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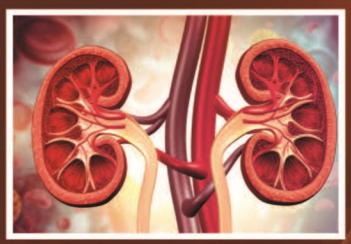
Basics of Medical Physiology

D Venkatesh | HH Sudhakar

Fifth Edition



Wolters Kluwer

Basics of
MEDICAL PHYSIOLOGY

Fifth Edition

Basics of MEDICAL PHYSIOLOGY

Fifth Edition

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Preface to the Fifth Edition

The COVID pandemic that affected the entire world had a tremendous negative impact on the educational environment, especially medical education. The students were distanced from the teachers. Much needed practical training, which is typically carried out in the physical presence of both teacher and taught, could not be completed due to compulsory isolation. The adverse situation arising due to the pandemic prompted us to explore alternative methods of imparting trainings including the practical and clinical skills. This led to innovations in teaching technology. However, these techniques still fell short to deliver the desired outcome in terms of quality. This brought about the need of a hybrid training model that gives emphasis to interactive training sessions and limits the online teaching-learning activities. The pandemic situation has improved significantly with signs of restoration of classroom teaching.

We were pleasantly surprised to receive appreciations from our beloved students and ever-dependable faculty colleagues as our book came in handy for students who were struggling to understand complex concepts on their own with limited help from the teachers. They appreciated the concise and lucid presentation of the topic which facilitates a comprehensive understanding of the complex concepts.

Keeping in mind the needs of the students, the fifth edition of the book has been revised extensively with enriched content and concepts explained with simple diagrams and flowcharts. However, we have resisted the urge to add complex graphs and additional content that can be a burden to undergraduate students. Recommendation of the book by newer institutions and continuation in the existing is a proof of its value to the end users.

We have taken a close look at the competency-based curriculum. In-line with the suggestions therein, we have added a chapter on integrated physiology containing very useful topics needed for the study of physiology. With this addition, the book will serve the needs of undergraduate students of physiology pursuing medical, dental, physiotherapy, ayurveda, homeopathy, medical electronics, and medical technician courses. This book will also serve as a useful tool for quick revision and exam preparation.

We look forward to meeting the changing needs of the students and the teachers from time to time. In order to meet this requirement, updated content, diagrams, flowcharts and lecture videos will be made available as online resource. This would help the students in keeping up to date about the recent developments in the chosen field without waiting for the next edition of the book.

We express our sincere thanks to Ms. Sangeetha, Sr. Publishing Manager, for closely monitoring the progress of the book. Our sincere thanks are also due to the editorial team for putting their best efforts in bringing out this edition and making all of us proud of the product.

We welcome suggestions from students, teachers and our well-wishers for adding value to future editions.

D Venkatesh
HH Sudhakar

Preface to the First Edition

We placed our first book *Basics of Medical Physiology* (level 2) in the hands of our beloved students and colleagues last year with an apprehension about its acceptability. Response to the book has been encouraging and the experience satisfying. With the patronage of our well wishers, we could bring out second edition of the book in less than a year with a lot of value additions. We express our sincere thanks to all those who made our maiden effort a great success.

It was our desire to present a book to bridge the gap between the ocean of information available and little knowledge about the subject for a beginner. The readers have opined that the contents in the book are balanced and presentation lucid. In short, it is student friendly. Although we have made a humble beginning, we feel that lot more needs to be accomplished.

Encouraged by the response for the earlier book, honoring our commitment to provide useful information to our students, we have decided to bring out this book *Basics of Medical Physiology* (level 3).

We have maintained the student-friendly features of the earlier book but made it richer in relevant content. Emphasis is laid on the applied physiology. Simple illustrative diagrams have been included. To help the students to prepare for examination, an extensive question bank and multiple choice questions have been provided.

We are confident that our students and colleagues will appreciate our effort and give all the support and encouragement for this book also.

We thank our editorial team, artists, and the printer for doing a neat job to bring out this book within a short time.

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Introduction

Physiology is the branch of science dealing with the study of the functions of living beings. It is a dynamic study of life describing the vital functions of the living organisms at organ, cellular, and molecular levels. The term physiology is a combination of Greek words *physis*, meaning "nature," and *logos*, meaning "science" or "study." Physiology is closely associated with medicine. Alteration in the normal physiology leads to causation of disease. Restoring the normal physiology is the essence of medical management.

Medical physiology deals with the functioning of the human body. It takes a global and holistic view of the human body, requiring an integrated understanding of events at the cellular and organ level. Physiology is the mother of several biological sciences responsible for the development of disciplines such as biochemistry, biophysics, and neurosciences. Hence, the boundaries of physiology are not sharply defined.

Physiologists have attempted to understand the intricate control systems and regulatory mechanisms that influence the body to function, survive, and maintain stability in the ever-changing external environment. The ability of the body to maintain constancy of the internal environment is termed **homeostasis**. The concept of homeostasis was developed by a French physiologist, Claude Bernard. The term homeostasis (*homoios*, meaning "the same," and *stasis*, meaning "standing") was suggested by an American physiologist, Walter B. Cannon, in the year 1932.

Cannon suggested that every regulatory mechanism of the body is aimed at maintaining constancy of the internal environment. The internal environment is not static. Even under constantly changing external environment, the internal environment is dynamically changing and is maintained relatively constant.

A wide range of fluctuation in the environmental temperature does not significantly alter the core temperature which is kept constant at about 37°C. This ability of the body to regulate its own function and return to normal condition forms the basis for understanding the mechanism of the disease.

The study of physiology is done by understanding the functions of the specific organ system. It is done at different levels: organ system, organelle, tissue, and cellular levels. A more complex and intricate physiological basis is understood at the molecular level. Later, an attempt is made to evaluate the integration of the organ system for smooth functioning of the body.

An important character of life is to respond to changes in the external environment. This property is termed **responsiveness**. Withdrawal of the limb from a painful stimulus is a classical example for this property. The living tissues transmit a wave of excitation from one region of the body to another region. This is **conduction of impulse**. Responsiveness and conduction are very well developed in the excitable tissues such as muscle and nerve.

The functions of the body are regulated by the nervous system and endocrine system. The endocrine glands produce specialized chemical messengers called **hormones**. These hormones modify the function of another organ, termed the **target organ**.

The tissues require energy to carry out their metabolic activities. The source of energy and a constant supply of oxygen are required for the generation of energy. The complex food

products ingested by animals are broken down into simpler substances, absorbed and assimilated by the digestive system. The simpler food substances such as glucose, fatty acids, and amino acids are used by individual cells to satisfy their energy requirement.

Every individual cell needs oxygen to a varying extent to produce energy. The cells are drawn away from the environment because of the complex structure of the organ system. The oxygen requirement of each cell is satisfied by a well-established transport system—cardiovascular system. It has a primer pump, the heart, and the channels in the form of blood vessels.

Blood which acts as a vehicle carrying oxygen and nutrients is transported to the individual cell by contraction of the heart and movement of blood through the blood vessels.

An alternate pathway for drainage exists in the form of lymphatic system composed of lymph, lymphatic vessels, lymph nodes, thymus, and spleen. It helps in the movement of fluid and large protein molecules from the tissue spaces, the fat-related substances from the digestive system to the blood.

The internal environment of a living being is threatened by foreign substances and invading microorganisms. The individual's ability to resist infection and fight cancer and other types of diseases depends on the effective functioning of the immune and lymphatic system. **Immunology** is the study of immune responses of the body.

The metabolic waste produced by the individual cell can damage the cell or hamper its function if it accumulates at the site of production. This undesirable side effect is prevented by the transport of metabolic waste through the blood to the various organs of excretion. The solid waste is excreted through the gastrointestinal tract, excess water and soluble waste through the renal system, and the gaseous waste through the respiratory system.

An increase in the size or number of groups of cells results in growth. Growth increases the size of an individual or an organ.

During life, the aging cells lose their capacity to perform functions at the desired level, and hence, they have to be replaced at periodic intervals. New cells have to be added to the different tissues to facilitate growth. Specialized cells have to be produced to repair the damaged tissues of the body. More importantly, new individuals having the same features as the ancestors have to be produced for the propagation of generation. The formation of the new individual and new cells is the function of the reproductive system.

In this book, efforts have been made to give an insight into the functional manifestation in the body, physiological control mechanisms, and integration of structures and functions.

CHAPTER

1 General Physiology

Outline

The Cell 4
Structure of Cell 5
Cytoskeleton 10
Intercellular Connections 11
Intercellular Communications 12
Cell Division 13
Genetics 15
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Homeostasis 28

Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the structure and functions of cell membrane, cell organelles, and nucleus.
- Describe the types and functions of cytoskeleton, intercellular connections, and molecular motors.
- Explain the process of cell division and components of chromosomes.
- Describe the process of transcription and translation. Discuss the basic principles of genetics and concept of apoptosis.
- Discuss the role of transport proteins in transport across cell membrane.
- Classify transport processes and explain the mechanism of each type.
- Explain active transport mechanisms and describe the structure and functions of sodium–potassium pump.
- Classify body fluids and explain the measurement of body fluids.
- Describe the mechanism of regulation of body fluid volume.
- Define homeostasis and discuss the concept of feedback mechanisms in the maintenance of homeostasis.
- Successfully answer the questions and MCQs at the end of this chapter.

The human body is composed of many organ systems, each performing a specific function. Each organ system consists of various organs and each of these organs is made of tissues. These tissues are made of cells. Though the tissue, organ, and organ system differ from each other in structure and function, the cells present in them have certain basic characteristics that are common and specific for that particular species. In fact, there is very little variation in the cellular architecture of different species. This is because all organisms originated from a single unicellular organism.

The chapter of general physiology deals with this basic common nature of the cell and other common fundamental mechanisms occurring throughout the body. The components of a cell are almost the same everywhere in the body, and only minor structural modifications occur in some parts of the body to suit the functioning of a particular organ. Even these structural modifications are generally superficial in nature and they are in addition to the basic components of the cell. For example, the muscle cell is modified to form a muscle fiber and it has contractile elements which are responsible for the functioning of

the muscular system, i.e., contraction of the muscle. However, this muscle cell also has all the components of a typical cell present anywhere else in the body.

The study of basic and general concepts in physiology helps us to easily understand the working of different organ systems. All the 75 trillion cells present in the human body have the same structure and organelles. Understanding the structure and function of these cellular components at the molecular level helps us to understand the various mechanisms operating in maintaining a particular function of an organ and the disease process that may occur in that organ.

The outer covering of these cells, the **cell membrane**, is responsible for the activities that are happening between the two major compartments of the body, i.e., intracellular and extracellular compartments. Transport of various substances occurs across the cell membrane and this is made possible by multiple routes. The study of various transport mechanisms operating at the cell membrane helps in better understanding of the differences in physiological processes occurring at various organs of the body.

THE CELL

Life started millions of years ago with a single cell. In the course of evolution through time, multicellular organisms with complex structures and functions have developed.

Human beings are creatures with complexities in structure and function. Each and every function of a human being is actually performed by a specific organ system of the body. Each organ system is made up of various tissues. Each tissue is made up of millions and millions of small units, termed cells.

COMPONENTS OF CELL

The cell is the basic unit of living beings. Our body is made up of 75 trillion cells.

Each cell contains

- water,
- electrolytes,
- proteins,
- lipids, and
- carbohydrates.

Water

Seventy to seventy-five percent of cell is made up of water. It contains dissolved chemicals and suspended particles. Water helps in the transport of substances from one part of the cell to another. Almost all the chemical reactions occurring in the cell take place in solution in water.

Electrolytes

Major electrolytes include potassium, magnesium, sodium, phosphate, sulfate, bicarbonate, chloride, and calcium. They are dissolved in water.

Electrolytes are necessary for cellular control mechanisms. Few important functions include regulation of water balance, contraction and relaxation of muscles, and transmission of nerve impulse.

Proteins

Proteins constitute 10–20% of the cell mass. They are of two types:

i. structural proteins and
ii. globular proteins

Structural Proteins

- Present in the form of long filaments
- Polymers of protein molecules
- Provide contractile mechanisms for muscles
- Form cytoskeleton of cilia, axons, and mitotic spindles
- Found in collagen and elastic fibers

Globular Proteins

- Made up of individual protein molecules
- Globular (shaped like a globe or a ball) in structure
- Mainly enzymes which catalyze various intracellular chemical reactions

Lipids

Lipids constitute 2% of cell mass. They are made up of phospholipids and cholesterol. They are insoluble in water.

Lipids form major constituents of the cell membrane. They also form barriers that separate various compartments of the cell. Some cells contain triglycerides in addition to phospholipids and cholesterol. They are present in large quantities in fat cells. The fat stored is used as energy whenever needed by the body.

Carbohydrates

Carbohydrates form around 1% of cell mass. They play a major role in providing nutrition to the cell. However, they do not play a major role in the structural function of the cell.

Carbohydrates are present in extracellular fluid (ECF) as glucose and are readily available for the cellular metabolism.

They are also stored as glycogen, which is used for providing energy to the body.

STRUCTURE OF CELL

A cell is the structural and functional unit of all living beings **(Fig. 1.1)**. Different cells of the body have different features. Even though the features are different, the basic component of all cells in the body remains the same.

The cell is made up of two major parts:

i. nucleus and
ii. cytoplasm

Cytoplasm is the fluid part of cell containing the organelles. It is covered by an envelope termed **cell membrane**.

CELL MEMBRANE

The cell membrane is a thin layer of membrane surrounding the cell **(Fig. 1.2)**. It covers both the nucleus and the cytoplasm. It is semipermeable and has a thickness of 7–10 nm.

The membrane is principally made up of proteins, lipids, and to a much lesser extent carbohydrates.

Composition of Cell Membrane	
Proteins	55%
Phospholipids	25%
Cholesterol	13%
Other lipids	4%
Carbohydrates	3%

Various theories have been proposed to explain the cell structure. The most accepted

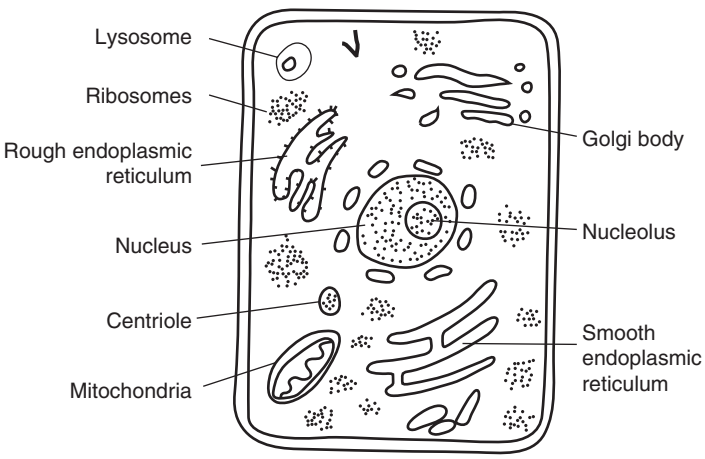


Figure 1.1 Structure of cell.

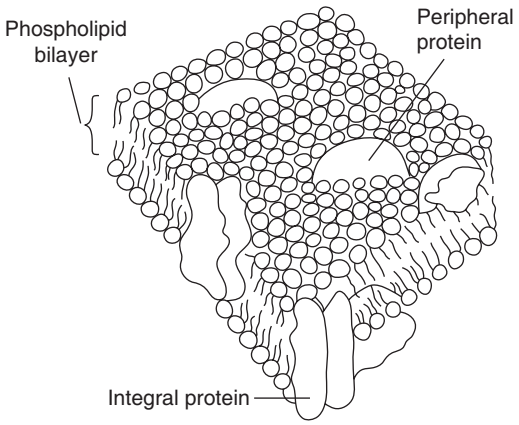


Figure 1.2 Cell membrane.

one is the **fluid mosaic model** proposed by Singer and Nicolson.

Lipids

The cell membrane is made up of two layers of lipids, which are only two molecules thick. It is mainly made up of phospholipids and cholesterol. The phosphate radical of phospholipid and the hydroxyl radical of cholesterol are water soluble, i.e., hydrophilic.

The fatty acid radical of phospholipid and the steroid nucleus of cholesterol are fat soluble, i.e., hydrophobic. The hydrophobic portion of both these molecules occupies the center of the membrane. The hydrophilic portion faces the surrounding water.

The lipid bilayer is impermeable to water-soluble substances such as ions and glucose, but is permeable to fat-soluble substances such as oxygen and alcohol. The cell membrane is a combination of fluid and solid. Therefore, the fluid portion of the membrane flows from one point to another along the cell membrane.

Functions of Lipids

- Form the cell membrane
- Selectively permeable; allow fat-soluble substances to pass through them easily
- Provide a framework for the arrangement of protein and carbohydrate molecules on the cell membrane

Proteins

Proteins are globular masses floating in the lipid bilayer. They are mostly glycoproteins. They are of two types:

(i) integral proteins and

(ii) peripheral proteins

Integral proteins pass through the entire thickness of the membrane. They are closely associated with membrane lipids. **Peripheral proteins** are attached only to the surface. They are concerned with the maintenance of cell shape and motility.

Functions of Proteins

- Act as structural proteins providing framework for the cell
- Act as pumps which help in active transport
- Act as carriers in facilitated diffusion
- Form ion channels
- Act as receptors
- Act as enzymes

Carbohydrates

Carbohydrates are present on the outer surface of the cell. They are glycoproteins or glycolipids. Carbohydrate molecules form a thin layer throughout the surface of the cell membrane which is called **glycocalyx**.

Functions of Carbohydrates

- Attach to glycocalyx of other cells
- Act as receptors for binding hormones
- Participate in immune reactions

NUCLEUS

The nucleus **(Fig. 1.3)** is a spherical structure covered by a nuclear membrane (nuclear envelope). It is the control center of the cell.

It controls

- chemical reactions occurring in the cell and
- reproduction of the cell

The nucleus contains nucleolus and chromatin material. It is mainly made up of water. 80% of dry weight is formed by proteins, 18% by DNA, and 2% by RNA. The nucleus

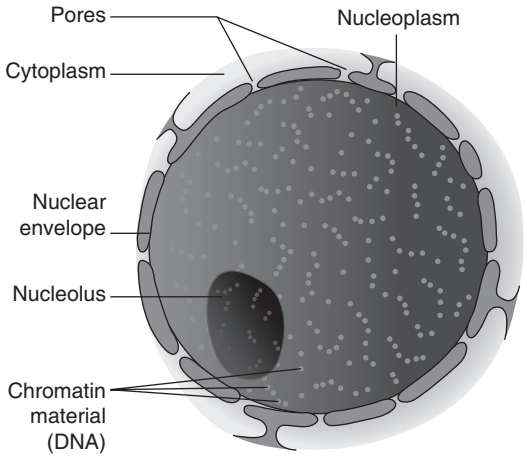


Figure 1.3 Structure of nucleus. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

contains a densely staining network of DNA and protein. This is called **chromatin**. The chromatin material gets organized and is readily identified as chromosomes during cell division. Each species has a fixed number of chromosomes. Human beings have 23 pairs of chromosomes.

Genes are the units of heredity. Each gene is a portion of the DNA molecule. They are present on the chromosomes.

Nuclear Membrane

The nuclear membrane has outer and inner layers. The outer layer is continuous with endoplasmic reticulum (ER). The space between the two nuclear membranes is continuous with the space inside the ER.

The nuclear membrane has several thousand nuclear pores. The central area of these pores is only around 9 nm in diameter as large protein molecules are attached to the edges of these pores. These pores allow low-molecular-weight substances to pass through them.

Nucleoli

Nucleoli are lightly stained structures in the nucleus. They synthesize and store RNAs and proteins. Later, they are transported to form mature ribosomes, which play an important role in protein synthesis.

CYTOPLASM

The cytoplasm contains a fluid portion of the cell in which organelles are present. The fluid portion is called **cytosol**. It contains dissolved proteins, glucose, and electrolytes. The contents of cytoplasm include cell organelles, inclusion bodies, and cytoskeleton.

Cytoplasm contains the following cellular organelles:

- Mitochondria
- Endoplasmic reticulum
- Ribosomes
- Golgi apparatus
- Lysosomes
- Centrosomes
- Cytoskeleton

Mitochondria

Mitochondrion is called powerhouse of the cell. It is present in the cytoplasm. It is a sausage-shaped structure made up of an outer membrane and an inner membrane **(Fig. 1.4)**.

The inner membrane is folded to form shelves called **cristae**. The membranes of mitochondria are similar to cell membrane. The inner portion of mitochondria is filled with matrix. The matrix contains dissolved enzymes required for the Krebs cycle. Its number varies depending on the energy requirement of the cell.

Mitochondria are self-replicative and produced in large numbers whenever extra energy is required by the cell.

They come almost entirely from the ovum in the zygote. Therefore, their inheritance is mostly maternal.

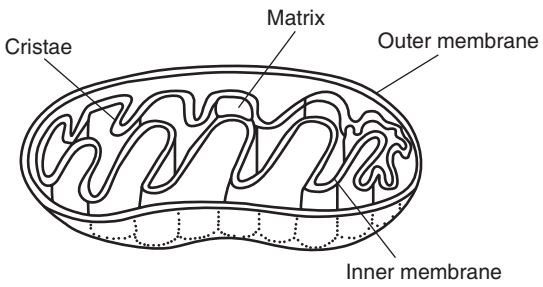


Figure 1.4 Mitochondrion.

Functions

Mitochondria contain large quantities of enzymes that convert food products to CO_2 and water by the citric acid cycle. The energy liberated during the reaction is used for the synthesis of high-energy molecules such as adenosine triphosphate (ATP). The ATP is transported out of mitochondria to the place where energy is required.

The rate of mutation for mitochondrial DNA is much higher than that for nuclear DNA since mitochondria do not have an effective DNA repair system. Therefore, a large number of rare DNA diseases occur due to mutation in mitochondrial DNA.

The symptoms of mitochondrial diseases include gastrointestinal dysfunction, susceptibility to infections, visual impairment, hearing problems, and cardiac and respiratory diseases.

Endoplasmic Reticulum

The endoplasmic reticulum (ER) is a network of tubular and flat vesicular structures interconnected with each other.

The spaces between the tubules and the vesicles are filled with watery fluid termed **endoplasmic matrix**. The surface area of ER is quite large. It is around 30–40 times the area of the cell membrane.

The endoplasmic reticulum is of two types:

i. rough endoplasmic reticulum **(Fig. 1.5)** and
ii. smooth endoplasmic reticulum **(Fig. 1.6)**.

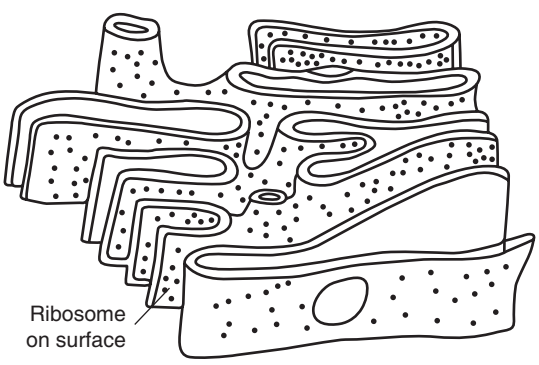


Figure 1.5 Rough endoplasmic reticulum.

