Contraception



Reproduction is a multidimensional subject with physiological, biochemical, genetic, psychological, emotional, social, economic, moral and many other aspects. The physiology of reproductive system begins with *sex determination*, i.e. genetic differentiation which occurs during fertilization. An ovum always contains 22 + X chromosomes, whereas a sperm may contain either 22 + X or 22 + Y chromosomes. Therefore, after fertilization, the zygote's chromosomal patterns can be either 44 + XX (i.e. female genotype) or 44 + XY (i.e. male genotype). The next step in reproductive physiology is *sex differentiation*, which begins at about 7–8 weeks of intrauterine life when the primitive, bipotential sex gland or gonad (gone = seed) differentiates into either testis or ovary depending on the genotype (gonadal differentiation). From this point onwards, there occurs development of male or female accessory sex organs *(genital differentiation or phenotype)*. After remaining quiescent during childhood, the gonads suddenly awaken into vigorous activity for a period of 3–4 years during which gonadal development and maturation reaches to the point where reproduction is possible for the first time. During this phase, there also occurs a sudden spurt of physical growth and the child grows into an adult. This transitional period between the childhood and adulthood is called period of *puberty*, during which the secondary sex characters develop.

The adult *male* and *female reproductive physiology* involves gametogenic and endocrinal functions of testes and ovaries, respectively. In a sexually active female, the *physiology of pregnancy* involves fertilization at a proper time and place (fallopian tube), development of the fetus in mother's womb and finally birth of a new human being, either male or female.

After childbirth, the mother continues to provide nourishment by breastfeeding for a further period of 6–9 months *(physiology of lactation)*.

The understanding of reproductive physiology is important not only for the promotion of conception and normal fetal growth but also for the prevention of conception *(physiology of contraception)* for population control, which is of global concern.

The point when reproductive physiology ends is called *climacteric* (literally meaning, a major turning point). In females it is *menopause*; but in males there is no sharp point.

9.1 Sexual Growth and Development

CHAPTER OUTLINE

Prepubertal Sexual Growth and Development
Sex Determination
Human Chromosomes
Human Gametes
Genetic Sex Determination
Sex Differentiation
Gonadal Differentiation
Genital Differentiation
Psychological Differentiation

Puberty and Adolescence
Introduction
Components of Puberty
Spurt of Physical Growth
Appearance of Secondary Sex Characters
Hormonal Changes during Puberty
Control of Onset of Puberty
Disorders of Puberty
Precocious Puberty
Delayed or Absent Puberty

PREPUBERTAL SEXUAL GROWTH AND DEVELOPMENT

In human embryo sexual growth involves two processes:

- Sex determination
- Sex differentiation

Sex Determination

Sex Determination, also known as *genetic differentiation*, refers to the genotype of the fetus, whether male or female. The genotype is determined by the presence of sex chromosomes, hence is also known as *chromosomal sex differentiation.*

Human Chromosomes Each cell (except ovum and sperm) in a normal adult male and female possesses 46 chromosomes (44 autosomes + 2 sex chromosomes) usually arranged in an arbitrary pattern (karyotype).

- *Sex chromosomes* are called X and Y chromosomes.
- *The females* possess 44 autosomes plus 2X chromosomes (44 + XX).
- *The males* possess 44 autosomes plus an X chromosome and a Y chromosome (44 + XY).

Human Gametes The mature male gametes are called sperms and mature female gametes are called ova. During gametogenesis there occurs meiosis (*reduction division*); therefore the mature sperm and ovum contain half the number of chromosomes, i.e. 23 (22 autosomes + one sex chromosome). This is called *haploid* number.

- The primitive female germ cells (*oogonia*) from which mature ova are formed contain 44 + XX chromosomes, so each ovum will contain 22 + X chromosomes (Fig. 9.1-1).
- The primitive male germ cells (spermatogonia) from which mature sperms are formed contain 44 + XY chromosomes, so half of the normal sperms will contain 22 + X and other half will have 22 + Y chromosomes (Fig. 9.1-1).

Genetic Sex Determination of the embryo occurs during fertilization, i.e. penetration of the ovum by the sperm as:

- When an ovum (22 + X) is fertilized by a sperm containing 22 + X chromosomes, the resultant zygote's chromosomal pattern will be 44 + XX (*female genotype*).
- When an ovum (22 + X) is fertilized by a sperm containing 22 + Y chromosomes, the resultant zygote's chromosomal pattern will be 44 + XY (*male genotype*).

Sex Differentiation

After fertilization, the normal sex differentiation in the embryo proceeds sequentially. The stages of sex differentiation are as follows:

- Gonadal differentiation
- Genital differentiation
- Psychological differentiation

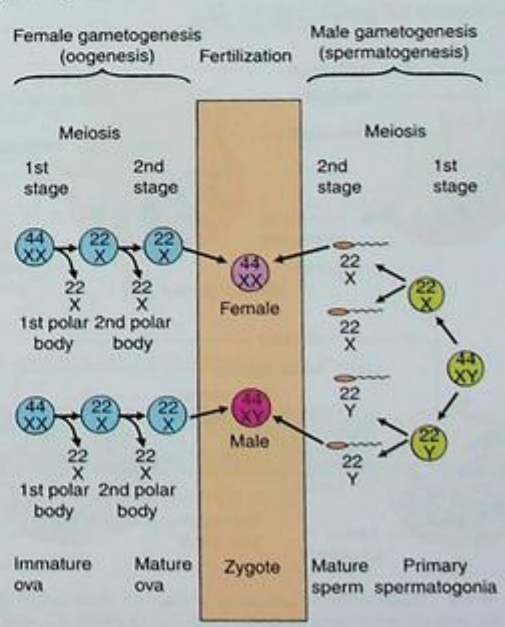


Figure 9.1-1 Basis of genetic sex determination.

Gonadal Differentiation

Gonadal differentiation or *gonadogenesis* refers to the formation of gonads, i.e. testes in males and ovaries in females. Gonadal sex differentiation is dependent on the genotype of the embryo.

Genital ridge or the urogenital ridge (the condensation of mesenchymal tissue present on each side near the adrenal glands) is the site where gonads develop.

Bipotential gonads. Bipotential gonads are also known as primordial or primitive or indifferent or ambisexual gonads. Up to 6 weeks of gestation the bipotential gonads are identical in both sexes, and have the rudiments of both male and female gonads.

Testicular Differentiation In genetic male (44 + XY) embryo, the bipotential gonads begin to differentiate into testes at approximately sixth week. The Y chromosome plays key role in the process of testicular differentiation.

Role of Y Chromosome in Testicular Differentiation

- Two transcription genes, one for testicular differentiation and another for the formation of Mullerian duct inhibitory substance (MIS), are present on the Y chromosome.
- The gene responsible for testicular differentiation is called SRY gene (SRY = sex-determining region of the Y chromosome).
- The SRY gene encodes the *testis-determining factor* (TDF), which triggers the testicular differentiation.
- The TDF gene product causes Sertoli cell differentiation, which is critically important for all events in male sexual differentiation.

Ovarian Differentiation

- In genetic female (44 + XX) embryo, by about 10th week of gestation, ovarian differentiation occurs in the absence of TDF.
- The ovaries develop on each side from the cortical region of the bipotential gonad (Fig. 9.1-2C).

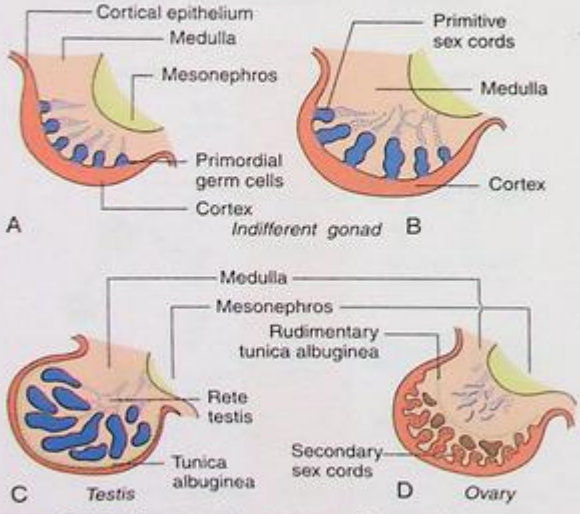


Figure 9.1-2 Diagrammatic structure of human bipotential gonad (A and B), and development of testis from the medulla (C) and ovary from the cortex (D).

Genital Differentiation

Genital sex differentiation, also known as *phenotypic sex differentiation*, refers to the differentiation of internal and external genitalia.

Differentiation of Internal Genitalia

- The internal genitalia differentiate from the *neutral sex anlagen*, which develops during sixth week of gestation along with the development of bipotential gonad.
- The primordia of internal genitalia are a paired set of Wolffian (male) ducts and a paired set of Mullerian (female) ducts. By 7th week of gestation, the embryo has both male and female primordial ducts (Fig. 9.1-3).

Differentiation of Male Internal Genitalia In the genetic male fetus (44 + XY) with functioning testes (Fig. 9.1-3B):

- The testosterone secreted by the Leydig cells stimulate the Wolffian ducts to form the epididymis, vas deferens and seminal vesicles.
- The Mullerian duct inhibitory substance (MIS) causes regression of the Mullerian ducts by apoptosis.

Differentiation of Female Internal Genitalia (Fig. 9.1-3C)

- In the genetic female fetus (44 + XX), in the absence of MIS, the female ducts (Mullerian ducts) proliferate and form oviduct (uterine tubes), uterus and upper two-thirds of vagina.
- In the absence of testosterone, Wolffian ducts degenerate.

Differentiation of External Genitalia The external genitalia in both sexes develop from *common anlagen*, which are the urogenital sinus, the genital sinus, the genital tubercle, the genital swelling and the genital (urethral) folds (Fig. 9.1-4).

The external genitalia derived from the common anlagen in male and female are shown in Table 9.1-1.

Psychological Differentiation

Psychological sex differentiation refers to a normal sexual behaviour in adult male and female. It is determined by the effect of androgens on the development of brain in the embryonic stage.

PUBERTY AND ADOLESCENCE

Introduction

Puberty and adolescence are the phases of growth between childhood and adulthood.

- Puberty refers to the stage of gonadal development and maturation to the point where reproduction is possible for the first time.
- Adolescence refers to the period of sudden spurt of physical growth between childhood and adulthood.

These two phases (adolescence and puberty) of growth are overlapping; hence, the terms are interchangeable. The total period of growth spurt ranges between 3 and 5 years. It starts from the age of 8 years. The average age of onset of puberty is 12 years in girls and 14 years in boys.

Components of Puberty

The two principal components of puberty are sudden spurt of physical growth and appearance of secondary sex characters.

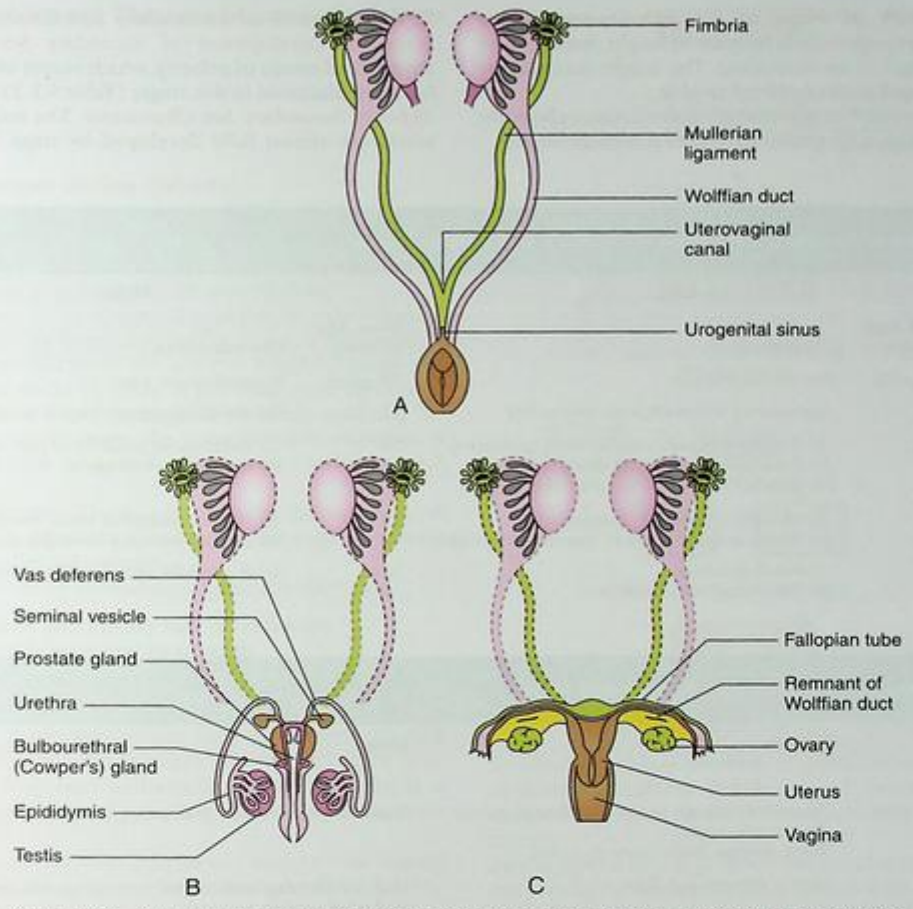


Figure 9.1-3 Development of male (B) and female (C) internal genitalia from primordial genital ducts (A).

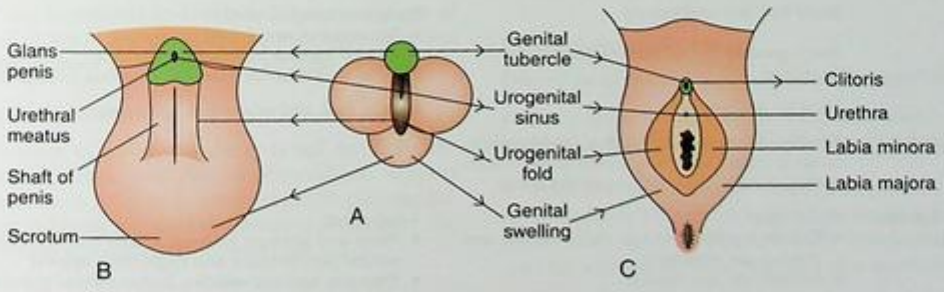


Figure 9.1-4 Differentiation of external genitalia in male (B) and female (C) from common anlagen (A).

TABLE 9.1-1 The Male and Female External Genitalia Derived from the Common Anlagen

Anlagen Part	Male Derivative	Female Derivative
Urogenital sinus	Prostate and prostatic urethra	Urethra
Urethral fold	Penile urethra and shaft of penis	Labia minora
Genital swelling	Scrotum	Labia majora
Genital tubercle	Glans penis	Clitoris

1. Sudden Spurt of Physical Growth During sudden spurt of physical growth there is increase in height, muscle mass and muscle strength of an individual. The height increases by 7–12 cm in boys and about 6–11 cm in girls.

The muscle mass and muscle strength also increase in both the sexes but the increase is far greater in boys as compared to girls.

2. Appearance of Secondary Sex Characters

Stages of Development of Secondary Sex Characters The sequence of events of puberty, which occurs in 3–5 years period, has been discussed in five stages (Table 9.1-2).

Types of Secondary Sex Characters The secondary sex characters are almost fully developed by stage 5 of the puberty

TABLE 9.1-2 Sequence of Events During Puberty in Male and Female

	Females		Males	
Stage of Puberty	Bone Age in Years	Characteristics	Bone Age in Years	Characteristics
Stage 1	Up to 7½	Pre-adolescent age	7½ years	Pre-adolescent age
Stage 2	10½	Appearance of breast buds (thelarche)	12	Genital development begins (enlargement of testis)
Stage 3	11½	(i) Axillary and pubic hair appear (pubarche) (ii) Enlargement of breast (elevation) (iii) Sudden increase in height (height spurt)	14	(i) Axillary and pubic hairs start appearing (ii) Enlargement of penis
Stage 4	13	(i) Menstruation starts (menarche) (ii) Breast areola begins to elevate and project	15	(i) Further growth of testis, penis and genitalia (ii) Sudden increase in height spurt
Stage 5	14	(i) Adult genitalia (ii) Secondary sex characters	16½	Adult genitalia and secondary sex characters

TABLE 9.1-3 Secondary Sex Characters in Female and Male

Group	Female	Male
A. Structural		
(i) Body configuration	Narrow shoulders, broad hips (broad pelvis) Thighs converge Arms diverge (wide carrying angle)	Shoulders are broader than pelvis
(ii) Skin	Skin is smooth and light	Skin is thick, dark and oily (sebaceous glands secretion thickens and predisposing to acne)
(iii) Hair growth on:		
• Body	Body hair fine and scanty	Body hair rough and dark
• Face	–	• Moustaches and beard appeared
• Scalp	Thick growth, frontal hairline rounded	• Frontal hairline indented at the side
• Pubic region	Concave	Convex and extends towards umbilicus (triangle with apex up)
(iv) Muscularity	Muscles are soft (+)	Muscle bulk and strength is far greater (+ + +)
(v) Subcutaneous fat	Female distribution of fat due to deposition of fat in breast and hips, which gives characteristic curves and contours to the body	
(vi) Genitalia and accessory sex organs	Adult type: • Clitoris increases in size, labia majora and minora get enlarged • Breasts are developed • Uterus and vaginal growth increases, and their activity starts	Adult type: • Penis and scrotum increase in size and become pigmented, scrotal skin thickens and rugal folds appear • Prostate, seminal vesicles, bulbourethral glands enlarge and their secretion begins
B. Functional		
(i) Voice	No change (remains soft and shrill)	Larynx enlarges and vocal cords get thickened; therefore, voice becomes loud, bass (low pitched), deep and breaks
(ii) Basal metabolic rate (BMR)	Lower	5%–10% higher than female
(iii) RBC count and Hb, concentration	Lower	Higher
(iv) Menstrual cycle	Begins	Absent
C. Psychological	Girls are more emotional, shy, introvert and sexually attracted towards males	Behaviour is more aggressive, extrovert, competitive and interested in opposite sex

both in male and females. These can be grouped as follows (Table 9.1-3):

- Structural
- Functional
- Psychological

Hormonal Changes during Puberty

Besides ovaries and testes, other endocrinal glands (adrenal, thyroid and anterior pituitary) also grow in size and their activity increases at the onset of puberty. The hormonal changes noticed at the time of puberty are discussed below.

1. Gonadotropins In both sexes, the levels of *gonadotropins* – follicle-stimulating hormone (FSH) and luteinizing hormone (LH) – secreted from the *anterior pituitary gland* rise slowly from birth of the child up to pre-adolescent age, but at the time of puberty (early teenage) their levels suddenly increase. In prepubertal stage, the gonadotropin secretion is not under the check of gonadal hormones (oestrogen and testosterone).

2. Adrenal Androgens There is increase in the secretion of adrenal androgens at puberty. The onset of this stage of increase or activation is called *adrenarche*.

Functions subserved by adrenal androgens at puberty are:

- Growth of public and axillary hair in both sexes
- Growth of muscle mass and its strength

3. Growth Hormone Normally from birth up to prepubertal stage, the growth hormone secretion is intermittent (a few peaks every 24 hour) but at the time of puberty, though basal level of growth hormone does not rise but there is an increase in the frequency and amplitude of the peaks. It is responsible for generalized growth spurt at adolescence (see page 307).

4. Thyroid Gland Secretions (thyroxine) also increase during puberty. Thyroxine is necessary for normal growth and development (see page 316).

5. Gonadal Hormones (sex hormones). There is slow increase in secretion of sex hormones in children between the age of 7 and 10 years. But, there is a rapid rise in oestrogen secretion (in girls) and testosterone in boys in early teenage.

Control of Onset of Puberty

The exact mechanism of onset of puberty is still not fully understood, but experimental and clinical observations support that the *hypothalamus* is intimately involved in this process, being a nodal point between nervous and hormonal circuits. The plausible mechanism involved is as follows (Fig. 9.1-5).

Role of Hypothalamus

From birth to pre-adolescent age. Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus is highly sensitive to feedback inhibition by circulating sex hormones (source being adrenal cortex and prepubertal testes). Therefore, there is very less or slow release of gonadotropins (FSH and LH) from the anterior pituitary.

At the time of puberty (12–14 years), hypothalamic cells become more mature and their sensitivity for circulating sex hormones (for negative feedback) decreases.

As a result, there occurs an increase in secretion of pituitary gonadotropins (FSH and LH). They act on gonads to release gonadal sex hormones.

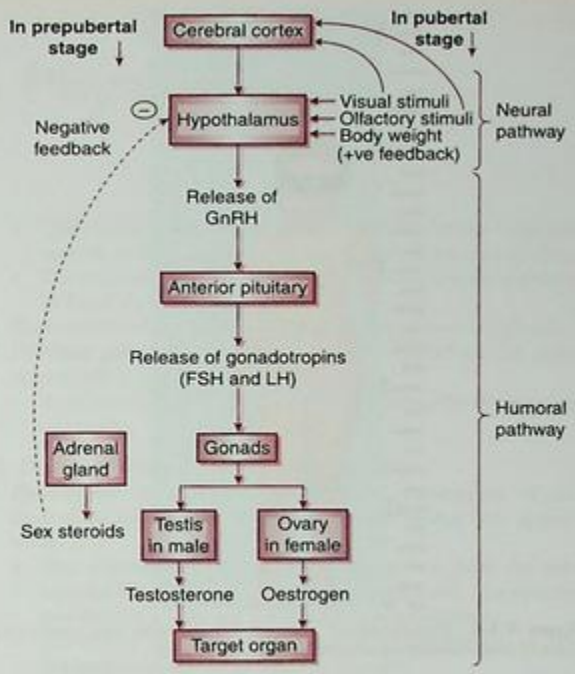


Figure 9.1-5 Neurohormonal mechanism of onset of puberty.

Awakening of hypothalamus. Hypothalamus at puberty is also positively stimulated (awakening of hypothalamus) by the critical body mass, visual, external, olfactory and other sensory stimuli.

Role of leptin. Leptin (a Greek word meaning thin) is a circulating protein formed in the fat cells. It acts on the hypothalamus by feedback control mechanism. Therefore, leptin acts as a link between critical body weight and onset of puberty.

Disorders of Puberty

Disorders of puberty are related to the time of its onset, e.g.

- Early onset of puberty (precocious puberty)
- Late onset of puberty (delayed or absent puberty)

1. Precocious Puberty Precocious puberty refers to the onset of puberty in a child before 8 years of age. It is more commonly seen in girls. There is early development of secondary sex characters and gametogenesis also starts earlier (Fig. 9.1-6).

2. Delayed or Absent Puberty Puberty is considered to be pathologically delayed in case of female, if menarche does not occur by 17 years of age, or in case of male, testicular development and maturation fails to occur by the age of 20 years.

Delayed puberty is more commonly observed in boys than in the girls. Delayed or absent puberty is a matter of great concern when it occurs in the following conditions:

- *Failure of hypothalamus/pituitary* to secrete gonadotropins, as in panhypopituitarism.
- *Primary gonadal failure.* It refers to the developmental failure or gonadal dysgenesis, which occurs in Klinefelter syndrome in males and Turner syndrome in females.

Figure 9.1-6 Photograph of a 7-year-old girl with true precocious puberty (well-developed secondary sex characters).

SELF-ASSESSMENT

1. Describe briefly the sex determination and sex differentiation.
2. Define puberty, stages of puberty and control of onset of puberty.
3. Write notes on:
   - Turner syndrome
   - Precocious puberty
   - Delayed puberty

9.2 Male Reproductive Physiology

CHAPTER OUTLINE

An Overview of Male Reproductive System

Functional Anatomy of Testes
Structure of Testes

Functions of Testes
Spermatogenesis
Endocrine Functions of Testes
Control of Testicular Functions

AN OVERVIEW OF MALE REPRODUCTIVE SYSTEM

The male reproductive system comprises the internal and external genital organs which can be functionally organized as follows (Fig. 9.2-1).

I. Gonads or Primary Male Sex Glands Gonads or primary male sex glands are a pair of testes. The principal functions of the testes are to produce sperms and secrete testosterone (male sex hormones).

II. Accessory Sex Glands

1. ***Seminal vesicles*** are two lobulated glands situated on either side of the prostate between the urinary bladder and rectum.

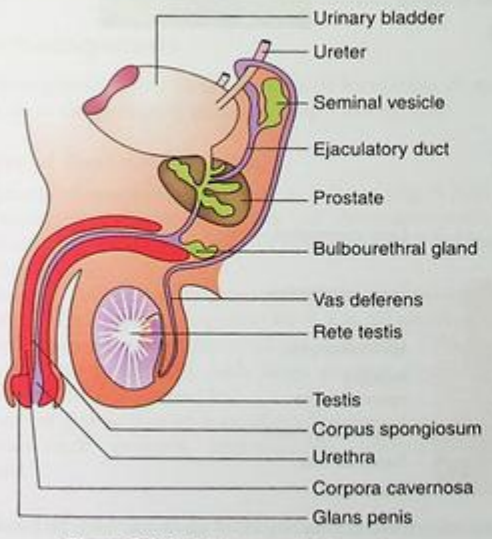


Figure 9.2-1 Male reproductive system.

- They secrete a thick alkaline fluid that mixes with the sperms as they pass into the ejaculatory ducts and urethra.
- The duct of each seminal vesicle joins the ductus deferens to form the ejaculatory duct.

2. ***Bulbourethral (Cowper's) glands*** are two pea-sized glands.
3. ***Prostate gland*** is the largest accessory gland of the male reproductive system.
   - It secretes a thin milky fluid which forms 30% the volume of semen.

III. Ducts of Male Reproductive System

1. ***Epididymis.*** It is formed by minute convolutions of the duct of the epididymis, so tightly compacted that they appear solid.
   - The efferent ductus transports the sperms from the rete testis to the epididymis where they are stored. The sperms can remain viable for a month in the epididymis.
   - Secretions of epididymis provide nourishment to the spermatozoa and help them to mature.
   - Nonmotile spermatozoa become motile after passing through epididymis.
2. ***Ductus deferens or vas deferens.*** It is the continuation of the tail of epididymis. It ends by joining to the duct of seminal vesicle. It serves as a secondary storehouse for spermatozoa, which will be released at the time of ejaculation.
3. ***Ejaculatory ducts.*** Each ejaculatory duct is a slender tube that arises by the union of the ductus deferens with the duct of seminal vesicle. The ejaculatory ducts open as minute slit-like opening into the prostatic urethra.
4. ***Urethra.*** The male urethra is a muscular tube (18–20 cm long) that conveys urine from the internal urethral orifice of the urinary bladder to the external urethral orifice at the tip of the glans penis. The urethra also provides an exit for semen (sperms and glandular secretions).

IV. Supporting Structures of Male Reproductive System

1. ***Spermatic cord.*** It suspends the testes in the scrotum and contains structures that pass through the inguinal canal to and from the testis, such as ductus deferens, vessels and nerves of the testis.
2. ***Scrotum.*** It is a cutaneous fibromuscular sac (can be considered an outpouching of the lower part of the anterior abdominal wall) which houses testes, epididymis and the lower ends of the spermatic cords.
   The scrotum maintains the temperature lower than the normal body temperature (about 32°C), which is necessary for normal spermatogenesis.
3. ***Penis.*** It is the male copulatory organ and the common outlet for urine and semen. Penis can be divided into three parts: root, body and glans penis. It is composed of cylindrical bodies of erectile cavernous tissue – the corpora cavernosa and corpus spongiosum.

FUNCTIONAL ANATOMY OF TESTES

The testes are ovoid bodies suspended by spermatic cords into the scrotum. In an adult male, the average weight of each testis is 25 g (range 10–40 g). Weight of testis decreases in old age.

Structure of Testes

Each testis is divided into many lobules by the fibrous septa (Fig. 9.2-2A). Each lobule of the testes consists of:

- Seminiferous tubular compartment
- Interstitial compartment

Seminiferous Tubular Compartment

The seminiferous tubular compartment of each lobule of the testis contains about two-to-three seminiferous tubules. The seminiferous tubules constitute about 80%–90% of the testicular volume.

Each seminiferous tubule is about 80 cm long and 150 μm in diameter. It consists of two parts: the convoluted part and the straight part. The convoluted part forms the loops and continues as two straight ends. Near the apex of the lobules, the straight ends join one another to form 20–30 larger straight tubules (tubule recti). The straight tubules pass through the fibrous tissue of mediastinal testis and unite to form a network called rete testis. At the upper end of each testis the rete testis gives of 10–20 efferent ductules which continue into the head of epididymis (Fig. 9.2-2A).

The epithelium contains mainly two types of cells (Fig. 9.2-2B):

- The germ cells (spermatogenic cells)
- Supporting cells or sustentacular cells (Sertoli cells)

Spermatogenic Cells The spermatogenic cells lie in between the Sertoli cells. These are arranged in an orderly manner in four to eight layers, which extend from the basal lamina to the lumen of the seminiferous tubule.

In a sexually mature individual, the spermatogenic cells of all stages of differentiation are seen arranged in an orderly manner (Fig. 9.2-2C).

Sertoli Cells Under electron microscope, each Sertoli cell appears as a slender cell of irregular pyramidal shape.

The functions attributed to Sertoli cells are given as follows:

1. ***Physical support and nutrition.*** The Sertoli cells provide physical support to maturing germ cells (present in the recesses on the side), nourish them (being rich in glycogen contents) and also remove waste products from the germ cells.
2. ***Phagocytic function.*** The residual cytoplasmic by-products, which are cast off from the spermatozoa during conversion of spermatids into sperms, are phagocytized by the Sertoli cells.

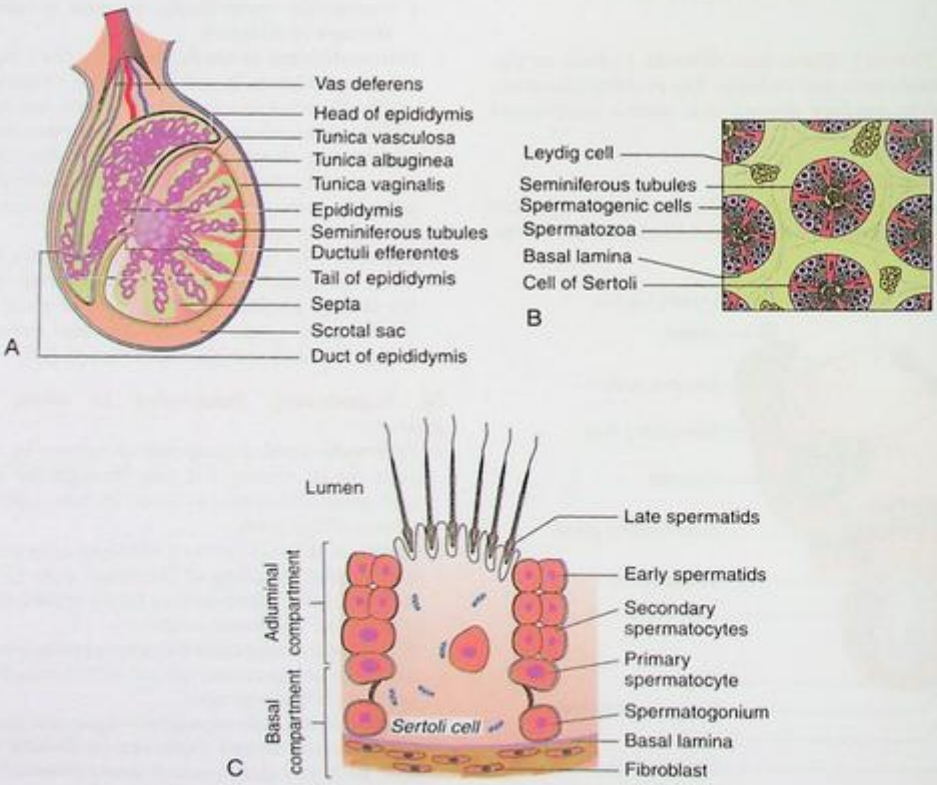


Figure 9.2-2 Structure of testis: (A) lateral view showing the cut section of testis, epididymis and distal part of spermatic cord; (B) histology of testis; and (C) electron microscopic structure of seminiferous epithelium.

3. ***Maintenance of blood–testis barrier.*** The tight junction forms effective permeability barrier within the seminiferous epithelium, which is defined in man as *blood–testis barrier.*
   Significance of blood–testis barrier. It limits the transport of many substances from blood to the seminiferous lumen:
   - This barrier maintains germ cells in a privileged location because mature sperm cells are very immunogenic when introduced into the systemic circulation. Thus blood–testis barrier protects the cells of different stages of spermatogenesis from blood-borne toxic substances and from circulating antibodies.
4. ***Secretory functions.*** Sertoli cells secrete the following hormones and substances:
   - *Mullerian duct inhibitory substance* (MIS) or Mullerian duct inhibition factor (MIF)
   - *Inhibin*
   - *Androgen-binding protein (ABP)* or androgen-binding globulin (ABG)
   - *Oestrogen*
   - *Transport proteins,* such as transferrins (the iron-transporting protein), and ceruloplasmin (copper-binding protein)
   - *Plasminogen activator*

Interstitial Compartment

The interstitial spaces between the seminiferous tubules constitute about 10%–20% volume of the testis. The interstitial compartment of each lobule is filled by loose connective tissue and Leydig cells. The Leydig cells or the so-called interstitial cells are present in groups. They have an endocrine function of secretion of male sex hormone (testosterone).

FUNCTIONS OF TESTES

The two principal functions of testes are as follows:

- Gametogenic function (spermatogenesis)
- Endocrine function

Spermatogenesis

Spermatogenesis refers to the process of formation of spermatozoa from the primitive germ cells (spermatogonia).

Phases of Spermatogenesis

The phases of spermatogenesis are as follows (Fig. 9.2-3).

1. Phase of Mitotic Division of Spermatogonia Each spermatogonium divides mitotically five times to form 32 spermatogonia.

2. Phase of Formation of Primary Spermatocytes by Mitotic Division The 32 spermatogonia (44 + X + Y) undergo mitosis to form 64 primary spermatocytes (44 + X + Y). Primary spermatocytes are large cells with large nucleus having diploid number of chromosomes (2n).

3. Phase of Formation of Secondary Spermatocyte by Meiotic Division Each primary spermatocyte undergoes meiotic division:

- After first reductional division (meiosis), the 64 primary spermatocytes are converted into 128 primary spermatocytes.
- The 128 primary spermatocytes undergo meiosis to form 256 secondary spermatocytes having haploid number of chromosomes (n), i.e. either 22 + X or 22 + Y. Therefore, 50% of sperms will have X chromosome and other 50% will have Y chromosome.

4. Phase of Formation of Spermatid Each secondary spermatocyte divides mitotically to give rise to two spermatids. Thus, a total of 512 spermatids are formed from a single spermatogonium.

5. Phase of Formation of Spermatozoon (Spermiogenesis) The spermatids do not divide further but undergo morphological changes to form sperms or spermatozoa. The spermatid undergoes changes in the shape and orientation of its organelles. The spermatids mature into spermatozoa in the deep folds of the cytoplasm of the Sertoli cells.

Structure of Spermatozoon A fully formed spermatozoon is about 55–65 μm in length. It comprises the following parts (Fig. 9.2-4).

1. Head The head is about 4–5 μm long. It is surrounded by acrosome.

Acrosome contains a number of enzymes (hyaluronidase, proteolytic enzymes and acid phosphatase), which help the sperm in penetrating ovum during fertilization.

2. Neck It is a narrow constricted part. It contains a funnel-shaped basal body and a spherical centriole.

3. Tail of the sperm is the motile portion and is also called the flagellum. It can be divided into three parts:

- Middle piece
- Principal piece
- End piece

Storage of Spermatozoa About 120 million sperms are formed each day. A small quantity of them is stored in the epididymis but most of them are stored in vas deferens and ampulla of vas deferens. They remain stored and maintaining their fertility for about a month.

Semen

Semen or the seminal fluid refers to the fluid ejaculated during the orgasm at the time of male sexual act.

Characteristic Features

- *Volume.* The average volume of semen per ejaculation is 2.5–3.5 mL after an abstinence of 2 days. Volume of semen decreases with repeated ejaculations.
- *Appearance* of semen is milky due to prostatic secretions.
- *Specific gravity* is about 1.028.
- *Reaction* is alkaline with a pH of 7.5. The alkalinity is due to the prostatic secretions.
- *Nature* of the semen when ejaculated is liquid but soon it coagulates in vitro or in the vagina, and finally undergoes secondary liquefication after.

Components of Semen and Their Characteristics The semen comprises following components.

1. Spermatozoa The normal sperm count varies from 35 to 200 million per mL of semen, with an average of 100 million per mL.

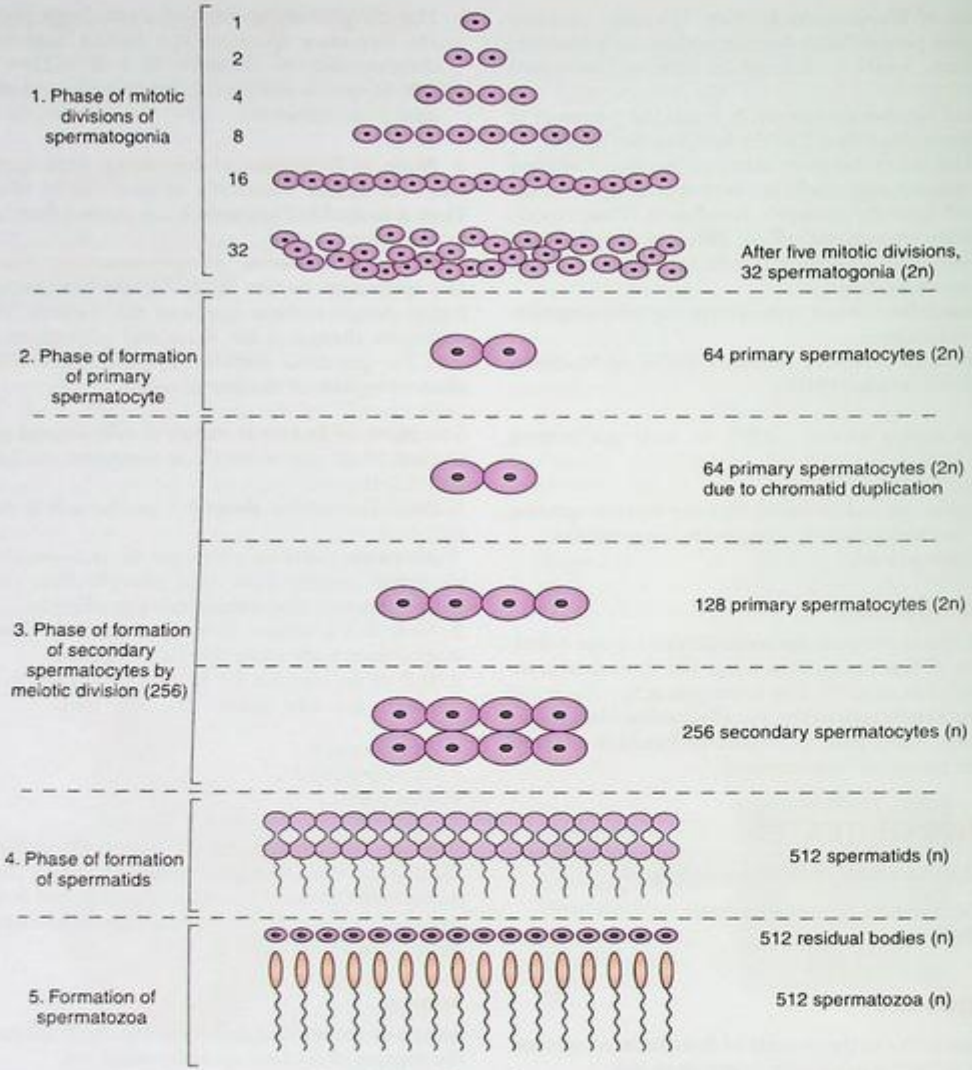


Figure 9.2-3 Phases of spermatogenesis.

2. Secretions of Seminal Vesicles Secretions of seminal vesicles contribute 60% of the semen volume:

- The secretion from seminal vesicles is mucoid and viscous fluid.
- It is neutral or slightly alkaline in nature.
- It contains fructose, phosphorylcholine, ergothioneine, ascorbic acid, flavins and prostaglandins.

Functions subserved by the seminal vesicle secretions are as follows:

Nutrition to sperms after being ejaculated into the female genital tract is provided by the fructose and other nutritive substances from the seminal vesicle secretions.

Clotting of semen soon after ejaculation into the female genital tract occurs due to fibrinogen present in the seminal vesicle secretions.

Fertilization of ovum may be enhanced by the prostaglandins present in the seminal vesicle secretion.

3. Secretion of Prostate Gland Secretion of prostate gland forms about 10% of the total semen bulk:

- It contributes milky and alkaline fluid part of the semen.

Functions subserved by prostatic fluid component of semen are as follows:

Maintenance of optimum pH for fertilization (6–6.5) is the function of alkaline prostate fluid, which neutralizes the acidity of vaginal secretion. At this pH, the sperms become motile and the chances of fertilization are enhanced.

Clotting of semen by converting fibrinogen (from seminal vesicles) into a coagulum is caused by the clotting enzymes present in the prostatic fluid.

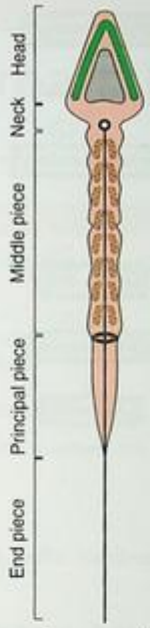


Figure 9.2-4 Structure of a mature human spermatozoon.

4. Secretion of Bulbourethral Gland Secretion of bulbourethral gland and other mucous glands provide mucoid consistency to the semen after puberty.

Endocrine Functions of Testes

Testes secrete the following androgens (male sex hormones).

1. Testosterone The most important testicular hormone is testosterone secreted by Leydig cells.

- A normal man secretes 4–9 mg of testosterone daily. More than 98% of secreted testosterone is bound to plasma proteins, 68% is bound to albumin and 30% is bound to testosterone-binding globulin, also called sex steroid-binding globulin (SSBG) or gonadal steroid-binding globulin (GBG) because it binds oestradiol as well. A very small percentage of the plasma testosterone is unbound. The free fraction alone is physiologically active in the target tissues.

2. Androstenedione is an important steroid precursor for blood oestrogens in men. It is secreted by the testes at a rate of about 2.5 mg/day.

3. Dihydrotestosterone (DHT) is another important androgen present in the blood.

Adrenal cortex also secretes androgens, normally testosterone, androstenedione and dehydroepiandrosterone (of these last one is more important). The actions of adrenal androgens are unimportant under normal physiological conditions because their quantity is insignificant.

Functions of Androgens

A. Functions of Androgens in Fetal Period (in Utero)

The testosterone is secreted by the fetal testes at about 2nd to 4th month of embryonic life. The functions of androgens in fetal period are as follows:

- *Gonadal sex differentiation* (as discussed on page 352) is dependent on the genotype of the embryo.
- *Genital differentiation* (see page 352).
- *Effect on descent of testes.* The testes developed in the abdominal cavity are pushed into the scrotum through inguinal canal just before birth. Testosterone is necessary for this descent of testes.

B. Functions of Androgens at Puberty

Effects on External Genitalia Testosterone causes pubertal enlargement of penis. Scrotum increases in size and becomes pigmented. Rugal folds appear in scrotal skin.

Effects on Accessory Sex Organs Testosterone (with or without DHT) causes enlargement of seminal vesicles, promotes growth of prostate and stimulates prostatic secretions.

Development of Male Secondary Sexual Characters

Anabolic and General Growth Promoting Effects Testosterone causes nitrogen retention in the body (positive nitrogen balance) and causes accelerated growth of the body and skeletal muscles in particular. Androgens increase the rate of linear growth of the bones causing a rapid increase in stature at puberty (pubertal growth spurt).

C. Functions of Androgens in Adults

1. ***Hair growth.*** Androgenic patterns of hair growth are maintained. With increasing age, male baldness may be initiated.
2. ***Psyche.*** Behavioural attitudes and sexual potency are maintained in postpubertal adults.
3. ***Bone.*** Bone loss and osteoporosis are prevented by the androgens in adult males.
4. ***Spermatogenesis*** is maintained in adulthood by testosterone along with follicle-stimulating hormone (FSH). The testosterone acts on both Sertoli cells and germ cells, and thus maintains spermatogenesis.
5. ***Haematopoiesis.*** Testosterone stimulates erythropoiesis. Therefore, accounts for the greater haemoglobin concentration and RBC count in males.
6. ***Effects on circulating and stored body fats.*** Testosterone increases circulating levels of low-density lipoprotein (LDL) cholesterol and decreases plasma high-density lipoprotein (HDL) cholesterol.
7. ***Regulation of gonadotropin secretion.*** Androgen suppression of LHRH and LH by negative feedback effect.

Control of Testicular Functions

The two principal functions of testes, such as spermatogenesis and secretion of testosterone, are controlled by the hypothalamic–hypophyseal–testicular axis.

Control of Spermatogenesis

The hypothalamic–hypophyseal–testicular (seminiferous tubular) axis controlling the spermatogenesis is as follows (Fig. 9.2-5).

I. Stimulatory Control

1. Role of Hypothalamus At puberty hypothalamic cells become more mature and their sensitivity for circulating sex hormones (negative feedback) decreases so much that there

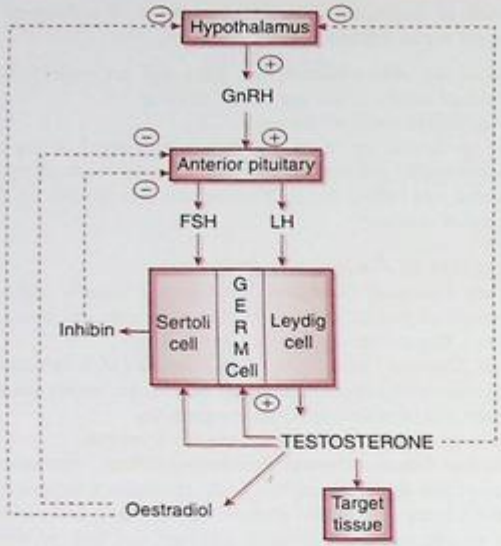


Figure 9.2-5 Stimulatory and feedback inhibitory control of secretion of spermatogenesis.

is a pulsatile release (8–14 pulses per day) of gonadotropin-releasing hormone (GnRH) from the *hypothalamus*. The GnRH stimulates anterior pituitary to secrete LH and FSH.

2. Role of Anterior Pituitary The anterior pituitary controls spermatogenesis through the gonadotropic (FSH and LH) and growth hormones.

FSH stimulates cells of Sertoli, which play the following roles during spermatogenesis:

- Sertoli cells help in conversion of spermatids to sperms.
- They secrete androgen-binding protein (ABP).
- FSH also promotes the synthesis of inhibin by Sertoli cells.

The *LH stimulates Leydig cells* to cause testosterone secretion. The testosterone is required for normal spermatogenesis.

3. Role of Growth Hormone Growth hormone specifically promotes early division of the spermatogonia themselves. In its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent.

4. Role of Testicular Hormones Testosterone secreted by Leydig cells by paracrine effect acts on both Sertoli cells and germ cells, and thus maintains spermatogenesis.

II. Feedback Inhibitory Control The spermatogenesis is controlled by the following negative feedback mechanisms (Fig. 9.2-5).

- *Inhibin* secreted by the Sertoli cells acts directly on the anterior pituitary and inhibits the secretion of FSH.

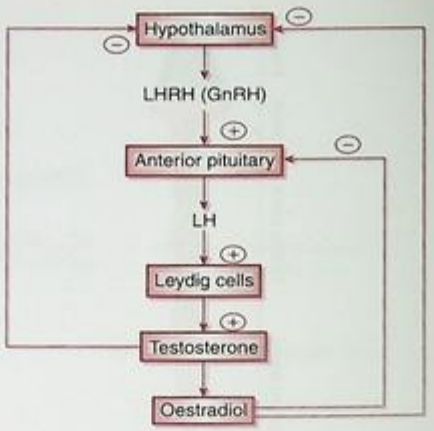


Figure 9.2-6 Stimulatory and feedback inhibitory control of secretion of testosterone.

- *Testosterone* has its feedback effect mainly at the hypothalamic (GnRH) level.

Control of Testosterone Secretion

I. Stimulatory Control The hypothalamic–hypophyseal–testicular (Leydig cell) axis controls the secretion of testosterone in adults as (Fig. 9.2-6).

Hypothalamus produces gonadotropin releasing hormone (GnRH), which stimulates anterior pituitary to secrete FSH and LH.

Anterior pituitary controls secretion of testosterone (steroidogenesis) primarily through LH.

II. Feedback Inhibitory Control Plasma testosterone level is maintained at a constant level by a feedback control exerted by testosterone and oestradiol independently to control LH (Fig. 9.2-6).

SELF-ASSESSMENT

1. Describe briefly:
   - Process of spermatogenesis and its control
   - Endocrinal functions of testes
2. Write notes on:
   - Sertoli cells
   - Semen
   - Functions of prostate
   - Sperm capacitation
   - Blood–testis barrier
   - Cryptorchidism
   - Testosterone

9.3 Female Reproductive Physiology

CHAPTER OUTLINE

An Overview of Female Reproductive System
Primary Sex Organs
Accessory Sex Organs
Female Internal Genitalia
Female External Genitalia

Ovaries
Functional Anatomy
Structure
Functions of Ovaries
Oogenesis
Endocrine Function

Female Sexual Cycle
Ovarian Cycle
Endometrial Cycle
Cyclic Changes in Cervix
Cyclic Changes in Vagina
Hormonal Control of Female Sexual Cycle

AN OVERVIEW OF FEMALE REPRODUCTIVE SYSTEM

The female reproductive system comprises internal and external genitalia, which can be organized as follows (Fig. 9.3-1).

I. Primary Sex Organs or Ovaries The primary sex organs are a pair of ovaries which correspond with testes in males. The principal functions of ovaries are as follows:

- To produce ova
- To secrete female sex hormones

II. Accessory Sex Organs The accessory sex organs of females include internal genital organs and external genitalia.

Female Internal Genitalia

The internal genital organs include uterus, fallopian tubes and vagina.

I. Uterus Uterus is a hollow, thick-walled muscular organ, situated between the urinary bladder and the rectum. It can be divided into two parts (Fig. 9.3-2).

1. Body of the Uterus It forms the upper two-third part of the uterus. Its lower limit is marked by a constriction which corresponds to narrowing of uterine cavity at *internal os*. Body of the uterus can be divided into two parts:

Fundus is the rounded part of the body that lies superior to the opening of the fallopian tubes.

Isthmus is the relatively constricted region of the body (approximately 1 cm long) just above the cervix.

2. Cervix of the Uterus It is the cylindrical lower part which protrudes into the uppermost part of vagina. It is approximately 2.5 cm long in an adult nonpregnant woman. Its cavity extends from the *internal os* to *external os*, which opens into the vagina.

Structure of Uterus The wall of body of uterus consists of three layers.

1. ***Perimetrium*** is the external serosal layer.
2. ***Myometrium*** is the middle muscular layer comprising bundles of smooth muscles amongst which there is connective tissue.
3. ***Endometrium*** is inner layer of uterus which consists of epithelial lining and the stroma (Fig. 9.3-3):

Functionally, the endometrium of body of uterus can be divided into two strata.

1. *Stratum functionale* includes the superficial two-third thickness of endometrium, which undergoes monthly cyclic changes

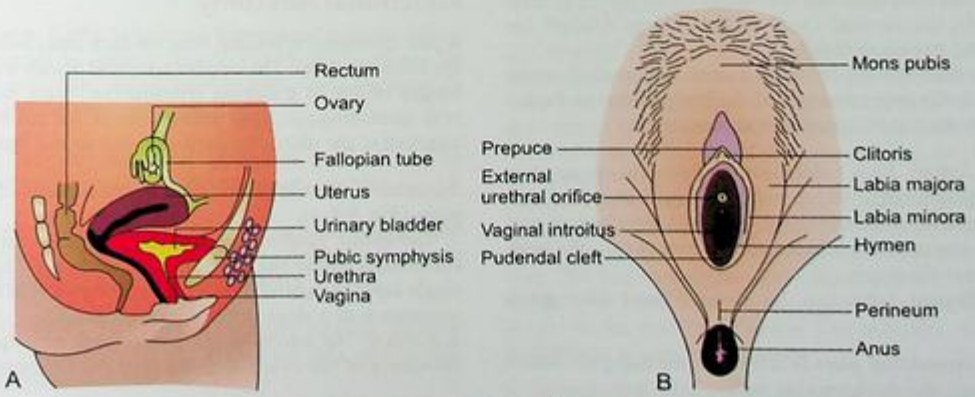


Figure 9.3-1 Female reproductive organs: (A) lateral view showing position of internal reproductive organs in relation to pelvic viscera and (B) female external genitalia.

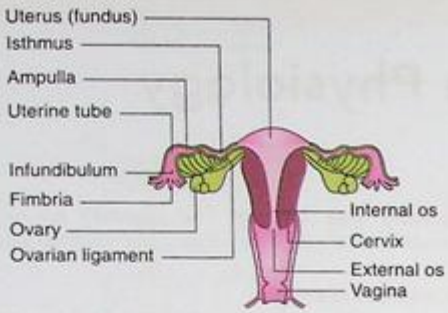


Figure 9.3-2 Parts of the uterus and fallopian tube

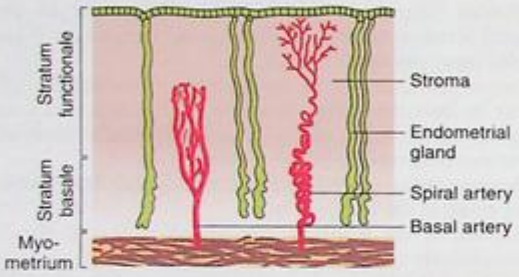


Figure 9.3-3 Histological structure of the endometrium.

in preparation for the implantation of fertilized ovum and is shed during menstruation. This portion of endometrium is supplied by long and spiral (coiled) arteries.

2. *Stratum basale* is the deeper one-third layer of endometrium. It does not participate in the cyclic changes but functions as a regenerative layer. This part of endometrium is supplied by short and straight *basal arteries.*

Structure of Cervix of the uterus is somewhat different from that of the body.

1. ***Perimetrium*** is the outermost serous layer.
2. ***Myometrium*** layer of the cervix is much less muscular as compared to the body of uterus and contains more connective tissue. During childbirth, when the myometrium of body of uterus contracts, the myometrium of cervix dilates; consequently, the cervical canal becomes large enough for the fetal head to pass through.
3. ***Endocervix*** refers to the innermost mucosal layer of cervix in contrast to the endometrium of the body of uterus. Endocervix is not shed at the time of menstruation.

II. Fallopian Tubes Each fallopian tube (also known as uterine tube) is approximately 10 cm in length and 8 mm in diameter. It has a medial or *uterine end,* which is attached to and opens into the uterus and a *lateral end* that opens into the peritoneal cavity near the ovary.

Parts Each fallopian tube can be divided into four parts (Fig. 9.3-2):

1. ***Uterine or interstitial part*** is the most medial part which passes through the thick uterine wall.
2. ***Isthmus*** is the relatively narrow and thick-walled part, which is just next to the uterine part. It is about 2.5 cm in length.
3. ***Ampulla*** is the next thin-walled and dilated part of the uterine tube. It is the largest part (7 cm) of uterine tube.
4. ***Infundibulum*** refers to the funnel-shaped lateral end of the tube. It is prolonged into a number of finger-like processes known as fimbria. One fimbria is longer than rest of the fimbriae, and is attached to the outer pole of ovary.

Structure Fallopian tubes consist of same three coats as of the uterus, i.e. endometrium, myometrium and perimetrium.

Functions

- The uterine tubes convey ova, shed by the ovaries, to the uterus. Ova enter the tube at its fimbriated end.
- Secretions present in the tubes provide nutrition, oxygen and other requirements for ova and spermatozoa passing through the tube.
- Fertilization takes place in the ampulla, and the fertilized ovum travels towards the uterus through the tube.

III. Vagina

- The vagina is a musculomembranous tube (about 8- to 10 cm long) located anterior to the rectum and posterior to the urethra and urinary bladder.
- Its upper end surrounds the lower part of the cervix and its lower end, i.e. vaginal orifice, opens into the vestibule of vagina (the cleft between the labia minora).

Functions The vagina serves the following functions:

- It serves as the excretory duct for menstrual fluid.
- It forms the inferior part of pelvic (birth) canal.

Female External Genitalia

The external genital organs include mons pubis, labia majora, labia minora, clitoris, vestibule of vagina, bulbs of vestibule and greater vestibular glands (Fig. 9.3-1B).

The synonymous terms vulva and pudendum include all these parts. The vulva serves:

- As sensory and erectile tissue for sexual arousal and intercourse
- To direct the flow of urine
- To prevent entry of foreign material into the urogenital tract

OVARIES

Functional Anatomy

A pair of ovaries is located (one on each side) behind and below the fallopian tubes. The ovaries are ovoid glands with a combined weight of 10–20 g during reproductive years, which decreases with increasing age. Each ovary is about 3–5 cm in length, and is attached to the uterus by the broad and round ligament of ovary.

Structure Histologically, each ovary consists of the following parts (Fig. 9.3-4).

1. Germinal Epithelium Germinal epithelium refers to the epithelium lining the outer surface of ovary and consists of a single layer of cuboidal cells. The term germinal epithelium is a misnomer, as it does not produce germ cells.

2. Cortex The cortex is the outer thick principal part of the substance of the ovary. It consists of the following tissues:

- ***Tunica albuginea*** is the outer condensation of the connective tissue present immediately below the germinal epithelium.

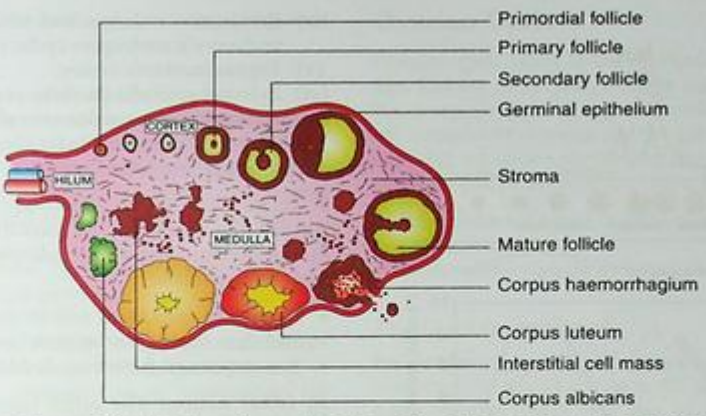


Figure 9.3-4 Schematic diagram of the histology of ovary depicting various stages of development of follicles and corpus luteum.

- ***Stroma*** of the cortex, present deep to the tunica albuginea.
- ***Ovarian follicles*** at various stages of development are scattered in the stroma. Each follicle contains a developing ovum.

3. Medulla The medulla is the inner small part of the substance of ovary. It consists of connective tissue in which numerous blood vessels (mostly veins), smooth muscles and elastic fibres are present.

4. Hilum The hilum refers to the area where ovary attaches to mesentery. It is the site for entry of blood vessels and lymphatics.

Functions of Ovaries

The two principal functions of ovaries are as follows:

- Gametogenic function, i.e. oogenesis
- Endocrine function, i.e. secretion of female hormones called ovarian hormones

Oogenesis

Oogenesis refers to the process of formation of ova from the primitive germ cells.

Primitive Germ Cells When the bipotential gonads differentiate into ovaries in genetic female (44 + XX) embryo by 10th week of gestation, the primitive germ cells increase in number by mitosis to form oogonia.

Oogonia are the stem cells from which ova are derived. The oogonia proliferate by mitosis to form primary oocytes.

Primary Oocytes, formed from the oogonia, enter a prolonged prophase (*diplotene stage*) of the first meiotic division and remain in this state until ovulation occurs after puberty.

Primordial Follicles The *diploid primary oocytes* become enveloped by a single layer of flat granulosa cells and in this form are called *primordial follicles.*

- After puberty, the oogenesis or formation of ovum occurs in a highly cyclic fashion, once every 28 days till menopause.
- Every month, in each ovary, more than one primordial follicles start undergoing maturation process, but only one reaches maturity and the rest undergo atresia at different stages of development.
- The different stages of maturation of primordial follicle into graafian follicle *(folliculogenesis).*

Endocrine Function of Ovaries

The endocrine function of the ovaries is to produce female sex hormones which include:

- Oestrogens
- Progesterone

Oestrogens

Oestrogens are (C-18) steroids. The naturally occurring oestrogens include:

- *Oestradiol.* It is the principal and physiologically most potent oestrogen. Ovarian oestradiol accounts for more than 90% of the circulating oestrogens.
- *Oestrone.* It is a weak ovarian oestrogen.
- *Oestriol.* It is the degradation product of oestradiol and oestrone. It is the weakest of all naturally occurring oestrogens.

Synthesis, Plasma Levels and Transport of Oestrogens

Sites In the normal female, oestrogens are mainly secreted by theca interna and granulosa cells of the ovarian follicles. A small quantity is also produced by the adrenal cortex, breast, some areas of brain, placenta (during pregnancy) and by Sertoli cells (in males).

Plasma Levels In a normal adult woman, the plasma levels of oestrogen vary in different phases of ovarian cycle (Fig. 9.3-5). As shown in Fig. 9.3-5D, there are two peaks of oestrogen secretion. The first occurs just before the ovulation (12th–13th day of sexual cycle) and is called *oestrogen surge*, and the second peak occurs in the mid-luteal phase. The secretion rate of oestrogen in different phases is as follows:

- In early follicular phase: 36 μg/day
- Just before ovulation: 380 μg/day
- During mid-luteal phase: 250 μg/day

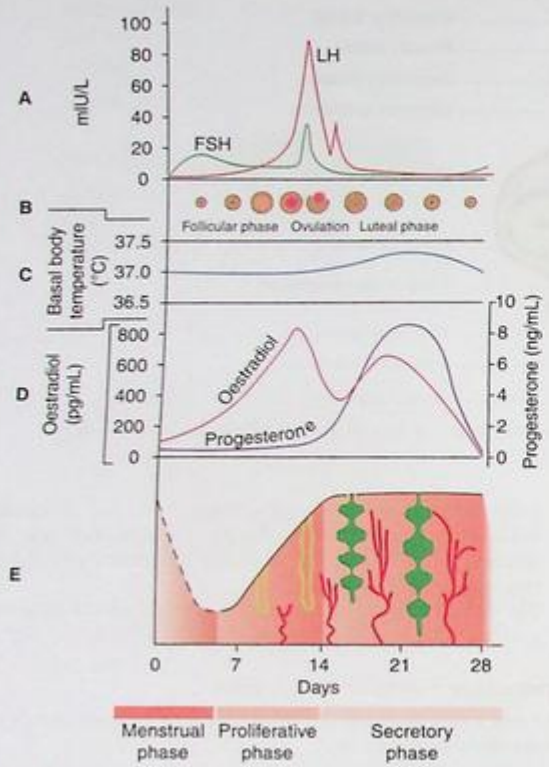


Figure 9.3-5 Correlation of plasma concentration of gonadotropins (FSH and LH) (A); ovarian cycle changes (B); basal body temperature (C); ovarian hormones (D); and endometrial changes (E) during female sexual cycle.

After menopause, oestrogen level falls to minimum of 50 µg/day.

Transport In the circulation, oestrogen is present in two forms: bound (98%) and free (2%). The oestradiol is mainly bound to albumin.

Metabolism and Excretion of Oestrogens

The liver is the principal site for metabolism of ovarian hormones. The degradation metabolites are excreted by kidney into the urine and a small amount of them is secreted into the bile.

Functions of Oestrogens

The functions of oestrogen for descriptive purposes can be grouped as reproductive actions and other actions.

I. Reproductive Actions

A. At Puberty oestradiol is secreted in larger amounts which cause the following changes.

1. ***Growth and development of genital organs***
   (i) *Ovaries* increase in size and complete ovarian cycle starts.
   (ii) *Fallopian tubes* become functional.
   (iii) *Uterus.* It enlarges in size; endometrium gets thickened due to increase in stroma and blood flow. The rhythmic cyclic changes (proliferative and secretory) occur with onset of menstrual cycle.
   (iv) *Cervix* also enlarges and with onset of menstrual cycle, endocervix undergoes cyclic changes (see page 368).
   (v) *Vagina* increases in size.
   (vi) *External genitalia* Increase in size.
2. ***Appearance of secondary sex characters***
   Oestrogen is responsible for the appearance of secondary sex characters (see page 354).

B. In an adult woman Oestrogens along with progesterone regulate the ovarian cycle, menstrual cycle and cyclic changes in the cervix, vagina and fallopian tubes (see page 368) in nonpregnant state.

- It plays an important role in the maintenance of pregnancy and then during parturition (see page 373).
- It is important for breast development.

II. Other Actions The other functions of oestrogens include the effects on the following:

1. ***Effects on bones***
   (i) Oestradiol accelerates the linear growth of bones at puberty by its osteoblastic activity.
   (ii) Oestradiol enlarges the hip and widens the inlet of the pelvic bone to facilitate childbirth.
2. ***Effects on metabolism***
   (i) *Protein metabolism.* Oestrogens cause positive nitrogen balance due to growth-promoting effect.
   (ii) *Fat metabolism.* Oestrogens cause fat deposition in subcutaneous tissues, in the breasts and the thighs.
3. ***Water and electrolyte balance.*** Oestrogens like other steroids, in general, cause salt and water retention in the body and produce premenstrual tension in some women.
4. ***Effects on skin.*** Oestrogens make the skin soft and more vascular. It makes the sebaceous glands, secretions thin. Therefore, synthetic oestrogens are used as a part of treatment in acne.

Progesterone

Progesterone is C-21 steroid meant for maintenance of pregnancy and is biologically called prostagen or gestagen.

Synthesis, Plasma Levels and Transport of Progesterone

Sites In a normal adult nonpregnant woman progesterone is mainly secreted by corpus luteum and during pregnancy by the placenta. A small amount is also secreted by the adrenal cortex and by testes in case of males.

Plasma Levels *In a normal adult woman,* the plasma levels of progesterone vary with different phases of sexual cycle (Fig. 9.3-5D).

In early follicular phase, plasma concentration of progesterone is very low (about 0.9 ng/mL or 9 ng/dL).
In midcycle (late follicular phase), its level starts rising due to secretion from the granulosa cells.
In luteal phase, it reaches to its peak value, i.e. 18 ng/mL.
At the end of cycle, its levels fall to its minimum value.
During pregnancy, the levels of progesterone further rise (see page 373).
After menopause, progesterone levels fall to its minimum (0.2 ng/mL) or even not detectable.

Transport In the plasma, progesterone is present in two forms:

Bound form. About 98% of progesterone in the blood is present in bound form with plasma proteins.

Unbound form or free form. Only 2% of circulating progesterone is present in this form.

Metabolism and Excretion of Progesterone

Metabolism In the liver, progesterone is metabolised to form pregnanediol and 17α-hydroxyprogesterone to pregnanetriol. The metabolites then conjugate with glucuronic acid and sulphuric acid to form water-soluble substances, which are excreted by the kidney into the urine and small amount into the bile.

Functions of Progesterone

The physiological actions of progesterone can be grouped as reproductive actions and other actions.

I. Reproductive Actions occur mainly on the reproductive organs primed by oestrogens, and these include the following.

1. Action on Uterus. The progesterone is responsible for the secretory phase of the endometrial cycle and prepares the endometrium to receive the zygote. It decreases the uterine motility.

2. Endocervix. The cervical secretions become thick and viscid, and ferning pattern disappears.

3. Vagina. Vaginal epithelium becomes thickened, cornified and infiltrated with leucocytes.

4. Fallopian Tubes. Progesterone increases the epithelial-cell secretions rich in nutritive materials to provide nutrition to shed ovum, incoming sperm or zygote, if fertilization occurs.

5. Breast. Progesterone causes lobular and alveolar growth of breast.

6. During Pregnancy. The principal function of progesterone is to maintain the pregnancy (see page 373).

II. Other Actions The other systemic effects of progesterone are as follows:

Thermogenic Effect. Progesterone is known as a thermogenic steroid, which increases the basal body temperature by 0.5°C in postovulatory phase.

Other Ovarian Hormones

Besides female sex steroids (oestrogen and progesterone), ovaries also secrete inhibin, activin, relaxin, and small amount of testosterone is also secreted by the ovaries during biosynthesis of oestrogen and progesterone.

These androgens are responsible for acne vulgaris, libido and pubic hair.

FEMALE SEXUAL CYCLE

With the onset of puberty the female sexual cycle starts, which repeats itself every 28 days. The occurrence of first menstrual cycle is called *menarche*. The permanent stoppage of menstrual cycle is called *menopause*, which occurs at the age of about 45–50 years. The period between menarche and menopause is called *reproductive period*. During this period, females have rhythmical sexual cycles.

Components of human female sexual cycle. During each female sexual cycle, rhythmical changes occur in ovaries and accessory sex organs – uterus, cervix and vagina.

Duration of female sexual cycle is usually 28 days. But under physiological conditions it may vary between 20 and 40 days. Traditionally, first day of the menstrual bleeding is taken as the first day of female sexual cycle.

Ovarian Cycle

Ovarian cycle refers to the rhythmic changes occurring in ovaries. During each cycle, a single mature ovum is released from the ovary. Ovarian changes occurring during the female sexual life completely depend on the gonadotropic hormones (FSH and LH), which are secreted by the anterior pituitary. The ovarian cycle can be divided into three phases:

- Pre-ovulatory phase or follicular phase
- Ovulation
- Postovulatory phase or luteal phase

Pre-Ovulatory Phase

Pre-ovulatory or follicular phase of the ovarian cycle extends from the 5th day of the cycle till the time of ovulation (which takes place at about 14th day of the cycle). Thus, this phase generally lasts for 8–9 days (but may vary from 10–25 days).

- Changes in the ovary during this phase are mostly under the influence of FSH from the anterior pituitary. Luteinizing hormone also helps in the maturation of the follicle in the latter part of follicular phase.
- During this phase of each cycle, some 10–15 primordial follicles start maturing, but only one follicle matures fully and the rest undergo atresia (atrophy) at different stages of development. A fully matured graafian follicle is characterized by (Fig. 9.3-4) the following features:
  - *Size* of the follicle increases markedly to about 2–5 mm.
  - *Antrum becomes larger* and distended with fluid. As a result the ovum covered by a layer of cells called *corona radiata* remains in contact with granulosa cells only at a hill like area called *cumulus oophorus*.
  - *Theca interna becomes more prominent.*
  - *Formation of secondary oocyte.* Just prior to ovulation, the primary oocyte of the fully matured graafian follicle completes the first meiotic division (which began in fetal life at about 20th, 28th week of gestation, i.e. before birth), and forms the secondary oocyte with a haploid nucleus and the first polar body.

Ovulation

Ovulation refers to the release of secondary oocyte from the ovary (following rupture of graafian follicle) into the peritoneal cavity. It usually occurs *14 days after the onset* of menstruation (Fig. 9.3-5B).

Postovulatory Phase

Postovulatory phase, also called luteal phase of ovarian cycle, is of remarkably constant period of about 14 days. This phase is characterized by the following events (Fig. 9.3-4).

Formation of Corpus Haemorrhagicum Following ovulation, the outer wall of the graafian follicle collapses and promptly fills with blood forming the so-called corpus haemorrhagicum.

Formation of Corpus Luteum Soon, the granulosa cells and theca cells of the follicle lining begin to proliferate, and the clotted blood is rapidly replaced with yellowish lipid-rich *luteal cells*. This process is called *luteinization* and the total mass of the cells is now called *corpus luteum*. LH is responsible for luteinization.

Formation of Corpus Albicans If there is no fertilization and pregnancy does not occur, the corpus luteum begins to involute (regress) after 24th day of the sexual cycle, and is eventually replaced by a whitish scar tissue called the corpus albicans. This involution occurs due to falling levels of FSH and LH and also the hormone *inhibin* secreted by the lutein cells.

Corpus Luteum of Pregnancy However, if the ovum released is fertilized and pregnancy occurs, then the corpus luteum formed during postovulatory phase persists and serves as the major source of oestrogen and progesterone till the third month of pregnancy when the placenta takes over its endocrine function.

Endometrial Cycle

Endometrial cycle refers to the cyclic changes occurring in the endometrium during active reproductive period (menarche to menopause) in females leading to recurrent monthly bleeding per vaginum (menstruation). These cyclic changes in the endometrium are brought about by the cyclic production of oestrogens and progesterone by the ovaries.

Phases of Endometrial Cycle

The endometrial cycle of 28 days can be divided into three phases (Fig. 9.3-5E):

- Menstrual phase (1st–5th day)
- Proliferative phase (6th–14th day)
- Secretory phase (15th–28th day)

For the purpose of better understanding, the menstrual phase is described last of all.

Proliferative Phase of endometrial cycle is from day 6th to 14th day. It follows the phase of menstruation, after which only a thin basal layer of original endometrium is left.

Hormone Responsible for the changes in the endometrium during this phase is oestrogen secreted by the developing graafian follicle in the ovary. Thus, proliferative phase of the endometrial cycle coincides with the follicular phase of ovarian cycle.

Changes in the Endometrium which occur during proliferative phase are as follows:

- Thickness of endometrium, which is less than 1 mm at the end of menstrual phase increases to 3–4 mm at the end of the proliferative phase.
- Angiogenesis in the stratum functionale leads to proliferation of blood vessels.
- Endometrial glands are stimulated to grow.

Secretory Phase also known as postovulatory phase of endometrial cycle is from day 15th–28th day.

Hormones Responsible for changes in the endometrium during this phase are both oestrogen and progesterone secreted by the corpus *luteum* formed after ovulation. Thus, the secretory phase of endometrial cycle coincides with the luteal phase of ovarian cycle.

Changes in the Endometrium which occur during this phase are as follows:

- There is elongation and coiling of the endometrial mucous glands. These glands become secretory and secrete thick viscous fluid containing glycogen.
- *Blood supply* of endometrium further increases as progesterone promotes spiralling of blood vessels.
- *Thickness* of endometrium increases to 5–6 mm at the end of secretory phase. Thus, the thickened endometrium with large amounts of nutrients is ready to provide appropriate conditions for implantation of ovum during this phase.
- *If fertilization does not occur* and there is no pregnancy, the corpus luteum in the ovary involutes to form corpus albicans, and on day 26th of the menstrual cycle the levels of oestrogen and progesterone fall suddenly and mark the end of secretory phase of endometrial cycle.

Menstrual Phase The menstrual phase of endometrial cycle is also called bleeding phase. The average duration of this phase is 3–5 days. About 24 hours before the end of menstrual cycle, there is sharp decline in the plasma levels of oestrogen and progesterone, which are responsible for menstrual bleeding. During menstrual phase, about two-thirds of the superficial endometrium is sloughed off and only a thin basal layer (2 mm thick) is left behind.

Cyclic Changes in Cervix

The mucosal lining of cervix (endocervix) also shows certain cyclic changes during sexual cycle. These are as follows.

During Menstruation Phase the mucosa of cervix does not undergo desquamation (shedding off) like that of endometrium.

During Proliferative Phase (oestrogen phase), the secretions of the mucosal cells of endocervix become thin, watery and alkaline. At the time of ovulation, the cervical mucus is thinnest and its elasticity is maximum. It can be stretched like a long, thin elastic thread up to 8–12 cm (*spinnbarkeit effect*). The mucus also produces a characteristic fern-like pattern when a drop of mucus is spread on the glass slide and allowed to dry (*Fern test*).

This characteristic nature of cervical mucus favours the transport of sperms in the female genital tract, and makes the conditions favourable for fertilization.

During Secretory Phase, under the influence of progesterone, cervical secretions decrease in quantity and become thick, tenacious and cellular, and fern pattern is not seen. These changes make a plug and prevent the entry of sperm through cervical canal.

Cyclic Changes in Vagina

Vaginal epithelium undergoes the following cyclic changes in the endometrial cycle:

In Proliferative Phase, vaginal epithelium becomes thickened (by adding up more and more layers of epithelium) and cornified.

In Secretory Phase, under the influence of progesterone, vaginal epithelium proliferates and gets infiltrated with leucocytes, and the vaginal secretions become thick and viscid.

Hormonal Control of Female Sexual Cycle

The hypothalamo–hypophyseal–gonadal axis regulates the cyclic changes occurring during the female sexual cycle. The role of each component of the axis is (Fig. 9.3-6).

Role of Hypothalamus

Hypothalamus regulates the secretions of gonadotropins (both FSH and LH) through the gonadotropin-releasing hormone (GnRH). The gonadotropin-releasing hormone (GnRH) is also known as luteinizing hormone-releasing hormone (LHRH). It reaches the anterior pituitary through hypothalamo–hypophyseal portal system, where it is stored as small granules. It stimulates the anterior pituitary cells to release gonadotropins.

Role of Anterior Pituitary

The anterior pituitary plays its role in the female sexual cycle regulation by releasing gonadotropins (FSH and LH). Gonadotropins in turn regulate the ovarian cycle, i.e. formation of graafian follicles (folliculosis), ovulation and formation of corpus luteum.

Regulation of Gonadotropins The secretion of both FSH and LH is regulated by the following.

1. Gonadal Hormones The gonadal hormones (oestrogen and progesterone) regulate gonadotropin secretion by their feedback effect (Fig. 9.3-6).

- ***High levels of oestrogen and progesterone*** in mid-luteal phase inhibit the secretion of FSH and LH (by negative feedback effect).
- ***Low levels of gonadal hormones*** (during menstruation phase) increase the secretion of both FSH and LH (by positive feedback effect).

The feedback effect (positive or negative) of ovarian hormones is brought about by its action either directly on anterior pituitary or through the hypothalamus (Fig. 9.3-6).

IMPORTANT NOTE

Oral contraceptives are the preparations containing high concentration of oestrogen and progesterone. These drugs inhibit gonadotropin release by negative feedback effect and prevent ovulation.

2. Human Chorionic Gonadotropin (HCG) It is a glycoprotein secreted by syncytiotrophoblasts during early pregnancy (12–16 weeks of gestation). Like LH, HCG also maintains the functional state of corpus luteum, and thus elevates gonadal hormones resulting in inhibition of gonadotropin release.

3. Prolactin It is a mammotropic hormone secreted from anterior pituitary during lactation. It inhibits GnRH release and thus lowers the basal secretion of FSH and LH (cause for lactation amenorrhoea).

4. Activin It is structurally quite similar to inhibin (secreted from ovary). It is synthesized in the cells of the anterior pituitary. It stimulates the synthesis and release of FSH by autocrine and paracrine actions.

Role of Ovaries

Ovaries play an important role in the regulation of ovarian cycle and endometrial cycle by secreting gonadal hormones (oestrogen and progesterone).

Oestrogen In each sexual cycle, the plasma concentration of oestrogen starts rising from first day of the cycle and reaches to its peak just before ovulation (at 12–13th day) called *oestrogen surge*.

- Oestrogen through its positive feedback effect is responsible for *ovulation* due to LH surge.
- Oestrogen is responsible for the proliferative phase of the endometrial cycle.

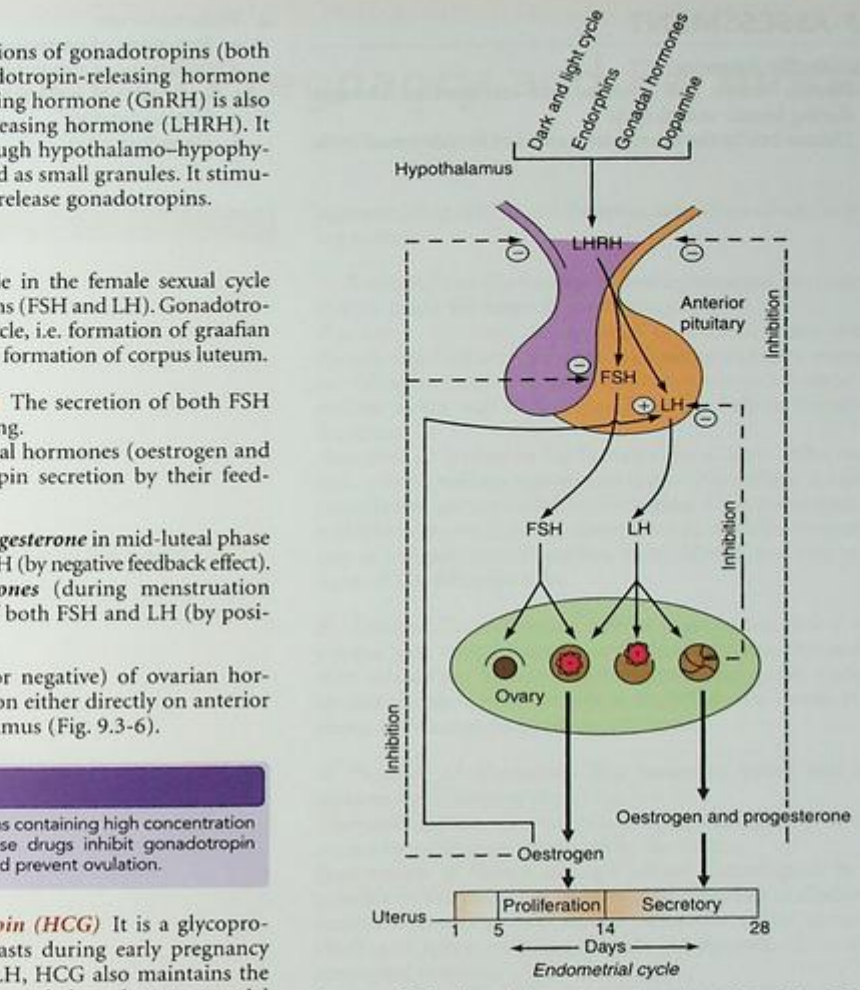


Figure 9.3-6 Hypothalamo–hypophyseal–ovarian axis regulating the female sexual cycle through positive and negative feedback mechanisms.

Progesterone In the luteal phase of ovarian cycle levels of both oestrogen and progesterone are high, but progesterone rises markedly.

Progesterone prepares the oestrogen-primed endometrium for implantation. Thus, it is responsible for the secretory phase of endometrial cycle.

If Fertilization Occurs the corpus luteum involutes, and levels of oestrogen and progesterone decline.

Withdrawal of hormones support results in menstruation, and at the same time negative feedback effect on anterior pituitary and hypothalamus is also abolished leading to further increase in gonadotropin, and next ovarian and endometrial cycle starts.

If Fertilization Occurs then HCG level rises, which maintains corpus luteum. Therefore, the levels of oestrogen and progesterone remain high, and by negative feedback effect gonadotropin levels (FSH and LH) remain low.

SELF-ASSESSMENT

1. Describe the following:
   - Discuss briefly the ovarian and endometrial changes during female sexual cycle
   - Discuss briefly the hormonal control of female sexual cycle
2. Write notes on:
   - Functions of oestrogen
   - Functions of progesterone
   - Indicators of ovulation
   - Corpus luteum
   - Gonadotropins

9.4 Physiology of Pregnancy and Parturition

CHAPTER OUTLINE

Physiology of Pregnancy
Fertilization and Implantation
Fertilization
Transportation of Gametes
Sperm Capacitation
Fusion of Gametes
Implantation
Placenta and Pregnancy Tests
Placenta
Placental Membrane
Functions
Pregnancy Tests
Physiological Changes in Mother during Pregnancy
Genital Organ Changes
Weight Gain
Haematological Changes
Cardiovascular System Changes
Respiratory System Changes
Urinary System Changes
Gastrointestinal System Changes
Metabolic Changes
Endocrine System Changes
Changes in the Skin
Psychological Changes

Physiology of Parturition
Mechanics of Parturition
Uterine Contractions
Cervical Dilatation
Control of Parturition
Hormonal Factors
Mechanical Factors

PHYSIOLOGY OF PREGNANCY

Physiology of pregnancy is mainly concerned with maternal adaptations to provide ideal atmosphere for fertilization, nutrition to the growing fetus and safe childbirth. The physiology of pregnancy can be discussed under the following headings:

- Fertilization and implantation
- Formation of placenta and its functions
- Physiological changes during pregnancy
- Applied aspects

Fertilization and Implantation

Fertilization

Fertilization refers to the fusion of male and female gametes (i.e. spermatozoon and ovum). It takes place in the middle segment (ampulla) of the fallopian tube. It involves the following events:

1. Transport of Gametes Before fertilization, the ovum and sperms reach the ampulla for fertilization.

Transport of Ovum At the time of ovulation, the ovum is directly expelled into the peritoneal cavity and then enters into the fallopian tube. The contractions of smooth muscle fibres present in the wall of fallopian tube also help in transport of the ovum.

Transport of Sperms in the Female Genital Tract After ejaculation, several million sperms (average – 200 million sperms per ejaculation) get deposited in the vagina. After ejaculation, normal sperm shows flagellar movements in the fluid medium at a rate of 1–4 mm/min. Therefore, in 30–60 minutes, they are able to reach the fallopian tube.

2. Sperm Capacitation Sperm capacitation refers to the process that makes a sperm to fertilize an ovum. Immediately after ejaculation in female genital tract, the sperm undergoes certain changes, which enable it to fertilize an ovum. It takes about 1–10 hours (capacitation period).

3. Fusion of Gametes The fusion of ovum and sperm involves the following steps (Fig. 9.4-1):

Chemoattraction Chemoattraction of the sperms to ovum occurs by substances produced by the ovum.

Penetration of Sperm through Ovum Coverings It is made possible by the release of enzyme hyaluronidase and other proteolytic enzymes present on the acrosome of the sperm. The binding of sperm to zona pellucida glycoprotein (ZP_3) triggers acrosomal reaction.

Acrosomal reaction (Fig. 9.4-1C). It involves release of acrosin (protease enzyme) from anterior membrane of acrosome of the sperm.

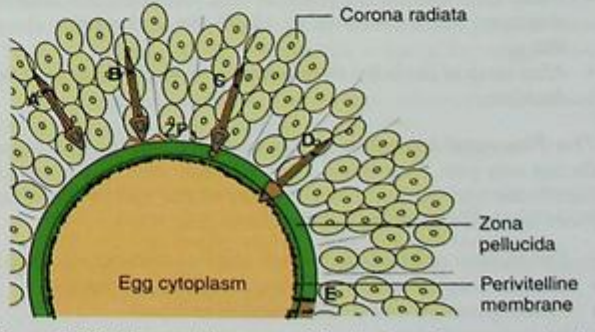


Figure 9.4-1 Sequential events of fertilization of an ovum by the sperm: (A) penetration of corona radiata; (B) binding of sperm to zona pellucida; (C) acrosomal reaction; (D) fusion of sperm with oocyte; and (E) discharge of cortical granules into the perivitelline space producing vitelline block to polyspermy.

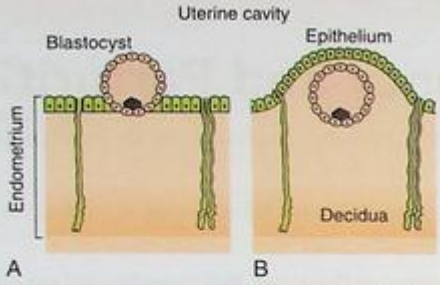


Figure 9.4-2 (A) Implantation of blastocyst in the endometrium and (B) decidual reaction.

Only one sperm can enter into the oocyte, and further entry of sperms is prevented by the activation of ovum.

Implantation

Implantation of a fertilized ovum involves the following steps.

1. Formation of Blastocyst The fertilized ovum starts dividing immediately and is called morula (16-cell stage) and blastocyst (100-cell stage).

2. Transportation of Blastocyst in Uterine Cavity In next 3–4 days, blastocyst is transported into the cavity of the uterus.

3. Implantation of Blastocyst in the Endometrium The blastocyst then erodes and burrows into the endometrium (Fig. 9.4-2). The blastocyst goes deeper and deeper into the uterine mucosa till whole of it lies within the endometrium.

4. Decidual Reaction After implantation, the endometrium is called decidua. The stroma cells of the endometrium get enlarged, become vacuolated and get filled with glycogen and lipids. These cells are called decidual cells. The stored glycogen and lipids are the source of nutrition for the embryo till placenta takes up this function. Therefore, this change in stroma cell is called decidual reaction.

Placenta and Pregnancy Tests

Placenta

Placenta is a temporary organ formed during pregnancy. It is an important link between the mother and the fetus.

- When fully formed, the placenta (Fig. 9.4-3) is a disc-shaped structure, has a diameter of 15–20 cm and weighs about 500 g.
- After birth of the baby, the placenta is shed off along with the decidua.

The Placental Membrane The maternal and the fetal blood do not mix with each other. They are separated by a placental membrane and made up of the layers of the wall of the villus. From the fetal side, these are as follows (Fig. 9.4-4):

- *Endothelium* of fetal blood vessels and its basement membrane
- Surrounding mesenchymal tissue (connective tissue)
- Cytotrophoblast and its basement membrane
- Syncytiotrophoblast

The total area of the membrane varies from 4 to 14 m^2. Its thickness is 0.025 mm in the beginning and it is reduced to 0.002 mm in the later part of pregnancy.

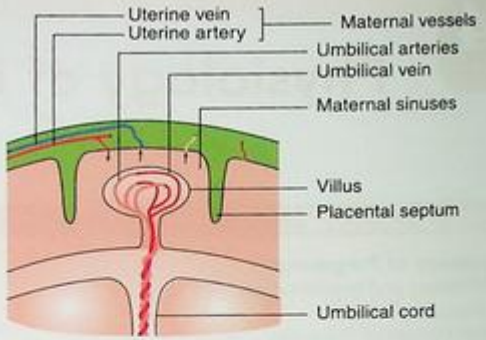


Figure 9.4-3 Schematic diagram showing structure of placenta.

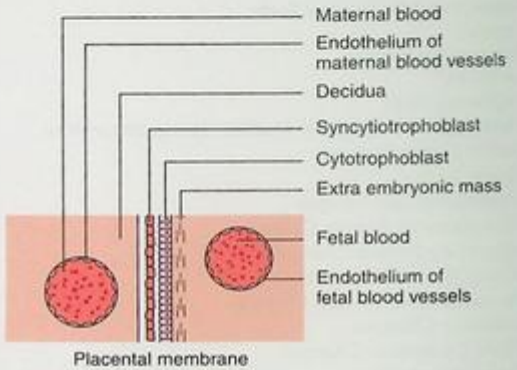


Figure 9.4-4 Structure of the placental membrane.

Functions of Placenta The fully functional placenta develops by the end of third month (12 weeks) of pregnancy. Placenta serves mainly three functions:

- Hormone secretion (endocrinal functions of placenta)
- Transport of substances between mother and fetus
- Protection of the fetus

A. Hormone Secretion The syncytiotrophoblast of the placenta serves as an endocrine gland. The hormones secreted by the placenta are as follows:

- Human chorionic gonadotropin (HCG)
- Human chorionic somatomammotropin (HCS)
- Human chorionic thyrotropin (HCT)
- Placental progesterone
- Placental oestrogens
- Relaxin

1. Human Chorionic Gonadotropins Human chorionic gonadotropin is a polypeptide (largest active peptide). It is secreted by syncytiotrophoblast; soon after fertilization, it is detected in the maternal blood as early as 6–8 days after conception, and reaches its peak between 60 and 90 days of gestation. After this the concentration falls to a very low level, and just before labour its level falls to zero (Fig. 9.4-5A). Its approximate peak value in human maternal blood during normal pregnancy is 5 mg/mL.

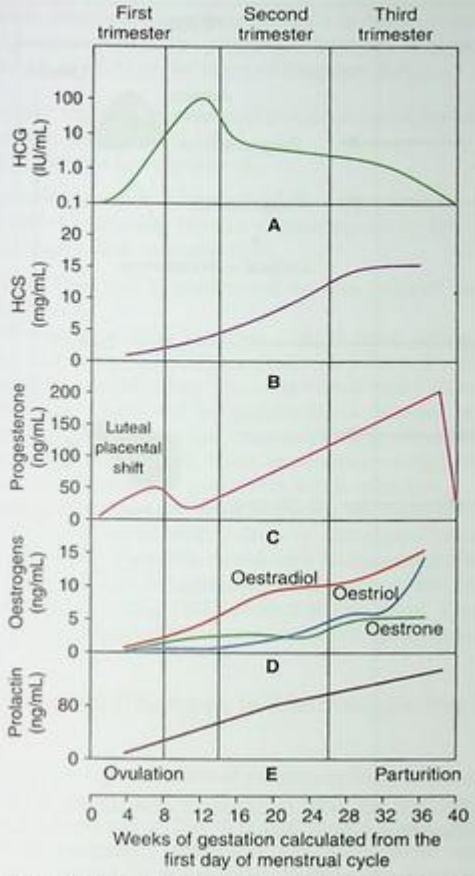


Figure 9.4-5 Profile of plasma concentration of hormones during normal pregnancy: (A) human chorionic gonadotropin (HCG); (B) human chorionic somatomammotropin (HCS); (C) progesterone; (D) oestrogens; and (E) prolactin.

Physiological effects of HCG are as follows:

- HCG is a luteotropic hormone. Its actions are similar to LH of anterior pituitary, hence are also called second *luteotropic hormone*. It maintains the functions of the corpus luteum up to 7 weeks after conception until fetoplacental unit is able to synthesize its own oestrogen and progesterone.
- HCG stimulates fetal testes in male fetus to secrete testosterone prior to fetal pituitary LH secretion. This testosterone and Mullerian regression factor secreted by the fetal testes is responsible for development of male genital organs and descent of testes during intrauterine life.

APPLIED ASPECTS

Clinical importance (application) of HCG are as follows:

The presence of HCG in the urine forms the basis of all the pregnancy tests. HCG appears in the urine as early as 10 days after gestation with 99% accuracy.
If fetus dies early then HCG disappears from the blood as well as from the urine.

2. Human Chorionic Somatomammotropin The syncytiotrophoblast cells of placenta also secrete a large amount of HCS. HCS is protein in nature and structurally resembles to growth hormone.

Plasma concentration. The secretion of HCS begins at 5th week of pregnancy. It increases gradually throughout pregnancy. Its peak reaches at term and peak value is 15 µg/mL (Fig. 9.4-5B).

It functions as maternal growth hormone of pregnancy, causes deposition of protein in the tissues and brings about nitrogen, calcium and potassium retention.

3. Human Chorionic Thyrotropin HCT secreted by the placenta has properties quite similar to that of thyroid-stimulating hormone (TSH). The physiological role of this substance is not very clear.

4. Placental Progesterone Progesterone is C-21 steroid hormone.

Synthesis. During early pregnancy, it is synthesized by corpus luteum of pregnancy and then by syncytiotrophoblasts of placenta (85% of total contribution).

- Placental syncytiotrophoblasts do not synthesize cholesterol. Therefore, cholesterol is mainly derived from maternal circulation and very little is contributed by the fetus.
- The fetus, placenta and mother – though they are independent, but constitute a functional unit called *fetoplacental maternal unit* (Fig. 9.4-6).

Plasma concentration. During pregnancy plasma concentration of progesterone rises steadily throughout gestation (Fig. 9.4-5C) reaching a maximum plateau at 30–40 weeks of gestation, and its level does not fall to zero like other placental hormones. Just before the onset of labour its level decreases.

Physiological effects of placental progesterone are as follows:

(i) It helps to preserve the pregnancy by promoting the growth of endometrium. It converts secretory endometrium of luteal phase of menstrual cycle to decidual during pregnancy.
(ii) Progesterone has a marked inhibitory effect on the contractions of uterus.
(iii) It causes development of alveolar system of mother's breast. Its synergic action with oestrogen prepares the breast for lactation after the birth of the baby.

5. Placental Oestrogens Placental oestrogens are C-21 steroid hormones; quantitatively oestriol is the major oestrogen of pregnancy with smaller amount of oestradiol and oestrone.

Plasma concentration. Like progesterone, plasma oestrogen (oestriol) concentration rises throughout the gestation. Its peak value (14 ng/mL) and secretory curve parallels as that of the progesterone, and maximum *plateau* is reached at 30–40 weeks of gestation.

The plasma concentration of oestriol reflects the functional status of fetoplacental maternal unit activity.

Physiological effects. It mediates the following effects:

(i) It causes growth and development of maternal reproductive organs (uterus increases in size, weight, length and volume both by hypertrophy and stretching of myometrium).
(ii) Oestrogen stimulates development of lactiferous ductal system in mammary glands.

B. Transport of Substances between the Mother and the Fetus

1. Transport of Nutrients The major function of placenta is to provide foodstuffs from mother's blood into the fetus.

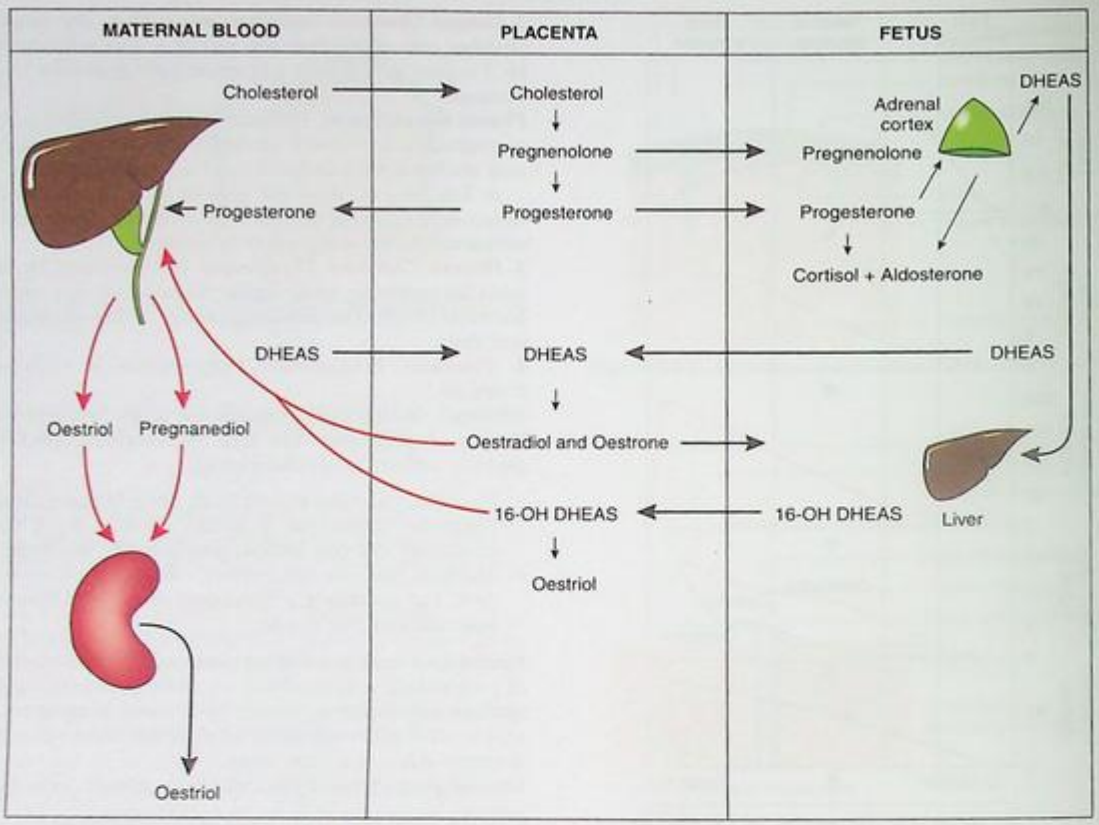


Figure 9.4-6 Fetoplacental maternal unit for steroid hormone synthesis.

By the 4th week of pregnancy, the placenta takes up the nutritive functions. The nutritive materials which are transported from mother's blood into the fetus are as follows:

- *Glucose.*
- *Fats.*
- *Amino acids.*
- *Calcium and inorganic phosphates.*
- *Potassium,* sodium and chloride ions, and substances with molecular weight less than 1000 can cross readily by simple diffusion.

2. Excretion of Waste Products through Placenta Excretory products, especially urea, uric acid and creatinines, etc. formed in the fetus are transported into the mother's blood and then excreted by mother's kidneys. Thus placenta also acts as a fetal kidney.

3. Diffusion of Respiratory Gases

(i) ***Oxygen transport.*** Dissolved oxygen from the maternal sinuses of placenta diffuses into the fetal blood along the pressure gradient (mean pO_2 in mother's blood is 50 mm Hg, whereas in fetal blood mean pO_2 is 30 mm Hg).

(ii) ***Transport of CO_2.*** Transport of CO_2 from fetus occurs by diffusion along the pressure gradient. The pCO_2 of fetal blood is 2–3 mm Hg higher than that of the maternal blood (as CO_2 is continuously being formed in the fetus and eliminated only through placenta). Thus, placenta acts as fetal lungs.

4. Transport of Antibodies Maternal immunoglobulins are transferred into the fetus and are responsible for innate immunity.

Rh agglutinins are easily transported as compared to ABO agglutinins, that is why the effects of Rh incompatibility are more severe.

5. Transport of Harmful Substances Certain viruses and many drugs (like nicotine and barbiturates) can easily cross the placental barrier and may produce harmful effect on the fetus. Therefore, as far as possible one should avoid these drugs and smoking during pregnancy.

C. Protection of the Fetus Placenta protects the fetus in many ways:

- It acts as a barrier for certain harmful substances.
- It provides nutrition to the fetus.
- Its hormonal secretion is responsible for the proper growth of the fetus.
- Placental progesterone decreases uterine contractions and thus protects the fetus from being expelled.

Pregnancy Tests

In an adult healthy woman, amenorrhoea is the first sign of pregnancy, but it occurs in many other conditions as well.

Therefore, detection of early pregnancy is made possible by certain pregnancy tests. The pregnancy detection tests are based on presence of HCG in the urine of pregnant lady.

Gravindex Test Immunological pregnancy tests are based on the antigenic properties of HCG.

The kit for this test consists of:

- Gravindex antigen (latex particles coated with HCG), Gravindex antibodies (serum containing antibodies against HCG) and a dark coloured slide.

Procedure This test is performed on the control and test samples of urine.

Control sample. A drop of urine sample from nonpregnant subject (containing no HCG) is mixed with a drop of antiserum containing HCG antibodies. Then it is mixed with HCG-coated latex particles. There will be agglutination because urine of nonpregnant subject does not contain antigen; therefore, antibodies are not neutralized. Thus, occurrence of agglutination indicates no pregnancy or pregnancy test is negative.

Test sample. A drop of urine of suspected pregnant lady (containing HCG) is mixed with a drop of antiserum (containing HCG antibodies). Then it is mixed with HCG-coated latex particles. There will be no agglutination because antibodies have been neutralized by the HCG present in the urine. Therefore, occurrence of no agglutination means positive pregnancy test.

Physiological Changes in Mother during Pregnancy

The normal average duration of pregnancy in human beings is 280 days (40 weeks) and is calculated from the first day of the last menstrual period or 256–270 days from the time of ovulation. As the pregnancy progresses, various types of extra demands are imposed on the mother's body by the growing fetus, which are met with by certain adaptations in almost all the organ systems of the body. These physiological changes include the following:

I. Changes in Genital Organs

1. Uterus To accommodate the growing fetus marked increase in the size of uterus takes place. The enlargement is mainly due to hypertrophy and to some extent hyperplasia of the myometrial smooth muscle fibres.

2. Ovaries The follicular changes and ovulation do not occur because FSH and LH of anterior pituitary are inhibited.

3. Cervix Endocervix gets hypertrophied, the cervical glands increase in number and their secretions form a plug that closes the cervical canal, and the tough cervix becomes soft.

4. Mammary Glands Under the influence of various hormones, breast enlarges in early pregnancy. Hyperplasia of ductal and alveolar tissue occurs, the areola becomes pigmented and many sebaceous glands become prominent in the areola. Nipples also become larger and pigmented.

II. Weight Gain

A woman may gain total of 10–12 kg of weight during normal pregnancy, which is contributed by:

- Fetus: 3 kg
- Placenta and amniotic fluid: 1.5 kg
- Uterus and breast enlargement: 1.0 kg
- Increase in blood volume and interstitial fluid: 1.5 kg
- Fat deposition: 3.5–4 kg

III. Haematological Changes

1. Blood Volume The total blood volume increases by 30%. The plasma volume increases relatively more than that of the red cell volume, which causes haemodilution; thus, there is physiological anaemia of pregnancy.

2. The Haematological Indices show the following changes:

- RBC count decreases.
- Hb concentration decreases.
- PCV decreases.
- ESR increases.
- Reticulocyte count increases.

3. Plasma Proteins The total concentration of plasma proteins decreases from 7.5 to 6 g% due to haemodilution. The fibrinogen level increases, but serum albumin level markedly decreases.

4. Leucocytes Total leucocyte count (TLC) increases and may reach up to 20,000/mm^3.

5. Platelets. There occurs a slight decrease in the platelet count.

6. Coagulation Factors Pregnancy seems to be a hypercoagulable state due to an increase in the following: fibrinogen, and factors VII, VIII, IX and X. The hypercoagulability of the blood plays a significant role of haemostasis at the time of separation of placenta during delivery.

IV. Cardiovascular System Changes

1. Position of Heart The gravid uterus pushes the diaphragm upwards resulting change in the position of heart.

2. Heart Rate Heart rate also increases by 10–12 beats/min.

3. Cardiac Output Cardiac output (CO) increases from 5 L/min to 7 L/min at 20 weeks of gestation.

4. Blood Pressure may show the following changes:

- ***Systolic blood pressure.*** In normal pregnancy, there is either no change in systolic pressure or some fall may occur.
- ***Diastolic pressure*** decreases and by 16–20 weeks of pregnancy its value is lowest. Then it starts rising and comes back to normal.

5. Blood Flow Blood flow to skin, uterus and kidneys increases to meet the demands.

6. Venous Pressure The gravid uterus exerts pressure on the pelvic veins, abdominal veins and femoral veins, thus increasing the venous pressure. The rise in femoral venous pressure results in oedema in feet (common occurrence).

V. Respiratory System Changes

1. Hyperventilation High levels of plasma progesterone during pregnancy increase the sensitivity of respiratory neurons to CO_2 resulting in hyperventilation.

2. Gas Exchange Gas exchange across the alveoli is greatly enhanced due to a marked increase in the pulmonary blood flow.

3. Oxygen Consumption Oxygen consumption of body increases by 15% to meet the demands of growing fetus and for the extra work of heart, uterus and other tissue.

VI. Urinary System Changes

Kidney functions show the following changes.

1. Renal Blood Flow There is a marked increase in renal blood flow due to increase in the cardiac output and vasodilatation.

2. Glomerular Filtration Rate (GFR) increases by 50% due to an increase in renal blood flow and solute load.

3. Renal Tubular Absorptive Capacity for sodium and chloride ions also increases by 50% due to high level of steroid hormones secreted by the placenta and the adrenal cortex.

4. Glycosuria is a common physiological phenomenon during pregnancy.

5. Proteinuria occurs due to increase in excretion of proteins.

6. Water Balance During later months of pregnancy, excess of water is retained due to:

- Decreased protein concentration
- Retention of sodium

7. Acid–base Balance Hyperventilation during pregnancy results in respiratory alkalosis. Kidneys, therefore, compensate for it by excreting more HCO_3^- ions in the urine.

VII. Gastrointestinal System Changes

1. GIT Secretions Hypochlorhydria is very common due to decreased gastric secretion.

2. GIT Motility decreases under the influence of hormones resulting in delayed gastric emptying.

3. Gall Bladder Functions The gall bladder increases in size and empties its contents at a very slow rate.

4. Liver Functions are also altered during pregnancy. The fibrinogen synthesis increases and albumin decreases; thus plasma A:G ratio is also altered.

5. Morning Sickness Anorexia, nausea and vomiting are very common in early pregnancy (first trimester) especially in the morning hours, hence is known as morning sickness. The cause for the morning sickness is not known.

VIII. Metabolic Changes

1. The Basal Metabolic Rate (BMR) of the pregnant woman increases by about 15% during later half of the pregnancy.

2. Protein Metabolism When the diet is balanced and adequate, then there is nitrogen retention and positive nitrogen balance. The proteins are deposited in the uterus, breast, fetus and placenta.

3. Carbohydrate Metabolism shows the following changes:

- Blood glucose level increases due to rapid absorption from the gut.
- *Glycosuria* is of common occurrence due to the increase in GFR and decrease in renal threshold for glucose.
- Ketosis may occur due to anorexia and excessive vomiting.

4. Fat Metabolism About 3–4 kg of fat is deposited in the body during pregnancy. There occurs an increase in plasma concentration of cholesterol, phospholipids and triglycerides.

5. Mineral Metabolism depicts the following changes:

- ***Calcium and phosphorus.*** In normal pregnancy, mother retains about 50 g of extra calcium and 30–40 g of phosphorus. These are deposited in the fetus and also retained in the mother stores (skeleton).
- ***Iron metabolism.*** Iron requirement tremendously increases during pregnancy and lactation.

IX. Endocrine System Changes

Almost all the endocrine glands of the mother react substantially during pregnancy. Firstly, due to increased metabolic load on the mother and secondly in response to the hormones produced by the placenta and fetus.

X. Changes in the Skin

1. Hyperpigmentation occurs on the face (butterfly pattern known as chloasma), areola, nipple and midline of abdomen (linea alba) extending from pubic symphysis to xiphisternum. The hyperpigmentation is related to increased secretion of ACTH and MSH during pregnancy.

2. Stria Gravidarum These are linear scars present on the lower abdomen due to stretching of skin.

XI. Psychological Changes

The nervous system shows mild changes in the form of craving for particular types of food item, alterations in the behaviour, emotions and mood. In few cases, true psychosis may also develop but cause is not known.

PHYSIOLOGY OF PARTURITION

Parturition is the process by which baby is born. It involves preparation for childbirth, act of childbirth and recovery from childbirth. It is difficult to predict the exact date of onset of labour. It may occur any time between 37th and 40th weeks of gestation. The uterine myometrium and cervix play an important role for this process.

Mechanics of Parturition

From the functional point of view, mechanics of parturition mainly involves:

- Uterine contractions
- Cervical dilatation

Uterine Contractions

The uterus, which remains quiescent during the period of pregnancy, becomes progressively more and more excitable towards the end of pregnancy, until finally it begins strong rhythmical contractions with such a force that it expels the fetus.

Cervical Dilatation

Throughout pregnancy cervix remains as a rigid structure, but at the time of parturition certain structural and biochemical changes occur and the cervix becomes soft. This is known as cervical ripening. It allows the cervix to stretch when uterine contractions start.

Control of Parturition

The mechanisms responsible for onset of labour in human are still not understood exactly. The control of parturition includes the role of:

- Hormonal factors
- Mechanical factors

A. Hormonal Factors

The hormonal changes that initiate the parturition and cause increased excitability of uterine musculature are given below.

1. Activation of Fetal Hypothalamic–pituitary–adrenal Axis Recently, it has been hypothesized that the initial signals for the onset of labour comes from the fetus only, and due to some unknown factors, corticotropin-releasing hormone (CRH) secretion in the fetus results in an increase in ACTH secretion few days before parturition. ACTH causes fetal adrenal cortex to secrete large amount of androgens.

The above changes lead to an altered oestrogen–progesterone ratio.

2. Role of Altered Oestrogen–progesterone Ratio The altered oestrogen–progesterone ratio also causes:

- An increase in release of oxytocin from maternal posterior pituitary
- An increase in number of oxytocin receptors in myometrium
- An increase in prostaglandin synthesis
- The prostaglandins enhance the force of oxytocin-induced uterine contractions

B. Mechanical Factors

Mechanical factors that increase the contractility of uterus include the following.

1. Stretch of Uterine Musculature usually increases its own contractility (myogenic theory). As the pregnancy advances with growing fetus, the stretch increases leading on to uterine contractility.

2. Positive Feedback Effect Stretching and irritation of cervix is particularly important because this positive feedback effect leads to further reflex increase in uterine contractility.

The positive feedback mechanism continues until the baby is expelled.

3. Role of Ferguson Reflex Once labour is started, the uterine contractions dilate the ripened cervix. The cervical dilatation, in turn, sets of signals in afferent nerves that increase oxytocin secretion from the posterior pituitary. This is called *Ferguson reflex*.

APPLIED ASPECTS

Clinical application. The obstetricians frequently induce labour by rupturing the membrane so that the head of the baby stretches the cervix more forcefully than usual and thus initiate it, leading to initiation of positive feedback effect and Ferguson reflex.

SELF-ASSESSMENT

1. Describe briefly the process of fertilization and implantation.
2. Describe briefly the functions of placenta.
3. Describe briefly the physiological changes in mother during pregnancy.
4. Write notes on:
   - Human chorionic gonadotropin
   - Immunological test of pregnancy
   - Placental membrane
   - Fetoplacental unit

9.5 Physiology of Lactation

CHAPTER OUTLINE

Functional Anatomy of Breast
Control of Breast Development and Growth

Physiology of Lactation
Phases of Lactation
Mammogenesis
Lactogenesis
Expulsion of Milk or Galactokinesis
Maintenance of Milk Secretion or Galactopoiesis

FUNCTIONAL ANATOMY OF BREAST

Breastfeeding is the characteristic feature of all the mammals including human beings. It has evolved as the best method of nourishing the newborn. The mammary glands (the secondary sex organs) play an important role in the lactation process.

Mammary glands are present in both the sexes; in males they remain rudimentary but in females they are well developed after puberty.

Gross Anatomy The fully developed breast is a soft, rounded, elevated structure present over the pectoral region having central dark pigmented area (areola). The central part of areola, projected above the surface, is called nipple.

Histological Structure Each mammary gland is covered by an overlying skin, and discrete masses of glandular tissue are present underlying it, in the connective tissue consisting of stroma and adipose tissue (Fig. 9.5-1).

- *The glandular tissue* mainly consists of alveoli having secretory cells.

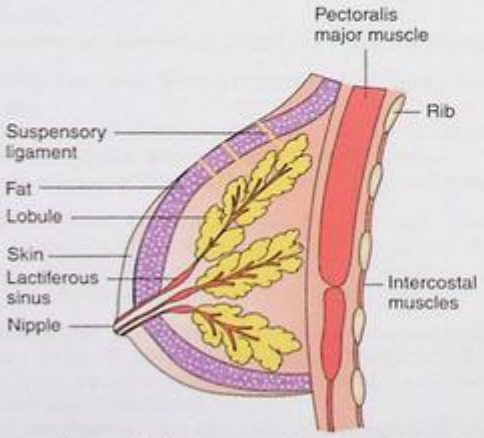


Figure 9.5-1 Structure of mammary gland.

- *The secretions* from these cells are poured by apocrine manner and exocytosis into the ducts (lactiferous ducts). About 15–20 ducts open at the summit of nipple, and just before opening lactiferous ducts show a dilatation called lactiferous sinus.
- *The smaller ductules* are lined by a single layer of columnar epithelial cells, whereas large ducts are lined by one or two layers of cells and near the opening at the nipple these are lined by squamous cells.
- *Around the alveoli,* ductules and lobules are present in the myoepithelial cells. They squeeze the contents and pour their secretions into the ductules.

Control of Breast Development and Growth

Various hormones necessary for full growth and development of mammary glands at various stages are as follows:

1. Oestrogen It is primarily responsible for the ductal growth and fat deposition. It also causes thickening of nipples.
2. Progesterone The development of glandular tissue mainly depends on progesterone. Both oestrogen and progesterone work best with cooperation of hypothalamo–pituitary–adrenal cortex axis.
3. Other Hormones including growth hormone, thyroxine, cortisol and insulin enhance overall growth and development of mammary glands at all stages.
4. Corpus Luteal and Placental Hormones, particularly oestrogen, progesterone and human chorionic somatomammotropic hormone (HCS or HPL) are essential for further growth of breast during pregnancy.
5. Prolactin It is another very important hormone for the development of breasts during pregnancy and lactation. It acts on mammary gland tissue, which has already grown under the influence of oestrogen and progesterone.

PHYSIOLOGY OF LACTATION

Phases of Lactation

The physiology of lactation can be divided into four phases:

- Preparation of breast for milk secretion (mammogenesis)
- Synthesis and secretion of milk (lactogenesis)
- Expulsion of milk (galactokinesis)
- Maintenance of lactation (galactopoiesis)

Mammogenesis

During pregnancy. The breast develops fully and is prepared for milk secretion after delivery (see page 375).

Lactogenesis

Stages of Lactogenesis The process of milk secretion occurs in two stages:

Stage I In later few weeks of pregnancy, a small amount of fluid is secreted in the alveolar cells. It is called colostrum. It occurs due to high plasma levels of prolactin and placental HCS. But due to suppressive lactogenic action of oestrogen and progesterone, free flow of milk never occurs during pregnancy.

Stage II It is the initiation of lactation after childbirth. Immediately after the baby is born, sudden loss of oestrogen and progesterone secretion by the placenta allows the lactogenic effect of prolactin.

Human Milk

Types of Human Milk The nature and composition varies with postpartum period. Therefore, the human milk is of three types:

1. ***Colostrum*** is deep-yellow coloured fluid secreted by the mammary glands during first few days of postpartum period.
2. ***Transition milk or intermediate milk.*** It is secreted from 6th to 15th day of postpartum period. The nature and composition of the secretion changes from colostrum to mature milk. Hence it is called transition milk.
3. ***Mature milk*** is formed from 15th day of postpartum onwards and continues during the whole lactation period (7–9 months).

Composition of Human Milk Human milk contains 88.5% water and about 11.5% solids. The solids include both organic and inorganic constituents. The composition of mature human milk, colostrum and cow's milk is shown in Table 9.5-1.

Note. Human milk is balanced diet as it contains first class proteins (caseinogen and lactalbumin), carbohydrates, fats, mineral salts and vitamins. Therefore, it is an ideal food for the baby.

Expulsion of Milk or Galactokinesis

Though milk is secreted continuously into the alveoli of the breast, but it does not flow continuously from alveoli into the duct system. It depends on the suckling reflex and some local mechanisms acting within the breast.

Suckling Reflex It is a neuroendocrinal reflex. The characteristic features and mechanism of suckling reflex (Fig. 9.5-2) are the following.

- When baby suckles, the sensory nerve endings or receptors located in skin of areola and nipple get stimulated.
- The sensory impulses are transmitted to the hypothalamus through somatic nerves (from nipple and areola to spinal cord, and then to hypothalamus). The activation of hypothalamus causes release of oxytocin and prolactin from the pituitary gland.
- The oxytocin is carried to the breasts through blood, where it causes contraction of myoepithelial cells that surround the outer wall of the alveoli. This process is called *milk ejection* or *milk expulsion* or *milk let down.*
- Another important observation is that suckling of one breast causes milk flow in the other breast also.
- Even stimuli such as sight, sound or crying of infant and thought of their infants also cause milk ejection, indicating the psychological component in the neuroendocrine reflex.

TABLE 9.5-1 Composition of Human Milk Colostrum, Mature Milk and Cow's Milk

Content	Human Milk		Cow's Milk (g/dL)
	Colostrum (g/dL)	Mature Milk (g/dL)	
1. Proteins	8.5	1.0–2.0	3.5
2. Carbohydrates (lactose)	3.5	6.5–8.5	4.7
3. Fat	2.5	3.0–5.0	3.5
4. Minerals: Na^+, K^+, P^+ and Cl^-	0.35	0.18–0.25	0.75
5. Calcium	–	0.03	0.14

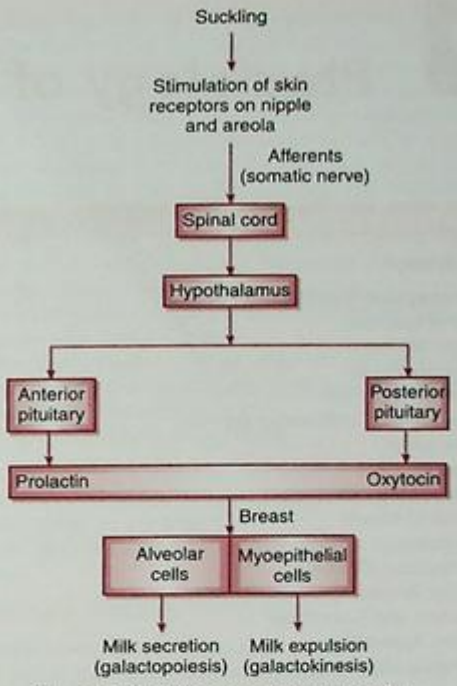


Figure 9.5-2 Mechanism of suckling reflex.

Maintenance of Milk Secretion or Galactopoiesis

Maintenance of milk secretion or galactopoiesis depends on the surge in prolactin secretion. After few weeks of childbirth, prolactin level falls to its basal value; however, in nursing mothers, neuroendocrine reflex causes 10- to 20-fold surge in prolactin secretion that lasts for 1 hour. Each time when baby suckles, the impulses from nipple and areolar receptors are transmitted by somatic nerves up to the hypothalamus, which cause 1- to 20-fold surge in the prolactin secretion.

The amount of milk production is related to infant's demand.

SELF-ASSESSMENT

1. Describe briefly Phases of lactation.
2. Write notes on:
   - Suckling reflex
   - Lactational amenorrhea

9.6 Physiology of Contraception

CHAPTER OUTLINE

Introduction

Contraceptive Methods in Females
Spacing Methods
Rhythm Method
Barrier Methods
Chemical Methods
Intrauterine Contraceptive Devices
Lippes Loop
Copper-T
Terminal Methods
Surgical Methods
Tubectomy
Laparoscopic Occlusion
Medical Termination of Pregnancy
Dilatation and Curettage
Vacuum Aspiration
Pregnancy Vaccines

Contraceptive Methods in Males
Spacing Methods
Natural Method
Barrier Methods
Chemical Methods (Drugs)
Terminal Methods
Vasectomy
No-scalpel Vas Occlusion

INTRODUCTION

Aims of Contraception Contraception refers to prevention of pregnancy. The aims of contraception are:

- The principal aim of contraception is family planning to check the enormous increase in population growth, which is the root cause of socioeconomic problems of poor and developing countries like India.
- Certain contraceptive measures are important to prevent the sexually transmitted diseases like AIDS.
- Contraceptives are also recommended on medical grounds to control the stress of pregnancy, labour and lactation in women suffering from heart diseases, etc.

Methods of Contraception can be broadly grouped as:
- Spacing methods
- Terminal methods

Both types of contraceptive measures are available for use by females as well as males; therefore, these can be described as:

- Contraceptive methods in females
- Contraceptive methods in males

CONTRACEPTIVE METHODS IN FEMALES

Spacing Methods

The spacing methods increase the gap between two pregnancies. These include the following:

- Rhythm method
- Barrier methods
- Chemical methods
- Intrauterine contraceptive devices

Rhythm Method

Rhythm method is also known as *calendar method* or *safe period method* or *natural method.* This method of contraception depends on the time of ovulation. In a woman having regular menstrual cycle, ovulation occurs on 14th day of the cycle. After ovulation, ovum remains viable for 48–72 hours. Similarly, after ejaculation sperms remain alive for 24–48 hours. Thus, pregnancy occurs only if coitus is performed during this period. This is the period of high fertility and is called *dangerous period.*

Therefore, to avoid pregnancy, intercourse should be avoided in the dangerous period. Rest of the cycle, i.e. 5–6 days after bleeding phase of menstrual cycle and 5–6 days before the next cycle, is the *safe period* (period of least fertility). This method of contraception is successful only if menstrual cycles are regular.

Barrier Methods

Barrier methods of contraception prevent the meeting of ovum and sperms after coitus. These include the following:

1. Mechanical Barriers The mechanical barriers used as contraceptive are diaphragm and cervical caps (Fig. 9.6-1).
Advantages. These devices are inexpensive and usually do not require any medical consultation.

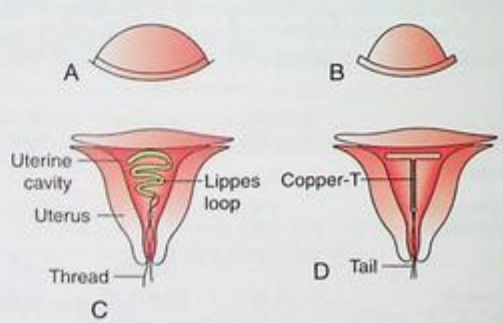


Figure 9.6-1 Female contraceptive devices: (A) vaginal diaphragm; (B) cervical cap; (C) Lippes loop; and (D) copper-T.

Disadvantages of mechanical barriers include the following:

- Failures are quite common because chances of displacement of the device are very high.
- Some women get cervicitis (inflammation of cervix) and local irritation.

2. Chemical Barriers Chemical barriers refer to spermicidal agents that can destroy the sperms when applied in the female genital tract before coitus. The common spermicidal agents used are as follows:

- Ricinoleic acid (oldest)
- Nonoxynol-9
- Octoxynol-3

These spermicidal agents are available in various forms such as foam tablets, pastes, creams, jellies and vaginal sponges. Vaginal sponge is a polyurethane sponge impregnated with nonoxynol-9. It is available by the trade name 'TODAY'.

3. Combined Methods As mentioned above, mechanical barriers (diaphragm and cervical caps) along with the spermicidal agents give good protection.

Chemical Methods

Chemical methods for contraception are used in various forms like locally applied chemicals (in the form of cream, jellies, etc.) and taken as drugs (either orally or in injectable form or as implants).

1. Oral Contraceptives Oral contraceptives/steroidal drugs are most widely used contraceptive measure by the women all over the globe. These are recommended in women of younger age group (up to 35 years).

Mechanism of Action In general, oral contraceptives contain synthetic preparation of oestrogen and progesterone, and when taken orally, the plasma concentration of these hormones rises. The raised levels of these hormones by their negative feedback effect act on the anterior pituitary to inhibit the release of gonadotropins (FSH and LH) and thus inhibit ovulation.

Types of Pills The oral contraceptives are available in different types of pills:

- Combined pill (classical pill)
- Sequential pill
- Minipill
- Postcoital (morning-after) pill

2. Depot Preparations Depot preparations are long-acting drugs and are highly effective. These are available in three forms:

- Injectable preparations
- Subdermal implants
- Vaginal rings

Advantages and Disadvantages of Depot Preparations

Advantages. As depot preparations are long-acting drugs, to avoid daily intake of oral pill, these preparations are preferred.

Disadvantages of depot preparation are that they sometimes lead to sterility and can alter menstrual bleeding pattern.

Intrauterine Contraceptive Devices

Intrauterine contraceptive devices (IUCDs) are inserted into the uterine cavity for long-term contraception. The devices are usually made up of inert materials like plastic, polythene and metal.

Lippes loop (Fig. 9.6-1C). It is a serpentine or S-shaped device made up of plastic to which is attached a fine nylon tail. The plastic used is nontoxic and nontissue reactive. A small amount of *barium sulphate* is also present in the plastic material to allow its radiographic observation. Lippes loop is available in different sizes.

Copper-T This is the most commonly used IUCD in India. As the name indicates, it is made up of copper and its shape resembles the letter T. Like Lippes loop, it is also attached with a nylon thread (tail) (Fig. 9.6-1D).

Insertion. Most ideal time for its insertion is during menstruation or within 10 days of the beginning of menstruation because the diameter of cervical cavity at this time is greater. It can also be inserted during first week after the delivery.

Mechanism of action. Copper-T.

Prevents implantation and growth of fertilized ovum by evoking aseptic inflammation and thus making endometrium unsuitable for implantation.

Advantages of IUCDs are as follows:

- This method of contraception is quite safe, effective and reversible. IUCDs can be easily pulled out or removed when contraception is not required.
- These provide long-term contraception without adverse effects.

Disadvantages of IUCDs are as follows:

- In some cases, these may cause heavy bleeding.
- The IUCD may come out accidentally, when not inserted properly.
- Risks of ectopic pregnancy are there.

Terminal Methods

Terminal method of contraception means permanent sterilization, which can be achieved either surgically or laparoscopically. The following methods have been employed.

Surgical Methods

Tubectomy Tubectomy is the permanent method of sterilization in female, and is recommended only when the family is completed. In tubectomy operation, fallopian tubes are cut, and then cut ends are ligated and buried as shown in Fig. 9.6-2.

Laparoscopic Occlusion In this procedure, the fallopian tubes are occluded using silicon rubber bands, Fallope rings or Hulka–Clemens clips. This method is much quicker and simple, and hospitalization is not required.

Medical Termination of Pregnancy

Medical termination of pregnancy (MTP or abortion) is allowed under MTP Act, 1971. Medical pregnancy act has laid down the following criteria:

- Conditions in which pregnancy can be terminated
- The person who can do termination
- Place, where it should be performed

Figure 9.6-2 Procedure of tubectomy (female sterilization).

Indications *Conditions in which pregnancy* can be terminated are as follows:

- *Medical.* When continuation of pregnancy is hazardous to the mother.
- *Eugenic.* When there is substantial risk to the child if born from that pregnancy.
- *Humanitarian grounds.* When pregnancy is the result of rape.
- *Failure of contraceptive measure.*

Methods Medical termination of pregnancy is possible only in first few months of pregnancy (from 7th week to beginning of second trimester). The following procedures have been employed depending on the duration of pregnancy.

1. Dilatation and Curettage (D and C) In this procedure, cervix is dilated with dilators and implanted ovum is removed by doing curettage of the endometrium.

2. Vacuum Aspiration Like D and C, in this procedure cervix is dilated and then implanted ovum is removed (aspirated) by applying suction. This method is employed only up to 12 weeks of gestation.

Pregnancy Vaccines

Pregnancy vaccines are under experimental trial. These have not yet been tried in women.

CONTRACEPTIVE METHODS IN MALES

Spacing Methods

The spacing methods of contraception used in males are as follows:

- Natural method
- Barrier methods
- Chemical methods

Natural Method or Coitus Interruptus

It is the oldest method of voluntary fertility control. In this method, male withdraws the penis before ejaculation into the vagina and tries to prevent deposition of semen into the vagina. This method needs practice and discipline. The failure rate is high because of the following reasons:

- Precoital secretions of the male may contain sperms and even a drop of semen is sufficient to cause pregnancy.
- Slightest mistake in timings of withdrawal may lead to deposition of certain amount of semen.

Barrier Methods

Condom This is the most widely used barrier by the males all around the world. In India, it is known by its trade name *Nirodh* (Fig. 9.6-3). It consists of a fine latex sheath and is electronically tested.

Mechanism of Action Condom prevents deposition of semen into the vagina, thus does not allow the sperms and the ovum to meet.

Figure 9.6-3 Condom.

Advantages

- They are easily available, safe and inexpensive.
- They also provide protection against sexually transmitted diseases.

Disadvantage

- It may slip off or tear off during coitus due to its incorrect use.

Chemical Methods

Antispermatogenic Drugs Few drugs which inhibit spermatogenesis have been available. These include male pill and calcium channel blockers.

1. Male Pill (Gossypol) contains gossypol, a phenolic derivative of cotton seed oil.

Mechanism of action. Gossypol acts as an effective azoospermic agent. Its exact mechanism of action is not yet known. In 99.9% of cases sperm count decreases to 4 million/mL.

2. Calcium Channel Blockers (e.g. nifedipine) block the Ca^{2+} channels on the cell membrane of the sperms. As a result, the sperm membrane becomes rigid and gets loaded with cholesterol. The rigid membrane of sperm prevents its binding to the zona pellucida of the ovum.

Terminal Methods

The permanent methods employed for sterilization in males are as follows:

- Vasectomy
- Vas occlusion using no scalpel technique

1. Vasectomy Vasectomy is a simple operation in which about 1 cm piece of vas deferens is removed after clamping. Then both the ends are ligated and sutured so that they face away from each other (Fig. 9.6-4). This procedure reduces the risk of recanalization later on.

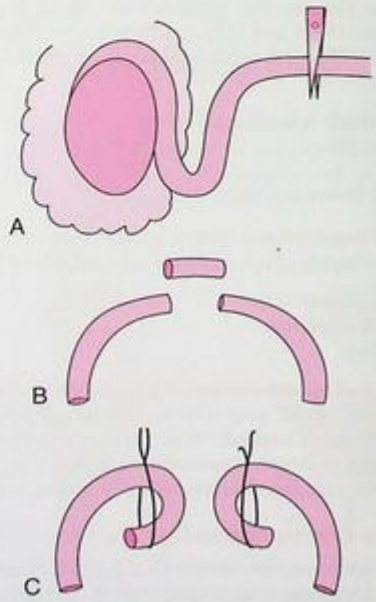


Figure 9.6-4 Procedure of vasectomy (male sterilization).

Advantages of vasectomy are that it is simpler, faster, less expensive procedure and no hospitalization is required. It is 100% effective.

Disadvantages *Failure rate* of vasectomy is only 0.15%, and that too because of wrong identification of vas deferens.

2. No-scalpel Vas Occlusion No-scalpel vas occlusion is a newer technique, which is quite safe, convenient and is acceptable to males.

Principle of Occlusion An elastomer is injected into the vas deferens; it gets hardened in situ within 20 minutes and plugs the vas deferens (occludes it).

Advantages. It is an easy procedure, and reversal is possible with 100% efficacy.

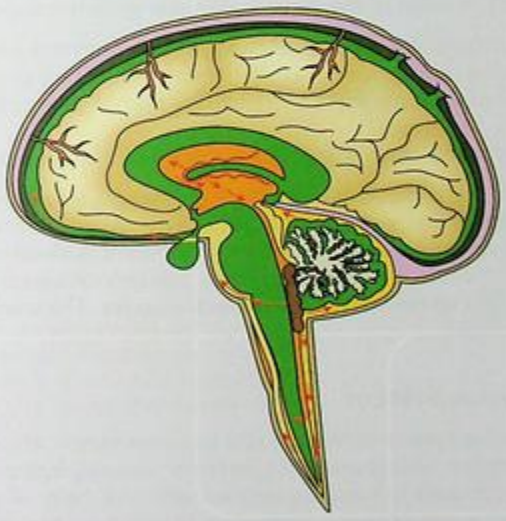
SELF-ASSESSMENT

1. Describe briefly methods of contraception in males.
2. Describe briefly methods of contraception in females.
3. Write notes on:
   - Mechanism of action of oral contraceptive pills
   - Safe period
   - Medical termination of pregnancy

Nervous System

SECTION OUTLINE

10.1 Central Nervous System
10.2 Synaptic Transmission
10.3 Somatosensory System
10.4 Somatic Motor System
10.5 Autonomic Nervous System
10.6 Meninges, Cerebrospinal Fluid, Blood–Brain Barrier and Cerebral Blood Flow
10.7 Limbic System and Physiology of Emotional, Behavioural and Motivational Mechanisms
10.8 Reticular Formation, Electrical Activity of the Brain, and Alert Behaviour and Sleep
10.9 Some Higher Functions of Nervous System



Organization of Nervous System

The nervous system acts as a control network within the body. The functional units of the nervous system are called *neurons*, which are responsible for the reception and response to changes in the internal and external environments. It is estimated that the human nervous system is composed of more than 100 billion neurons, which are linked together in a highly intricate manner. Thus, the various parts of the nervous system are interconnected, but for the convenience of description, the nervous system can be divided anatomically and functionally into different divisions.

Anatomical Divisions of the Nervous System

The nervous system is broadly classified into two divisions: central nervous system and peripheral nervous system.

1. **Central nervous system (CNS),** which occupies the central axis of the body, includes the brain and spinal cord.
2. **Peripheral nervous system (PNS)** is the part of the nervous system which lies outside the CNS. The PNS consists of peripheral nerves and the ganglia associated with them. Peripheral nerves attached to the brain are called *cranial nerves* (12 pairs), and those attached with the spinal cord are called *spinal nerves* (31 pairs).

Functional Divisions of the Nervous System

Functionally, the nervous system can be divided into the following two parts:

- Somatic nervous system
- Autonomic nervous system

Somatic Nervous System

The sensory division of the somatic nervous system collects the information about the changes that take place in the external environment and interprets the meaning of these changes. The sensory division of the somatic nervous system consists of the following:

- It consists of *sensory receptors* that receive stimulus from the external environment. The stimulus may be mechanical, chemical, thermal, auditory or visual.
- It consists of *afferent neurons* that carry impulses from the receptors to the brain and spinal cord.
- It consists of *parts of the brain* that primarily deal with the processing of information.

The *motor division* of the somatic nervous system executes appropriate actions with the help of skeletal muscles in response to changes in external environment detected by *the sensory division*. It also coordinates the actions of different skeletal muscles of the body.

Motor division of the somatic nervous system consists of neurons that carry signals away from the brain and spinal cord to the skeletal muscles. The somatic nervous system is under voluntary control.

Autonomic Nervous System

The autonomic nervous system (ANS) collects the information about the changes that take place in the internal environment (i.e. internal viscera), interprets these changes, guides the action and gets the plan executed with the help of smooth muscles of viscera, *cardiac muscles* and *secretory epithelium* of glandular *tissues* (which are effector organs of ANS). In other words, ANS is responsible for *activities* of the organs of digestion, circulation, excretion, respiration and *reproduction*, as well as of *adrenal medulla, sweat, salivary* and *lacrimal glands*. It also controls the activities of smooth muscles of *iris, ciliary body* and *arrectores pilorum*.

The word autonomous is taken from the Greek words '*autos*' meaning self and '*nomos*' meaning control. Thus, ANS is an involuntary system.

Divisions of ANS: ANS has two main divisions: sympathetic and parasympathetic, each having a central and a peripheral component.

10.1 Central Nervous System

CHAPTER OUTLINE

Brain
Forebrain
Midbrain
Hindbrain
Cerebrum
External Features
Lobes and Functional Areas
Histological Structure of Cerebral Cortex
Interior of Cerebrum
Basal Ganglia
White Matter
Diencephalon
Thalamus
Hypothalamus

Brainstem
Medulla Oblongata
Pons
Midbrain
Hindbrain
Cerebellum

Spinal Cord
Anatomy of Spinal Cord
Tracts of Spinal Cord
Functions
Lesions
Hemisection of the Spinal Cord

BRAIN

The central nervous system (CNS) consists of the brain and the spinal cord (Fig. 10.1-1). The brain is the largest and most complex mass of nervous tissue in the body. It is contained in the cranial cavity and weighs about 1380 g in the adult male and about 1250 g in the adult female.

Parts of Brain

The brain has the following three parts:

1. ***Forebrain*** (prosencephalon) consists of the following:
   - Cerebral hemispheres (telencephalon)
   - Diencephalon (thalamus plus hypothalamus)
2. ***Midbrain*** (mesencephalon)
3. ***Hindbrain*** (rhombencephalon) consists of the following:
   - Pons
   - Medulla oblongata
   - Cerebellum

Spinal cord traced upwards becomes medulla oblongata. Above the medulla, a broad bridge – the pons – connects the two hemispheres of the cerebellum, which lie behind the pons and medulla. The midbrain connects the forebrain with hindbrain. Medulla oblongata, pons and midbrain together constitute the *brainstem.*

Cerebrum

External Features

Cerebrum consists of two cerebral hemispheres, which are separated from each other in the upper part by a median longitudinal fissure in which the *falx cerebri* (a fold of dura mater) invaginates. In the lower part, the two cerebral hemispheres are connected by the largest white commissure called *corpus callosum.*

Sulci and Gyri

The surface of cerebral hemisphere is covered by a thin layer (2–4 mm thick) of grey matter called the cerebral cortex. The

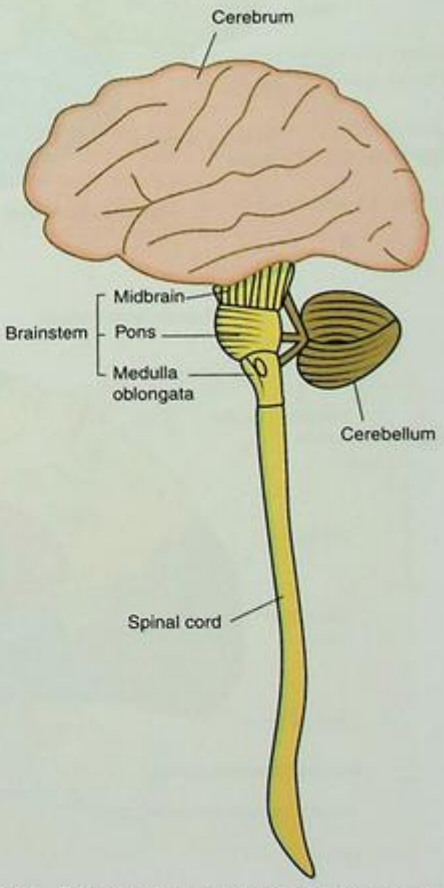


Figure 10.1-1 Diagram showing parts of the central nervous system.

entire surface of cerebral hemisphere is folded with intervening grooves of fissures. The folds or convolutions are called gyri and the intervening fissures are called sulci. The cerebral cortex follows the contour of the sulci and gyri of the hemisphere. As a result of the folding of the cerebral surface, the cerebral cortex acquires a much larger surface area (about 2200 cm^2).