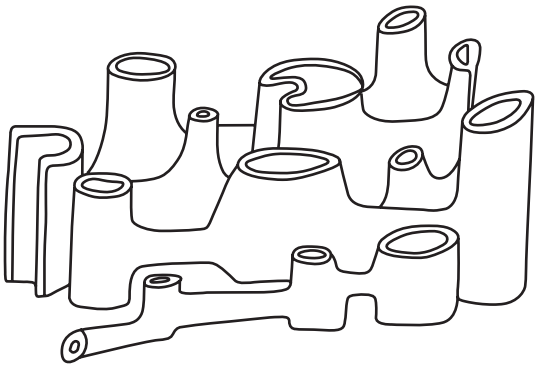


Figure 1.6 Smooth endoplasmic reticulum.

Rough Endoplasmic Reticulum

Endoplasmic reticulum with granular structure (ribosomes) on its outer surface is called rough endoplasmic reticulum. It is well developed in cells actively involved in protein synthesis.

The Nissl granules of neurons and acinar cells of pancreas have well-formed rough ER.

Function Rough ER helps in the synthesis of proteins.

Smooth Endoplasmic Reticulum

Smooth ER does not have ribosomes on its surface. It is found in abundance in Leydig cells of the testis and cells of the adrenal cortex.

In skeletal and cardiac muscles, smooth ER is modified to form sarcoplasmic reticulum.

Functions Smooth ER helps in the synthesis of lipids, drug degradation, glycogen metabolism, and control of calcium ion concentration.

Ribosomes

Ribosomes are spherical particles found in both free and bound forms. The bound form is present on the outer surface of ER. Ribosomes are made up of RNA and proteins.

Functions

Ribosomes help in the synthesis of proteins. Ribosomes that are attached to ER synthesize all transmembrane proteins, most of the

secreted proteins, and proteins stored in Golgi apparatus, lysosomes, and endosomes.

Free ribosomes synthesize cytoplasmic proteins such as hemoglobin and proteins found in peroxisomes and mitochondria.

Golgi Apparatus

The Golgi apparatus resembles the smooth ER. It is made up of multiple layers of thin, flat vesicles lying near the nucleus (**Fig. 1.7**). The Golgi apparatus is a polarized structure with *cis* and *trans* sides. Vesicles containing proteins bud off from the rough ER and fuse with the cistern on the *cis* side of the Golgi apparatus. Later, they are passed to the *trans* side from where the vesicles branch off into the cytoplasm by exocytosis. Vesicles are carried to their destination by v-SNARE and t-SNARE proteins.

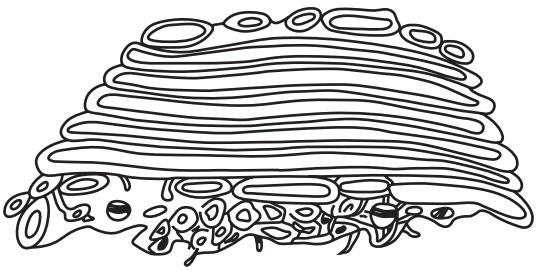


Figure 1.7 Golgi apparatus.

Functions

- Concentrates protein and polysaccharide
- Helps in the synthesis of the carbohydrate portion of glycoprotein
- Is the site for the formation of lysosomal enzymes
- Transports substances to other parts of the cell

Lysosomes

Lysosomes are formed by the Golgi apparatus and are present throughout the cytoplasm. They are more acidic than the remaining parts of the cell because of the presence of H^+ ATPase in their membrane.

Lysosomes are filled with hydrolytic enzymes. They get attached to the phagocytic vesicles and empty their contents into these vesicles. The enzymes digest the material inside the vesicle. Amino acids, glucose, and other substances formed diffuse out of the membrane. The undigested matter is excreted by exocytosis.

Functions

- Help in the removal of unwanted, damaged substances and foreign bodies such as bacteria
- Are responsible for regression of tissues, e.g., regression of uterus after pregnancy and mammary glands after lactation

Deficiency of lysosomal enzymes leads to lysosomal storage diseases.

Peroxisomes

Peroxisomes are similar to lysosomes formed from smooth ER. They contain oxidases and catalases.

Functions

- Peroxisomes cause breakdown of fatty acids by the process of beta oxidation.
- Oxidases generate and catalases break down hydrogen peroxide.
- Peroxisomes form the major site for oxygen utilization in the cell.

Centrosomes

Centrosomes are structures present near the nucleus. They are made up of structures called **centrioles**. Centrioles are two short cylinders arranged at right angle to each other. They are visible only during cell division.

Microtubules in groups of three run longitudinally in the walls of each centriole.

Centrosomes divide into two during cell division and move to the opposite poles of the mitotic spindle.

Function

Centrosomes control the steps of cell division.

CYTOSKELETON (Fig. 1.8)

Cytoskeleton is a system of fibers that maintains the structure of cell and permits the cell to change its shape. It helps in the movement of cell.

Cytoskeleton is made up of

- microfilaments,
- intermediate filaments, and
- microtubules

Microfilaments

Microfilaments are long, solid fibers 4–6 nm in diameter. They are made of actin molecules and provide elastic support to the cell membrane. The actin molecules are G-actin. These G-actins polymerize to form F-actin. F-actin is the microfilament. These actin fibers polymerize and depolymerize in vivo.

Actin fibers attach to various parts of the cytoskeleton and interact with the membrane-bound proteins. They reach the tip of microvilli in the intestinal epithelial cells. They interact with integrin receptors to form a focal adhesion complex. Microfilaments also serve as tracks for some molecular motors.

Intermediate Filaments

Intermediate filaments are 8–14 nm in diameter and made up of various subunits. They connect the nuclear membrane to the cell membrane. They are found in all types of cells.

Intermediate filaments form flexible folds in the cell, which helps in resisting external pressure. Absence of intermediate filament results in easy rupture of the cell.

Microtubules

Microtubules are long, hollow structures with a diameter of 15 nm. They are formed by the organization of two globular protein subunits: α- and β-tubulin. These subunits aggregate to form long tubes made of stacked rings with each ring containing 13 subunits.

Microtubules provide tracts for the transportation of vesicles and organelles such as mitochondria from one part of the cell to another. Substances can be transported in both directions along the microtubules. They form a spindle which moves the chromosomes during mitosis.

Microtubules assemble and disassemble as and when required. Warmth facilitates assembly and cold facilitates disassembly.

Some anticancer drugs such as vinblastine and colchicine prevent assembly of microtubules while others such as paclitaxel make them so stable that organelles cannot move inside them. Both the situations result in the death of the cell.

Molecular Motors

Molecular motors are ATPases that move proteins, organelles, and other contents of cells from one part to the other. They bind to

(*Contd.*)

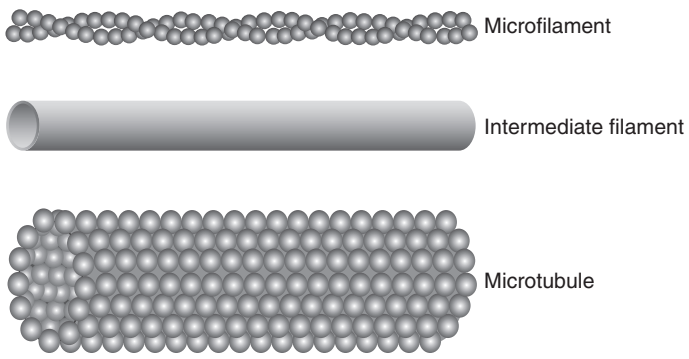


Figure 1.8 Cytoskeleton.

microtubules or microfilaments and bring about the movement of substances. They include kinesin, dynein, and myosin.

Kinesin

Kinesin is a double-headed molecule. One head binds to the microtubule and the other head swings forward and binds to the substance carried. Kinesins are associated with mitosis and meiosis.

Dyneins

Dyneins are of two types: (i) cytoplasmic dynein and (ii) axonemal dynein. The functions of cytoplasmic dynein are similar to those of kinesin. Axonemal dynein is responsible for beating of flagella and cilia. Dyneins also have two heads.

Myosin

Myosin is present in multiple forms. Its functions include muscle contraction and cell migration.

INTERCELLULAR CONNECTIONS

Intercellular connections are junctions formed between the cells. Types of intercellular connections include tight junctions, anchoring junctions, and gap junctions **(Fig. 1.9)**.

Tight Junctions

Tight junctions are also known as *zonula occludens*. They are present in the apical zone of the cell. They are commonly seen in cells lining the intestinal mucosa, renal tubules, and choroid plexus. They are formed by proteins belonging to occludin, junctional adhesion molecules, and claudin family.

Functions

- Provide strength to the tissues by holding the neighboring cells together
- Permit the passage of some ions and other solutes
- Prevent the movement of proteins in the plane of the membrane
- Form blood–brain barrier in the brain capillaries

Anchoring Junctions

Anchoring junctions are of two types: (i) cell-to-cell anchoring junctions and (ii) cell-to-basal lamina anchoring junctions.

Cell-to-cell junctions include zonule adherens and desmosomes.

Cell-to-basal lamina anchoring junctions are hemidesmosomes and focal adhesions.

Zonula Adherens

Zonula adherens is present on the basal side of zonula occludens and is the major site for attachment of actin fibers. The transmembrane

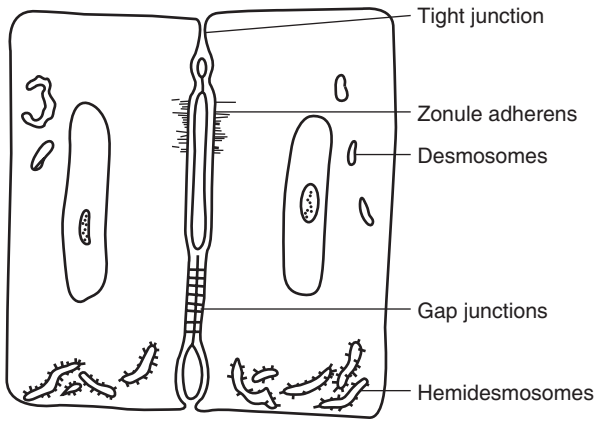


Figure 1.9 Intercellular connections.

proteins involved are cadherins. They provide strong attachment to the neighboring cells.

Desmosomes

Desmosomes are spot-like patches present on the membranes of the two adjacent cells. Intermediate filaments are attached to them.

Hemidesmosomes

Hemidesmosomes attach cells to the basal lamina. Intracellularly, they are attached to intermediate filaments. The transmembrane proteins involved are integrins.

Focal Adhesions

Focal adhesions are dense plaques which also attach cells to the basal lamina. They are structures associated with actin filaments inside the cell and play an important role in cell movement.

Gap Junctions

Gap junctions are channels formed by protein units called **connexons (Fig. 1.10)**. Each connexon is made up of six subunits surrounding a channel. The diameter of a channel is around 2 nm.

The diameter of channels is regulated by intracellular calcium ions. An increase in intracellular calcium causes a reduction in the diameter of the channel. The diameter of the channel is also affected by pH, hormones, and various neurotransmitters.

The intercellular space narrows from 25 nm to 3 nm at the gap junctions. These junctions enable substances such as ions and sugars to pass between the cells without entering ECF.

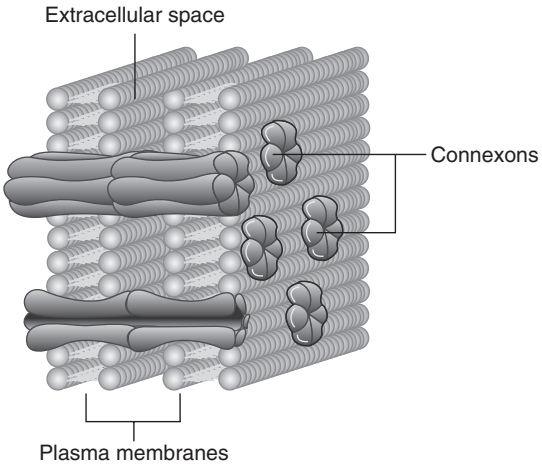


Figure 1.10 Connexons. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

They also permit rapid propagation of electrical activity from one cell to another.

Cell Adhesion Molecules

Cell adhesion molecules (CAM) are substances which attach cells to the basal lamina and also to each other. They are important in embryonic development and formation of the nervous system and other tissues. They are useful in holding the cells together in adults, in the process of inflammation, in wound healing, and in the metastasis of tumors.

CAMs are divided into four broad groups:

1. **Integrins**: Heterodimers that bind to various receptors
2. **Adhesion molecules**: IgG superfamily of immunoglobulins
3. **Cadherins**: Calcium-dependent molecules that mediate cell-to-cell adhesion by homophilic reactions
4. **Selectins**: Bind carbohydrates

INTERCELLULAR COMMUNICATIONS

Communication between cells occurs by various mechanisms:

1. **Neural communication:** In this form of communication, neurotransmitters are released at the synaptic junctions from nerve cells. They act on a postsynaptic cell across a narrow synaptic cleft.
2. **Endocrine communication:** In this type, hormones and growth factors reach cells through blood circulation.

3. **Paracrine communication:** The product of cells diffuses in the ECF to affect the neighboring cells which are some distance away.
4. **Autocrine communication:** In this type, cells secrete chemical messengers that bind to receptors on the same cell.

In all forms of communication, the substance used is a chemical messenger. These chemical messengers commonly include amines, steroids, polypeptides, and amino acids. The chemical messenger can function in different parts of the body in different ways. It can function as a neurotransmitter, a neural hormone, and an endocrine hormone.

Chemical messengers act in various ways. These include the following:

1. opening or closing of ion channels, e.g., acetylcholine;
2. through cytoplasmic or nuclear receptors to increase transcription of selected mRNA, e.g., thyroid hormones;
3. activation of phospholipase C with intracellular production of IP_3 and other inositol phosphates, e.g., angiotensin II;
4. increasing cGMP in the cell, e.g., atrial natriuretic peptide;
5. activation of adenylyl cyclase causing increased production of cAMP, e.g., norepinephrine via α_1-adrenergic receptor;
6. inhibition of adenylyl cyclase causing decreased production of cAMP, e.g., norepinephrine via α_2-adrenergic receptor;
7. increasing tyrosine kinase activity, e.g., insulin.

In most instances, these chemical substances (ligands) which act extracellularly trigger the release of intracellular mediators. The extracellular ligands are called **first messengers** and intracellular mediators are called **second messengers**.

Following the recognition of the primary messenger by the receptor, second messenger changes will be activated in the cell. This results in a cell signaling pathway which amplifies the primary signal and distributes it to appropriate targets within the cell. Second messengers bring about short-term changes in cell function by altering enzyme function and triggering exocytosis. They also act by altering transcription of various genes.

The second messengers generally activate protein kinase enzymes. These enzymes add phosphate groups to proteins causing change in protein configuration. This alters the function of proteins and thereby alters the functions of the cell.

Examples of second messengers include cyclic AMP, cyclic GMP and calcium.

CELL DIVISION

All multicellular organisms start from a single cell. Human cells have 46 chromosomes (23 pairs). Of this, 22 pairs are autosomes and 1 pair is sex chromosomes.

Transformation from a single cell to a multicellular organism involves the processes of cell division and cell differentiation.

The cell divides in two phases: (i) interphase and (ii) mitosis.

INTERPHASE

Interphase is a preparation period for mitosis. It is subdivided into G_1, S, and G_2 phases.

G_1 Phase

The decision for cell division is confirmed during this stage. The cell performs all its normal functions.

S Phase

There is duplication of DNA material. The DNA double helix separates. Two strands synthesize its complement and therefore two DNA double helixes are formed.

G_2 Phase

In this phase, the volume of cytoplasm increases.

MITOSIS

Mitosis begins at the end of the G_2 phase. It has four phases **(Fig. 1.11)**:

1. Prophase
2. Metaphase
3. Anaphase
4. Telophase

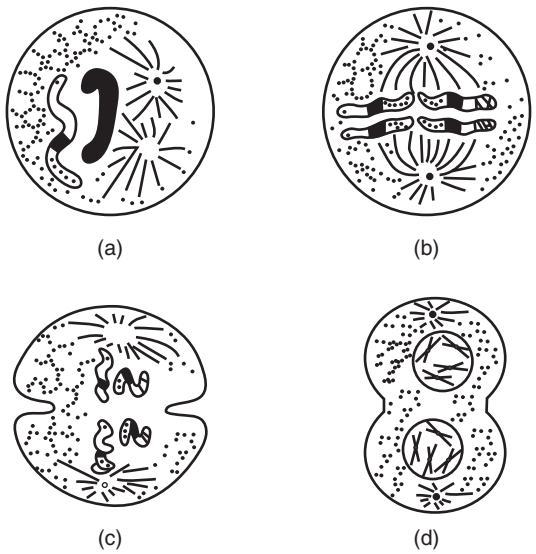


Figure 1.11 Stages of mitosis: (a) prophase, (b) metaphase, (c) anaphase, and (d) telophase.

Prophase

Centrioles move apart and form poles of mitotic spindle. Chromatin material condenses into chromosomes. Each chromosome is made up of a pair of chromatids attached to the centromere. There is dissolution of nuclear membrane and nucleoli.

Metaphase

Chromosomes move to the equator of the spindle. Centromeres split and chromatids get separated. Centrioles duplicate resulting in two centrioles at each pole of the spindle.

Anaphase

Separated chromatids move toward opposite poles with the help of spindles. A constriction appears in the middle of the cell indicating the formation of two daughter cells.

Telophase

Chromosomes are converted to a chromatin network. Nucleoli reappear, new nuclei are formed, and nuclear membrane reappears. Spindle fibers disappear and finally two daughter cells are formed.

MEIOSIS

Meiosis is a process where four daughter cells with half the number of chromosomes are formed. Sex cells (gametes) are produced by this method.

Gamete formation occurs in two stages: (i) meiosis I and (ii) meiosis II.

In the first division, two cells with a haploid number of chromosomes are formed. In the second division, four cells are formed from these two cells without reduction in the number of chromosomes. Meiosis also occurs in four phases as seen in mitosis.

Stages (Fig. 1.12)

Prophase I

It is the longest phase of meiosis. Centrioles move apart. Chromatin material condenses into chromosomes. The chromosomes separate and are attached at a few points. Exchange of genetic material occurs between the chromatids.

Metaphase I

The homologous pairs of chromosomes move toward the equator with the help of microtubules attached to the centromere.

Anaphase I

One chromosome from each homologous pair moves toward the opposite pole with the help of spindles. Therefore, 23 chromosomes move to one pole while the other 23 chromosomes move to the other pole.

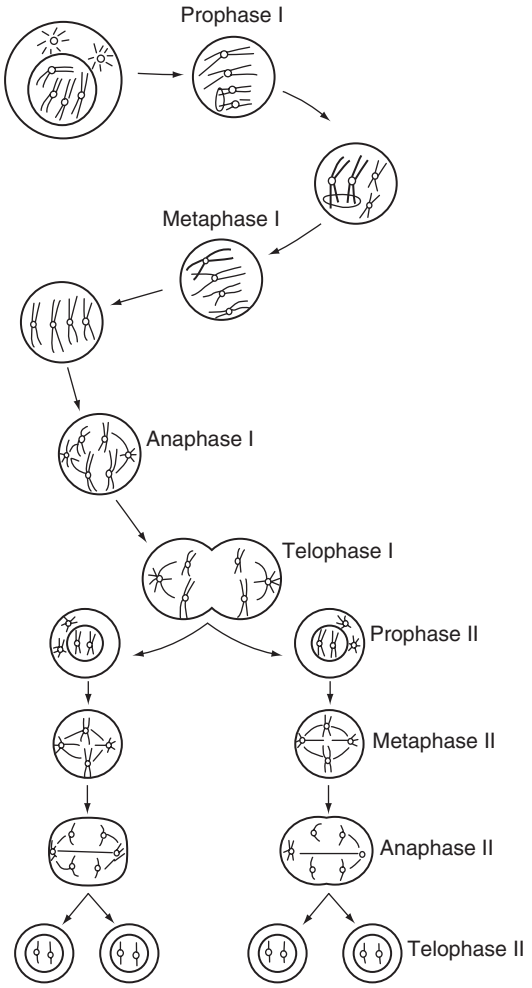


Figure 1.12 Stages of meiosis.

Telophase I

The cytoplasm divides, nuclei are formed, and two cells develop. The spindle network disappears. The cell has 23 chromosomes, each chromosome with a pair of chromatids.

Prophase II

This occurs after telophase I. There is formation of a new spindle at right angle to the earlier one.

Metaphase II

A pair of chromatids moves toward the equator with the help of microtubules attached to the centromere.

Anaphase II

The two chromatids move toward the opposite poles with the body of spindles.

Telophase II

It is marked by decondensation and lengthening of the chromosomes. The spindle disappears. The chromatids form a network. New nuclei are formed. One cell divides into two. Finally, four daughter cells are formed from one mother cell.

GENETICS

Genetics is a branch of biology devoted to the study of genes and heredity. The science of genetics has made great advance in the recent past. The foundation for modern-day genetics was laid down by Gregory Mendel. Later, hundreds of researchers have contributed to this field and have helped in revolutionizing the study of genetics.

CHROMOSOMES

The term *chromosome* was coined by Waldeyer in 1888. Chromosomes are thin, thread-like structures present in the nucleus of eukaryotic cells during cell division.

Chromosomes are responsible for the transmission of hereditary characters from one generation to the next.

The number of chromosomes in every cell is constant for a given species. There are 46 chromosomes (23 pairs) in all the human cells of which 22 pairs are autosomes and one pair is sex chromosome. Gametes (sperm and ovum) contain only 23 chromosomes. The chromosome is composed of a pair of chromatids connected at the centromere which

divides the chromosome into two sections, or "arms" (**Fig. 1.13**). The short arm of the chromosome is labeled "p arm." The long arm of the chromosome is labeled "q arm." The location of the centromere on each chromosome gives the characteristic shape and can be used to describe the location of specific genes.

Chromosomes are mainly composed of DNA. They also contain RNA, basic proteins called histones, complex proteins, and inorganic salts.

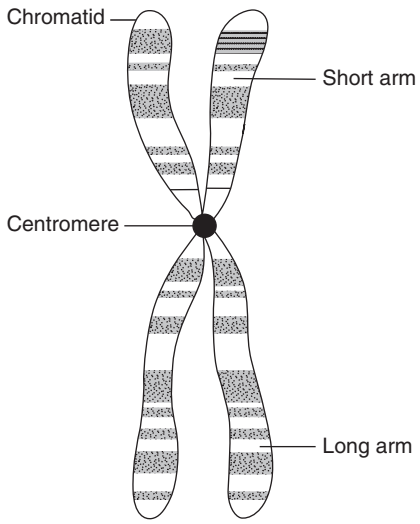


Figure 1.13 Structure of a chromosome. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

DNA

DNA (deoxyribonucleic acid) is a long, double-stranded helical structure containing simple chemical compounds bound together in a regular pattern **(Fig. 1.14)**.