Lobes and Functional Areas

Each cerebral hemisphere is divided into the following four lobes (Fig. 10.1-2A):

- Frontal lobe
- Parietal lobe
- Temporal lobe
- Occipital lobe

Frontal Lobe

The frontal lobe lies in front of the central sulcus and above the posterior ramus of the lateral sulcus (Fig. 10.1-2). It forms about one-third of cortical surface. On the basis of functions, the frontal lobe is subdivided into the following two main areas:

- Precentral cortex
- Prefrontal cortex

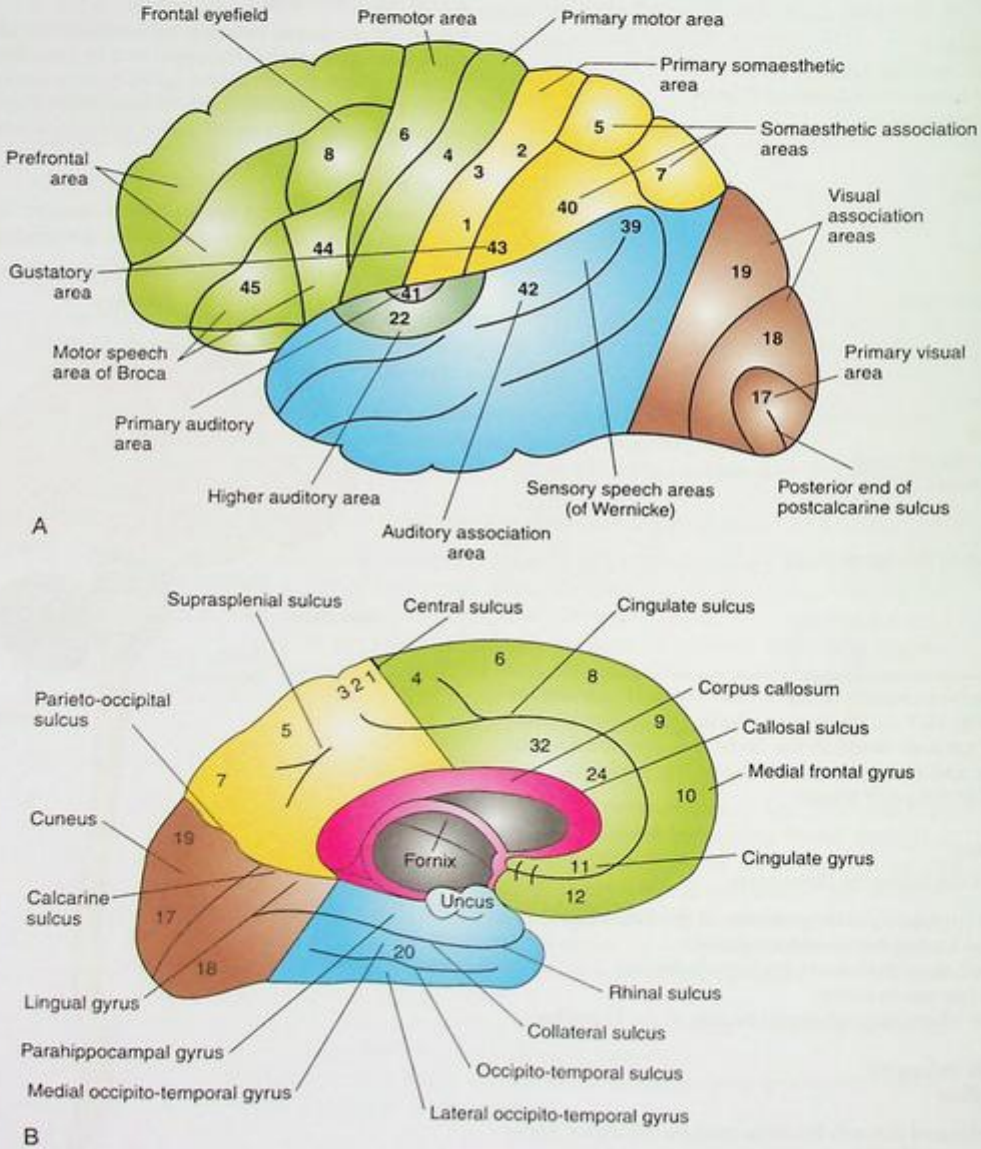


Figure 10.1-2 Left cerebral hemisphere showing lobes, sulci and gyri: (A) superolateral surface and (B) medial surface.

I. Precentral Cortex

Precentral cortex refers to the posterior part of the frontal lobe that includes the lip of central sulcus, precentral gyrus and posterior part of superior, middle and inferior frontal gyri. The precentral cortex is also called the excitomotor area of cortex.

Nowadays, the motor cortex and sensory cortex are together known as the *sensorimotor cortex.*

Areas in Precentral Cortex The precentral cortex includes the following important areas:

- Primary motor area (Brodmann's area 4)
- Premotor area (Brodmann's area 6, 8, 44 and 45)
- Supplementary motor area

1. **Primary motor area (area 4)** It lies in the precentral gyrus extending into the paracentral lobule on the medial surface (Fig. 10.1-2). Different parts of the contralateral half of the body are represented separately in more or less inverted order. Those parts of the body which carry out the most skilled movements, e.g. the fingers and thumb, have the largest areas of cortical representation. The body is represented upside down (however, the face not represented in an inverted manner) (Fig. 10.1-3A).
   Functions: It is concerned with initiation of voluntary movements of the contralateral half of the body and initiation of speech.
2. **Premotor area** Premotor area lies anterior to the primary motor area and includes Brodmann's area 6, 8, 44 and 45.
   - ***Area 6:*** It abuts on the primary motor cortex both above and behind. Cells from this area contribute fibres to pyramidal tracts. The topographical organization of this area is roughly the same as that of the primary motor cortex.
   - ***Area 8:*** It is also called the *frontal eye field.* It lies anterior to area 6. It is concerned with control of eye movements.
   - ***Area 44 and 45 or Broca's motor speech area:*** It is a special region of premotor cortex situated in the inferior frontal gyrus.

Functions: This area, especially in the dominated hemisphere (left hemisphere in a right-handed person), is concerned with movements of those structures which are responsible for the production of voice and articulation of speech.

II. Prefrontal Cortex

Location Prefrontal cortex, also called the prefrontal lobe or orbitofrontal cortex, is the anterior part of frontal lobe lying anterior to areas 8 and 44 (Fig. 10.1-2).
Major areas: Prefrontal cortex has different Brodmann's areas such as 9–14, 23, 24, 29 and 32, 44–47.
Functions of prefrontal cortex are as follows:

1. ***Centre for planned actions:*** Prefrontal-association areas in close association with motor cortex plan complex patterns and the sequence of motor movements.
2. ***Centre for higher functions:*** This forms the centre for higher functions like emotions, learning, memory and social behaviour.
3. ***Seat of intelligence:*** Short-term memories are registered in prefrontal cortex. It can keep track of many bits of information and also has the ability to recall this information bit by bit for subsequent thoughts. It is therefore called the seat of intelligence or an organ of mind.
4. ***Control of intellectual activities:*** The prefrontal cortex has the following intellectual abilities:
   - It allows us to prognosticate.
   - It allows us to plan the future.
   - It allows the person to concentrate on the central theme of thought. It helps in depth and abstractness of thought, and thereby in elaboration of thought.
   - It allows to delay action in response to incoming sensory signals so that sensory information can be weighed until the best response is obtained.
   - It allows to consider the consequence of motor actions before their performance.

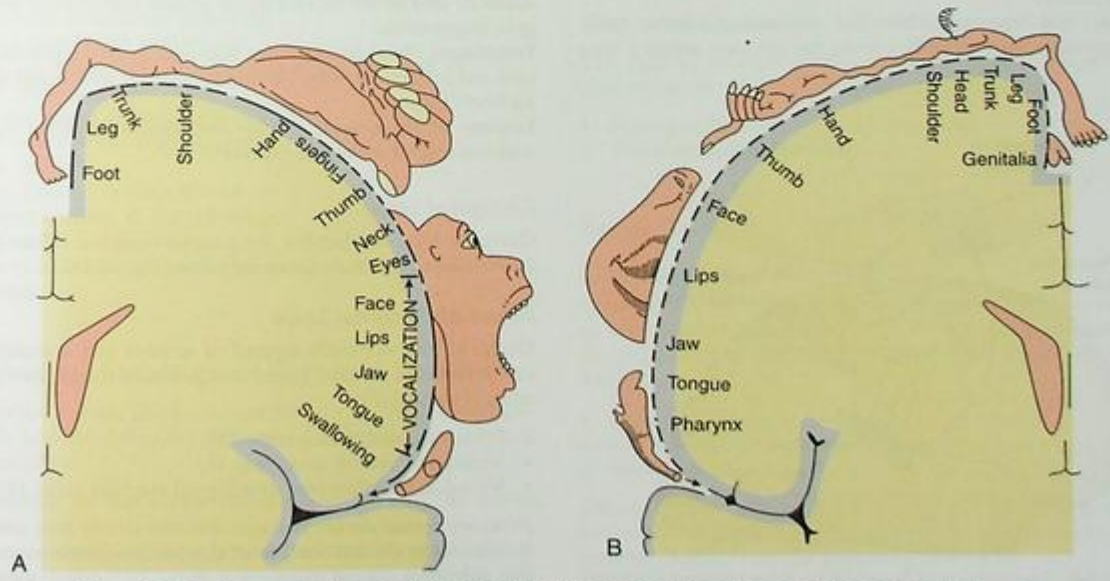


Figure 10.1-3 Topographical representation (homunculus) of motor (A) and sensory (B) areas in cerebral cortex.

- It plays a role in solving complicated mathematical, legal and philosophical problems.
- It allows to correct avenues of information in diagnosis of rare disease.
- It allows to control one's activity according to the moral laws.

Parietal Lobe

Parietal lobe (Fig. 10.1-2) lies between the central sulcus and parieto-occipital sulcus, and at the upper part of first imaginary line.

Areas of Parietal Lobe

Functionally, the parietal lobe can be divided into the following three parts:

- Primary sensory area (which corresponds to Brodmann's areas 3, 1 and 2)
- Secondary sensory area
- Sensory association areas (Brodmann's area 5 and 7)

Primary Sensory Area (First Somatic Sensory Area)

Location: The first somatic sensory area (SI) occupies the posterior wall of the central sulcus, the postcentral gyrus and the postcentral part of the paracentral lobule (Fig. 10.1-4).
Major areas It includes Brodmann's area 3, 1 and 2.
Topographical organization The primary sensory cortex receives sensory inputs from the opposite half of the body. The representation of the body within this area is similar to that already noted in the primary motor cortex (Fig. 10.1-3B).

Secondary Sensory Area

Location: Secondary sensory area, also called the second somatic sensory area (SII), is situated in the postcentral gyrus below the area of the face of first somatic sensory area. Most of it is buried in the superior wall of the Sylvian fissure (lateral cerebral sulcus).
Topographical representation The secondary sensory (SII) area receives sensory impulses from the primary sensory area (SI) as well as from the thalamus directly (Fig. 10.1-4). Like SI, the SII area also manifests a dermatomal (point-to-point) sequence of representation (although there is more overlap). Thus, the body is represented twice in the somatic sensory cortex, i.e. in area SI as well as in area SII.

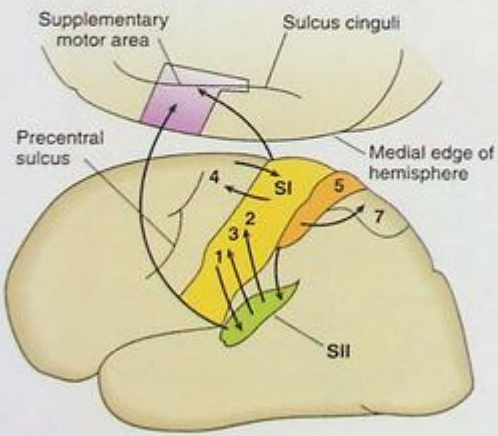


Figure 10.1-4 Connections of parietal lobe areas involved in somatic sensations.

Sensory-Association Areas

The sensory-association areas include areas 5 and 7. Area 40 is a higher association area.

Temporal Lobe

Temporal lobe (Fig. 10.1-2) lies below the posterior ramus of lateral sulcus and its continuation to the second imaginary line.

Areas of Temporal Lobe

The major areas in the temporal lobe are (Fig. 10.1-2) given below.

Primary Auditory Area

The Primary auditory area, also called the audiosensory area, includes Brodmann's areas 41 and 42, and forms the centre for hearing.
Functions: This area perceives the nerve impulses as sound, i.e. auditory information such as loudness, pitch, source and direction of sound.

Auditory-Association Area

The auditory-association area corresponds to Brodmann's areas 22, 21 and 20.
Area 22, also called Wernicke's area, is a sensory speech centre situated in the posterior part of superior temporal gyrus behind areas 41 and 42 in the categorical hemisphere, i.e. dominant hemisphere.
Functions: It performs the following functions:

- Interpretation of the meaning of what is heard
- Comprehension of spoken language and formation of ideas that are to be articulated in speech

Areas 21 and 20 are located in the middle and inferior temporal gyri, respectively.
Functions: These areas receive impulses from the primary area, and are concerned with the interpretation and integration of auditory impulses.
Lesions of these areas impair auditory, short-term memory without impairing visual memory.

Occipital Lobe

Occipital lobe lies behind the parieto-occipital sulcus and its continuation down an imaginary line (Fig. 10.1-2).

Areas of Occipital Lobe

Occipital lobe is mostly formed of sensory and association areas. It contains a visual cortex composed of the following three areas (Fig. 10.1-2):

- Primary visual cortex (area 17)
- Visual-association area (area 18)
- Visual-association area or occipital eye field (area 19)

Primary visual cortex is also called the striate area (area 17). It lies on the medial surface of the occipital lobe in and near the calcarine sulcus occupying parts of lingual gyrus and cuneus.

Peristriate area, also called the visual-association area (area 18), lies in the walls of lunate sulcus.
Parastriate area (area 19) is also a visual-association area. It lies in the cortex in front of the lunate sulcus.
Functions: Functions of visual cortex of:

- *Primary visual area (area 17)* is concerned with the perception of visual impulses.
- *Visual-association areas* (areas 18 and 19) are concerned with the interpretation of visual impulses. These are involved in the recognition and identification of objects in light of past experience.
- *Occipital eye field area* (area 19) is concerned with the movements of eyeball.

Summary of Cortical Functional Areas

Classically, cortical functional areas are subdivided into the following areas (Fig. 10.1-2):

Motor areas include the following:
- Primary motor area (Brodmann's area 4)
- Premotor area (area 6)
- Frontal eye field (area 8)
- Supplementary motor area

Sensory areas include the following:
- Primary somaesthetic areas (areas 3, 1 and 2)
- Secondary (supplementary) somaesthetic area
- Somaesthetic-association areas (areas 5 and 7 and higher association area 40)

Auditory areas include the following:
- Primary auditory area (area 41) or auditory area I
- Auditory-association area (area 42) or auditory area II
- Higher auditory-association area (area 22)

Visual areas include the following:
- Primary visual area (area 17) or visuostriate area of visual area I
- Visual-association area 18 (peristriate area)
- Visual-association area 19 (parastriate area)

Speech areas include the following:
Motor speech area comprises:
- Anterior area (Broca's area) or areas 44 and 45
- Superior area

Sensory speech areas comprise:
- Area 39 (or reading centre)
- Area 40
- Area 22 (Wernicke's area)

Smell area consists of the following:
- Area 28

Gustatory area consists of the following:
- Area 43

Histological Structure of Cerebral Cortex

The cerebral cortex, also known as pallium, is divided phylogenetically into the following three types: allocortex, mesocortex and neocortex.

1. ***Allocortex*** or old cortex forms about 10% of the entire cortex.
   Since most of the allocortex is located around the peripheral margin of the diencephalon in the form of a ring, it is also called *limbic cortex.*
2. ***Mesocortex,*** which is the transitional zone between allocortex and neocortex, comprises the *cingulate gyrus*, part of *parahippocampal* gyrus and *subiculum.*
3. ***Neocortex***, also called an isocortex, comprises rest of 90% of the cerebral cortex in human brain. The extent of neocortex has increased with the evolution of mammals.

Histologically, the cerebral cortex is composed of nerve cells and fibres. The following three types of cells may be identified in the cerebral cortex:

1. Pyramidal cells
2. Stellate or granule cells
3. Fusiform cells

Laminae of Neocortex The six laminae of neocortex numbered I–VI are (Fig. 10.1-5) as follows:

1. ***Molecular or plexiform layer:*** It mainly consists of transverse nerve fibres dispersed with occasional horizontal cells.
2. ***External granular layer:*** It contains numerous stellate or granule cells. It is traversed by afferent and efferent projection fibres.
3. ***Outer pyramidal layer:*** It mainly consists of pyramidal neurons, and some stellate and basket cells.
4. ***Internal granular layer:*** This layer consists of densely packed stellate cells. The inner zone of this layer is traversed by transversely running fibres called the external band of Baillarger.
5. ***Inner pyramidal (ganglionic) layer:*** This layer consists of large pyramidal cells. It is specially developed in the motor cortex, where these cells are called giant cells or Betz cells. This layer is traversed by aggregation of transversely running fibres called the internal band of Baillarger.
6. ***Polymorphous or multiform layer:*** This layer contains many spindle-shaped cells called fusiform cells. This layer merges with the white matter of cerebral cortex.

Interior of Cerebrum

The interior of each cerebrum, below the thick layer of grey matter (cerebral cortex), consists of the following:

- *Basal ganglia*, the masses of grey matter
- *White matter* of cerebrum

Basal Ganglia

Components of Basal Ganglia

Basal ganglia are subcortical nuclear masses. They are so named as they develop in the basal part of cerebral hemisphere. From the physiological viewpoint, the term basal ganglia include the following:

- Corpus striatum
- Subthalamic nucleus (body of Luys)
- Substantia nigra

Corpus striatum (Fig. 10.1-6) comprises subcortical masses of grey matter, which is divided almost completely by the fibres of internal capsule into the following two parts:

(i) Caudate nucleus (medial part)

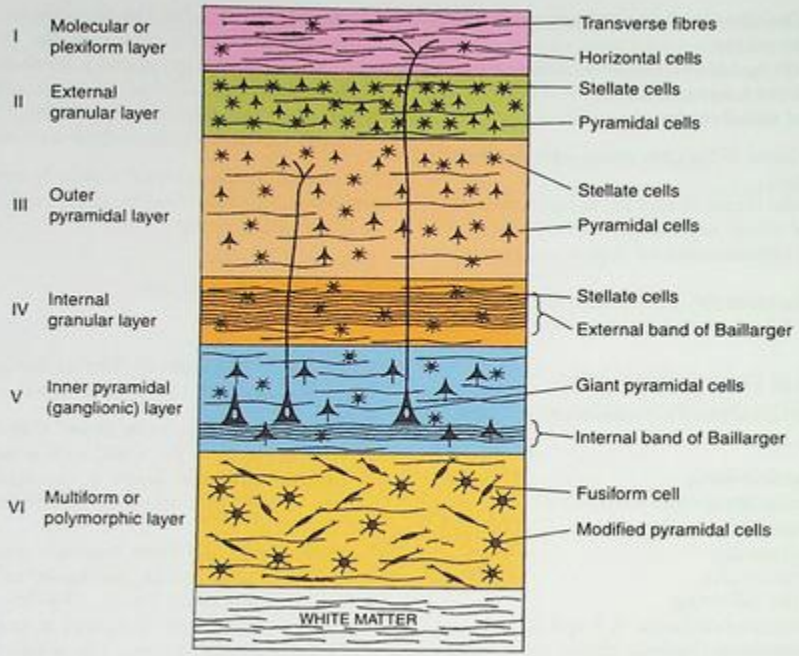


Figure 10.1-5 Histological structure of neocortex.

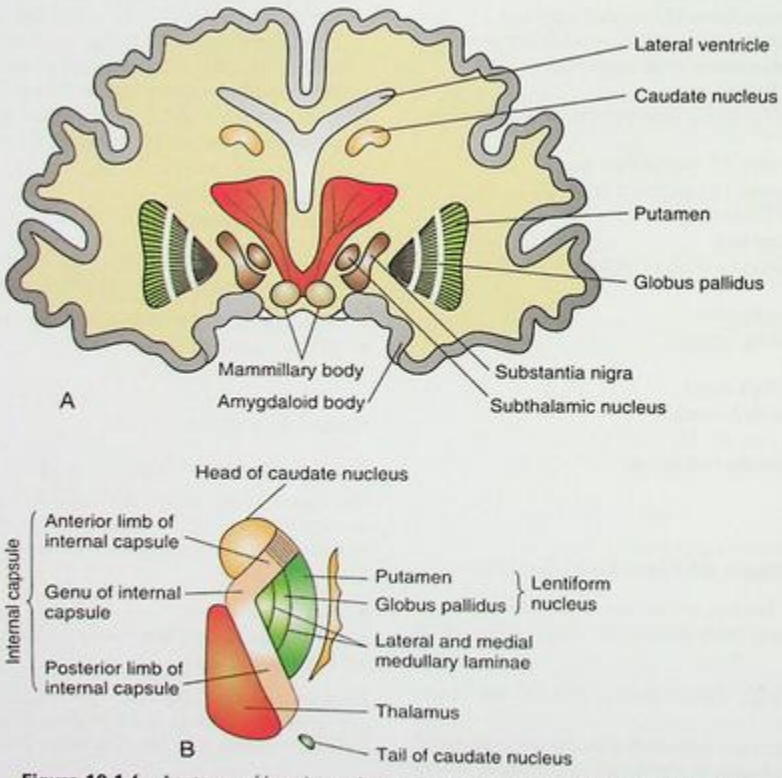


Figure 10.1-6 Anatomy of basal ganglia: (A) frontal section and (B) horizontal section.

(ii) Lenticular nucleus (lateral part), which is further subdivided into the following two parts:
- Putamen (an outer part)
- Globus pallidus (an inner part)

Phylogenetically and functionally, the corpus striatum can be divided into the following two parts:

1. ***Neostriatum or striatum*** Phylogenetically, the caudate nucleus and putamen are of more recent origin and hence called neostriatum or striatum.
2. ***Paleostriatum*** refers to globus pallidus, which is an older and primitive part. It is also called pallidum, as it is pale (pallid).

Subthalamic nucleus (body of Luys) is a biconvex mass of grey matter, which is situated lateral to the red nucleus and dorsal to the substantia nigra in the mesencephalon.

Substantia nigra is a sheet made up of pigmented nerve cells. It appears dark as the neurons contain the pigment neuromelanin.

Functions of Basal Ganglia

Control of Voluntary Motor Activity Basal ganglia control the voluntary movements, which are initiated by the motor cortex.

The role of basal ganglia in controlling voluntary motor activity includes the following:

(i) ***Cognitive control of motor activity:*** The basal ganglia, like the cerebellum, are involved in the planning and programming of the movement.
Most of the motor actions occur as a consequence of thoughts generated in mind. This process is known as cognitive control of motor activity.

(ii) ***Timing and scaling of the intensity of movements:*** Two important capabilities of brain in controlling the movements are as follows:
- Timing of the movements, i.e. how rapidly the movements should be performed
- Scaling of the intensity of movements, i.e. how large the movement should be

(iii) ***Subconscious execution of some movements:*** Basal ganglia subconsciously execute some movements during the performance of trained motor activities, i.e. skilled activities. Examples of movements executed subconsciously at the level of basal ganglia are as follows:
- Swinging of arm while walking
- Crude movement of facial expression that accompany emotions
- Movements of limbs while swimming
- Control of clutch and brake while driving (constant attention is required during initial stages; however, they are carried out subconsciously by basal ganglia as they become routine)

Importance: By subconscious control of activities, the basal ganglia relieve cortex from routine acts so that cortex can be free to plan its actions.

Control of Reflex Muscular Activity The basal ganglia exert an inhibitory effect on spinal reflexes and regulate the activity of muscles which maintain posture.

Control of Muscle Tone Muscle spindles and the γ motor neurons of spinal cord (which are responsible for maintaining the tone of the muscles) are controlled by basal ganglia, especially substantia nigra. In the lesion of basal ganglia, muscle tone increases. Rigidity (lead-pipe type) is a characteristic feature of Parkinson disease.

Role in Arousal Mechanism Globus pallidus and red nucleus are involved in the arousal mechanism because of their connections with reticular formation. Extensive lesions in globus pallidus are associated with drowsiness, leading to sleep.

Disorders of Basal Ganglia

Parkinson Disease Parkinson disease, also called *paralysis agitans* or shaking palsy, was first described by James Parkinson in 1817. Parkinson disease occurs in elderly people due to a steady loss of dopamine and dopamine receptors with age in the basal ganglia in normal individuals.

Pathogenesis A current view of the pathogenesis of Parkinson disease is that there is an imbalance between excitation and inhibition in the basal ganglia created by the loss of the dopaminergic inhibition of the putamen.

Clinical features Parkinson disease has both hypokinetic and hyperkinetic features. Its cardinal features are a triad of akinesia, rigidity and tremor of which akinesia is a hypokinetic feature, whereas rigidity and tremors are hyperkinetic features.

1. ***Akinesia or hypokinesia:*** The patient is unable to initiate the voluntary movements (akinesia) or the voluntary movements are decreased (hypokinesia).
Manifestations of akinesia or hypokinesia include the following:
   - Delayed motor initiative
   - Slow performance of voluntary movements (bradykinesia)
   - Mask-like facial expression due to decrease in movements of facial muscles
   - Absence of normal associated movements, e.g. swinging of arms during walking
   - Shuffling or festinant-type gait, in which the patient is bent forwards and walks quickly with short steps as if trying to catch up the centre of gravity or preventing himself or herself from falling
   - Retropulsion, i.e. when a walking patient is suddenly pulled backwards, he begins to walk backwards and is unable to stop.
2. ***Rigidity:*** It refers to an increase in tone of the muscles.
Characteristic features of rigidity occurring in Parkinson disease are as follows:
   - Due to rigidity, the posture becomes that of flexion attitude in which the back is flexed, arms are abducted and flexed, and the knees are bent.
   - In advanced cases, the rigidity may increase to such an extent that a statue-like appearance is produced with complete absence of movements.
   - Rigidity differs from spasticity seen in lesions of pyramidal tracts (see Table 10.1-1).

Cause of rigidity: An increased discharge of γ-efferents supplying the muscle spindle causes rigidity.
In patients with Parkinson disease, lack of dopaminergic activity due to degeneration of neurons in the substantia nigra shifts the balance towards excitatory cholinergic fibres. As a result, hyperkinetic features of Parkinson disease appear.

TABLE 10.1-1 Differences between Spasticity and Rigidity

Feature	Spasticity	Rigidity
1. Lesion	Occurs in pyramidal tract lesions, commonest site being internal capsule	Occurs in basal ganglia lesion, therefore, called the extrapyramidal rigidity
2. Muscles involved	One group of muscles, either agonist or antagonist (usually antigravity muscles), involved	Both agonist and antagonist muscles are involved producing a uniform hypertonia often resulting in general attitude of flexion of the limbs and trunk
3. Characteristics of hypertonia	Clasp-knife type of hypertonia is seen in muscles involved, i.e. on passive flexion, initially, there is marked resistance but then there is sudden completion of movement without much resistance (similar to closure of a pocket knife)	Usually, there occurs a uniform resistance to flexion giving a feeling as if lead pipe is being bent (lead-pipe rigidity); sometimes, there is a series of catches during passive motion of the limb (cogwheel rigidity)
4. Relation of hypertonia to stretch	Spasticity is stretch-sensitive, i.e. degree of hypertonia developed during any passive stretch is proportional to the speed of stretch applied	Rigidity is not stretch-sensitive

3. ***Tremors:*** Tremors (i.e. involuntary rhythmic oscillatory movements of the distal parts of limbs and head) seen in Parkinson disease have the following characteristics:
   - The tremors are present at rest, but disappear during activity. It is a hallmark of Parkinson disease and so popularly known as resting (static) tremors.
   - Frequency of tremors ranges from four to six times per second.
   - It is frequently seen as frill-rolling movements of the hand, i.e. rhythmic contraction of thumb over first two fingers.
   - Tremors are suppressed during sleep and exaggerated by stress, anxiety and excitement.

The tremors are observed as rhythmic movements of pronation and supination in fingers, hands, lips or tongue.

Treatment ***L-DOPA*** is used in the treatment of Parkinson disease. It can cross the blood–brain barrier and reaches the brain tissue, where it is concentrated into dopamine and thus compensates its deficiency.

White Matter of Cerebrum

Passing through, between and around the subcortical masses of grey matter of cerebrum, are tracts of white fibres. The white fibres of cerebrum are of the following three types (Fig. 10.1-7):

- Association fibres
- Commissural fibres
- Projection fibres

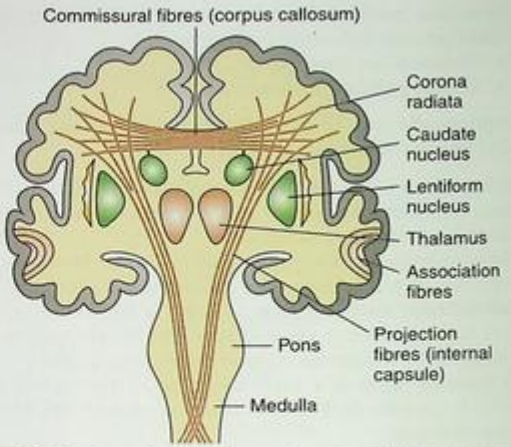


Figure 10.1-7 Frontal view of coronal section of brain showing the position of association, commissural and projection fibres.

1. ***Association fibres*** Association fibres connect the different gyri of the same hemisphere (Fig. 10.1-7).
2. ***Commissural fibres*** Commissural fibres connect the corresponding parts of two cerebral hemispheres with each other. There are five bundles of commissural fibres (Fig. 10.1-7):
   - Corpus callosum
   - Anterior commissure
   - Posterior commissure
   - Habenular commissure
   - Hippocampal commissure
3. ***Projection fibres*** Projection fibres connect the cerebral hemispheres with other parts of CNS, e.g. thalamus, brainstem and spinal cord. Projection fibres include the afferent and efferent tracts contained in the corona radiata and internal capsule.

   Corona radiata: Corona radiata (fountain of fibres) refers to that part of projection fibres that radiates from the upper end of internal capsule to cerebral cortex (Fig. 10.1-7). It contains both the ascending and descending fibres.

   Internal capsule: Internal capsule is a thick curved band of projection fibres (ascending and descending) that occupy the space between the thalamus and caudate nucleus medially and the lentiform nucleus laterally. Superiorly, it fans out as corona radiata and inferiorly the fibres descend into the crus cerebri.

   Parts: The internal capsule can be divided into the following parts (Fig. 10.1-8):
   - Anterior limb
   - Genu
   - Posterior limb
   - Retrolenticular or caudal part
   - Sublentiform part

APPLIED ASPECTS

In an internal capsule, fibres are densely crowded in a narrow area. Pyramidal fibres being compressed in this little space are particularly vulnerable to effects of even a pinpoint vascular lesion.

Damage to an internal capsule from infarction and haemorrhage is a common form of stroke, resulting in loss or decrease in sensations and movements of the opposite half of the body (*hemianaesthesia* and *hemiplegia*).

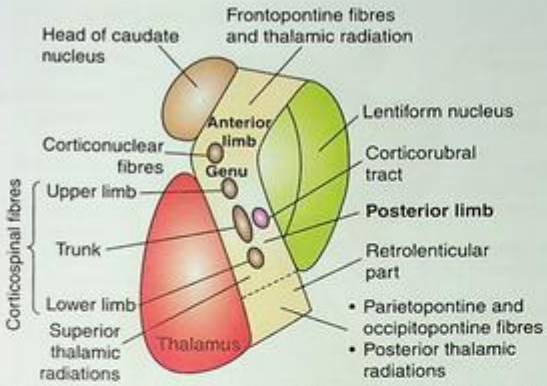


Figure 10.1-8 Parts of internal capsule: disposition of motor fibres and thalamic radiations passing through it.

Diencephalon

The diencephalon consists of the following:

- Thalamus
- Hypothalamus

Thalamus

The thalamus is a large ovoid structure placed immediately lateral to the third ventricle (Figs 10.1-9 and 10.1-10).

- ***Posterior end*** (or pole) is expanded and is called pulvinar.
- ***Dorsal or superior surface*** of the thalamus is convex and forms the part of floor of the central part of lateral ventricle (Fig. 10.1-10).
- ***Medial surface*** forms the greater part of the lateral wall of third ventricle, and is lined by ependyma. The medial surfaces of the two thalami are connected by a short bar of grey matter called the *interthalamic adhesion*. Inferiorly, the medial surface is separated from the hypothalamus by *hypothalamic sulcus* (Fig. 10.1-9).
- ***Lateral surface*** of thalamus is related to the posterior limbs of internal capsule.

Internal Structure

Like other parts of brain, thalamus consists of grey matter (mainly) and white matter (Fig. 10.1-11).

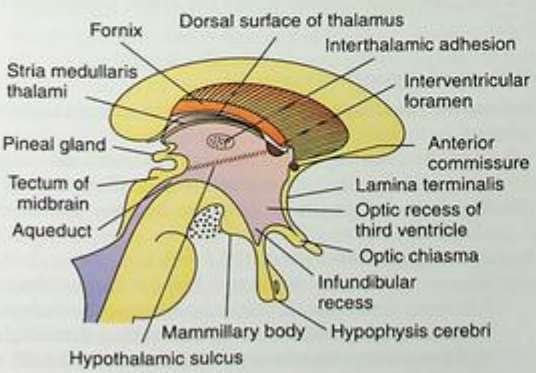


Figure 10.1-9 Median section through the brain showing the medial surface of thalamus and hypothalamus.

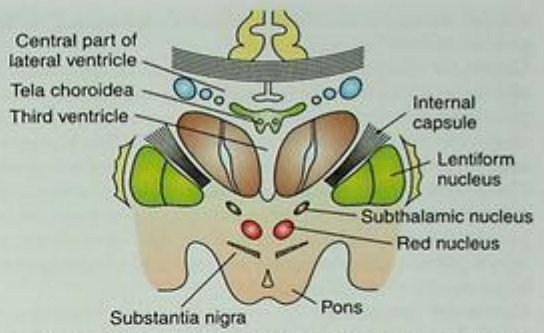


Figure 10.1-10 Coronal section through the brain passing through the basilar part of pons showing the relations of ventral surface of thalamus and subthalamic structures.

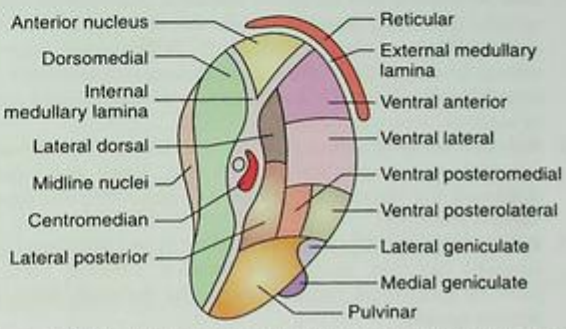


Figure 10.1-11 Horizontal section of right thalamus (superior aspect) showing nuclear subdivisions.

White matter: White matter is scanty in thalamus and includes the following:

- *Stratum zonale* is a thin layer of white matter covering the superior surface of thalamus.
- *External medullary lamina* is a thin layer of white matter covering the lateral surface of thalamus. It consists of thalamocortical and corticothalamic fibres.
- *Internal medullary lamina* is a Y-shaped sheet of white matter placed vertically in the grey matter of thalamus. It consists mainly of internuclear thalamic connections.

Grey matter: Grey matter of thalamus is divided into the following three masses of nuclei by the Y-shaped internal medullary lamina:

- Anterior group of nuclei
- Lateral group of nuclei
- Medial group of nuclei

Functionally, the thalamic nuclei can be grouped under the following two divisions:

- Nonspecific projection nuclei
- Specific projection nuclei

Functions and Connections

Various functions of thalamus along with the connections through which these functions are mediated are summarized below.

1. ***Sensory relay centre:*** Almost all the sensory impulses (except olfactory) reach the thalamic nuclei, which relay them to the cerebral cortex by thalamic radiations (ascending thalamocortical

system). Because of this, thalamus is usually considered the *head ganglion* of all the sensory system.

2. ***Centre for integration of sensory impulses:*** The thalamus also forms a major centre for integration and modification of peripheral sensory impulses before the impulses are projected to specific areas of cerebral cortex. Because of this, thalamus is usually considered as a *functional gateway* of cerebral cortex.
3. ***Crude centre for perception of sensations:*** Thalamus also acts as a crude centre for sense perception. Pain sensation is perceived in the thalamus itself. To decide whether a sensation is pleasant or unpleasant and agreeable or disagreeable is the function of thalamus.
4. ***Centre for integration of motor function:*** Thalamus receives the output from the basal ganglia and the cerebellum before projecting it to the motor cortex, thereby helping in integration of motor functions by unconscious regulation of muscle tone.
5. ***Role in arousal and alertness reaction:*** Majority of nonspecific ascending impulses from the reticular activating system (RAS) are relayed to thalamus before proceeding to cortex. Through these fibres, the thalamus is involved in controlling the level of consciousness and maintaining state of alertness and wakefulness.
6. ***Role in emotional aspect of behaviour:*** Because of intimate connections between thalamus, frontal cortex and hypothalamus, the thalamus is involved in subjective feeling of various emotions.
7. ***Role in language:*** Thalamus is also concerned with language (speech) function. Integration between different cortical parts by subcortical connections in the thalamus helps to achieve speech.
8. ***Role in synchronization of electroencephalogram:*** Thalamus also plays an important role in the genesis of synchronization of electroencephalogram (EEG).
9. ***Centre for integration of visceral and somatic functions:*** Thalamus receives somatic as well as autonomic sensations, and is also connected with hypothalamus. Because of this, it also acts as a centre for integration of visceral and somatic functions.
10. ***Centre for sexual sensations:*** Thalamus also acts as a centre for perception of sexual sensations.
11. ***Centre for reflex activity:*** All the sensory fibres relay in thalamus, so it forms the centre for many reflex activities.

APPLIED ASPECTS

Thalamic syndrome: The thalamic syndrome is a disturbance of emotional responses to sensory experience characterized by symptoms and signs which occur on the opposite side of the body. These include the following:

1. Astereognosis, which occurs due to loss of tactile localization, tactile discrimination and stereognosis
2. Thalamic over-reaction, i.e. the threshold for pain, touch and temperature is decreased and the sensations become exaggerated and disagreeable
3. Ataxia, decreased muscle tone and profound muscular weakness
4. Involuntary movements

Hypothalamus

The hypothalamus is a bilateral diencephalic diffuse nuclear mass situated below the thalamus. It is the most important organ of integration in the homeostatic control of internal environment.

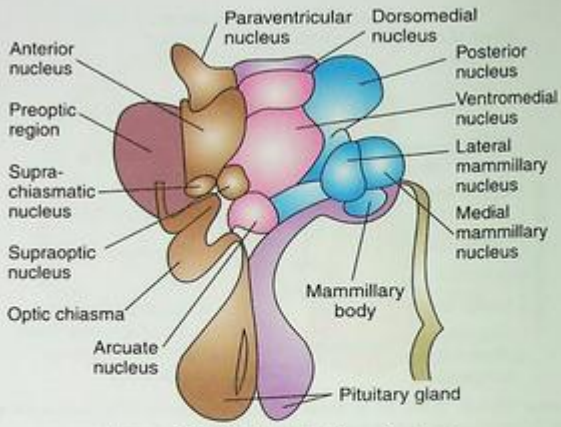


Figure 10.1-12 Nuclei of hypothalamus.

Subdivisions and Nuclei of Hypothalamus

For the convenience of description, the hypothalamus can be divided as follows:

From medial to lateral, into the following two zones:

- Medial zone
- Lateral zone

From anterior to posterior, the hypothalamic nuclear mass is arranged in the following four regions (Fig. 10.1-12):

- Preoptic region
- Supraoptic region
- Tuberal region
- Mammillary region

Connections of Hypothalamus (Fig. 10.1-13)

The hypothalamus serves as the main integrator of the autonomic nervous system, is concerned with visceral functions and is, therefore, connected to other areas having a similar function. These include the various parts of the limbic system, the reticular formation, and autonomic centres in the brainstem and spinal cord.

Apart from its neural connections, the hypothalamus also acts by releasing secretions into the blood stream and into the CSF.

Functions of Hypothalamus

1. ***Autonomic functions*** subserved by the hypothalamus are as follows:
   (i) *Cardiovascular regulation* through cardiovascular control centres in the reticular regions of medulla and pons
   (ii) *Regulation of peristaltic and secretomotor functions of alimentary tract*
2. ***Endocrinal functions*** include the following:
   (i) *Control of anterior pituitary:* Hypothalamus does the following functions through the releasing hormones:
   - Controls the metabolism by controlling thyroid gland
   - Controls the metabolism of different foodstuffs and maintains electrolyte balance through its influence over adrenal cortex

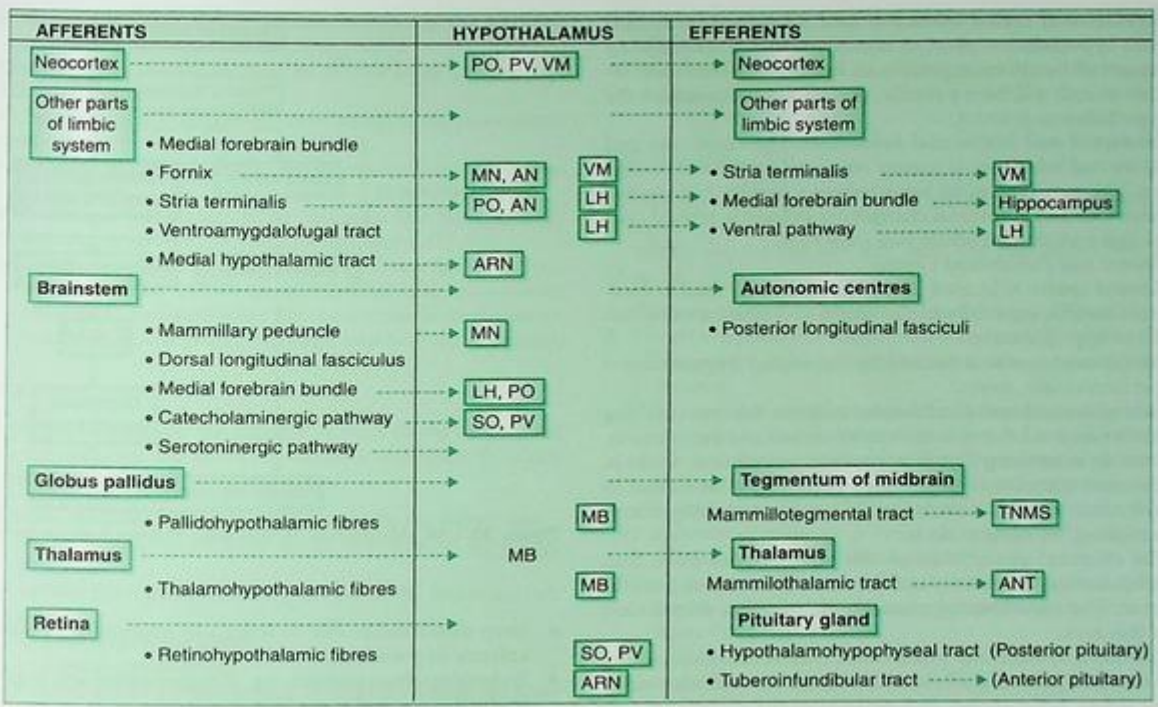


Figure 10.1-13 Simplified scheme of main afferent and efferent connections of hypothalamus. PO, preoptic; PV, paraventricular; VM, ventromedial; MN, medial nucleus; AN, anterior nucleus; LH, lateral hypothalamus; SO, supraoptic; ARN, arcuate nucleus; MB, mammillary body.

- Keeps the gonads inhibited till the physical growth is complete, which inhibition is removed once physical growth is complete so that gonads start functioning and gametes are produced (propagation of species)
- Controls the formation of milk by the breasts by controlling prolactin secretion (see page 307).

(ii) *Regulation of posterior pituitary functions*: It exercises neural control of posterior pituitary with the secretion of antidiuretic hormone (ADH) in regulation of water balance by controlling water excretion by kidneys (see page 238)

(iii) *Regulation of uterine contractility and regulation of milk ejection from the breast*: Oxytocin secretion increases the contractility of uterus, especially at the end of the pregnancy and thus helps during parturition. It also contracts the myoepithelial cells that surround the alveoli of breast and cause milk ejection. When the baby suckles the breast, signals from nipple to hypothalamus cause reflex oxytocin release, which causes expulsion of milk through nipples.

3. ***Control of circadian rhythm*** (biological clock): Circadian rhythm refers to rhythmic fluctuations in certain physiological parameters of the body. These are called circadian rhythms because they often show 24-hour cycles (circadian around a day). *Common rhythmic variations* in homeostatic regulatory mechanism are as follows:
   - Rhythmic secretion of ACTH (see page 330)
   - Rhythmic secretion of growth hormone (see page 306)
   - Rhythmic secretion of melatonin (see page 346)
   - Sleep–wake cycles (see page 457)
   - Body temperature rhythm
   - Rhythmic gonadotropin secretion (see page 369)
4. ***Regulation of food intake:*** The regulation of food intake is an essential vegetative function of the hypothalamus, which keeps the body weight of an individual relatively constant over a long period. To regulate the food intake, hypothalamus has two centres: *feeding centre* and *satiety centre*, located in the tuberal region.
   - *Feeding centre:* The lateral hypothalamic nucleus subserves as the feeding centre or hunger centre. When this is stimulated, in animals, it creates a sensation of hunger and leads to increased food intake (hyperphagic). Normally, the feeding centre is always active and its activity is inhibited by the satiety centre after food intake. The destruction of feeding centre leads to loss of appetite (anorexia).
   - *Satiety centre:* Satiety is opposite to hunger, i.e. it is a feeling of fulfilment after food intake. The *ventromedial nucleus* of hypothalamus acts as a satiety centre. Stimulation of this in animals causes sensation of food intake (fulfilment). The cells of satiety centre act as glucoreceptors (also called glucostats); therefore, the activity of satiety centre is governed by glucose utilization of these cells.

   Role of neurotransmitters in food intake: Food intake is increased by the stimulation of α_2 adrenergic receptors in medial hypothalamus and centrally acting opioids. Food intake is decreased by the stimulation of β adrenergic and dopaminergic in lateral hypothalamus and by stimulation of serotonergic pathways.

5. ***Regulation of sexual behaviour and reproduction:*** In animals, hypothalamus plays an important role in maintaining the sexual functions, especially in females. A decorticate female animal will have a regular oestrous cycle, provided the hypothalamus is intact.
6. ***Emotional and instinctual behaviour:*** The emotional and instinctual behaviour is mainly regulated by the limbic cortex. The two centres in hypothalamus involved in such a behaviour and emotional changes are called the reward centre and punishment centre (see page 453).
   Reward and Punishment Centres
   Reward centre is located along the course of medial forebrain bundle, especially in the lateral and ventromedial nuclei of hypothalamus.
   Punishment centre is located in the medial hypothalamus (periventricular zone).
   Role of reward and punishment centres: Almost anything that we do is related in some way to reward and punishment. If we do something that is rewarding, we continue to do it. Electrical stimulation of this area encourages the animal to seek more of such stimulation. If we do something that is punishing, we cease to do it.
   The electrical stimulation of this area leads to pain, fear, defence, escape reactions and the other elements of punishment. The experimental animal avoids further stimulation of this area.
   Therefore, *reward and punishment centres constitute one of the most important of all the controllers of our bodily activities, our drives, our aversions and our motivation.*
7. ***Regulation of body temperature:*** The hypothalamus acts as the principal integrating centre for heat regulation. By adjusting a balance between heat production and heat loss, it helps to maintain body temperature at 37°C. Hypothalamus accomplishes this function by two centres: heat loss centre and heat gain centre (see page **164**).
8. ***Role in regulation of water balance:*** Hypothalamus regulates water balance of the body by the following two mechanisms (Fig. 10.1-14):
   - Through the thirst centre by controlling water intake
   - Through osmoreceptors in supraoptic nucleus by controlling water loss

   (i) *Through thirst centre:* Thirst centre located in the lateral nucleus of hypothalamus is stimulated by plasma hypertonicity (which occurs when the water content of the body is reduced). This causes intense desire for water, and animal drinks large quantities of water.

   (ii) *Through osmoreceptors in supraoptic nucleus:* The increased plasma osmolality also stimulates osmoreceptors in the supraoptic nucleus. The stimulated neurons of supraoptic nucleus, in turn, send impulses to the posterior pituitary gland to secrete the hormone ADH. This hormone reaches the kidney tubules through blood and causes increased absorption of water from the collecting ducts of the kidneys. Thus, water loss is decreased. When the body has excess water, exactly opposite events occur.

Applied Aspects

Disturbances in hypothalamic lesions include the following:

- Autonomic disturbances
- Disturbances of body temperature regulation

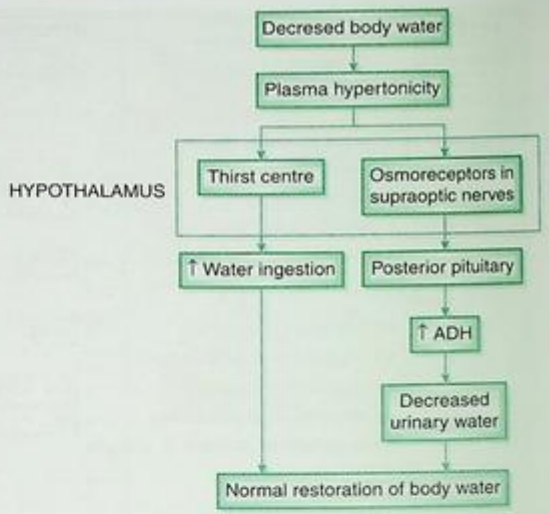


Figure 10.1-14 Mechanism of regulation of water balance by hypothalamus.

- Sleep disturbances due to lesions in mammillary body and anterior hypothalamus
- Endocrine abnormalities, e.g. hypogonadism and hypothyroidism
- Disturbance in sexual functions due to involvement of mid-hypothalamus
- Disturbance of body water balance due to damage to supraoptic nuclei or infundibular stalk, characterized by excessive thirst and polyuria
- Emotional disturbances leading to sham rage due to lesions in ventromedial and posterolateral parts

BRAINSTEM

The brainstem consists (from below upwards) of the medulla oblongata, pons and midbrain.

Medulla Oblongata

The medulla oblongata is conical in shape and connects to the pons above and the spinal cord below.

Functions

1. ***Pathway for ascending and descending tracts:*** The medulla oblongata forms the main pathway for the ascending and descending tracts of spinal cord.
2. ***House of vital centres:*** The medulla oblongata houses many important centres which control the vital functions of the body:
   - *Respiratory centres* (inspiratory and expiratory) control the normal rhythmic respiration (page 202).
   - *Vasomotor and cardiac centres* control the blood pressure and functions of the heart and vascular system (page 150).
   - *Deglutition centre* controls the pharyngeal and esophageal phases of deglutition (page 259).
   - *Vomiting centre* is responsible for inducing vomiting in disorders of gastrointestinal tract (page 268).

- *Superior and inferior salivary nuclei*, located in the medulla, control the salivary secretion (page 257).

3. ***Cranial nerve nuclei*** located in the medulla control the following functions:
   - *Twelfth cranial (hypoglossal) nerve* controls the movements of tongue.
   - *Eleventh cranial (accessory) nerve* controls the movements of shoulder.
   - *Tenth cranial (vagus) nerve* controls the functions of important viscera, i.e. heart, lungs and GIT.
   - *Eighth cranial nerve* controls the auditory function (cochlear division of the nerve has the relay in medulla oblongata) and vestibular function (medial and inferior vestibular nuclei extend through much of the medulla).

Pons

The pons is situated on the anterior surface of the cerebellum below the midbrain and above the medulla oblongata. Pons can be divided into the following two parts:

1. ***Ventral (basilar) part of the pons*** contains the following:
   - *Transverse fibres* laterally form the middle cerebellar peduncle.
   - *Vertical fibres* present in the pons are of the following two types:
     - Corticopontine fibres
     - Corticospinal fibres
   - *Pontine nuclei* are the groups of neurons which are scattered amongst the nerve fibres.
2. ***Dorsal (tegmental) part of pons*** contains the following:
   - Decussations of trapezoid body
   - Nuclei of the Vth, VIth, VIIth and VIIIth cranial nerves
   - Pontine reticular formation
   - Number of descending and ascending tracts, the most prominent ascending tracts being the four lemnisci: medial, trigeminal, spinal and lateral.

Functions

Pons subserves the following functions:

1. Connecting the pathway between cerebral cortex and cerebellum
2. Pathway for ascending and descending tracts of spinal cord and medulla oblongata
3. Joining station for medial lemniscus with fibres of the Vth, VIIth, IXth and Xth cranial nerves
4. Contains pneumotaxic and apneustic centres for regulation of respiration (page 203)

Midbrain

The midbrain is a narrow part of the brain that connects forebrain to hindbrain.

Midbrain can be divided into the following two parts (Fig. 10.1-15):

1. ***Tectum:*** It consists of superior and inferior colliculi.
2. ***Cerebral peduncles:*** Each cerebral peduncle, in turn, consists of three parts, which from the anterior to posterior side are as follows:
   (i) *Crus cerebri* (or basis pedunculi): It consists of a large mass of vertically running descending fibres from cerebral cortex, which include frontopontine fibres, corticospinal and corticonuclear fibres, and temporopontine, parietopontine and occipitopontine fibres (occupying the lateral one-sixth of crus).
   (ii) *Substantia nigra* is a mass of pigmented grey matter (therefore appears dark in colour).
   (iii) *Tegmentum* of the two sides is continuous across the midline. It contains the following important masses of grey matter and nerve fibres:
     - Red nucleus
     - Nuclei of the IIIrd, IVth and Vth cranial nerves
     - Reticular formation of midbrain
     - Fibre bundles of the tegmentum
     - Three decussations

Hindbrain

The hindbrain consists of the following:

- Pons (described above)
- Medulla oblongata (described above)
- Cerebellum

Cerebellum

Cerebellum, the largest part of hindbrain, consists of two lateral parts called the *cerebellar hemispheres* connected in the midline

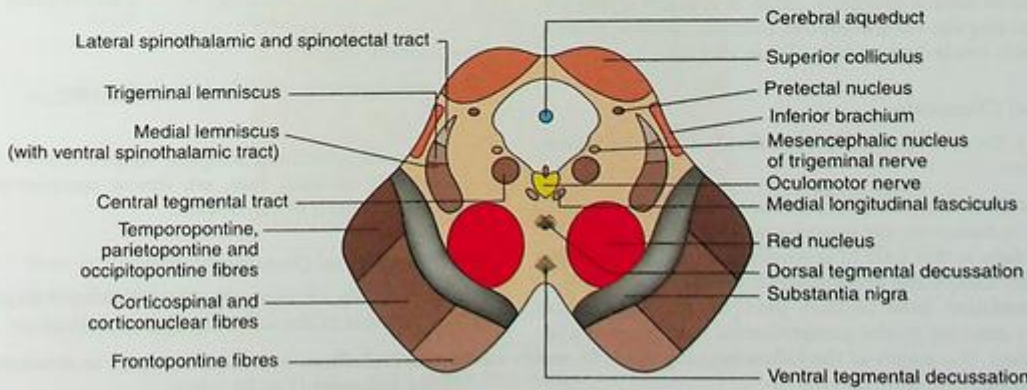


Figure 10.1-15 Main features of internal structure of midbrain exhibited by transverse section at the level of superior colliculi.

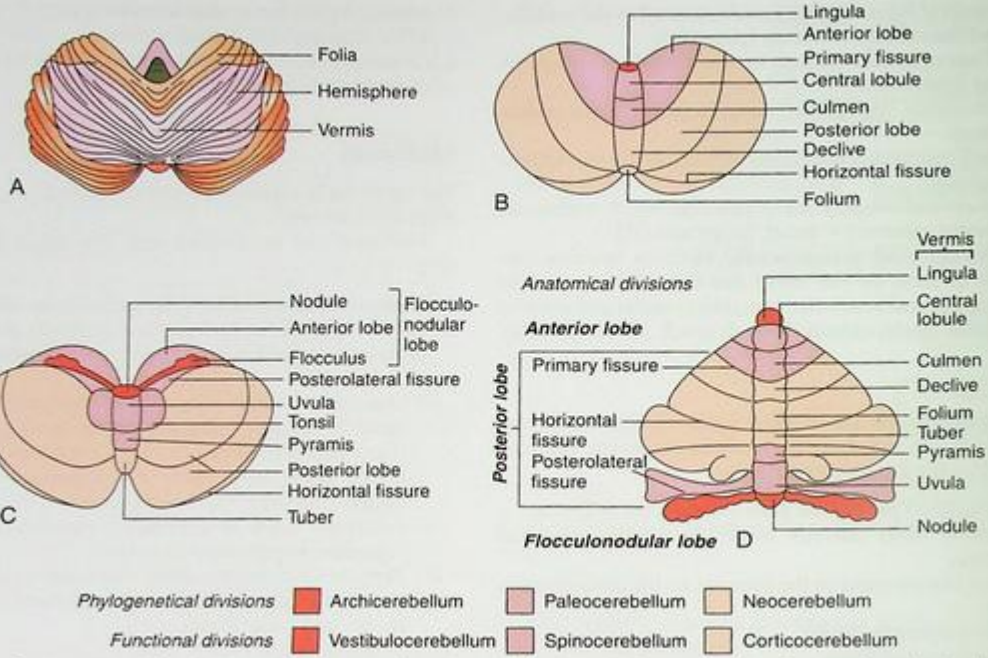


Figure 10.1-16 Gross anatomy of cerebellum: (A) superior surface showing folia; (B) and (C) superior and inferior surface showing fissures, lobes and parts of vermis; and (D) schematic diagram to show the parts of vermis and hemisphere in an opened unrolled cerebellum.

by a narrow central region called the *vermis*. The cerebellum is thrown into numerous transverse folds called folia. The surface of the cerebellum presents the following three main fissures (Fig. 10.1-16):

- ***Primary fissure:*** It is V-shaped, with the opening being in the forward direction. It forms the posterior limit of the anterior lobe.
- ***Horizontal fissure*** separates the superior surface of the cerebellum from its inferior surface.
- ***Posterolateral fissure*** is situated anteriorly on the inferior surface of the cerebellar hemisphere, and separates the posterior lobe from the flocculonodular lobe.

Vermis is so named because it resembles a worm which is bent on itself to form a complete circle. It consists of the following parts: lingula, central lobule, culmen, declive, folium, tuber, pyramis, uvula and nodule (Table 10.1-2).

Anatomical Divisions

Anatomically, the cerebellum has been divided into the following three lobes:

1. ***Anterior lobe*** is that part of cerebellum which lies in front of the primary fissure on the superior surface (Table 10.1-2).
2. ***Posterior lobe*** is that part of cerebellum which lies between the primary fissure and posterolateral fissure.
3. ***Flocculonodular lobe*** is that part of the cerebellum which lies anterior to the posterolateral fissure on the inferior surface. It consists of the following (Fig. 10.1-16 and Table 10.1-2):
   - *Nodule* is the rostral part of the vermis.
   - *Flocculi*, which are irregular-shaped masses attached to nodule on each side, are almost completely separated from the rest of cerebellum.

TABLE 10.1-2 Lobes of Cerebellum and Parts of Vermis and Hemisphere Forming Them

Lobes of Cerebellum	Part of Vermis	Part of Hemisphere
Anterior lobe	Lingula Central lobule Culmen	No lateral projection Alae Anterior quadrangular lobule
Primary fissure		
Posterior lobe	Declive Folium	Posterior quadrangular lobule Superior semilunar lobule
Horizontal fissure		
	Tuber Pyramis Uvula	Inferior semilunar lobule Biventral lobule Tonsil
Posterolateral fissure		
Flocculonodular lobe	Nodule	Flocculus

Phylogenetical Divisions

Phylogenetically, i.e. according to evolutionary stages, the cerebellum consists of the following three subdivisions:

1. ***Archicerebellum:*** It is the oldest part to develop. It consists of the following (Fig. 10.1-16):
   - Flocculonodular lobe

- Lingula

2. ***Paleocerebellum:*** Phylogenetically, it is the next part to appear. It consists of (Fig. 10.1-16) the following:
   - Entire anterior lobe except lingula and parts of posterior lobe – pyramis, uvula and paraflocculus
3. ***Neocerebellum:*** It is the latest part to develop. It consists of the whole of the posterior lobe except pyramis and uvula (Fig. 10.1-16).

Functional Divisions

Functionally, cerebellum can be divided into the following three categories:

1. ***Vestibulocerebellum:*** It includes the flocculonodular lobe, which is its principal component and has vestibular connections only.
   - Nucleus fastigial is its effector nucleus.
   - It is concerned with the control of body posture and equilibrium.
2. ***Spinocerebellum:*** It includes the parts forming paleocerebellum, i.e. the entire anterior lobe except lingula and some parts of posterior lobe (pyramis, uvula and paraflocculus).
   - *Nucleus interpositus:* Nucleus globossus and nucleus emboliformis are its effector nuclei.
   - It receives proprioceptive inputs from the spinal cord and is concerned with control of axial (trunk) and limb muscle postural reflexes.
3. ***Corticocerebellum:*** Corticocerebellum, also called central cerebellum, includes the whole of the posterior lobe except pyramis and uvula.
   - Nucleus dentatus is its effector nucleus.
   - It occupies the more lateral regions of the cerebellar cortex and receives information from the cerebral cortex and pons.
   - It is concerned with smooth performance of highly skilled voluntary movements.

Histological Structure

Histologically, cerebellum consists of the following (Fig. 10.1-17):

- Cerebellar cortex (outer grey matter layer)
- White matter (formed by afferent and efferent nerve fibres of cerebellum) forming medullary core
- Deep cerebellar nuclei (masses of grey matter embedded in the medullary core)

I. Cerebellar Cortex *Microscopically*, the grey matter of cerebellar cortex consists of five main types of neurons (stellate cells, basket cells, Purkinje cells, granule cells and Golgi cells), which are arranged in the following three layers:

- ***Molecular layer*** (most superficial) is composed of two types of neurons (stellate and basket cells) and unmyelinated nerve fibres.
- ***Purkinje cell layer:*** It is composed of a single layer of large, flask-shaped Purkinje cells and dendrites of Purkinje cells.
- ***Granule cell layer*** consists of granule and Golgi cells, with their processes and sensory mossy fibres with their synaptic glomeruli.

II. White Matter of Cerebellum The cerebellar cortex, i.e. outer grey matter, surrounds the inner medullary core of white matter (an arrangement opposite to what is seen in spinal cord). White matter is formed by both afferent and efferent fibres. These fibres can be classified into the following three groups:

1. ***Projection fibres*** of the cerebellum leave or enter the cerebellum. These are arranged in the following three bundles:
   - *Inferior cerebellar peduncle* consists of fibres connecting cerebellum with medulla.

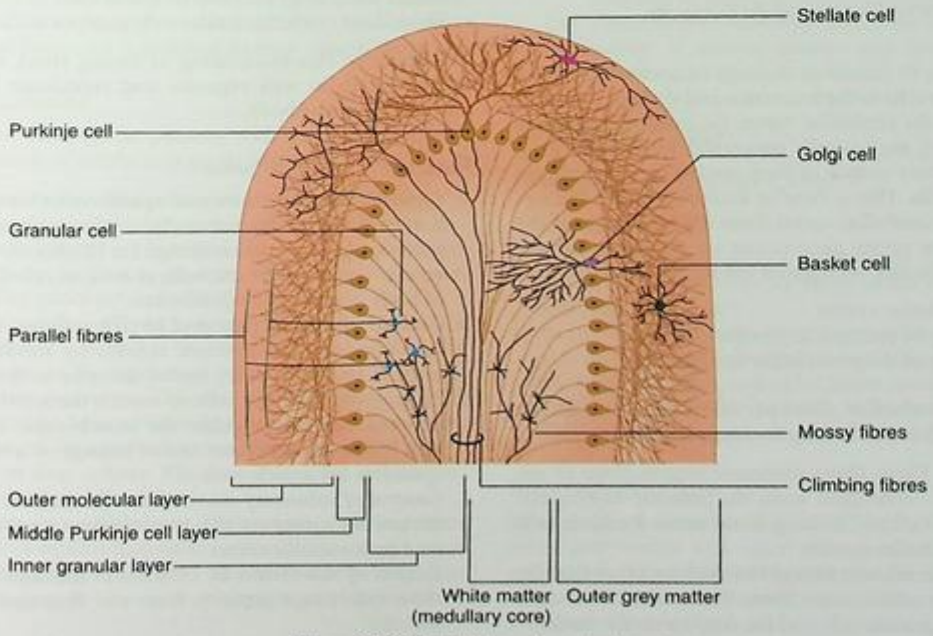


Figure 10.1-17 Histology of cerebellar cortex.

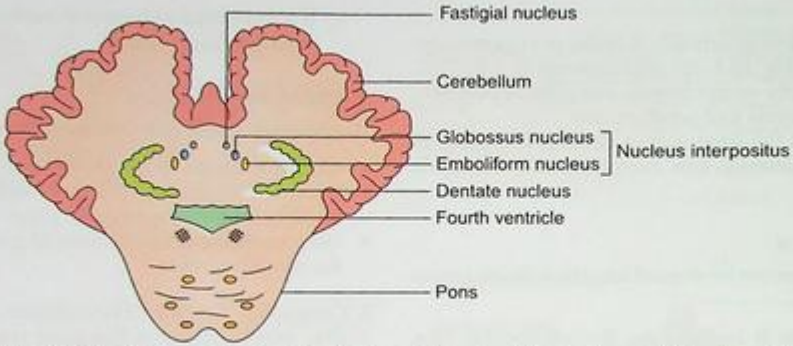


Figure 10.1-18 Diagrammatic view of nuclei of cerebellum in relation to the roof of fourth ventricle.

- *Middle cerebellar peduncle* contains the fibres connecting cerebellum with pons.
- *Superior cerebellar peduncle* connects the cerebellum with midbrain.

2. ***Association fibres*** connect different regions of the same cerebellar hemisphere.
3. ***Commissural fibres*** connect the areas of two halves of cerebellar cortex with each other.

III. Deep Cerebellar Nuclei Within the white matter of medullary core of cerebellum are embedded four pairs of masses of grey matter called deep cerebellar nuclei (Fig. 10.1-18):

1. *Dentate nucleus*
2. *Emboliform nucleus*
3. *Globossus nucleus*
4. *Fastigial nucleus*

Neural Circuits and Neuronal Activity in Cerebellum

Cerebellum executes its functions through excitatory output of the deep cerebellar nuclei to the brainstem and thalamus. Neural connections within the cerebellar cortex, i.e. intrinsic cerebellar circuit (Fig. 10.1-19), are basically concerned with modulating or timing the excitatory output of deep cerebellar nuclei via the fibres of Purkinje cells. This is done in accordance with the signals received by the cerebellar cortex from different parts of the brain and body. The entire process can be discussed, for the purpose of understanding only, under the following headings:

- Afferents to cerebellar cortex
- Neuronal activity of intrinsic cerebellar circuitry
- Neuronal activity of deep cerebellar nuclei

Afferents to Cerebellar Cortex Afferents to cerebellar cortex reach through the following two types of fibres:

1. ***Climbing fibres:*** These fibres represent terminations of axons reaching the cerebellum from the inferior olivary nucleus (Fig. 10.1-19). The climbing fibres excite Purkinje cells and the deep cerebellar nuclei.
2. ***Mossy fibres:*** All the afferent fibres of cerebellum, other than the olivocerebellar, are called mossy fibres. The mossy fibres excite the Purkinje cells, granule cells and the deep cerebellar nuclei.

Neuronal Activity of Intrinsic Cerebellar Circuitry As a result of excitatory input from the climbing fibres or mossy fibres (Fig. 10.1-19), the following activity is set up in the intrinsic cerebellar circuitry:

- Feed-forward inhibition of Purkinje cells
- Feed-forward inhibition of granule cells
- Feedback inhibition of granule cells
- Reverberating circuit

Neuronal Activity of Deep Cerebellar Nuclei The deep cerebellar nuclei receive excitatory inputs via collaterals from the mossy fibres, climbing fibres and also other excitatory inputs.

The neuronal activity in the cerebellar cortex plays an important role in modulating the excitatory signals of the following pathways:

- From deep cerebellar nuclei to thalamus, then to cerebral cortex and motor pathway to spinal cord
- From deep cerebellar nuclei to brainstem nuclei

Because of this modulating or timing effect, the cerebellar cortex is able to well organize and coordinate the different movements of the body.