It is the component of chromosomes that carries the genetic message (hereditary characteristics) from the parent to the offspring.

DNA is made of phosphoric acid, deoxyribose sugar, and four nitrogenous bases—adenine, guanine, thymine, and cytosine.

Phosphoric acid and deoxyribose sugar form the helical strands and nitrogenous bases connect the two strands. These strands are linked together by hydrogen bonds between the specific nitrogenous bases.

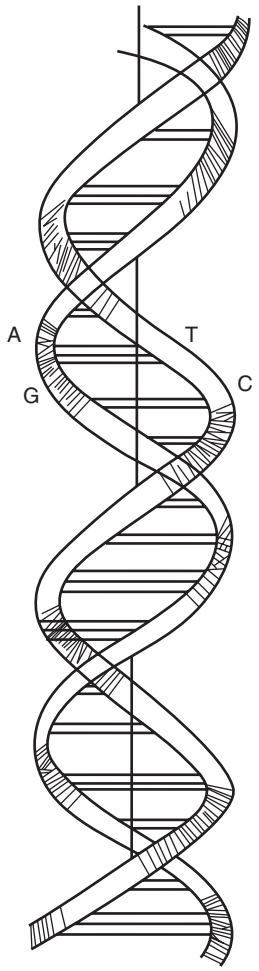


Figure 1.14 Structure of a DNA molecule.

Adenine pairs with thymine and guanine pairs with cytosine.

There are an estimated 30,000 genes in the human genome. The collection of genes with full expression of DNA from an organism is called **genome**.

DNAs which code for proteins are called **exons**. They make up only 3% of the human genomes. The remaining 97% of DNAs are called **introns**. Their function is not yet known. They are also referred to as **junk DNAs**.

RNA

RNA is similar to DNA except that the sugar present is ribose. Nitrogenous base thymine is replaced by uracil. During RNA synthesis, the

DNA Fingerprinting

The character of DNA varies from individual to individual. A common form of variation is repetition of base pairs. This causes variation in the length of the DNA chain where it is cut by restriction enzymes. This process is termed **restriction fragment length polymorphism** (RFLP). Analysis of RFLP is DNA fingerprinting. It is very accurate in differentiating two individuals since the chance of RFLP matching due to chance is 1 in 1 million to 1 in 1 lakh. DNA fingerprinting can be carried out in small quantity of specimens of semen and blood, as well as of tissues.

Mutation

Mutation is a change in the DNA structure of a gene. It leads to the formation of an abnormal protein causing abnormal cell function and sometimes cell death. The factors that produce mutation are called mutagens. They include X-rays, UV rays, and certain chemicals.

two strands of DNA separate and one of the strands is used as a template for RNA molecule synthesis. RNA is essential in various biological roles in coding, decoding, regulation, and expression of genes.

There are three types of RNAs:

1. mRNA (messenger RNA)
2. tRNA (transfer RNA)
3. rRNA (ribosomal RNA)

mRNA

mRNA carries the genetic code from the nucleus to the cytoplasm for controlling protein synthesis. It is composed of several hundred to several thousand nucleotides in a single unpaired strand. It contains codons that are complementary to triplets of DNA genes. It enters the cytoplasm and arranges itself on the ribosomes.

tRNA

tRNA contains about 80 nucleotides. It is folded to form a clover leaf. It transports amino acids to protein molecules as the protein is being synthesized. tRNA combines with amino acids that are to be incorporated into proteins. Then it acts as a carrier to transport these amino acids to the ribosomes where protein is formed.

In the ribosomes, each specific type of tRNA recognizes a particular codon on mRNA and thereby delivers the correct amino acid for the protein molecule which is newly formed.

rRNA

rRNA is synthesized in the nucleus. It constitutes about 60% of the ribosomes. The remaining 40% of the ribosomes is composed of proteins. rRNA functions in association with tRNA and mRNA. tRNA transports amino acids to the ribosome for incorporation in the protein. mRNA provides the necessary information for arranging the amino acids in a proper order.

TRANSCRIPTION

Transcription is the process of formation of mRNA. It occurs under the influence of the RNA polymerase enzyme.

Steps in the Transcription Process

The DNA strand contains a sequence of nucleotides called promoter. RNA polymerase recognizes this promoter and attaches to it. It unwinds the DNA helix and separates the two strands. The DNA strand on which the synthesis of RNA occurs is called a template strand. The other DNA strand is called a coding strand. As unwinding goes on, a new RNA nucleotide is added to the newly formed RNA chain. The newly formed RNA chain breaks away from the DNA template. It is released into the nucleoplasm. The DNA strand rebonds with its own complementary DNA strand.

TRANSLATION

Translation is the process of formation of the polypeptide chain from mRNA. The mRNA molecule comes in contact with the ribosomes. As it travels through the ribosomes, a protein molecule is formed. The protein molecule formation ends when the chain-terminating codon passes through the ribosome. This protein molecule is released into the cytoplasm.

GENES

Genes are the functional units of DNA. The portion of chromosome which codes a particular character is called a **gene**. The position of a gene on a chromosome is called **locus**. The loci of genes for different characteristics are also constant for a given species. The sequence of nitrogenous bases in the DNA constituting a given gene is also very similar in all individuals of a species. However, minor individual differences in the sequence of nitrogenous bases in the DNA constituting some genes account for the variety within the species.

In sexual reproduction, the progeny receives two genes for each character, one from the mother and another from the father. If both parents transmit the same type of genes, the progeny is homozygous for the character concerned. If both parents transmit different types of genes, the progeny is heterozygous. In the heterozygous state, only one trait is expressed in the progeny (dominant trait). The other trait remains hidden (recessive trait). However, the heterozygous individual passes on the dominant or recessive trait with equal probability to its own progeny.

GENETIC CODE

The genetic code consists of triplets of bases. A triplet is made up of three successive bases. This triplet is termed a **code word**. The successive triplets finally control the sequence of amino acids present in a protein.

Two strands of DNA molecules split apart, exposing the purine and pyrimidine bases on each of the strands. The genetic code is formed in these exposed bases.

GENE EXPRESSION

Each and every cell of the human body contains the entire genetic information. There is a great differentiation and specialization in human cells.

The genetic information is normally maintained in a repressed state and only small parts of the information are transcribed. This is mediated by transcription factors.

CLINICAL NOTES

Genetic engineering has a wide variety of application in the field of medicine.

It includes

- production of hormones such as insulin, growth hormone, and erythropoietin;
- manufacture of vaccines, clotting factors, and interferons;
- rapid laboratory diagnosis of diseases such as AIDS;
- correction of various genetic defects;
- prenatal diagnosis of genetic disorders;
- settling of paternity disputes; and
- DNA fingerprint that helps in detection of crimes.

Apoptosis

Apoptosis is programmed cell death. It is a form of coordinated and planned cell death which occurs under genetic control. Apoptosis occurs whenever the cell is no longer required by the body. This process involves a series of specific proteolytic reactions that causes condensation and shrinkage of the cells. The cytoskeleton is disassembled and the cell surface is altered. This causes a neighboring macrophage to attach to the cell, resulting in phagocytosis.

Apoptosis occurs both during fetal development and in adulthood.

In the fetus, it causes removal of webs between fingers and regression of the duct system during sexual development. It causes the death of a large number of neurons during the development of CNS. It causes the death of inappropriate clone of immune cells.

In adults, it causes breakdown of endometrium during menstruation and death of enterocytes present at the tips of intestinal villi.

Abnormal apoptosis occurs in cancer, neurodegenerative diseases such as Alzheimer's disease, and autoimmune disorders.

TRANSPORT ACROSS CELL MEMBRANE

The chemical composition of extracellular fluid (ECF) is quite different from that of intracellular fluid (ICF). This difference is extremely important for the survival of cell.

Passage of substances through the cell membrane can be divided into two categories:

1. Direct passage through the membrane
2. Passage through carrier proteins and channels

The lipid bilayer of the cell membrane allows lipid-soluble substances such as oxygen, carbon dioxide, nitrogen, and alcohol to pass through it.

Lipid-insoluble substances such as electrolytes, glucose, and amino acids are selectively transported by protein molecules present in the cell membrane. These proteins are called **transport proteins**.

TRANSPORT PROTEINS

Transport proteins are of two types:

i. channel proteins and
ii. carrier proteins.

Channel Proteins

Channel proteins have watery spaces through the molecule and therefore allow free movement of certain ions and molecules. They are of two types:

1. Ion channels
2. Water channels

Ion channels are formed by polypeptide subunits. These subunits are arranged around an aqueous pore. Ions pass from one side of the membrane to the other through this aqueous pore, e.g., sodium channel and potassium channel.

Water channels are called **aquaporins**. They are mainly present in kidneys; however, they are also found in liver, lungs, spleen, leukocytes, and lacrimal glands.

Channel proteins allow movement of water, ions, and molecules. Substances such as water can easily pass through these protein channels. Transport of other substances depends on the character of the protein channels.

Protein channels have two important characteristics:

1. They are selectively permeable to certain substances.
2. Many of the channels are opened or closed by gates.

Selective Permeability

Protein channels are highly selective for the transport of ions or molecules. It depends on the diameter, shape, and electrical charge of the channel.

Gating (Fig. 1.15)

Gates are actually extensions of the transport protein molecule. These gates provide means for controlling the permeability of the channels. A conformational change in the shape of the protein molecule causes either opening or

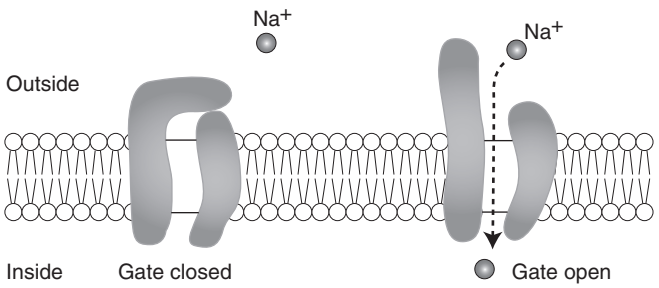


Figure 1.15 Gating of channels.

closing of the gate. Opening and closing of the gate are controlled by three mechanisms:

1. Voltage gating
2. Chemical gating (ligand gating)
3. Mechanical gating

Voltage Gating Here, the molecular conformation of the gate responds to changes in the electrical potential across the cell membrane.

Chemical Gating In this type of gating, protein channels are opened with the binding of another molecule (ligand) to the protein (receptor).

Mechanical Gating Some of the channels are mechanosensitive. They respond to stretch, e.g., ion channels in the hair cells of the vestibular apparatus.

Carrier Proteins

Carrier proteins bind to substances that are to be transported and undergo conformational change. This causes movement of substances from one side of the membrane to the other.

Types of carrier-mediated transport **(Fig. 1.16)** are as follows:

- **Uniport:** There is transport of only one substance. For example, sodium channels transport Na^+ and potassium channels transport K^+.
- **Symport:** There is transport of two substances in the same direction, e.g., sodium and glucose transport.
- **Antiport:** There is movement of two substances in opposite directions. Example is the Na^+–K^+ pump.

Both the carrier and channel proteins are highly selective in allowing the passage of ions or molecules across the membrane.

METHODS OF TRANSPORT

Transport of ions or molecules occurs by two basic processes:

1. Passive transport
2. Active transport

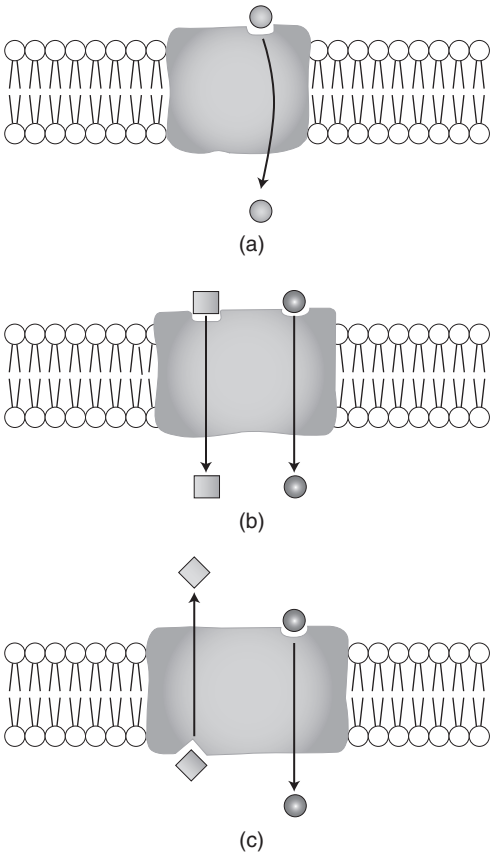


Figure 1.16 Types of carrier-mediated transport: (a) uniport, (b) symport, and (c) antiport.

The mechanism of passive transport includes the following:

- Simple diffusion
- Facilitated diffusion
- Osmosis
- Filtration
- Bulk flow
- Solvent drag

The active transport mechanisms are

- Primary
- Secondary

Other transport mechanisms are

1. Vesicular transport
   - Exocytosis
   - Endocytosis
2. Transport across epithelia
   - Transcellular transport
   - Paracellular transport

Passive Transport

The main features of passive transport are as follows:

- Transport occurs downhill (along the electrochemical gradient)
- It does not require expenditure of energy (ATP)

The substances are transported on both the sides; however, the net movement occurs down the electrochemical gradient.

Diffusion

Diffusion is the continuous movement of molecules among one another in a liquid or in a gaseous state.

Diffusion is of two types:

1. Simple diffusion
2. Facilitated diffusion

Simple Diffusion (Fig. 1.17) Diffusion is the movement of molecules or ions through the cell membrane without involvement of carrier proteins. It occurs from the region of higher concentration to the region of lower concentration.

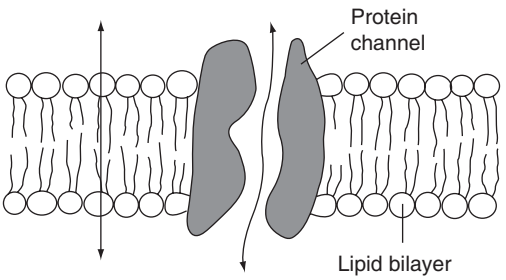


Figure 1.17 Simple diffusion.

Diffusion depends on the following:

- Permeability of cell membrane
- Concentration gradient
- Electrical gradient
- Pressure gradient

Simple diffusion occurs through the lipid bilayer and protein channels.

Diffusion Through the Lipid Layer Substances such as O_2, CO_2, alcohol, and N_2 dissolve directly in the lipid layer and diffuse through the cell membrane. The rate of diffusion of these substances is directly proportional to their lipid solubility.

Diffusion Through Protein Channels Substances such as water can easily pass through these protein channels. Transport of other substances depends on the character of protein channels.

Facilitated Diffusion It is also called *carrier-mediated diffusion*. The substances are transported with the help of a specific carrier protein, e.g., glucose and amino acids **(Fig. 1.18)**. Like simple diffusion, facilitated diffusion is also a downhill transport and does not require energy.

Features of Facilitated Diffusion

- Faster rate of transport
- Saturation
- Specificity
- Competitive inhibition

Differences between simple and facilitated diffusion are given in **Table 1.1**.

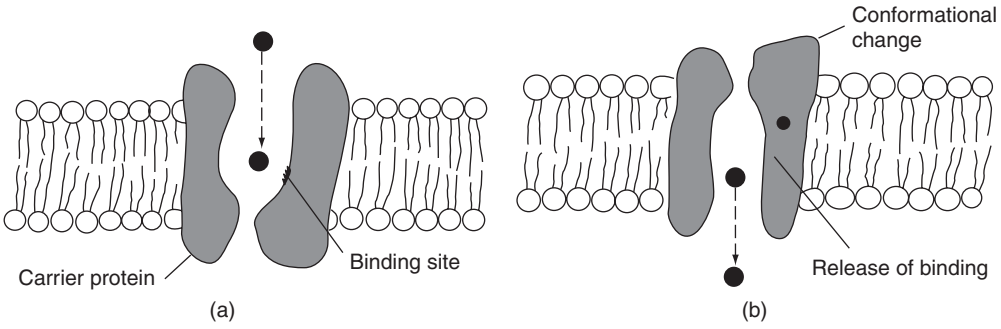


Figure 1.18 Facilitated diffusion.

Table 1.1 Differences Between Simple Diffusion and Facilitated Diffusion

Features	Simple Diffusion	Facilitated Diffusion
Carrier molecule	Not involved	Involved
Rate of diffusion	Slow	Fast
Saturation kinetics	Not present	Present
Competitive inhibition	Absent	Present
Type of substance transported	Small, nonpolar particles	Large/polar particles

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

Osmosis

Osmosis is a special type of diffusion. It is the movement of water across a semipermeable membrane from a region of lower solute concentration to a region of higher solute concentration **(Fig. 1.19)**.

Osmotic Effectiveness Some substances are said to be osmotically effective and some are osmotically ineffective. Substances which do not freely diffuse through the cell membrane are called osmotically effective substances, e.g., plasma proteins and dextran.

Substances that freely diffuse through the cell membrane are called osmotically ineffective substances, e.g., urea.

Osmotic Pressure The pressure required to prevent osmosis is called **osmotic pressure**. Osmotic pressure depends on the number of particles in the solution and not on the type or size of the particle.

The osmotic pressure exerted by colloidal substances in the body is called **colloidal osmotic pressure**.

Colloidal osmotic pressure due to plasma colloids is called **oncotic pressure**. The normal value is 25 mm of Hg.

Other forms of passive transport include

- filtration,
- bulk flow, and
- solvent drag

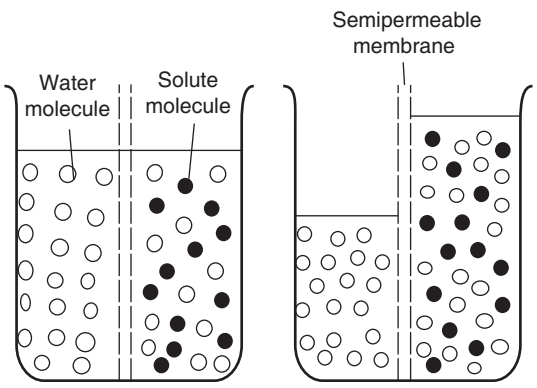


Figure 1.19 Osmosis.

Filtration

Filtration is a process by which fluid is forced through a membrane because of pressure difference on two sides.

Bulk Flow

Bulk flow is the process of movement of large quantities of water.

Solvent Drag

Solvent drag occurs during bulk flow. In this process, dissolved particles are also carried with water.

Active Transport

Active transport is a process by which molecules or ions move uphill across the cell membrane against a concentration gradient.

Features of Active Transport

- Uphill transport—occurs against the electrochemical gradient
- Utilization of energy—requires energy which is derived from breakdown of ATP
- Exhibits saturation kinetics—reaches saturation point due to limited availability of carrier proteins

Active transport is divided into two types: (i) primary and (ii) secondary.

Primary Active Transport

In primary active transport, energy is derived directly from the breakdown of ATP or

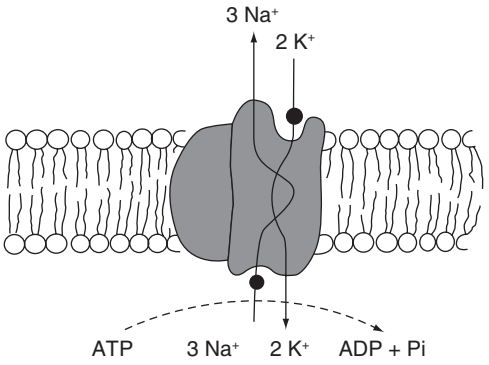


Figure 1.20 Primary active transport.

some other high-energy phosphate compound **(Fig. 1.20)**.

Important primary active transport processes are

- sodium–potassium pump,
- potassium–hydrogen pump, and
- calcium pump

Sodium–Potassium (Na^+–K^+) Pump It is present in all the cells of the body. This pump transports sodium ions from inside the cell to the exterior. At the same time, it transports potassium ions from outside to inside of the cell.

Structure The Na^+–K^+ pump is a carrier protein **(Fig. 1.21)**. It is made up of two globular protein subunits: α and β.

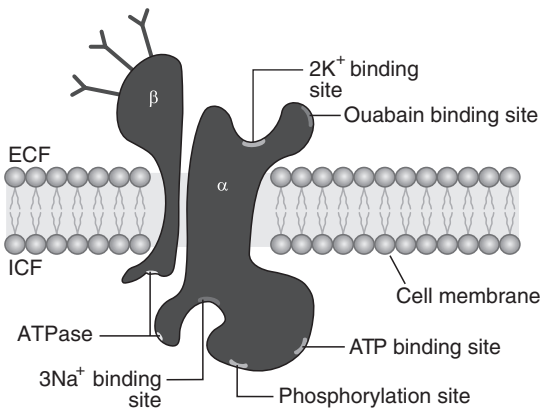


Figure 1.21 Structure of the Na^+–K^+ pump. *ECF*, extracellular fluid; *ICF*, intracellular fluid. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The α subunit is larger than the β subunit. The β subunit is mainly concerned with sodium–potassium transport.

This pump has

- *three intracellular binding sites:* one for three Na^+ ions, another for ATP, and third is the phosphorylation site;
- *two extracellular sites:* one for binding two K^+ ions and another for ouabain.

This pump has three receptor sites for binding sodium ions on the inside. It has two receptor sites for binding potassium ions on the outside. The inner portion near the sodium-binding sites has ATPase activity.

Functions The Na^+–K^+ pump causes electronegativity inside the cell. It prevents accumulation of water inside the cell.

Potassium–Hydrogen (K^+–H^+) Pump It is present in two places: (i) at the parietal cells of gastric glands and (ii) at the renal tubules.

The K^+–H^+ pump present in the parietal cells actively transports H^+ ions out of the cells into the lumen of gastric glands and K^+ ions from the lumen into the cell.

The K^+–H^+ pump present in the cells of the distal tubule of nephron secretes large amounts of H^+ ions into the tubules to eliminate H^+ from the body.

Calcium Pump This is another important active transport mechanism. Like the Na^+–K^+ pump, it also operates with the help of a carrier protein which has ATPase activity. The calcium pump helps in maintaining extremely low concentration of calcium in the intracellular fluid.

Secondary Active Transport

The energy derived from the transport of one substance helps the movement of the other substances. This transport is of two types:

1. Cotransport
2. Countertransport

Cotransport (Symport) Two substances are simultaneously transported across the cell membrane in the same direction.

Examples include sodium–glucose cotransport and sodium–amino acid cotransport.

Countertransport (Antiport) A single carrier is used to transport two substances in opposite directions. Examples include sodium–calcium countertransport (occurs throughout the body) and sodium–hydrogen countertransport (occurs in the distal convoluted tubule).

Vesicular Transport Mechanisms

Vesicular transport mechanisms are involved in the transport of substances such as protein molecules which cannot pass through the cell membrane either by diffusion or by active transport. They include

- exocytosis,
- endocytosis, and
- transcytosis

Exocytosis (Fig. 1.22a)

Exocytosis is a process by which intracellular substances are extruded out of the cell. Granules and vesicles present inside the cell move toward the cell membrane. The membranes of granules and vesicles fuse with the cell membrane releasing the contents to the exterior. Release of hormones and enzymes by the secretory cells of the body occurs by exocytosis.