Functions of Cerebellum

1. ***Control of body posture and equilibrium:*** Vestibulocerebellum includes the flocculonodular lobe as its principal component, and the nucleus fastigii (as its effector nucleus) and vermal region of the cerebellum are concerned with control of body posture and equilibrium.
2. ***Control of muscle tone and stretch reflexes:*** Spinocerebellum regulates the postural reflexes by modifying muscle tone. It facilitates the γ motor neurons in the spinal cord. The γ motor neurons reflexly modify the activity of γ motor neurons, and thus regulate the muscle tone. Thus, cerebellum forms an important site of linkage of α–γ systems responsible for muscle tone.
3. ***Control of voluntary movements:*** Cerebellum is not able to initiate any motor activity, but coordinates movements initiated by the motor cortex.

Control of movements by cerebellum includes regulation of time, rate, range (extent), force and direction of muscular activity.

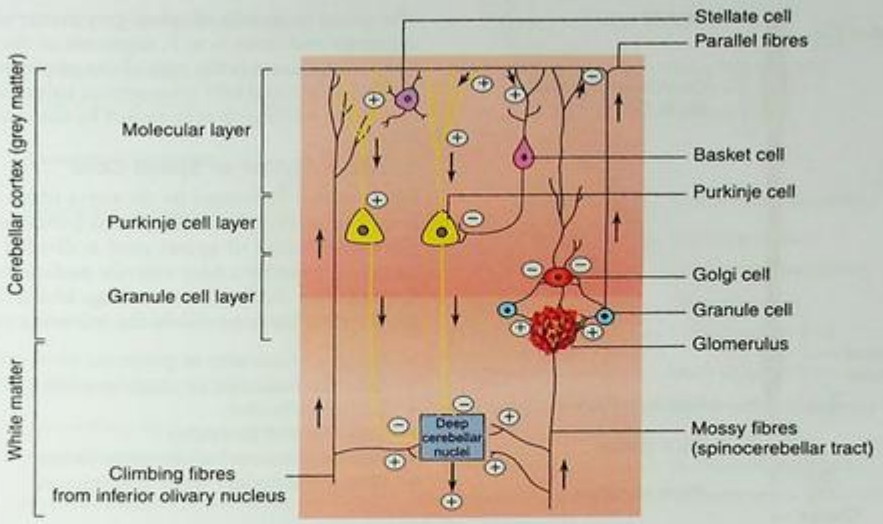


Figure 10.1-19 Intrinsic cerebellar circuitry.

4. ***Other functions of cerebellum:*** Recent studies have shown that the importance of the cerebellum is as follows:
   (i) *Influence on autonomic system:* It has been postulated that the cerebellum may influence autonomic functions and thus respiratory, cardiovascular, pupillary and urinary bladder responses.
   (ii) *Influence on conduction in ascending sensory pathway* may be exerted by the cerebellum through the reticular formation and thalamus.
   (iii) *Control of eyeball movements:* The oculomotor, trochlear and abducent nuclei, which supply extraocular muscles of eye movements, are brought under the cerebellar control through vestibular nuclei. Medial longitudinal fasciculus is involved in these connections.

Cerebellar Lesions

Common signs observed in patients with cerebellar dysfunction due to lesions of cerebellum are as follows:

1. ***Disturbances in tone and posture*** include the following:
   (i) *Atonia or hypotonia:* Hypotonia refers to reduction and atonia to loss of tone in muscles. It occurs due to reduction of the facilitatory neocerebellar output to the descending inhibitory reticular formation.
   (ii) *Attitude changes:* Trunk is bent with concavity towards the affected side; this is because the weight of the body is thrown on the unaffected leg.
   (iii) *Deviation movement:* The arm held straight out in front of the body deviates laterally when the eyes are closed. In bilateral lesions, both arms deviate.
   (iv) *Effect on deep reflexes:* The deep or tendon reflexes become weak and pendular.
2. ***Disturbances in equilibrium:*** The patient suffering from disturbance of equilibrium walks on a wide base, sways from side-to-side (drunken-like gait) and is unable to maintain the upright posture due to involvement of the vestibular system.
3. ***Disturbances in movements*** include the following:
   (i) *Ataxia*, i.e. lack of coordination of movements, is the hallmark of cerebellar disorder.
   (ii) *Intention tremors* become evident during purposeful movements and diminish or disappear with rest. These tremors become more marked as the hand approaches the object (i.e. are observed at the end of movement) and are coarse, oscillating, to and fro and rhythmic.
   (iii) *Nystagmus* refers to regular and rhythmic to and fro involuntary oscillatory movements of the eyes, occurring due to incoordination of extraocular muscles.
   (iv) *Dysarthria* or scanning speech occurs due to incoordination of various muscles and structures involved in speech.

SPINAL CORD

Anatomy of Spinal Cord

Gross Anatomy

- The spinal cord (Fig. 10.1-20) extends from the upper border of the first cervical vertebra to the lower border of the first lumbar vertebra.
- Its upper end becomes continuous with medulla oblongata and its lower end called *conus medullaris* becomes continuous with a fibrous cord called *filum terminale*.
- The spinal cord, like the brain, is surrounded by three meninges: dura mater, arachnoid mater and pia mater.

Internal Structure

As seen on cross-section (Fig. 10.1-21), the spinal cord presents inner grey matter and outer white matter. The grey matter is composed of the nerve cell bodies, dendrites and parts of axons, whereas the white matter is formed by the myelinated and unmyelinated nerve fibres.

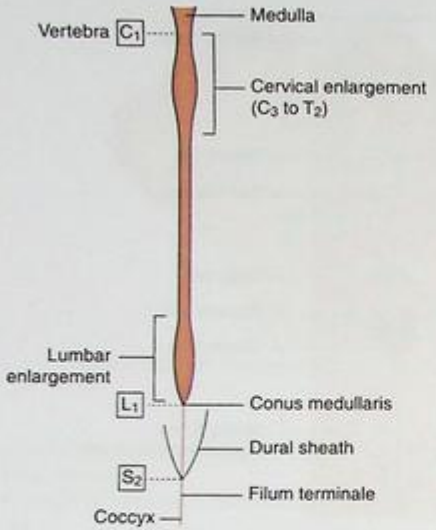


Figure 10.1-20 Gross appearance of the spinal cord and its relation with vertebrae.

1. Spinal Grey Matter

In a transverse section, the grey matter of spinal cord forms an H-shaped mass in the centre of which is present a canal called the spinal canal. The *spinal grey* matter exhibits the following parts:

Dorsal horn or posterior grey column refers to the posterior horn-like projection of the H-shaped grey matter in each lateral half of the cord.
The dorsal horn neurons of spinal grey matter are involved in sensory functions.
Ventral horn or anterior grey column refers to the anterior projection of the grey matter in each lateral half of the cord.
The ventral horn neurons of spinal grey matter are involved in motor functions and send motor nerve fibres to the muscles and other effector organs.
Lateral horn or intermediate horn or lateral column refers to a small lateral projection between the ventral and dorsal grey columns present in the thoracic segments and first two lumbar segments only.

The lateral horn cells of spinal grey matter extend from T_1 to L_2 segments and from S_2 to S_4 segments of the spinal cord.
Grey commissure is the part of the grey matter which connects the two (right and left) symmetrical halves of spinal grey matter across the midline. It is traversed by the central canal.

2. White Matter of Spinal Cord

White matter is formed by the nerve fibres which are arranged as ascending and descending tracts (described later). In general, the white matter of spinal cord is divided into right and left halves, in front by a deep *anterior median fissure* and behind by the *posterior median septum* (Fig. 10.1-21). In each half, the spinal white matter exhibits the following parts:

- Posterior funiculus or posterior white column
- Anterior funiculus or anterior white column
- Lateral funiculus
- Anterolateral funiculus
- Ventral (anterior) white commissure
- Dorsal (posterior) white commissure

Tracts of Spinal Cord

Ascending Tracts

Ascending tracts convey impulses arising in various parts of body to different parts of the brain. The ascending tracts present in the spinal cord (Fig. 10.1-22) can be grouped as follows:

1. ***Posterior (dorsal) column–medial lemniscus pathway:*** *Fasciculus gracilis and fasciculus cuneatus* are often referred to as the *posterior column tracts*. Fasciculus gracilis is situated medial to fasciculus cuneatus (see page 421).
2. ***Spinothalamic pathways:*** *Anterior and lateral spinothalamic tracts*, the spinothalamic tracts, are formed by the axons of the second-order sensory neurons of the pathway of crude touch and pressure (anterior spinothalamic tract) and pain and temperature (lateral spinothalamic tract). For more details, see page 422.
3. ***Spinoreticular tract:*** This tract is located in the anterolateral white funiculus (Fig. 10.1-22). The fibres of the spinoreticular tract are the components of ascending RAS and are concerned with arousing consciousness or alertness.

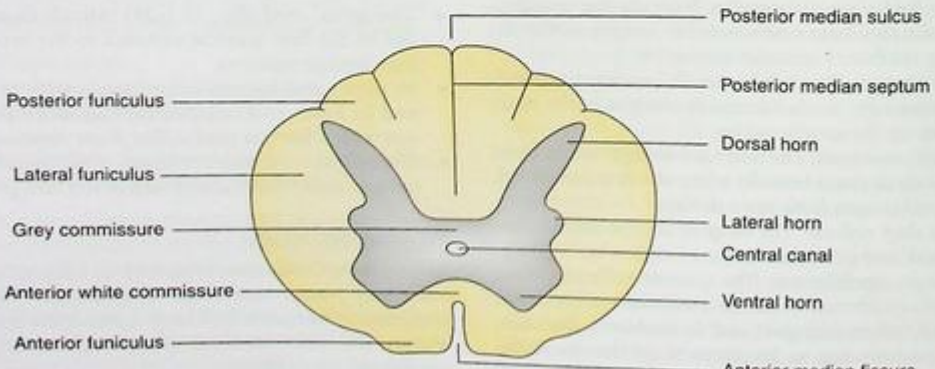


Figure 10.1-21 Cross-section of the thoracic segment of the spinal cord.

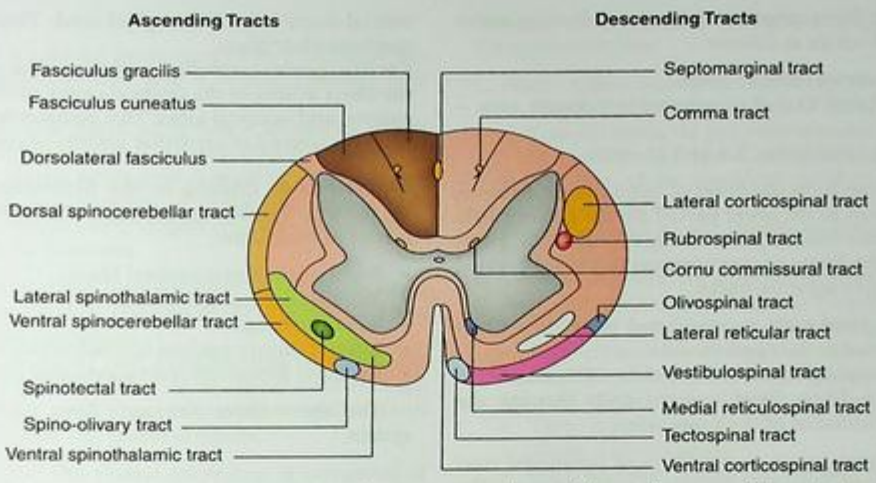


Figure 10.1-22 Schematic diagram to show the position of the main ascending and descending tracts of the spinal cord and brainstem.

4. ***Spinotectal tract:*** This tract is located in the lateral side of lateral white funiculus anterior to the lateral spinothalamic tract (Fig. 10.1-22). These fibres form an alternate route for conduction of *slow pain*, and are also concerned with *spino-visual reflexes*.
5. ***Spinoolivary tract:*** This tract is located in the anterolateral part of white funiculus and occupies mostly the anterior white funiculus (Fig. 10.1-22). This tract is concerned with proprioception.
6. ***Spinocerebellar tracts:*** The spinocerebellar tracts carry proprioceptive impulses arising in the lower part of the body to the cerebellum. Some exteroceptive sensations (e.g. touch) may reach the cerebellum through these pathways. The spinocerebellar pathway is organized into the ventral and dorsal tracts.

Ventral spinocerebellar tract: It is located in the lateral white funiculus of the spinal cord (Fig. 10.1-22) and is constituted by the second-order neurons of a proprioceptive pathway.
Dorsal (posterior) spinocerebellar tract: This tract is located in the lateral funiculus. It is situated posterior to the ventral spinocerebellar tract (Fig. 10.1-22).
The peripheral processes of *first-order neurons* receive impulses from the muscle spindles, Golgi tendon organs and other proprioceptive receptors.
Cuneocerebellar tract: The central processes of some first-order neurons (related to cervical segments) reach the *accessory cuneate nucleus* in the medulla. The central processes of the second-order neurons located in the accessory cuneate nucleus form the cuneocerebellar tract. This tract brings the *conscious proprioception* impulses from the upper limb. Thus, it may be regarded as the forelimb equivalent of the dorsal spinocerebellar tract.

Descending Tracts

The descending tracts are concerned with the various motor activities of the body and formed by the motor nerve fibres arising from the brain and descending into the spinal cord and brainstem (Fig. 10.1-22).

Descending tracts ending in spinal cord: Traditionally, the descending tracts ending in the spinal cord have been divided into the following two groups:

- Pyramidal tracts
- Extrapyramidal tracts

1. Pyramidal tracts The pyramidal tracts refer to the corticospinal tracts, which are constituted by the axons that transmit motor signals directly from the cortex to spinal cord (Fig. 10.1-23).

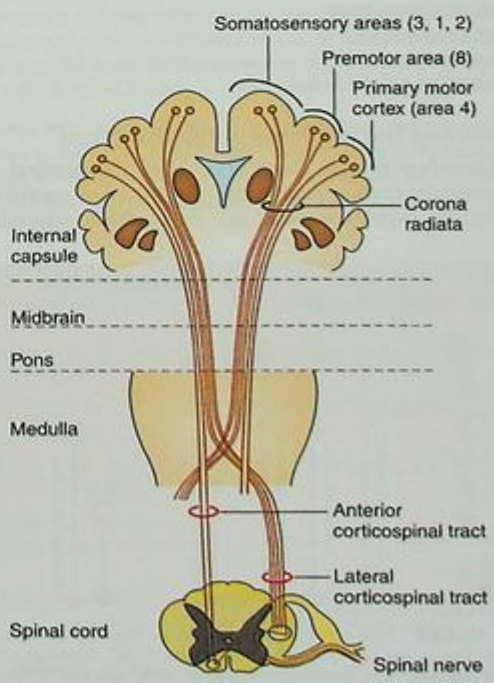


Figure 10.1-23 Pathway of corticospinal tracts.

Corticospinal tract fibres originate from the following nerve cells in the cerebral cortex as follows:

- Primary motor cortex (area 4) – 30%
- Premotor area (area 8) and supplementary motor area – 30%
- Somatic sensory areas (areas 3, 1 and 2) – 40%

All the above fibres form the fibres of upper motor neurons of the motor pathway. In the lower part of medulla, about 90% fibres decussate in the midline to reach the opposite side. From here downwards, the fibres of corticospinal tracts are divided into the following two separate tracts:

- ***Lateral corticospinal tract*** is constituted by 80% of fibres which have crossed to the opposite side.
- ***Anterior corticospinal tract*** is formed by 20% uncrossed pyramidal fibres. These fibres descend down through the anterior white funiculus of the same side.

The neurons giving origin to the fibres of pyramidal tract along with their axons constitute the *upper motor neurons*. The ventral motor neurons in the spinal cord along with their axons constitute the *lower motor* neurons.

Functions: The cerebral cortex controls voluntary fine skilled movements of the body through the corticospinal tracts. Interruption of the tract anywhere in its course leads to paralysis of the muscles concerned.

2. Extrapyramidal tracts The descending tracts of spinal cord other than the pyramidal tracts are collectively called extrapyramidal tracts. These include the following (Figs 10.1-22 and 10.1-24):

- Rubrospinal tract
- Vestibulospinal tract
- Reticulospinal tract
- Tectospinal tract
- Olivospinal tract
- Medial longitudinal fasciculus

Descending Tracts Ending in the Brainstem

Corticonuclear tracts: These arise from the cerebral cortex along with the corticospinal tracts. The nuclei of cranial nerves that supply skeletal muscles are functionally equivalent to ventral horn cells of the spinal cord. These are controlled by corticonuclear fibres.

Cortico–ponto–cerebellar pathway: This pathway consists of the fibres arising in the cerebral cortex of the frontal, temporal, parietal and occipital lobes. This pathway forms the anatomical basis for control of cerebellar activity of cerebral cortex.

Other Fibres Ending in the Brainstem Other fibres arising from the cerebral cortex end in the following masses of grey matter of brainstem:

- Red nucleus (corticorubral fibres)
- Tectum (corticotectal fibres)
- Substantia nigra
- Inferior olivary nucleus (corticoolivary fibres)
- Reticular formation (corticoreticular fibres)

The above fibres ultimately form part of extrapyramidal system.

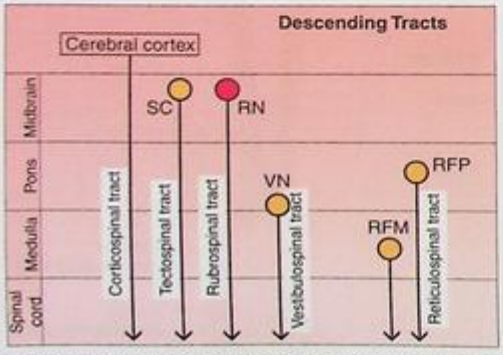


Figure 10.1-24 Schematic drawing to show the various descending tracts ending in the spinal cord and brainstem. SC, superior colliculus; RN, red nucleus; VN, vestibular nucleus, RFP, reticular formation of pons; RFM, reticular formation of medulla.

Spinal Segments and Spinal Nerves

Spinal Segments

Spinal cord, though a continuous structure, can be considered to consist of 31 spinal segments, each giving attachment to rootlets of the ventral and dorsal roots of each spinal nerve (Fig. 10.1-25). The 31 segments of spinal cord correspond symmetrically to 31 spinal nerves and are named as follows:

- ***Eight cervical segments*** give attachment to eight cervical nerves.
- ***Twelve thoracic segments*** give attachment to 12 thoracic nerves.
- ***Five lumbar segments*** give attachment to five lumbar nerves.
- ***Five sacral segments*** give attachment to five sacral nerves.
- ***One coccygeal segment*** gives attachment to one coccygeal nerve.

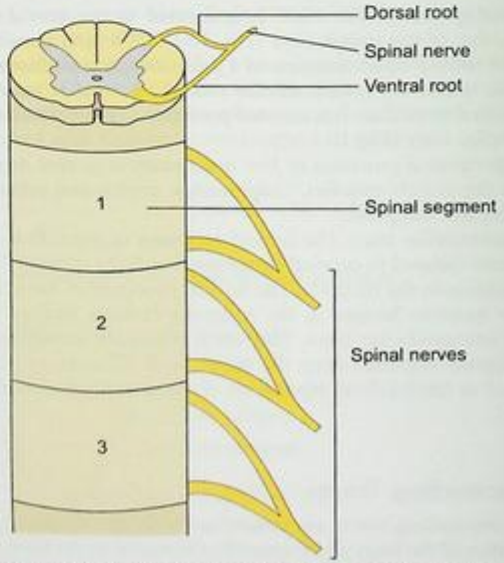


Figure 10.1-25 Scheme to illustrate the concept of spinal segments and roots of spinal nerve.

Spinal Nerves

Each spinal nerve is a mixed nerve formed by a union of two roots: a dorsal (sensory) root and a ventral (motor) root (Fig. 10.1-25).

1. Dorsal nerve root The dorsal nerve root is formed by several rootlets. All sensory fibres reach the spinal cord through dorsal nerve roots. Each dorsal nerve root is marked by a swelling called dorsal nerve root ganglion or spinal ganglion. Dorsal root ganglion is composed of T-shaped unipolar neurons with peripheral and central processes.

Peripheral process of dorsal root ganglion cells extends up to sensory receptors in the skin. The area of the skin supplied by a spinal nerve is called *dermatome*.

Central processes of dorsal root ganglion cells constitute the dorsal nerve root, which is attached to spinal cord through various rootlets. Each rootlet just before entering the spinal cord divides into medial and lateral divisions.

2. Ventral nerve root The ventral nerve root is composed of axons of motor neurons present in the ventral grey horn. The ventral root also contains the autonomic fibres originating from the lateral (intermediate) horn of the spinal grey matter.

Functions of Spinal Cord

1. Sensory Functions

All the somatic afferent impulses enter the spinal cord through the dorsal nerve root.

After entering the spinal cord, all the somatic sensations are conveyed to the brain (postcentral gyrus) by ascending tracts (see page 421).

2. Motor functions

Spinal cord performs motor functions through the pyramidal and extrapyramidal tracts. Motor functions served by the spinal cord are as follows:

- Control of tone and power of muscles
- Control of movement of muscles and joints
- Control of deep (tendon) reflexes
- Control of superficial reflexes

3. Autonomic functions

Visceral afferent impulses in the spinal cord travel through dorsal nerve roots to lateral horns of T_1–L_2 and S_2–S_4 spinal segments.

Autonomic efferents travelling through the spinal cord supply the visceral organs and control the activity of smooth muscles, heart, glands of GIT, sweat glands and adrenals. The spinal cord also regulates the body temperature. In other words, spinal cord helps in maintaining the optimal internal environment of the body through its autonomic function.

Lesions of Spinal Cord

Transection of Spinal Cord

Complete Transection of Spinal Cord

The effects (symptoms and signs) produced by complete transection of the spinal cord occur in the following three stages:

A. Stage of spinal shock Spinal shock refers to cessation of all the functions and activity below the level of the section immediately after injury. *Characteristic effects during shock* are summarized below:

1. ***Motor effects*** include the following:
   - Paralysis of the muscles below the level of section
   - Loss of tone in the paralysed muscles: The muscles become atonic or flaccid. This is called the state of flaccid paralysis.
   - Areflexia: All the superficial and deep reflexes are markedly decreased or lost.
2. ***Sensory effects:*** All the sensations are lost below the level of transections.
3. ***Vasomotor effects:*** The sympathetic vasoconstrictor fibres leave the spinal cord between T_1 and L_2. Therefore, depending on the site of lesion, the vasomotor effects produced are as follows:
   - Extremities are cold and blue (cyanotic).
   - Skin becomes dry and scaly and bed sores may develop.
4. ***Visceral effects*** produced are as follows:
   - There is retention of urine.
   - There is constipation.
   - Penis becomes flaccid and erection becomes impossible.

B. Stage of reflex activity After about a 3-week period, depending largely on the general health of the patient, the reflex activity begins to return to the isolated segments of spinal cord below the level of lesion. Various developments which take place are as follows:

- Smooth muscles regain functional activity first of all.
- Sympathetic tone of the blood vessels is regained and blood pressure is restored to normal.
- Skeletal muscle tone then recovers slowly after 3–4 weeks.
- Reflex activity begins to return after a few weeks of recovery of muscle tone.
- Flexer reflexes return first. The reflex which elicited first is *Babinski's reflex* (Babinski sign is positive).
- Extensor reflexes return after a variable period of 1–5 weeks.
- Mass reflex can be elicited in some cases by scratching the skin of the lower limb or anterior abdominal wall depending on the level of lesion.

Note: The mass reflex can be utilized to provide paraplegic patients a degree of bladder and bowel control. Patients can be trained to initiate urination and defecation by intentionally producing mass reflex with the help of a stroke or a pinch on their thighs.

C. Stage of reflex failure The failure of reflex activity may occur when the general condition of the patient starts deteriorating.

Hemisection of the Spinal Cord (Brown–Sequard Syndrome)

Hemisection of the spinal cord refers to a lesion involving one lateral half of the spinal cord.

The effects of hemisection of the spinal cord can be described in the following two stages:

- Immediate effects
- Late effects

Immediate Effects Immediate effects following the hemisection of the spinal cord are those of 'spinal shock'.

Late Effects If the patient survives, typical motor and sensory changes develop after recovery from the spinal shock.

These changes constitute the *Brown–Sequard syndrome* and can be described as follows:

- Changes at the level of section
- Changes below the level of section

Changes at the Level of Hemisection

I. Changes on the Same Side

- All the sensations are lost (complete anaesthesia) at the level of hemisection on the same side because of complete damage to posterior nerve root, posterior horn cells and spinothalamic fibres (which cross to the opposite side).
- *Lower motor neuron* (LMN) type paralysis (flaccid paralysis) is seen due to damage to the anterior horn cells.
  - All the reflexes are lost.
  - Muscle power is lost.
- *Permanent vasomotor paralysis* occurs due to damage of the lateral horn cells.

II. Changes on the Opposite Side

- There occurs some loss of pain, temperature and crude touch sensations due to injury to the fibres of spinothalamic tract, which cross horizontally in the same segment.
- Usually no motor change occurs.

SELF-ASSESSMENT

1. Describe briefly:
   - Organization of central nervous system
   - The functional areas of cerebral lobes and their functions
   - The components of basal ganglia and its role in control of motor activity
   - The functions of thalamus
   - The role of hypothalamus in regulation of body temperature
   - Role of hypothalamus in emotional and instinctual behaviour
   - Functions of medulla oblongata
   - The functional divisions of cerebellum and their functions
2. Write notes on:
   - Role of cerebellum in body posture and equilibrium
   - Role of cerebellum in maintenance of muscle tone
   - Functions of spinal cord
   - Parkinson disease
   - Brown–Sequard syndrome
3. Differentiate between:
   - Spasticity and rigidity
   - Upper motor and lower motor neuron lesion
   - Pyramidal and extrapyramidal tracts

10.2 Synaptic Transmission

CHAPTER OUTLINE

Synapse: Definition and Types
Anatomical Types
Physiological Types

Chemical Synapse
Structure
Process of Chemical Synaptic Transmission
Properties of Synaptic Transmission

Neurotransmitters
Definition
Classification
Biochemical Classification
Physiological Classification

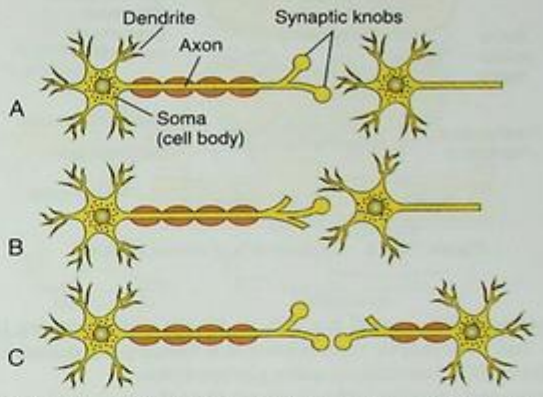


Figure 10.2-1 Types of synapses depending on the manner an axon terminates on the other neuron: (A) axo-dendritic synapse; (B) axo-somatic synapse; and (C) axo-axonic synapse.

SYNAPSE: DEFINITION AND TYPES

Definition

The synapse is the anatomic site where the nerve cells communicate among themselves. There is no anatomical connection or continuity between different neurons. They are connected only functionally. So, synapse is the functional junction between two neurons.

Types of Synapses

A. Anatomical Types Depending on the manner an axon terminates on the other neurons, the synapses can be of the following types (Fig. 10.2-1):

*1. **Axo-dendritic Synapse*** (Fig. 10.2-1A) is the synapse between the axon of a neuron and dendrite of another neuron. It is the most common type of synapse.

*2. **Axo-somatic Synapse*** (Fig. 10.2-1B) refers to the synapse between the axon of a neuron and the soma (body) of another neuron.

*3. **Axo-axonic Synapse*** (Fig. 10.2-1C) is the synapse between the axon of a neuron and the axon of another neuron.

In some parts of the brain (e.g. thalamus), some synapses are seen in which the presynaptic element is dendrite instead of an axon. Such synapses may be *dendro-axonic* or *dendro-dendritic*.

B. Physiological Types Depending on the process of transmission of impulse, the synapses can be classified as follows:

*1. **Chemical Synapses*** are those in which transmission is carried out by the *neurotransmitter*. Most synapses in the human nervous system are of this type. Chemical synapses conduct information only in one direction. These synapses are more vulnerable to fatigue on repeated stimulation (*synaptic fatigue*) and to the effects of hypoxia and pH changes. Chemical synaptic transmission is definitely slower than the velocity of nerve conduction, resulting in the synaptic delay.

*2. **Electrical Synapses*** are those at which transmission occurs through gap junctions. Transmission at electrical synapses is essentially electrotonic conduction between two neurons. It is similar to the process of nerve conduction. The electrical synapses can conduct in both directions. The speed of transmission at electrical synapses is the same as that of nerve conduction.

Electrical transmission is seen in a few locations (e.g. within the retina and olfactory bulb) in the human nervous system.

*3. **Conjoint Synapse*** refers to a synapse where both the chemical and electrical transmissions coexist.

CHEMICAL SYNAPSE

Structure of a Chemical Synapse

A typical chemical synapse between the axon of one neuron and dendrite of other neuron exhibits the following characteristics (Fig. 10.2-2):

Synaptic knob or button: As the axon of neuron approaches the synapse, it loses the myelin sheath and divides into a number of fine branches which end in small swellings called the synaptic knobs or synaptic buttons. Each synaptic knob contains a large number of mitochondria and synaptic vesicles containing neurotransmitter. Mitochondria provide ATP required for the synthesis of neurotransmitter.

Presynaptic membrane refers to the axonal membrane lining the synaptic knobs. On the inner aspect of presynaptic membrane are present *zones of dense cytoplasm*.

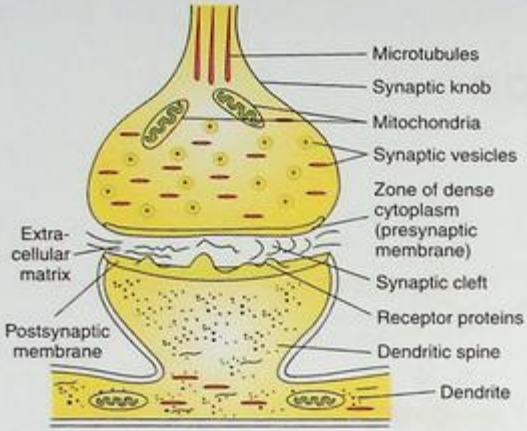


Figure 10.2-2 Structure of a chemical synapse.

Synaptic cleft is a small gap (20- to 40-nm wide) between the pre- and postsynaptic membranes. It is filled by the extracellular fluid (ECF) containing some glycoproteins.

Postsynaptic process is the name given to the region of receiving neuron (e.g. dendritic spine) where the synaptic knob synapses.

Postsynaptic membrane is the membrane lining the postsynaptic process. On the inner aspect of postsynaptic membrane is present a *zone of dense cytoplasm*, which constitutes the active zone of a synapse. Postsynaptic membrane contains a large number of receptor proteins, which protrude outwards in the synaptic cleft. Neurotransmitter released in the synaptic cleft binds with these receptor proteins to cause the effect.

Process of Chemical Synaptic Transmission

The sequence of events which occurs during chemical synaptic transmission is as follows.

A. Release of Neurotransmitter

- When the nerve impulse (action potential [AP]) travelling in a nerve fibre (axon) reaches the nerve terminal (synaptic knobs), there occurs depolarization of the presynaptic terminal.
- As a result of depolarization, the voltage-gated Ca^{2+} channels present on the presynaptic membrane open up, increasing its permeability to Ca^{2+} ions. Consequently, the Ca^{2+} ions present in the ECF of synaptic cleft enter the axon terminal.
- The elevated Ca^{2+} levels in the cytosol of axon terminal results in marked increase in exocytosis of vesicles, releasing neurotransmitter into the synaptic cleft.
- Neurotransmitter then diffuses across the synaptic cleft and binds to the postsynaptic receptors.

B. Development of Excitatory Postsynaptic Potential and Inhibitory Postsynaptic Potential

Binding of the neurotransmitter to the postsynaptic receptors causes the opening of channels through which ions can flow.

Excitatory Postsynaptic Potential Excitatory postsynaptic potential (EPSP), i.e. depolarization of the postsynaptic membrane, is produced by the excitatory neurotransmitters. The most common excitatory neurotransmitter within the CNS is *glutamate*.

Ionic Basis of EPSP The excitatory neurotransmitter binds with a specific receptor protein and opens the ligand-gated Na^+ channels on the postsynaptic membrane. As a result, the Na^+ ions diffuse inwards and depolarize the membrane. However, a very small area of postsynaptic membrane develops increased Na^+ permeability, so the amount of Na^+ influx is able to produce only a brief depolarization followed by a slower decline to the resting potential.

Conduction of EPSP The EPSP does not transmit over the cell. However, it can depolarize the adjacent membrane. This occurs passively due to local currents which are set up.

Summation of EPSP The EPSP is a graded response. It does not follow all-or-none law like AP. It shows temporal and spatial summation.

Temporal summation occurs when repeated stimuli are applied at very short intervals (i.e. before the EPSP because previous stimulus has decayed) (Fig. 10.2-3A).

Spatial summation occurs when the postsynaptic membrane receives impulses from a large number of presynaptic terminals

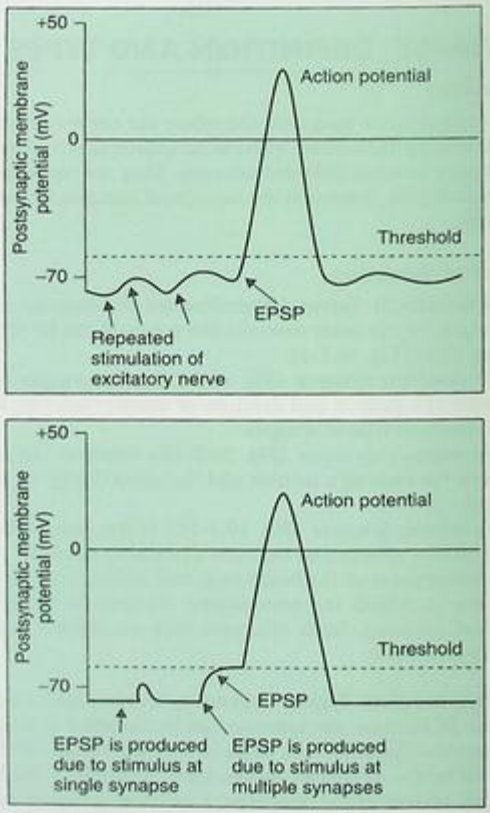


Figure 10.2-3 Excitatory postsynaptic potential (EPSP) summation resulting in action potential (AP) when a threshold is reached: (A) temporal summation and (B) spatial summation.

simultaneously. The effect of all the impulses is added up and enough transmitter substance is released to cause a greater response (Fig. 10.2-3B).

Both types of summations occur simultaneously in the neuronal pool. When the temporal or spatial summation brings the membrane potential of the cell to the firing level, an AP is fired and propagated in the postsynaptic neuron.

Inhibitory Postsynaptic Potential Inhibitory postsynaptic potential (IPSP), i.e. hyperpolarization of the postsynaptic membrane, is produced by the inhibitory neurotransmitters released in the synaptic cleft. The most common inhibitory neurotransmitters within the CNS are *glycine* and *γ-aminobutyric* acid (GABA).

Ionic Basis of IPSP The inhibitory transmitter released at the synaptic cleft causes opening of either K^+ channels or Cl^- channels in the postsynaptic membrane, leading to diffusion of a large number of K^+ ions from the neuron to the ECF or a large number of Cl^- ions to diffuse to the interior of the neuron. This causes postsynaptic membrane potential to become more negative (*hyperpolarization*). This change in potential is called IPSP.

C. Inactivation of Neurotransmitter from the Synaptic Cleft

The neurotransmitter released in the synaptic cleft from the presynaptic terminal is soon inactivated in one of the following three ways:

- Diffusion of the transmitter out of the cleft
- Enzymatic degradation of the transmitter, e.g. dissociation of acetylcholine by acetylcholinesterase
- Active transport back into the presynaptic terminal (transmitter re-uptake), e.g. active re-uptake of norepinephrine at sympathetic postganglionic nerve endings

D. Development of Action Potential

The development of AP from EPSP can be considered to happen in the following three steps:

- Synaptic integration
- Generation of the initial segment spike
- Generation of propagated signals, i.e. AP

Synaptic Integration Synaptic integration refers to the phenomenon of summation (temporal as well as spatial, as described above) of both EPSP and IPSP produced at the postsynaptic membrane. It is the net algebraically summated potential, which determines whether synaptic transmission will occur or not.

Generation of Initial Segment Spike The summated potential spreads passively to the initial segment, which comprises axon hillock and the proximal part of the unmyelinated nerve fibres. If the summated potential is large enough to depolarize the initial segment of neuron to a threshold level of about 6–10 mV (the threshold of initial segment is lowest as compared to the other parts of the nerve fibre), a spike potential called the *initial* spike (IS) is generated (Fig. 10.2-4).

Generation of Propagated Signals, i.e. Action Potential The initial spike requires a relatively low degree of depolarization for its own production (due to a low threshold value of initial segment), but once initiated, it itself produces a further depolarization of 30–40 mV by opening the voltage-gated channels

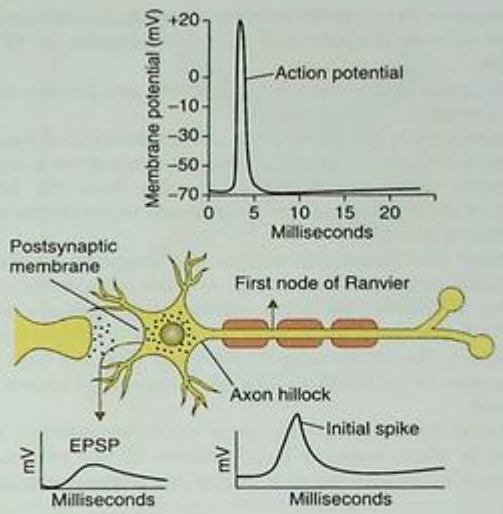


Figure 10.2-4 Summated postsynaptic potential producing initial spike (IS) and action potential (AP).

on the axon hillock (the sodium channels are in plenty in axon hillock than in any other part of the soma). Thus, the initial spike, in turn, triggers the generation of the AP spike (Fig. 10.2-4). Once generated, the AP travels in both directions, i.e. peripherally in the axon as a nerve impulse and also retrogradely over the cell membrane of soma and dendrites. This backward-conducted AP is called the soma dendritic (*SD) spike*. The SD spike helps to clear the existing EPSP so that the cell is ready to react to another set of stimuli.

Properties of Synaptic Transmission

Some characteristic features of synaptic transmission are as follows:

1. One-way Conduction The chemical synapse allows only one-way conduction of an impulse, i.e. from the presynaptic to the postsynaptic neuron and never in the opposite direction. This is called the *law of dynamic polarity* or *Bell–Magendie law.*

Cause: One-way conduction occurs because only the presynaptic nerve terminals contain the chemical neurotransmitter, whereas the postsynaptic membrane contains the specific receptor sites. Therefore, an impulse conducted antidromically in an axon dies out at the soma due to the absence of the chemical transmitter in the cell body.

Significance: The synapses act like a valve and are responsible for the orderly conduction of impulse in one direction only.

2. Synaptic Delay Synaptic delay refers to a time lapse, which occurs between the arrival of nerve impulse at the presynaptic terminal and its passage to the postsynaptic membrane. Normally, synaptic delay occurs by approximately 0.5 ms (almost always less than 1 ms).

Causes of synaptic delay include the time taken for the neurotransmitter to release and to act on postsynaptic membrane.

Significance: The synaptic delay is one of the causes for the latent period of the reflex activity. The number of neurons involved in the reflex can be estimated from the duration of reaction time of a reflex action.

3. Summation Property of Synapse A synapse exhibits the property of both temporal and spatial summation of EPSP and IPSP.

4. Convergence and Divergence properties are present in a chemical synapse.

Convergence refers to a phenomenon of termination of signals from many sources (i.e. many presynaptic neurons on a single postsynaptic neuron). Information coming from the large number of presynaptic neurons is integrated to decide the onward effect (Fig. 10.2-5).

Divergence: One presynaptic neuron may terminate on many postsynaptic neurons. Thus, a single impulse is converted into a number of impulses going to a number of postsynaptic neurons, which may travel in the same tract or into multiple tracts (Fig. 10.2-6). This causes magnification and therefore helps in amplification of an impulse. This phenomenon is known as divergence.

5. Occlusion Phenomenon The term occlusion describes the situation in which response to stimulation of two presynaptic neurons is less than the sum total of the response obtained when they are stimulated separately. This happens because of the fact that some postsynaptic neurons are common to both the presynaptic neurons (Fig. 10.2-7). Thus occlusion is due to overlapping of afferent fibres in their central distribution.

6. Subliminal Fringe Effect An afferent nerve fibre divides into many hundred branches. Of these, a large number may terminate on one efferent neuron, whereas a smaller number may terminate on another efferent neuron lying nearby. When afferent neuron is stimulated, the efferent (postsynaptic) neuron which has many presynaptic terminals is excited to a threshold level and AP is fired. Others in the peripheral zone (fringe area) are excited to a subthreshold level only, i.e. their excitability is increased but an AP is not fired. This is known as *subliminal* fringe effect. Thus, the postsynaptic neurons that are fired are said to be in a discharging zone and those which are not fired are said to be in a subliminal fringe (i.e. not in the discharging zone).

This is exactly opposite to occlusion (Fig. 10.2-8).

Physiological significance: As a result of the summation, occlusion and subliminal fringe effect, the patterns of impulses in

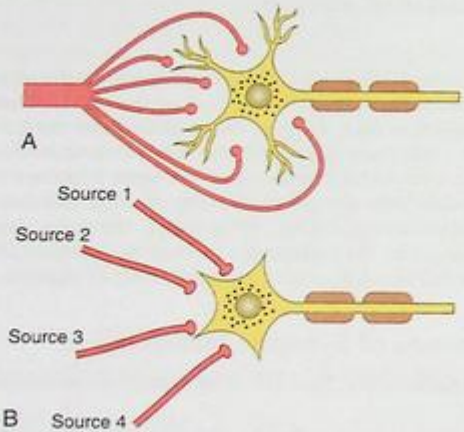


Figure 10.2-5 Convergence of signals on a single neuron: (A) convergence from a single source and (B) convergence from multiple sources (e.g. ventral horn cell of spinal cord).

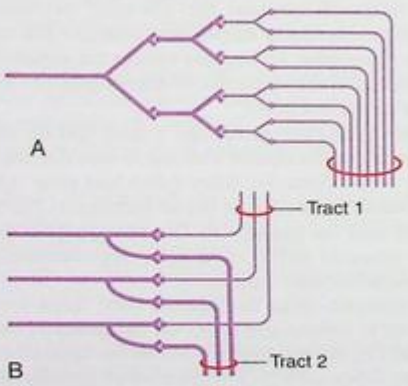


Figure 10.2-6 Phenomenon of divergence: (A) divergence in the same tract and (B) divergence into multiple tracts.

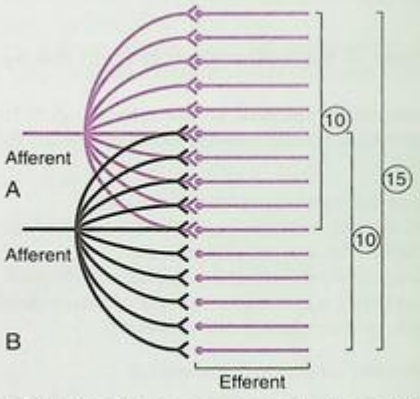


Figure 10.2-7 Occlusion phenomenon: stimulation of afferent neuron A and B each excites 10 efferent neurons. Simultaneous stimulation of neuron A and B together excite 15 efferent neurons because five efferent neurons are common to both.

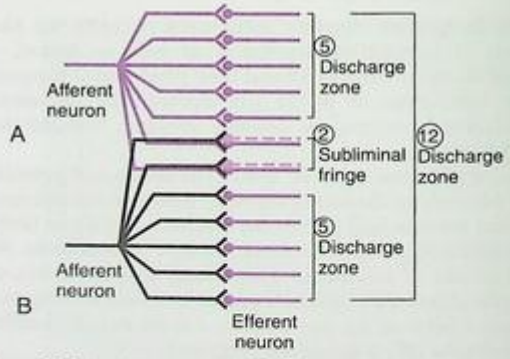


Figure 10.2-8 Subliminal fringe effect: stimulation of afferent neurons A and B, each exciting five efferent neurons and subliminal fringe effect on two efferent neurons (which are common to both A and B neurons). Simultaneous stimulation of neurons A and B excites 12 efferent neurons because the subliminal fringe effect on two neurons gets summated to produce threshold stimulation.

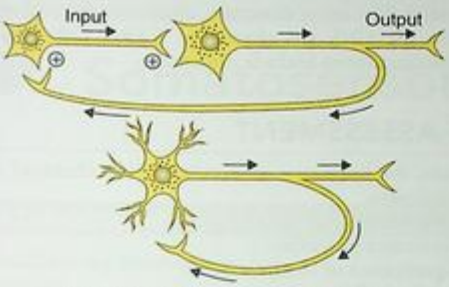


Figure 10.2-9 Reverberating circuit.

peripheral nerves are usually altered as they pass through synapses on the way to brain. One such effect is the phenomenon of referred pain.

7. Facilitation When the presynaptic axon is stimulated with several consecutive individual stimuli, each stimulus may evoke a larger postsynaptic potential than that evoked by the previous stimulus. This phenomenon is known as facilitation.

8. Synaptic Fatigue When the presynaptic neuron is stimulated separately, the rate of impulse discharge in the postsynaptic neuron is initially high, but within a few seconds, there occurs a gradual decrease and finally disappearance of the postsynaptic response. This phenomenon is called *synaptic* fatigue or *habituation*. Fatigue is a temporary phenomenon.

Mechanism: Fatigue mainly occurs due to *exhaustion* of chemical neurotransmitter.

9. Synaptic Plasticity and Learning Plasticity refers to the capability of being easily moulded or changed. Synaptic transmission can be increased or decreased on the basis of past experience. The changes in the synaptic transmission can occur due to alterations at the presynaptic or postsynaptic location.

10. Reverberation Reverberation refers to the phenomenon of passage of impulse from presynaptic neuron and again back to presynaptic neuron to cause a continuous stimulation of presynaptic neuron (Fig. 10.2-9).

11. Reciprocal Inhibition Reciprocal inhibition refers to a phenomenon in which an afferent signal activates an excitatory neuron to a group of muscles and simultaneously activates inhibitory signals to other group of muscles, usually antagonistic muscles. For example, during flexion of a joint the afferent stimulus causes excitation of the neurons, supplying the flexor muscles of the joint, and at the same time a branch of afferent fibre excites an inhibitory interneuron, which synapses with the motor neuron, supplying the extensor muscles of the joint (Fig. 10.2-10) (see page 432).

12. After Discharge After discharge of a synapse refers to a phenomenon in which a single instantaneous input results into sustained output signals (i.e. a series of repetitive discharges). Input signals last only for 1 ms and output signals last for many milliseconds.

NEUROTRANSMITTERS

Definition

Neurotransmitters are the chemical substances which are responsible for transmission of an impulse through a synapse.

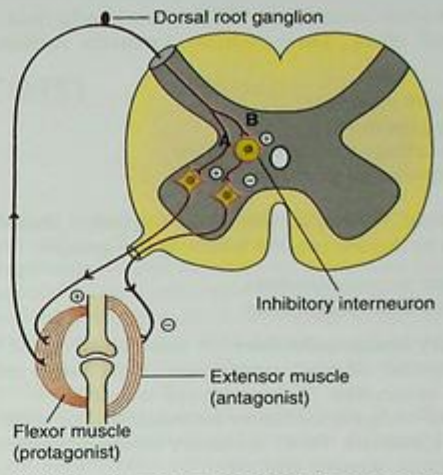


Figure 10.2-10 Neuronal arrangement of reciprocal inhibition. An afferent stimulus producing contraction of flexors of a joint (through A) and causes inhibition of extensors (through B) by intervention of an inhibitory neuron.

Neuromediators or neurohormones: These are chemical substances which are synthesized in neurons and poured into the blood stream through terminals resembling synapses in structure.

Neuromodulators are the chemical substances which are associated with synapses but do not influence synaptic transmission directly.

Classification

Generally, these substances are classified in the following two ways:

Biochemical Classification Biochemically, neurotransmitter can be divided into the following two groups:

A. Small Molecule Neurotransmitters These act rapidly and cause acute response. These are synthesized and packed into synaptic vesicles in the axon terminal. Important small molecule neurotransmitters with their site of release (given in *parentheses*) are as follows:

I. ***Acetylcholine (Ach)***
- Neuromuscular junction
- All preganglionic autonomic neurons
- All postganglionic parasympathetic neurons
- Postganglionic sympathetic neurons to sweat glands and skeletal muscle blood vessels
- Some amacrine cells of retina
- Many parts of CNS

II. ***Biogenic amines***
- Catecholamines: epinephrine (EP), norepinephrine (NE), dopamine (DA)
- Serotonin (5 hydroxytryptamine [5HT])
- Histamine

III. ***Amino acid neurotransmitters***
- Gamma-aminobutyric acid (GABA)
- Glycine
- Glutamic acid or glutamate
- Aspartic acid or aspartate

B. Neuropeptide transmitters These act slowly and have a prolonged effect. These neurotransmitters include the following:

- Neuroactive peptides
- Pituitary peptides
- Peptides acting on the gut and brain
- Neuropeptides from other tissues

Physiological Classification Physiologically, neurotransmitters can be divided into the following two groups:

- Excitatory neurotransmitters
- Inhibitory neurotransmitters

1. ***Excitatory neurotransmitters*** can cause an AP (if the target cell is another neuron), contraction (if the target cell is a muscle) or secretion (if the target cell is a gland).
   The most common excitatory neurotransmitter within the CNS is glutamate. Other excitatory neurotransmitters are acetylcholine, aspartic acid, etc.
2. ***Inhibitory neurotransmitters*** reduce or block the activity of the postsynaptic cell. They produce a hyperpolarization of the postsynaptic membrane called the inhibitory postsynaptic potential. The most common inhibitory neurotransmitters within the CNS are *glycine* or *GABA*. Other inhibitory neurotransmitters include dopamine.

SELF-ASSESSMENT

1. Discuss the sequence of events during chemical synaptic transmission.
2. Write notes on:
   - Generator potential
   - Significance of synaptic delay
   - Subliminal fringe
   - Occlusion property
   - Reciprocal inhibition
3. Define a neurotransmitter. Give classification of neurotransmitters. Write a note on functions of acetylcholine as a neurotransmitter.
4. Differentiate between:
   - EPSP and IPSP
   - Temporal and spatial summation
   - Convergence and divergence
   - Neurotransmitter and neuromediator

10.3 Somatosensory System

CHAPTER OUTLINE

General Sensory Mechanism
Introduction
Sensations
Components of Sensory System
Receptors
Classification
Sensory Transduction
Properties of Receptors

Somatosensory System
Somatic Sensations
Touch, Pressure and Vibration Sensations
Temperature Sensation
Pain Sensation
Other Sensations
Pathways in Somatosensory System
Neurons of Sensory Pathway
Sensory Nerves and Dermatomes
Ascending Sensory Tracts
Role of Thalamus in Somatosensory System
Somatic Sensory Cortex
Encoding: Recognition of Type of Sensation
Encoding of Stimulus Intensity
Encoding of Stimulus Location
Encoding of Stimulus Quality

GENERAL SENSORY MECHANISM

Introduction

Sensations

Sensory division of the human nervous system is concerned with the collection of the information about the outside world and changes occurring within the body itself. Sensation refers to conscious perception of sensory information reaching the brain. Sensations may be broadly classified into the following two groups:

1. Special Senses These include visual sensations, auditory sensations, gustatory (taste sensation) and olfactory (smell) sensations.
2. Somaesthetic Senses These, depending on their point of origin, can be classified into the following three types:

A. ***Exteroceptive sensations***, also known as cutaneous sensations, arise from the surface of the body and these include the following:
- Tactile sensation
- Pressure sensation
- Pain sensation
- Temperature sensation

B. ***Visceral sensations*** arise from the viscera, i.e. internal organs and is called visceral sensation.

C. ***Proprioceptive and kinaesthetic sensations*** arise from the muscles, tendons and joints. These include the following:
Proprioceptive sensations: These are concerned with the physical state of the body, i.e. the sense of position, tendon and muscle sensations, deep pressure and sense of equilibrium.
Kinaesthetic sensations or kinaesthesia: It is the conscious recognition of rate of movement of different parts of the body. Kinaesthetic sensations include the following:
- Conscious kinaesthetic sensations
- Unconscious kinaesthetic sensations

Components of Sensory System

The sensory division of the human nervous system includes the following components:

1. Sensory Receptors These are specialized cells that transduce stimulus energy into neural signals.
2. Afferent Neurons These carry sensory impulses to the sensory cortex and constitute the neural pathway.
3. Sensory Cortex It includes the sensory areas of cerebral cortex. The information received in the sensory cortex results in a conscious perception of the stimulus, i.e. a sensation.

Receptors

Sensory receptors are specialized cells that receive stimuli from the external or internal environment and transduce these signals into neural signals. A *stimulus* is a change of environment of sufficient intensity to evoke a response in an organism. The external stimuli may be mechanical, chemical, thermal, auditory or visual.

Classification of Receptors

Receptors for somatic sensations include:

A. Receptors for Cutaneous Sensations

1. ***Mechanoreceptors*** or receptors of touch, pressure and vibration sensation provide information about these stimuli to skin. In general, these receptors consist of an unmyelinated axon surrounded by lamellated connective tissue corpuscles. These include (Fig. 10.3-1) the following:
   - Pacinian corpuscles
   - Meissner's corpuscles
   - Merkel's discs
   - Ruffini's end organs
   - Hair end organs
   - Krause's end bulbs
   - Free nerve endings

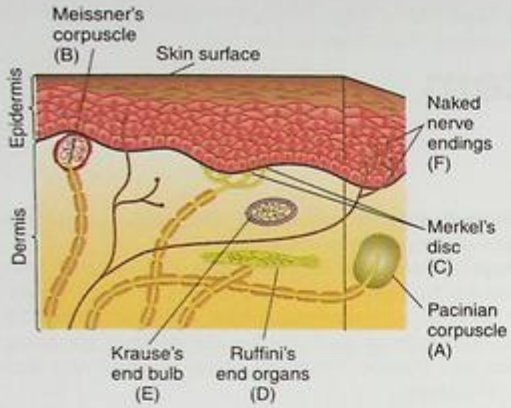


Figure 10.3-1 Sensory receptors.

2. ***Thermoreceptors:*** Thermoreceptors are responsible for detecting temperature sensation. Free nerve endings of unmyelinated C fibres form the *warm receptors* and that of *small myelinated* Aδ fibres form the *cold receptors.*
3. ***Nociceptors:*** Nociceptors or pain receptors refer to a special type of free nerve endings of the following:
   - Aδ myelinated fibres
   - C unmyelinated nerve fibres

B. Receptors for Proprioceptive and Kinaesthetic Sensations The receptors concerned are called *proprioceptors* and include the following:

- There are muscle spindle or stretch receptors (see page 429).
- Joint receptors located in the joint capsules and ligaments around the joints: Ruffini's end organs are the most important receptors for this function. A few Pacinian corpuscles are also involved.
- There is a Golgi tendon organ (see page 431).
- There is a vestibular receptor (see page 438).

C. Receptors for Visceral Sensation The visceral receptors are present in the visceral organs.

Sensory Transduction

Sensory transduction refers to the phenomenon of transduction of environmental signals into neural signals by the receptors. Steps of sensory transduction are as follows:

- Arrival of stimulus to receptor
- Production of generator or receptor potential
- Production of action potential in sensory nerve

Arrival of Stimulus to Receptor The stimulus arriving at the given sensory receptor may be in the form of the following:

- ***Mechanical force*** causing depression of the skin, which stimulates mechanoreceptors
- ***Light or electromagnetic wave***, which stimulates photoreceptors of the retina
- ***Chemical***, e.g. a molecule of NaCl on the tongue, which stimulates chemoreceptors
- ***Cold or warm temperature*** stimulating thermoreceptors
- ***Sound energy*** stimulating auditory receptors, and so on and so forth

Production of Receptor Potential When a stimulus excites the receptor, it changes the potential across the membrane of the receptors. This change in the potential is called receptor or generator potential.

Mechanism of Development of Receptor Potential *(Fig. 10.3-2)* The change in membrane potential in a receptor is caused by a change in permeability of membrane of the unmyelinated terminals to Na^+. The resultant influx of Na^+ causes development of generator or receptor potential.

Usually the current is inwards, which produces *depolarization of the receptor.* The exception is in the photoreceptors, where light causes *hyperpolarization.*

Production of Action Potential in a Sensory Nerve The receptor potential developed in an unmyelinated nerve ending (transducer region) depolarizes the sensory nerve at the first node of Ranvier (spike generator region) by electrotonic depolarization current sink action. When the receptor potential rises above the threshold level (i.e. above 10 mV), it brings the membrane potential of the first node of Ranvier to the firing level, causing production of action potential, which is propagated in the nerve fibre (Fig. 10.3-2D). Thus, the first node of Ranvier (spike generator region) converts the graded response of the receptor into action potential. The greater the magnitude of receptor potential, the greater is the rate of discharge of action potentials in the nerve fibre.

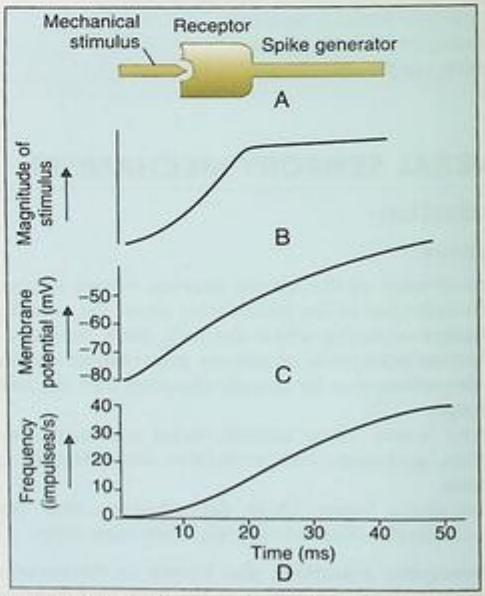


Figure 10.3-2 Mechanism of development of generator potential and its relationship with intensity of stimulus. (A) Stimulus to mechanoreceptor causes its deformation, which opens up channels which are permeable to Na^+ causing membrane depolarization; (B) the magnitude of stimulus intensity; (C) the receptor potential (generator potential) follows the time course; and (D) the action potential. *Note:* The magnitude of generator potential and frequency of action potential are proportionate to the magnitude of the stimulus.

Properties of Receptors

1. Specificity of Response Each receptor is easily stimulated (has low threshold) by only one type of appropriate (adequate) specific stimulus. This specificity of response by a particular receptor is also called *law of adequate stimulus*. Although each receptor is exquisitely sensitive to its adequate stimulus, receptors can respond to other forms of energy if the intensity is high enough. Examples include the following:

Adequate stimulus for rod and cones of retina is light. Pressure on the eyeball can also stimulate retinal receptors, but the threshold of these receptors to pressure is much higher than the threshold of the pressure receptors in skin.

2. Production of Receptor Potential on Stimulation It has been described in detail above.

3. Adaptation When a receptor is continuously stimulated with the same strength of stimulus, the frequency of action potential in its sensory nerve decreases progressively. This property is called adaptation. Depending on the rate of adaptation, the receptors are of the following two types:

Tonic receptors: These receptors keep on firing action potentials continuously during stimulus application. Such receptors are important for life as they keep the brain constantly apprised of status of the body and its relation to its surroundings. Examples of such receptors are as follows:

- Muscle spindles
- Pain and cold receptors
- Baroreceptors and chemoreceptors

Phasic receptors: These are *rapidly adapting* receptors. These transmit signals only when the stimulus strength is changed. Examples of phasic receptors include the following:

- Meissner's corpuscles, Pacinian corpuscle and olfactory receptors

4. Effect of Strength of Stimulus Receptor potential amplitude depends on the strength of stimulus. During the stimulation of a receptor, if the response given by the receptor is to be doubled, the strength of stimulus must be increased 10 times. This phenomenon is called *Weber–Fechner law*.

5. Effect of Velocity of Stimulus The magnitude of the receptor potential rises with rate of change of stimulus application. It also applies to removal of stimulus, e.g. off response.

6. Projection When any part of sensory path is stimulated, conscious sensation referred to the location of receptor is produced. This is called *law of projection* (for more details, see Encoding of Sensation, see page 424).

SOMATOSENSORY SYSTEM

Somatosensory system can be discussed under the following headings:

- Somatic sensations
- Pathways in somatosensory system
- Role of thalamus in somatosensory system
- Somatosensory cortex
- Encoding: recognition of type of sensation

Somatic Sensations

Touch, Pressure and Vibration Sensations

Mechanoreceptors provide information about touch, pressure and vibration stimuli to skin (Fig. 10.3-1).

The salient features of main mechanoreceptors are summarized in Table 10.3-1.

Functions of Touch and Pressure Mechanoreceptors

1. Detection of Touch, Pressure and Vibration Sensations by Mechanoreceptors Touch, pressure and vibration are considered to be a different form of the same sensation.

2. Two-point Discrimination It is the ability to distinguish two touch stimuli separately. The minimum distance by which two touch stimuli can be perceived as separate stimuli varies from a 2–3 mm on the lips and fingertips to over 60 mm on the back of the trunk. The difference in the distance between the two points seems to be related to the density of touch receptors in different parts of the body.

3. Stereognosis Stereognosis refers to the ability to recognize familiar objects such as a key, coins, pen, pencil and spoons by merely handling them without looking at them.

TABLE 10.3-1 Salient Features of Cutaneous Mechanoreceptors

Receptors	Main Descriptive Feature	Receptive Field Size	Adaptation Sensation	Encoded
Pacinian corpuscles	Onion-like capsule surrounding unmyelinated nerve ending	Large	Very rapid	Vibration, tapping
Meissner's corpuscles	Small encapsulated, present in nonhairy skin	Small	Rapid	Speed of stimulus application
Merkel's disc	Transducer is on epithelial cells	Small	Slow	Location of stimulus
Ruffini's end organs	Multibranched, encapsulated, liquid-filled collagen corpuscle	Large	Slow	Magnitude and duration of stimulus (pressure)
Hair end organs	Hair and its basal nerve	Small	Rapid	Movement of object on the surface of body
Krause's end bulbs		Small	Rapid	Touch and pressure

Temperature Sensation

Thermoreceptors

Location Thermoreceptors are located in the skin of all parts of the body. However, the density of thermoreceptors is greatest in the lips, moderate in the fingertips and least in the skin of trunk.

Stimulus Thermoreceptor responds to the temperature of subcutaneous tissue surrounding them and not to the environmental temperature as such. Because of this reason, cold metal objects feel colder than wooden objects of the same temperature. The metal being good conductor conducts heat away from the skin more rapidly and cools the subcutaneous tissue to a greater degree than the wood.

The salient features of response exhibited by warm and cold receptors are given below.

Warm Receptors They are activated when skin temperature is between 30°C and 43°C (Fig. 10.3-3). The firing rate of warm receptors reaches a peak at temperatures of approximately 42°C.

Cold Receptors

- They are activated when the skin temperature is between 10°C and 40°C (Fig. 10.3-3). The steady-state firing rate of cold receptors reaches a peak at temperatures between 25°C and 30°C.
- Paradoxically, temperatures between 45°C and 50°C stimulate cold fibres as well as pain fibres, producing a mixed sensations of cold and pain (Fig. 10.3-3).
- Cold temperature below 10°C stimulates only pain receptors (Fig. 10.3-3).
- Thus, between 30°C and 40°C both cold and warm receptors are stimulated, which help the person in fine gradation of temperature. Therefore, between 30°C and 40°C (neutral or comfort zone), complete perceptual adaptation occurs (i.e. awareness of temperature disappears).
- Thermoreceptors show a moderate degree of adaptation.

Pain Sensation

Definition and Purpose Pain refers to an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

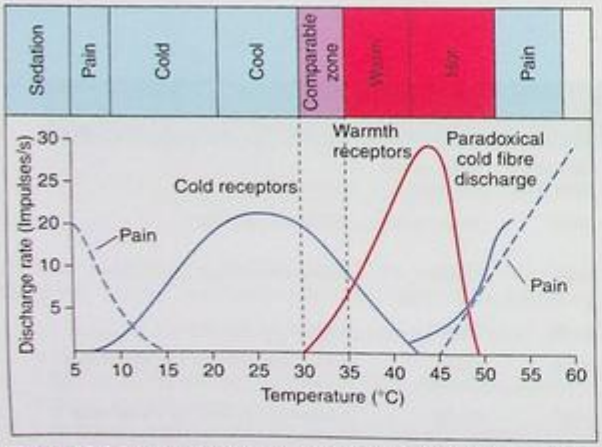


Figure 10.3-3 Impulse discharge rate of cold and warm receptors as a function of temperature.

Pain sensation is different from other sensations because its purpose is to inform the brain that the stimulus is physically damaging. Therefore, though the pain sensation is unpleasant, it is useful in the following ways:

- It makes one aware of a harmful agent in close contact with the body and body gives preferential treatment to this information.
- It causes the individual to react to remove the pain stimulus to prevent further damage to the tissues.
- Pain receptors are nonadaptable receptors; therefore, they keep the person apprised of damaging stimulus as long as it persists. Thus, pain sensation has a protective function.

Pain Receptors, Stimuli and Chemical Mediators of Pain

Nociceptors Nociceptors refer to the following special types of free nerve endings:

- Aδ myelinated nerve fibres
- C unmyelinated nerve fibres

Types Nociceptors can be broadly grouped as somatic nociceptors and visceral nociceptors.

1. ***Somatic nociceptors*** are free nerve endings of Aδ and C fibres as mentioned above.
2. ***Visceral nociceptors***: Visceral pain is not produced by many tissue-damaging stimuli such as localized cutting, clamping or burning. However, widespread inflammation, ischaemia, mesenteric stretching, or spasm or dilatation of hollow viscera produce pain.

Pain Stimuli Pain receptors are activated by three types of noxious stimuli: mechanical, thermal and chemical.

Chemical stimuli: Damaged tissue releases certain chemicals which act on nociceptors and cause pain sensations. *Chemical mediators of pain include the following*:

- K^+, *ATP* and *ADP* are released following cell death.
- *Bradykinin* is released by dying cells.
- *Leukotrienes* are released from mast cells.
- *Serotonin* is released from platelets.
- *Histamine* is released from mast cells.
- *Lactic acid* is accumulated in tissues due to anaerobic mechanism during ischaemia.
- *Substance P* and *calcitonin gene-related peptide* (CGRP) are released.
- *Prostaglandins and substance P* enhance the sensitivity of pain endings but do not directly excite them.
- *Nociceptin* is released.

Qualitative Types of Pain Sensations Qualitatively, pain sensations are of two types: fast pain and slow pain.

1. Fast Pain Fast pain is a sharp, well-localized, pricking sensation that results from activation of the nociceptors on the Aδ fibres. The fast pain sensations travel faster and thus appear within 0.1 ms after the application of stimulus.

Accompaniments of fast pain are as follows:

- *Withdrawal reflex*, which causes the individual to move the involved body part away from the source of painful stimulus
- *Sympathetic response*, i.e. increased blood pressure, tachycardia and mobilization of body energy supply

2. Slow Pain Slow pain is a poorly localized, dull, throbbing, burning sensation that results from activation of nociceptors

on the C fibres. It appears after 1 second or more following the application of stimulus.

Accompaniments of slow pain are as follows:
- *Emotional perception* in the form of unpleasantness, and in long-standing cases in the form of irritation, frustration and depression
- *Autonomic symptoms* in the form of nausea, profuse sweating, vomiting and lowering of blood pressure
- *Generalized reduction in skeletal muscle tone*

Clinical Types of Pain In clinical practice, pain sensations can be classified as follows:

- Somatic pain
- Visceral pain
- Referred pain
- Radiating pain
- Projected pain
- Hyperalgesia

1. Somatic Pain Somatic pain, as the name indicates, arises from the tissues of the body other than viscera. It is of the following two types:

Superficial somatic pain arises from the skin and superficial tissues. Its features are usually similar to the *fast pain*.
Deep somatic pain arises from the muscles, joints, bones and fascia. Usually, its features are similar to that of *slow pain*.

2. Visceral Pain
Features of visceral pain are as follows:
- This is *poorly localized* because of comparatively fewer pain receptors in viscera.
- This is *unpleasant* because of emotional perception.
- *Autonomic symptoms* include nausea, vomiting, profuse sweating and lowering of blood pressure.
- *Reflex contraction of skeletal muscle* of abdominal wall, clinically known as guarding, is a common association, especially when inflammation of viscera involves peritoneum. It is a protective reflex which helps to protect the underlying inflamed structures from unintentional injury.
- It *radiates* or is referred to other site (see Referred Pain).

3. Referred Pain Referred pain as the name indicates is that pain which originates due to irritation of a visceral organ and is felt not only in the organ but also in some other somatic structure (usually skin) supplied by the same neural segment.

Characteristic features of referred pain are as follows:
1. Such a pain is said to be referred to the second structure. Examples include the following:
   - In *myocardial ischaemia*, pain is referred to the left shoulder and arm.
   - Pain due to *stone in lower part of ureter* is usually referred to the corresponding testis and inner thigh.
   - *Inflammation of diaphragm* secondary to pleurisy or severe cholecystitis produces pain at the tip of shoulder.
2. Pain is usually referred to a structure with *common embryonic origin*, and hence are innervated by a common neural segment. This principle is called the *dermatomal rule*. For example, embryologically the heart and the left arm have the same segmental origin. Similarly, the testes and kidney develop from the same primitive urogenital ridge.

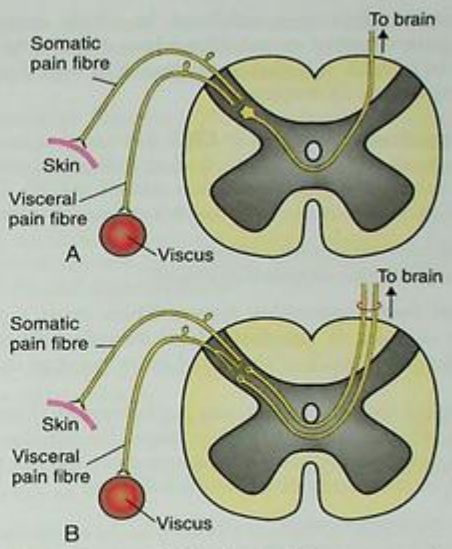


Figure 10.3-4 Theories of referred pain: (A) convergence theory and (B) facilitation theory.

Theories of referred pain are discussed below.
1. *Convergence theory*: According to this theory, when the first-order neurons carrying pain sensation from a somatic area and a visceral organ converge on a common second-order neuron (Fig. 10.3-4A), the brain is unable to identify the source of pain. Somatic pain is far more common, so the brain interprets all pain as somatic pain even when the source is actually visceral.
2. *Facilitation theory*: According to this theory, the visceral irritation is inadequate for producing pain by itself. However, it facilitates pain fibres from somatic structures (Fig. 10.3-4B) so that even minor somatic irritation produces perceptible pain.

4. Radiating Pain Sometimes visceral pain is experienced both locally and also at a distant point (referred pain). In fact, pain seems to spread from the local area to the distant site. This is called radiating pain. Example of radiating pain are as follows:

- *In appendicitis*, pain starts in the right iliac fossa and radiates towards centre of abdomen.

5. Projected Pain When the sensory fibres carrying pain sensations are stimulated anywhere in their course to the sensory cortex, the pain sensations evoked are projected to the area where receptors are located. This is called *projected pain*. It follows the *law of projection* (see page 417). Examples of projected pain are as follows:

- After amputation of a limb, sometime patient complains of intense pain in the absent limb (phantom limb). The pain sensations are produced due to irritation of nociceptive fibres at the stump but are projected to the area where receptors used to be located.
- Striking the elbow causes pain to be projected to the hand.

6. Hyperalgesia Hyperalgesia refers to enhanced painful response to a stimulus.

Causalgia Causalgia is a condition in which spontaneous burning pain sensation occurs after a long time in the area of even trivial injuries. It is also accompanied by *hyperalgesia* and reflex sympathetic dystrophy.

Pain Suppression Systems in CNS The degree of reaction to painful stimuli varies from individual to individual, mainly because of existence of pain suppression systems in CNS. The pain suppression consists of the following two major components:

- Spinal pain suppression system
- Supraspinal pain suppression system

A. Spinal Pain Suppression System There exists a pain inhibitory complex in the dorsal horn of spinal cord, which blocks the pain signals at the initial entry point to the spinal cord.

Gate Control Hypothesis has been put forward by (Metzak and Wall in 1965). According to this hypothesis, the dorsal grey horn acts as gate for transmission of pain sensation, and this gate can be partly or completely closed by the following:

- Segmental suppression
- Supraspinal suppression

1. ***Segmental suppression***: It has been observed that activation of large myelinated touch fibres (Aβ) reduces pain. Aβ fibres give collaterals, which cause *presynaptic inhibition* (primary afferent depolarization) of pain carrying (both type C and Aδ) fibres, where they synapse in the dorsal horn (Fig. 10.3-5). Although poorly understood, such circuitry probably explains the relief of pain achieved by the following manoeuvres:
   - Rubbing or massage or pressure in the vicinity of painful area
   - Local application of warmth or cold
   - Local application of counterirritants, i.e. stimulation of skin
   - Acupuncture
   - Transcutaneous electric nerve stimulation (TENS) in which the pain site or the nerves leading from it are stimulated by electrodes placed on the surface of skin
2. ***Supraspinal suppression*** is caused by the supraspinal suppression system described below.

B. Supraspinal Pain Suppression System There exist the following three different supraspinal descending pain modulation pathways:

- Descending serotonergic and opioid inhibitory system
- Descending purinergic inhibitory system
- Descending adrenergic inhibitory system

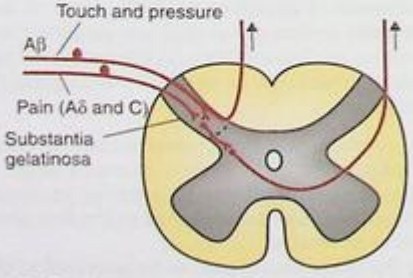


Figure 10.3-5 Spinal pain suppression system. Note that the collaterals from Aβ fibres from touch receptors cause presynaptic inhibition of pain afferent Aδ and C fibres.

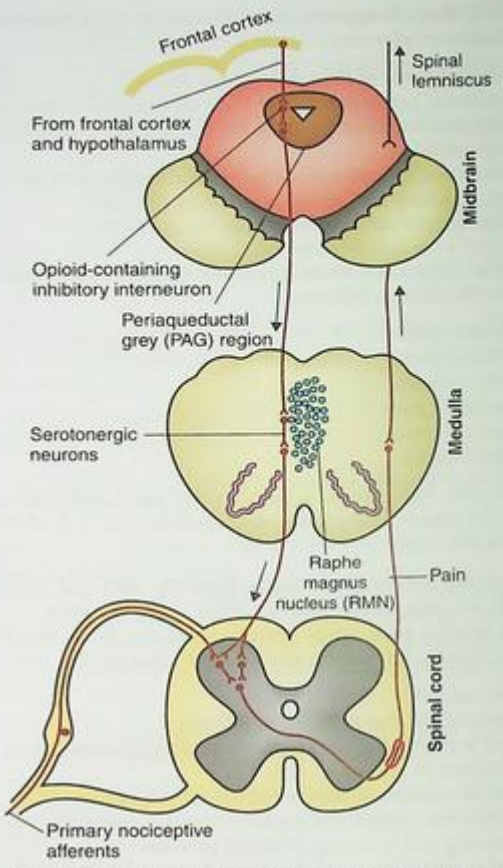


Figure 10.3-6 Supraspinal serotonergic and opioid pain inhibitory system.

1. Descending Serotonergic and Opioid Inhibitory System Components of this system (Fig. 10.3-6) are as follows:

(i) ***Raphe magnus nucleus (RMN):*** The *serotonergic neurons* of the RMN project down the dorsolateral column to influence the neurons in dorsal horn of spinal cord, which are excited by primary nociceptive afferents. The serotonergic fibres are believed to exert their effect by *postsynaptic inhibition.*

(ii) ***Periaqueductal grey (PAG) area in the midbrain:*** It inhibits pain by stimulating the RMN. Neurons of PAG have opioid receptors on their surface membranes. When *opioid receptors* are stimulated by exogenously administered opioid compounds (analgesics) or by endogenous opioid neurotransmitters (endorphins and enkephalins) found in the brain, the pain suppression circuitry is activated and this leads to reduced pain perception.

Conditions under which descending serotonergic and opioid pain inhibitory system is stimulated are as follows:

(i) *When limbic system is stimulated*: Limbic system is the seat of emotions. Fibres from the limbic system supply the PAG. This explains why a soldier wounded in the battlefield may feel no pain during the heat of battle.

(ii) *Autofeedback*: When the spinothalamic tract (STT) is stimulated, the collaterals from STT stimulate the descending inhibitory pathway.

2. Descending Purinergic Inhibitory System It is composed specifically of adenosine. Adenosine exhibits both pre- and postsynaptic actions, and produces antinociception by indirect interaction with excitatory amino acid release.
3. Descending Noradrenergic Inhibitory System Fibres of this system originate from the *locus coeruleus* and medullary reticular formation, and descend in dorsolateral fasciculus. Environmental factors such as stress may activate this descending inhibitory mechanism.

Other Sensations

This group includes the following sensations (excluding somatic sensations like touch, pressure, pain and temperature):

- Itch
- Tickle
- Synthetic senses

Itch It is an irritative skin condition which occurs due to mild stimulation (especially when something moves across the skin). *Characteristic Features are as follows:*

1. It occurs only in the skin, eyes and certain mucous membranes but not in the deep tissue and viscera.
2. It originates due to stimulation of *itch receptors*, which are naked nerve endings of unmyelinated C fibres. The receptors are stimulated by the following two ways:
   - By repeated local mechanical stimulation of skin
   - By certain chemical agents (e.g. bile salts, histamine and kinins)
3. Scratching relieves the itching: The mechanism is the same as that of the gate control hypothesis in pain sensation.

Tickle Tickle is regarded as a pleasurable feeling as compared to itching (which gives annoying feeling) and pain (is an unpleasant feeling).

Synthetic Sense The combinations of various cutaneous sensations produce different experiences, which are entirely different from primary sensation. Therefore, the new experience is regarded as synthetic sense.

Pathways in Somatosensory System (Transmission of Sensations)

Neurons of Sensory Pathway

Pathways in the somatosensory system are formed by a chain of three neurons, which ultimately reach the sensory cortex.

First-order Neurons These are the primary afferent neurons that receive the transduced signals from the sensory receptors and carry them to the spinal cord or brainstem. The cell bodies of the primary afferent neurons are located in *dorsal root ganglia*. These are T-shaped unipolar neurons with peripheral and central processes. The peripheral processes reach the sensory receptors and form the sensory part of *spinal nerves* (which are mixed nerves). Central processes constitute the *dorsal nerve root* of the spinal nerve. The fibres of first-order neurons in the spinal nerves and dorsal nerve root comprise Aα-, Aβ-, Aδ- and C-type fibres and are often referred to group I, II, III and IV, respectively, by the sensory physiologists.

Second-order Neurons The second-order neurons are located in the dorsal horn of spinal grey matter. Axons of the second-order neurons form the *ascending sensory tracts*.

Third-order Neurons Third-order neurons of the sensory pathway are located in specific nuclei of thalamus. From here the encoded sensory information ascends to sensory cortex through the thalamic radiations.

Sensory Nerves and Dermatomes

Sensory Nerves All sensory fibres reach the CNS through their cranial equivalents.
Dorsal Nerve Roots in Spinal Cord Each dorsal nerve root is attached to the spinal cord through various rootlets. Each rootlet just before entering the spinal cord divides into medial and lateral divisions.

Medial divisions of each rootlet consist of myelinated group I and II fibres, which include the following:
- Proprioceptive fibres from muscles
- Sensory fibres conveying touch, pressure and vibratory sensations

Lateral divisions of each rootlet is composed of the following:
- Thin myelinated group III (Aδ) fibres, which carry fast and discriminative pain and temperature sensations
- Unmyelinated group IV (type C) fibres, which carry slow pain and visceral sensations

Dermatomes Dermatome refers to the area of skin supplied by one dorsal root (spinal cord segment). It is important to note that dermatomes are quite different from the peripheral nerve fields because fibres from one dermatome may be present in different peripheral nerves.

During the embryo stage, the body is divided into orderly metameres. In the postnatal life, owing to excessive growth of limbs, the metamere arrangement, excepting in the trunk, is no longer present. Therefore, dermatomes are remnants of orderly metameric arrangement, which has survived only in the trunk, where the dermatomes consist of a series of 12 narrow overlapping bands running from the vertebral column to the midventral line (Fig. 10.3-7). However, this apparent complexity of the dermatomes in man is simplified if the man is visualized as a quadruped animal (like monkey, the ancestor of man) (Fig. 10.3-8). The knowledge of dermatomes is utilized to know the level of spinal cord injury by mapping the area of altered sensation produced.

Ascending Sensory Tracts

The major ascending sensory tracts in the spinal cord have been grouped as follows:

- Dorsal (posterior) column sensory pathway
- Anterolateral sensory pathway
- Dorsolateral column sensory pathway

Dorsal Column Sensory Pathway Dorsal column sensory pathway (Fig. 10.3-9) in man is well developed and completely myelinated.

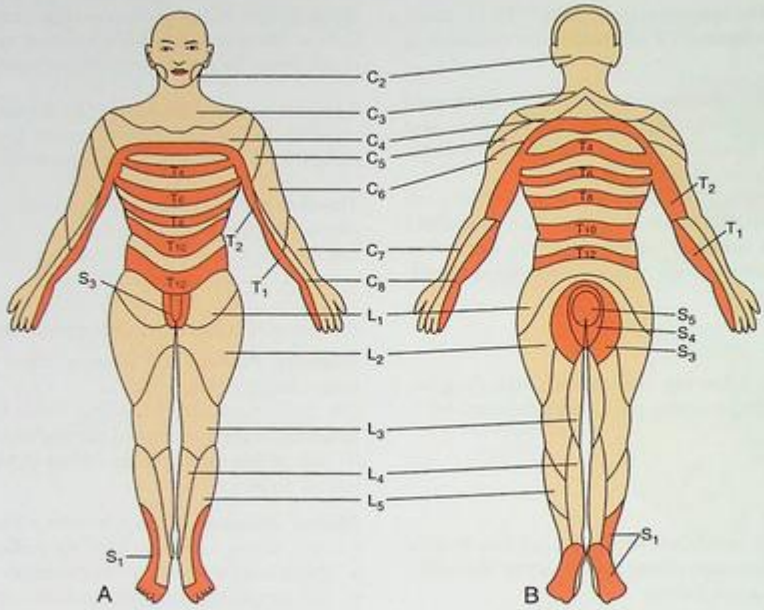


Figure 10.3-7 Dermatomes as seen from (A) front and (B) back.

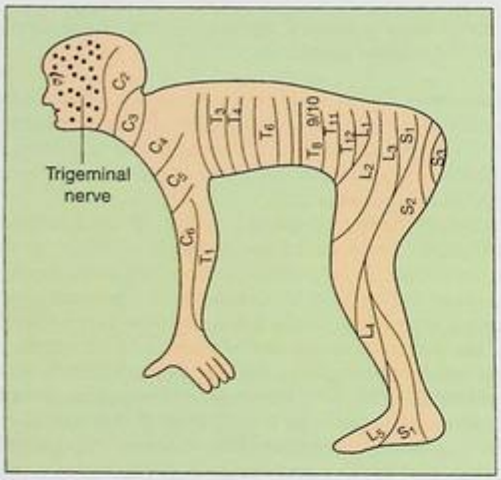


Figure 10.3-8 Dermatomes in man, visualized as a quadruped animal (like ancestors), to clarify the apparent complexity and to memorize the various dermatomes.

First-order neurons: These carry sensations of fine touch, tactile localization, two-point discrimination, vibration, pressure with intensity discrimination, and sense of position and proprioception. These fibres run in the spinal cord through *dorsal column* as fasciculus gracilis and fasciculus cuneatus (Fig. 10.3-9) to end in the *nucleus gracilis* and *nucleus cuneatus*, respectively. Many fibres of the dorsal columns, on their way up, terminate or relay in the dorsal grey horn.

Second-order neurons arise from the nucleus gracilis and nucleus cuneatus located in medulla oblongata. These decussate in the medulla as *internal arcuate fibres* and ascend up in the brainstem as medial lemniscus. The fibres of *medial lemnisci terminate* in the *ventroposterior lateral* (VPL) nucleus of thalamus.

Third-order neurons are from the VPL nucleus of thalamus. These ascend to the sensory cortex through the thalamic radiations.

Spatial Orientation of Nerve Fibres in Dorsal Column In the dorsal column, fibres coming from lower parts of the body are in the centre, whereas those coming from progressively higher segmental level form successive layers laterally.

Anterolateral Sensory Pathway

First-order neurons of anterolateral pathway carries sensations of pain, temperature and crude touch, and finally terminate on the *nucleus proprius* of the spinal cord.

Second-order neurons arise from the nucleus proprius and cross in the anterior commissure of the spinal cord to the opposite side in the anterior and lateral white columns in which they run upwards to the brain as anterior and lateral spinothalamic tracts, respectively.

Anterior spinothalamic tract mainly carries sensation of crude touch, tickle and itch, etc. Higher up in the brainstem, the anterior spinothalamic tract joins the medial lemniscus of thalamus.

Lateral spinothalamic tract consists of the fibres carrying pain and temperature sensation, and higher up in the brainstem, it is called the spinal lemniscus (Fig. 10.3-10).

Third-order neurons arise from thalamus and carry tactile signals to the somatic sensory area of the cortex along with the fibres of dorsal column.

Dorsolateral Column Sensory Pathway Dorsolateral column pathways carry proprioceptive impulses arising from the muscles and joint receptors of the lower part of the body to the

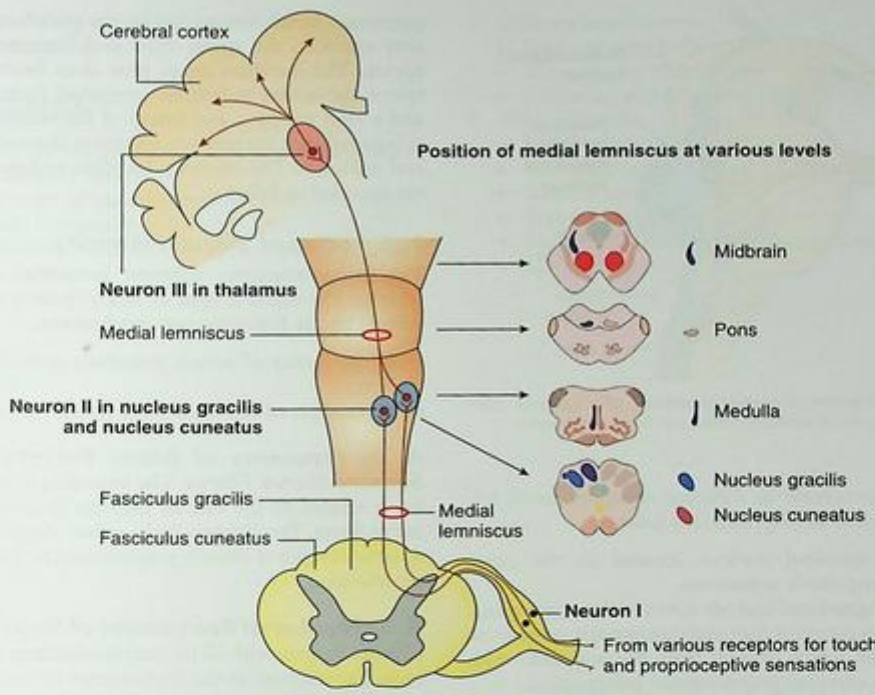


Figure 10.3-9 Dorsal column sensory pathways. Fibres carrying touch, pressure and proprioceptive sensations are arranged as fasciculus gracilis and fasciculus cuneatus in the dorsal column of spinal cord.

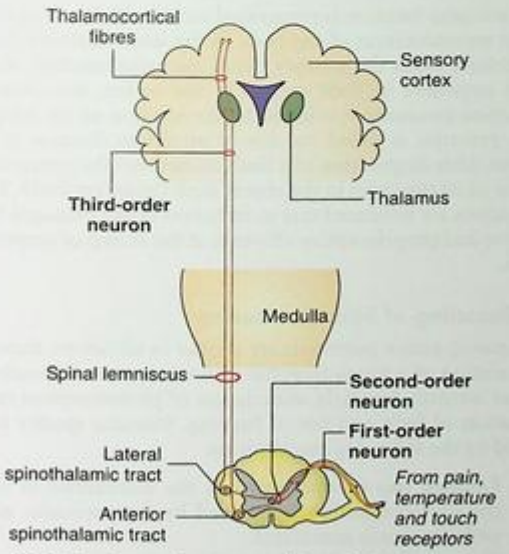


Figure 10.3-10 Course of anterior and lateral spinothalamic tracts.

cerebellum. Recent investigations have shown that touch may also reach the cerebellum through these pathways.

First-order neurons receive impulses from muscle spindles, Golgi tendon organs and other proprioceptive receptors. Some fibres are related to end organs concerned with exteroceptive sensations (touch and pressure).

Second-order neurons are located in the junctional area between the ventral and dorsal grey column (laminae V, VI and VII) in the lumbar and sacral segments of spinal cord. Their axons form the following:

- Ventral spinocerebellar tract
- Dorsal spinocerebellar tract

Pathway of Sensations from Face and Oral Cavity The sensations of touch, pain and temperature from the face and oral cavity, including teeth, and proprioceptive information from the jaw muscles are carried by trigeminal nerve.

First-order neurons are located in the *trigeminal ganglion*, which is equivalent to dorsal nerve root ganglia in the spinal cord. The peripheral processes of these neurons form three divisions of the trigeminal nerve: ophthalmic, maxillary and mandibular, which innervate different areas of the facial skin (Fig. 10.3-11). The central processes of these neurons of

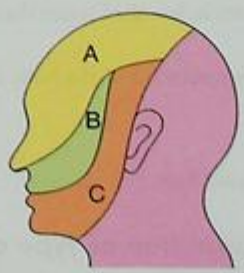


Figure 10.3-11 The areas of face innervated by three divisions of the trigeminal nerve: (A) ophthalmic; (B) maxillary; and (C) mandibular.

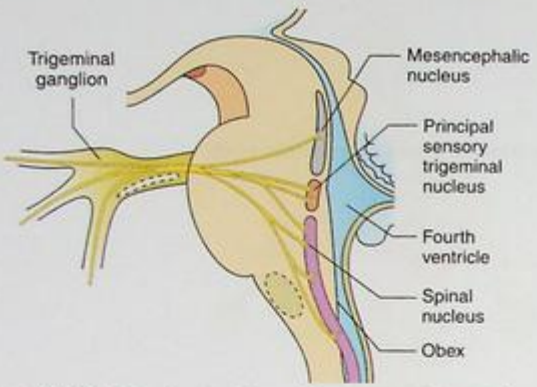


Figure 10.3-12 Termination of central processes of trigeminal ganglion in three components of sensory nucleus of trigeminal nerve.

trigeminal ganglia terminate in different components of trigeminal sensory nucleus as (Fig. 10.3-12) follows:

Principal sensory trigeminal nucleus, located in the pons, receives fibres carrying *tactile* sensations.
Spinal nucleus is elongated and extends down to the upper spinal cord. It receives fibres carrying *pain* and *temperature* sensations.
Mesencephalic nucleus, which extends from the pons into midbrain, receives fibres carrying *proprioceptive* information.

Second-order neurons: Axons of these neurons cross to the opposite side and ascend as *trigeminal lemniscus* to the ventroposterior medial (VPM) nucleus of thalamus.
Third-order neurons are located in the VPM nucleus of thalamus. All the sensations reaching this nucleus are carried primarily to the sensory area of cerebral cortex by fibres passing through the posterior limb of internal capsule (*superior thalamic radiations*).

Role of Thalamus in Somatosensory System

Ventral posterior nucleus of thalamus is concerned with the somatosensory system. It has the following two divisions:

- Ventral posterior lateral (VPL) nucleus
- Ventral posterior medial (VPM) nucleus

For more details, see page 395.

Somatic Sensory Cortex

Somatic sensory cortex is described under the following headings:

- Areas
- Topographical organization of the body in somatic sensory cortex
- Connections
- Functions

For more details, see page 390.

Encoding: Recognition of Type of Sensation

As discussed above, the sensory receptors transduce all forms of sensory stimuli into a common type of neural signal, i.e. action potentials, which are carried by the peripheral nerves and sensory tracts in the spinal cord and brainstem to the sensory cortex. The question arises how does brain differentiate between the action potentials generated from a touch receptor and a pain receptor, and interpret the sensation accordingly. It is believed that the sensory receptors themselves act as peripheral analysers. The intensity, location and quality of a stimulus are encoded as follows:

1. Encoding of Stimulus Intensity

The brain interprets different intensities of sensation (i.e. whether the touch is light or heavy; pain is mild, moderate or severe) by the following two mechanisms:

- By frequency of action potentials generated in the sensory fibres
- By number of recruitment of sensory units

A. By Frequency of Action Potential Generated in Sensory Nerve Fibres The encoding of intensity of stimulus is related to the rate of impulse discharge in the sensory nerve fibres. The *'Weber–Fechner law' states that the magnitude of sensation felt is directly proportional to the log of intensity of the stimulus.*

B. By Number of Recruitment of Sensory Units A single afferent neuron with all its receptor endings makes up a *sensory unit*. The increase in the recruitment of sensory units is interpreted as increase in the intensity of the stimulus.

2. Encoding of Stimulus Location

The stimulus location is recognized accurately due to point-to-point representation of the body in the somatosensory cortex. Therefore, when the sensory fibres are experimentally stimulated anywhere in their course to the cortex, the conscious sensation produced is referred to the location of the receptor. This principle is called the *law of projection*. Because of this reason, after amputation of a limb, sometimes the patient complains of intense pain in the absent limb (*phantom limb*). These sensations are produced due to irritation of the damaged nociceptive and proprioceptive afferents at the stump of amputated limb.

3. Encoding of Stimulus Quality

In general, action potentials are similar in all nerves, then why stimulation of a touch receptor causes sensation of touch and not of warmth. Similarly, stimulation of photoreceptors causes sensation of light and not of hearing. Stimulus quality is encoded by the following mechanisms:

(i) ***Labelled line mechanism:*** It is the mechanism in which the stimulus quality is encoded by the particular neural pathway that is stimulated.
The specificity of sensory pathway from the receptors to the sensory cortex has been called the *Muller's doctrine of specific nerve energies.*
(ii) ***Pattern of activity within the neural pathway*** that is carrying information to the brain is used to encode stimulus quality.
(iii) ***Feature detectors*** are used in the most sophisticated mechanism of sensory coding. Feature detectors are neurons within the brain that integrate information from a

variety of sensory fibres and fire to indicate the presence of a complex stimulus.

SELF-ASSESSMENT

1. Define sensation, classify sensations and give an account of components of sensory system.
2. Give a brief account of classification of sensory receptors. How does sensory transduction occur?
3. Define pain sensation, its receptors, types of pain and how it is perceived.
4. Differentiate between:
   - Fast and slow pain
   - Somatic and visceral pain
   - Radiating and projected pain
5. Write notes on:
   - Referred pain
   - Pain suppression system
   - Neutral zone
   - Weber's Fechner law
   - Muller's doctrine of specific nerve energies
   - Law of projection

10.4 Somatic Motor System

CHAPTER OUTLINE

Introduction

Components of Somatic Motor Control System
Highest Level of Motor Control
Middle Level of Motor Control
Lowest Level of Motor Control

Skeletal Muscles: The Effector Organ of Somatic Motor System
Motor Unit
Muscle Sensors
Muscle Tone

Reflex Activity
General Considerations
Reflex Arc
Classification of Reflexes
Spinal Cord Reflexes
Stretch Reflex
Golgi Tendon Reflex
Withdrawal Reflex
Clinical Reflexes
Physiological Reflexes
Pathological Reflexes

Regulation of Posture
Mechanisms Involved in Maintenance of Posture
Muscle Tone
Postural Reflexes
Role of Different Regions of Nervous System in Maintenance of Posture
Role of Spinal Cord
Role of Brainstem
Role of Midbrain
Role of Cerebellum
Role of Basal Ganglia
Mechanism of Standing in Man

Vestibular Apparatus and Equilibrium
Functional Anatomy
Vestibular Receptors
Mechanism of Functioning of Vestibular Apparatus
Vestibular Pathways
Vestibular Reflexes
Functions of Vestibular Apparatus
Applied Aspects

INTRODUCTION

The execution, planning, coordination and adjustments of the movements of the body are under the influence of different parts of the nervous system, which together constitute the somatic motor system, which is organized as a three-tier system consisting of a highest level of motor control, middle level of motor control and lowest level of motor control (Fig. 10.4-1).

1. ***Highest level of motor control*** involves activities of various areas of cerebral cortex. It is mainly concerned with the generation of the idea of voluntary movements (motor plan) and issuing the motor commands for their execution.
2. ***Middle level of motor control*** involves activities of various subcortical centres such as basal ganglia, some brainstem nuclei and cerebellum. The middle level of motor control is concerned with developing and perfecting each motor programme and subprogramme for bringing out a motor act. It also supervises the implementation of motor programme.
3. ***Lowest level of motor control*** is exerted by cranial nerve nuclei in the brainstem and spinal cord. The spinal cord contains the final common pathway through which a movement is executed.

Feedback signals to the central nervous system (CNS) from the proprioceptors in muscles, joints, skin and other sensory receptors are used to adjust the motor commands during somatic motor activity.

In view of the above background, the somatic motor control system is discussed in detail under the following headings:

- Components of somatic motor control system
- Skeletal muscles: the effector organ of somatic motor system
- Reflexes
- Regulation of posture and equilibrium

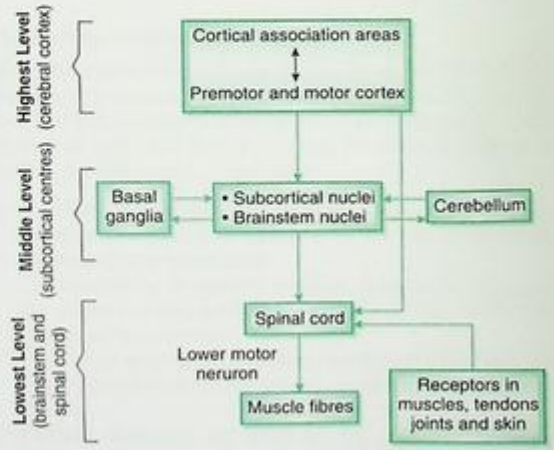


Figure 10.4-1 Integration of the highest, middle and lowest levels of somatic motor control system.

COMPONENTS OF SOMATIC MOTOR CONTROL SYSTEM

I. Highest Level of Motor Control

Motor Cortex

Areas of motor cortex include (Fig. 10.1-2) the following:

- *Primary motor cortex* (Brodmann's area 4)
- *Premotor cortex*, which includes Brodmann's areas 6, 8, 44 and 45
- *Supplementary motor cortex*

Note: For more details on motor cortex, see page 389.

Functional Role of Motor Cortex in Control of Voluntary Movements

Supplementary motor cortex is responsible for generating the idea for a movement. Then, it plans the movements. Lateral cerebellum and basal ganglia are also involved in the planning and programming of movements.

Primary motor cortex is responsible for the execution of movement.

Premotor cortex coordinates the voluntary activity.

Plasticity property of motor cortex: The motor system 'learns by doing', and performance improves with repetition. This involves synaptic plasticity. The motor cortex shows plasticity. This has been confirmed by PET and functional MRI (fMRI) in intact experimental animals and humans.

Descending Motor Pathways from Motor Cortex

A. *Pyramidal tracts* include the tracts which are constituted by the axons that transmit motor signals directly from the cortex to spinal cord (corticospinal tracts) and cranial nerve nucleus (corticobulbar tracts). Corticospinal fibres are divided into the following two tracts (Fig. 10.1-23, see page 405):

Lateral corticospinal tract is constituted by 80% of fibres, which cross the midline in the medullary pyramids. These fibres are responsible for making skilled precision movements (e.g. the muscles that move the fingers and hands, and the muscles that produce speech) (*lateral motor system*).

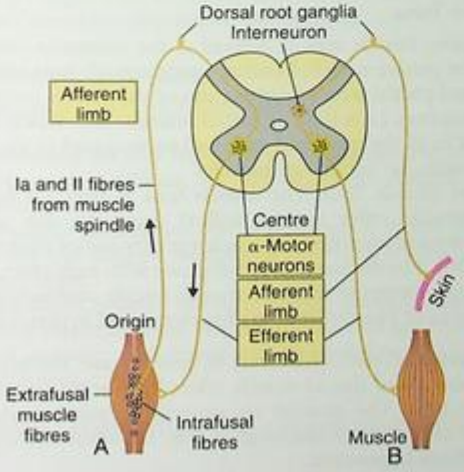


Figure 10.4-2 (A) Components of reflex arc in a monosynaptic and (B) disynaptic reflex.

Anterior corticospinal tract is formed by 20% uncrossed fibres, which descend ipsilaterally in the ventral white column of the spinal cord. This pathway controls the axial (trunk muscles) and proximal limb muscles that are concerned with posture and equilibrium (*medial motor system*).

B. ***Extrapyramidal tracts:*** Extrapyramidal pathways are chiefly concerned with regulation of muscle tone, and posture and equilibrium.

II. Middle Level of Motor Control

The middle level of motor control specifies the postures and movements necessary to carry out the desired acts. It involves activities of basal ganglia, cerebellum and brainstem.

A. Basal Ganglia

Physiologically, basal ganglia include corpus striatum (caudate nucleus and lenticular nucleus having two parts, e.g. putamen and globus pallidus), subthalamic nucleus and substantia nigra (see page 391).

Role of Basal Ganglia in Somatic Motor Activity

- Cognitive control of motor activity is executed by the basal ganglia.
- It performs timing and scaling of the intensity of the movements.
- It performs subconscious execution of some movements.
- It controls reflex muscular activity.
- It controls muscle tone.

Note: For more details on basal ganglia, see page 393.

B. Cerebellum

Functionally, the cerebellum has been divided into three divisions, vestibulocerebellum, spinocerebellum and corticocerebellum, which play an important role in different motor activities.

1. Control of Voluntary Movements Corticocerebellum, also called cerebral cerebellum, is intimately associated with control of timing, rate, range (extent), duration, direction and strength of a movement. Corticocerebellum performs this function by the following actions:

(i) ***Comparator function:*** The cerebellum receives inputs from the command neurons about the sequential intended plan of movements for the next fraction of second. It also gets feedback (afferents) from the proprioceptive endings of muscles, tendons and joints about what actual movements result. All this information is integrated and the corrective signals are sent to the motor cortex. This happens through the closed feedback loop.

(ii) ***Damping action:*** Corticocerebellum sends impulses to the cerebral cortex to discharge appropriate signals to the muscles so that any extra or exaggeration of muscular activity does not occur, and thus overshooting is prevented.

(iii) ***Timing and programming of the skilled movements*** is done by the corticocerebellum feedback loop, which modulates the motor command of pyramidal tracts through two-way communication.

(iv) ***Servomechanism:*** Cerebellum allows the cerebral cortex to discharge the signals which are already programmed and stored at the sensory motor cortex, and does not influence

much. However, if there is any disturbance or interference, the corticocerebellum immediately influences the cerebral cortex and corrects the movements. This action of corticocerebellum is known as servomechanism.

2. Control of Body Posture and Equilibrium is done by vestibulocerebellum (see page 432).
3. Control of Muscle Tone and Stretch Reflex is the function of spinocerebellum (see page 436).

Note: For more details about cerebellum, see page 399.

C. Brainstem

Reticular formation and vestibular nuclei are important components of the motor control system present in the brainstem.

Reticular Formation The *motor control centres* within the reticular formation are a relay station for all descending motor commands, except those requiring the greatest precision, which are transferred directly from the cortex to spinal cord.

Vestibular Nuclei Vestibular nuclei, located within the brainstem and cerebellum, receive information from *vestibular receptors* via vestibular nerve fibres (VIIIth cranial nerve). Vestibular system reflexes perform the following activities:

- Maintain tone in antigravity muscles
- Coordinate the adjustments made by the limbs and trunk to maintain balance
- Adjust the position of the eyes to maintain visual fixation when the position of head changes

III. Lowest Level of Motor Control

The lowest level of motor control is exerted by motor nuclei of cranial nerves and spinal cord. The spinal cord contains the *final common pathway* through which a movement is executed.

Spinal Cord

Motor Neurons

Motor neurons of spinal cord present in the ventral horn are as follows:

1. Alpha Motor Neurons (α-motor Neurons) These are the largest neurons. These are responsible for contraction of muscles in upper limbs, trunk and lower part of the body.
2. Gamma Motor Neurons (γ-motor Neurons) These neurons innervate the intrafusal fibres of the muscle spindles and are responsible for maintenance of muscle tone.
3. Interneurons The interneurons actually receive the bulk of synaptic input that reaches the spinal cord, either as incoming sensory information or signals descending from higher centres in the brain.
4. Renshaw Cells are interneurons that receive input from collateral branches of the axons of α-motor neurons. Their axons carry the impulses back to the cell bodies of the same α-motor neurons. These are inhibitory neurons, which play an important role in synaptic inhibition at the spinal cord.

Motor Functions Motor functions served by the spinal cord are as follows:

- Control of movement of muscles and joints
- Control of tone and power of muscles
- Control of deep (tendon) reflexes
- Control of superficial reflexes

SKELETAL MUSCLES: THE EFFECTOR ORGAN OF SOMATIC MOTOR SYSTEM

The motor activity, be it in the form of walking, physical labour, skilled work like typing, performing surgical operations or even expression of thoughts and feelings through gesture or speech, is a result of highly coordinated movements produced by the skeletal muscles. The skeletal muscles thus form the effector organ of the somatic motor system. The physiology of skeletal muscle has been discussed in Chapter 2.3. However, certain aspects which need elaboration of skeletal muscle as an effector organ and are relevant to complete the study of somatic motor system are as follows:

- Motor unit
- Muscle sensors (proprioceptors)
- Muscle tone

Motor Unit

The motor unit is the functional module used by the motor control system to carry out a movement. The movement produced by a skeletal muscle basically depends on the pattern and ratio of discharge of motor neurons supplying the muscle. A *motor unit consists* of a single motor neuron and the muscle fibres that it innervates (see page 47).

Muscle Sensors

Muscle sensors refer to the proprioceptors present in the muscles, tendons of muscles, joints, ligaments and fasciae. Proprioceptors are the receptors which give information about the change in position of different parts of the body in space, especially joints or tension of muscles at any given moment. The muscle sensors are as follows:

- Muscle spindle
- Golgi tendon organ
- Pacinian corpuscle
- Free nerve endings

In addition to the above proprioceptors, the labyrinth also contains proprioceptors.

Muscle Tone

Definition Muscle tone is defined as the resistance offered to active or passive stretch. In other words, muscle tone refers to a sustained partial state of contraction of the muscle under resting condition, i.e. a state of partial tetanus. The muscle tone is present in all the muscles, but is well pronounced in the extensor muscles, i.e. antigravity muscles.

Basis of Muscle Tone The muscle tone is purely a function of myotactic reflex (stretch reflex) occurring due to low-frequency and asynchronous discharge of γ-motor neurons (see page 430). The discharge is out of phase with each other, which ultimately merges to produce smooth muscle contraction.

Anomalies of Muscle Tone are hypotonia and hypertonia.

1. ***Hypotonia*** refers to decrease in muscle tone. The hypotonic or also called flaccid muscle offers little or no resistance to stretching. The muscles are generally hypotonic when the rate of γ-efferent discharge is low, i.e. when stretch reflex becomes hypoactive.
2. ***Hypertonia*** refers to increase in muscle tone. The hypertonic or spastic muscle offers high resistance to stretch. The muscles

are generally hypertonic when the rate of γ-efferent discharge is high, i.e. when stretch reflex becomes hyperactive. Hypertonia is of the following two types:

- *Spasticity* refers to hypertonia which is confined to only one group of muscles. For example, lesions of internal capsule and upper motor neuron lesions produce spasticity.
- *Rigidity* refers to hypertonia which involves both groups of muscles, i.e. extensor as well as flexors equally. For example, lesions of basal ganglia produce rigidity.

REFLEX ACTIVITY

General Considerations

A reflex is an involuntary response to a peripheral nervous stimulation. In other words, it is a mechanism by which sensory impulse is automatically converted into a motor effect through the involvement of CNS. It is a type of protective mechanism which tries to protect the body from irreparable damage.

Reflex Arc

The pathway for a reflex activity is called the reflex arc. It consists of (Fig. 10.4-2) the following:

- Afferent limb
- Centre
- Efferent limb

1. *Afferent Limb* of each reflex arc consists of a receptor and an afferent or sensory nerve.

2. *Centre* This is the part of CNS (spinal cord or brain) where the afferent limb ends and either synapses directly with efferent motor neuron or establishes connection with the efferent neuron via interneurons (internuncial or intercalated neurons).

3. *Efferent Limb* of a reflex arc consists of the following:

- *Efferent nerve* transmits motor impulses from the centre to the effector organ.
- *Effector organ* may be in the form of a muscle or a gland which shows the response to the stimulus.

Classification of Reflexes

Reflexes can be classified in different ways.

I. Depending on the Number of Synapses *(Fig. 10.4-2)*

1. ***Monosynaptic reflexes***, e.g. stretch reflexes (biceps, triceps or knee jerk)
2. ***Disynaptic reflexes***, i.e. one interneuron is placed between afferent and efferent neurons of the reflex arc, e.g. inverse stretch reflex
3. ***Polysynaptic reflexes***, characterized by more than one interneuron placed between afferent and efferent neurons of the reflex arc, e.g. withdrawal reflex, cross-flexor reflex and cross-extensor reflex.

II. Clinical Classification Clinically, reflexes are classified as follows:

- Superficial
- Deep
- Visceral
- Pathological reflexes

Spinal Cord Reflexes

Spinal cord reflexes, according to the receptors from which they originate the spinal cord reflexes, can be categorized into muscle reflexes and cutaneous reflexes.

Muscle reflexes: Two important reflexes which originate in muscles are as follows:

- Stretch reflex
- Lengthening reaction or Golgi tendon reflex

Cutaneous reflexes: The most important of the cutaneous reflexes is the following:

- Withdrawal (flexor, pain) reflex

1. Stretch Reflex

Stretch reflex, also known as myotactic reflex, refers to reflex contraction of a muscle that is stretched. It is the best-known monosynaptic reflex in the body. *Stimulus* that evokes the reflex response is 'stretch' to the muscle. *Stretch reflex is well developed* in antigravity muscles such as an extensor group of muscles of legs and flexor groups of muscles of arm. *Examples of stretch* reflexes include knee jerk, ankle jerk, biceps jerk and triceps jerk (see page 433).

Reflex Arc of Stretch Reflex (Fig. 10.4-2)

1. Afferent Limb Afferent limb consists of a receptor muscle spindle and an afferent nerve.

Structure of muscle spindle (Fig. 10.4-3): Each muscle spindle consists of 3–10 small muscle fibres (called intrafusal muscle fibres) encapsulated in a thin connective tissue capsule containing fluid. The muscle spindles are present in between and parallel to the extrafusal fibres. Either end of the muscle spindle is attached to the endomysium of the extrafusal muscle fibres.

Intrafusal muscle fibres consist of a central noncontractile portion and are devoid of striations. The central part of each intrafusal fibre is the sensory portion. Intrafusal fibres are of the following two types:

- *Nuclear bag fibres*
- *Nuclear chain fibres*

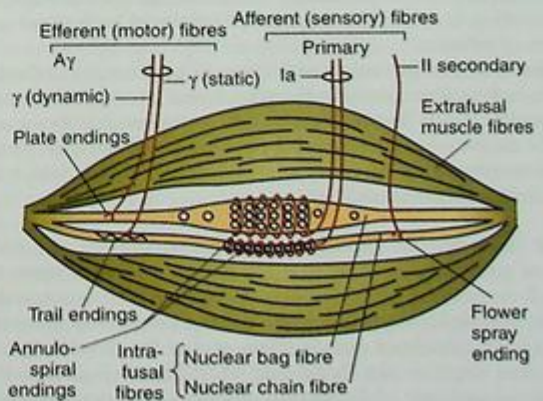


Figure 10.4-3 Structure of a muscle spindle.

Nerve Supply of the Muscle Spindle The muscle spindle is innervated by both sensory and motor nerve fibres.

(i) *Sensory Nerve Supply* The following are the two types of sensory fibres:

Group Ia fibres, also known as primary sensory endings, supplying central receptor portions of both nuclear bags as well as nuclear chain fibres. The primary endings are stimulated when the muscle spindle is stretched.

Type II fibres, also known as secondary sensory endings, innervate the receptor portion of mainly nuclear chain fibres. These nerve endings respond mainly to sustained stretch, therefore measuring the muscle length.

(ii) *Motor Supply* The efferent fibres to the muscle spindle are called *gamma fibres* because their axons belong to the Aγ group of fibres. The following are the two types of gamma fibres:

- ***Dynamic gamma fibres*** primarily innervate the striated poles of nuclear bag fibres. These fibres increase the sensitivity of the Ia afferent fibres to stretch.
- ***Static gamma fibres*** primarily innervate the striated poles of nuclear chain fibres. They increase the tonic activity in the Ia afferent fibres at any given muscle length.
- ***Afferent nerve***: The afferent nerve fibres emerging from the muscle spindle travel along the spinal nerve, enter the spinal cord through the dorsal root and send branches to every α-motor neuron that goes to the muscle from which the Ia originated.

2. Centre Centre for stretch reflex is the ventral grey horn area where the afferent nerve ends and synapses directly with the α-motor neuron.

3. Efferent Limb Consists of the following:

- ***Efferent nerve***: The axons of α-motor neurons form the efferent nerve fibres, which leave the spinal cord through the ventral root and supply the skeletal muscle fibres.
- ***Effector organs***: Both extensor and flexor muscles exhibit stretch reflexes.

Reciprocal Innervation in Stretch Reflex The stretch reflex is characterized by reciprocal innervation, i.e. excitation of one group of muscles is associated with inhibition of the antagonistic group of muscles on the same side, allowing the agonistic muscles to contract without interference. Reciprocal innervation is one of the important features of both flexor and extensor reflexes.

Pathway of Reciprocal Innervation is biphasic. A collateral from each Ia fibre passes in the spinal cord to an inhibitory interneuron (Golgi bottle neuron) that synapses directly on one of the motor neurons supplying the antagonist muscles. Reciprocal innervation is very important in spinal reflexes, which are involved in locomotion.

Role of γ-Motor Neurons As discussed above, the firing rate of primary nerve endings (Ia fibres) increases when the muscle is stretched (Fig. 10.4-4B), and causes reflex contraction of the muscle by increased α-motor neuron activity. Contraction of the extrafusal muscle fibres makes the muscle spindle slack and decrease the firing rate of Ia fibres (Fig. 10.4-4C). The decreased rate of Ia afferent discharge that occurs during muscle contraction is called *unloading of muscle spindle* and is

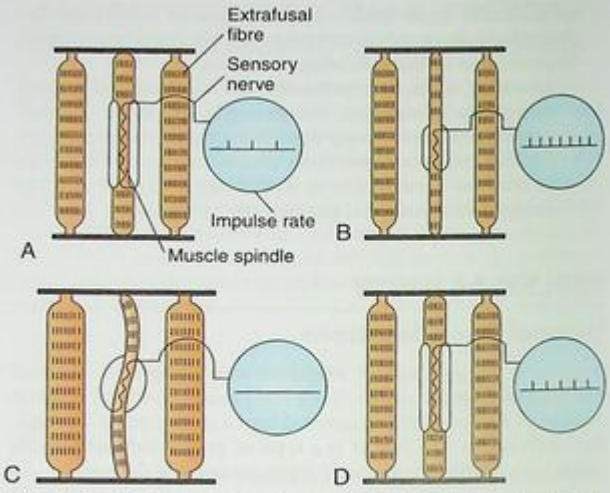


Figure 10.4-4 Firing rate of primary nerve endings (Ia) under different conditions: (A) muscle at rest; (B) muscle stretched; (C) muscle contracted; and (D) muscle contracted with increased gamma (γ) efferent discharge.

functionally disadvantageous because the CNS stops receiving information about the rate and extent of muscle shortening. However, by the activity of γ-motor neurons, this unloading is prevented (Fig. 10.4-4D). The γ-motor neurons cause the striated poles of intrafusal fibres of muscle spindle to shorten along with shortening of extrafusal fibres during muscle contraction. As a result of contraction of the striated polar regions of intrafusal fibres, the central receptor region of the intrafusal fibres remains stretched during muscle contraction, and unloading does not occur. In this way, the γ-motor neuron activity adjusts the sensitivity of the muscle spindle so that it will respond appropriately during muscle contraction as well. Furthermore, the γ-motor neurons control both dynamic and static activities of muscle spindle.

Higher Control of Stretch Reflex Although the stretch reflex is a spinal reflex, the activity in the reflex arc can be modified (inhibited or facilitated) by higher centres through their influence on the nerve fibres involved in stretch reflex.

Some of the important brain areas that facilitate or inhibit the stretch reflex are (Fig. 10.4.5) as follows:

- ***Facilitatory reticular formation*** is a large area in the brainstem which discharges spontaneously in response to afferent input. This increases discharge of γ-motor neurons, and stretch reflex becomes hyperactive.
- ***Inhibitory reticular formation*** is a small area which does not discharge spontaneously. It acts by inhibiting γ-efferent neuron discharge, thereby decreasing the spindle sensitivity.
- ***Cerebral motor cortex and cerebellum*** reflexly inhibits the stretch reflex by stimulating the inhibitory reticular formation.

Other Factors which Influence γ-efferent Discharge are as follows:

- ***Anxiety*** causes an increased discharge, a fact that probably explains the hyperactive tendon reflexes sometimes seen in anxious patients.

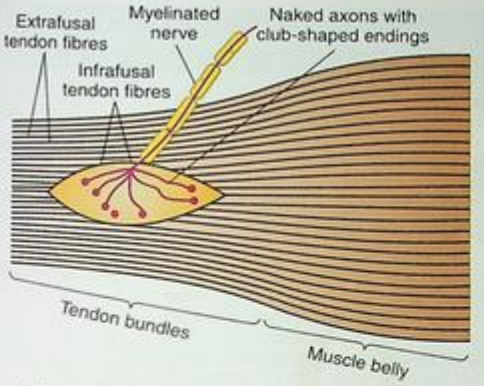


Figure 10.4-5 Structure of Golgi tendon organ.

- ***Stimulation of skin***, especially by noxious agents, increases γ-efferent discharge. This fact is sometimes used as reinforcement to elicit deep tendon reflexes (such as knee jerk), which are not being elicited otherwise. For it, the individual is asked to pull the hands apart when the flexed fingers are hooked together; this facilitates the knee jerk (*Jendrassik's* manoeuvre). It is contributed to increased γ-efferent discharge initiated by afferent impulses from the hands.

Functions of Stretch Reflex

- Role in maintaining muscle tone
- Role in maintaining posture
- Role in control of voluntary movement

2. Golgi Tendon Reflex (Disynaptic Reflex)

The Golgi tendon reflex, also called 'inverse stretch reflex', is a disynaptic reflex. The receptors involved are the Golgi tendon organs.

Golgi Tendon Organs Golgi tendon organs (Fig. 10.4-5) are high-threshold stretch receptors located in the tendons and musculoaponeurotic junction. They are placed in series between the muscle fibres and the tendon, and are thus stretched whenever the muscle contracts.

The Golgi tendon organs are supplied by *Ib type sensory nerve fibres.*

Pathway and Activity of Reflex (Fig. 10.4-6)

- When a muscle contracts, the muscle tension increases. The Golgi tendon organ detects the muscle tension and sends impulses through afferent (group Ib) fibres, which enter the spinal cord through the dorsal root.
- In the spinal cord, the group Ib afferents stimulate the inhibitory interneurons.
- The inhibitory interneurons, in turn, release inhibitory mediator glycine, which inhibits α-motor neurons and causes relaxation of the muscle that was originally contracted.
- At the same time, due to reciprocal innervation, the antagonistic muscles are excited.

Physiological role or the functions of Golgi tendon reflex have been described as a protective reflex in which a strong and potentially damaging muscle force reflexively inhibits the muscle,

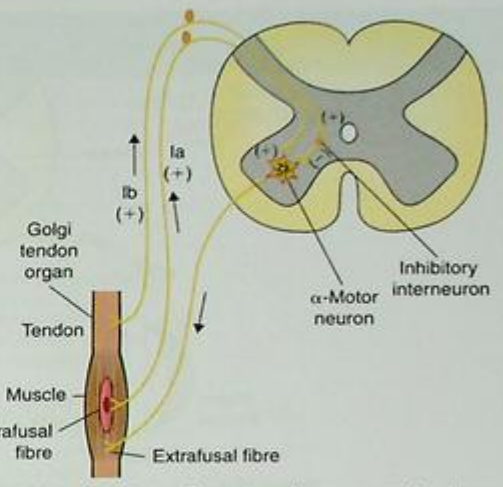


Figure 10.4-6 Pathway of stretch and inverse stretch reflexes.

causing the muscle to lengthen instead of trying to maintain the force and risking damage.

- It regulates tension during normal muscle activity.

Clasp–knife reflex refers to an exaggerated form of the Golgi tendon reflex, which can occur with disease of the corticospinal tracts (hypertonicity or spasticity). For example, when the arm is hypertonic, the increased sensitivity of the muscle spindles in the extensor muscles (triceps) causes resistance to flexion of the arm. Eventually, tension in the triceps increases to the point at which it activates Golgi tendon reflex, causing triceps to relax and the arm to flex closed like a jack knife, hence the name clasp–knife reflex. The physiological name for it is *lengthening reaction* because it is the response of a spastic muscle to lengthening.

3. Withdrawal Reflex (Polysynaptic Reflex)

Definition and Receptors

Definition Withdrawal reflex, also known as flexor reflex, is a cutaneous reflex which occurs in response to nociceptive (pain) stimuli and is characterized by removal of a body part from painful stimulus.

Receptors for withdrawal reflex are *nociceptors* located in free nerve endings of Aδ and C fibres.

Pathway (Reflex Arc) of Withdrawal Reflex *(Fig. 10.4-7)*

- The pain fibres carrying impulses, upon entering the spinal cord, synapse on many interneurons. Some of these also convey information to CNS. Others several reflex pathways are given below:
- Some of the interneurons project onto α-motor neurons on the ipsilateral side and stimulate the flexors, which withdraw the limbs.
- Some of the interneurons form an inhibitory pathway and terminate on α-motor neurons supplying the extensor muscles on the ipsilateral side, producing their relaxation.
- Some of the interneurons cross to the opposite side of spinal cord and end on the α-motor neurons supplying the extensors on contralateral side. In the case of need, this pathway produces extension of the opposite limbs (crossed extensor reflex).

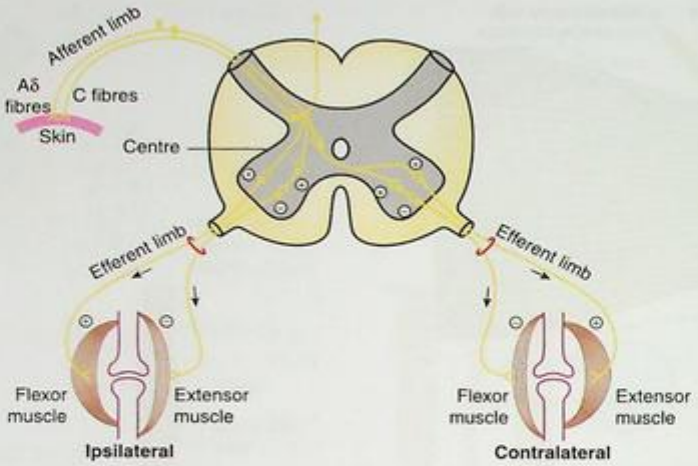


Figure 10.4-7 Reflex arc of a polysynaptic reflex (withdrawal reflex or crossed extensor reflex).

Effector Organs The effector organs of the withdrawal reflex are the skeletal muscles that cause withdrawal of the limb.

Response in Withdrawal Reflex The reflex response to a painful stimulus varies from just withdrawal of the affected part to withdrawal of the whole body depending on the strength of painful stimulus and location of the stimulus.

Crossed Extensor Reflex Response (two-limb response): When a strong stimulus is applied to a limb, the response includes not only flexion and withdrawal of the limb but also extension of the opposite limb. This crossed extensor response is produced by the interneuronal pathway, which crosses to the opposite side of spinal cord. In lower limbs, crossed extensor reflex allows one limb to support the body, while the other is raised off the ground.

Clinical Reflexes

Clinically, the reflexes can be grouped as follows:

I. Physiological Reflexes

1. Superficial Reflexes These reflexes are initiated in response to stimulation of receptors on skin (cutaneous reflexes, e.g. plantar, abdominal, cremasteric, bulbocavernous) or mucous membranes (mucous membrane reflexes), e.g. corneal, conjunctival and palatal reflex. The superficial reflexes are summarized in Table 10.4-1.

2. Deep Reflexes These reflexes are basically stretch reflexes and are elicited on stroking a tendon, so called tendon reflexes (e.g. knee jerk, ankle jerk); the stretch reflex has been described in detail on page 433; however, the various clinically known stretch reflexes are summarized in Table 10.4-1.

3. Visceral Reflexes are elicited from the visceral organ, or at least one part of the reflex arc is formed by the autonomic nerve, e.g. carotid sinus reflex (see page 155) and micturition reflex (see page 249). A few of clinically known visceral reflexes are summarized in Table 10.4-1.

II. Pathological Reflexes The pathological reflexes are abnormal reflexes which are not found normally. They are elicited in pathological conditions, e.g. Babinski sign, mass reflex, clonus and pendular movements.

REGULATION OF POSTURE

Physiologically, posture refers to subconscious adjustment of tone in different muscles so as to maintain balance during displacement of the body caused by gravity or acceleration.

For the purpose of understanding, the regulation of posture can be discussed under the following two main headings:

- Mechanisms involved in maintenance of posture
- Role of different regions of nervous system in maintenance of posture

Mechanisms Involved in Maintenance of Posture

The two main mechanisms involved in the maintenance of posture are as follows:

- Muscle tone
- Postural reflexes

Role of Tone in Antigravity Muscles in Maintenance of Posture

Largely, the posture is maintained through reflex adjustments of tone in the antigravity muscles. The basic postural reflex involved in the control of muscle tone is stretch reflex, which is described in detail.

Posture control is required not only for holding the body in an erect position but also for fixation of the body parts over adjoining body segments. The centre of gravity of head passes in front of the atlanto-occipital joint. Thus, the head has always got a tendency to roll forwards. To hold the head in an erect position, cervico-occipital muscles are to be maintained in a state of constant tension.

In the upright position, gravity tends to displace the body downwards, stretching quadriceps muscles as the legs flex at the

TABLE 10.4-1 Characteristic Features of Clinical Reflexes

Reflex	Method to Elicit	Response	Spinal Segment/Cranial Nerve and Centre Involved
I. Superficial reflexes			
(a) Cutaneous reflexes			
1. Plantar reflex	Strike the outer aspect of the sole of the foot with a blunt object (e.g. key) and move towards the ball of small toes	Plantar flexion of the foot and toes	L_5–S_1
2. Abdominal reflex	Lightly stimulate the wall of abdomen by stroking with key or some blunt object from out to inside (parallel to costal margin) in upper quadrants and (parallel to inguinal ligament) in lower quadrants of the abdomen	Contractions of the underlying abdominal muscle ***Note:*** The reflex is difficult to elicit in elderly individuals, obese persons and in multipara	T_7–T_{12}
3. Cremasteric reflex	Stimulate the skin of upper and inner part of the thigh	Pulling upwards of scrotum and testicles due to contraction of cremasteric muscles; this reflex may not be elicited in elderly individuals	L_1 and L_2
4. Scapular reflex	Stroke the skin of interscapular region	Contraction of supra- and infraspinatus muscles	C_5–T_1
5. Anal reflex	Gently stimulate the skin of perianal region	Contraction of external and internal anal sphincters	S_2–S_4
6. Bulbocavernous reflex	Gently pinch the dorsum of glans penis	Contraction of bulbocavernous muscle	S_3–S_4
(b) Mucous membrane reflexes			
7. Corneal reflex	Touch the cornea with wisp of cotton from lateral aspect	Closure of eye of same and of opposite side	*Afferents:* Via ophthalmic division of the Vth (trigeminal) cranial nerve *Centre:* In the pons *Efferents:* Via facial nerve to orbicularis oculi muscle
8. Conjunctival reflex	Touch the conjunctiva with wisp of cotton	Closure of the eyes	Pathway is the same as for corneal reflex
9. Palate reflex	Touch on the either side of posterior pharyngeal wall with a swab stick	The contraction of the palate	*Afferents:* IXth cranial nerve *Centre:* Nucleus ambiguous *Efferents:* Xth cranial (vagus) nerve
II. Deep reflexes (tendon reflexes)			
1. Knee jerk	The subject is in lying or in sitting position; place the left hand under the knee (to be tested); tap the tendon of the quadriceps midway between its origin and insertion with knee hammer	Observe the extension of knee due to contraction of quadriceps femoris muscle; sometimes if unable to elicit then apply reinforcement. (Jendrassik's manoeuvre, page 431)	Femoral nerve (L_2–L_4)
2. Ankle jerk	With foot slightly everted and dorsiflexed, strike on the tendo-Achilles	Plantar flexion of the foot occurs due to contraction of calf muscle	S_1 and S_2
3. Triceps jerk	Keep the forearm of the subject to rest across his chest; then tap the triceps tendon with broader side of the patellar hammer	Contraction of triceps with extension of the elbow	C_6 and C_7
4. Biceps jerk	Keep the position of elbow at right angle with forearm and the forearm is semipronated; examiner places his thumb or index finger on the tendon of the biceps muscle and strikes on the finger (kept on biceps tendon) with patellar hammer	Contraction of biceps with flexion of elbow	C_5 and C_6
5. Supinator	Tap the lower end of the radius at the styloid process, keeping the position of elbow the same as for biceps jerk	Supination of forearm and flexion of elbow	C_5 and C_6
6. Jaw jerk	Ask the subject to open the mouth slightly; then place one finger firmly below the lower lip and tap on the finger in the downward direction	Contraction of masseter muscle causes closure of the jaw	Afferent and efferents are carried by trigeminal nerve; centre lies in the pons

knees. The muscle stretch evokes discharge from the muscle spindles of the quadriceps, leading to its reflex contraction. This ensures that the knee joints, i.e. the main weight-bearing joints, do not give way under the effect of gravity. This maintains the leg as a pillar of support and thus counteracts the gravitational displacement of the body.

In general, the antigravity muscles of the body are endowed with a somewhat higher muscle tone than the other muscles of the body.

In human beings, flexors of upper extremity and extensors of lower extremity are the main antigravity muscles. Retractors of neck, the elevators of joint, supraspinatus, the extensors of back, rectal muscles of abdominal wall, extensors of knee and ankle are the muscles which exhibit a greatest degree of tone. When these muscles completely relax (as in unconscious person), the body collapses.

Various postural reflexes (described below) influence the medial motor system and the motor neurons of antigravity muscles.

Maintenance of Muscle Tone

Stretch reflex, as mentioned earlier, plays the main role in the maintenance of muscle tone (page 430).

The centre for muscle tone lies in anterior motor neurons (α-motor neurons) of spinal cord, which are stimulated through a constant γ-motor neuron discharge. Activity of γ- and α-motor neurons is modified by both extrapyramidal and pyramidal fibres, which terminate on them (directly or through interneurons). Mainly, the extrapyramidal system is responsible for maintaining tone (Fig. 10.4-8).

Postural Reflexes

The postural reflexes help to maintain the body in an upright and balanced position. They also provide adjustments

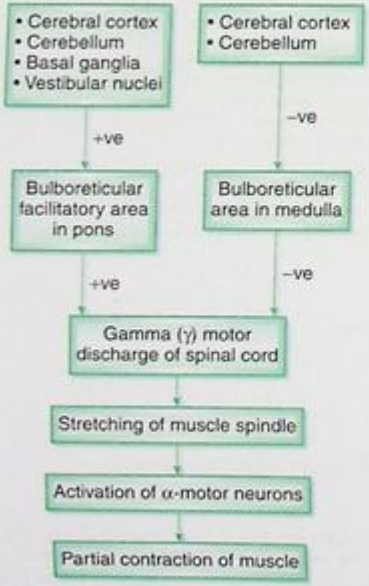


Figure 10.4-8 Flowchart depicting control of muscle tone.

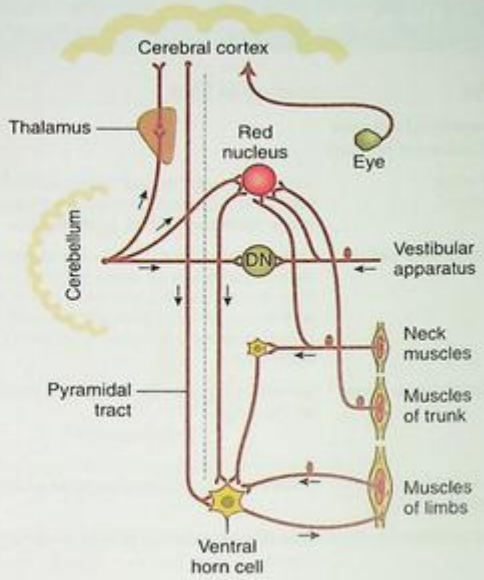


Figure 10.4-9 Neuronal pathway of postural reflexes. DN, Deiter nucleus.

necessary to maintain a stable posture during voluntary activity.

Reflex arc of postural reflexes is as follows *(Fig. 10.4-9)*:

Afferent pathways of reflex arc come from the eyes, the vestibular apparatus and the proprioceptors.

Integrating centres are formed by neuronal networks in the brainstem and spinal cord.

Efferent pathways consist of α-motor neurons supplying the various skeletal muscles which form the effector organs.

Types of postural reflexes Broadly, postural reflexes are of the following two types:

Static reflexes: These are elicited by gravitational pull and involve sustained contraction of muscles.

Statokinetic reflexes: These reflexes, also called phasic reflexes, are elicited by acceleratory displacement of the body. They maintain a stable postural background for voluntary activity.

Both these types of postural reflexes are integrated at various levels in the CNS from the spinal cord to cerebral cortex and are affected largely by pyramidal pathways.

The various postural reflexes are summarized in Table 10.4-2.

Role of Different Regions of Nervous System for Maintenance of Posture

The role of different regions of the nervous system for the maintenance of posture can be experimentally investigated (usually in a cat) by producing a transection in the neuraxis at various levels.

Role of Spinal Cord: Spinal Animal

Spinal Animal The role of spinal cord in the maintenance of posture can be studied in a spinal animal. The spinal animal can be

TABLE 10.4-2 **Various Postural Reflexes**

Reflex	Stimulus	Response	Receptors	Integrating Centre in CNS
A. Static reflexes				
I. Local static reflexes				
• Stretch reflex	Stretch	Contraction of antigravity muscles	Muscle spindles	Spinal cord and midbrain
• Positive supporting reflex	Contact of skin of the sole of foot with ground	Contraction of flexors and extensors of the limb	Touch and pressure receptors from skin of sole of foot; proprioceptors from distal flexors	Spinal cord
• Negative supporting reaction	Stretch of extensor muscles	Disappearance of positive supporting reaction	Proprioceptors in extensors	Spinal cord
II. Segmental static reflexes				
• Crossed extensor reflex	Painful stimulus	Contraction of flexors of the ipsilateral limb and extensors of contralateral limb to support the body	Nociceptors	Spinal cord
III. General static reflexes				
1. Attitudinal reflexes				
• Tonic labyrinthine reflex	Gravity (alteration of position of head relative to horizontal plane)	Extensor rigidity	Otolith organs	Vestibular and reticular nuclei present in the medulla oblongata
• Tonic neck reflex	Stretch of neck muscles due to alteration of position of head relative to body	Flexion of forelimbs and extension of hind limbs on ventroflexion of head (turning down); extension of fore limbs and flexion of hindlimbs on upward turning of head; flexion of ipsilateral limbs and extension of contralateral limbs on turning the head side ways	Pacinian corpuscles in the ligaments of cervical joint (atlanto-occipital joint) and muscle spindles of neck muscles	Medulla
2. Long-loop stretch reflex	Stretch of the muscle due to swaying of body	Continuous moment-to-moment corrections of sways, which occur during standing	Muscle spindles (monosynaptic reflex); visual receptor (long-loop reflex)	Spinal cord; cerebral cortex
3. Righting reflexes				
• Labyrinthine righting reflex	Gravity	Brings the head in upright level	Otolith organs in saccules of labyrinth	Midbrain
• Body righting reflex (body on head righting reflex)	Pressure on side of body (differential stimulation of deep structures of the body wall)	Righting of head	Exteroceptors	Midbrain
• Neck righting reflex (neck on body righting)	Stretch of neck muscles	Righting of thorax and shoulders and then pelvis	Muscle spindles	Midbrain
• Body on body righting reflex	Pressure on side of the body	Righting of body even when righting of head is prevented	Exteroceptors	Midbrain
• Limbs righting reflex	Stretch of limb muscles	Appropriate posture of limbs	Muscle spindles	Midbrain
• Optical righting reflex	Visual cues	Righting of head	Eyes	Cerebral cortex
B. Statokinetic reflexes				
• Vestibular placing reaction	Linear acceleration	Foot placed on supporting surface in position to support body	Receptors in utricle and saccule	Cerebral cortex
• Visual placing reaction	Visual cues	Foot places on supporting surface	Eyes	Cerebral cortex
• Hopping reactions	Lateral displacement while standing	Hops, maintains the limb in position to support the body	Muscle spindle	Cerebral cortex

produced by a transection in the spinal cord at the cervical region, and respiration is maintained artificially by a respiratory pump. In this way, most of the cord functions can be studied in a spinal animal. If the spinal cord is transected below the origin of phrenic nerve in the mid-thoracic region, then diaphragmatic respiration continues and so the artificial respiration is not required.

Effects of spinal cord transection: As described earlier, the effects produced by a complete spinal cord transection reflect in three stages. For more details, see page 407.

Posture in Spinal Animal during Stage of Reflex Activity

Except the basic stretch reflex and supporting reflexes which are integrated in spinal cord (Table 10.4-2), all other postural reflexes are absent, as they require the integrity of upper motor neurons coming from various levels of neuraxis.

- *Though stretch reflex* and supporting reactions are present, but they are very weak and cannot support the weight of the animal. Therefore, the animal cannot stand on its legs.
- *Muscle tone* returns first in flexor muscles; therefore, flexors become less hypotonic than extensors, producing *paraplegia in flexion* (both lower limbs are in a state of flexion).

Role of Brainstem: Bulbospinal Animal or Decerebrate Animal

Decerebrate Animal Decerebrate animal is one in whom the brainstem is transected at an intercollicular level (between superior and inferior colliculi).