Endocytosis (Fig. 1.22b)

Endocytosis is the reverse of exocytosis. It is a process by which substances are taken into the cell. A region of the membrane is pinched off to form an endocytic vesicle that causes internalization of the substance into the cell.

Types of endocytosis are phagocytosis and pinocytosis.

Phagocytosis (Fig. 1.23) It is a process in which bacteria and dead tissue are engulfed by the cells.

Phagocytosis has three broad steps:

1. Attachment of the foreign molecule to the cell membrane **(Fig. 1.23a)**
2. Engulfment of the foreign molecule in the form of endocytic vesicle **(Fig. 1.23b)**
3. Killing or degradation of the ingested material **(Fig. 1.23c** and **d)**

Pinocytosis It is similar to phagocytosis, but the substances ingested are in fluid form. It is, therefore, called **cell drinking**.

Transcytosis

Transcytosis is vesicular transport within the cell. It is also called **cytopempsis**. Transcytosis makes use of caveolin-coated vesicles.

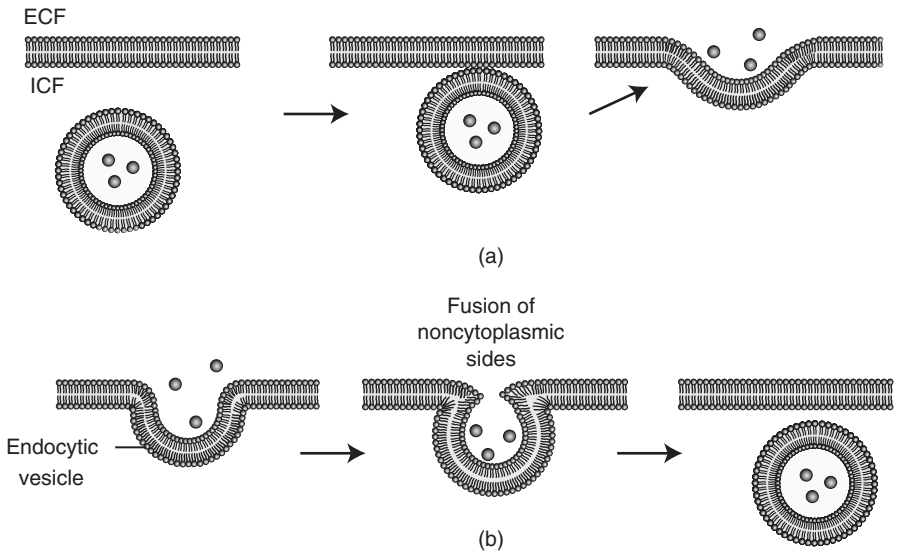


Figure 1.22 (a) Exocytosis and (b) endocytosis.

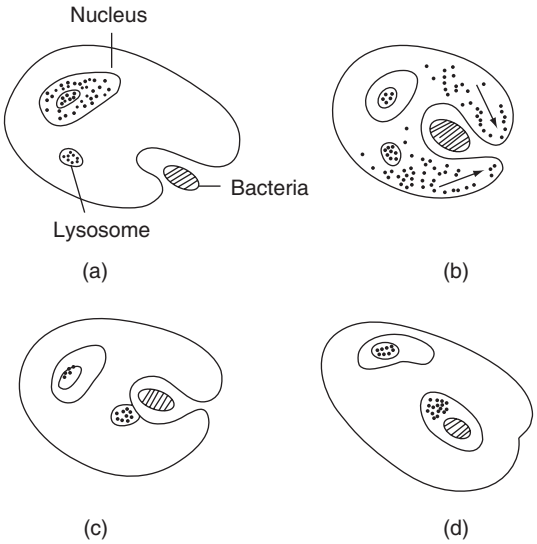


Figure 1.23 Phagocytosis.

Transport Across Epithelia

There are two mechanisms of transport across epithelia:

1. Transcellular transport
2. Paracellular transport

Transcellular Transport

Transcellular transport is transport through the cell. Initially, there is transport from the lumen into the cytoplasm through the apical surface and later from the cytoplasm through the basolateral membrane into the interstitial fluid.

Paracellular Transport

Paracellular transport is transport through the tight junctions. It occurs at the intestinal epithelia, proximal renal tubules, and gallbladder.

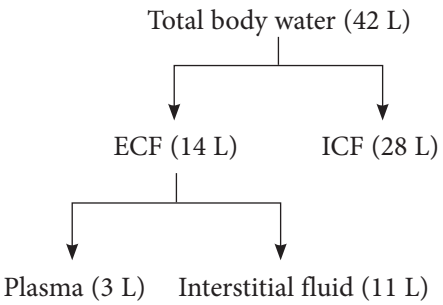
BODY FLUIDS

Water is an essential component of our body. The major portion of our body is composed of water. The total body water (TBW) is around 60% of the body weight, i.e., 42 L in a 70-kg adult male. The total body water is about 10% less in a normal adult female as compared to a male. This is due to relatively greater amounts of fat tissue in females. TBW decreases with age.

Electrolytes constitute about 7% of the total body weight. They are distributed widely in different body fluid compartments.

Body fluids are divided into two compartments:

1. Intracellular fluid (ICF)
2. Extracellular fluid (ECF)



INTRACELLULAR FLUID

Intracellular fluid is the total amount of fluid present inside the 75 trillion cells of our body. Although the fluid is distributed among the 75 trillion cells of our body, it is considered one single unit because the composition of fluid in all these cells is similar. The ICF compartment comprises about 40% of the body weight.

The normal volume of ICF is 28 L.

Constituents of ICF: ICF contains large numbers of potassium, phosphate, magnesium, and sulfate ions. It contains a small number of sodium and chloride ions and almost no calcium ions. It also contains large amounts of protein.

EXTRACELLULAR FLUID

Extracellular fluid (ECF) is the fluid present outside the cells. It constitutes about 20% of the body weight. The normal volume of ECF is 14 L.

It has two parts: (i) interstitial fluid (11 L) and (ii) plasma (3 L).

Interstitial Fluid

Interstitial fluid surrounds the cells. It is found in the spaces between cells. It is similar to plasma except that it has very little protein. Interstitial fluid is an ultrafiltrate of plasma.

Plasma

Plasma is the noncellular part of blood. It forms 25% of the ECF. Plasma communicates continuously with interstitial fluid through the pores in the capillaries resulting in exchange of water, ions, and small solutes. Therefore, plasma and interstitial fluid have almost similar composition.

Constituents of ECF: ECF contains large amounts of sodium and chloride ions, and moderate amounts of bicarbonate ions. Potassium, calcium, magnesium, and phosphate ions are present in very minute quantities.

Transcellular Fluid

Transcellular fluid is a special type of ECF. It includes synovial, peritoneal, pericardial, intraocular, and cerebrospinal fluid.

In total, the transcellular fluid constitutes 1–2 L.

Composition of Body Fluids

	ECF ($mOsm/L\ H_2O$)	ICF ($mOsm/L\ H_2O$)
Na	142	14
K	4.2	140
Ca	1.3	0
Mg	0.8	20
Cl	108	4
Protein	1.2	4

MEASUREMENT OF BODY FLUIDS

Body fluids can be measured by substances that remain in the particular compartment to be measured.

Total Body Water

Total body water (TBW) is measured by using radioactive water, heavy water, and antipyrine. These substances mix well with body water within a few hours after injection. TBW is calculated by estimating the degree of dilution of these substances:

$$TBW = \frac{\text{Amount of substance injected}}{\text{Concentration of the substance after dilution}}.$$

Extracellular Fluid

Extracellular fluid is measured by using substances that disperse in ECF and plasma but do not enter the cell. Substances used are radioactive sodium, sucrose, thiosulfate ion, and inulin.

Plasma Volume

Substances that remain in the vascular system but do not readily pass through the capillary are used to measure the plasma volume, e.g., serum albumin labeled with radioactive iodine and Evans blue (a dye) by the dilution technique.

Intracellular Fluid

Intracellular fluid is the fluid present within the cells. It cannot be measured directly. It is calculated from

$$ICF = TBW — ECF.$$

Interstitial Fluid

Like ICF, the interstitial fluid also cannot be measured directly. It can be calculated from values of ECF volume and plasma volume.

REGULATION OF BODY FLUID VOLUME

Control of body fluid volume involves

1. water balance and
2. electrolyte balance.

WATER BALANCE

Water balance is mainly through the kidneys and is achieved by balancing water input and output.

Input of water is from two sources: (i) exogenous and (ii) endogenous. Exogenous water gain is achieved by drinking water and ingestion of water in food. The amount of water gain by drinking ranges from 0.5 to 8 L/day depending on the environmental conditions. Around 1–1.5 L of water is ingested through food every day. Endogenously, water is produced in the body during tissue oxidation. This accounts for about 300–400 mL of water per day.

Output of water is by loss of water from the body through urine, feces, sweat, and insensible form. About 1–1.5 L of water is lost through the urine and 200 mL through the feces. Water loss through sweat is influenced by environmental conditions and physical activity. It is around 100 mL/day at 23°C and 1400 mL/day at 38°C. Insensible loss occurs by evaporation from skin surface and respiratory passage.

Factors Influencing Water Balance

Water balance is controlled by two factors:

1. Plasma osmolality
2. Blood volume

Plasma osmolality controls water balance by stimulating thirst center and secretion of antidiuretic hormone (ADH) through osmoreceptors situated in the hypothalamus. Plasma osmolality depends on the presence of osmotically active substances such as NaCl, proteins, and glucose.

A change in blood volume is detected by volume receptors present in the atria. When blood volume is low, impulses are sent to the hypothalamus and pituitary to secrete ADH. This causes conservation of water by kidneys.

BODY ELECTROLYTES

Electrolytes constitute about 7% of the total body weight. Their distribution varies widely in different compartments.

In the ICF, the main cations are K^+ and Mg^{2+}. The main anions are PO_4^{3-} and proteins. The ICF has low concentrations of Na^+ and Cl^-.

In the ECF, the main cation is Na^+ and the main anions are Cl^- and HCO_3^-.

All the body K^+ is in an exchangeable pool. However, only 65% of Na^+ is in an exchangeable pool. Almost all of the body Ca^{2+} and Mg^{2+} are non-exchangeable. Only exchangeable solutes are osmotically active.

Functions of Electrolytes

- Are the main solutes of body fluids that maintain acid–base balance
- Maintain proper osmolality

ELECTROLYTE BALANCE

Sodium is the chief electrolyte present in ECF and potassium is the chief electrolyte present in ICF.

Sodium

Sodium is the main electrolyte of the ECF compartment. Its concentration in the ECF is about 142 mmol/L and in ICF it is 10 mmol/L. Normally, Na^+ is taken along with food, drinks and water and as common salt.

Excretion occurs through urine, stool, and sweat.

It is responsible for the maintenance of ECF volume. It is also responsible for the production of action potentials.

Sodium balance is maintained by aldosterone, atrial natriuretic peptide, and glomerulotubular balance.

Potassium

Potassium is the main electrolyte of the ICF compartment.

Its concentration in ECF is 4.2 mmol/L and in ICF it is 140 mmol/L. Our diet is rich in potassium; fruits in particular are a rich source.

Potassium is excreted through urine and stools.

It influences the electrical activity of excitable tissue.

Potassium balance is maintained by excretion rather than intake.

HOMEOSTASIS

Homeostasis is defined as the "maintenance of constancy of the internal environment of the body." All the organs present in our body function optimally and help to maintain the constant environment.

In human beings, about 60% of the total body weight is water, which means a person weighing 70 kg has a total water content of about 42 L, of which 28 L is present inside the cells and 14 L is present outside the cells. The electrolyte composition of the fluid present outside the cell, the extracellular fluid (ECF), roughly resembles that of sea water, which is rich in sodium and chloride.

In 1857, Claude Bernard, a French physiologist, designated this fluid (ECF) in the body as the internal environment (or the milieu interieur) to differentiate it from the external environment of the body.

Later in 1929, an American physiologist, WB Cannon, coined the term **homeostasis** (homoios means "like" and stasis means "standing still" to describe phenomenon of the constancy of the internal environment.

The human body containing 75 trillion cells is organized into different structures called the **organs**. Each organ contributes to the maintenance of homeostatic conditions in the extracellular fluid which is termed the **internal environment**.

Homeostatic Regulatory Mechanisms

Homeostatic regulation is generally achieved through feedback mechanisms.

Feedback mechanisms are of two types:

1. Negative feedback mechanism
2. Positive feedback mechanism

Negative Feedback Mechanism

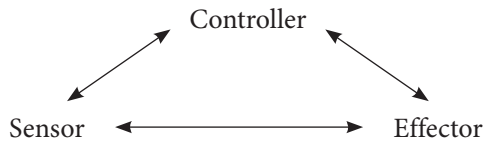
Majority of the control systems of the body act by negative feedback mechanism. The negative feedback system generally operates to maintain the physiological variable at a constant level. It consists of a sensor, a controller, and an effector.

The stimulus for this feedback system is a change in the level of variable. This change is detected by a sensor that activates the control system. This in turn causes a response to bring the variable back to the normal range and restore homeostasis.

Sensor The negative feedback control system requires a sensor for its operation. Sensors are receptors that continuously monitor the change of a variable and regularly provide information to the controlling center, e.g., receptors in aortic arch and carotid sinus that detect change in blood pressure.

Controller Controller is usually located in the brain as groups of nuclei. It receives inputs from various parts of the body by the way of afferent signals. For example, the vasomotor center located in the medulla regulates the heart rate.

Effector Effector is the target organ that carries out the command given by the controller to achieve an effective response. For example, blood vessels and heart are the effector organs for regulation of blood pressure.



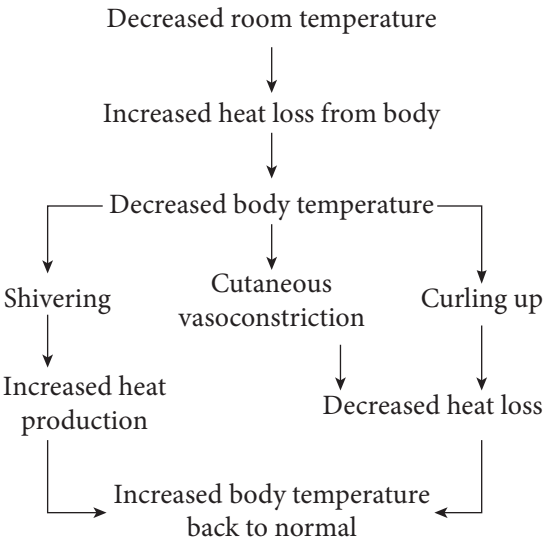
Depending on the signals received from the center, the effector organs constantly change their activity to achieve the desired effect. When the deviation observed is an increase in a variable above the set point, the effector will be inhibited and this inhibition continues until the variable is brought back to normal. A reverse process is initiated whenever the variable is reduced below the set point.

Temperature regulation is an example of negative feedback mechanism.

Temperature Regulation A decreased atmospheric temperature tends to decrease the

body temperature. This triggers events in the body resulting in cutaneous vasoconstriction and curling up which decrease heat loss from the body and shivering which increases heat production. This restores the body temperature to the normal level.

Negative feedback mechanism operating in regulation of body temperature



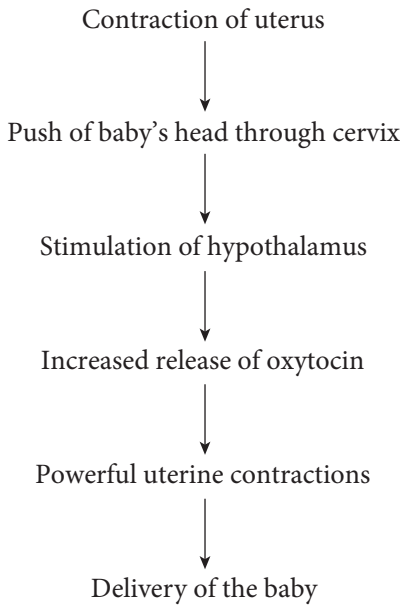
Positive Feedback Mechanism

In a positive feedback system, an increase in the variable triggers various processes that further increase the quantity of the variable. Positive feedback mechanism is a vicious cycle that terminates only when the stimulus applied to trigger the system is withdrawn or the process itself is self-terminated.

Parturition reflex is an example of positive feedback regulation.

Parturition Reflex When the uterine contractions become strong enough, the baby's head begins to push through the cervix. This stretching of the cervix sends signals to the uterus, causing even more powerful contractions. This process is repeated until contractions become very powerful and cause expulsion of the baby.

Positive feedback mechanism operating in the delivery of the baby



REVIEW QUESTIONS

Long Essay

1. Give the normal value of total body water? Classify its various compartments giving the normal values. Explain the methods of measurement of various compartments.
2. Describe the various transport mechanisms occurring across the cell membrane.

Short Essay

1. Explain the structure and functions of the following cellular components:
   a. Cell membrane
   b. Nucleus
   c. Mitochondria

   d. Golgi apparatus
   e. Endoplasmic reticulum
   f. Lysosomes
2. Explain the different types of intercellular connection. What are its functions?
3. Describe the phases of mitotic cell division.
4. Describe the phases of meiotic cell division.
5. What are the types of RNA? Add a note on their functions.
6. Describe the proteins that help in transport across the cell membrane.
7. Describe different mechanisms of passive transport across the cell membrane.
8. Describe different mechanisms of active transport across the cell membrane.
9. Describe the sodium–potassium pump.
10. Explain the various types of intercellular communications.
11. Explain the distribution of fluid in various compartments of the body.
12. Describe the methods of measurement of different fluid compartments of the body.
13. Explain apoptosis.
14. Describe homeostasis with examples.

Short Answer

1. What are peroxisomes? List their functions.
2. What are molecular motors? Give two examples.
3. Cell adhesion molecules
4. Gap junctions
5. Molecular motors
6. List the functions of microtubules
7. Channel proteins
8. Carrier proteins
9. Facilitated diffusion
10. What is cotransport? Give two examples.
11. What is countertransport? Give two examples.
12. Transcytosis
13. Transcellular fluid
14. Negative feedback mechanism
15. Positive feedback mechanism

CHAPTER

2 Blood

Outline

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Specific Learning Objectives

After studying this chapter, you should be able to:

- List the constituents and functions of blood. Explain the types and functions of plasma proteins.
- Describe the morphology of erythrocytes. Explain the stages of erythropoiesis and the factors affecting it.
- Define, classify, and explain the different types of anemia. Describe polycythemia.
- Describe the structure, types, and compounds of hemoglobin.
- Explain ESR, PCV, and blood indices. Discuss their clinical significance.
- Classify leukocytes, describe leukopoiesis, and describe the morphology of leukocytes. Explain the variations in leukocyte count.
- Describe the monocyte–macrophage system and its functions.
- Define, classify, and explain the different types of immunity. Discuss its clinical implications.
- Describe the complement system. Review the circulation and functions of the lymphatic system.
- Explain the mechanism of hemostasis. Describe the structure, functions, and clinical importance of platelets.
- List the clotting factors. Describe the mechanism of blood coagulation and anticoagulation.
- Describe the different blood group systems. Interpret the concept of ABO and Rh incompatibility, and universal donors and recipients.
- List the hazards of blood transfusion. Outline the concept of blood grouping, cross-matching, and collection and storage of blood.
- Successfully answer the questions and MCQs at the end of this chapter.

Blood is a fluid connective tissue present in the circulatory system.

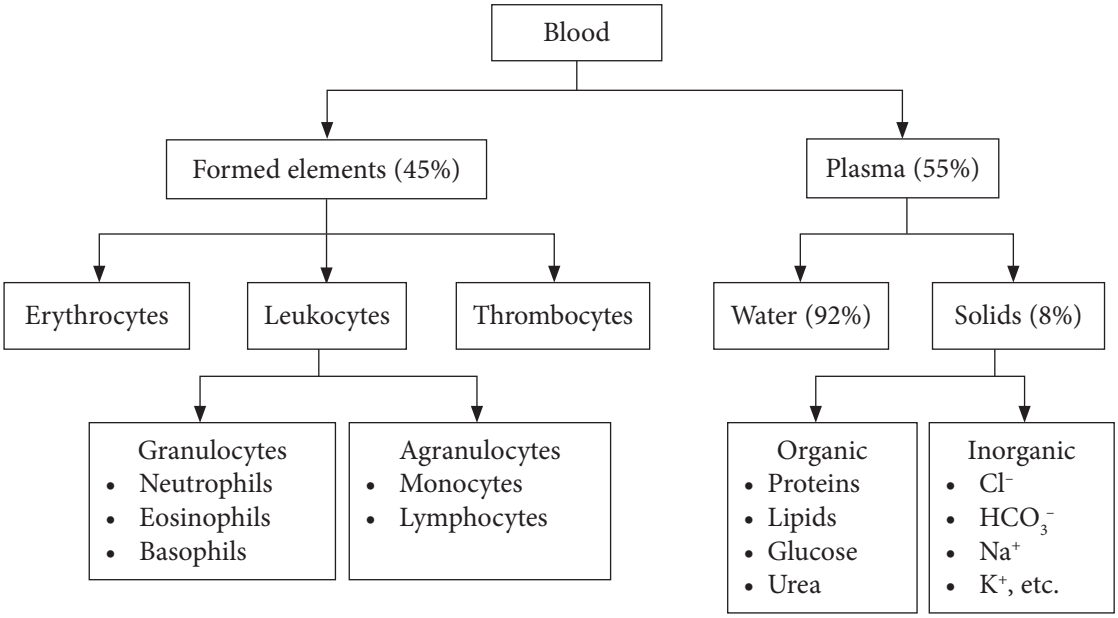
It is red in color due to the presence of hemoglobin. The normal blood volume in adults is around 5 L.

Blood is made up of the following:

1. **Fluid component**: Plasma
2. **Formed elements**: Erythrocytes (RBCs), leukocytes (WBCs), and thrombocytes (platelets) (Flowchart 2.1)

Plasma constitutes 55% of blood and formed elements constitute 45%.

The pH of blood is 7.4. Its specific gravity is 1055–1060.



Flowchart 2.1 Constituents of blood.

FUNCTIONS OF BLOOD

1. **Transport of oxygen and carbon dioxide**: Blood helps in the transport of oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs.
2. **Supply of nutrition to various tissues**: Blood supplies absorbed food materials from the gastrointestinal tract to the tissues.
3. **Transport of waste products**: Metabolic waste products such as urea, uric acid, and creatinine are transported by blood to the kidneys and other excretory organs.
4. **Transport of hormones, vitamins, drugs, and chemicals**: Blood is the vehicle through which various substances such as hormones and drugs are transported from one part of the body to the other.
5. **Maintenance of acid–base balance**: Blood has various buffers which maintain the acid–base balance.
6. **Regulation of body temperature**: Blood distributes the heat generated at a particular organ to all parts of the body.
7. **Protection against infection**: Leukocytes present in the blood help in protecting the body against invading microorganisms.
8. **Helps in blood clotting**: Blood forms a clot during injury, preventing blood loss.
9. **Storage**: Blood is the storehouse for water, electrolytes, and nutrients.