Characteristic Features of a decerebrate animal are as follows:

1. ***Decerebrate rigidity,*** i.e. spasticity in all the antigravity muscles, occurs immediately after decerebration. Characteristic features of decerebrate rigidity (Fig. 10.4-10) are as follows:
   - Hyperextension of all the four limbs
   - Dorsiflexion (hyperextension) of tail and head
   - Extreme hyperextension of the spine (opisthotonus), producing concave configuration of the back
2. ***Postural reflexes present in a decerebrate animal*** are those which have their integration centre in the spinal cord or medulla or pons. These include the following:
   - Stretch reflexes
   - Positive supporting reaction
   - Negative supporting reaction
   - Crossed extensor reflex
   - Tonic neck and tonic labyrinthine
3. ***Righting reflexes are absent***; therefore, a decerebrate animal can stand on its four legs but slight displacement causes the decerebrate animal to topple over.

Role of Midbrain: Mesencephalic Animal or High-Decerebrate Animal

A mesencephalic or high-decerebrate animal is one in which the brainstem is transected at the rostral border of midbrain.

Characteristic Features of a mesencephalic animal are as follows:

1. ***Decerebrate rigidity***, similar to that of bulbospinal animal, is present, but it disappears when the limb is performing a reflex activity.
2. ***No spinal shock.***
3. ***Animal can not only stand*** but also reflexly perform typical quadrupedal walking movements.
4. *Righting reflexes* having an integration centre in the midbrain are present. These include the following:
   - Labyrinthine righting reflex
   - Neck righting reflex
   - Body on head righting reflex
   - Body on body righting reflex

By means of the righting reflexes, the midbrain animal can bring its head right way up and get the body into the erect position under all circumstances.

Role of Cerebellum

Spinocerebellum regulates the postural reflexes by modifying muscle tone. The γ-motor neurons reflexly modify the activity of α-motor neurons and thus regulate the muscle tone. Thus, cerebellum forms an important site of linkage of α–γ systems responsible for muscle tone.

Role of Basal Ganglia: Decorticate Animal

Decorticate animal is one in which the whole cerebral cortex is removed but the basal ganglia and brainstem are left intact.

Postural Characteristics of a Decorticate Animal

Moderate rigidity is present due to loss of the cortical area that inhibits spinal γ-motor neurons discharge via reticular formation. It is seen only when the animal is at rest. This is because the basal ganglia, which are intact in a decorticate animal, activate the descending inhibitory reticular formation and thereby prevent hypertonia.

Typical posture in a decorticate man consists of full extension of legs, arms lying across the chest, with semiflexion at elbow, slight pronation of forearm, and flexion of wrist and fingers (Fig. 10.4-11).

Postural reflexes: In a decorticate man or animal, the following reflexes can be elicited:

- ***Typical neck reflexes***
- ***Righting reflexes***
- ***Postural reflexes*** which are seriously disrupted by decortication are as follows:
  - Hopping reactions
  - Placing reactions

Mechanism of Standing in Man

As mentioned earlier, the tall human being has to stand over a narrow base of feet; therefore, maintenance of erect posture is more difficult than the quadruped animals. Mechanisms which play important role in an erect standing posture are discussed below:

Reflex Adjustment in Muscle Tone of Antigravity Muscles undoubtedly plays the most important role in making the man stand erect. A continued contraction of most of the trunk and leg muscles keeps the posture upright.

The Effect of Gravity has to be opposed by reflex contraction of some of the antigravity muscles all the time; otherwise, a standing man may fall in any direction (forwards, backwards or sideways). The different antigravity muscles which contract sufficiently to restore the balance to oppose the fall under various circumstances are as follows:

- ***Extensors of the trunk and flexors of the legs*** maintain the balance when the body sways forwards.

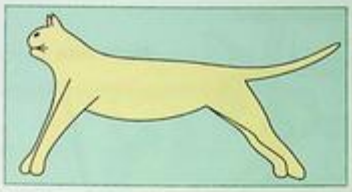


Figure 10.4-10 Characteristic features of decerebrate rigidity in cat.

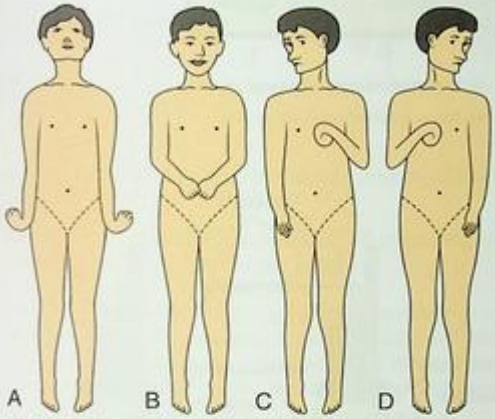


Figure 10.4-11 (A) Decerebrate and (B, C and D) decorticate rigidity in human.

- ***Recti abdominis and leg extensors*** maintain the balance when the body sways backwards.
- ***Contralateral external oblique abdominal muscles*** maintain the balance when the body leans sideways.
- ***Head has a tendency to sway more than the trunk;*** therefore, to hold the head in an erect position, the cervico-occipital muscles are to be maintained in a state of constant tension.

Reflex changes in antigravity muscles described above are induced by the following:

- ***Stretch receptors*** are present in the trunk and leg muscles.
- ***Visual afferents*** also play an important role in reflex of upright posture in man. This is why, when the eyes are closed, the upright posture is less steady and there occurs more swaying (bending) of the trunk.
- ***Vestibular afferents*** help in maintaining the erect position of head.

VESTIBULAR APPARATUS AND EQUILIBRIUM

Functional Anatomy

The internal ear or labyrinth is situated in the petrous part of the temporal bone. It consists of bony labyrinth and membranous labyrinth (Fig. 10.4-12).

Bony labyrinth consists of vestibule, semicircular canals and the cochlea.

Membranous labyrinth is lodged within the bony labyrinth. It consists of the following:

- *Utricle and saccule*, which are lodged in the bony vestibule, and are collectively called *otolith organs*

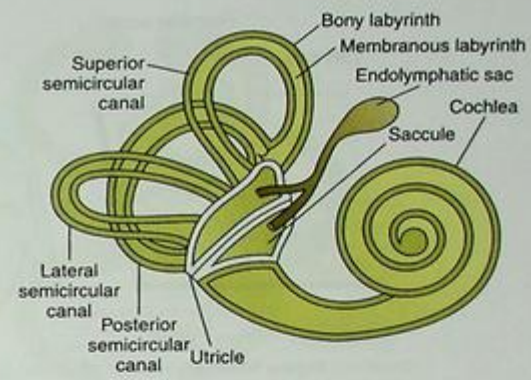


Figure 10.4-12 Vestibular apparatus: semicircular canals and otolith organs.

- *Three semicircular ducts*, which lie within the body of semicircular canals
- *Duct of cochlea*, which lies within the bony cochlea

Vestibular Apparatus The semicircular canals and the utricle and saccule collectively form the vestibular apparatus. The vestibular apparatus plays an important role in maintaining posture and equilibrium.

Semicircular Canals The three semicircular canals are arranged at right angles to each other so that all the three planes are represented as (Fig. 10.4-13) follows:

- *Anterior semicircular canal* is vertical and placed at right angles to the long axis of the petrous bone.
- *Posterior semicircular canal* is also vertical but is placed parallel to the long axis of the petrous bone.
- *Lateral semicircular canal* is set in a horizontal position making an angle of about 30° with the horizontal plane.

It is important to note the following:

- The right anterior and left posterior canals lie in the one plane, whereas the left anterior and right posterior canals lie in the other plane.
- One end of each semicircular canal is dilated and is called *ampulla*. The ampulla contains the receptor organ known as *crista ampullaris* (Fig. 10.4-14).
- The semicircular canals open into the utricle by means of five orifices. The ampullary end of each canal and narrow end of horizontal canal open independently, whereas narrow ends of anterior and posterior canals open jointly by a common orifice.

Otolith Organ refers to the combination of two vestibular sacs called the utricle and saccule.

Utricle is the larger of the two vestibular sacs in which the three semicircular canals open. It is indirectly connected to the saccule and ductus endolymphaticus. The *ductus endolymphaticus* ends in a small bag-like structure called *endolymphatic sac* (Fig. 10.4-12).

Saccule is a globular sac which is connected to utricle indirectly through the ductus utriculosaccularis, and to the cochlea via the *ductus reunion* (Fig. 10.4-12).

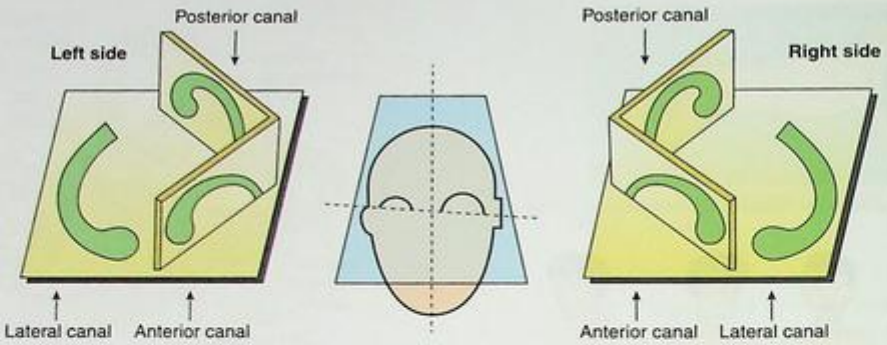


Figure 10.4-13 Position of semicircular canals when the head is tilted forward at 30°.

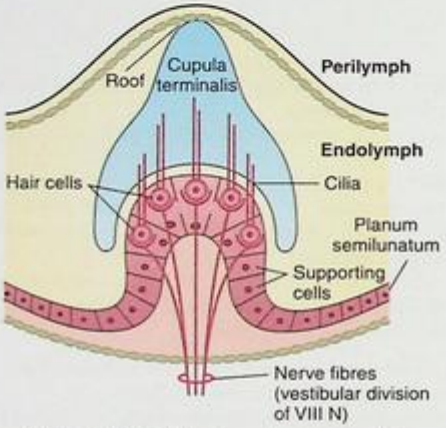


Figure 10.4-14 Structure of crista ampullaris.

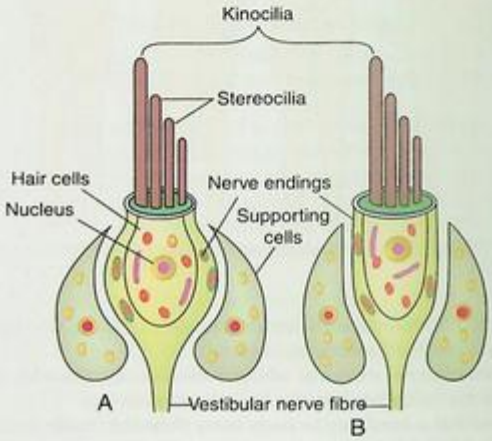


Figure 10.4-15 Structure of hair cells: (A) type I and (B) type II.

Vestibular Receptors

The receptor cells of the vestibular system are called hair cells, which are slowly adapting mechanoreceptors.

Hair Cells The vestibular hair cells are of the following two types:

- *Type I hair cells* are flask shaped.
- *Type II hair cells* are cylindrical in shape.

Cilia of hair cells (Fig. 10.4-15)**:** From the apex of each hair cell arise about 40–60 cilia. These cilia are called *stereocilia*, which are motile. A large, nonmotile cilium located at one end of the cell is called *kinocilium*.

Activity of Hair Cells The hair cells are polarized cells. When the stereocilia are bent towards the kinocilium, the cell depolarizes, and when the stereocilia are bent away from the kinocilium, the cell hyperpolarizes. The changes in the activity of hair cells are conveyed to CNS by afferent fibres, which form the vestibular part of the VIIIth cranial nerve.

Receptors in Semicircular Canals The receptors, i.e. the hair cells of the semicircular canals, are located on a raised mass of tissue in the ampulla called the *crista ampullaris*. The crista ampullaris consists of the following structures (Fig. 10.4-14):

Neuroepithelium is formed by the hair cells (described above), which are innervated by the primary afferent fibres of vestibular nerve.

Secretory epithelial cells surround the hair cells.

Cupula is a dome-shaped large mass of gelatinous material in which are embedded the cilia arising from the hair cells.

Stimulation of Receptors in Semicircular Canals The movements produced in the endolymph by the angular movements of head push the cupula backwards, causing the cilia of hair cells to bend. Depending on whether the stereocilia are pushed towards or away from the kinocilium, the hair cell depolarizes or hyperpolarizes.

It is important to note that cupula is unaffected by linear acceleration force, as it has the same specific gravity as the endolymph.

Receptors in Otolith Organs The receptors (hair cells) of the otolith organs (utricle and saccule) are located in a raised

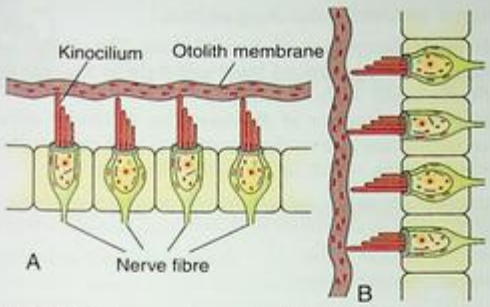


Figure 10.4-16 Structure of macula: (A) utricle (horizontally placed) and (B) saccule (vertically placed).

mass of tissue called macula. The macula consists of the following (Fig. 10.4-16):

- *Neuroepithelium* of macula like that of crista ampullaris is formed by hair cells (both type I and II).
- It consists of *supporting cells*.
- *Otolith membrane*: It is a flat gelatinous membrane covering the hair cells. This contains crystals of calcium carbonate called *otoliths or otogonia*, which increase its specific gravity as compared to endolymph. The cilia of hair cells project in the gelatinous membrane.

Stimulation of Receptors in Otolith Organs The movements produced in the otolith membrane by linear acceleration of the head cause the cilia of hair cells to bend. This leads to excitation of vestibular afferents supplying these cells.

Orientation of the macula is (Fig. 10.4-16) as follows:

- *Macula of utricle* is directed horizontally so its cilia are in a vertical plane, which are stimulated by horizontally directed linear acceleration, e.g. moving in a car.
- *Macula of saccule* is directed vertically, so its cilia are in a horizontal plane and are stimulated by vertically directed linear acceleration, e.g. moving in a lift.

Mechanism of Functioning of Vestibular Apparatus

Salient Features of Functioning of Semicircular Canals

- *Receptors* of semicircular canals are stimulated by rotatory movements or *angular acceleration* of the head.
- *Semicircular canals are oriented* in three different planes, so the movement of the head in any direction generates a unique pattern of activity.
- Receptors of horizontal canals are stimulated during the rotation of head in a vertical axis, whereas receptors of vertical canals are stimulated during the rotation of head in an anteroposterior or transverse axis.
- Receptors of semicircular canals are stimulated only at the beginning and at the stoppage of rotatory movements (Fig. 10.4-17).

Salient Features of Functioning of Utricle and Saccule

- These provide information about linear acceleration and change in head position relative to the force of gravity.
- The effective stimulus is the pull of gravity on the otolith membrane. These receptors discharge tonically even in the absence of head movement.

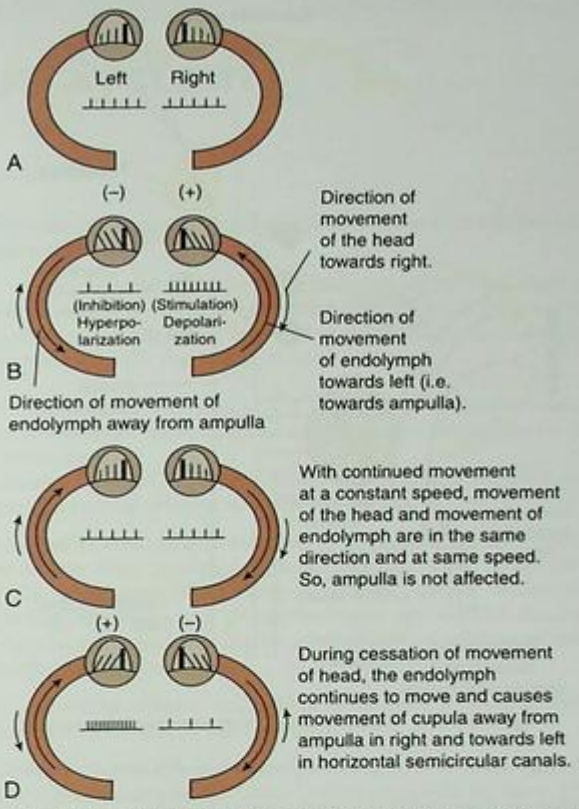


Figure 10.4-17 Mechanism of stimulation of receptors in horizontal (lateral) semicircular canal during rotation of head towards right: (A) resting position; (B) when head begins to rotate to right; (C) after 15–20 seconds of continued movement of head at a constant speed; and (D) when the head stops moving.

- During linear acceleration of the head, the otolith membrane having more specific gravity lags behind due to inertia. This causes cilia of hair cells embedded in the otolith membrane to bend. This leads to excitation of vestibular afferents supplying these cells.
- The hair cells of utricle are stimulated during dorsiflexion or ventroflexion of the head, i.e. by nodding the head up and down (as in signifying yes).
- The hair cells of saccule are stimulated when the head is tilted sideways.

Vestibular Pathways

First-order Neurons The afferent fibres carrying impulses from the hair cells are dendrites of the bipolar cells having their cell bodies in the vestibular or Scarpa's ganglion situated in the internal auditory meatus. Axons of these cells form the vestibular division of vestibulocochlear (VIIIth cranial) nerve, which enters the medulla. These axons end in the vestibular nuclei of the same side (Fig. 10.4-18).

Vestibular Nuclei The vestibular nuclei contain cell bodies of the second-order neurons of the vestibular pathway.

Afferent Connections In addition to the main afferents from vestibular apparatus, the vestibular nuclei also receive inhibitory fibres from the cerebrum and cerebellum.

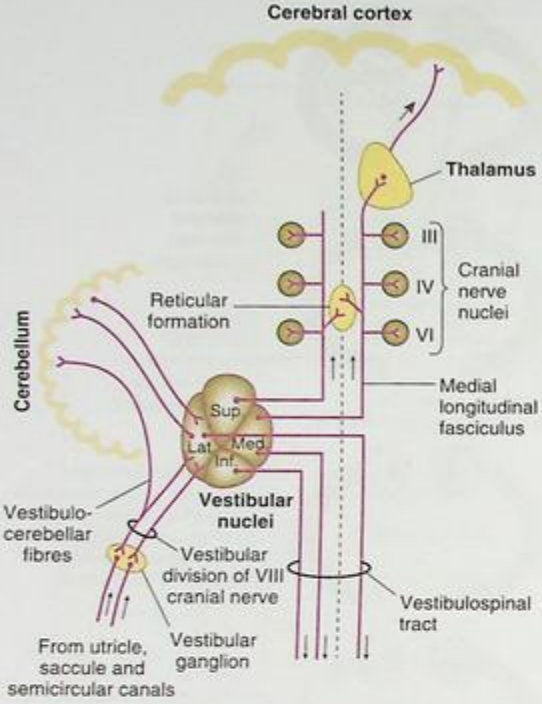


Figure 10.4-18 Neural pathway from vestibular apparatus.

Efferents from vestibular nuclei are as follows:

- Vestibulospinal tract
- Vestibulo-ocular tract
- Vestibulocerebellar fibres
- Vestibuloreticular spinal tract
- Vestibulo–rubro–spinal tract
- Vestibulo–thalamo–cortical fibres

Vestibular Reflexes

1. Vestibulo-ocular Reflex The vestibulo-ocular reflex maintains visual fixation during movements of the head by producing reflex nystagmus.

Nystagmus For example, when the head is rotated to the left, the eyes move slowly towards the right in order to keep the image on the fovea. When the eyes have rotated as far as they can, they are rapidly returned to the centre of the socket. These reflex movements of the eyes are called nystagmus.

2. Otolith Reflexes Otolith organs initiate a reflex that prevents leg injuries when an individual walks downstairs or jumps from a platform. While making such a descent, the muscles of the leg begin to contract before the feet reach the ground to cushion the force of impact.

Functions of Vestibular Apparatus

1. Role in Maintenance of Equilibrium The otolith organs detect change in position of head and help in maintenance of equilibrium under static condition.

2. Role in Maintenance of Posture The vestibular apparatus plays an important role in the maintenance of posture through vestibular reflexes, which include the following:

- Vestibular placing reaction
- Righting reflexes
- Vestibulo-ocular reflex
- Vestibulo-otolith reflex

Applied Aspects

1. Motion Sickness The motion sickness is a symptom complex occurring due to excessive and repeated stimulation of vestibular apparatus while travelling in automobile, ship, aircraft or spacecraft.

Characteristic features of motion sickness are unpleasant sensation of rotation accompanied by nausea, vomiting, sweating, pallor, salivation, headache, disorientation and even diarrhoea.

Prevention: Motion sickness can be prevented by taking antiemetic drugs such as Avomine, and by avoiding greasy and bulky food before travelling.

2. Meniere Disease It is caused by overdistension of the membranous labyrinth, probably due to oversecretion (*endolymphatic hydrops*).

Characteristic features of Meniere disease are as follows:

- Fluctuating deafness of sensorial type
- Tinnitus, which may be very troublesome
- Episodic attacks of rotatory vertigo

SELF-ASSESSMENT

1. Describe the components of the somatic motor control system of body and their functions.
2. Define muscle tone and how it is maintained in antigravity muscles.
3. Define reflex activity, its components and classification of reflexes with examples.
4. Define stretch reflex, its receptors and significance in maintenance of muscle tone.
5. Discuss regulation of body posture.
6. Discuss the role of vestibular apparatus in maintenance of body equilibrium.
7. Differentiate between the following:
   - Superficial and deep reflexes
   - Stretch reflex and inverse stretch reflex
   - Monosynaptic and polysynaptic reflex
8. Write a note on the following:
   - Golgi tendon reflex
   - Planter reflex
   - Withdrawal reflex
   - Otolith organs
   - Vestibulararocular reflex
   - Motion sickness

10.5 Autonomic Nervous System

CHAPTER OUTLINE

Anatomical Considerations
Autonomic Nervous System: Divisions
General Organization of the ANS
Neurons of ANS
Physiological Anatomy of Sympathetic Nervous System
Physiological Anatomy of Parasympathetic Nervous System

Physiological Considerations
Autonomic Neurotransmitters and Receptors

ANATOMICAL CONSIDERATIONS

Autonomic Nervous System: Divisions

The word autonomous is taken from Greek words the *autos* meaning 'self' and the *nomos* meaning 'control'. Thus, the autonomic nervous system (ANS) is an involuntary system. It controls the vegetative functions, so it is also called the vegetative system.

The ANS collects the information about the changes that take place in the internal environment (i.e. internal viscera), interprets these changes, guides the actions and gets the plan executed with the help of smooth muscles of viscera, cardiac muscles and secretory epithelium of the glandular tissues (which are the effector organs of ANS).

Divisions of ANS

ANS has the following two main divisions:

Sympathetic division, also called the thoracolumbar division, consists of thoracic and lumbar chains of sympathetic ganglia.
Parasympathetic division, also called the craniosacral division, consists of the ganglia associated with the IIIrd, VIIth, IXth and Xth cranial nerves.

General Organization of the Autonomic Nervous System

The ANS is organized as follows:

I. Autonomic Areas in the Cerebral Hemispheres The autonomic areas, controlling visceral functions, located in the cerebral hemisphere are as follows:

Higher brain centres, such as the limbic cortex and parts of the cerebral cortex, can influence the activity of ANS by sending signals to the hypothalamus and lower brain area.
Hypothalamus is the site of integration of somatic, autonomic and endocrine functions. Such an integration is essential for the maintenance of homeostasis during stresses like extreme hot, extreme cold, stress of surgical operation, stress of injuries and haemorrhage.

Hypothalamus plays an important role in the regulation of autonomic activity, so it has been called the main ganglion of ANS. However, it is now known that the limbic cortex is equally important in the regulation of ANS.

II. Autonomic Centres in the Brainstem These are located in the reticular formation and in the general visceral nuclei of cranial nerves.
General Visceral Nuclei of Cranial Nerves These include both general visceral afferent and efferent nuclei.

General visceral afferent nucleus is represented by the *nucleus of solitary tract* (nucleus solitarus tractus) present in the medulla. It receives fibres carrying general visceral sensations through the vagus and glossopharyngeal nerves. This nucleus plays an important role in the reflex control of respiratory and cardiovascular functions.

According to some authorities, some general visceral afferents end in the dorsal vagal nucleus.

General visceral efferent nuclei give origin to the preganglionic fibres that constitute the cranial parasympathetic outflow. *The general visceral efferent nuclei* include the following:

- *Edinger–Westphal nucleus* (of oculomotor nerve) situated in the midbrain
- *Salivary nucleus* (superior and inferior) located in the pons
- *Dorsal nucleus of vagus* present in the medulla

III. Autonomic Centres in the Spinal Cord These are located in the intermediolateral grey column of spinal cord at the following two levels:

1. Neurons present in the thoracic and upper two or three lumbar segments of spinal cord (T_1–L_3) constitute the preganglionic neurons of the sympathetic nervous system (*thoracolumbar outflow*).
2. Neurons present in the second, third and fourth sacral segments of spinal cord (S_2–S_4) are the preganglionic neurons of the sacral part of parasympathetic system, which along with the cranial part constitute the *craniosacral outflow*.

IV. Peripheral Part of ANS This is made up of all autonomic nerves and ganglia throughout the body. In fact, autonomic fibres are intimately related to different cranial and spinal nerves.

Neurons of ANS

Unlike motor nerves, where a single motor neuron travels all the way from the spinal cord or cranial nuclei to the muscle, the autonomic efferent pathway from the spinal cord or cranial nuclei is made up of two neurons: preganglionic and postganglionic.

Preganglionic Neurons The cell body of the preganglionic neuron is located in either the brainstem or the spinal cord. The axon of this visceral motor neuron projects as a thin myelinated preganglionic fibre to an autonomic ganglion.

Postganglionic Neuron The cell body of the postganglionic neuron is located in the autonomic ganglion and sends an unmyelinated axon, the postganglionic fibre, to the visceral effector cells.

In general, sympathetic ganglia are located close to the central nervous system, whereas parasympathetic ganglia are located close to the effector tissues. Therefore, the sympathetic pathway has short preganglionic fibres and long postganglionic fibres, whereas the parasympathetic pathway has long preganglionic fibres and short postganglionic fibres.

Physiological Anatomy of Sympathetic Nervous System

Sympathetic Preganglionic Neurons The cell bodies of the sympathetic preganglionic neurons are located in the intermediolateral horn of the spinal cord from level T_1 to L_2. The myelinated axons of these visceral motor neurons leave the spinal cord via the ventral root and then pass via the white rami communicantes to the paravertebral ganglia of the sympathetic trunk (Fig. 10.5-1). After reaching the sympathetic trunk, preganglionic fibres may pass on to one of the following three destinations:

- They may terminate in the ganglion at the level of entrance by synapsing with an excitor cell in the ganglion (Fig. 10.5-2).
- They may travel up or down in the sympathetic trunk to terminate in the ganglia located at a higher or lower level (Fig. 10.5-2).
- They may travel through the sympathetic trunk and exit without synapsing via the splanchnic nerve and terminate in a prevertebral ganglion (Fig. 10.5-2).

Preganglionic fibres that innervate the adrenal medulla travel through the sympathetic trunk exit without synapsing via the greater splanchnic nerve and end directly on the cells of suprarenal medulla. These medullary cells may be regarded as modified sympathetic excitor cells that secrete epinephrine and norepinephrine into the bloodstream. These secretory cells of the adrenal medulla are derived embryologically from the nervous tissue and are analogous to the postganglionic neurons.

Sympathetic Ganglia The sympathetic ganglia are of the following three types:

- Paravertebral ganglia
- Prevertebral or collateral ganglia
- Peripheral or terminal ganglia

Paravertebral Ganglia are arranged along the entire length of two sympathetic trunks (right and left placed on either side of vertebral column throughout its length). Paravertebral ganglia of sympathetic trunk are divided into the following:

- ***Cervical ganglia***: These are three in number: superior, middle and inferior.
- ***Thoracic ganglia***: These are 11–12 in number.
- ***Lumbar ganglia***: These are four in number.

Note: In all, there are 22 or 23 ganglia on each trunk. The inferior cervical ganglion and the first thoracic ganglion are often fused to form a large stellate ganglion.

The two sympathetic trunks end below by joining together to form a single ganglion, the *ganglion impar.*

Prevertebral or Collateral Ganglia are three in number (coeliac ganglion, inferior mesenteric ganglion and superior mesenteric ganglion).

Peripheral or Terminal Ganglia are located within or close to structures innervated by them. Heart, bronchi, pancreas and urinary bladder are innervated by the terminal ganglia.

Postganglionic Sympathetic Neurons are located primarily in ganglia on the sympathetic trunks. Some are located in the prevertebral ganglia and the peripheral autonomic plexus (Figs 10.5-1 and 10.5-2). Axons arising from these neurons behave in one of the following ways:

- *The axons may pass through a grey ramus communicantes* and re-enter the ventral root to reach a spinal nerve (Fig. 10.5-1).

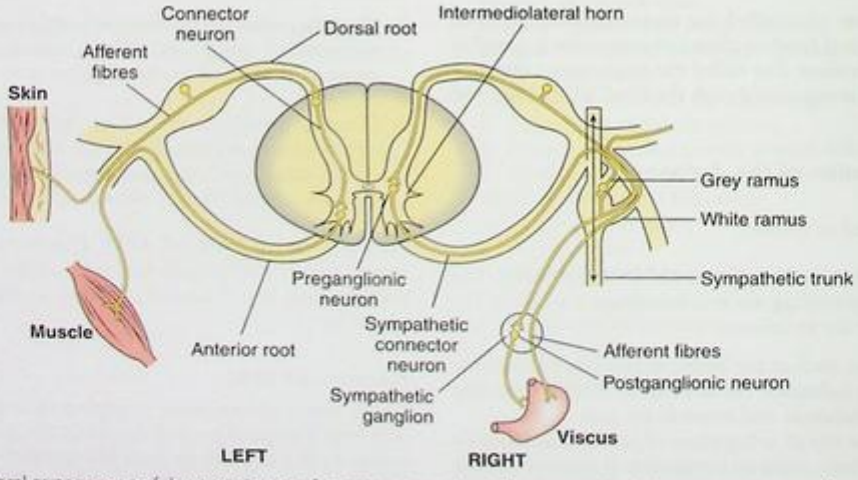


Figure 10.5-1 General arrangement of the somatic part of nervous system (on left) compared with the autonomic part of nervous system (on right).

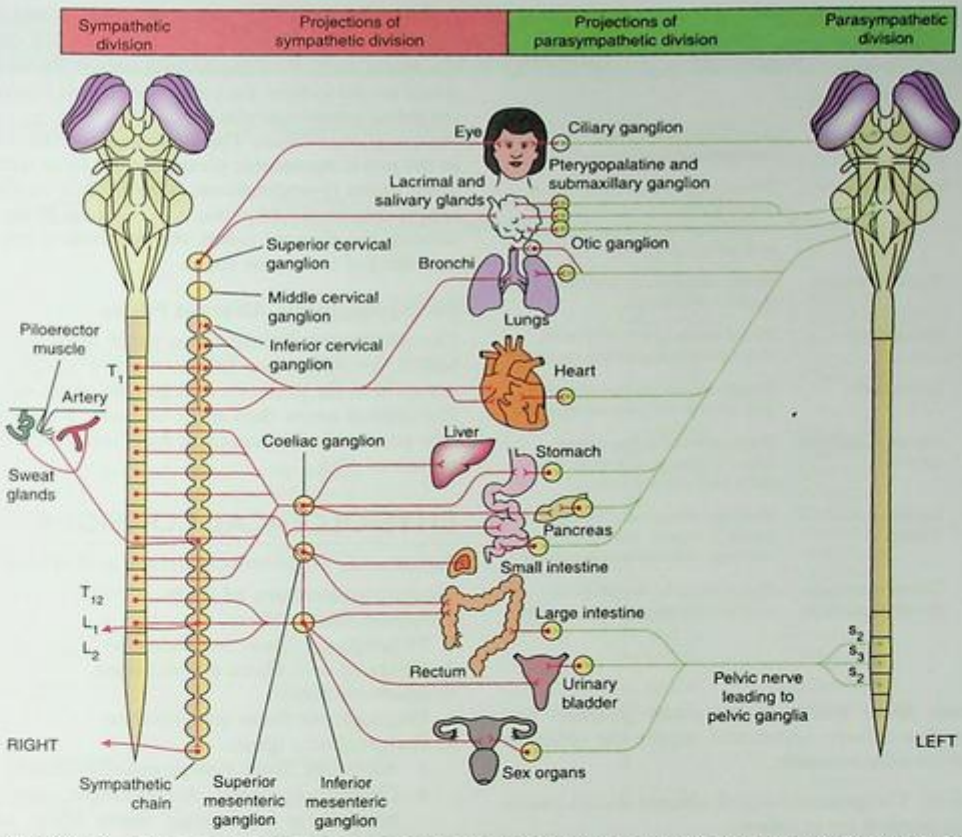


Figure 10.5-2 Efferent part of the autonomic nervous system: parasympathetic (on left) and sympathetic (on right).

In the spinal nerve, the postganglionic fibres travel through its branches to innervate sweat glands and arrectores pilorum muscles of the skin in the region to which spinal nerve is distributed.

- *The axons may reach a cranial nerve* through a communicating branch and may be distributed through it as in the case of spinal nerve.
- The axons may pass into a vascular branch and may be distributed to branches of the vessel.
- Some fibres from these plexuses may pass to other structures in the neighbourhood of the vessel.
- *The axons of postganglionic neurons arising* in the sympathetic ganglia may travel through vascular branches and through autonomic plexus to reach some viscera (e.g. the heart).
- *The axons of postganglionic neurons located in the peripheral autonomic plexus innervate neighbouring viscera.*

Sympathetic Afferent Fibres The afferent myelinated fibres travel from the viscera through the sympathetic ganglia without synapsing (Fig. 10.5-1). They enter the spinal nerve via the white rami communicantes and reach their cell bodies in the posterior root ganglia of the corresponding spinal nerve. The central axons then enter the spinal cord and may form the afferent component of a local reflex arc. Others may pass up to higher autonomic centres in the brain.

Distribution of Sympathetic Preganglionic Neurons and Postganglionic Fibres The distribution of preganglionic neurons and postganglionic fibres is given in Table 10.5-1 and illustrated Fig. 10.5-2.

Physiological Anatomy of Parasympathetic Nervous System

Parasympathetic Preganglionic Neurons The parasympathetic fibres form the *craniosacral outflow*, consisting of cranial parasympathetic outflow and sacral parasympathetic outflow.

I. Cranial Parasympathetic Outflow The cell bodies of the neurons are located in the general visceral efferent nuclei. Cranial parasympathetic outflow can be further divided into the following:

- Midbrain or tectal outflow
- Bulbar outflow

1. Midbrain or Tectal Outflow The general visceral efferent nucleus associated with the midbrain outflow is the Edinger–Westphal nucleus.

Edinger–Westphal nucleus: It lies in the midbrain and is closely related to the oculomotor nucleus complex.

- ***Preganglionic fibres*** arising from the Edinger–Westphal nucleus pass through the oculomotor (IIIrd cranial) nerve and relay in the ciliary ganglion.

TABLE 10.5-1 Distribution of Preganglionic Neurons and Postganglionic Fibres

Segmental Level of Preganglionic Neurons	Area of Distribution	Final Distribution of Postganglionic Fibres
T_1, T_2	Head and neck	Dilator pupillae muscle, superior and inferior, Muller's muscles of eyelids, blood vessels and sweat glands
T_3, T_4	Thoracic viscera	Heart, esophagus, trachea, bronchi and lungs
T_5–T_6	Upper limb	Blood vessels, sweat glands and arrectores pilorum muscles
T_{10}–L_2	Lower limb	Blood vessels, sweat glands and arrectores pilorum muscles
T_5–T_{12}	Upper abdominal viscera	Gastrointestinal tract, liver, spleen capsule, adrenal medulla and urinary tract
L_1, L_2	Lower abdominal viscera	Bladder, uterus and fallopian tubes (or testis, vas deferens, seminal vesicles and prostate)
T_1–T_{12}	Thoracic and abdominal parietes	Blood vessels, sweat glands and arrectores pilorum muscles

- ***Postganglionic fibres*** arising in the ciliary ganglion pass through the short ciliary nerves and supply the sphincter pupillae and the ciliary muscle.

2. Bulbar Outflow The general visceral efferent nuclei associated with bulbar outflow are as follows:

(i) ***Superior salivary nucleus*** *Preganglionic fibres* arising from the superior salivary nucleus enter the facial (VIIth cranial) nerve and ultimately relay in the *submandibular ganglion*. Postganglionic fibres pass to the submandibular and sublingual salivary glands to which they are secretomotor.

(ii) ***Lacrimal nucleus*** of the VIIth cranial nerve sends preganglionic fibres to the *pterygopalatine* (sphenopalatine) ganglion. The postganglionic fibres reach the lacrimal gland to which they are secretomotor.

(iii) ***Inferior salivary nucleus*** sends preganglionic fibres into the glossopharyngeal (IXth cranial) nerve. These fibres relay in the otic ganglion, from where the postganglionic fibres go to parotid gland to which they are secretomotor.

(iv) ***Dorsal (motor) nucleus of the vagus*** About 75% of all parasympathetic fibres arise from dorsal nucleus.
Preganglionic fibres travelling in the vagus nerve end in ganglia (or nerve plexuses) closely related to the visceral organs, such as heart, lungs, bronchi, esophagus, stomach, small intestine and large intestine, up to two-thirds of transverse colon.
Postganglionic fibres arise in these ganglia and run a short course to supply smooth muscles and glands in these organs.

II. Sacral Parasympathetic Outflow

Preganglionic Fibres Cell bodies of the preganglionic neurons of sacral parasympathetic outflow are located in the intermediolateral grey horn of the second, third and fourth sacral segments (S_2, S_3 and S_4) of spinal cord (Fig. 10.5-2). Their axons form the preganglionic fibres which pass out through the ventral spinal root of corresponding nerves. These axons leave the spinal nerves to form the pelvic splanchnic nerves, which end in the pelvic autonomic plexuses.

Postganglionic Fibres The postganglionic neurons are located in the pelvic autonomic plexuses close to or within the viscera. Their axons (postganglionic fibres) run a very short course to supply the concerned pelvic viscera. These fibres also supply the rectum, the sigmoid colon, the descending colon and the left one-third of transverse colon.

Parasympathetic Afferent Fibres

The afferent myelinated fibres travel from viscera to their cell bodies, located either in the sensory ganglia of the cranial nerves or in the posterior root ganglia of the sacrospinal nerves. The central axons then enter the central nervous system and take part in the formation of local reflex arc or pass to higher centres of ANS.

PHYSIOLOGICAL CONSIDERATIONS

Autonomic Neurotransmitters and Receptors

Neurotransmitters of ANS

Parasympathetic Fibres

1. Preganglionic fibres: acetylcholine
2. Postganglionic fibres: acetylcholine

Sympathetic Fibres

1. Preganglionic fibres: acetylcholine
2. Postganglionic fibres:
   - Adrenergic fibres: Norepinephrine (mainly) or epinephrine
   - Cholinergic fibres: Acetylcholine (the postganglionic sympathetic cholinergic nerve fibres supplying sweat glands, blood vessels in heart and skeletal muscles)

Autonomic Receptors The autonomic neurotransmitters (acetylcholine or norepinephrine) produce their effects on the organs by combining with specific protein molecules known as receptors, which are of the following types:

1. Cholinergic Receptors On the basis of their pharmacologic properties, these are of the following two types:

(i) Nicotinic Receptors These receptors are located in/at the following:

- Autonomic ganglia of sympathetic and parasympathetic nervous system
- Neuromuscular junction
- Adrenal medulla

Activation: Nicotinic receptors are activated by the following:

- Acetylcholine (ACh)
- Nicotine

Effect: These receptors produce excitation.

Blockage: Ganglion blockers (e.g. hexamethonium, trimethaphan) block the nicotinic receptors for ACh in the autonomic ganglia, but not at the neuromuscular junction.

(ii) Muscarinic Receptors These receptors are located in the following:

- Heart
- Smooth muscles (except vascular smooth muscle)
- Glands

TABLE 10.5-2 Responses of Effector Organs to Sympathetic and Parasympathetic Stimulation

S. No.	Effector Organ	Parasympathetic Effect	Sympathetic Effect	
			Receptor Type	Response
1.	***Eyes***			
	• Dilator pupillae muscle	–	α	Contraction (mydriasis)
	• Sphincter pupillae muscle	Contraction (meiosis)	–	–
	• Ciliary muscle	Contraction (produces accommodation for near vision)	β_2	Relaxes (flattens lens for far vision)
2.	***Heart***			
	• SA node	↓ Heart rate, vagal arrest	β_1 and β_2	↑ Heart rate
	• Atria	↓ Contractility ↓ Conductivity	β_1 and β_2	↑ Contractility ↑ Conductivity
	• AV node and conduction system	↓ Conduction velocity	β_1 and β_2	↑ Conduction velocity
	• Ventricles	↓ Contractility	β_1 and β_2	↑ Contractility
3.	***Arterioles***			
	• Coronary	–	α_1 and α_2	Constriction
			β_2	Dilatation
	• Cutaneous and mucosal	No supply	α_1 and α_2	Constriction
	• Skeletal muscle	No supply	α_1	Constriction
			β_2	Dilatation
	• Cerebral	Dilatation	α_1	Constriction
	• Pulmonary	Dilatation	α_1	Constriction
			β_2	Dilatation
	• Abdominal viscera	No supply	α_1	Constriction
	• Renal	No supply	α_1 and α_2	Constriction
			β_1 and β_2	Dilatation
	• Salivary glands	Dilatation	α_1 and α_2	Constriction
4.	***Systemic veins***	No supply	α_1 and α_2	Constriction
			β_2	Dilatation
5.	***Lungs***			
	• Bronchial muscles	Contraction	β_2	Relaxation
			α_1	Inhibition
	• Bronchial glands	Stimulation	β_2	Stimulation
6.	***Salivary glands***	Stimulation (profuse watery secretion)	α_1	Stimulation (thick viscous secretion)
7.	***Stomach***			
	• Motility and tone	Increases	α_1, α_2, β_2	Decreases
	• Sphincters	Relaxation	α_1	Contraction
	• Secretion	Stimulation	α_2	Inhibition
8.	***Gall bladder***	Contraction	β_2	Relaxation
9.	***Liver***	–	α_1, β_2	Glycogenolysis
10.	***Pancreas***			
	• Exocrine glands	Stimulates secretion	α_1	Inhibits secretion
	• Endocrine glands	–	α_2	Inhibits insulin secretion
			β_2	Stimulates glucagon
11.	***Spleen capsule***	–	α_1	Contraction
			β_2	Relaxation
12.	***Adrenal medulla***	Secretion of epinephrine and norepinephrine	–	–
13.	***Urinary bladder***			
	• Detrusor muscle	Contraction	β_2	Relaxation (usually)
	• Sphincter	Relaxation	α_1	Contraction
14.	***Uterus***	Variable	α_1	Contraction (pregnant)
			β_2	Relaxation (nonpregnant)
15.	***Male sex organ***	Erection	α_1	Ejaculation
16.	***Lacrimal glands***	Secretion	–	–
17.	***Skin***			
	• Pilomotor muscle	–	α_1	Contraction (erection of hair)
	• Sweat glands	Generalized (cholinergic sweating)	α_1	Localized (adrenergic) sweating

Continued

TABLE 10.5-2 Responses of Effector Organs to Sympathetic and Parasympathetic Stimulation—cont'd

S. No.	Effector Organ	Parasympathetic Effect	Sympathetic Effect	
			Receptor Type	Response
18.	*Nasopharyngeal glands*	Secretion	–	–
19.	*Adipose tissue*	–	α_1, β_1, β_3	Lipolysis, release of FFA
20.	*Juxtaglomerular cells*	–	β_1	Increased renin secretion
21.	*Pineal gland*	–	β_1	Increased melatonin synthesis and secretion
22.	*Skeletal muscles*	–	β_2	Increased glycogenolysis
23.	*Basal metabolic rate*	–	β_2	Increased
24.	*Mental activity*	–	–	Increased

Activation: These receptors are activated by the following:

- Acetylcholine (ACh)
- Muscarine

Effects produced by their stimulation are as follows:

- *Inhibitory in the heart*, e.g. decreased heart rate and decreased conduction velocity in atrioventricular (AV) node
- *Excitatory* in smooth muscle and glands (e.g. increased gastrointestinal motility and increased secretion)

Blockage: Muscarinic receptors for acetylcholine are blocked by atropine.

2. Adrenergic Receptors On the basis of their pharmacologic properties, adrenergic receptors are of the following two types:

- *Alpha (α) adrenergic receptors* (which are of further two types: α_1 and α_2)
- *Beta (β) adrenergic receptors* (which are of further three types: β_1, β_2 and β_3)

(i) α_1 Receptors are located in the following:

- Vascular smooth muscles of skin and splanchnic regions
- Gastrointestinal and bladder sphincters
- Radial muscles of the iris

Effect: These receptors produce excitation, e.g. contraction or constriction.

(ii) α_2 Receptors are located in the following:

- Presynaptic nerve terminals
- Platelets
- Fat cells
- Walls of the gastrointestinal tract

Effect: They often produce inhibition (e.g. relaxation or dilatation).

(iii) β_1 Receptors are located in the following:

- Sinoatrial (SA) node
- Atrioventricular (AV) node
- Ventricular muscles of the heart

Effect: These receptors produce excitation (e.g. increased heart rate, increased conduction velocity and increased contractility).

Catecholamine sensitivity: β_1 receptors are sensitive to both norepinephrine and epinephrine, and are more sensitive than the α_1 receptors.

(iv) β_2 Receptors are located in the following:

- Vascular smooth muscle of skeletal muscle
- Bronchial smooth muscle
- Walls of the gastrointestinal tract
- Bladder

Effect: These receptors produce relaxation (e.g. dilation of vascular smooth muscle, dilation of bronchioles and relaxation of bladder wall).

Sensitivity to epinephrine is more than to norepinephrine. These are more sensitive to epinephrine than the α_1 receptors.

(v) β_3 Receptors: These receptors are located in the adipose tissue and cause lipolysis.

Note: The type of adrenergic receptors present in various organs and the effects produced by their stimulation are given in Table 10.5-2.

SELF-ASSESSMENT

1. Discuss the organization of the autonomic nervous system.
2. Differentiate between:
   - Activity of sympathetic and parasympathetic systems
   - Adrenergic and cholinergic receptors
   - Preganglionic and postganglionic fibres
   - Muscarinic and nicotinic receptors

10.6 Meninges, Cerebrospinal Fluid, Blood–Brain Barrier and Cerebral Blood Flow

CHAPTER OUTLINE

Meninges of the Brain
Pia Mater
Arachnoid Mater
Dura Mater

Cerebrospinal Fluid
Composition, Volume and Pressure
Formation, Circulation and Absorption
Functions
Clinical Applications

Blood–Brain and Blood–CSF Barriers
Blood–brain Barrier
Blood–CSF Barrier

Cerebral Blood Flow
Normal Cerebral Blood Flow

MENINGES OF THE BRAIN

The brain is enclosed within the cranial cavity by three concentric connective tissue layers, pia mater, arachnoid mater and dura mater, which constitute the meninges of the brain (Fig. 10.6-1).

Pia Mater covering closely and continuously the external surface of the brain, is a thin and highly vascular membrane. Folds of pia mater enclose tufts of capillaries called choroid plexuses to form tela choroidea in relation to the ventricles of brain.

Arachnoid Mater is connected to the pia mater by many filamentous fibres. The subarachnoid space between these two layers is filled with cerebrospinal fluid (CSF).

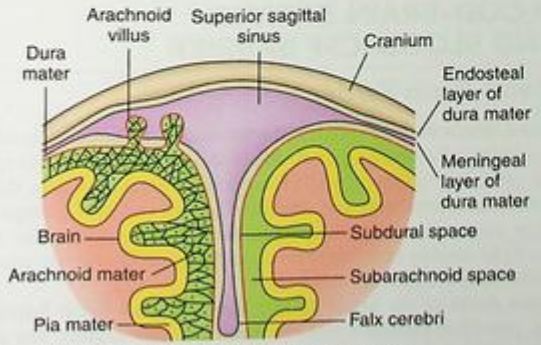


Figure 10.6-1 Meninges of brain.

Dura Mater is composed of two layers: outer endosteal and inner meningeal. These are fused except where folds form (e.g. falx cerebri), or venous sinuses (e.g. superior sagittal sinus) are enclosed between them. *Subdural space* separates the dura mater from the arachnoid mater. The arachnoid mater has minute protrusions (*arachnoid villi*), which pass through fenestrae in the dura mater and project into the venous sinuses to allow escape of CSF into the venous sinuses.

CEREBROSPINAL FLUID

CSF cushions the brain, and along with the blood–brain barrier, the buffering function of neuroglia and regulation of central nervous system (CNS) circulation controls the extracellular environment of neurons. Within the substance of brain in the *ventricular system*, there are series of spaces filled with CSF.

Composition, Volume and Pressure of CSF

Composition of CSF The extracellular fluid within the CNS communicates directly with the CSF. Thus, the composition of CSF indicates the composition of the extracellular environment of the neurons in the brain and spinal cord. The composition of CSF vis-á-vis blood is given in Table 10.6-1. The CSF differs from blood in having a lower concentration of K^+, glucose and protein and a higher concentration of Na^+ and Cl^-. CSF normally lacks blood cells. The increased concentration of Na^+ and Cl^- enables the CSF to be isotonic to blood, despite the much lower concentration of proteins in the CSF.

CSF Volume and Pressure The cranial cavity contains about 140 mL CSF.

The volume of CSF within the cerebral ventricles is approximately 40 mL, and that in the subarachnoid space is about 100 mL. The pressure in the CSF column is about 120–180 mm H_2O when a person is recumbent. Rate of CSF formation (about 0.35 mL/min) is independent of CSF pressure as well as systemic blood pressure.

TABLE 10.6-1 Composition of CSF vis-á-vis Blood

Constituent	Lumbar CSF	Blood
Na^+ (mEq/L)	148	136–145
K^+ (mEq/L)	2.9	3.5–5
Cl^- (mEq/L)	120–130	100–106
Glucose (mg/dL)	50–75	70–100
Protein (mg/dL)	15–45	6.8×10^3
pH	7.3	7.4

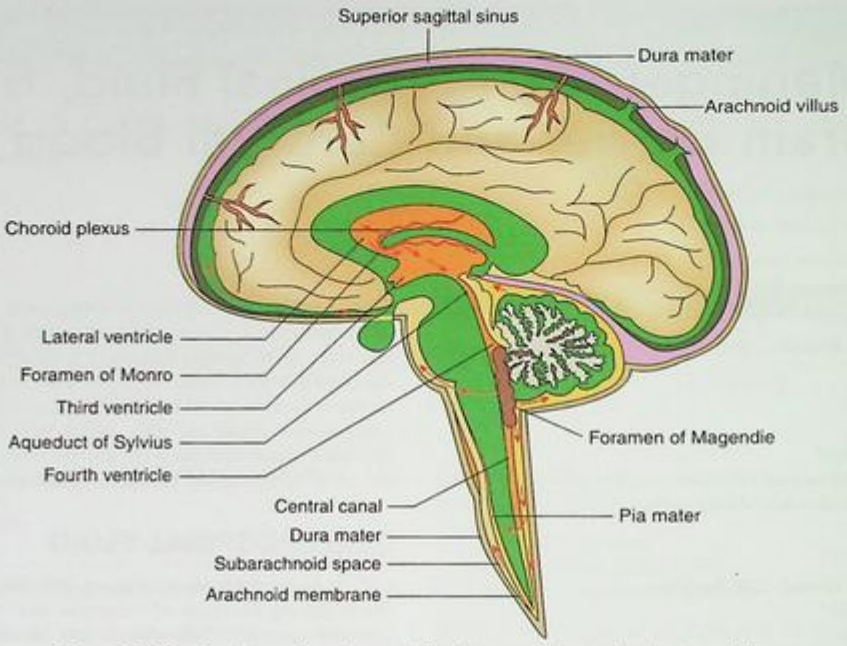


Figure 10.6-2 Circulation of cerebrospinal fluid. Arrows indicate the direction of flow.

Formation, Circulation and Absorption of CSF

Formation of CSF The CSF is mainly formed by the choroidal plexuses, which are covered by specialized ependymal cells. The *choroidal plexuses* are located in the cerebral ventricles (lateral, third and fourth). About 500 mL of CSF is secreted per day.

Circulation of CSF (Fig. 10.6-2) CSF formed in the lateral ventricles passes through the interventricular foramina of Monro into the third ventricle. Thence, the fluid flows through the cerebral aqueduct of Sylvius into the fourth ventricle. From the fourth ventricle, some CSF passes into the central canal of spinal cord, but most escapes into the subarachnoid space (surrounding the brain and spinal cord) through the median aperture (foramen of Magendie) of the fourth ventricle and the two lateral apertures of the fourth ventricle (foramina of Luschka).

Subarachnoid cistern refers to the regions where subarachnoid space is distended to form pools of CSF. An example is the *lumbar cistern*, which surrounds the lumbar and sacral spinal roots below the level of termination of spinal cord. The lumbar cistern is the target for lumbar puncture – a procedure used clinically to sample the CSF.

Absorption of CSF A large part of CSF is removed by bulk flow through the valvular *arachnoid villi* into the dural venous sinuses in the cranium. Unlike the rate of formation, the absorption rate of CSF is a direct function of the CSF pressure.

Functions of CSF

Protection to CNS by acting as a 'water jacket' as it absorbs shock in the event of blow

Removal of Waste Products of brain metabolism

Regulating the Extracellular Environment for the neurons of CNS

Transporting hormones and hormone-releasing factors

Clinical Applications

Hydrocephalus Hydrocephalus refers to an abnormal accumulation of CSF in the cranium.

Causes of hydrocephalus include the following:

- Obstruction to CSF circulation
- Excessive production of CSF
- Interference with absorption of CSF

Lumbar and Cisternal Puncture

Lumbar puncture refers to the tapping of CSF from the lumbar cistern. CSF examination is required in many disorders of CNS. It is performed by inserting a needle in between the L_2 and L_3 or L_3 and L_4 vertebrae.

Cisternal puncture refers to the tapping of CSF from the cisterna magna. To do this, a needle is passed through the posterior atlanto-occipital membrane forwards and upwards to a depth of 4.5 cm from the surface.

BLOOD–BRAIN BARRIER AND BLOOD–CSF BARRIER

Blood–Brain Barrier

Blood–brain barrier restricts the movement of large molecules and highly charged ions from the blood into the brain and spinal cord. It is formed by CNS capillary endothelial cells, their intercellular junctions and a relative lack of vesicular transport. Most substances that must cross the blood–brain barrier are not lipid soluble and therefore cross by a specific carrier-mediated transport system.

Some areas of the brain do not have a blood–brain barrier, e.g. posterior pituitary and circumventricular organs. The absence of blood–brain barrier in these regions is consistent with

their physiological functions. These leaky regions are isolated from the rest of the brain by specialized ependymal cells called *tanycytes*.

APPLIED ASPECTS

Disruption of blood–brain barrier occurs in a variety of pathological situations, such as brain tumours and bacterial meningitis. This fact can be exploited radiologically by introducing into the circulation a substance that normally cannot penetrate the blood–brain barrier. If the substance can be imaged, its leakage into the region occupied by the brain tumour can be used to demonstrate the distribution of tumour.

Blood–CSF Barrier

Blood-CSF barrier is formed by the capillaries that traverse the choroidal plexuses which are freely permeable to plasma solutes. However, a barrier (blood–CSF barrier) exists at the level of epithelial cells that make up the choroid plexuses. This barrier is responsible for carrier-mediated active transport.

CEREBRAL BLOOD FLOW

Functioning of the brain is closely related to the level of cerebral blood flow. Total cessation of blood flow to the brain causes unconsciousness within 5–10 seconds because of the decrease in oxygen delivery and the resultant cessation of metabolic activity.

Normal cerebral blood flow in an adult averages 50–65 mL/100 g or about 750–900 mL/min. Thus, the brain receives approximately 15% of the total resting cardiac output.

Details of cerebral blood flow are given on page 163.

10.7 Limbic System and Physiology of Emotional, Behavioural and Motivational Mechanisms

CHAPTER OUTLINE

Limbic System
Physiological Anatomy
Functions of Limbic System

Physiology of Emotions
Components of Emotions
Theories of Genesis of Emotions
Emotional Behaviour
Neural Substrate of Emotions

Physiology of Motivation
Neural Mechanism
Concept of Reward and Punishment
Role of Neurotransmitters

LIMBIC SYSTEM

Physiological Anatomy

Components of Limbic System The term limbic has been derived from the word *'limbus'*, which means a ring. Thus, the term limbic system is applied for those parts of the cortex (limbic cortex or limbic lobe) and subcortical structures that form a ring around the brainstem. The components of limbic system are (Fig. 10.7-1) as follows:

Limbic cortex, or the so-called limbic lobe, surrounds the subcortical structures of the limbic system. Phylogenetically, limbic cortex is an older part of the cerebral cortex (allocortex), having primitive histological structures. Limbic cortex is composed of (Figs 10.7-1 and 10.7-2) the following:

- Orbitofrontal cortex
- Subcallosal gyrus
- Cingulate gyrus
- Parahippocampal gyrus
- Uncus

Subcortical structures included in the limbic system are as follows:

- Hypothalamus
- Septum
- Paraolfactory area
- Anterior nuclei of thalamus
- Amygdala
- Portions of basal ganglia
- Hippocampus

Connections

Papez circuit refers to a closed circuit formed by connections between the cingulate gyrus (located in the prefrontal lobe), hippocampus, mammillary bodies and anterior nucleus of thalamus (Fig. 10.7-3). This circuit is responsible for resting EEG and for those emotions and aspects of behaviour that are related to preservation of the individual and species.

Efferent projection of limbic system is shown in Fig. 10.7-4.

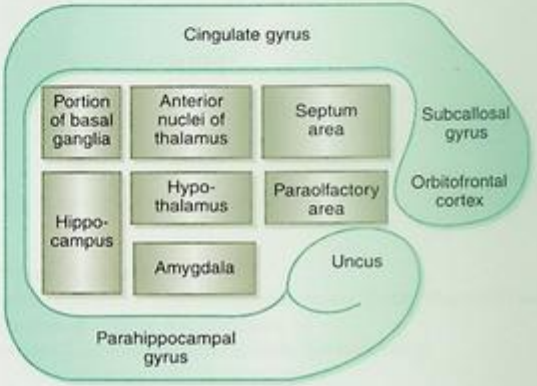


Figure 10.7-1 Diagrammatic representation of the structures forming the limbic system.

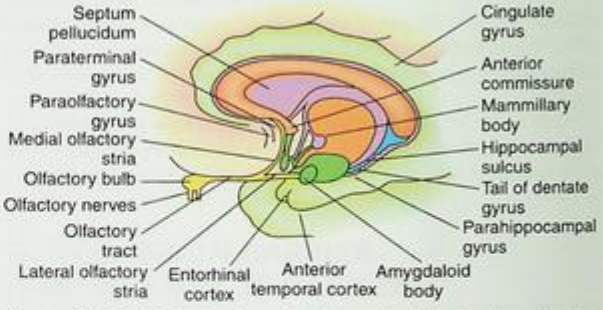


Figure 10.7-2 Medial surface of right cerebral hemisphere showing limbic cortex (limbic lobe) and other components of the limbic system.

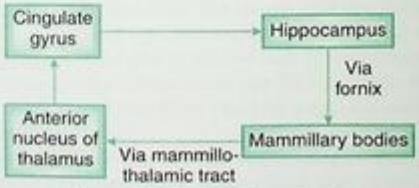


Figure 10.7-3 The Papez circuit.

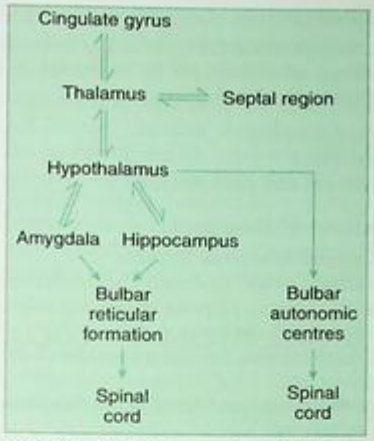


Figure 10.7-4 Efferent projection of the limbic system.

Characteristic Features of Limbic System Connections

- *Limbic system has very little connection with the neocortex.* Because of this, emotional and instinctual behaviour is not under voluntary control, especially in lower animals. Thus, from a functional point of view, neocortical activity does modify the emotional behaviour, but it cannot be turned on and off at will.
- *Prolonged after discharge* is shown by the anatomic closed circuit of the limbic system following a sensory experience. Therefore, the emotional responses are usually prolonged, i.e. continue long after the end of the stimuli that produce them.

Functions of Limbic System

Most of the functions of limbic system are intimately related to the functions of hypothalamus, which have been described in Chapter 10.1, page 398.

1. Autonomic Functions Stimulation of many parts of the limbic system, especially that of amygdala, produces autonomic responses, such as changes in cardiovascular, respiratory and gastrointestinal system through hypothalamus. Such changes are also observed during the emotional states. Autonomic functions of hypothalamus are described on page 396.

2. Regulation of Feeding Behaviour Limbic system regulates the feeding behaviour mainly through hypothalamus and amygdala.

3. Regulation of Sexual Behaviour and Reproduction Sexual behaviour, the basic sex drive (urge to copulate), is an instinctual behaviour as food intake. It is the function of limbic system and hypothalamus, which, in turn, are influenced by gonadal hormones and cerebral cortex.

4. Maternal Behaviour Maternal behaviour is the function of cingulate gyrus and the retrosplenial portion of the limbic cortex. In animals, maternal behaviour is primarily neurogenic, i.e. it depends on the olfactory, auditory, visual and thermotactile stimuli arising from the young ones. Prolactin and oxytocin, though absolutely not essential, have been reported to facilitate maternal behaviour. In general, the maternal behaviour is concerned with the nursing (breastfeeding) and protection of the offspring by the mother.

5. Emotional Behaviour Emotional behaviour is one of the most important functions of limbic system. It has been discussed separately in the section entitled 'Physiology of Emotions'.

6. Motivational Behaviour Motivational behaviour is also an important function of the limbic system and has been discussed separately in the section entitled 'Physiology of Motivation'.

PHYSIOLOGY OF EMOTIONS

Components of Emotions

Emotions refer to an aroused state involving intense feeling, autonomic activation and related behaviour, which accompany many of our conscious experiences. Emotions have two major components: mental and physical.

I. Mental or Sensory Component Mental or sensory component of emotions comprises cognition, affect and conation.

Cognition: It refers to a phenomenon by which one becomes aware (sees) and recognizes a situation. For example, when an individual hears a sudden loud noise and from his experience recognizes it to be a bomb blast. This is called cognition.

Affect: It is a German word, which means development of a feeling. In the above example, the person after cognizing the loud sound as a bomb blast is frightened; this feeling of frightening is called affect.

Conation: It is the force which directs or urges to take some action. For example, the desire to run away from the site of loud noise after getting frightened is conation.

II. Physical or Expressive or Peripheral Component Physical or expressive or peripheral component of the emotions consists of two subcomponents: somatic and autonomic.

Somatic part of the physical component of emotions is basically comprises changes in the skeletal muscles. The accomplishment of the act of running away from the site of noise in the above example constitutes the somatic part of the physical component.

Autonomic part of the physical component of emotions involves the coordinated activity of the sympathetic and parasympathetic nervous systems. For example, the occurrence of tachycardia, raised blood pressure, increased respiration rate, etc., after getting frightened from the sudden loud noise constitutes the autonomic part of the physical component.

Sympathetic expression: Fear (as in the above example) is associated with sympathetic expression, which is characterized by an increase in the heart rate, increase in respiration rate, cutaneous vasoconstriction, sweating (cold sweat), piloerection, pupillary dilatation and dryness of mouth.

Parasympathetic expression is noticed during grief or pleasure.

Note: In many instances, the somatic part of the physical component of emotions may be absent. For example, after getting insulted and provoked, one may beat the insulter (somatic part present), whereas the other individual may feel enraged,

develop high blood pressure plus tachycardia but restrains oneself and does not show any somatic side of expression (indeed, this is common in civilized societies).

Function served by the peripheral component of emotions is that the body is prepared for action.

Theories of Genesis of Emotions

Physical changes are secondary to the emotional feelings or vice versa, and have been the matter of debate. Various theories have been put forward from time to time in this regard. The genesis of emotions as explained by Arnold is as follows.

Arnold Theory This theory of genesis emotions (Fig. 10.7-5) states the following:

- By *cognition*, one becomes aware and recognizes a situation.
- By *unconscious evaluation*, the situation is judged as to be harmful or beneficial.
- *Affect* is conscious reflection of unconscious appraisal. A feeling is thus generated consciously in response to unconscious evaluation of a situation. Such a feeling may be in the form of fear, joy, grief or rage.

Thus, according to Arnold's theory, emotions have their own logic and that the peripheral component of emotions results from an unconscious evaluation of situation as potentially harmful or harmless. Therefore, in response to a particular situation, different individuals react differently, e.g. in response to a bomb blast by terrorist attacks:

- Some will be frightened.
- Proterrorist persons will have a feeling of joy.
- Antiterrorists will develop a feeling of rage, and so on.

Furthermore, Arnold pointed out that the autonomic responses are not an essential component of emotions.

Emotional Behaviour

Different emotions produce different sets of behaviour. Behaviour is considered an expression of emotions. Some of the emotional behaviours are as follows:

- Rage, fear and placidity
- Sexual behaviour
- Feeling of reward and punishment

Neural Substrate of Emotions

1. Role of Central Nervous System

(i) Role of Cerebral Cortex especially the frontal, cingulate and parahippocampal cortices, plays an important role in the *affective component of emotions*.

(ii) Role of Hypothalamus has been considered the main seat of emotions.

***Areas of hypothalamus** associated with behavioural control* functions are as follows:

- Increased level of general activity, leading to *rage and aggression*: It occurs when lateral hypothalamus is stimulated.
- *Feelings of reward, tranquillity and pleasure* are appreciated when the reward centre is stimulated.
- *Fearing, feeling of punishment and aversion* are felt when the punishment centre is stimulated.

Lesions of hypothalamus are associated with the following:

- Extreme passivity and loss of drive
- Rage and violent behaviour
- Excessive eating and drinking

(iii) Role of Amygdala As far as emotions are concerned, Amygdala coordinates the affective component of emotions (function of cerebral cortex) with the autonomic response to emotions (function of hypothalamus) through the *ventral amygdalofugal pathway* and *stria terminalis*.

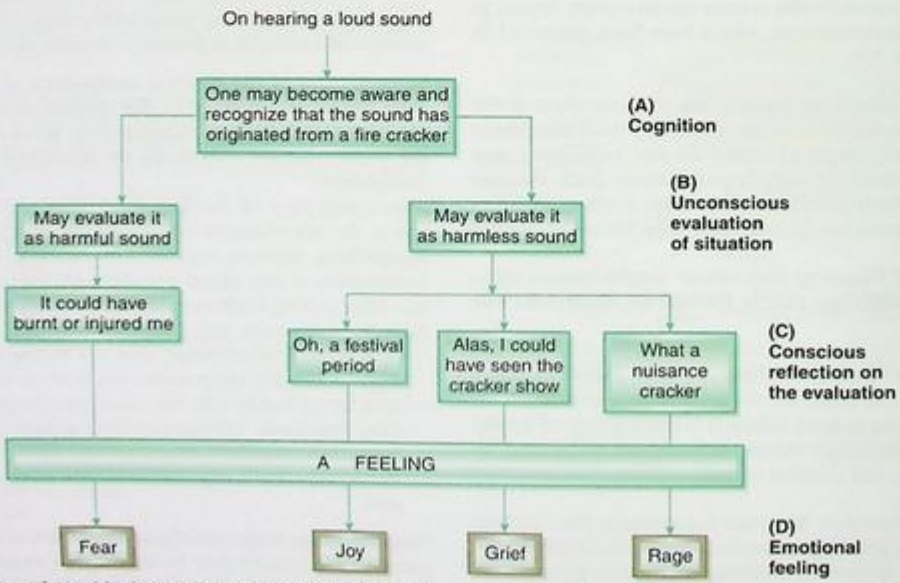


Figure 10.7-5 Steps of Arnold's theory of emotions: (A) cognition; (B) unconscious evaluation of situation; (C) conscious reflection on the evaluation; and (D) emotional feeling.

2. Role of Peripheral Nervous System Autonomic as well as the somatic motor peripheral nervous system is involved in the peripheral expression of the emotions.

(i) ***Autonomic nervous system*** is the chief mediator of the emotional output. Cannon described the emotional response to an emergency or involving diffuse sympathetic activation and outpouring into the blood of excitatory substances, i.e. the catecholamines.

(ii) ***Somatic motor nervous system*** is involved in the somatic part of the physical component of emotions, which is basically comprises changes in the skeletal muscles.

PHYSIOLOGY OF MOTIVATION

Motivation is that component of behaviour which is responsible for accomplishing a particular task.

Neural Mechanism of Motivation

Neural mechanisms involved in the motivation are based on the concept of reward and punishment. It has been elucidated by the effects of self-stimulation of brain.

Concept of Reward and Punishment

Almost anything that we do is related in some way to reward and punishment. If we do something that is rewarding, we continue to do it. If we do something that is punishing, we cease to do it.

Reward and Punishment Centre: It appears that conditions which result in stimulation of reward centre produce motive to do a job.

Role of Neurotransmitters

Neurotransmitters involved in the pathway that stimulate the *reward centre* are as follows:

- Catecholamines (norepinephrine and dopamine)
- Morphine
- Enkephalin

Drugs that increase stimulation of reward centre are those which increase synaptic activity in catecholamine pathway, e.g.

- *Amphetamine* causes increased release of dopamine.
- *Nicotine and alcohol* increase the amount of dopamine.
- *Cocaine* inhibits the re-uptake of dopamine and norepinephrine.

APPLIED ASPECTS

- *Addiction*: Tobacco, alcohol, cannabis, opiates, LSD, cocaine and amphetamine are well known to produce addiction. These drugs act by increasing dopaminergic activity in the reward centre. Thus, a strong motive develops to use them again and again.
- *Learning*: Catecholamines and enkephalins are also involved in the pathways responsible for learning (page 463). Therefore, it seems that reward and punishment constitute the incentives for learning.

Drugs that decrease stimulation of reward centre are those which lower synaptic activity in the catecholamine pathway, e.g. chlorpromazine hydrochloride (Largactil).

SELF-ASSESSMENT

1. Describe the components and functions of limbic system.
2. Write notes on:
   - Papez circuit
   - Amygdala
   - Reward and punishment

10.8 Reticular Formation, Electrical Activity of the Brain, Alert Behaviour and Sleep

CHAPTER OUTLINE

Reticular Formation and Reticular Activating System
Reticular Activating System
Functions of Reticular Formation

Electrical Activity of the Brain
Evoked Cortical Potentials
Electroencephalogram
Normal EEG
Abnormal EEG Waveforms

Wakefulness and Sleep
Wakefulness
Neural Substrate for Wakefulness
Chemical Mediators of Wakefulness
Sleep
Sleep–wake Cycle and Factors Affecting Sleep
Types and Stages of Sleep
Non-REM
REM Sleep
Sleep Cycle
Physiological Significance of Sleep

RETICULAR FORMATION AND RETICULAR ACTIVATING SYSTEM

Reticular formation (RF) refers to the complex network of neurons and nerve fibres, which occupy the midventral portion of brainstem around the central cavity. The brainstem RF can be considered to be composed of medullary RF, pontine RF and midbrain RF. Structurally, brainstem RF consists of the following:

- Neuronal aggregates
- Afferent connections and reticular pathway
- Efferent connections

Reticular Activating System

Reticular activating system (RAS), also known as the ascending reticular activating system (ARAS), is a complex polysynaptic pathway that projects diffusely from the brainstem RF to the cerebral cortex.

Collaterals to RAS funnel from the following sources (Fig. 10.8-1):

- Long ascending sensory pathways, such as spinothalamic tracts, are the important sources of collaterals to RAS. The fibres of the tracts conveying slow pain send the richest collateral connections to RAS.

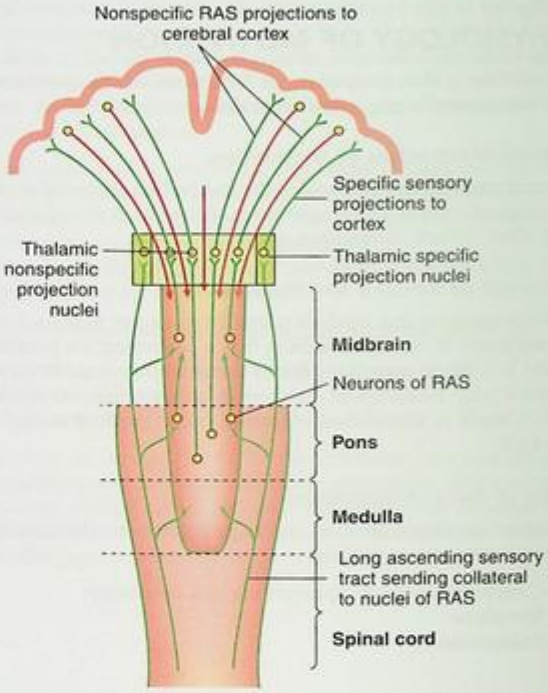


Figure 10.8-1 Diagrammatic depiction of reticular activating system vis-á-vis specific sensory projections.

- In addition to long ascending sensory tracts, collaterals to RAS also funnel from the trigeminal, auditory, visual and olfactory pathway systems.

Efferent Projections from RAS are as follows:

- Majority of RAS fibres end in nonspecific thalamic nuclei (intralaminar and midline nuclei), and from there projected diffusely and nonspecifically to the whole neocortex (Fig. 10.8-1).
- Another part of RAS bypasses the thalamus to project diffusely to the cortex.

The RAS fibres occupy the core portion of the brainstem (Fig. 10.8-1), whereas the specific fibres occupy the lateral parts of brainstem.

Stimulation of RAS: RAS is stimulated by impulses funnelled into it through the collateral described above. Thus, RAS is a *nonspecific system*, which can be excited by any sensation.

Functions of Reticular Formation

1. Sleep–wakefulness The RAS of RF is the neural substrate of the consciousness.

- RAS sends a strong facilitatory drive to the central neurons, raising their background excitability and increasing their responsiveness to specific stimuli. Thus, when RAS is stimulated, there is wakefulness and alertness of the subject, and the subject becomes fully conscious. This alertness is necessary even for proper sense perception. Conversely, when RAS is inhibited, the subject is asleep.
- *Lesions of RAS* in experimental animals produce interminable sleep and coma. In human beings also, lesions in RAS (e.g. tumours) cause prolonged sleep.
- *Many agents producing sedation*, hypnosis and anaesthesia (e.g. benzodiazepine and barbiturates) act by preventing synaptic transmission in RAS, and thus inhibiting RAS.

2. Selective Attention and Sensory Inattention RF is also responsible for selective attention and sensory inattention through the corticofugal control of sensory input and due to habituation.

3. Conditioning and Learning RF is an integral part of the neural substrate for conditioning and learning (for details, see page 462).

4. Control of Muscle Tone and Regulation of Postural Reflex Changes RF modulates the tone of extensor (antigravity) muscles (for details, see page 434).

5. Autonomic Functions The visceral regulating centres are an integral part of RF. The influence of higher neurons over the viscera and autonomic functions are mediated through the visceral centres in RF.

6. Modulation of Pain By affecting the transmission of pain impulses through the substantia gelatinosa of the spinal cord, the serotonergic neurons modulate the perception of pain (for details, see page 420).

7. Control of Neuroendocrine System The RF projections play a role in the control of neuroendocrine systems in the hypothalamus.

ELECTRICAL ACTIVITY OF THE BRAIN

Evoked Cortical Potentials

Evoked potential refers to the surface electrical activity recorded from the surface of the scalp in response to a specific and adequate stimulus – auditory, visual or somatosensory. Stimulation by a specific adequate stimulus produces two types of electrical activity in the cerebral cortex, known as primary evoked potential and diffuse secondary response.

Primary Evoked Potential This is the initial, brief (lasting for a few milliseconds) and localized response over the specific sensory cortex. The primary evoked potential is characterized by (Fig. 10.8-2) the following:

- There is a latency of about 5–12 ms (average 10 ms).
- First, there appears a surface positive wave, which is followed by a small negative wave.
- The primary evoked potential is highly specific in its location and can be observed only where the pathway from a particular sensory organ ends; that is, it is produced by the conduction of sensory signals through the specific sensory pathways.

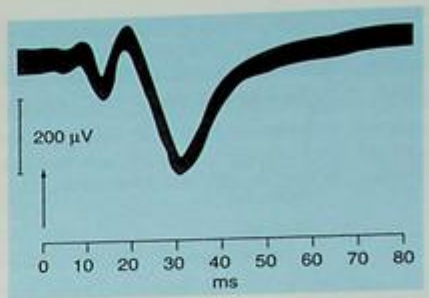


Figure 10.8-2 Response evoked in the contralateral sensory cortex by stimulation of the sciatic nerve in a cat. The upward deflection is surface negative.

Diffuse Secondary Response is characterized by the following:

- There is a latency of about 20–80 ms (average 50 ms), i.e. it appears for about 50 ms of sensory stimulus.
- Positive–negative wave sequence of secondary diffuse response is frequently larger and more prolonged than the positive–negative wave sequence of primary evoked potential.
- The surface-positive diffuse secondary response, unlike the primary, is not highly localized. It can be recorded at the same time from most of the cerebral cortex. It is due to spread of impulses through RAS to the cerebral cortex.

Types of Evoked Potentials

Depending on the type of stimulus, the evoked potential can be any of the following:

- Visual evoked potential (VEP)
- Brainstem auditory evoked potential (BAEP)
- Somatosensory evoked potential

Depending on the latency of response, evoked potential can be classified into the following:

- Stimulus-related potentials (short, mid and long latency)
- Event-related or endogenous potentials

Electroencephalogram

The term electroencephalogram (EEG) (introduced by the German psychiatrist *Hans Berger*) refers to the record of spontaneous electrical activity of the brain taken from the surface of scalp (cf. evoked potential, which is the surface electrical activity recorded in response to a specific and adequate stimulus). The spontaneous electrical activity of the brain is largely due to graded or summated postsynaptic potentials in the many hundreds or thousands of brain neurons that underlie the recording electrode at the surface of scalp.

Normal Electroencephalogram EEG consists of waves, which are oscillations in the electrical potential of brain, having the following characteristics:

- The oscillations differ in frequency and amplitude at different points on the scalp and during different stages of mental alertness.
- Different waves recorded in a normal person, depending on their frequency, are classified as alpha-, beta-, theta- and delta-waves (α-, β-, θ-, δ-) (Table 10.8-1, Fig. 10.8-3).

TABLE 10.8-1 Classification of Brain Waves Depending on Frequency of Oscillations

Frequency (Hz)	Type of EEG Wave	Amplitude (μV)
1–4	Delta (δ)	20–200
4–7	Theta (θ)	10
8–13	Alpha (α)	50
14–30	Beta (β)	5–10

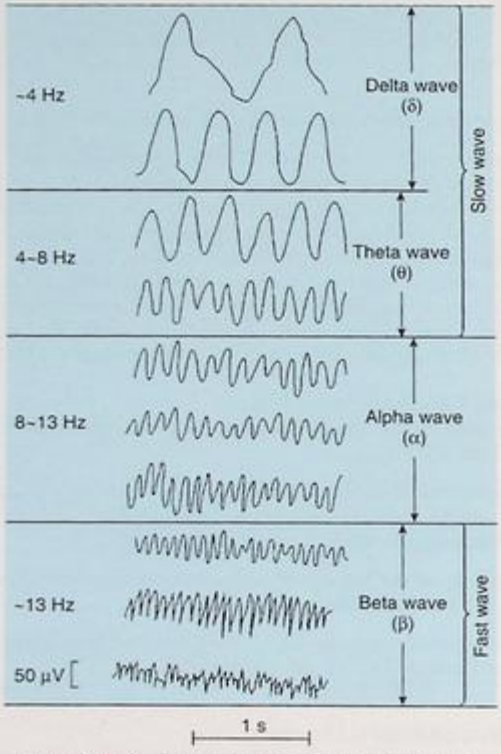


Figure 10.8-3 Different types of normal EEG waves.

Waves of EEG (Fig. 10.8-3)

Alpha-Waves These are the most prominent component of EEG obtained from adult humans who are awake but quiet and at rest with the eyes closed. α-waves are said to result from spontaneous activity of a nonspecific thalamocortical system.

Characteristic features of α-waves are as follows:

- *Frequency* of α-waves varies from 8 to 13 Hz. The mean peak frequency in a large number of normal adults is 4.2 Hz.
- *Amplitude* of these waves slowly waxes and wanes, but the average amplitude is about 50 μV.
- *Location*: α-waves are most significant in the parieto-occipital area of the scalp, though these are observed sometimes from other locations as well.
- They *disappear* during sleep.

Causes of decreased frequency of α-waves are as follows:

- Old age, due to decreased cerebral perfusion, leading to decreased cerebral metabolism
- Low blood glucose level
- Low body temperature
- Low levels of adrenal glucocorticoids
- High arterial partial pressure of CO_2
- Sleep

Causes of increased frequency of α-waves are as follows:

- High blood glucose level
- Rise in body temperature
- Low arterial pCO_2
- High levels of adrenal glucocorticoids
- Alerting states

Alpha Block (α-block) or alpha attenuation refers to a phenomenon in which α-waves attenuate and are replaced by the fast, irregular waves of low amplitude. α-block occurs in the following cases:

- The person opening their eyes
- When the individuals engage in conscious mental activity, such as doing mathematical calculations
- When any form of stimulation is applied (Fig. 10.8-4)

The term *aroused* or *alerting response* is also used to denote α-block, because it is correlated with arousal or alerting response.

Beta-Waves

- *Frequency* of β-waves is usually between 14 and 30 cycles/s.
- *Amplitude* (voltage) of β-waves (5–10 μV) is much lower than the α-waves (50 μV).
- *Location*: They are frequently recorded from the parietal and frontal regions.
- They are *seen under* the following conditions:
  - Tension and CNS activation
  - Arousal response (or α-block)
  - Infants having fast β-like activity in EEG, and occipital rhythm being slow of 0.5–2/s patterns

Theta-Waves θ-waves usually do not occur in normal waking individuals (except in newborn infants).

Characteristic features of θ-waves are as follows:

- *Frequency* is between 4–7 Hz.
- *Amplitude* (10 μV) is slightly larger than the α-waves.
- *Location*: They are recorded from the temporal and parietal regions in children.

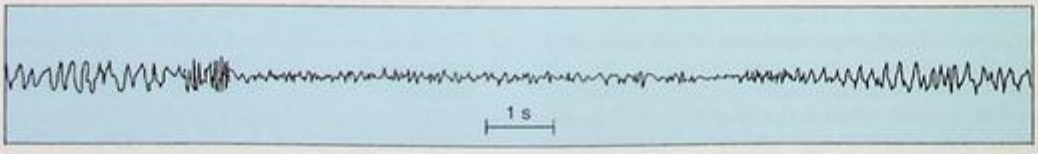


Figure 10.8-4 Electroencephalography depicting α-block produced by olfactory stimulus in a rabbit.

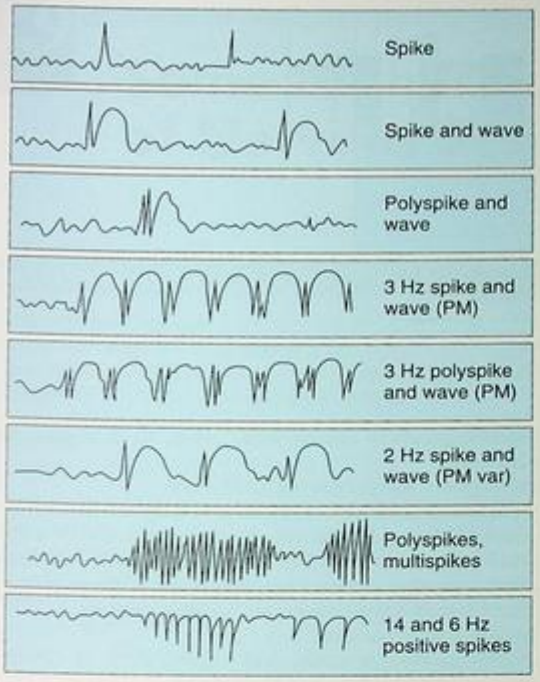


Figure 10.8-5 EEG waveform of epilepsy. PM, petit mal.

Delta-Waves δ-waves do not occur in normal waking individuals. These are seen in the following conditions:

- Deep sleep (stages III and IV of non-REM sleep)
- Infancy
- Serious brain damage

Characteristic features of δ-waves (Fig. 10.8-4) are as follows:

- *Frequency* is less than 4 Hz.
- *Amplitude* is very high (20–200 μV).
- They *can be produced* by overbreathing.

Abnormal EEG Waveforms

1. Epilepsy Electroencephalographic inspection is indispensable to the diagnosis of epilepsy. The waveforms of epilepsy (Fig. 10.8-5) include idiopathic abnormal waves, such as a spike, sharp wave, and spike and slow wave complex.

2. Organic Brain Dysfunction An abnormal wave appears when a functional trouble occurs in the brain due to cerebral tumour, brain blood vessel trouble (bleeding, clogging, artery/vein leakage, hardened brain artery, etc.) or brain injury caused by an external wound of the head.

3. Brain Death Criteria for labelling brain death are important because of the desire to obtain organs for transplant operations and the desire to remove the heroic life-support system. An individual is declared dead when brain cells stop activity, the EEG waveform becomes flat in all channels and finally disappears.

WAKEFULNESS AND SLEEP

Wakefulness

The RAS of RF is the neural substrate of the consciousness and sleep–waking cycle. As described earlier, RAS is a complex polysynaptic pathway that projects diffusely from the brainstem RF to the cerebral cortex both directly and via thalamus (for details, see page 457).

Neural Substrate for Wakefulness

The neural substrates of wakefulness generating systems are as follows:

1. Reticular Activating System, as discussed above, is mainly responsible for the tonic maintenance of the cortical activation and behavioural arousal of the wakefulness.
2. Thalamus: The nonspecific thalamic system is involved in the activation of the entire cerebral cortex. These nuclei get tonic drive from RF, and, in turn, project diffusely to the cerebral cortex.
3. Hypothalamus and Subthalamus The posterior hypothalamus also acts as the waking centre, as its stimulation causes wakefulness. Conversely, lesions of posterior hypothalamus result in coma.

Chemical Mediators of Wakefulness

Chemical mediators of wakefulness include the following:

- Catecholamines
- Acetylcholine
- Histamine
- Glutamate
- Substance P
- Hypothalamic releasing factors
- Vasoactive intestinal peptide (VIP)
- Glucocorticoids

Sleep

Sleep refers to a state of unconsciousness from which the individual can be aroused by sensory or other stimuli. When asleep, an individual is not aware of the environment and is unable to perform activities that require consciousness.

Sleep–Wake Cycle and Factors Affecting Sleep

Sleep and wakefulness, like many of the body's regulatory mechanisms, have a circadian rhythm of about 24 hours. In a normal adult, the sleep–wake cycle consists of 7–8 hours of sleep and 16–17 hours of wakefulness. A newborn infant has many cycles of sleep and wakefulness in 24 hours, but after the age of 2 years, a single sleep–wake cycle is established.

Factors Affecting Sleep The factors which favour the onset of natural sleep are as follows:

- Darkened room
- Comfortable surrounding temperature
- Silence
- Physical and mental relaxation
- Consumption of a basic urge, such as hunger or sex
- Low-frequency stimulation, such as by patting or knocking in a cradle or sitting in a moving vehicle

The above-described factors have only a modest effect, if any. The only behavioural factor that reliably and substantially

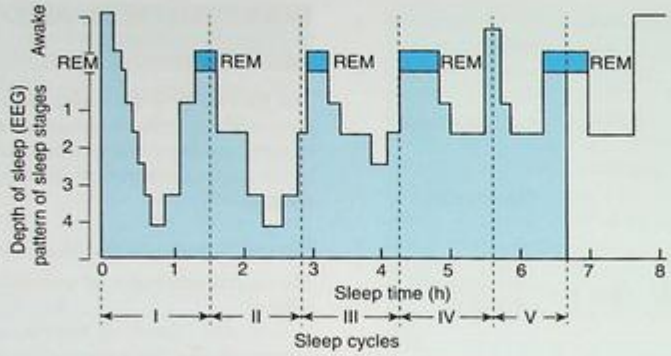


Figure 10.8-6 Typical sleep cycles in an adult individual.

increases sleep is prior sleeplessness. On the other hand, anxiety and emotional stimuli by release of epinephrine cause activation of RAS and make sleep more difficult.

Types and Stages of Sleep

Sleep is of two types: non-REM sleep and REM sleep, which alternate in a sleep cycle.

Non-REM Sleep i.e. nonrapid eye movement sleep, is also known as *slow* wave sleep (SWS) because in this type of sleep brain waves are very slow.

In normal adults, sleep mostly begins with non-REM sleep. It is a rest type of sleep, which a person experiences during the first hour of sleep after having been kept awake for many hours.

Stages and EEG Patterns of Non-REM Sleep

State of Quiet, Awake rest with Eyes Closed State of quiet, awake rest with eyes closed is the period between the stage of wakefulness and stage of sleep characterized by α-waves, which are highly synchronized.

State of Non-REM Sleep When an individual from the state of quiet rest with eyes closed enters the state of non-REM sleep, the consciousness is reduced. The non-REM sleep progresses in an orderly way from light to deep sleep in four stages. EEG pattern also changes and delta wave occurs during stage III and IV of non-REM sleep.

Physiological Changes during Non-REM Sleep

- Muscle tone decreases progressively.
- Heart rate and blood pressure are decreased.
- Respiration rate is also decreased.
- Eyes begin a slow, rolling movement until they finally stop in stage 4 (deep sleep) with eyes turned upwards.
- Body metabolism is lowered.
- Pituitary shows pulsatile release of growth hormone and gonadotropin.

REM Sleep i.e. 'rapid eye movement' sleep, is also called 'fast wave (desynchronized) sleep' or 'paradoxical sleep' or 'dream sleep' or 'deepest sleep' (as explained below). In adults, the REM sleep follows non-REM sleep.

EEG Pattern of REM Sleep During REM sleep, EEG is characterized by a high-frequency and low-amplitude pattern (β-rhythm), i.e. some desynchronized pattern that is seen in the waking state. Because of the EEG pattern of wakefulness, the REM is also called 'paradoxical sleep'.

Dreaming occurs during REM sleep, so it is also called 'dream sleep'.

Physiological Changes during REM Sleep

- REMs are the hallmark of this state of sleep and that is why the name REM sleep. REMs (saccadic eye movements) are bursts of small jerky movements that bring the eye from one fixation point to another to allow a sweeping of visual images of dreams.
- Heart rate and respiration rate become irregular.
- Muscle tone is reduced.
- Penile erection in males and engorgement of clitoris in females may occur during REM sleep.
- Teeth grinding (bruxism) may be seen in children.

Sleep Cycle

In a normal adult individual, the average sleep period of about 7–8 hours is divided into about five cycles during which non-REM sleep and REM sleep alternate with each other. There is an orderly progression of sleep states and stages during a typical sleep cycle (Fig. 10.8-6).

Physiological Significance of Sleep

Sleep is an indispensable phenomenon. Its physiological significance is as follows:

- Sleep may serve as a period of the body's rest and metabolic restoration.
- Sleep is necessary for certain forms of learning.
- REM sleep is necessary for mental well-being.
- REM sleep plays an important role in the homeostatic mechanism.

SELF-ASSESSMENT

1. Discuss in brief the reticular formation, reticular activating system and its functional significance.
2. Define electroencephalogram. What are various waves and their significance?
3. Write notes on the following:
   - Sleep cycle
   - Wakefulness
4. Differentiate between the following:
   - REM and non-REM sleep

10.9 Some Higher Functions of Nervous System

CHAPTER OUTLINE

Language and Speech
Neurophysiology of Language and Speech
Development of Speech
Mechanism of Speech and Speech Centres
Speech Disorders
Dysarthria
Aphasia

Learning and Memory
Learning
Non-associated Learning
Associated Learning
Memory
Types of Memory
Mechanism of Memory
Interhemispheric Transfer of Learning and Memory

Higher Intellectual Functions of the Prefrontal Association Cortex

LANGUAGE AND SPEECH

Neurophysiology of Language and Speech

Communication through language is a unique faculty which places the humans much above the animals. Language refers to that faculty of nervous system which enables the humans to understand the spoken and printed words, and to express ideas in the form of speech and writing. There are two aspects of communications: language input (the sensory aspect) and language output (the motor aspect). The sensory aspect of language includes the visual, auditory and proprioceptive impulses, whereas the motor aspect includes the mechanisms concerned with the expression of spoken (sound) language and written language.

Development of Speech

Development of speech involves coordinated activity of three important areas of cerebral cortex: Wernicke's area, Broca's area and motor areas of the categorical (dominant) hemisphere.

Development of speech in a child occurs in the following two stages:

First Stage In this stage, there occurs association of certain words with visual, tactile, auditory and other sensations, aroused by objects in the external world, which is stored in the memory.

Second Stage This stage of development of speech involves establishment of new neuronal circuits. When a definite meaning has been attached to certain words, a pathway between the auditory area (area 41) and motor area for the muscles of articulation, which helps in speech, (area 44) is established, and the child attempts to formulate and pronounce the words, which are learnt.

Mechanism of Speech and Speech Centres

Speech is of two types: spoken and written.

Spoken speech involves both understanding of spoken words and expressing ideas in the form of spoken words.
Written speech also involves both understanding of written words and expression of ideas in the form of written words. Mechanism of speech involves coordinated activities of central speech apparatus and peripheral speech apparatus. The central speech apparatus consists of cortical and subcortical centres. The peripheral speech apparatus includes larynx or sound box, pharynx, mouth, nasal cavities, tongue and lips. All the structures of peripheral speech apparatus work in coordination with the respiratory system, under the influence of motor impulses from the respective motor areas of the cerebral cortex.

Mechanism of speech and the centres concerned with can be described separately for the following purposes:

- Understanding of speech
- Expression of speech

Understanding of Speech (Sensory Aspects of Communication)

Understanding of Spoken Speech Understanding of the spoken words is accomplished by the following activities:

1. ***Hearing of the spoken words*** requires an intact auditory pathway from the ears to primary auditory areas.

   Primary auditory areas, also called auditory sensory areas, include Brodmann's areas 41 and 42 and form the centre for hearing. Primary auditory areas are located in the middle of superior temporal gyrus on the upper margin and on its deep or insular aspect (Fig. 10.9-1). This area perceives the nerve impulses as sound, i.e. auditory information, such as loudness, pitch, source and direction of sound.
2. ***Recognition and understanding of the spoken words*** is carried out by *auditory association areas* (21 and 20) located in the middle and inferior temporal gyri, respectively (Fig. 10.9-1).These areas receive impulses from the primary area and are concerned with interpretation and integration of auditory impulses.
3. ***Interpretation and comprehension of the speech ideas*** It involves the activities of *Wernicke's area.* Wernicke's area (area 22) is a *sensory* speech centre located in the posterior part of the superior temporal gyrus behind the

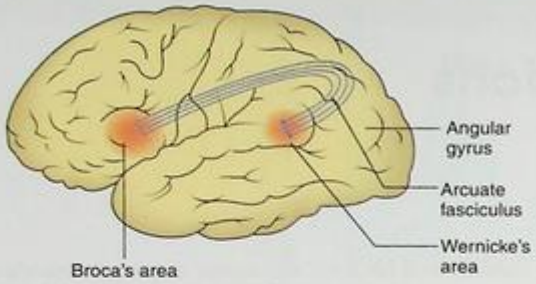


Figure 10.9-1 Lateral surface of left (categorical) hemisphere showing the location of primary areas of language.

areas 41 and 42 (Fig. 10.9-1) in the categorical hemisphere, i.e. dominant hemisphere. *Functions* of this area are as follows:

- Interpretation of the meaning of what is heard
- Comprehension of the spoken language and the formation of ideas that are to be articulated in speech

Understanding of Written Speech The understanding of the written speech is accomplished by the following activities (Fig. 10.9-2):

1. *Perception of written words* requires an intact visual pathway from eyes to primary visual cortex.
   Primary visual cortex, also called the striate area (area 17), or the centre of vision lies on the medial surface of occipital lobe. The optic radiations bring impulses from parts of both retina.
2. *Interpretation of written speech* ***Visual association areas*** (areas 18 and 19) are concerned with the interpretation of written words. These areas are involved in the recognition and identification of the written words in light of past experience.
3. *Generation of thoughts/ideas in response to written speech* ***Dejerine's area*** (area 38), located in the angular gyrus behind Wernicke's area in the dominant hemisphere, is involved in the activity of generation of thoughts/ideas in response to the written speech. This area is also called the *visual speech centre* and along with Wernicke's areas (auditory speech centre) forms the so-called sensory speech centre.

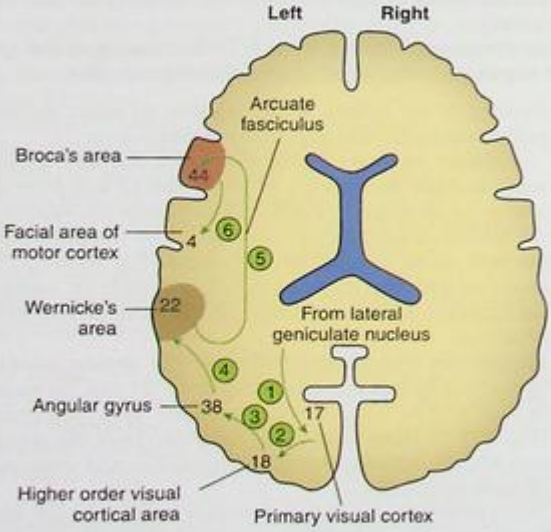


Figure 10.9-2 Neural pathway in brain involved in the understanding and expression of written speech.

Expression of Speech (Motor Aspect of Communication)

The expression of speech in response to both spoken speech and written speech can be in the form of spoken speech or written speech or both. It involves the activities of *motor speech centres*, which include Broca's area (area 44) and Exner's area.

1. Expression in the Form of Spoken Speech Expression in the form of spoken speech involves the activities of motor speech (Broca's area) area (area 44).

Functions: This area, especially in the dominant hemisphere (left hemisphere in a right-handed person), processes the information received from the sensory speech centres (Wernicke's area and Dejerine's area) into a detailed and coordinated pattern for vocalization, which is then projected to motor cortex for implementation. Thus, Broca's area is concerned with the movements of those structures which are responsible for the production of voice and articulation of speech, i.e. it causes activation of vocal cords simultaneously with movements of mouth and tongue during speech; lesions of this area cause motor aphasia.

2. Expression in the Form of Written Speech The expression in the form of written speech is the function of Exner's area (Fig. 10.9-2).

Exner's area (motor writing centre) is situated in the middle frontal gyrus in the categorical (dominant) hemisphere in the premotor cortex. It processes the information received from Broca's area into a detailed and coordinated pattern, and then along with the motor cortex (area 4) initiates the appropriate muscle movements of the hand and fingers to produce written speech.

Concept of Dominant Hemisphere for Language

In human cerebral cortex, the interpretive functions of Wernicke's area, the angular gyrus and the frontal motor speech areas (i.e. the ability to understand or express oneself by spoken or written speech) are more highly developed in one hemisphere called the *dominant hemisphere*. How one hemisphere comes to be dominant is not yet understood. It is important to note the following:

- In approximately 95% of all individuals, the left hemisphere is dominant, regardless of handedness.
- The motor area concerned with the hand movements is closely associated with the centre for speech, so this explains the right handedness in over 90% of the individuals.
- Right hemisphere dominance is seen in only 15% of left handers.
- About 70% of left handers also have left hemisphere dominance.

Concept of Categorical and Representational Hemisphere

Presently, it is believed that the left hemisphere is not really dominant over the right hemisphere. In fact, the two halves of the brain have independent capabilities of consciousness, memory storage, and control of motor activities and speech. The corpus callosum and anterior commissure connect the two halves of brain. By these connections, information stored in one

hemisphere is made available to the other hemisphere and then the activities of two hemispheres are coordinated.

As summarized below, some specialized higher functions are allowed to each hemisphere. Therefore, the terms 'dominant' and 'nondominant' have been replaced by *categorical* and *representational* hemispheres, respectively.

Functions Allotted to Left Hemisphere in a Right-Handed Person

- Right-hand control
- Spoken language
- Written language
- Mathematical skills
- Scientific skills
- Reasoning

Functions Allotted to Right Hemisphere in a Right-Handed Person

- Left-hand control
- Music awareness
- Three-dimensional awareness
- Art awareness
- Insight
- Imagination

Speech Disorders

Dysarthria

Dysarthria is a disorder of speech in which articulation of words is impaired, but the comprehension of spoken and written speech is not affected.

Aphasia

Aphasia refers to the inability to understand spoken or written speech or inability in expressing the spoken or written speech in the absence of mental confusion or motor deficit. The aphasia may be any of the following:

- Sensory aphasia
- Motor aphasia
- Global aphasia

Sensory Aphasia Sensory aphasia, also known as Wernicke's aphasia, is the result of a lesion in Wernicke's area.

Characteristic features of sensory aphasia are as follows:

1. There is *difficulty in understanding the meaning of speech.*
2. *Motor speech* is intact and the patients talk very fluently, which is why it is also called *fluent aphasia.* However, the speech does not make much sense.
3. *Impairment in reading and writing:* The patient cannot comprehend the written words (*word blindness*), so he/she is unable to read aloud or copy print into writing.

Motor Aphasia Motor aphasia, also known as Broca's aphasia, results from lesions involving Broca's motor speech area (area 44) in the frontal lobe.

Characteristic features of Broca's aphasia are as follows:

1. *Comprehension of written or spoken* speech is good.
2. There is *difficulty in speaking.*
3. *Speech is nonfluent; nonfluent aphasia* or *expressive aphasia.*
4. There is *inability to write (agraphia).*

Global Aphasia Global aphasia refers to the total inability to use language communication. This condition is produced as a result of loss of both Wernicke's and Broca's areas.

LEARNING AND MEMORY

Learning

Learning and memory are closely related. Learning is impossible without memory and memory has no meaning without learning. In fact, learning and memory are two sides of a coin. Learning refers to a neural mechanism by which the individual changes his or her behaviour on the basis of the past experience. Two patterns of learning are reflex and incidental learning.

Reflex learning: The learning is associated with immediate behavioural changes.

Incidental learning: The behavioural change is not immediately apparent. The individuals acquire information about the world, while attending incidentally to sensory inputs, and thereby develop the potential to behave differently.

The two broad classes of learning are as follows:

- Nonassociative learning
- Associative learning

A. Nonassociative Learning

In nonassociative learning, the subject learns about the properties of a single stimulus. It results when an animal or person is repeatedly exposed to a single type of stimulus. Two forms of nonassociative learning are common in everyday life: habituation and sensitization.

Habituation

Habituation refers to a decrease in response to a benign (neutral type) stimulus when the stimulus is presented repeatedly. When the stimulus is applied for the first time, it is novel and evokes reaction. This response is called *orientation reflex* or 'what is it' response. However, due to habituation, lesser and lesser response is evoked on repeated stimulation. Eventually, the subject totally ignores the stimulus and thus gets habituated to it.

Sensitization

Sensitization is opposite to habituation. In it, repeated application of a distinctly pleasant or unpleasant (strong) stimulus produces greater and greater response. Thus, in sensitization, learning occurs in a direction opposite to that seen in habituation.

B. Associative Learning

In associative learning, the subject learns about the relationship between two stimuli or between a stimulus and a behaviour. The following two forms of associative learning have been distinguished based on the experimental procedures used to establish the learning:

- Classical conditioning
- Operant conditioning

Classical Conditioning

Classical conditioning involves learning a relationship between two stimuli. Classical conditioning is also termed Pavlovian conditioning, conditioned reflex type I or type-S conditioning.

Characteristic Features of a Classical Conditioned Reflex

- A conditioned reflex is a reflex response to stimulus that is *acquired by repeatedly pairing the stimulus with another stimulus* that normally does produce the response. It depends for its appearance on the *formation of new functional connections in CNS.*
- *Reinforcement*, i.e. a process of following a conditioned stimulus (CS) with the basic unconditional stimulus (US), is must for retaining a conditioned reflex; otherwise, it will get *extinct.*

Pavlov's experiment to demonstrate classical conditioned reflex is as follows:

- When food, i.e. US is presented to a hungry dog, it produces salivation (an unconditioned response).
- If a bell is rung (a CS), just before the food (US) is presented, the dog learns to associate the bell (CS) with the food (US).
- Eventually, ringing the bell (CS) alone causes salivation.
- Of course, if the food fails to appear consistently when the bell is rung, the conditioned response fades away, a process called *extinction* or *internal inhibition.* Thus, a conditioned reflex needs to be reinforced frequently; otherwise, it dies out.

Physiological Basis of Conditioned Reflexes Physiologically, the occurrence of conditioned reflex is explained by the formation of a new functional connection in the nervous system.

Operant Conditioning

Operant conditioning is also termed instrumental conditioning, type II conditioning, type-R conditioning or trial-and-error conditioning. Operant conditioning is of the following two types:

- ***Reward conditioning***: In it, a naturally occurring response is strengthened by positive reinforcement (reward).
- ***Adversive conditioning***: In it, a naturally occurring (innate) response is weakened by a negative reinforcement (punishment).

Experiment to Demonstrate Operant Conditioning A hungry animal (e.g. rat) is placed in a cage with a lever (bars) protruding in the cage. Because of naturally occurring (innate) response, the rat will randomly press the lever.

- If the pressing of lever is not associated with any event, then the pressing of the lever will be at a random rate.
- If the pressing a lever is associated with a positive reinforcement, i.e. reward (e.g. food), the rate of pressing the lever will be much more than the random rate (*reward conditioning*).
- If the pressing of lever is associated with a negative reinforcement, i.e. punishment (e.g. electric shock), the lever-pressing rate will be much less than the random rate (*adversive conditioning*).

Memory

Memory refers to the acquisition, storage and retrieval of sensory information, whereas learning is the change in behaviour based on the sensory information stored in the brain. Brain has different sites and mechanisms for handling different types of information.

Types of Memory

Memory can be classified in the following two ways:

I. Physiologically: On the Basis of How Information Is Stored and Recalled

Implicit memory, also called nondeclarative or reflexive memory, refers to the information about how to perform something. It is not associated with awareness and does not involve processing in the hippocampus in most instances. Examples of implicit memory include motor skills, habits, behavioural reflexes and the learning of certain types of procedures and rules, which, once acquired, become unconscious and automatic.

Explicit memory: Explicit memory, also termed as *declarative* or *recognition memory*, refers to the factual knowledge of people, places, things and what these facts mean. This is recalled by a deliberate conscious effort. Explicit memory is highly flexible and involves the association of multiple bits and pieces of information. In contrast, implicit memory is more rigid and tightly connected to the original stimulus conditions under which the learning occurred.

II. Depending on Permanency of Storage

Depending on permanency of storage, memory is short-term, intermediate and long-term.

1. ***Short-term memory,*** also termed *primary memory*, lasts for seconds to hours. Examples of short-term memory include the memory of a new telephone number after calling the operator or after looking into the directory. Most of the times such a telephone number is forgotten after a few minutes.
2. ***Intermediate long-term memory*** (or secondary memory) lasts for days to weeks, but is eventually lost.
3. ***Long-term memory*** (or tertiary memory), which once stored, can be recalled years later or for a lifetime.

Mechanism (Physiological and Cellular or Molecular Basis) of Memory

Studies of memory retention and disruption of memory have revealed that both explicit and implicit memories are stored in stages by different mechanisms. Input to the brain is processed into *short-term memory* before it is transformed through one or more stages (intermediate long-term memory) into more permanent long-term storage.

Mechanism of Implicit Memory

Mechanism of Short-Term Storage of Implicit Memory

Mechanism for simple forms of learning results from *changes in the effectiveness of synaptic transmission*:

- Habituation (page 461)
- Sensitization (page 461)

Mechanism of Long-Term Storage of Implicit Memory

The process by which transient short-term memory is converted into a stable long-term memory is called consolidation. Consolidation of long-term implicit memory for simple forms of learning involves the following three processes:

- Gene expression
- New protein synthesis
- Growth (or pruning) of synaptic connections

Interhemispheric Transfer of Learning and Memory

Much information is transferred between the two hemispheres through the corpus callosum, although some is transmitted through other commissures (e.g. the anterior commissure or hippocampal commissure).

HIGHER INTELLECTUAL FUNCTIONS OF THE PREFRONTAL ASSOCIATION CORTEX

Prefrontal cortex refers to the portion of frontal lobes in front of the motor cortex. This area, like other association areas, is better developed in man than in any other species. The functions thought to be performed by prefrontal cortex are as follows:

- Role in thought process
- Site of working memory and intellectual functions (for more details, see page 389)

SELF-ASSESSMENT

1. Discuss in brief the mechanism of speech.
2. Discuss in brief the physiology of learning.
3. Differentiate between:
   - Sensory speech and motor speech
   - Sensory and motor aphasia
   - Habituation and sensitization
   - Associative and nonassociative learning
   - Implicit and explicit memory
   - Long-term and short-term memory

SECTION 11

Special Senses

SECTION OUTLINE

11.1 Sense of Vision
11.2 Sense of Hearing
11.3 Chemical Senses: Smell and Taste

11.1 Sense of Vision

CHAPTER OUTLINE

Introduction and Functional Anatomy
Introduction
Functional Anatomy
Maintenance of Clear Refractive Media of the Eye
Image-Forming Mechanism
Optics of the Eye
Accommodation
Common Defects of the Image-Forming Mechanism
Physiology of Vision
Photoreceptors and Visual Pigments
Photoreceptors
Visual Pigments
Phototransduction
Processing and Transmission of Visual Impulse in Visual Pathway
Processing and Analysis of Visual Impulse in the Visual Cortex
Visual Perception
Light Sense
Form Sense
Colour Sense
Field of Vision and Binocular Vision
Field of Vision
Binocular Single Vision
Aqueous Humour and Intraocular Pressure
Aqueous Production
Drainage of Aqueous Humour
Maintenance of Intraocular Pressure
Glaucoma
Physiology of Pupil
Pupillary Reflexes

INTRODUCTION AND FUNCTIONAL ANATOMY

Introduction

Sense of vision is a complex function of the two eyes and their central connections. The eyeballs are able to perform their function with the help of the following physiological activities:

- Maintenance of clear media of the eye
- The image-forming mechanism
- Physiology of vision
- Physiology of binocular vision
- Maintenance of normal intraocular pressure
- Physiology of pupil

Functional Anatomy

The Eyeball

Each eyeball (Fig. 11.1-1), though generally referred to as a globe, is not a sphere but an oblate spheroid.

Coats of the Eyeball

1. The Outer Fibrous Coat The fibrous coat (Fig. 11.1-1) is a dense strong wall which protects the intraocular contents. Anterior one-sixth of this fibrous coat is transparent and is called *cornea*. The average diameter of the cornea is 11–12 mm. The posterior five-sixth opaque white part is called *sclera*. Junction of the cornea and sclera is called *limbus*.

The sclera is relatively avascular structure of about 1 mm in thickness.

2. The Middle Vascular Coat (Fig. 11.1-1) also known as uveal tract, from anterior to posterior, can be divided into three parts.

Iris The iris is a coloured, circular diaphragm with a central aperture of 3–4 mm size known as *pupil*. The pupil regulates the light reaching the retina. The pupil constricts and dilates by the contraction of sphincter pupillae and dilator pupillae muscles of the iris, respectively. The sphincter pupillae is supplied by the parasympathetic nerves, whereas the dilator pupillae is supplied by the sympathetic nerves.

Ciliary Body The ciliary body is the middle part of the uveal tract. It contains a nonstriated muscle called the ciliary muscle which is supplied by parasympathetic fibres and takes part in the process of accommodation of the eye.

There are about 70–80 finger-like projections from the ciliary body called *ciliary processes*. They are the site of aqueous humour production – a watery fluid which maintains the intraocular pressure of the eyeball.

Choroid The choroid is a dark brown highly vascular layer situated in between the sclera and retina. It supplies nutrition to the outer layers of retina.

3. The Inner Nervous Coat (Retina) Retina is a thin, delicate, transparent membrane. It is the most highly developed tissue of the eye. It is concerned with the visual functions. Grossly, retina exhibits three distinct areas: optic disc, macula lutea and peripheral retina (Fig. 11.1-2).

Optic Disc It is a well-defined, circular, pink coloured disc of 1.5 mm diameter. It has only nerve fibre layer, so it does not excite any visual response. It produces *blind spot* in the field of vision.

Macula Lutea (Yellow Spot) It is a comparatively dark area situated at the posterior pole temporal to the optic disc. Its central depressed area of 1.5 mm diameter is called *fovea centralis*, which is the most sensitive part of the retina. Visual acuity is maximum in this part of the retina.

Ora Serrata It is the anterior serrated margin where the retina ends.

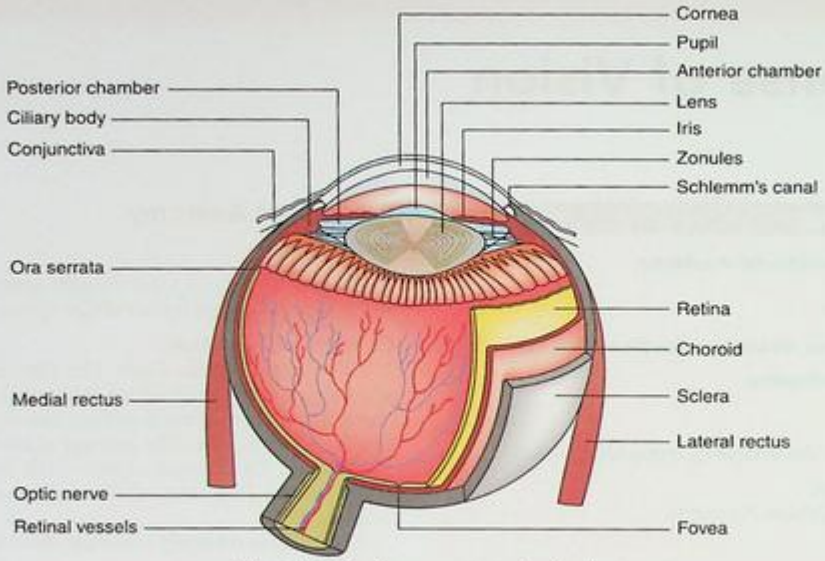


Figure 11.1-1 Gross anatomy of eyeball.

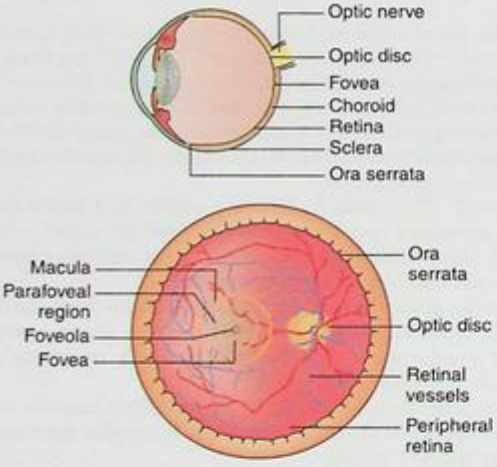


Figure 11.1-2 Gross anatomy of retina.

Microscopic Structure Retina consists of 10 layers, which from outwards to inwards are listed as follows (Fig. 11.1-3):

1. Layer of Pigment Epithelium It is a single layer of hexagonal cells containing melanin pigments. The principal function of the layer is to absorb stray light, and thereby to reduce light scatter.

2. Layer of Rods and Cones It consists of the outer segments of the photoreceptors (rods and cones). Photoreceptors are the end organs of vision.

3. External Limiting Membrane It is not a separate membrane. In fact, the numerous connections made between Muller cells and inner segments of photoreceptors give the appearance of a continuous membrane under light microscopy.

4. Outer Nuclear Layer This layer contains the nuclei of rods and cones.

5. Outer Plexiform Layer This layer contains presynaptic and postsynaptic elements of synapses that exist between the photoreceptors, bipolar cells and horizontal cells.

6. Inner Nuclear Layer It contains the cell bodies and nuclei of bipolar cells, amacrine cells and horizontal cells.

7. Inner Plexiform Layer It is the layer of synapse between bipolar cells, ganglion cells and amacrine cells.

8. Ganglion Cell Layer It consists of ganglion cells, which are the output cells of the retina. They transmit visual information to the brain.

9. Nerve Fibre Layer It consists of the axons of ganglion cells which pass through lamina cribrosa to form the optic nerve. These fibres remain unmyelinated in the retina, but become myelinated in the optic nerve.

10. Inner Limiting Membrane It is formed by projections of the Muller's cells and separates the retina from vitreous.

Interior of the Eyeball The interior of the eyeball consists of anterior and posterior chambers containing the aqueous humour, the lens and the vitreous. *Anterior chamber* is the space bound anteriorly by the back of cornea and posteriorly by the anterior surface of iris. *Posterior chamber* is the space between the front of crystalline lens and the back of iris.

MAINTENANCE OF CLEAR REFRACTIVE MEDIA OF THE EYE

The major factor responsible for transparency of the ocular media is their avascularity. The structures forming refractive media of the eye from anterior to posterior are tear film, cornea, aqueous humour, crystalline lens and vitreous humour.

- ***Tear film.*** It keeps the cornea moist, and provides oxygen and nutrients.
- ***Cornea.*** It forms the principal refracting medium of the eye.

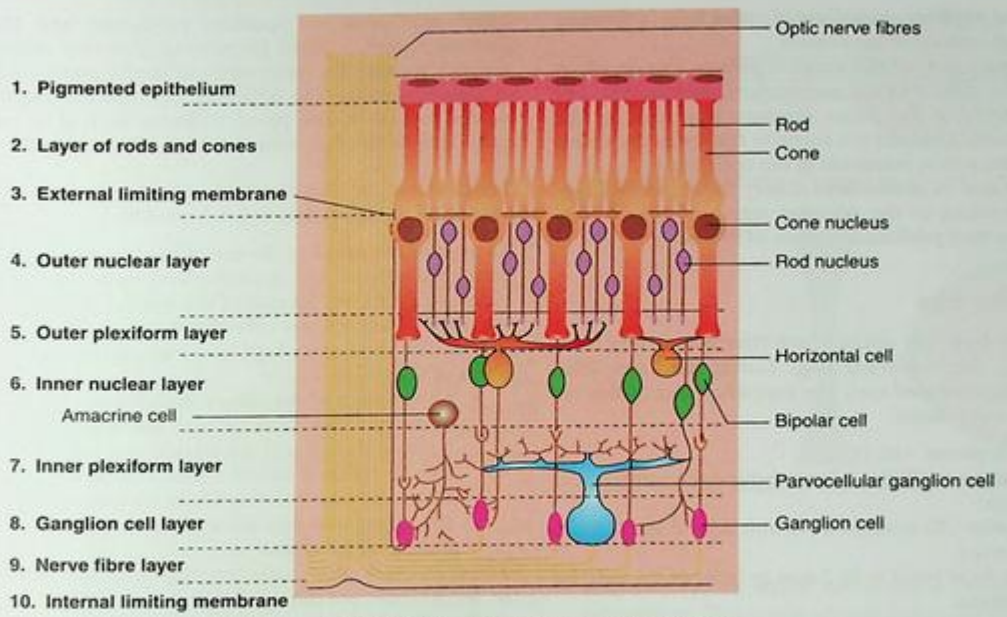


Figure 11.1-3 Microscopic structure of retina.

- ***Aqueous humour.*** It is a clear watery fluid filling the anterior chamber and posterior chamber of the eye.
- ***Crystalline lens.*** It is a biconvex lens which has been provided with a unique mechanism of changing its power *(accommodation)*. Due to this characteristic, it helps in sharp focussing of the images of the objects present at varying distances from the eye.
- ***Vitreous humour.*** It is clear jelly-like material that fills posterior four-fifth of cavity of eyeball, which in addition to being a refractive medium also helps in maintaining the shape of the eyeball.

Crystalline lens is a transparent, biconvex, crystalline structure placed between the iris and the vitreous. It is suspended from the ciliary body by the suspensory ligaments or zonules of Zinn. Refractive power of the lens is about 15–16 diopter (D). Lens is elastic in nature and its power changes with accommodation.

THE IMAGE-FORMING MECHANISM

The functioning of the eye as an optical instrument can be compared with a close-circuit colour television camera (Fig. 11.1-4) in which:

- ***Eyelids*** act as a shutter of the camera.
- ***Cornea and crystalline lens*** act as a focussing system of the camera.
- ***Iris*** acts as a diaphragm, which regulates the size of the aperture (pupil) and therefore the amount of light entering the eye.

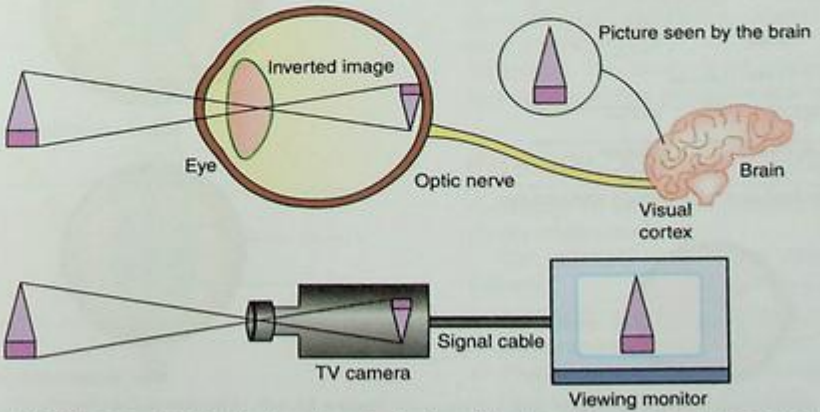


Figure 11.1-4 The sense of sight in many ways is similar to a close-circuit colour TV system. It is superior in all respects except ease of replacement.

- ***Choroid and pigment epithelium of retina*** help in forming the darkened interior of the camera.
- ***Neural retina*** acts as a light-sensitive plate or film on which images of the objects in the environment are focussed. The light rays striking the retina generate potentials in the rods and cones. Thus the eye converts energy in the visible spectrum into action potentials in the optic nerve.
- ***Optic nerve and its connections*** convey the impulses generated in the retina to the occipital region of the cerebral cortex where they produce sensation of vision.

Optics of the Eye

The Reduced Eye The optics of eye otherwise is very complex. However, for understanding, Listing has simplified the data (***Listing's reduced eye***). The simplified data of this eye (Fig. 11.1-5) are as follows:

- Total dioptric power +60 D.
- The principal point (P) lies 1.5 mm behind the anterior surface of cornea.
- The nodal point (N) is situated 7.2 mm behind the anterior surface of cornea.
- The anterior focal point is 15.7 mm in front of the anterior surface of cornea.
- The posterior focal point (on the retina) is 24.4 mm behind the anterior surface of cornea.
- The anterior focal length is 17.2 mm (15.7 + 1.5) and the posterior focal length is 22.9 mm (24.4 – 1.5).

Accommodation

Our eyes have been provided with a unique mechanism by which we can even focus the diverging rays coming from a near object on the retina in a bid to see clearly (Fig. 11.1-6). This mechanism is called accommodation. In it, there occurs an increase in the power of the crystalline lens.

Far Point, Near Point, Range and Amplitude of Accommodation The nearest point at which small objects can be seen clearly is called *near point* or punctum proximum and the distant (farthest) point is called *far point* or punctum remotum. The distance between the near point and the far point is called *range of accommodation*. The difference between the dioptric power needed to focus at near point (P) and to focus at far point (R) is called *amplitude of accommodation* (A). Thus, A = P − R.

Mechanism of Accommodation in Human In man the process of accommodation is achieved by:

Change in the shape of the lens When the eye is at rest (unaccommodated) the lens is compressed in its capsule (which is elastic structure) by tension of the zonules. The surfaces of the compressed lens are less curved and change the dioptric power in lens. The zonules are kept under tension by the relaxation of fibres of the ciliary muscle.

- ***Contraction of the ciliary muscle*** causes the ciliary ring to shorten and move forward the equator of the lens. As a result, the zonules are relaxed, the tension on the capsule is relieved and the lens attains a more spherical shape. Increase in convexity of the lens increases its dioptric power, and thus allows the near objects to be focused clearly on the retina.

The principal change in the lens during accommodation is seen in the anterior surface of the lens as compared to posterior surface (Fig. 11.1-7).

Pupillary constriction and convergence of eyes In addition to the changes in the lens and zonular system, the pupil constricts and the eyes converge, almost simultaneously. These changes occur in a bid to achieve clear vision for near objects.

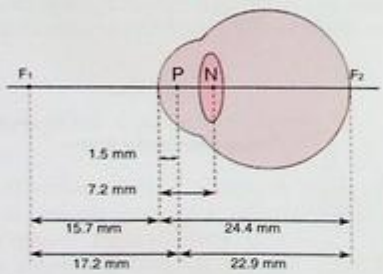


Figure 11.1-5 Cardinal points of Listing's reduced eye.

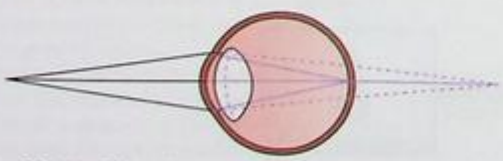


Figure 11.1-6 Effect of accommodation on divergent rays entering the eye.

Common Defects of the Image-Forming Mechanism

Emmetropia The emmetropia (optically normal eye) can be defined as a state of refraction when the parallel rays of light

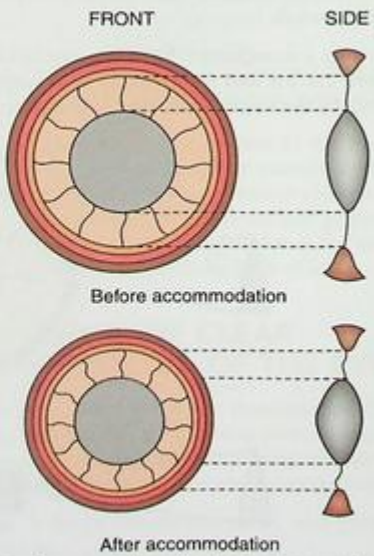


Figure 11.1-7 Changes in the ciliary body ring zonules and shape of lens during accommodation.

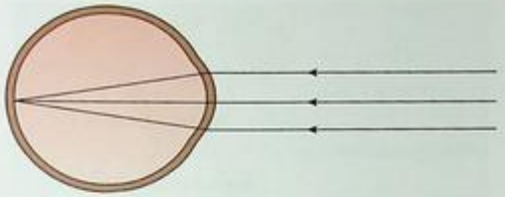


Figure 11.1-8 Refraction in an emmetropic eye.

coming from infinity are focused at the sensitive layer of retina with the accommodation being at rest (Fig. 11.1-8).

Ametropia The ametropia (a condition of refractive error) is defined as a state of refraction when the parallel rays of light coming from infinity (with accommodation at rest) are focused either in front or behind the sensitive layer of retina in one or both the meridia. The ametropia includes myopia, hypermetropia and astigmatism.

Hypermetropia The hypermetropia (hyperopia) or long sightedness is the refractive state of the eye wherein parallel rays of light coming from infinity are focused behind the retina with accommodation being at rest (Fig. 11.1-9). Persons with mild-to-moderate hypermetropia, in their young age, can see the distant objects clearly using their accommodation. This is why hypermetropia is also called far sightedness or long sightedness.

Optical Correction Basic principle of treatment of hypermetropia is optical correction with convex (plus) lenses, so that the light rays are brought to focus on the retina (Fig. 11.1-10).

Myopia The myopia or short sightedness is a type of refractive error in which parallel rays of light coming from infinity are focused in front of the retina when accommodation is at rest

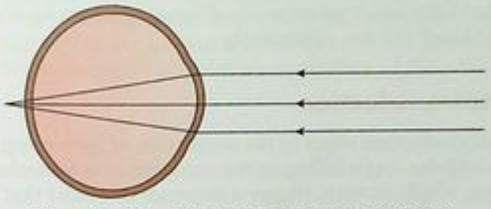


Figure 11.1-9 Refraction in a hypermetropic eye.

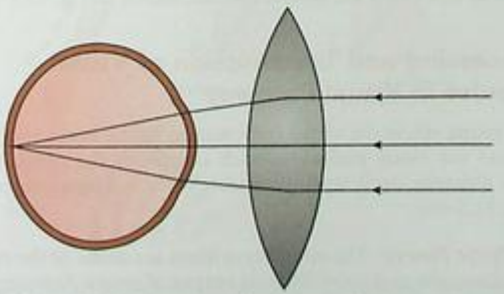


Figure 11.1-10 Refraction in a hypermetropic eye corrected with convex lens.

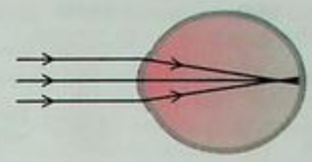


Figure 11.1-11 Optics of myopia parallel rays are focussed in front of retina.

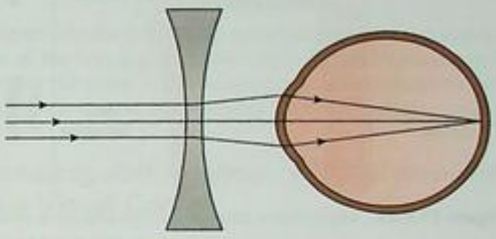


Figure 11.1-12 Refraction in a myopic eye corrected by concave lens.

(Fig. 11.1-11). Therefore, the myopic persons cannot see the distant objects. This is why myopia is also called *short sightedness.*

Optical Correction Basic principle of treatment of myopia is optical correction with concave (minus) lenses, so that clear image is formed on the retina (Fig. 11.1-12).

Astigmatism It is a type of refractive error wherein the refraction varies in the different meridia. Consequently, the rays of light entering the eye cannot converge to a point focus but form focal lines.

Presbyopia The presbyopia (eyesight of old age) is not an error of refraction but condition of physiological insufficiency of accommodation, leading to failing vision for near.

We usually keep the book at about 25 cm, so we can read comfortably up to the age of 40 years. After the age of 40 years, the near point of accommodation recedes beyond the normal reading or working range. This condition of failing near vision due to age-related decrease in the amplitude of accommodation or increase in punctum proximum is called presbyopia. It occurs due to (i) decrease in the elasticity of the crystalline lens and (ii) age-related decrease in the power of ciliary muscles.

Treatment The treatment of presbyopia is the prescription of appropriate convex glasses for near work.

PHYSIOLOGY OF VISION

Physiology of vision is a complex phenomenon which is still poorly understood.

The principal mechanisms concerned with vision are as follows:

- ***Initiation of vision*** (phototransduction), a function of photoreceptors (rods and cones).
- ***Processing and transmission of visual sensation***, a function of the image processing cells of retina and visual pathway.

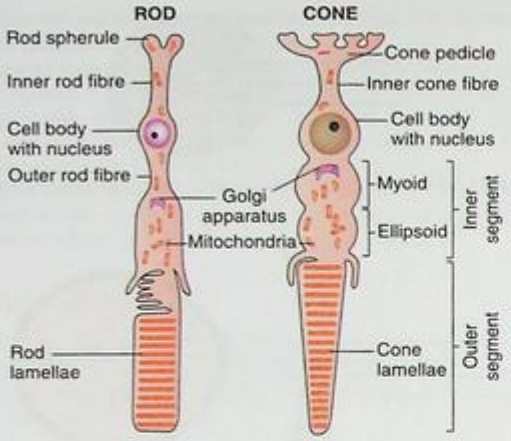


Figure 11.1-13 Microscopic structure of rod and cone cells.

- ***Visual perceptions***, a function of visual cortex and related areas of cerebral cortex.

Photoreceptors and Visual Pigments

Photoreceptors

Structure of Photoreceptor Each *photoreceptor* consists of a cell body and a nucleus (which lie in the outer nuclear layer), a cell process that extends into outer plexiform layer and inner and outer segments (which form the layer of rods and cones) (Fig. 11.1-13). The long axis of the photoreceptor is oriented perpendicular to the retinal surface.

Visual Pigments

Rhodopsin (Visual Purple) Rhodopsin is the photosensitive visual pigment present in the discs of the rod outer segments. It consists of a protein opsin (called scotopsin) and a carotenoid called retinal (the aldehyde of vitamin A).

The absorption spectrum of rhodopsin, as shown in Fig. 11.1-14, depicts that its peak sensitivity to light lies within the narrow limits of 493–505 nm. It absorbs primarily yellow wavelength of light, transmitting violet and red to appear purple by transmitted light; it is therefore also called visual purple.

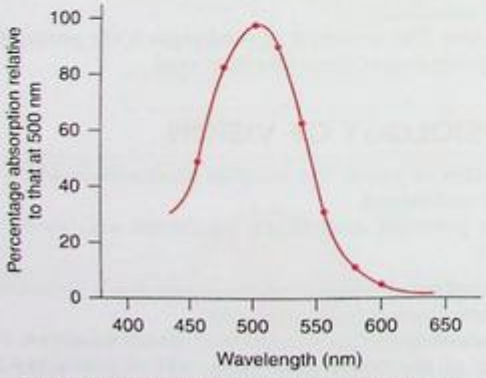


Figure 11.1-14 Absorption spectrum of rhodopsin.

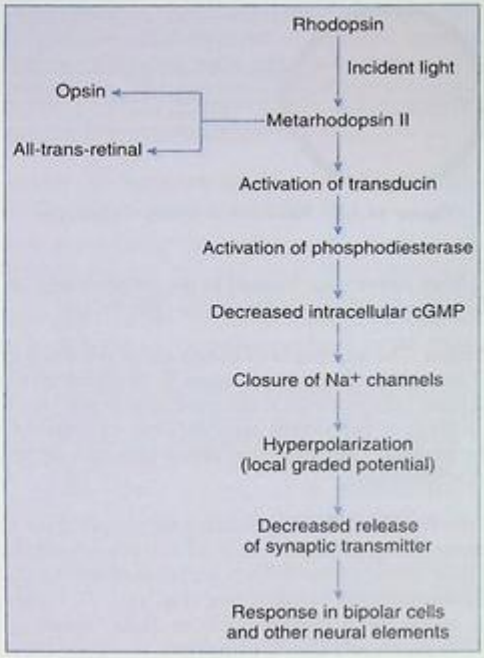


Figure 11.1-15 Sequence of events involved in phototransduction process in the photoreceptors.

Cone Pigments There are three kinds of cones in primates. Cone pigments are somewhat different from the rhodopsin, in a way that they respond to specific wavelength of light, giving rise to colour vision. These differences are present in the opsin portion of the molecule, whereas the chromophore 11-cis-retinal remains the same. The peak absorbance wavelengths of the 'blue', 'green' and 'red' sensitive cones lie at about 435, 535 and 580 nm, respectively.

Phototransduction

Phototransduction refers to the conversion of light energy into nerve impulse. Light falling on the retina initiates *photochemical changes*, which, in turn, trigger a sequence of events that cause phototransduction. The photochemical changes occurring in the rods and cones are similar and are shown in Fig. 11.1-15.

Processing and Transmission of Visual Impulse in Visual Pathway

The retina relays the visual information to the brain (occipital cortex) via visual pathway, which comprises the optic nerve, optic chiasma, optic tract, geniculate body and optic radiations (Fig. 11.1-16).

1. Optic Nerve The optic nerve fibres are axons of the retinal ganglion cells and carry the total output of retina. Arrangement of nerve fibres in the optic nerve head and distal region of the optic nerve (behind the eyeball) is exactly same as in the retina.

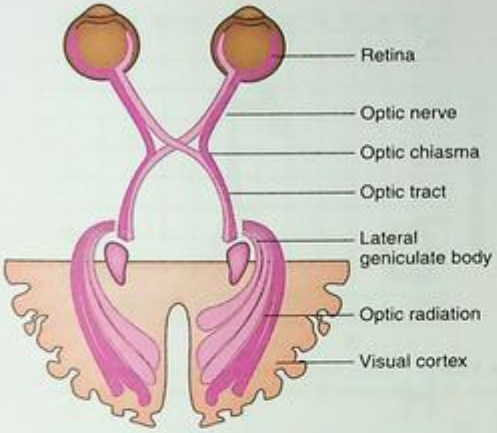


Figure 11.1-16 Components of visual pathway.

2. *Optic Chiasma* It is flattened structure lying above the pituitary fossa. Fibres originating from the nasal halves of the retinae decussate at the chiasma, whereas the fibres from temporal halves of retinae remain uncrossed. This implies that visual impulse from the temporal half of visual field goes to the opposite side, whereas the input from the nasal half of the visual field remains on the same side (Fig. 11.1-16).

3. *Optic Tracts* These are cylindrical bundles of nerve fibres which originate from the posterolateral angle of chiasma and run outwards and backwards to end in the lateral geniculate body (LGB). They consist of temporal fibres of the same side and nasal fibres of the opposite side.

4. *Lateral Geniculate Bodies* These are oval structures situated at the posterior termination of the optic tracts.

Each LGB contains six well-defined layers. On each side, layers 1, 4 and 6 receive input from the nasal half of the contralateral eye, whereas layers 2, 3 and 5 receive input from the temporal half of the ipsilateral eye (Fig. 11-1-17). In each layer, there is precise point-to-point representation of the retina.

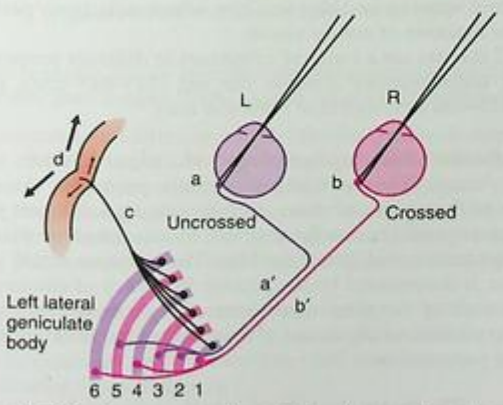


Figure 11.1-17 Arrangement of termination of axons of ganglion cells (second-order neurons) of two eyes in the lateral geniculate body (LGB) (for explanation, see text).

Functions of LGB. Two principal functions served by LGB are as follows:

1. ***Relay station.*** LGB serves as a relay station to relay the visual information from the ganglion cells to the visual cortex via parvocellular and magnocellular pathways. The signals from the two eyes are kept apart in LGB.
2. ***Visual perception and to 'gate' the transmission of signals,*** i.e. to control how much of the signals be allowed to pass to the cortex.

5. *Optic Radiations* The optic radiations are composed of axons of the lateral geniculate relay cells, which project to visual cortex on the same side. The optic radiations maintain a *retinotopic organization* in their passage to visual cortex.

Processing and Analysis of Visual Impulse in the Visual Cortex

Retinotopic Organization

Just as the ganglion cell axons project a detailed spatial representation of the retina on the LGB, the LGB projects a similar point-to-point representation on the visual cortex. The visual cortex is, therefore, also called the *cortical retina*, because a true copy of the retinal image is formed here. It is only in the visual cortex that impulses originating from corresponding points of two retinae meet.

Visual Areas

Classical Nomenclature Classically, the visual cortex has been divided into three parts.