BLOOD VOLUME

Blood volume is the total amount of blood present in the body.

- The total volume of blood is around 5 L in an average adult male (70 mL/kg body weight).
- Females have a lower blood volume than males.
- In children, the blood volume is 85 mL/kg.
- Blood volume is also expressed in relation to the body surface area. It is 2.8 L/m^2.

VARIATIONS

- Blood volume varies with the size of the individual. Greater the size, greater is the blood volume.
- Blood volume increases during pregnancy, after meals, and at high altitudes.
- It decreases on prolonged standing.

Pathological Variation

Blood volume increases in polycythemia and congestive cardiac failure.

It decreases after hemorrhage, burns, vomiting, and diarrhea.

DETERMINATION

Blood volume is determined by measuring the plasma volume and cell volume separately. It can also be determined by measuring the plasma volume and calculating the volume of formed elements (hematocrit).

Determination of Cell Volume

The RBCs from O^- (blood group O negative) individuals can be tagged with radioactive compounds such as radioactive iron and radioactive phosphorus. A known amount of these tagged RBCs is injected into the individuals whose blood volume is to be measured. The RBC with radioactive substance is diluted in the blood of the individual, and from this dilution, the RBC volume can be calculated.

Determination of Plasma Volume

Plasma volume can be determined by the dye dilution technique. In this method, a known amount of nontoxic dye is injected into the individual. Time is allowed for the distribution of the dye. After a reasonable time, a plasma sample is collected and the concentration of the dye in plasma is measured. The plasma volume is measured by the following formula:

$$\text{Plasma volume} = \frac{\text{Amount of dye injected}}{\text{Concentration of dye in plasma}}.$$

The total blood volume is calculated by using the formula

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{100 - \text{Hematocrit}} \times 100.$$

PLASMA

Plasma is the fluid portion of blood. Its normal volume is 3,500 mL. It is mainly composed of water (92%).

Other substances present in plasma are as follows:

1. **Inorganic substances**: Na^+, K^+, Ca^{++} ions, iron, and copper
2. **Organic substances**: Proteins, lipids, glucose, urea, and creatinine

Serum is plasma without clotting factors. The fluid that remains after allowing the blood to clot and later removing the clot is called serum.

PLASMA PROTEINS

Plasma proteins are the proteins present in plasma. They constitute about 7% of plasma, made up of albumin, globulin, fibrinogen, and prothrombin.

Formation

Most of the plasma proteins are synthesized in the liver. Albumin, prothrombin, and fibrinogen are synthesized in the liver. Globulin is formed by the reticuloendothelial cells, plasma cells, and lymphocytes.

Types

Important plasma proteins are

- **albumin**,
- **globulin**,
- **fibrinogen**, and
- **prothrombin**.

Albumin

Albumin has a molecular weight of 66,000. It is produced in the liver. The plasma half-life of albumin is 19 days. Albumin is mainly responsible for the maintenance of colloidal osmotic pressure. It also helps in the transport of bilirubin, hormones, and drugs.

Globulin

Globulin has a molecular weight ranging from 90,000 to 1,56,000. Globulins include transport proteins, lipoproteins, and immunoglobulins. There are three fractions:

1. α-globulin
2. β-globulin
3. γ-globulin

Fibrinogen

Fibrinogen has a molecular weight of 3,40,000. It plays an important role in blood coagulation. It is mainly responsible for the viscosity of blood due to its asymmetrical shape.

Prothrombin

Prothrombin is the inactive precursor of thrombin. It is a plasma protein with a molecular weight of 68,700. The normal concentration of prothrombin in plasma is 15 mg/dL. It is formed in the liver with the help of vitamin K.

Total proteins	6.0–8.0 g/dL
Albumin	3.5–5.5 g/dL
Globulin	1.3–2.5 g/dL
Fibrinogen	0.2–0.4 g/dL
Prothrombin	0.1 g/dL
Albumin/globulin ratio	1.7:1

FUNCTIONS

1. **Maintenance of colloidal osmotic pressure**: The normal colloidal osmotic pressure of plasma is 25 mm Hg. Plasma proteins are responsible for this pressure. The capillary wall is impermeable to plasma proteins. Therefore, water is drawn into the blood vessel from the extravascular compartment.
2. **Maintenance of viscosity of blood**: Blood is four to five times more viscous than water. The viscosity of blood depends on the shape and size of the protein molecules in plasma.
3. **Buffering action**: Plasma proteins act as buffers. They maintain pH at 7.4 by accepting or donating H^+ ions. They are responsible for 15% of the buffering capacity of the blood.
4. **Protein reserve**: The plasma proteins present in the blood act as a reservoir of the proteins. They are especially helpful during starvation.
5. **Immunity**: γ-Globulins are antibodies that protect the body against the invading microorganism.
6. **Blood clotting**: Fibrinogen and prothrombin are responsible for blood coagulation.
7. **Transport**: Plasma proteins transport hormones, drugs, and metabolites by forming a loose bond with them.

Separation

The separation of plasma proteins is done to study them and also to diagnose diseases.

The different methods for separation of plasma proteins are

- salt separation,
- paper electrophoresis,
- Cohn's fractional precipitation,
- immunoelectrophoresis, and
- ultracentrifugation technique

Plasmapheresis

Plasmapheresis was an experiment performed in dogs by Whipple to determine the role of plasma proteins in diet. In this experiment, the whole blood is withdrawn and the cellular elements are injected back into the body. The process is repeated till plasma protein levels

fall to 4 g/100 mL. Thereafter, different diets are given and their effect on protein synthesis is studied.

The technique of plasmapheresis is clinically used to remove excess of plasma proteins and certain antibodies harmful to the body.

CLINICAL NOTES

- **Hypoproteinemia** is a condition with a decrease in the level of plasma proteins. Plasma protein levels decrease in prolonged starvation and malabsorption. They also decrease in liver and kidney diseases.

  In liver diseases, plasma protein levels decrease due to the reduced synthesis. The normal albumin/globulin ratio is reversed in liver diseases.

  In renal diseases, more amounts of proteins are lost in the urine. Clinically, edema develops in these patients due to a decrease in the plasma oncotic pressure which causes movement of fluid into extravascular compartment.
- **Afibrinogenemia** is a disease due to congenital deficiency of fibrinogen. It is characterized by defective blood clotting.

  Clinically, the symptoms include bruising, bleeding in joints, nose, and excessive bleeding after injury.

RED BLOOD CELLS (ERYTHROCYTES)

The erythrocytes or RBCs are the most abundant cells present in blood. They are red in color due to the presence of the pigment, hemoglobin.

RBCs contain 61% water, 28% Hb, 7% lipids, 3% carbohydrates, electrolytes, and metabolites.

The RBC surface has a negative charge. RBCs do not have nucleus, mitochondria, or ribosomes. Therefore, a mature RBC cannot divide. RBCs contain the pigment hemoglobin in jelly form.

The normal life span of an RBC is about 120 days.

Normal Erythrocyte Count	
Males	5–5.5 million cells/mm^3
Females	4.5–5 million cells/mm^3
Infants	6–7 million cells/mm^3

STRUCTURE

The mean red cell diameter is 7.2 μ (**Fig. 2.1**). The thickness is 2.2 μ at the periphery and 1 μ at the center. Its surface area is 135 μ^2. The normal volume is 80–94 μ^3.

RBCs are flexible cells, but their membrane is not elastic. They have a biconcave shape.

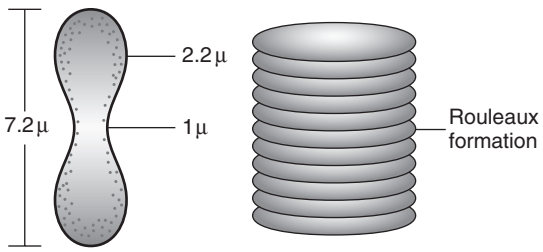


Figure 2.1 RBC.

The advantages of a biconcave shape are as follows:

- The cells can easily pass through narrow capillaries because the biconcave shape offers greater flexibility.
- The biconcave shape increases the surface area for exchange of gases.
- The cells can withstand lysis when exposed to hypotonic solutions.

The RBC membrane is made up of lipids and proteins.

- **Lipids**: Cholesterol, phospholipid, and glycolipids
- **Proteins**: Spectrin, actin, ankyrin, and band 3 and 4 proteins

The glycolipids constitute the ABO blood group substances (agglutinogens).

METABOLISM

The metabolic need of RBCs is very less. It is met by the glucose metabolism through the anaerobic Embden–Meyerhof (EMF) pathway (90%) and the pentose phosphate shunt (10%).

FUNCTIONS

The functions of RBCs are due to the presence of Hb. They include

- transport of oxygen from lungs to tissues,
- transport of CO_2 from tissues to lungs,
- regulation of acid–base balance, and
- maintenance of viscosity of blood

FATE OF RED BLOOD CELLS

The old and fragile RBCs are phagocytosed by the reticuloendothelial system. They are broken down in the reticuloendothelial cells, and Hb is released.

Subsequently, Hb is broken down into heme and globin. Globin is added to the amino acid pool. Iron liberated from heme is used again for the synthesis of new Hb.

The remaining portion of heme after breakdown is called **biliverdin**. It is reduced by biliverdin reductase to bilirubin in the liver and secreted through the bile.

ERYTHROPOIESIS

Erythropoiesis is the process of formation of RBCs. Continuous production of RBCs is required since old and damaged RBCs are regularly destroyed. Bone marrow maintains a relatively constant number of RBCs by producing the required number of cells which are destroyed by the body.

Sites

Erythropoiesis starts in the third week of intrauterine life in the mesoderm of the yolk sac.

From the third month of intrauterine life, erythropoiesis takes place in the liver and spleen.

After the fifth month of intrauterine life, the fetal bone marrow starts producing RBCs.

By birth, the bone marrow becomes the only place of erythrocyte production.

Bone marrow is of two types:

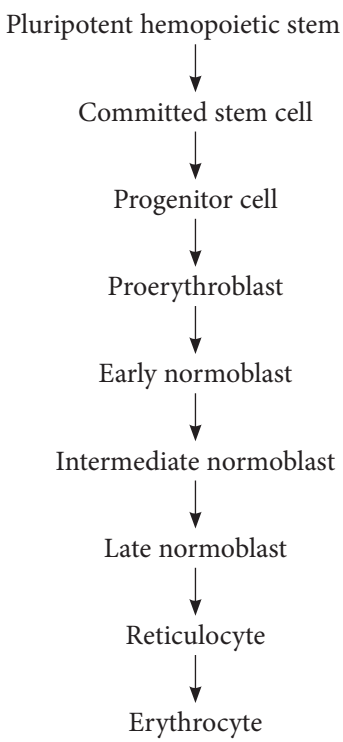
1. Red bone marrow
2. Yellow bone marrow

Red bone marrow produces RBCs. At birth, it is present in all the bones. In adults, it is present in flat bones (membranous bones) such as cranial bones, vertebrae, pelvic bones, ribs, sternum, and upper ends of long bones such as femur and humerus.

Yellow bone marrow is mainly made up of adipose (fat) tissue.

Stages of Erythropoiesis (Fig. 2.2)

All blood cells are produced from stem cells. They have the capacity to form different types of blood cells and are termed **pluripotent hemopoietic stem cells**.



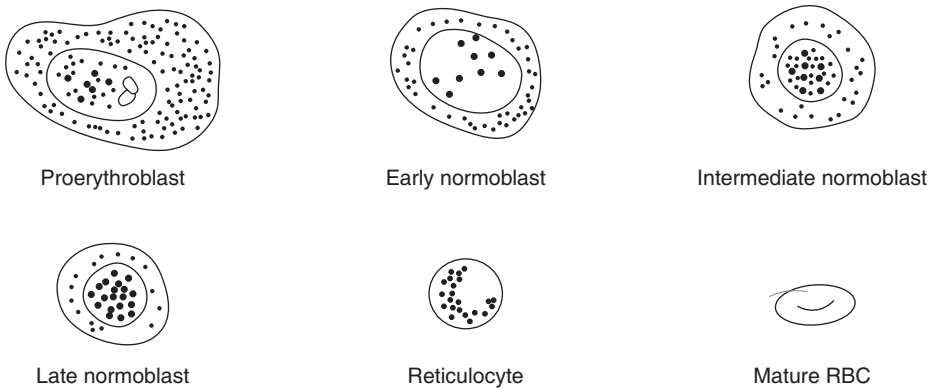


Figure 2.2 Stages of erythropoiesis.

Pluripotent Stem Cells

The pluripotent stem cells are not specific for producing a particular type of cell. They differentiate to form the committed stem cells.

Committed Stem Cells

Committed stem cells are of two types:

1. Stem cells of myeloid series
2. Stem cells of lymphoid series

The committed stem cell of the myeloid series gives rise to all blood cells except the lymphocytes.

The committed stem cells for the erythrocyte give rise to the progenitor cells.

Progenitor Cells

The progenitor cells are of two types:

1. BFU-E (burst-forming units)
2. CFU-E (colony-forming units)

BFU-E They form large, multilobulated colonies from progenitor cells. The development of colonies requires the presence of factors called burst-promoting activity (BPA).

The cells are immature blast cells, oval in shape with moderately basophilic cytoplasm, occasional pseudopods, fine chromatin, and nucleoli. BFU-E is the progenitor of CFU-E.

CFU-E They form small colonies. They do not require BPA but require other factors such as erythropoietin. BFU-E give rise to CFU-E. CFU-E cells give rise to blast cells.

CFU-E cells are more mature than BFU-E cells. Morphologically, they are similar to BFU-E cells.

Proerythroblast

These cells develop from CFU-E. They are large cells, 15–20 μ in diameter. The nucleus is large, containing basophilic nucleoli. It occupies 80% of the cells. The cytoplasm is scanty and basophilic. These cells actively divide by mitosis. They do not have hemoglobin.

Early Normoblast

These cells are 10–16 μ in diameter. They also show active mitosis. The nucleus is large, the cytoplasm is basophilic, and hemoglobin begins to appear. The nucleoli disappear and condensation of chromatin begins in this stage.

Intermediate Normoblast

These cells are 10–14 μ in diameter. The nucleus becomes small. Mitosis stops at this stage. Hemoglobin concentration increases and cells become acidophilic due to Hb. The condensation of nuclear chromatin increases in this stage.

Late Normoblast

These cells are 8–10 μ in diameter. The cytoplasm is acidophilic. The nucleus is very small, becomes pyknotic (small), and is lost by extrusion.

Reticulocyte

Reticulocyte is a flat, disk-shaped, non-nucleated cell, slightly bigger than the mature RBC. It is slightly basophilic. The Hb content increases to reach the level of the mature cell. The remaining chromatin is organized in the form of a network (reticulum); hence, it is called a reticulocyte. RBC attains maturity in 1–2 days after the loss of the basophilic material.

Erythrocyte

Erythrocyte is a mature cell, 7.2 μ in diameter, eosinophilic, non-nucleated; it resembles a biconcave disk.

The process of erythropoiesis takes 7 days.

Factors Influencing Erythropoiesis

Erythropoietin

Erythropoietin is a glycoprotein hormone that stimulates erythropoiesis. It increases RBC production, enhances synthesis of Hb, and hastens maturation of RBC.

Erythropoietin has a molecular weight of 46,000. It is made up of 74% protein and 26% carbohydrate.

Formation Erythropoietin is mainly formed in the kidney and partly in the liver. In the kidney, it is produced by the endothelial cells of the peritubular capillaries.

Functions

- Increases RBC production
- Enhances synthesis of Hb
- Hastens maturation of RBC

Factors Influencing Erythropoietin Production The basic stimulus for erythropoietin production is hypoxia.

- Androgens increase erythropoietin production.
- Estrogens depress erythropoietin production.
- Products of RBC destruction increase erythropoietin production.
- Vasoconstrictors produce renal hypoxia. They cause formation of erythropoietin.

Erythropoietin is inactivated in the liver and is excreted through the kidneys.

Androgens

Androgens stimulate erythropoiesis. Therefore, men have a higher RBC count compared to women. Androgens stimulate the production of erythropoietin. In addition, they directly stimulate erythropoiesis.

Estrogens

Estrogens have inhibitory effect on the erythropoiesis by suppression of erythropoietin production.

Hormones

Thyroxine, cortisol, and growth hormone are necessary for RBC production. Interleukin 1, 3, and 5, granulocyte macrophage colony-stimulating factor (GM-CSF), and BPA all act as local hormones and help in the conversion of stem cells to progenitor cells.

Dietary Factors

Iron is necessary for Hb synthesis. The deficiency of iron leads to hypochromia (less color than normal) and decrease in the size of RBC (microcytic).

Vitamin B_{12} and folic acid are necessary for maturation of RBC.

Vitamin B_{12}, vitamin C, copper, and cobalt act as cofactors.

Intrinsic Factor

The intrinsic factor is produced from the parietal cells of the gastric mucosa. It helps in the absorption of vitamin B_{12}.

ANEMIA (Flowchart 2.2)

Anemia is a clinical condition wherein the RBC count or Hb% or both are decreased. In anemia, the O_2-carrying capacity of blood is reduced.

CLASSIFICATION

Depending on the cause of anemia, they are classified as

- anemia due to decreased RBC formation,
- anemia due to increased RBC destruction, and
- anemia due to blood loss.

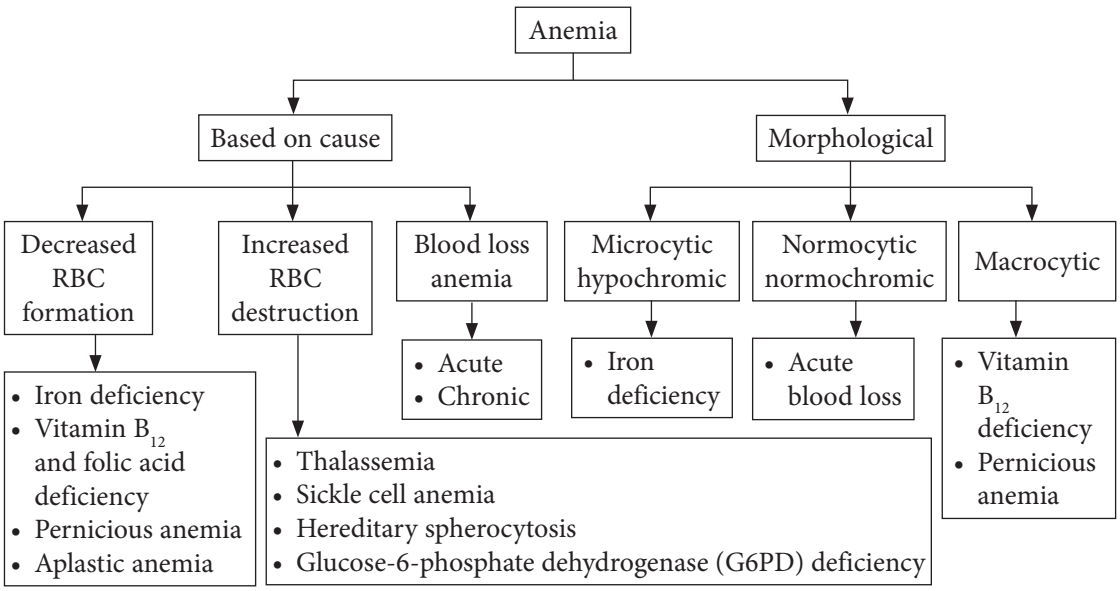
Anemia due to Decreased RBC Formation

- **Iron-deficiency anemia**: Iron is required for the formation of hemoglobin. Nutritional deficiency of iron causes anemia. This is the commonest type of anemia occurring in India. RBCs are **microcytic** and **hypochromic**.
- **Vitamin B_{12} and folic acid deficiency**: Vitamin B_{12} and folic acid are required for the development and maturation of RBCs. Deficiency of these vitamins causes megaloblastic anemia. RBCs are **macrocytic** and **normochromic**.
- **Pernicious anemia**: Vitamin B_{12} requires intrinsic factor for its absorption. The deficiency of intrinsic factor leads to pernicious anemia.
- **Aplastic anemia**: This is caused due to suppression of bone marrow by drugs, toxins, and exposure to X-rays.

Anemia due to Increased RBC Destruction

This is also termed hemolytic anemia.

- **Thalassemia**: There is a defect in the synthesis of the globin chain of Hb. This causes premature destruction of red cell due to membrane damage.
- **Sickle cell anemia**: RBCs contain abnormal hemoglobin termed HbS. Valine replaces glutamic acid at the sixth position in the β chain. This leads to a sickle-shaped deformity on exposure to hypoxia, resulting in early rupture and destruction of the cell.
- **Hereditary spherocytosis**: In this condition, RBCs become excessively permeable to Na^+. They assume a biconvex shape and are prone to hemolysis.



Flowchart 2.2 Anemia.

- **Glucose-6-phosphate dehydrogenase (G6PD) deficiency**: The deficiency of this enzyme causes damage to the RBC membrane leading to hemolysis. G6PD is required for the formation of NADPH which maintains glutathione in a reduced state. The decreased concentration of reduced glutathione causes damage of the RBC membrane.

Anemia due to Blood Loss

- **Acute blood loss**: Hemorrhage occurs due to accidents or during surgery. Sudden blood loss results in RBCs being **normocytic** and **normochromic**. However, anemia is due to reduction in its number.
- **Chronic blood loss**: It is seen in peptic ulcer, hemorrhoids, hookworm infestation, and menstrual irregularities. The RBCs are **microcytic** and **hypochromic**.

MORPHOLOGICAL CLASSIFICATION

- **Microcytic hypochromic anemia**: In this type of anemia, RBCs are smaller in size. The Hb content of the cell is also reduced and RBCs look pale.

  Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) are reduced, e.g., iron-deficiency anemia.
- **Normocytic normochromic anemia**: In this type of anemia, RBCs are normal in size, the Hb content is also normal, but the number of cells is reduced. MCV, MCH, and MCHC are within the normal range, e.g., anemia due to hemorrhage.
- **Macrocytic anemia**: RBCs are larger in size. The Hb content of these cells is normal or reduced. MCV is above normal, e.g., vitamin B_{12} deficiency anemia.

CLINICAL MANIFESTATIONS

The clinical signs and symptoms are not found in mild anemia. They are manifested only in moderate and severe anemia.

Patients have

- pallor, dyspnea, palpitations, and heart murmurs;
- headache, vertigo, restlessness, and muscle weakness;
- glossitis, atrophy of papillae of tongue, mouth ulcers, and dysphagia.

POLYCYTHEMIA

Polycythemia is a condition where the RBC count is increased above 8 million cells/mm^3.

There are two types of polycythemia:

1. Polycythemia vera
2. Secondary polycythemia

Polycythemia Vera

Polycythemia vera is produced due to genetic abnormality. The blast cells produce too many cells. This increases the hematocrit value, total blood volume, and viscosity of blood.

It is chronic and progressive, and ultimately it is fatal.

Secondary Polycythemia

Secondary polycythemia is of two types:

i. physiological and
ii. pathological.

Physiological Polycythemia

Physiological polycythemia occurs at high altitude due to hypoxia. This is seen in people who live at altitudes of 17,000–18,000 ft. Their RBC count is around 6–7 million/mm^3 and hematocrit reaches 60–70%.

Pathological Polycythemia

Pathological polycythemia occurs in

- chronic pulmonary diseases,
- chronic smokers,
- congenital heart diseases with a right-to-left shunt,
- renal tumors,
- tumors of the liver,
- brain tumors, and
- hydronephrosis.

HEMOGLOBIN

Hemoglobin (Hb) is a conjugate protein present in the RBC. It forms 95% of the dry weight of RBC.

Normal Value	
Males	14–18 g/dL
Females	12–16 g/dL
Infants	Up to 20 g/dL

VARIATIONS IN HEMOGLOBIN CONCENTRATION

Decreased Hb

- **Physiological**: Lower in children, females, and during pregnancy
- **Pathological**: Anemia

Increased Hb

- **Physiological**: High altitude
- **Pathological**: Severe diarrhea, vomiting, polycythemia vera, congenital heart disease, and emphysema

STRUCTURE

The molecular weight of Hb is 64,450. It is made of two components: heme and globin **(Fig. 2.3)**.

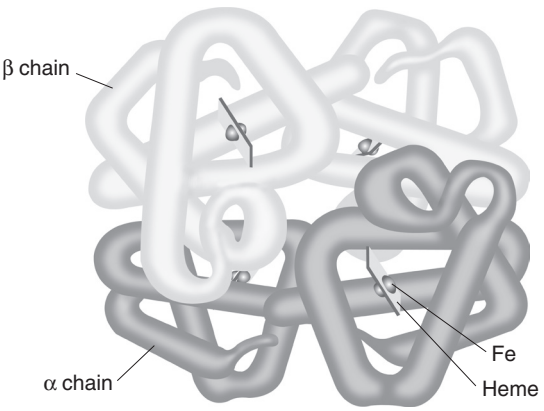


Figure 2.3 Structure of hemoglobin. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Heme is a tetrapyrrole structure with a central iron atom attached to four nitrogen atoms, one each from four pyrrole rings. This provides red color to the hemoglobin molecule. Each pyrrole has four atoms of carbon and one atom of nitrogen.

Globin is a protein containing two pairs of polypeptide chains (two α-globin and two β-globin subunits). It binds to the same iron atom that binds to the pyrrole rings.

One heme and one globin chain form a subunit. Four such subunits form a hemoglobin molecule.

SYNTHESIS

The substances required for the synthesis of heme are succinyl-CoA and glycine. Heme is synthesized in the normoblastic stage of the developing RBC.

Two molecules of succinyl-CoA and two molecules of glycine combine to form a pyrrole ring. Four pyrroles combine together to form protoporphyrin IX. Protoporphyrin IX combines with iron and polypeptide chain to form the hemoglobin chain. Four such hemoglobin chains make up a hemoglobin molecule.

Heme is located in the periphery of the Hb molecule which helps in its easy binding to O_2.

Steps in Hb formation

2 Succinyl-CoA + 2 Glycine

↓

Pyrrole —— 4 Pyrrole

↘

Protoporphyrin IX + Ferrous iron

↓

Heme + Globin

↓

Hemoglobin

TYPES OF HEMOGLOBIN

HbA

HbA constitutes 97% of Hb in adults. In adults, Hb is made up of α and β polypeptide chains. Therefore, HbA is $\alpha_2\beta_2$. Though it is present in small quantities in fetal life, HbA replaces HbF in the first few months after birth. This replacement is complete by 6 months.

HbA_2

HbA_2 constitutes about 3% of total Hb in adults. It has α_2 and δ_2 polypeptide chains.

HbF

HbF is the major hemoglobin present in fetal life. It has α_2 and γ_2 polypeptide chains. Fetal hemoglobin is replaced by adult Hb soon after birth. The O_2-binding capacity of fetal Hb is greater than the adult Hb. This helps in the movement of O_2 from maternal to fetal circulation.

FUNCTIONS

- Hemoglobin carries oxygen from the lungs to the tissues. (1 gram of hemoglobin carries 1.34 mL of oxygen when it is fully saturated.)
- It is also involved in the transport of CO_2.
- It acts as a buffer.

COMPOUNDS OF HEMOGLOBIN

Oxyhemoglobin

Hemoglobin combines with oxygen readily and reversibly to form oxyhemoglobin.

The affinity of Hb to O_2 depends on various factors such as temperature, pH, and 2,3-diphosphoglyceric acid (2,3-DPG)/ 2,3-bisphosphoglycerate (2,3-BPG).

Methemoglobin

Iron in Hb is converted from ferrous to ferric state to form methemoglobin. It occurs normally within the body to some extent.

The ferric form is converted back to ferrous form by methemoglobin reductase. Deficiency of this enzyme results in methemoglobinemia.

Carboxyhemoglobin

The combination of Hb with carbon monoxide forms carboxyhemoglobin. The affinity of Hb to CO is much greater than its affinity for O_2. Therefore, CO displaces O_2 from Hb causing the reduced O_2-carrying capacity of blood.

Carbaminohemoglobin

CO_2 combines with the globin part of Hb to form carbaminohemoglobin.

Acid Hematin

The combination of acid with Hb forms acid hematin. This forms the basis for estimation of hemoglobin by Sahli's method.

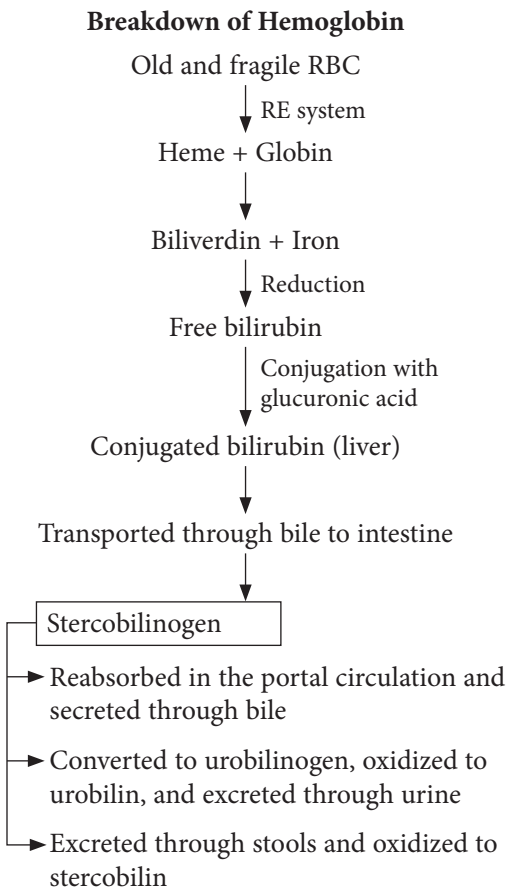
Glycosylated Hemoglobin

Combination of glucose with hemoglobin forms glycosylated or glycated hemoglobin. Normally, it is present in minor concentrations (<4 mg/dL). Its concentration increases in conditions where blood glucose is chronically elevated (like in diabetes mellitus). Therefore, glycosylated hemoglobin is known to be a good indicator of blood glucose levels.

BREAKDOWN OF HEMOGLOBIN

Breakdown of hemoglobin occurs after the RBCs are destroyed in the reticuloendothelial system.

Hemoglobin is broken down to heme and globin. Globin enters the amino acid pool where it is reused. Heme is converted to biliverdin by heme oxidase. Biliverdin is reduced to bilirubin.



ABNORMAL HEMOGLOBIN

Abnormal hemoglobin is produced due to the defective synthesis of either heme or globin portions.

The defect in the heme part is usually rare. The defect in the globin chain is more frequent.

There are two major types of inherited disorders of hemoglobin synthesis: hemoglobinopathies and thalassemias.

Hemoglobinopathies

The defects are due to the abnormalities in the polypeptide chain. The abnormal hemoglobins produced are HbS, HbC, and HbE.

HbS

In this type of hemoglobin, valine replaces glutamic acid at the sixth position in the β chain. When HbS is exposed to hypoxia, it becomes insoluble leading to a change in the shape of RBC. The sickle-shaped deformity developed in RBC results in its excessive destruction.

HbS are less flexible than normal RBCs. This leads to the blocking of capillaries. The homozygous individuals suffer from this condition leading to sickle cell anemia. The heterozygous individuals have sickle cell trait. They do not suffer severely with this problem. HbS individuals are resistant to one form of malaria.

Thalassemia

In this condition, α and β chains of globin are normal, but they are produced in lesser number or absent.

The decrease in α chain synthesis is called **α-thalassemia**.

α-Thalassemia is of two types: (i) α-thalassemia major and (ii) α-thalassemia minor.

α-Thalassemia major is usually incompatible with life. In α-thalassemia minor, the persons have a less number of α chains than normal and are usually symptom free.

β-**Thalassemia** is caused due to reduced synthesis of β chains.

It is of two types: (i) β-thalassemia major and (ii) β-thalassemia minor.

In β-thalassemia major, the patients suffer from anemia due to rapid destruction of RBCs. They need frequent blood transfusion. They accumulate iron. There is increased bone marrow activity, leading to frontal bossing, splenomegaly, repeated fever, and failure to thrive.

IRON

The normal iron content of an adult is 3–5 grams. It is more in males than females.

About 60–70% of the total body iron is in hemoglobin. About 4% is in the form of myoglobin. 15–30% is stored in the reticuloendothelial system and liver for later use.

Iron is derived from the breakdown of RBCs. It is carried by iron-binding protein transferrin and reutilized for hemoglobin synthesis.

Biological Forms

Tissue Iron

Tissue iron is nonavailable iron present in myoglobin and enzymes such as cytochrome, catalase, and peroxidase.

Storage Iron

The storage iron (available iron) can be utilized for Hb synthesis. The storage iron is 1–2 grams.

It is stored as

- ferritin and
- hemosiderin.

Ferritin is normally predominant. Iron is stored in reticuloendothelial cells, hepatic parenchymal cells, and skeletal muscles.

Hemosiderin is an iron storage complex. It is not found in circulation. Iron present within hemosiderin is poorly available when required.

Plasma Iron

Three to four milligrams of iron present in the plasma are bound to a transport protein called transferrin.

Absorption

Only 10% of iron in the diet is absorbed. A major portion of iron is reused in the body. Iron absorption occurs in the duodenum and proximal jejunum.

The liver produces a substance called **apotransferrin**. This flows through the bile into the duodenum. In the intestine, apotransferrin binds with iron to form transferrin. Transferrin is absorbed into the epithelial cells and later released into the blood in the form of plasma transferrin.

Functions

Iron is required for the synthesis of hemoglobin, myoglobin, and heme enzymes such as cytochrome C and catalase.

Iron Balance

The total content of iron in the body remains within a narrow range of variation. The loss of iron from the body is matched by its absorption from the gastrointestinal tract (GIT). Iron is not excreted from the body. It is lost during the removal of epithelial cells of GIT.

Daily Requirement

Human beings require around 1 mg of iron every day. Females in the reproductive age require little more iron compared to males due to its loss during menstruation.

Certain foods such as phytates, which are present in grains, inhibit iron absorption. Calcium, zinc, and cadmium also interfere with the absorption of iron.

Iron is lost mainly in feces. The daily loss of iron in man is about 0.6 mg. In women, it averages around 1.3 mg/day due to additional menstrual loss.

HEMATOLOGICAL INVESTIGATIONS

Erythrocyte sedimentation rate (ESR) and packed cell volume (PCV) are two important hematological investigations of clinical importance. ESR is helpful in knowing the prognosis of a disease and PCV gives an idea of the anemic status of the individual.

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) is the rate at which red blood cells settle down. It is the measure of supernatant plasma separated out at the end of 1 hour when a column of blood (mixed with an anticoagulant) is kept undisturbed.

Normal Value
0–5 mm at the end of 1 hour in males
0–8 mm at the end of 1 hour in females

Variations of ESR

1. **Physiological**
   - Age: ESR is more in newborns and in infants.

- Sex: ESR is more in females.
- Pregnancy: ESR is increased in pregnancy.
- ESR is increased during menstruation and during labor.

2. **Pathological**: ESR is increased in
   - infections such tuberculosis,
   - rheumatoid arthritis,
   - malignancy,
   - anemia, and
   - collagen diseases such as SLE.

   ESR decreases in
   - polycythemia,
   - sickle cell anemia,
   - hereditary spherocytosis, and
   - hypofibrinogenemia.

Factors Affecting ESR

- Alteration in the biconcave shape of RBC reduces ESR.
- Increase in the size of rouleaux increases ESR.
- Increased fibrinogen content of the blood increases ESR.
- Increased globulin levels in the plasma increases ESR.
- Viscosity of the blood decreases ESR.

Significance of ESR

ESR is of prognostic importance rather than of diagnostic value.

It helps to assess the effect of treatment and progress of the disease. It has limited value in detecting a disease.

Determination of ESR

ESR can be determined by two methods:

1. **Westergren's method**: Westergren's tube is 300 mm long, open at both ends. Blood mixed with anticoagulant is filled in Westergren's tube and placed vertically in a stand and left undisturbed. The height of the column of plasma separated is read directly from the tube at the end of 1 hour.
2. **Wintrobe's method**: Wintrobe's tube is a short tube open at one end and closed at the other. Blood mixed with anticoagulant is filled in the tube and placed vertically in a stand for 1 hour. The value is read directly at the end of 1 hour.

Packed Cell Volume

Packed cell volume (PCV) is the percentage of red cells present in the blood. It is also called hematocrit value.

Normal Value	
Males	42–48%
Females	38–42%

- PCV is increased in polycythemia, diarrhea, and excessive vomiting.
- It is decreased in anemia and pregnancy.

Determination

PCV can be determined by the following method:

- **Wintrobe's method**: Wintrobe's tube is filled with blood mixed with anticoagulant. The tube is then centrifuged at 3000 RPM for 20 minutes. The red cells settle at the bottom and the clear plasma is separated at the top.

  A buffy coat is present between the packed cells and the supernatant plasma containing WBCs and platelets. The mark up to which red cells are packed indicates the PCV.

Blood Indices

Blood indices indicate the health status of an individual. They also help in the diagnosis of various types of anemia.

Blood indices include MCV, MCH, MCHC, and CI.

Mean Corpuscular Volume

Mean corpuscular volume (MCV) is the average volume of a single, red cell. It ranges from 87 to 93 μ^3.

MCV is reduced in microcytic anemia. It is increased in megaloblastic anemia.

$$\text{MCV} = \frac{\text{PCV (per 100 mL of blood)}}{\text{RBC in millions/mm}^3 \text{ of blood}} \times 10.$$

Mean Corpuscular Hemoglobin

Mean corpuscular hemoglobin (MCH) is the average Hb present in a single, red cell. The normal value ranges from 28 to 32 pg (pico grams). It is reduced in microcytic anemia.

$$\text{MCH} = \frac{\text{Hb in g per 100 mL of blood}}{\text{RBC in millions/mm}^3 \text{ of blood}} \times 10.$$

Mean Corpuscular Hemoglobin Concentration

Mean corpuscular hemoglobin concentration (MCHC) is the relative percentage of Hb in a single red cell. The normal value is 33%.

It is decreased in megaloblastic anemia.

$$\text{MCHC} = \frac{\text{Hb in g per 100 mL of blood}}{\text{PCV per 100 mL of blood}} \times 100.$$

Color Index

Color index (CI) is the ratio of Hb% to RBC%.

It is reduced in hypochromic anemia.

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

The normal range is 0.85–1.15.

$$\text{Hb\%} = \frac{\text{Hb measured}}{\text{Normal Hb (15 g\%)}}.$$

$$\text{RBC\%} = \frac{\text{RBC counted}}{\text{Normal RBC count (5 million/mm}^3\text{)}}.$$

Microcyte	RBC with reduced volume (size)
Macrocyte	RBC with increased volume (size)
Hypochromia	Hb less than normal (reduced color)

LEUKOCYTES (WBCs)

We are exposed to a variety of harmful pathogens such as bacteria, viruses, fungi, and parasites which can cause diseases. To combat these pathogens, we have a specific defense system in the body. Leukocytes or white blood cells form a major part of this defense mechanism.

CLASSIFICATION

Based on the presence or absence of granules, leukocytes are classified as

- granulocytes and
- agranulocytes

Granulocytes

Based on the color of granules on staining, granulocytes are further classified as follows:

Neutrophils	60–65%
Eosinophils	1–4%
Basophils	0–1%

Agranulocytes

Lymphocytes	25–30%
Monocytes	2–8%

The percentages mentioned in the previous text indicate the number of each type of leukocyte in 100 cells. This is termed **differential count**.

It is helpful in the diagnosis of various diseases since a particular type of leukocyte is increased or decreased in a disease condition.

FUNCTIONS

- Neutrophils and monocytes are phagocytic.
- Eosinophils are antiallergic and antiparasitic.
- Basophils liberate heparin and histamine.
- Lymphocytes are involved in immunity.

LEUKOPOIESIS (Fig. 2.4)

Leukocytes develop from the pluripotent stem cells of the myeloid series. These cells give rise to committed stem cells, also called progenitor cells. These committed stem cells differentiate into various types of leukocytes.

Two different lineages of leukocytes are formed:

1. Myelocytic lineage
2. Lymphocytic lineage

The neutrophils, eosinophils, basophils, and monocytes are formed from the myelocytic lineage. Lymphocytes are formed from the lymphocytic lineage.

1. **Myelocytic lineage**
   - ***Myeloblasts***: They are large cells, 12–18 μ in diameter. They have a round nucleus

Pluripotent stem cell
↓
Committed stem cell
↓
CFU-GM
(colony-forming units—
granulocyte-monocyte)
↓
Myeloblast
↓
Promyelocyte
↓
Myelocyte
↓
Metamyelocyte
↓
Leukocyte

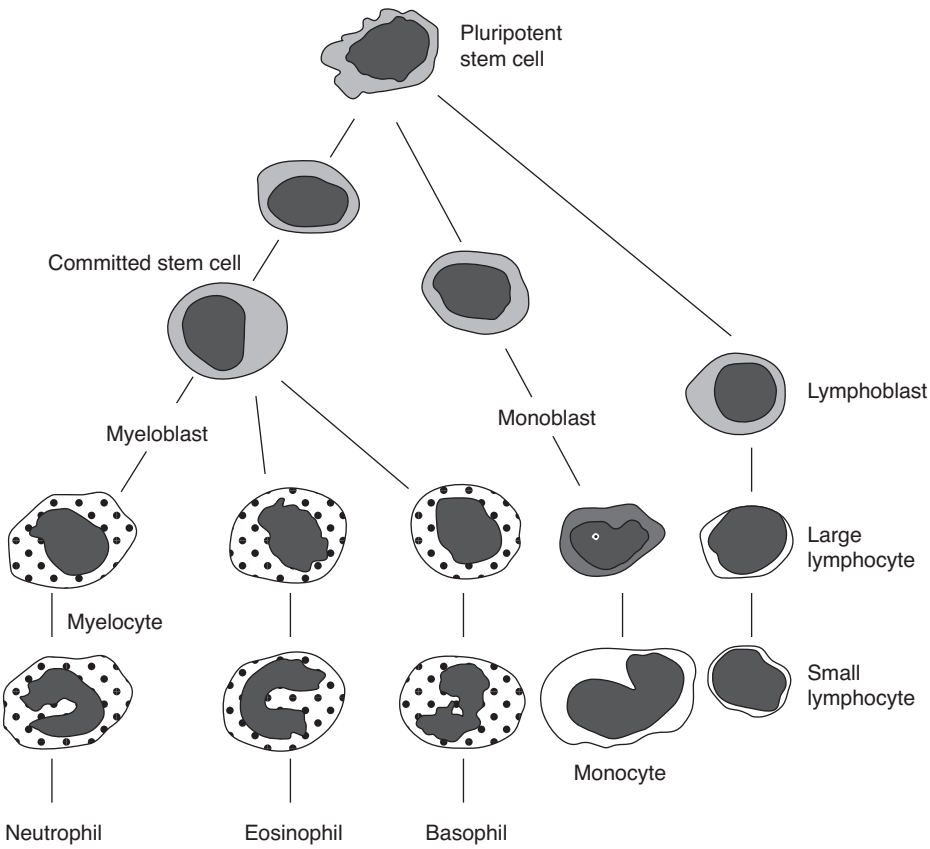


Figure 2.4 Leukopoiesis.

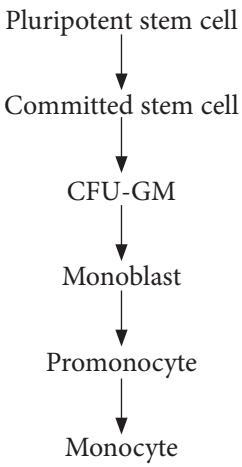
with 1–5 nucleoli, are nonmotile, and do not contain granules. They are actively mitotic.

- ***Promyelocytes***: The cells are slightly larger in size (12–20 μ). They have a round nucleus and their nucleoli decrease in number. The chromatin begins to condense.
- ***Myelocytes***: The cells multiply, the cytoplasm becomes less basophilic, and the granules appear in the cytoplasm. The size of the nucleus decreases and nucleoli disappear. The chromatin condenses further.

  Mitosis is reduced but still continues in this stage.
- ***Metamyelocytes***: The nucleus develops lobes, and cells stop multiplying and start maturing. They become fully mature and functional to form a leukocyte.

  The formation of granulocyte from myeloblast takes around 10 days.

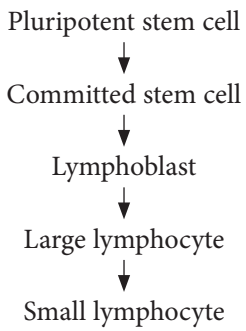
  Monocytes are also formed from the myelocytic lineage. They are produced from the same committed stem cells responsible for the formation of neutrophils.



Monocytes require 6 days for their formation.

2. **Lymphocytic lineage**: Lymphocytes are produced in the bone marrow and processed in the thymus.

They are finally lodged in the peripheral lymphoid organs such as the lymph node, spleen, tonsils, and the lymphoid tissues of the intestine.



- ***Lymphoblasts***: They are large cells, 12–20 μ in diameter with a round nucleus. These cells undergo division to form large lymphocytes.
- ***Large lymphocytes***: They stop dividing and only mature. They appear in circulation.
- ***Small lymphocytes***: They are formed by further maturation of large lymphocytes.

Regulation of Leukopoiesis

Leukopoiesis is influenced by specific proteins, colony-stimulating factor, interleukins, and prostaglandins.