1. ***Primary visual cortex,*** also called striate cortex or area 17, lies in the medial surface of the occipital lobe in and near the calcarine sulcus occupying parts of the lingual sulcus and coneum.
2. ***Peristriate cortex*** or visual association area 18 lies in the walls of lunate sulcus.
3. ***Parastriate cortex*** or visual association area 19 lies in the cortex in front of the lunate sulcus.

Visual Perception

It is a complex integration of light sense, form sense, sense of contrast and colour sense.

The Light Sense

It is awareness of the light. The minimum brightness required to evoke a sensation of light is called the *light minimum*. It should be measured when the eye is dark adapted for at least 20–30 minutes.

The human eye in its ordinary use throughout the day is capable of functioning normally over an exceedingly wide range of illumination by a highly complex phenomenon termed as the *visual adaptation*. The process of visual adaptation primarily involves:

- *Dark adaptation* (adjustment in dim illumination)
- *Light adaptation* (adjustment to bright illumination)

Dark Adaptation It is the ability of the eye to adapt itself to a decreasing illumination. When one goes from a bright sunshine into a dimly lit room, one cannot perceive the objects

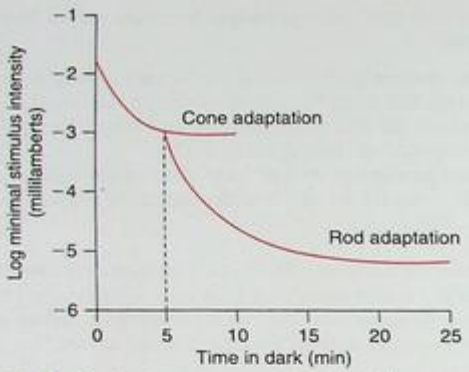


Figure 11.1-18 Dark adaptation curve plotted with illumination of test object along the vertical axis and duration of dark adaptation along the horizontal axis.

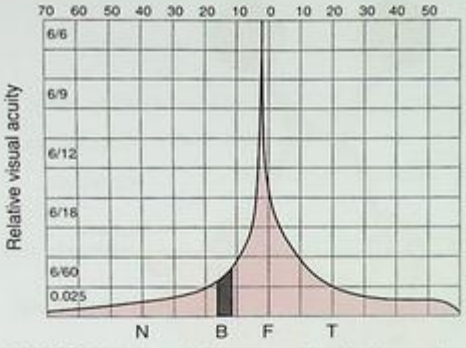


Figure 11.1-19 Visual acuity (form sense) in relation to the regions of the retina: N, nasal retina; B, blind spot; F, foveal region and T, temporal retina.

in the room until some time has elapsed. During this period, eye is adapting to low illumination. The time taken to see in dim illumination is called *dark adaptation time*. The rods are much more sensitive to low illumination than cones. Therefore, rods are used more in dim light (*scotopic vision*) and cones in bright light (*photopic vision*).

Dark Adaptation Curve Plotted with an illumination of test object in vertical axis and duration of dark adaptation along the horizontal axis shows that visual threshold falls progressively in the darkened room for about half an hour until a relative constant value is reached (Fig. 11.1-18).

Dark Adaptation and Vitamin A Deficiency Severe deficiency of vitamin A elevates the threshold for dark adaptation due to depletion of the photosensitive pigment. *Nyctalopia,* i.e. night blindness is another important feature of vitamin A deficiency.

Light Adaptation When one passes suddenly from a dim to a brightly lit environment, the light seems intensely and even uncomfortably bright until the eyes adapt to the increased illumination and the visual threshold rises. The process by means of which retina adapts itself to the bright light is called *light adaptation.* Unlike dark adaptation, the process of light adaptation is very quick and occurs over a period of 5 minutes. Strictly speaking, light adaptation is merely the disappearance of dark adaptation.

The Form Sense

It is the ability to discriminate between the shapes of the objects. Cones play a major role in this faculty. Therefore, form sense is most acute at the fovea, where there is maximum number of cones and decreases very rapidly towards the periphery (Fig. 11.1-19). Visual acuity recorded by Snellen's test chart is a measure of the form sense.

Visual Acuity Measurement of the threshold of discrimination of two spatially separated targets (a function of the fovea centralis) is termed visual acuity.

Snellen's test types In clinical practice, the measurement of visual acuity is considered synonymous with measurement of minimal resolvable. To measure the minimal resolvable, Snellen constructed certain test types, which are now routinely used to test the distant central visual acuity.

The fact that two distant points can be visible as separate only when they subtend an angle of 1 minute (1/60th of a degree) at the nodal point of the eye, forms the basis of Snellen's test types. It consists of a series of black capital letters on a white board, arranged in lines, each progressively diminishing in size. The lines comprising the letter have such a breadth that they will subtend an angle of 1 minute at the nodal point. Each letter of the chart is so designed that it fits in a square, the sides of which are five times the breadth of the constituent lines. Thus at the given distance, each letter subtends an angle of 5 minutes at the nodal point of the eye (Fig. 11.1-20) The letter of the top line of Snellen's chart (Fig. 11.1-21) should be read clearly at a distance of 60 m. Similarly, the letters in the subsequent lines should be read from a distance of 36, 24, 18, 12, 9, 6, 5 and 4 m.

The Colour Sense

Colour sense is the ability of the eye to discriminate between colours excited by light of different wavelengths. Some broad facts about colour vision are:

- Colour vision is a function of cones and thus better appreciated in photopic vision.
- There are three different types of cones, such as red sensitive, green sensitive and blue sensitive, which collectively perform the function of colour vision.
- All colours are a result of admixture in different proportion of three primary colours: the red (725–645 nm), green (575–490 nm) and blue (490–450 nm).

Mechanism (Neurophysiology) of Colour Vision

Trichromatic Theory Young–Helmholtz postulates the existence of three kinds of cones, each containing a different photopigment and maximally sensitive to one of three primary colours such as red, green and blue. The sensation of any given colour is determined by the relative frequency of the impulse from each of the three cone systems. In other words, a given colour consists of admixture of the three primary colours in different proportions.

Colour Blindness An individual with normal colour vision is known as *trichromate.* In colour blindness, faculty to appreciate one or more primary colours is either defective (anomalous) or

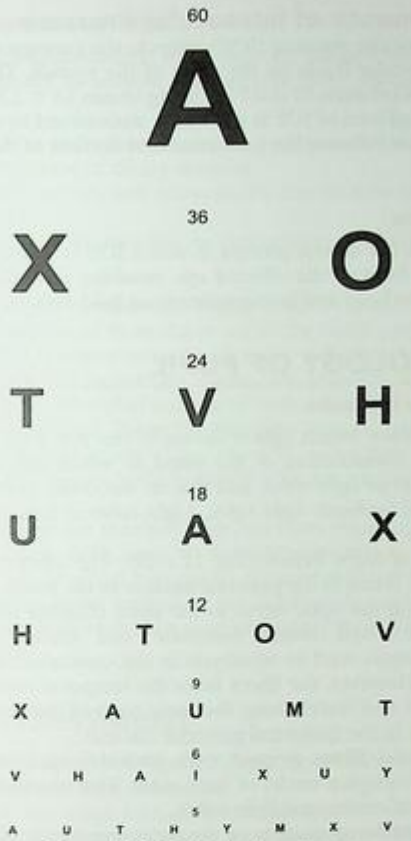


Figure 11.1-20 Snellen's test types.

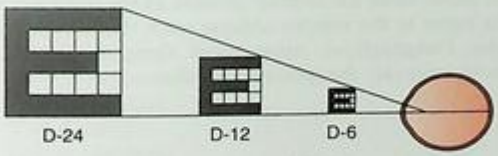


Figure 11.1-21 Principle of Snellen's test type.

absent (anopia). It is an inherited condition affecting males more (3%–4%) than females (0.4%). It may be of the following types.

1. **Anomalous trichromatism** Here the mechanism to appreciate all the three primary colours is present but is defective for one or two of them. It may be of the following types:
   - ***Protanomalous***, i.e. defective red colour appreciation.
   - ***Deuteranomalous***, i.e. defective green colour appreciation.
   - ***Tritanomalous***, i.e. implies defective blue colour appreciation.
2. **Dichromatism** In this condition, faculty to perceive one of the three primary colours is completely absent. Such individuals are called dichromates and may have one of the following types of defects:
   - ***Protanopia***, i.e. complete red colour defect.
   - ***Deuteranopia***, i.e. complete defect for green colour.
   - ***Tritanopia***, i.e. absence of blue colour appreciation.

Figure 11.1-22 Ishihara charts.

Tests for Colour Vision

1. Pseudo-isochromatic Chart Test It is the most commonly employed test using Ishihara's plates (Fig. 11.1-22). In this, there are patterns of coloured and grey dots which reveal one pattern to the normal individuals and another to the colour deficients. It is quick method of screening colour blinds from the normals.

2. The Lantern Test In this test, the subject has to name the various colours shown to him by a lantern and the judgement is made by the mistake he makes. Eldridge–Green lantern is most popular.

3. Holmgren Wool Test In this, the subject is asked to make a series of colour matches from a selection of skeins of coloured wools.

FIELD OF VISION AND BINOCULAR VISION

Field of Vision

The visual field is a three-dimensional area that can be seen around an object of fixation. The extent of normal visual field with a 5 mm white colour object is superiorly 60°, inferiorly 70°, nasally 60° and temporally 90° (Fig. 11.1-23). The field for blue and yellow is roughly 10° less and that for red and green

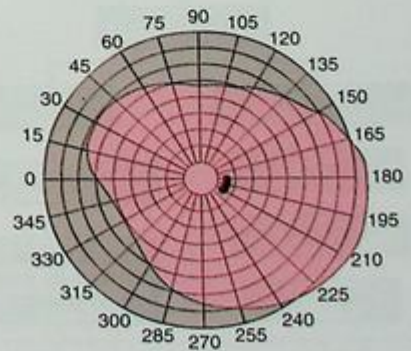


Figure 11.1-23 Extent of normal visual field.

colour is about 20° less than that for white. Perimetry with a red colour object is particularly useful in the diagnosis of bitemporal hemianopia due to chiasmal compression and in the central scotoma of retrobulbar neuritis.

Binocular Single Vision

Definition When a normal individual fixes his visual attention on an object of regard, the image is formed on the fovea of both the eyes separately; but the individual perceives a single image. This state is called binocular single vision. It is a conditioned reflex which is not present since birth but is acquired during first 6 months and is completed during first few years. The process of its development is complex and partially understood.

Binocular single vision plays an important role for depth perception.

AQUEOUS HUMOUR AND INTRAOCULAR PRESSURE

Aqueous Production

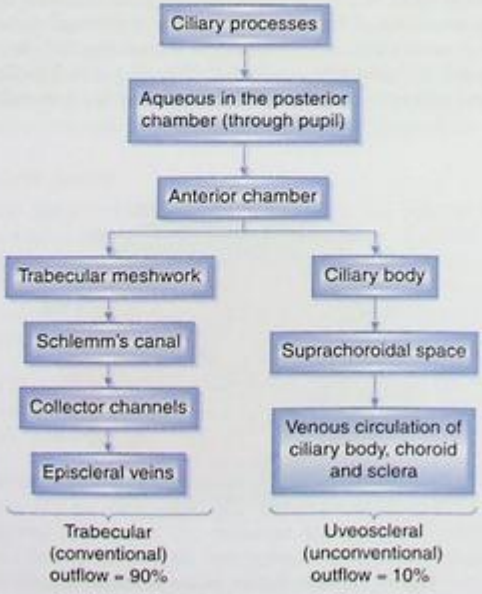
The aqueous humour is a clear, watery fluid filling the anterior chamber (0.25 mL) and posterior chamber (0.06 mL) of the eyeball. *In addition to its role in* maintaining a proper intraocular pressure, it also plays an important metabolic role by providing substrates and removing metabolites from the avascular cornea and lens.

Aqueous humour is derived from plasma within the capillary network of ciliary processes.

Drainage of Aqueous Humour

Aqueous humour flows from the posterior chamber into the anterior chamber through the pupil against the slight physiologic resistance. From the anterior chamber, the aqueous is drained out by two routes as shown:

- Trabecular (conventional outflow)
- Uveoscleral (unconventional) outflow



Maintenance of Intraocular Pressure

The intraocular pressure (IOP) refers to the pressure exerted by the intraocular fluids on the coats of the eyeball. The normal IOP varies between 10 and 21 mm Hg (mean 16 ± 2.5 mm Hg). The normal level of IOP is essentially maintained by a dynamic equilibrium between the formation and outflow of the aqueous humour.

Glaucoma

Glaucoma is a disease process in which IOP is raised above the tolerance limit of the affected eye, resulting in damage to the optic nerve head and irreversible visual field defects.

PHYSIOLOGY OF PUPIL

Pupillary Reflexes

Light Reflex When light is shown in one eye, both the pupils constrict. Constriction of the pupil to which light is shown is called *direct light reflex* and that of the other pupil is called *consensual (indirect) light reflex*. Light reflex is initiated by rods and cones.

Pathway of Light Reflex (Fig. 11.1-24). The *afferent fibres* extend from retina to the pretectal nucleus in the midbrain. These travel along the optic nerve to the optic chiasma where fibres from the nasal retina decussate and travel along the opposite optic tract to terminate in the contralateral pretectal nucleus. However, the fibres from the temporal retina remain uncrossed and travel along the optic tract of the same side to terminate in the ipsilateral pretectal nucleus.

Internuncial fibres connect each pretectal nucleus with the Edinger–Westphal nuclei of both sides. This connection forms the basis of consensual light reflex.

Efferent pathway consists of the parasympathetic fibres which arise from the Edinger–Westphal nucleus in the midbrain and travel along the third (oculomotor) cranial nerve. The preganglionic fibres enter the inferior division of the third nerve and via the nerve to the inferior oblique reach the ciliary ganglion to relay. Postganglionic fibres travel along the short ciliary nerves to innervate the sphincter pupillae.

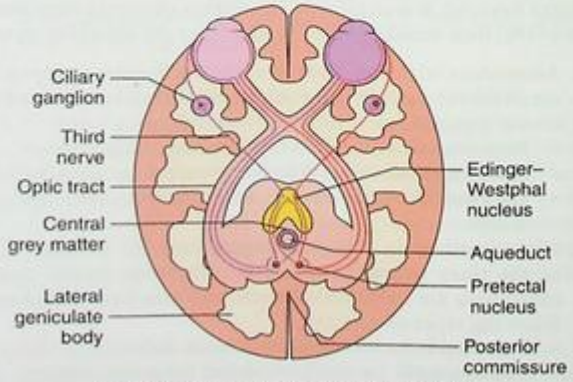


Figure 11.1-24 Pathway of the light reflex.

Accommodation Reflex

During accommodation, when eyes are focused from distant to near object to achieve clear vision, three reactions occur, such as:

- Changes in the radius of curvature of the lens (more convex) by contraction of ciliary muscles
- Pupillary constriction (meiosis) by contraction of sphincter pupillae
- Convergence of eyes due to contraction of medial recti of eye balls

Pathway of Accommodation Reflex (Fig. 11.1-25). The afferent impulses extend from the retina to the visual cortex via the optic nerve, chiasma, optic tract, optic radiations and striate cortex. From the parastriate cortex, the impulses are relayed to the Edinger–Westphal nucleus of both sides via the occipitomesencephalic tract. From the Edinger–Westphal nucleus, the efferent impulses travel along the 3rd nerve and reach the sphincter pupillae and ciliary muscle after relaying in the ciliary ganglia.

For convergence reaction impulses from visual cortex reach the frontal eye field (area 8) through association fasciculus (superior longitudinal fasciculus). From frontal eye field the corticonuclear fibres project to the third nerve nuclei of both sides and through oculomotor nerves supply the medial recti of the eye balls.

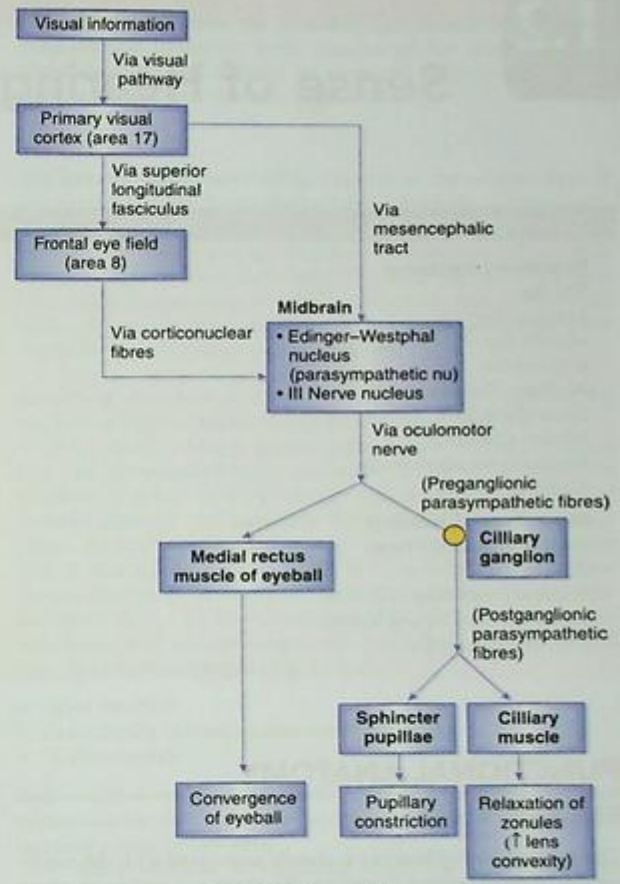


Figure 11.1-25 Pathway of the near reflex.

SELF-ASSESSMENT

1. With the help of well-labelled diagram, describe the coats of an eyeball and their functions.
2. Describe the image formation mechanism.
3. Describe the process of photo transduction.
4. Write notes on:
   - Accommodation
   - Refractive errors
   - Presbyopia
   - Visual pigments
   - Optical pathway
   - Dark adaptation
   - Visual acuity
   - Colour blindness
   - Formation of aqueous humour
   - Intraocular pressure
   - Pupillary reflex

11.2 Sense of Hearing

CHAPTER OUTLINE

Functional Anatomy
The Ear
External Ear
Middle Ear
Internal Ear
Auditory Pathways
Spiral Ganglion
Inferior Colliculus
Medial Geniculate Body
Auditory Cortex

Physiology of Hearing
Stimuli or Sound Waves
Definitions
Physical Properties of Sound
Conduction of Sound Waves
Role of External Ear
Role of Middle Ear
Impedance Matching
Attenuation Reflex
Transduction of Sound Waves
Vibration of Basilar Membrane
Stimulation of the Hair Cells
Membrane Potential Changes in the Hair Cells
Neural Transmission of Signals
Neural Processing of Auditory Information
Encoding of Sound Frequency
Encoding of Intensity
Localization of Sound in Space

Applied Aspects
Noise and Masking
Hearing Loss, Deafness and Tinnitus

FUNCTIONAL ANATOMY

The Ear

The mechanism of hearing is closely associated with the mechanism of equilibrium; therefore, the inner ear acts as an organ of hearing and equilibrium. For hearing, the sound waves have to pass through the three subdivisions of the ear, which are as follows (Fig. 11.2-1):

- External ear
- Middle ear
- Internal ear

External Ear

The external ear consists of the pinna (auricle) and the external auditory meatus.

Pinna or auricle consists of a single convoluted plate of elastic cartilage covered by skin. In humans, the pinna is not movable.

External auditory meatus extends from the pinna to the tympanic membrane. It is lined with skin, which secretes wax (from the ceruminous glands) and oil (from the sebaceous glands).

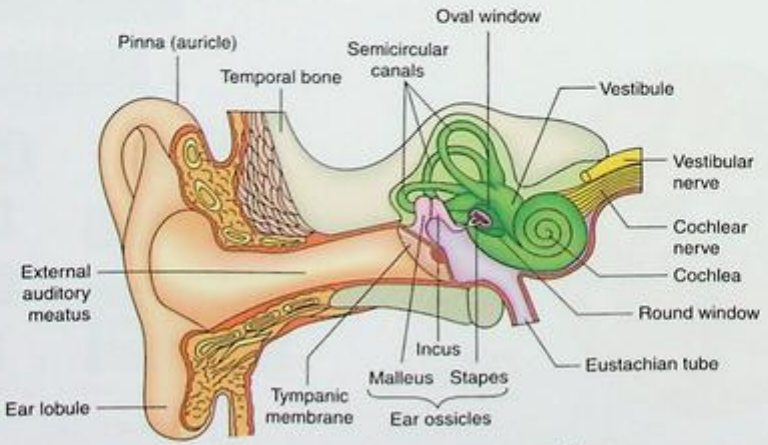


Figure 11.2-1 Structure of three subdivisions of the ear.

Middle Ear

The middle ear or the tympanic cavity is an air-filled rectangular space in the petrous part of temporal bone. It consists of the following structures.

Tympanic Membrane The tympanic membrane is a cave-shaped structure with concavity directed towards the external auditory meatus. Point of maximum convexity is called umbo. It consists of connective tissue covered with skin on the outside and mucous membrane on the inside.

Eustachian Tube Eustachian tube or the pharyngotympanic tube connects the middle ear cavity with pharynx. Air can pass through this tube into the middle ear. Therefore, it serves the function of equalization of pressure on two sides of tympanic membrane.

Ear Ossicles The three ear ossicles (auditory ossicles) include malleus, incus and stapes. They are attached to each other by ligaments and form a chain (Fig. 11.2-2).

Malleus. It resembles hammer and consists of a head, neck and three processes:

- *Manubrium* (handle) of the malleus is connected to the inner surface of the tympanic membrane.
- *Head* articulates with incus posteriorly.

Incus is the middle ossicle that resembles an anvil in shape. It consists of a body and two processes. The body of incus articulates with the head of malleus.

Stapes. It resembles a stirrup. Its head articulates with the incus and the oval footplate contacts the membrane of the oval window of the cochlea.

Windows Medial wall (labyrinthine wall) of the middle ear contains two windows (Fig. 11.2-1):

- ***Oval window*** (fenestra vestibuli) is present above, in which foot plate (face plate or stapes) is attached. It leads to the vestibule of the internal ear and transmits the sound vibrations of the ossicles to the perilymph of scala vestibuli.
- ***Round window*** (fenestra cochlea) is present in the lower part and is closed by a thin membrane called *secondary tympanic membrane.* It accommodates the pressure waves transmitted to the perilymph of the scala tympani.

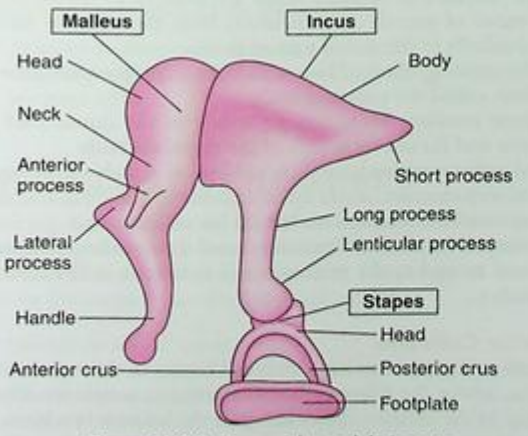


Figure 11.2-2 Ear ossicles and their parts.

Muscles The middle ear contains two muscles: the tensor tympani and stapedius. Both muscles of the middle ear act simultaneously and reflexly in response to loud sound and attenuate the sound (see also page 483).

Internal Ear

The internal ear or labyrinth is situated in the petrous part of the temporal bone. It consists of bony labyrinth and membranous labyrinth. *Bony labyrinth* consists of three parts: vestibule, semicircular canals and the cochlea. *Membranous labyrinth* is lodged within the bony labyrinth. The inner ear can be divided into two principal parts: vestibular apparatus and auditory receptor apparatus. The vestibular apparatus is concerned with equilibrium and is described on page 437.

Auditory Apparatus The auditory apparatus is formed by the *duct of cochlea*, which lies within the bony cochlea.

Cochlea *Bony cochlea* is a spiral tube, which in humans has a two and three-fourth turns around a central bone called the *modiolus*. The base of the modiolus is directed towards internal acoustic meatus, and transmits vessels and nerves to the cochlea. Around the modiolus and winding spirally, like the thread of a screw, is a thin plate of bone called *osseous spiral lamina*. It divides the bony cochlea incompletely and gives attachment to the basilar membrane. Two membranes (*basilar membrane* and *Reissner's membrane*) divide the bony cochlea into three compartments (Fig. 11.2-3):

- Scala vestibuli
- Scala media (membranous cochlear duct)
- Scala tympani

Scala vestibuli and scala tympani are filled with perilymph and communicate with each other at the apex of cochlea through an opening called *helicotrema*.

- ***Scala vestibuli*** is separated from the scala media by *Reissner's membrane* and is closed by the footplate of stapes, which separates it from the air-filled middle ear (Figs 11.2-3 and 11.2-4).
- ***Scala tympani*** is separated from the scala media by the *basilar membrane* and is closed by *secondary tympanic*

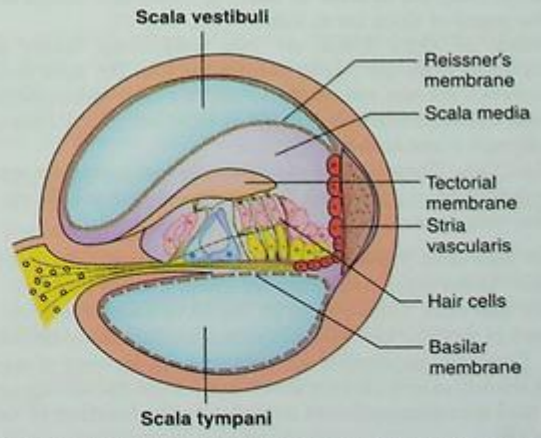


Figure 11.2-3 Vertical section through cochlea showing scala vestibuli, scala media (cochlear duct) and scala tympani. Note the location of organ of Corti over the basilar membrane in the cavity of cochlear duct.

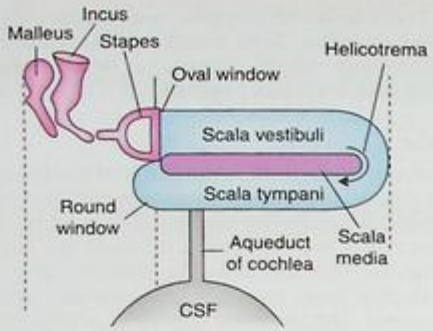


Figure 11.2-4 Diagrammatic depiction of arrangement of perilymphatic system, three compartments of cochlea (scala vestibuli, scala media and scala tympani) and ear ossicles of the middle ear. Note the CSF passes into scala tympani through aqueduct of cochlea.

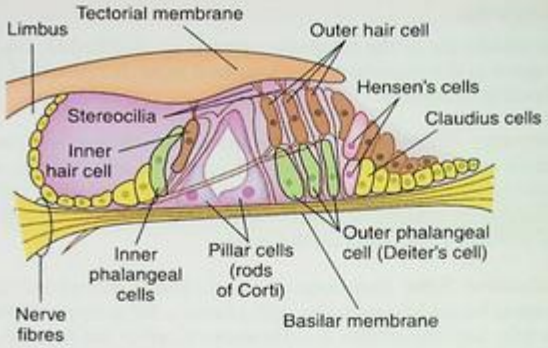


Figure 11.2-5 Structure of organ of Corti. Note the connections between tectorial membrane and cilia of hair cells.

membrane. It is also connected with a subarachnoid space through the aqueduct of cochlea (Figs 11.2-3 and 11.2-4).

- ***Scala media or cochlear duct*** or *membranous cochlea* appear triangular on cross-section. Its three walls are formed by the following (Fig. 11.2-3):
  - Basilar membrane
  - Reissner's membrane
  - Stria vascularis

Perilymph and Endolymph

Perilymph is the fluid present in the scala tympani and scala vestibuli compartments of the cochlea. Its composition is similar to the extracellular fluid (ECF) in that it is high in Na^+ and low in K^+.

Endolymph is the fluid present within the scala media or the membranous cochlea. Its composition is similar to the intracellular fluid (ICF) in that it is high in K^+ and low in Na^+. It is secreted by the stria vascularis, which forms the lateral wall of the scala media.

Organ of Corti The organ of Corti, the sense organ of hearing, is situated on the top of the basilar membrane in the scala media (Fig. 11.2-3). It contains the auditory receptors or the peripheral receptors of sense of hearing. Important components of the organ of Corti are as follows (Fig. 11.2-5).

1. Rods of Corti These are two projections (inner and outer rods) from the basilar membrane into the scala media. In-between the two rods is the *tunnel of Corti*, which contains a fluid called cortilymph. The exact function of the rods and cortilymph is not known.
2. Hair Cells These are the receptor cells that transduce sound energy into electrical energy. Two groups of hair cells lie on the basilar membrane (Fig. 11.2-5).

Inner hair cells. These form a single row of cells internal (i.e. medial) to the inner rod. These are about 3500 in number.

Outer hair cells. These are about 20,000 in number and are arranged in three or four layers external (i.e. lateral) to the outer rod. These are responsible for *detecting the presence of sound*. They mainly receive efferent innervation from the olivary complex and are concerned with modulating the function of inner hair cells.

Structure of a hair cell. The inner hair cells are flask shaped, whereas the outer hair cells are cylindrical. On the upper surface of the hair cells are present tiny cilia (*stereocilia*) which protrude into the overlying tectorial membrane.

- *Supporting cells* support the inner and outer hair cells.
- *Tectorial membrane* consists of gelatinous matrix with delicate fibres. This membrane is attached to the upper surface of spiral lamina.

The shearing force between the hair cells and tectorial membrane produces the stimulus to hair cells.

Auditory Pathways

Auditory pathways comprise following relay stations (Fig. 11.2-6).

Spiral Ganglion

First-order neurons are the bipolar cells of the *spiral ganglion*.

- *Dendrites* of these bipolar cells constitute the afferent fibres innervating the hair cells.
- *Axons* of these bipolar cells form the cochlear division of VIIIth cranial nerve. The cochlear nerve ends in the cochlear nuclei in the medulla.

Cochlear Nuclei

Second-order neurons have their cell bodies in the cochlear nuclei (dorsal and ventral) which are situated in the medulla. The axons of second-order neurons from the cochlear nuclei pass medially in the dorsal part of pons.

- The crossing fibres of two sides form a conspicuous mass of fibres called the *trapezoid body*.
- Some crossing fibres run separately in the dorsal part of pons and do not form part of the trapezoid body.

Third-order neurons have their cell bodies mainly in the *superior olivary complex* (made up of a number of nuclei), and also in trapezoid nucleus and nucleus of lateral lemniscus.

The fibres from these collections ascend through lateral *lemniscus*, and ascend to the midbrain and terminate in the inferior colliculus.

Inferior Colliculus

Fourth-order neurons have their cell bodies in the *inferior colliculus*, where the fibres of lateral lemniscus terminate. Fibres arising in the inferior colliculus enter the inferior brachium to reach the medial geniculate body.

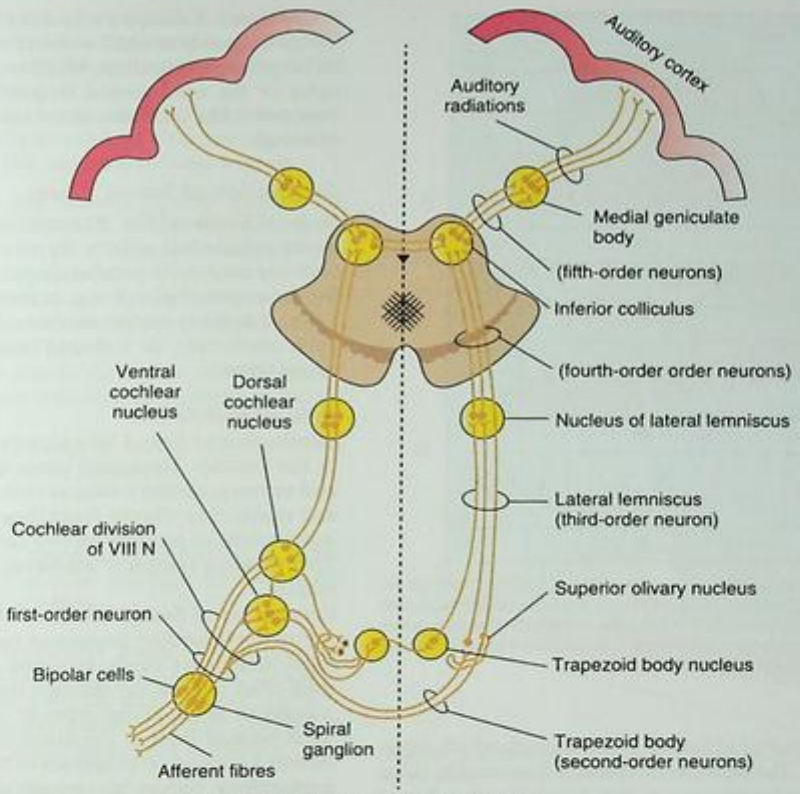


Figure 11.2-6 Central auditory pathways.

Medial Geniculate Body

Fifth-order neurons have their cell bodies in the medial geniculate body where most of the fibres arising in inferior colliculus terminate. Fibres arising in the medial geniculate body form the *acoustic radiation*, which ends in the acoustic area of the cerebral cortex.

Auditory Cortex Major areas constituting auditory cortex present in the temporal lobe are as follows:

- Primary auditory cortex (areas 41 and 42)
- Auditory association areas (areas 22, 21 and 20) (for details, see page 390)

PHYSIOLOGY OF HEARING

Hearing, i.e. detection of sound waves, may serve to warn of impending danger or localize friends. But most importantly audition allows social communication. Physiology of audition can be discussed under the following headings:

- Stimuli or sound waves
- Conduction of sound waves
- Transduction of sound waves
- Neural transmission of signals
- Encoding of signals

Stimuli or Sound Waves

Definition Stimuli for the receptors of hearing are sound waves. Sound is a form of energy produced by a vibrating object. A sound wave consists of alternating phases of compression and rarefaction of molecules of the medium (air, liquid or solid) in which it travels.

Physical Properties of Sound Physical properties of sound and certain terms which are frequently used in audiology and acoustics are the following (Fig. 11.2-7).

1. Speed of Sound Speed or velocity of the sound waves is different in different media:

- *In the air*, at 0°C, at sea level, sound travels at a rate of approximately 330 m/s (1100 feet/s), whereas at 20°C, it travels at a rate of 349 m/s (1150 feet/s).
- *In the water*, at 20°C, sound travels at much faster speed of 1450–1500 m/s. The speed is faster in salt water as compared to the fresh water. Furthermore, the speed of sound in water slightly increases with temperature and altitude.

2. Frequency of Sound refers to the number of waves per second.

- The *unit* of frequency is hertz (Hz).
- Range of human hearing is approximately 20–20,000 Hz.
- Range of average speaking voice is approximately 2000–5000 Hz.

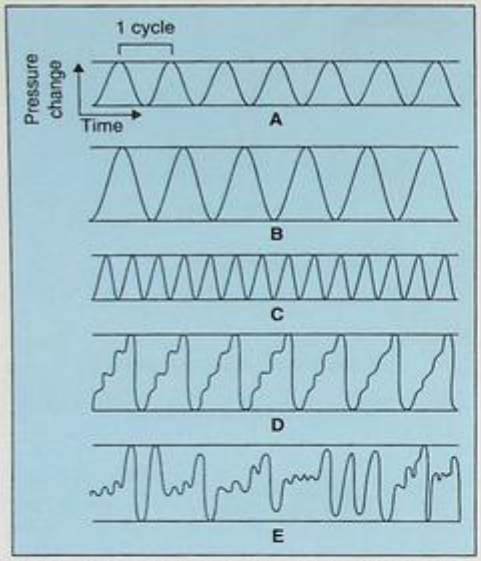


Figure 11.2-7 Characteristics of sound wave: (A) pure tones; (B) increase in amplitude (intensity) of sound wave, thus the sound is louder; (C) increase in frequency (pitch); (D) complex waveform due to mixture of pure tones and overtones determines the quality of sound (timbre); and (E) aperiodic irregular waveform (noise).

3. Amplitude (intensity) of Sound is the strength which determines its loudness. The intensity of sound is measured in terms of maximum pressure change at the tympanic membrane, which is more commonly expressed as *sound pressure level* (SPL). The unit of SPL is decibel (dB).

Reference (standard) pressure is 0.0002 dynes/cm^2. It is defined as a sound pressure that is just detectable, i.e. auditory *threshold.*

Thus, sound intensities are measured on a ratio scale using a subjective intensity (i.e. the threshold). Intensities of some common sounds at a distance of 1 m are as follows:

- Whisper: : 30 dB
- Normal conversation: : 60 dB
- Rock music: : 90 dB
- Discomfort of the ear is produced by sounds: : 120 dB
- Pain in the ear is produced by sound of above (10^7 times threshold): : 140 dB

4. Pure Tone A single-frequency sound is called a pure tone, e.g. a sound of 25–50 or 100 Hz.

5. Complex Sound refers to that with more than one frequency. For example, human voice is a complex sound.

6. Pitch It is the subjective sensation produced by the frequency of sound. Higher the frequency greater is the pitch.

- Pitch of average male voice is 120 Hz and that of female is 250 Hz.
- An average individual can distinguish about 2000 different pitches.

7. Overtones A complex sound is a mixture of pure tones. The lowest frequency at which a source vibrates is called *fundamental (or primary) frequency.* All other frequencies which are multiples of the fundamental frequency are called *overtones* or *harmonics.* The overtones determine the quality or the timbre of sound.

Conduction of Sound Waves

Role of External Ear External ear captures the sound waves. *Pinna* collects and reflects the sound waves into the external auditory meatus. Its peculiar shape, in humans, aids in discerning the source of sound (e.g. in front versus behind the head). *External auditory meatus* conducts the sound waves to the tympanic membrane. Its S-shaped course helps in amplifying the sound waves.

Role of Middle Ear

Conduction of Sound Stimulus by the Tympanic Membrane to Ear Ossicles The sound waves that pass through the pinna and external auditory meatus strike the tympanic membrane and enable it to vibrate. Eustachian tube does the function of equalization of pressure on two sides of tympanic membrane. The vibrating tympanic membrane causes the ear ossicles to vibrate.

Conduction of Sound Waves Mechanically from the Middle Ear to the Inner Ear *Impedance matching mechanism.* The air-filled middle ear conducts sound waves mechanically to the fluid-filled internal ear through the ossicular system. Effective transfer of sound energy from an air to a fluid medium is difficult because most of the sound is reflected as a result of the different mechanical properties of the two media, i.e. *impedance mismatching.* Nature has compensated for it by providing impedance matching mechanism to middle ear by the following mechanisms (Fig. 11.2-8):

1. ***Lever action of ossicles*** increases the force of movement by 1.3 times.
2. ***Hydraulic action of the tympanic membrane*** is exerted because the effective vibratory area of the tympanic membrane (about 55 mm^2) is much greater than the stapes – oval

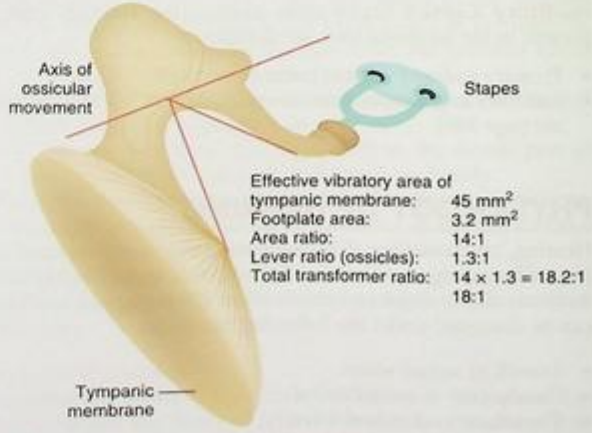


Figure 11.2-8 Amplification of sound pressure by the combined hydraulic effect of tympanic membrane and leverage effect of ear ossicles.

window surface area (about 3.2 mm^2). This size difference means that the force produced by the sound is concentrated over a smaller area, thus amplifying the pressure exerted on the oval window (17 folds).

3. ***Curved membrane effect.*** Movements of the tympanic membrane are more at the periphery than at the centre where malleus handle is attached. This too provides some leverage.

Thus, the above three mechanisms together increase the sound pressure 22 fold (i.e. 17 × 1.3). In this way, the impedance mismatching between the air-filled middle ear and fluid-filled inner ear is mostly compensated.

Attenuation Reflex Attenuation reflex, also called tympanic reflex or acoustic reflex, reduces sound pressure amplitude.

Stimulus for this reflex is loud sound.

Reflex activity. The two muscles of the middle ear (tensor tympani and stapedius) contract reflexively in response to the intense sound.

It prevents occurrence of damage to cochlea from the intense sounds like that of loud music, jet aircraft, etc.

Transduction of Sound Waves

Transduction of mechanical sound wave into electrical signal occurs in the organ of Corti of inner ear. Steps involved in the process of transduction are as follows.

Vibration of Basilar Membrane Sound waves from the middle ear are passed on to the inner ear through the oval window (Fig. 11.2-9) and spread along the scala vestibuli as a travelling wave. As the sound energy passes from scala vestibuli to scala tympani, it causes the basilar membrane to vibrate.

Stimulation of the Hair Cells The up-and-down movements of the basilar membrane in turn cause the organ of Corti to vibrate up and down. The top of the hair cells in the organ of Corti are held rigid by the reticular lamina and the hair of the outer hair cells are embedded in the tectorial membrane (Fig. 11.2-10). Because the tectorial and basilar membranes are attached at different points on the limbus (Fig. 11.2-10A), they slide past each other as they vibrate up and down.

Owing to the shear forces set up by the relative displacement of basilar membrane and the tectorial membrane, the stereocilia of hair cells bend back and forth. The bending of stereocilia stimulates (excites) the hair cells.

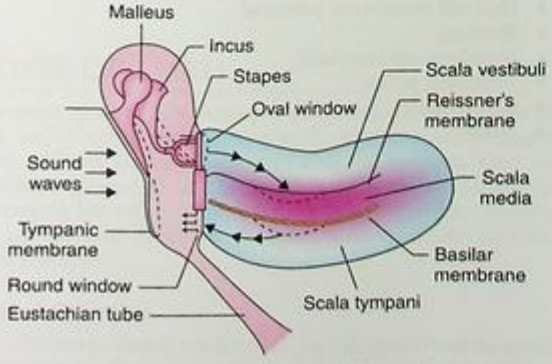


Figure 11.2-9 Diagrammatic depiction of the mechanism of vibrations of basilar membrane produced by in-and-out motion of stapes (for details, see text).

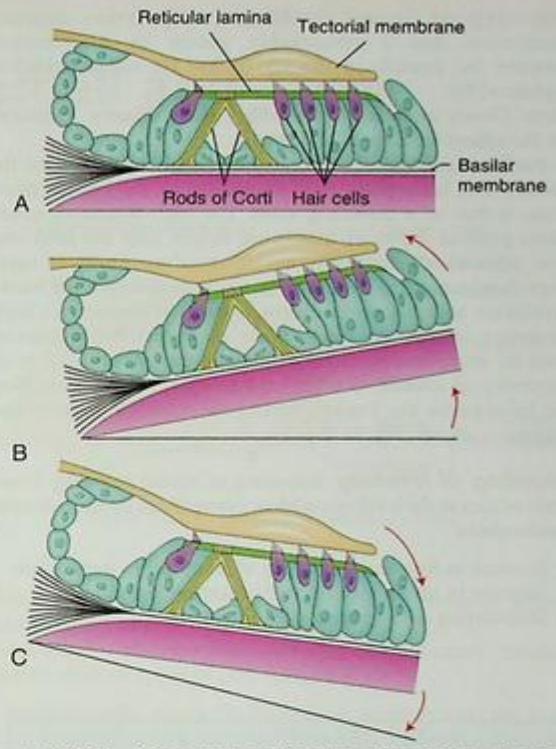


Figure 11.2-10 Demonstration of bending of stereocilia with movement of organ of Corti: (A) the tectorial membrane and basilar membrane are attached to limbus at different points; (B) upward movement of organ of Corti causes bending of cilia away from limbus; and (C) downward movement of organ of Corti causes cilia to bend towards limbus.

Membrane Potential Changes in the Hair Cells On stimulation the bending of the stereocilia produces a change in the membrane potential of the hair cells proportionate to the degree of displacement (generator potential). The changes in membrane potential of the hair cells result from changes in cation conductance at their apical ends. The gating of K^+ channels is controlled by bending of stereocilia.

Action potential of the auditory nerve. When the hair cell depolarizes, it initiates the release of a synaptic transmitter, which activates receptor sites on the terminals of the afferent neuron and cause the generation of action potentials in the neuron.

The frequency of action potentials in a single auditory nerve fibre depends on the intensity of sound wave.

Neural Transmission of Signals

The electrical signals from hair cells are transmitted through a complex auditory pathway, which consists of the following relay stations (Fig. 11.2-6).

Neural Processing of Auditory Information

Neural processing of auditory information involves the following:

- Encoding of frequency (pitch determination)
- Encoding of intensity (determination of loudness)
- Localization of sound in space

Encoding of Sound Frequency The human auditory mechanism has a remarkable power to discriminate between the sounds in the 60–20,000 Hz range, which is explained by:

Place Theory or Bekesy's Travelling-Wave Theory Following are the salient features of this theory:

Basilar membrane is a mechanical analyser of source frequency. The basic pattern of movement of the basilar membrane is that of a travelling wave. The high-frequency sound waves produce waves of maximum height near the oval window, whereas low-frequency sounds produce waves of maximum height near the helicotrema. Correspondingly, the basilar membrane near the oval window vibrates in response to high-frequency sounds. As the distance of the basilar membrane from the oval window increases there is gradual decrease in the frequency of sounds to which the membrane responds. Near the helicotrema the basilar membrane responds to very low-frequency sound (Fig. 11.2-11).

Encoding of Intensity Encoding of sound intensity (loudness) occurs at the level of cochlear nerve fibres by the following mechanisms:

- Increase in frequency of firing of an auditory nerve fibre
- Increase in number of nerve fibres stimulation
- Stimulation of inner hair cells

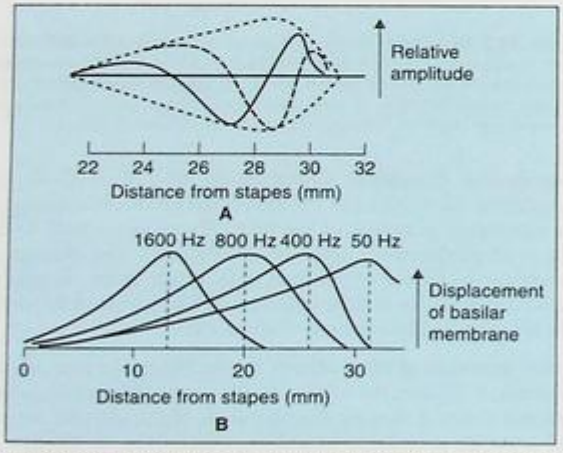


Figure 11.2-11 Amplitude pattern of vibration of basilar membrane for a medium-frequency sound wave (A) and displacement of the basilar membrane by the waves generated by stapes vibrations of frequencies shown at the top of each curve (B).

Location of Sound in Space A human can distinguish sounds originating from the sources separated by as little as one degree. Binaural receptive fields (which is a feature of most auditory neurons above the level of cochlear nuclei) contribute to sound localization. The auditory system uses the following clues to judge the origin of sound:

- Time lag between the entries of sound in two ears
- Differences in the intensity that reaches the two ears

APPLIED ASPECTS

Noise and Masking

Noise is defined as an aperiodic complex sound.

Masking refers to a phenomenon in which the presence of one type of sound decreases the ability of the ear to hear another type of sound.

Hearing Loss and Deafness

Hearing loss refers to the impairment of hearing and its severity may vary from mild to profound.

Deafness is labelled when there is little or no hearing at all.

Types of hearing loss. Hearing loss can be of two types.

1. Conductive Hearing Loss Any disease process which interferes with the conduction of sound from external ear to cochlea causes conductive hearing loss. Characteristically, hearing loss is partial and never complete because skull bones themselves conduct sound to the cochlea (bone conduction) and the basilar membrane can be set into vibrations.

2. Sensorineural Hearing Loss Sensorineural (SN) hearing loss results from lesions of cochlea (*sensory type*) or VIIIth cranial nerve and its central connections (neural type). Usually loss of hearing is complete.

SELF-ASSESSMENT

1. Describe the functions of middle ear.
2. Briefly discuss physiology of hearing.
3. Describe the pathway of auditory conduction.
4. Write notes on:
   - Organ of Corti
   - Impedance matching
   - Hair cell membrane potential
   - Masking
   - Membranous labyrinth
   - Tympanic reflex
   - Bony ossicles
   - Noise

11.3 Chemical Senses: Smell and Taste

CHAPTER OUTLINE

Sense of Smell
Site of Olfaction
Olfactory Mucosa
Olfactory Pathways
Olfactory Nerves
Olfactory Bulb
Olfactory Tracts
Olfactory Cortex
Physiology of Olfaction
Odoriferous Stimuli
Olfactory Receptors
Steps of Transduction in the Olfactory Receptor Neurons
Processing of Olfactory Sensations in the Olfactory Bulb
Transmission of Odorant Information to the Olfactory Cortex and Neocortex
Factors Influencing Olfactory Function
Applied Aspects
Abnormalities of Olfaction

Sense of Taste
Site of Taste
Papillae
Taste Buds
Taste Pathways
First-order Neurons
Second-order Neurons
Third-order Neurons
Physiology of Taste
Gustatory Stimuli
Transduction of Gustatory Stimuli
Transmission of Information about Taste to the Cortex
Sensation of Flavours
Abnormalities of Taste Sensations

SENSE OF SMELL

The sense of smell or olfaction is well developed in animals like dog and rabbit to give warning of the environmental dangers. Such animals are called *macrosmatics*. In humans, apes and monkeys (primates), the sense of smell is comparatively less developed, but still it is important for pleasure and for enjoying the taste of food. Therefore, the humans and primates are called *microsomatics*.

Site of Olfaction

The olfactory stimuli are detected by the specialized receptors located on the free nerve endings of the olfactory nerves, which are located in the olfactory mucosa of nose in human beings and vomeronasal organ in reptiles and certain mammals.

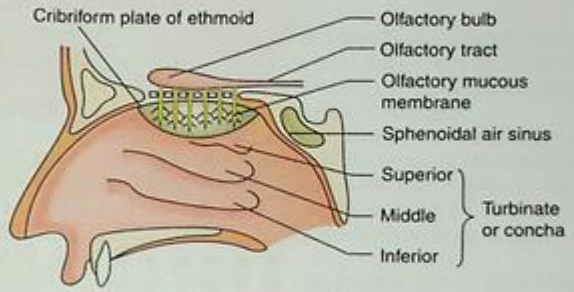


Figure 11.3-1 Location of olfactory mucosa.

Olfactory Mucosa In humans, the olfactory mucosa is confined to upper one-third of nasal cavity (Fig. 11.3-1).

Histological Structure Histologically, the olfactory mucosa consists of three types of cells (Fig. 11.3-2).

1. ***Receptor cells.*** About 10–20 million receptor cells are present in the olfactory mucosa. These cells are bipolar neurons, which lie between the supporting (sustentacular) cells. Their axons are fine unmyelinated fibres, which form the olfactory nerves.
2. ***Supporting cells*** also known as sustentacular cells are columnar in shape. These cells secrete mucus.
3. ***Basal cells*** are stem cells from which new receptor cells are formed. There is a continuous replacement of receptor cells by mitosis of the basal cells.

Olfactory Pathways

Olfactory pathways comprise the following:

1. Olfactory Nerves About 15–20 olfactory nerve filaments which consist of the axons of the bipolar olfactory neurons pierce the cribriform plate on either side to reach the olfactory bulb.

2. Olfactory Bulb (Fig. 11.3-2). It is an oval flattened strip of grey matter lying on the cribriform plate which receives the olfactory nerve filaments. There is point-to-point representation of olfactory mucosa in the olfactory bulb. The olfactory bulb contains three types of cells: *mitral cells, tufted cells* and interneurons (*granule cells* and *periglomerular cells*). The mitral and tufted cells constitute second-order neurons. *Axons of the mitral and tufted cells* leave the olfactory bulb and run in the olfactory tract.

3. Olfactory Tract It lies in the olfactory sulcus on the orbital surface of the frontal lobe and proceeds backwards from each olfactory bulb to the region of anterior perforated substance on the base of brain where it divides into lateral, intermediate and medial olfactory striae (Fig. 11.3-3).

Anterior olfactory nucleus. It is made up of scattered neurons within the olfactory tract. Neurons in this structure receive

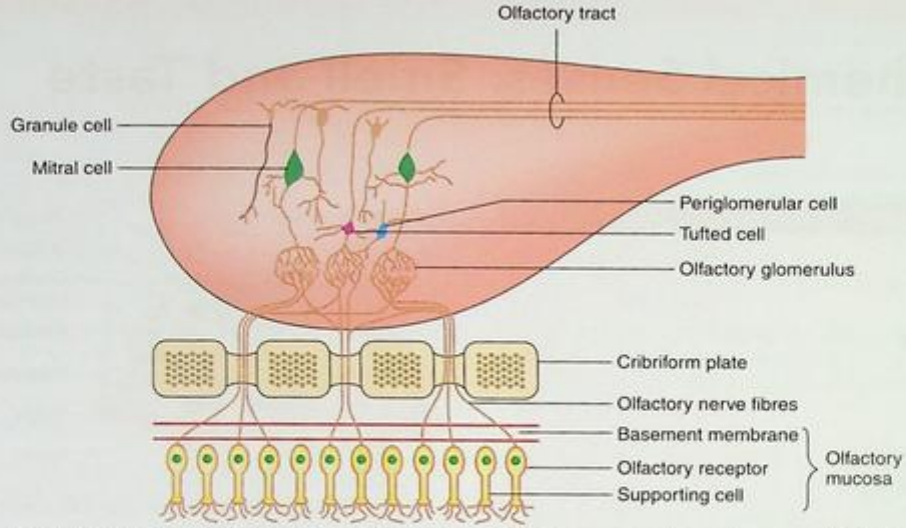


Figure 11.3-2 Diagrammatic depiction of the synapses between axons of olfactory neurons (first-order neurons) with the dendrites of mitral and tufted cells (second-order neurons) to form the olfactory glomeruli which lie in the olfactory bulb. The inhibitory neurons present in the olfactory bulb are granule cells and periglomerular cells.

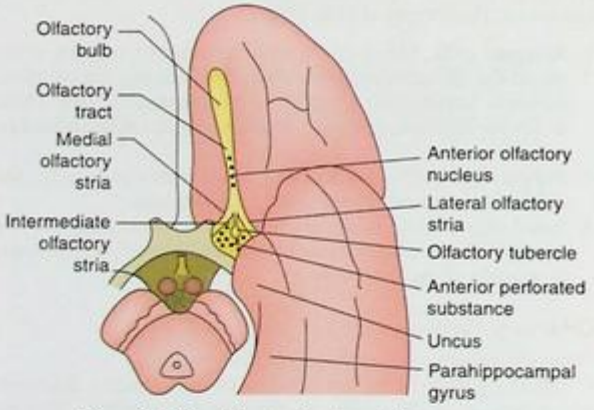


Figure 11.3-3 Olfactory bulb and olfactory tract.

synaptic connections from neurons of the olfactory bulb and send axons through the anterior commissure to excite inhibitory neurons on the contralateral olfactory bulb.

Olfactory striae. Three striae that are derived from each olfactory tract (Fig. 11.3-3) are as follows:

- Lateral olfactory stria
- Medial olfactory stria
- Intermediate olfactory stria

4. Olfactory Cortex It includes the anterior olfactory nucleus, prepiriform cortex, olfactory tubercle and amygdala. All these are the parts of limbic system.

Physiology of Olfaction

Odoriferous Stimuli The odoriferous (smell-producing molecules) stimuli enter the nasal cavity while breathing. Through eddy currents they reach the olfactory epithelium. The odorant molecules must dissolve in the mucous layer (lining the olfactory mucosa) before they can come in contact with the olfactory receptors.

Types of Odorant Stimuli There seems to be over 50 *primary smell sensations.* Although the olfactory capability of humans is somewhat limited, compared with that of macrosomatic animals, nevertheless, humans are able to perceive more than 10,000 different odorous molecules.

Olfactory Receptors The cilia of the olfactory neurons are specialized for odour detection. They have specific receptors for odorants.

Steps in Transduction in the Olfactory Receptor Neurons

- ***Binding of odorant molecule to receptors.*** It has been suggested that the mucous layer covering the olfactory mucosa contains one or more odorant-binding protein that concentrate and transfer the odorant molecules to the receptors present on the cilia of olfactory neurons.
- ***Depolarization receptor potential.*** The increased intracellular cAMP opens cyclic-nucleotide-gated (CNG) cation channels, leading to cation influx and a change in membrane potential in the cilium membrane, i.e. produces a depolarizing receptor potential.
- ***Action potentials.*** The receptor potential depolarizes the initial segment of the axon to threshold leading to the generation of action potentials in the sensory axon and the *transmission of signal to olfactory bulb.*

Processing of Olfactory Sensation in the Olfactory Bulb The odorant information is extensively processed and perhaps refined in the olfactory bulb before it is sent to the olfactory cortex.

Transmission of Odorant Information to the Olfactory Cortex and Neocortex

- From the olfactory bulb, the odorant information is first transmitted to the *olfactory cortex*, which includes piriform cortex, parts of amygdala, the olfactory tubercle and parts of entorhinal cortex.
- From the olfactory cortex, information is relayed to the frontal cortex (directly) and orbitofrontal cortex (via thalamus).

Role played by different regions of cerebral cortex involved in processing of olfactory information is summarized as follows:

- *Amygdala* and hypothalamus are probably involved with the emotional and motivational responses to olfactory stimuli as well as many of the behavioural and physiological effects of odour.
- *Entorhinal cortex* is concerned with olfactory memories.
- *Neocortex (orbitofrontal and frontal cortex)* is thought to be concerned with conscious discrimination of odours.

Factors Influencing Olfactory Function

1. Threshold of Olfactory Receptors The threshold of olfactory receptors varies from substance to substance. For example, methyl mercaptan, a substance which gives garlic its characteristic odour, has extremely low threshold. It can be smelled at a concentration of less than 500 pg/L of air (Table 11.3-1).
2. Intensity/Concentration of the Odour The concentration of an odoriferous substance must be changed by about 30% before a difference can be detected.
3. Adaptation. Olfactory sensation adapts very rapidly with continued exposure to an odour.

Applied Aspects

Abnormalities of Olfaction

1. Anosmia and Hyposmia Anosmia is total loss of sense of smell, whereas hyposmia refers to a diminished olfactory sensitivity.
2. Paraosmia or Dysosmia It refers to a distortion or perversion of smell. In it the person interprets the odours incorrectly. Often these persons complain of disgusting odours.

TABLE 11.3-1 Threshold Concentration of Some Odoriferous Substances

Substance	Concentration (mg/L) of Air
Ethyl ether	5.83
Chloroform	3.30
Pyridine	0.03
Oil of peppermint	0.02
Iodoform	0.02
Butyric acid	0.009
Propyl mercaptan	0.006
Artificial musk	0.00004
Methyl mercaptan	0.0000004

SENSE OF TASTE

Sense of taste (gustation) is a chemical sense that is stimulated by food and drink. It contributes considerably to the quality of life and is important stimulant for digestion. Taste must be distinguished from flavour, which includes the olfactory, tactile and thermal attributes of food in addition to taste.

Site of Taste

The taste (gustatory) stimuli are detected by specialized chemoreceptors called taste receptors or taste cells. The taste receptors are clustered in the taste buds located on the tongue, palate, pharynx, epiglottis and upper-third of esophagus.

Tongue, the principal site of taste detection, contains numerous taste buds on its dorsal surface. The mucous membrane of the dorsal surface of tongue exhibits numerous papillae, which increase the surface area of the mucosa available for taste receptors. The taste buds are located in the walls of these papillae.

Papillae Papillae, present on the tongue, are of four types (Fig. 11.3-4).

1. Circumvallate Papillae These are large (2–4 mm in diameter) papillae, about 10–12 in number, forming a single row in front of the sulcus terminalis. Sulcus terminalis is V-shaped groove (with apex posteriorly), which separates the anterior two-thirds of the dorsum of tongue from the posterior one-third. Each circumvallate papilla is surrounded by a groove. About 200 taste buds are located along the sides of each circumvallate papilla.
2. Fungiform Papillae These are bright red, flat, dot-like structures (each of about 1 mm in diameter) located on the anterior two-thirds of tongue along the edges, dorsum and tip. There are 8–10 taste buds on each papilla.
3. Foliate Papillae These are transverse mucosal folds, found on the posterolateral surfaces of the tongue anterior to the

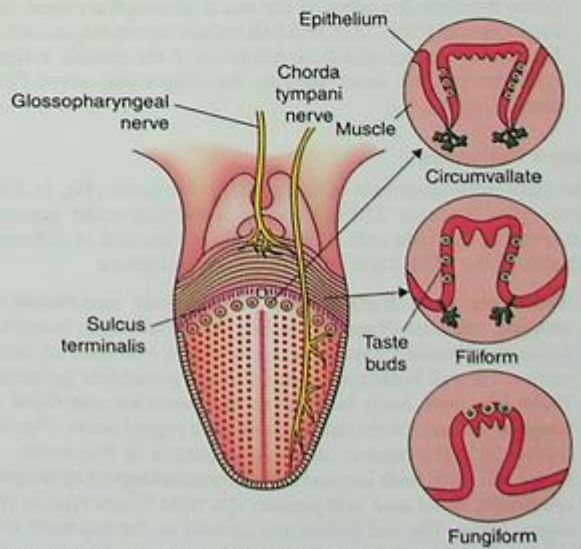


Figure 11.3-4 Structure and distribution of papillae on the tongue and arrangement of taste buds in the three types of papillae. Innervation by the cranial nerves is also indicated.

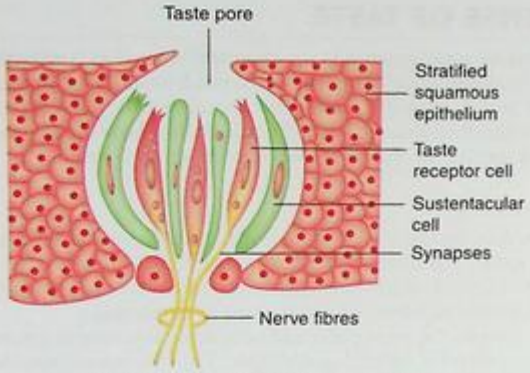


Figure 11.3-5 Structure of a taste bud.

circumvallate papillae. Each foliate papilla has numerous taste buds.

4. Filiform Papillae These are small conical projections covering the entire remaining surface of the dorsum of the anterior two-thirds of tongue, giving it a velvety appearance. They are not gustatory structures, i.e. *do not contain taste buds.*

Taste Buds The taste buds are concerned with sensation of taste. Each taste bud is barrel shaped and measures about 50–70 μm in diameter. It consists of cluster of cells with a small opening (taste pore) on the surface. It consists of the following cells (Fig. 11.3-5).

1. ***Receptor cells.*** These are modified epithelial cells.
2. ***Supporting cells.*** In addition to the taste cells and basal cells, the taste buds contain supporting or sustentacular cells.

Innervation

- The special sensory nerve fibres innervating the taste cells come from the branches of the facial, glossopharyngeal and vagus nerve (VIIth, IXth and Xth cranial nerve, respectively).
- The tactile and temperature receptors of the mouth, tongue and pharynx are innervated by the trigeminal nerve (Vth cranial nerve).

Taste Pathways

The taste pathways consist of three orders of neurons (Fig. 11.3-6).

First-order Neurons The cell bodies of the first-order neurons innervating the taste cells in taste buds are located in different ganglia of the VIIth, IXth and Xth cranial nerves as:

- ***From the taste buds located on anterior two-thirds of tongue,*** the taste fibres run in lingual nerve which branches from the chorda tympani nerve, which is a branch of facial nerve. The cell bodies are located in the geniculate ganglion.
- ***From the taste buds located on the posterior one-third of tongue,*** the taste fibres run in glossopharyngeal nerve. The cell bodies lie in the *superior and inferior ganglia* of this nerve.
- ***From the taste buds located on pharyngeal aspect of tongue, epiglottis, hard and soft palate,*** the taste fibres run in the vagus nerve. The cell bodies are located in the superior and inferior ganglia of the vagus nerve.
- ***Termination of first-order neurons.*** Ultimately, all the taste fibres travelling in different cranial nerves join the tractus solitarius to terminate in the nucleus of tractus solitarius (Fig. 11.3-6).

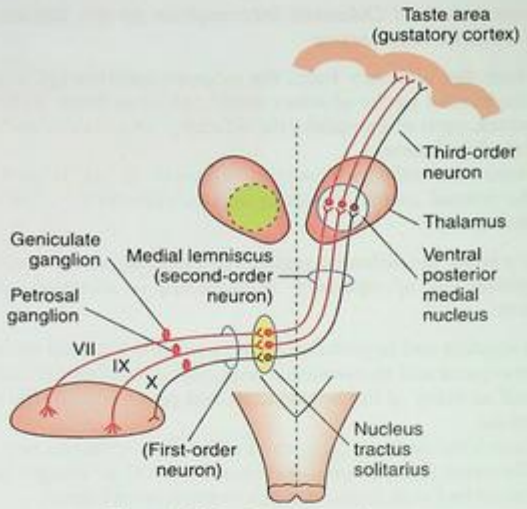


Figure 11.3-6 The taste pathways.

Second-order Neurons The cell bodies of second-order neurons of taste pathways are located in the *nucleus of tractus solitarius* in the medulla. Axons of the second-order neurons cross the midline to join the medial lemniscus and terminate with Vth cranial nerve fibres (carrying pain, touch and temperature fibres) in the ventral posterior medial nucleus of thalamus.

Third-order Neurons The cell bodies of third-order neurons are located in the *ventral posterior medial nucleus of thalamus.* Axons of third-order neurons proceed to terminate in the inferior part of the postcentral gyrus, i.e. the part of sensory cortex called taste cortex.

Physiology of Taste

Gustatory Stimuli Substances producing primary (basic) taste sensations are as follows:

1. ***Sweet Sensation.*** It is produced by a number of organic molecules including sugars, glycols, alcohols, aldehydes, esters, etc. Saccharin is a chemical that is 600 times as sweet as sucrose. Tip of the tongue was considered the area most sensitive to sweet stimuli.
2. ***Salty Sensation.*** It is produced by the anions of ionizable salts especially the sodium chloride. The front half of each side of the tongue was thought to be the area most sensitive to salty stimuli.
3. ***Sour Sensation.*** It is produced by acids; and the intensity of this sensation relates, to some degree, to the pH of stimulus solutions. The posterior half of each side of the tongue was the area considered most sensitive to sour stimuli.
4. ***Bitter Sensation.*** It is produced by alkaloids such as quinine, caffeine, nicotine and strychnine.
5. ***Umami Sensation.*** It has been recently added to the four basic taste sensations. It is produced by glutamate particularly by monosodium glutamate (MSG) used extensively in Asian cooking. This taste is pleasant and sweet but differs from the standard sweet taste.

Transduction of Gustatory Stimuli Transduction of gustatory stimuli into electrical signals is initiated at the level of receptors. The taste receptors are chemoreceptors, which are stimulated by the substances dissolved in the mouth by saliva.

Transmission of Information about Taste to the Cortex As described in the taste pathway (Fig. 11.3-6), the signals carried by sensory fibres travel through several different nerves to the gustatory cortex.

Sensation of Flavours The multitude of different sensation of flavours that one experiences results from a combination of gustatory, olfactory and somatosensory inputs.

Abnormalities of Taste Sensations

1. ***Ageusia*** It refers to the absence of taste sensation.
2. ***Hypogeusia*** It refers to a diminished taste sensitivity.
3. ***Dysgeusia*** It refers to a disturbed sense of taste.

SELF-ASSESSMENT

1. Describe briefly the physiology of olfaction.
2. Write notes on:
   - Olfactory transduction
   - Factors affecting olfactory function
   - Taste buds
   - Gustatory stimuli and taste pathway

A

A band, 42f
Absolute refractory period, 113
  in cardiac muscle, 113
  in skeletal muscle, 44t
Absorption, 286–287
  calcium, 291
  carbohydrate, 287
  iron, 291
  lipids, 289f
  minerals, 290–292
  proteins, 288–289
  vitamins, 292
  water and electrolytes, 290–292
Absorption spectrum, 472f
Accessory pancreatic duct, 271
Accommodation, 30
  eye, 470
  to hypoxia, 213
Acetoacetic acid, 247
Acetylcholinesterase, 39, 411
Achalasia, 260
Acid, 241
  hydrochloric, 262
Acid–base balance, 241–245
  disturbances, 244–245
Acidophil cells, 262
  stomach, 262
Acidosis, 244–245
  diabetic, 344
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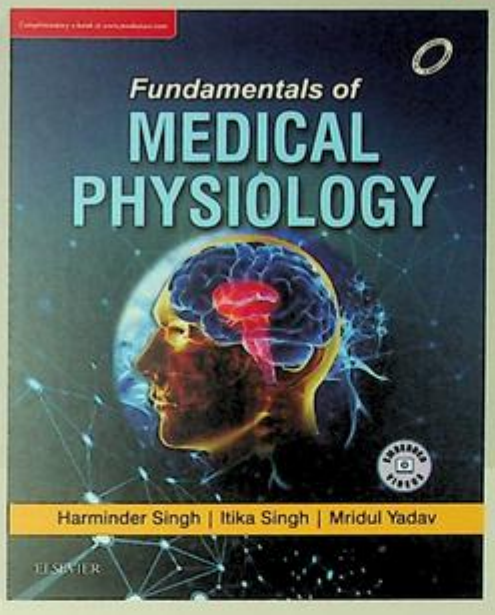

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About the Authors

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ISBN: 978-81-312-5299-4

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