- The protein formed by the ***scl* gene** (stem cell leukemia) is responsible for the production of a pluripotent stem cell.
- Colony-stimulating factor is a protein produced by the T-lymphocytes, fibroblasts, macrophages, and endothelial cells.
- It is of three types:
  i. **CSF-GM** stimulates the production of neutrophils, monocytes, eosinophils, erythrocytes, and megakaryocytes.
  ii. **CSF-G** stimulates the production of neutrophil.
  iii. **CSF-M** stimulates the production of monocytes.
- **Interleukins** are hormone-like substances regulating immune responses. Interleukin-1,

-3, and -6 convert pluripotent uncommitted stem cells to committed stem cells.
- Prostaglandins, cortisol, and adrenocorticotropic hormone (ACTH) play an important role in control of leukopoiesis.

MORPHOLOGY OF LEUKOCYTES

Neutrophils (Fig. 2.5)

Neutrophils are about 10–12 μ in diameter. They form about 60–65% of the total leukocytes. The nucleus is multilobed. The number of lobes varies from 2 to 7. The number of lobes increase as the neutrophil gets older. Cytoplasm contains fine granules. It appears violet in color when stained with Leishman's stain. These granules take up both acidic and basic stains. The granules are of two types:

1. **Primary azurophilic granules**: They contain various proteolytic substances, myeloperoxidase enzymes, and lysosomal enzymes.
2. **Secondary granules**: They contain lactoferrin, alkaline phosphate, and vitamin B_{12}-binding protein.

The life span of a neutrophil is about 6–7 hours in the blood and 1–4 days in the tissues.

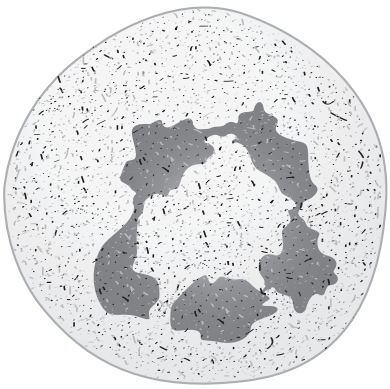


Figure 2.5 Neutrophil. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Functions

The main function of a neutrophil is destruction of microorganisms by phagocytosis. These cells are considered the first line of defense against infection.

Substances called **selectins** attract the neutrophils toward the vascular endothelium.

Attachment of the neutrophils to the endothelium is **margination**.

Later, the neutrophils squeeze through the pores of blood vessels by the process of **diapedesis**.

The neutrophils are attracted to the site of inflammation by a process called **chemotaxis**.

The invading bacteria are coated with certain plasma factors which make it suitable for phagocytosis. This process is called **opsonization**.

Neutrophils project pseudopodia in all directions around the bacteria and it is engulfed. This process is termed **phagocytosis**.

Phagocytosis

Phagocytosis is a process of ingestion and destruction of microorganisms by the phagocytic cells.

It is the most important function of neutrophils and macrophages.

The phagocytes first recognize the microorganism to be phagocytosed. The immune system of the body develops an antibody to the microorganism. The antibodies adhere to the membrane of the microorganism. It also combines with the C3 product of the complement system. These C3 molecules attach to the membrane of the microorganism.

Neutrophils approach these antibody-coated microorganisms and attach to them. They project pseudopodia in all directions around the microorganism. The pseudopodia fuse to form a closed cavity inside the cytoplasm of neutrophil. This is called a **phagocytic vesicle**.

A neutrophil can phagocytose 3–20 bacteria before it dies.

Macrophages are more powerful phagocytes than neutrophils. They engulf as many as 100 bacteria. They phagocytose red cells and malarial parasites.

(*Contd.*)

Digestion of an Ingested Particle

Once ingestion has occurred, the proteolytic enzymes present in the neutrophils and macrophages come in contact with the phagocytic vesicle and empty the digestive enzymes into it. This causes digestion of a foreign particle.

The phagocytic vesicle is converted into a digestive vesicle.

Eosinophils (Fig. 2.6)

Eosinophils are around 10–14 μ in diameter. They constitute 1–4% of the total leukocytes. The nucleus has two (spectacle-shaped) lobes. The cytoplasm contains coarse granules, oval or round in shape, which take up acid stain and appear orange/brick red colored with eosin.

The eosinophilic granules contain major basic protein, eosinophilic peroxidase, eosinophilic cationic protein, arylsulfatase B, and lysophospholipase.

They stay in blood for 6–8 hours and in the tissues for 4–5 days.

Functions

Eosinophils are antiallergic in function.

The eosinophil count increases during parasitic infestations. They migrate toward the larvae of the parasite, bind to it, and destroy them by releasing hydrolytic enzymes, major basic proteins, and by forming superoxides.

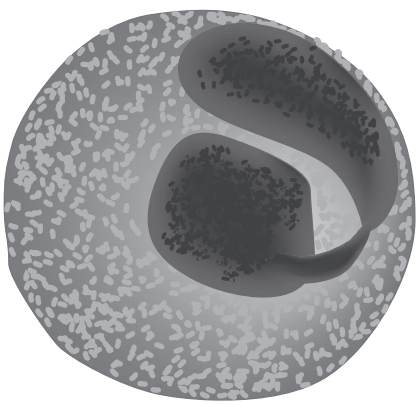


Figure 2.6 Eosinophil. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Eosinophils are attracted toward the site of inflammation by various chemotactic factors. These eosinophils cause detoxification of inflammation-inducing substances released by the mast cells and basophils.

They provide local immunity in the mucosa of GIT, respiratory tract, and urinary tract.

Basophils (Fig. 2.7)

Basophils are the least numerous of leukocytes forming less than 1% of the total leukocytes. They are around 8–10 μ in diameter. The nucleus is irregular or S-shaped; the cytoplasm contains coarse granules which take up the basophilic stain. The granules appear deep purplish blue in color.

Basophils remain in blood for short duration and later migrate to the tissues.

The granules of basophils contain histamine, heparin, acid peptides, and protease.

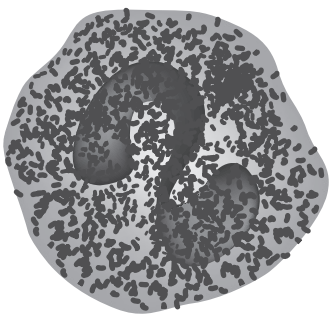


Figure 2.7 Basophil. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Functions

Basophils liberate heparin, which is an anticoagulant substance.

They liberate histamine, which produces allergic reactions.

They also liberate small quantities of bradykinin and serotonin, which participate in the inflammatory process.

Monocytes (Fig. 2.8)

Monocytes are very large cells, around 12–18 μ in diameter. They constitute 2–8% of the

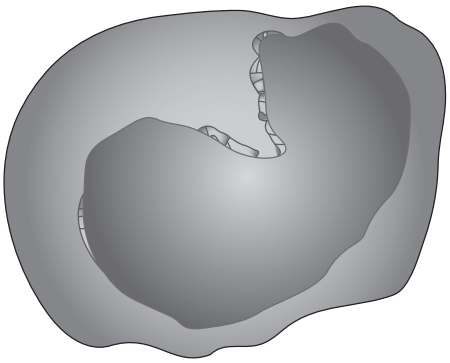


Figure 2.8 Monocyte. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

total leukocytes. The nucleus is indented (kidney-shaped or horseshoe-shaped) and does not have lobes. The nucleus occupies half of the cell and is eccentrically placed.

The cytoplasm is pale blue on staining and does not contain granules. It has ground glass appearance.

The life span of monocytes in blood is around 10–20 hours and later they migrate to the tissues.

In the tissues, they become large in size to form the **tissue macrophages**. They remain in the tissues for months to years.

Functions

Monocytes form the second line of defense. They are also phagocytic. They are immature cells in the blood and do not have the full ability to fight against infection. But once they enter the tissues, they are converted to tissue macrophages which enlarge to attain a size of about 80 μ.

A single macrophage can digest around 100 bacteria. After digestion, the digested particles are extruded out. Thus, macrophages can survive for months.

The dead neutrophils, macrophages, necrotic tissue, and dead bacteria all combine together to form the **pus**.

Lymphocytes (Fig. 2.9)

Lymphocytes constitute around 25–30% of the total leukocytes.

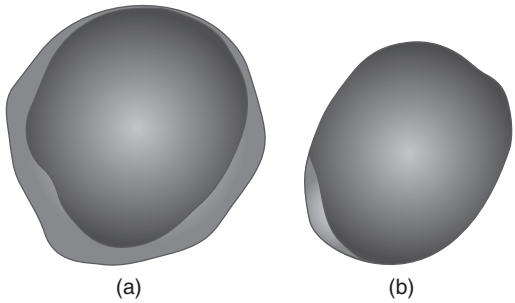


Figure 2.9 Lymphocyte: (a) large and (b) small. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Morphologically, they are of two types:

i. large and
ii. small lymphocytes.

1. **Large lymphocytes** are about 10–12 μ in diameter. The quantity of cytoplasm is more compared to that of small lymphocytes.

   There are no granules in the cytoplasm. They constitute 65% of the total lymphocytes.
2. **Small lymphocytes** have a diameter of about 7 μ. They have a large nucleus occupying the major part of the cell with a thin rim of pale basophilic cytoplasm. They constitute 35% of the total lymphocytes.

Functions

Lymphocytes are involved in immunity. Functionally, lymphocytes are of two types:

1. **T-lymphocytes**: Processed in the thymus.
2. **B-lymphocytes**: Processed in bursa of Fabricius in lower animals. They are also processed in fetal liver and bone marrow in humans. These are equivalent to bursa of Fabricius.

T-lymphocytes are concerned with cell-mediated immunity.

They are of four types:

- Cytotoxic T cells
- Helper T cells
- Memory T cells
- Suppressor T cells

B-lymphocytes get transformed into **plasma cells** when they are activated.

They form immunoglobulins and are responsible for humoral immunity.

LEUKOCYTE COUNT AND ITS VARIATIONS

The normal WBC count is 4,000–11,000 cells/mm^3 of blood.

Physiological Variations

The leukocyte count is increased in

- emotion;
- exercise;
- menstruation, pregnancy, and labor; and
- newborns and infants.

It is decreased in

- starvation and
- severe cold.

Diurnal Variation

Leukocyte count is lowest in the morning and increases during evening.

Pathological Variations

Leukocytosis

Leukocytosis is an increase in the leukocyte count above 11,000 cells/mm^3.

Leukocytosis occurs in acute bacterial infections, hemorrhage, burns, and malignancy.

Neutrophilia An increase in the neutrophil count in blood is termed neutrophilia. It is caused due to acute bacterial infection, severe burns, and myocardial infarction.

Eosinophilia An increase in the eosinophil count in blood is eosinophilia. It is caused due to parasitic infestations, asthma, hay fever, and skin diseases.

Basophilia An increase in the basophil count in blood is basophilia. It is caused due to influenza and chicken pox.

Lymphocytosis An increase in the lymphocyte count in blood is lymphocytosis. It is caused due to tuberculosis, measles, and mumps.

Monocytosis An increase in the monocyte count in blood is monocytosis. It is caused due to Hodgkin's disease and Crohn's disease.

Leukopenia

A decrease in the WBC count below 4000 cells/mm^3 is termed leukopenia.

Neutropenia A decrease in the neutrophil count in blood is called neutropenia. It is caused due to typhoid fever, paratyphoid fever, and bone marrow depression.

Eosinopenia A decrease in the eosinophil count in blood is called eosinopenia. It is caused due to injection of ACTH and excess of cortisol.

Basopenia A decrease in the basophil count in blood is called basopenia. It is caused due to prolonged exposure to radiation and drug-induced reaction.

Monocytopenia A decrease in the monocyte count in blood is called monocytopenia. It is caused due to AIDS and prolonged use of immunosuppressants.

Lymphocytopenia A decrease in the lymphocyte count in blood is called lymphocytopenia. It is caused due to Hodgkin's disease and AIDS.

Leukemia

An abnormal, uncontrolled increase in leukocytes is termed leukemia. It is a malignant condition associated with an increased number of premature cells in the blood.

Leukemia is classified into two main types:

1. Myeloid leukemia
2. Lymphocytic leukemia

Both of these types of leukemia are further classified into acute and chronic types.

Acute leukemia includes acute lymphoblastic and acute myeloblastic types.

Chronic leukemia includes chronic myeloid and chronic lymphocytic leukemia.

RETICULOENDOTHELIAL SYSTEM (MONOCYTE MACROPHAGE SYSTEM)

The reticuloendothelial (RE) system consists of monocytes, wandering macrophages, tissue macrophages, and specialized endothelial cells in the bone marrow, spleen, and lymph nodes.

Monocytes wandering in the blood enter the tissues and become larger. These cells are called **macrophages**. These macrophages get attached to the tissues and phagocytose bacteria, viruses, and necrotic tissue.

Macrophages remain in the tissues for months and years. Some of the macrophages can break away from their attachments and again become mobile.

Macrophages are present as tissue macrophages in the lymph nodes, alveolar macrophages in the lungs, Kupffer cells in the liver, macrophages in the spleen, histiocytes in the skin, and glial cells in the CNS.

TYPE OF MACROPHAGES

Tissue Histiocytes

When the skin is broken and gets infected, local tissue macrophages attack and destroy the infective agents.

Macrophages in Lymph Nodes

The microorganisms which are not destroyed at the tissues enter the lymphatic stream. These microorganisms are trapped in the lymph nodes. Macrophages present in the lymph nodes destroy these microorganisms.

Alveolar Macrophages

Alveolar macrophages are present in the alveolar walls of lungs. These cells invade and destroy the microorganisms which enter the body through lungs.

Kupffer Cells

Kupffer cells are present in the liver sinusoids. They destroy bacteria which enter the body through the GIT. Large numbers of bacteria get absorbed through the mucosa of the gastrointestinal wall and enter the portal circulation. They are destroyed by the Kupffer cells.

Macrophages in Spleen and Bone Marrow

If the microorganism succeeds in entering the general circulation, macrophages present in the spleen and bone marrow trap and destroy them.

Glial Cells

Glial cells are present in the CNS. They destroy the microorganisms which gain entry into the CNS.

FUNCTIONS OF MACROPHAGES

Phagocytosis

Macrophages play an important role in the defense mechanism of the body. They engulf microorganisms such as bacteria and viruses and destroy them.

Destruction of RBC

The RE cells in the spleen destroy the old and fragile RBC.

Secretion of Interleukins

Macrophages secrete various interleukins which regulate immune response. They play an important role in inflammation. They form a colony-stimulating factor which increases the production of blood cells. They ingest and process the antigen which stimulates the formation of antibody.

Storage of Lipids

The cells of the monocyte-macrophage system help in storage of excess lipids.

IMMUNITY

Immunity is the ability of the body to resist invasion by the microorganism and influence of the toxins that cause tissue damage.

FACTORS INFLUENCING IMMUNITY

- **Age:** Newborn and old people have low levels of immunity. The immune mechanisms in a newborn are not fully developed. In old age, there is a gradual decrease in immune response.
- **Hormones:** A change in hormonal levels leading to various endocrine disorders increases the susceptibility to infections due to reduced immunity.
- **Nutrition:** Immunity is reduced in malnutrition.

CLASSIFICATION

Immunity is divided into two broad categories (Flowchart 2.3):

1. innate immunity (nonspecific) and
2. acquired immunity (specific).

Innate Immunity

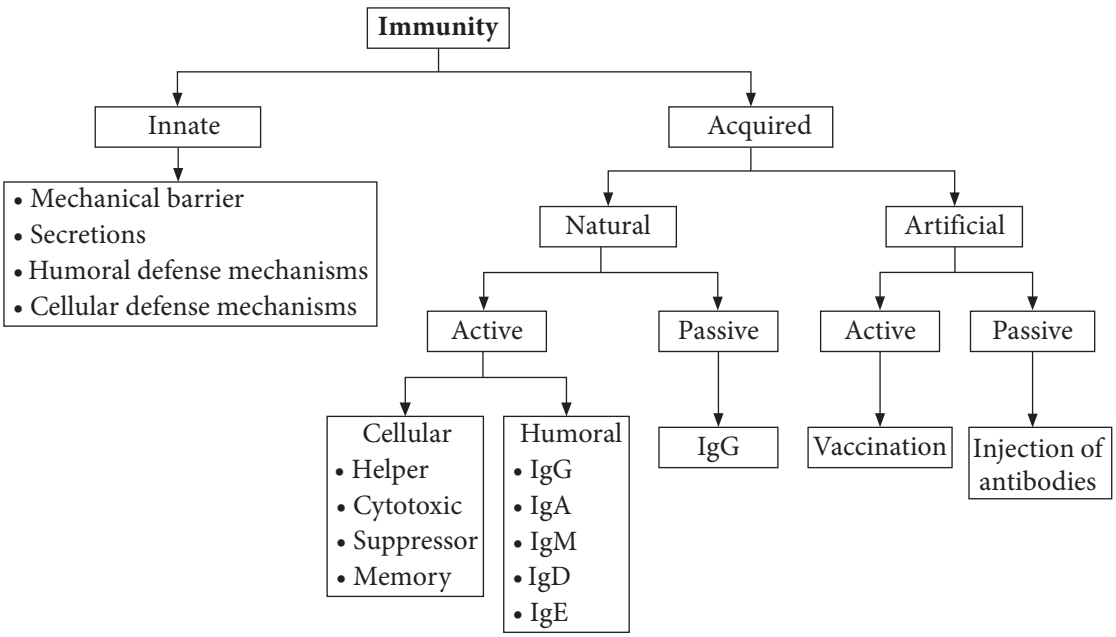
Innate immunity is present since birth. It is effective against all invading organisms and is not specific to a particular type of organism. It does not depend on previous contact with a microorganism. Innate immunity consists of nonspecific defense mechanisms and a few relatively specific defense mechanisms.

This type of immunity includes

- phagocytosis of bacteria by neutrophils and macrophages,
- skin and mucus membrane acting as a barrier against infections,
- acid secretion by the stomach which destroys the swallowed pathogenic organisms,
- lysosomes present in blood,
- complement system of the body, and
- natural killer cells which recognize and destroy tumor cells and infected cells.

Acquired Immunity

Acquired immunity is the ability of the body to develop specific immunity against invading



Flowchart 2.3 Classification of immunity.

agents such as bacteria, viruses, and foreign substances.

It is of two types:

1. Humoral immunity
2. Cell-mediated immunity

HUMORAL IMMUNITY

Humoral immunity is mediated by immunoglobulins. These immunoglobulins are produced by B-lymphocytes. B-lymphocytes specific for the antigen enlarge to form lymphoblast in response to a challenge by an antigen. Lymphoblast differentiates into plasma blast and plasma blast produces *plasma cells*.

The mature plasma cells produce *immunoglobulins,* or antibodies.

Lymphoblast
↓
Plasma blast
↓
Plasma cell
↓
Immunoglobulins

Immunoglobulins are of five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins, in general, contain four polypeptide chains. Two long chains are called *heavy chains* and the two short chains are called *light chains*. In different types of immunoglobulins, there is variation in heavy chains (**Fig. 2.10**).

- **IgG**: This consists of γ (gamma) heavy chain. It is present in plasma and ECF. It is the most abundant immunoglobulin. IgG passes through the placenta. It is involved in complement activation and phagocytosis.
- **IgA**: It contains α (alpha) heavy chain. It is called the secretory antibody. It is present in body secretions (milk, tears, saliva, and gastrointestinal secretions).
- **IgM**: This contains μ (mue) heavy chain. It is responsible for complement activation. It also forms ABO antibodies.

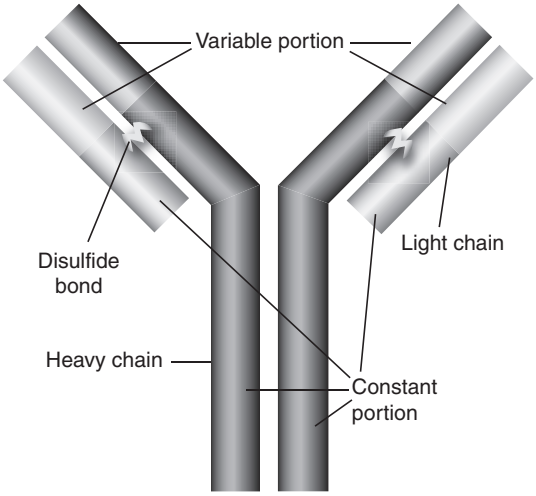


Figure 2.10 Immunoglobulin structure. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- **IgE**: It contains ε (epsilon) heavy chain. It causes the release of histamine from basophils and mast cells. It is increased in atopic allergy and parasitic infestations.
- **IgD**: This contains δ (delta) heavy chain. It is involved in the antigen recognition by B cells.

Activation of humoral immunity involves

- presentation of antigen,
- activation of B cells and conversion to plasma cells,
- proliferation of plasma cells and production of antibody,
- killing of invaders by antibodies, and
- formation of memory B cells.

Antibodies destroy the invading organisms by various mechanisms:

- Immobilizing bacteria
- Neutralizing antigens
- Complement system activation
- Precipitation of antigens
- Facilitation of phagocytosis

CELL-MEDIATED IMMUNITY

Cell-mediated immunity is produced by T-lymphocytes.

T-lymphocytes are of four types:

1. **Helper T cells**: These cells constitute about 75% of T-lymphocytes. They form a series of protein mediators called **lymphokines**. These lymphokines cause
   - stimulation and growth of cytotoxic and suppressor T cells,
   - stimulation and growth of B cells with the formation of antibodies,
   - activation of the macrophage system, and
   - feedback stimulation of other helper T cells.
2. **Cytotoxic T cells**: These cells directly attack and kill the microorganisms. The cells get attached to the microorganism. They create holes in the cell membrane of the microorganism and release cytotoxic substances causing death of the microorganism.
3. **Suppressor T cells**: They are capable of suppressing the functions of both the cytotoxic and the helper T cells. They prevent excessive immune reactions that might damage the body. Thus, they act as regulatory cells.
4. **Memory T cells**: After exposure to an antigen, a small number of T cells (and also B cells) persist as memory cells. Whenever the same antigen enters the body, these cells are activated to produce a rapid antibody response.

Mechanism of Cell-Mediated Immunity The process of cell-mediated immunity (CMI) occurs in three major steps:

1. Antigen recognition, processing, and presentation
2. Activation and proliferation of T cells
3. Elimination of the invader

T and B cells have the ability to recognize an antigen entering into the body. The antigen is processed and presented by antigen-presenting cells to the appropriate receptor on T cells. During processing, the antigen-presenting cell membrane includes antigen fragment and major histocompatibility (MHC) complex.

Activation of T cells occurs when the T cell receptor comes in contact with the MHC–antigen complex. The activated T cells undergo proliferation and differentiation into T cytotoxic cells and T memory cells.

Elimination of the invader is done by cytolysis, secretion of lymphokines, or secretion of interferon.

Cell-mediated immunity acts against

- viral infections,
- chronic bacterial infections,
- fungal infections,
- parasitic infestations,
- tumor cells, and
- transplanted cells.

Natural Killer Cells These are the third type of lymphocytes present in the body apart from T- and B-lymphocytes.

They are large lymphocytes that make up for 10–15% of the circulating lymphocytes and are present in spleen, lymph nodes, bone marrow, and blood.

Functions Natural killer cells destroy malignant cells in the body, thereby preventing cancerous growth. They attack viruses and destroy them.

Differences between humoral immunity and cell-mediated immunity are listed in **Table 2.1**.

Antigen

Antigen is a substance which stimulates the production of an antibody with which it reacts specifically in the body. Antigens are normally proteins or haptens.

Antibody

Antibody is the substance produced in the body in response to an antigenic stimulation.

Antigen–Antibody Reaction

It is the specific reaction between the antigen and the antibody in an observable manner.

Table 2.1 Differences Between Humoral Immunity and Cell-Mediated Immunity

	Humoral Immunity	Cell-Mediated Immunity
Cells involved	B lymphocytes	Macrophage
	T lymphocytes	Helper T cells
	Macrophage	Natural killer T cells Cytotoxic T cells
Percentage of lymphocytes	10–20% of circulating lymphocytes	60–70% of circulating lymphocytes
Maturation	Originates and matures in bone marrow	Originates in bone marrow and matures in thymus
Onset	Rapid	Delayed
Antibodies	Formed	Not formed
End result of activation	Differentiation of B cells into antibody-secreting cells called plasma cells	Secretes locally acting proteins called cytokines
Protect against	Extracellular microbes and their toxins	Intracellular microbes

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

COMPLEMENT SYSTEM

The complement system is a system of proteins present in the serum that are activated by the antigen–antibody interaction. They play an important role in killing the invading microorganism. They include enzymes, cell surface proteins, and regulatory membrane proteins.

These enzymes or proteins have been designated with numbers and letters. The components of the main pathway are named C1 to C9. The components of the alternate pathway are named in capital letters, for example, factor D, B, etc.

Complement is present in the body in an inactive form. The antigen–antibody reaction activates the complement.

Activation of complement occurs through two pathways:

1. Classic pathway
2. Alternate pathway

Classic Pathway

The classic pathway is a chain of events in which components of complement react in a specific sequence ending in immune cytolysis. Activation of C3 by C3 convertase is the major step in this pathway.

Alternate Pathway

In alternate pathway, activation of C3 occurs without C3 convertase. Properdin pathway is an example for this pathway.

Biological Effects of Complement

- Mediates immunological membrane damage causing bacteriolysis or cytolysis
- Amplifies the inflammatory response
- Participates in the pathogenesis of certain hypersensitivity reactions
- Exhibits antiviral activity
- Promotes phagocytosis

Cytokines

Cytokines are hormone-like substances produced from lymphocytes and macrophages. Cytokines with known amino acid sequences are called **interleukins**.

Earlier, substances secreted by lymphocytes were called **lymphokines**. Since these

substances are also secreted from other cells, they are now called **cytokines**.

Effects of Interleukins

- B-cell proliferation and immunoglobulin production
- Activation of phagocytes
- Inflammation and febrile response
- Eosinophil formation and function

Cytokines such as tumor necrosis factors α and β cause necrosis of tumor and blood vessels.

CLINICAL NOTES

AIDS (Acquired Immune Deficiency Syndrome)

AIDS is caused due to infection by a retrovirus called human immunodeficiency virus (HIV).

Infection occurs when the virus enters the body of the person and comes in contact with a suitable host cell-like T_4 lymphocyte. It causes destruction of helper T cells and reduces their number. Loss of helper T cells results in decreased activity of B cells and cytotoxic T cells.

Clinical Features

The infected person after an acute illness with low-grade fever and headache is asymptomatic for months to years. Later, the patient develops unexplained fever, diarrhea, weight loss, and generalized lymphadenopathy. The patient is more prone to opportunistic infections and malignancies.

Autoimmunity

Autoimmunity occurs due to a process of failure of the immune system to ignore self-antigens. This results in an immune reaction against the body's own antigens, causing autoimmune diseases.

Autoimmune Diseases

In this condition, the body produces antibodies against its own proteins. There is widespread destruction of antigenic substance by the antigen–antibody reaction.

Autoimmune diseases include Type I diabetes mellitus, myasthenia gravis, Grave's disease, and rheumatoid arthritis.

Allergy and Hypersensitivity

Antigenic substances present in chemicals, drugs, and cosmetics can cause allergy by activation of T cells. This is characterized by skin rashes due to the release of histamine.

Urticaria, hay fever, and asthma are examples of hypersensitivity.

Anaphylaxis

Anaphylaxis is a widespread allergic reaction affecting the vascular system and related tissues. It is caused by IgE antibodies reacting with the antigens.

Tissue Transplantation

Tissues such as skin or kidney transplanted from one person to another are rejected after some time. This is due to the development of cell-mediated immunity. Transplant rejection is prevented by immunosuppressive drugs, glucocorticoid therapy, and cycloserine.

Vaccination (Immunization)

Vaccination is a simple, safe, and effective method used to produce acquired immunity against specific diseases.

Vaccines

Vaccines are prepared from live attenuated or killed microorganisms or their products. They are used for immunization.

Live Vaccines

Live vaccines (e.g., BCG, measles, and oral polio) cause a low-grade infection without producing disease. Immunity lasts for years. They can be given orally (polio vaccine) or parenterally (measles).

Inactivated (Killed) Vaccines

The vaccines are produced by killing/inactivating the microorganism by heat or chemical treatment. Killed vaccines (e.g., rabies, pertussis [whooping cough], hepatitis A vaccines) are less immunogenic than live vaccines and protection lasts only for a short period. Therefore, they have to be administered repeatedly. At least two doses are required. The first dose is called primary dose. Subsequent doses are called booster doses. Killed vaccines are usually administered through injections. Diphtheria, pertussis, and tetanus vaccine (DPT vaccine) is a trivalent vaccine. It contains toxoids of *Corynebacterium diphtheriae* and *Clostridium tetani*, and killed cells from *Bordetella pertussis*.

LYMPHATIC SYSTEM

The lymphatic system is an accessory route through which fluid flows from the interstitial spaces into the blood. Almost all tissues of the body have lymphatics, exceptions being the skin, brain, and bones.

LYMPH

Lymph is a modified tissue fluid derived from interstitial fluid. It flows in the lymphatic channels.

Composition

Lymph contains proteins, fats, clotting factors, ions such as Na^+, K^+, Cl^-, Ca^{++}, lymphocytes, few RBCs, and platelets.

Flow

Lymph from the lower parts of the body and from the upper left parts of the body pass through lymphatic channels and empty into the venous system through the thoracic duct.

Lymph from the upper right part of the body enters the right lymphatic duct which later empties into the venous system at the junction of right subclavian and internal jugular veins.

Formation

Lymph is formed from the interstitial fluid. Therefore, the composition of lymph is initially similar to interstitial fluid.

Most of the fluid filtered from the blood capillaries flows around the cells and is reabsorbed back at the venous end of the capillaries. About 10% of the fluid flows through the lymphatic capillaries and forms lymph.

The normal lymphatic flow is 2–4 L/day.

Lymphatic flow is determined by two factors:

1. **Interstitial fluid pressure**: An increase in the interstitial fluid pressure increases lymph flow. Increased capillary pressure and decreased interstitial fluid colloid osmotic pressure increase the interstitial fluid pressure causing an increase in lymph flow.
2. **Activity of the lymphatic pump**: Lymphatic channels have valves. These valves prevent backflow of lymph. The portion of lymphatic channels between two valves forms a segment. Stretch of these segments by lymph causes contraction of the smooth muscles causing pumping of lymph into the next segment. This continues in the subsequent segments until the fluid is emptied into the veins.

   The lymphatic pump can generate pressures up to 100 mm Hg.

Functions

- **Absorbs nutrients from the GIT**: Lymph is an important route through which nutrients, especially lipids, are absorbed into the body.
- **Maintains the normal interstitial fluid pressure**: The extra fluid present in tissue spaces is absorbed by lymphatics and returned back to the circulation. Therefore, accumulation of fluid in the interstitial space is prevented.
- **Transport proteins**: Lymph returns the proteins leaked into the interstitial space back into the circulation.
- **Defense mechanism**: Bacteria, toxins, and foreign particles present in the tissue are removed by lymph and transported to the nearest lymph node. Phagocytes present in lymph nodes destroy these bacteria and foreign particles.

CLINICAL NOTES

Edema

Edema is accumulation of abnormally large quantities of fluid in the interstitial space. Reduced lymphatic drainage causes edema. This is due to the leakage of protein into the interstitial space that raises the colloid osmotic pressure of the interstitial fluid.

Edema is seen in diseases of lymphatics caused by infections such as filariasis or surgical removal of lymph nodes (radical mastectomy).

HEMOSTASIS

An injury causes rupture of the blood vessel resulting in hemorrhage (bleeding). The body mechanisms try to arrest the bleeding. This is termed **hemostasis**.

Hemostasis is achieved by several mechanisms:

- Vascular spasm or vasoconstriction
- Formation of a platelet plug
- Formation of a blood clot as a result of blood coagulation
- Deposition of fibrous tissue in the clot and permanent closure of defect in the blood vessel

Vasoconstriction

Rupture of blood vessel results in vasoconstriction. This causes reduction of blood flow through that vessel.

Vasoconstriction is produced by nervous reflexes, local myogenic reflexes, humoral factors released from traumatized tissues, and blood platelets.

Formation of a Platelet Plug

Platelets aggregate at the site of damage to the blood vessel. If the damage in the blood vessel is small, it is sealed by the formation of a platelet plug.

Formation of Blood Clot

This is a powerful mechanism for hemostasis. In severe trauma, there is rupture of blood vessel and blood gets exposed to the exterior (**Fig. 2.11**). Blood, when it is shed, forms a semisolid jellylike substance in about 15–20 seconds. Within 3–6 minutes, the opening in the vessel is filled with clot. After 20 minutes to an hour, the clot retracts and completely seals the defect in the blood vessel.

Formation of Fibrous Tissue in the Clot

After the blood clot is formed, either it is invaded by fibroblasts or it dissolves.

Fibroblasts are formed within a few hours following clot formation. Later, in 1–2 weeks, the clot is completely organized into the fibrous tissue.

The clot dissolves by the action of thrombolytic agents. This occurs in places where the clot is not required and the patency of the vessel has to be maintained.

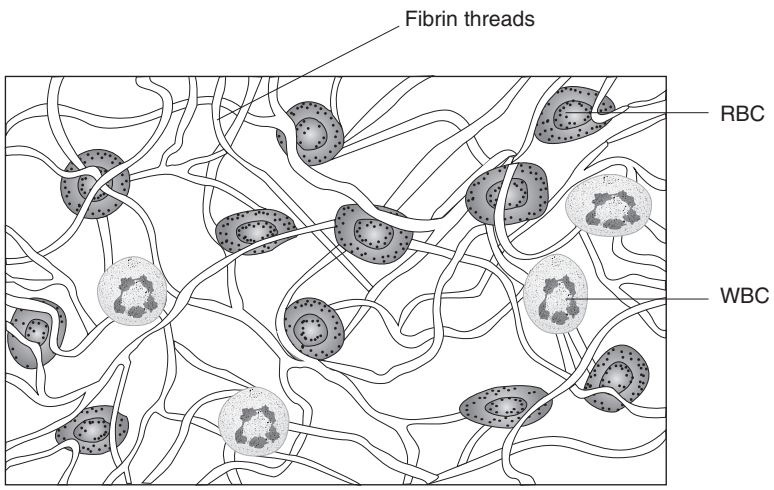


Figure 2.11 Clot formation.

THROMBOCYTES (PLATELETS)

Thrombocytes are small, colorless, round, or oval disks, 2–4 μ in size. They do not have a nucleus (**Fig. 2.12**). However, other cellular organelles are present. They also have a well-developed cytoskeletal system.

The normal count is 1.5–4 lakh cells/mm^3.

Their life span is 9–12 days.

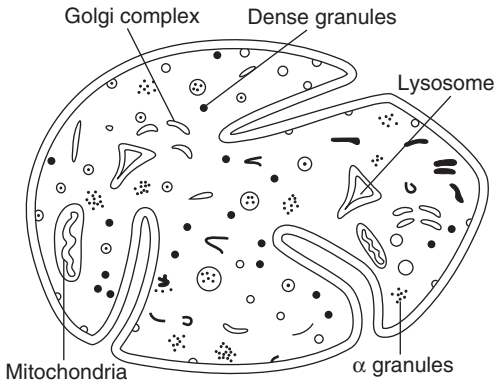


Figure 2.12 Thrombocyte (platelet).

FORMATION

Thrombocytes are formed in the bone marrow from megakaryocyte, which is a large multinucleated cell.

Megakaryocytes develop pseudopod-like extensions that break into fragments to form platelets. One megakaryocyte forms around 2000–4000 platelets.

Pluripotent uncommitted stem cell
↓
Committed stem cell
↓
Promegakaryoblast
↓
Megakaryoblast
↓
Megakaryocyte
↓
Platelet

STRUCTURE AND CONTENTS

The cell membrane of a platelet has a coating of glycoprotein that prevents adhesion to the normal endothelium. It also contains large amounts of phospholipids. The platelet membrane contains receptors, which attach them to the von Willebrand factor, collagen, and fibrinogen. Platelets contain mitochondria and various enzymes that form ATP and ADP. They contain contractile proteins: actin, myosin, and thrombosthenin.

Platelets contain three types of granules: α granules, dense granules, and lysosomal granules. The α granules have platelet-derived growth factor, von Willebrand factor, and thrombospondin. Dense granules contain nonprotein substances such as serotonin, ADP, ATP, and Ca^{++}.

FUNCTIONS

- Help in hemostasis by forming a platelet plug
- Cause vasoconstriction by releasing serotonin and thromboxane A_2
- Accelerate the process of clotting
- Involved in phagocytosis of antigen–antibody complexes and viruses
- Help in the repair of damaged endothelium
- Store and transport 5-hydroxytryptamine and histamine
- Play a role in inflammation

PLATELET REACTION

An injury to the blood vessel exposes its endothelium. Platelets adhere to the vessel wall. These adherent platelets become activated. They change their shape, become motile, and release their granular contents. Platelets become stickier and promote adhesion of a greater number of platelets to the vessel wall. They ultimately form a platelet plug (**Fig. 2.13**). This plug helps in the arrest of bleeding in small

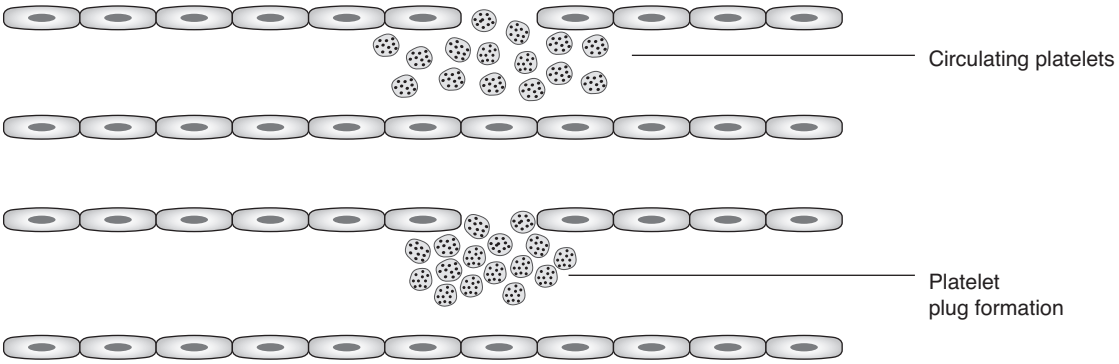


Figure 2.13 Platelet plug formation.

blood vessels. If the damage is large, bleeding is arrested by the formation of a clot.

Injury to blood vessel
↓
Platelet adhesion
↓
Platelet activation
↓
Release of platelet contents
↓
Platelet aggregation
↓
Platelet plug formation

Mechanism of Platelet Reaction

Injury to the blood vessel causes exposure of collagen. Platelets attach to the exposed collagen. The integrins and selectins also help in attachment of platelets. This causes platelet activation. The activated platelets secrete large amounts of ADP and form thromboxane A_2. The ADP and thromboxane A_2 increase platelet aggregation. Later, more and more platelets are attracted and activated resulting in the formation of a platelet plug.

CLINICAL NOTES

Thrombocytopenia

Thrombocytopenia is a condition of a reduced number of platelets in circulation. Individuals with thrombocytopenia have a tendency to bleed. This bleeding is from small capillaries.

Causes

- Viral infections such as dengue fever
- Bone marrow depression
- Drug reactions
- Hypersplenism

Thrombocytopenic Purpura

The disease is characterized by the formation of purplish spots beneath the skin due to spontaneous bleeding. In this condition, clot retraction is delayed and there is poor constriction of ruptured vessels.

In this condition, the bleeding time is prolonged but the clotting time is normal. Manifestation of disease is seen when the platelet count is less than 50,000 cells/mm^3.

Thrombasthenic Purpura

This is a condition with a normal platelet count but the circulating platelets are abnormal.

Treatment

Infusion of fresh blood or infusion of platelet concentrate.

In nonresponding cases, splenectomy (removal of spleen) is advised.

BLOOD COAGULATION

About 50 different substances that affect blood coagulation have been identified. The substances that promote coagulation are called **procoagulants**. The substances inhibiting coagulation are called **anticoagulants**. In a normal state, the anticoagulants predominate over procoagulants and therefore blood does not clot. But whenever the vessel ruptures, the procoagulants in that area become activated and override the effect of anticoagulants producing the clot.

MECHANISM OF BLOOD COAGULATION

Clotting or coagulation occurs in three basic stages:

1. The rupture of blood vessel results in a cascade of chemical reactions in blood involving 12 coagulation factors. They finally form a complex of activating substances called the **prothrombin activator**.
2. Prothrombin activator catalyzes the conversion of **prothrombin** to **thrombin**.
3. Thrombin acts as an enzyme to convert **fibrinogen** to **fibrin**.

Fibrin forms a mesh in which the blood cells, platelets, get entangled and form a clot.

Clotting Factors

The formation of prothrombin activator requires 12 different coagulation factors. They are as follows:

- **Factor I—fibrinogen**: Fibrinogen is a soluble plasma protein having a molecular weight of 3,30,000. Plasma contains about 100–700 mg/dL.

  It is acted upon by thrombin to form an insoluble fibrin clot. The absence of factor I is termed **afibrinogenemia**.
- **Factor II—prothrombin**: Prothrombin is the inactive precursor of thrombin. It is a plasma protein with a molecular weight of 68,700. The normal concentration in plasma is 15 mg/dL. It is formed in the liver with the help of vitamin K.
- **Factor III—thromboplastin**: This converts prothrombin to thrombin in the presence of factors V, VII, X, Ca^{++}, and phospholipids.
- **Factor IV—calcium**: Ionic calcium is required for clotting. This is required for the formation of prothrombin activator, for the conversion of prothrombin to thrombin, and for the formation of an insoluble fibrin clot.
- **Factor V—labile factor (proaccelerin)**: This is required for the conversion of prothrombin to thrombin by tissue extract and plasma factors.
- **Factor VI**: Absent.
- **Factor VII—stable factor (proconvertin)**: This is required for the formation of prothrombin activator from tissue extracts.
- **Factor VIII—antihemophilic factor A**: This is required for the formation of prothrombin activator by tissue extract. Absence of this factor leads to disease termed *hemophilia.*
- **Factor IX—Christmas factor (antihemophilic factor B)**: This is needed for the formation of prothrombin activator from blood constituents. Lack of factor IX results in Christmas disease.
- **Factor X—Stuart–Prower factor**: This is also required for the formation of prothrombin activator. Absence of this factor leads to hemorrhage.
- **Factor XI—plasma thromboplastin antecedent (antihemophilic factor C)**: This is required for the formation of prothrombin activator from blood constituents. Absence of this factor leads to hemorrhage.
- **Factor XII—Hageman factor**: Deficiency of this factor leads to delayed clotting. This factor is activated by glass and water-wettable surfaces. It also takes part in the formation of prothrombin activator.
- **Factor XIII—fibrin-stabilizing factor**: This is a plasma protein which causes polymerization of soluble fibrin to produce insoluble fibrin.

Clotting Mechanisms

Clotting occurs by two pathways:

1. Extrinsic pathway
2. Intrinsic pathway

Clotting factors are necessary for the formation of the prothrombin activator. The prothrombin activator is formed by the two pathways.

Extrinsic Pathway

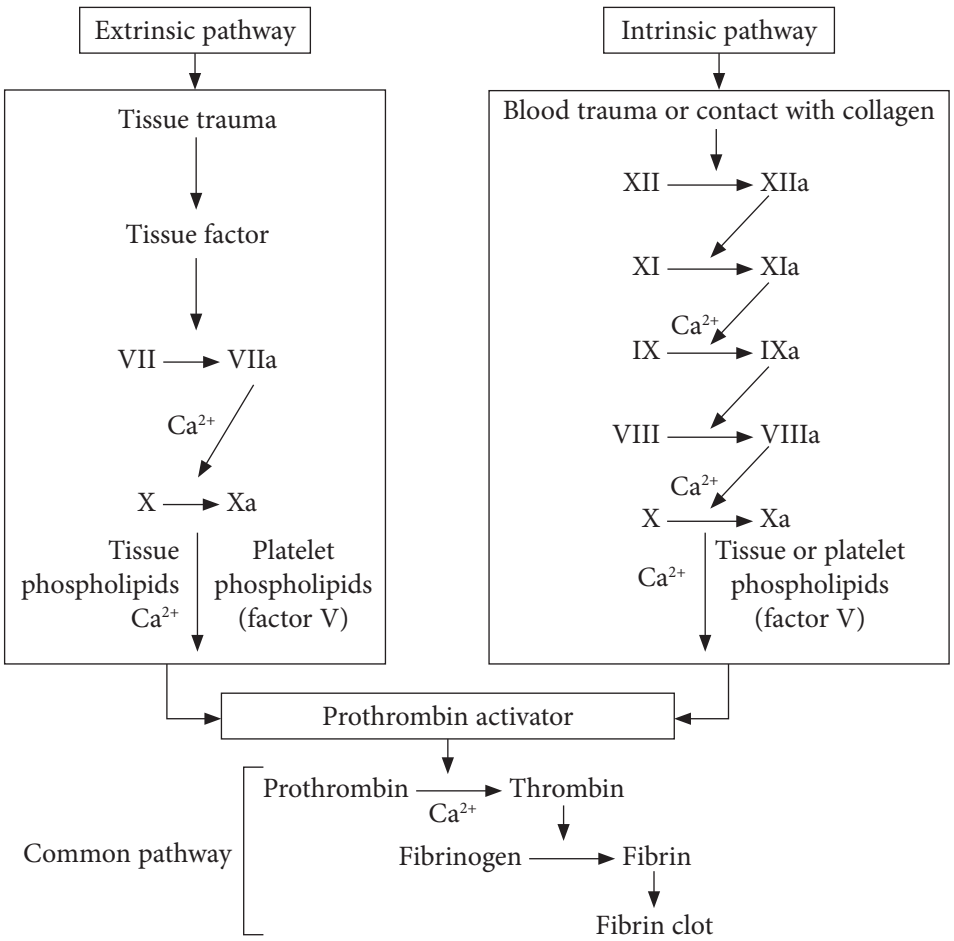
Trauma to the tissue releases complex tissue factors composed of phospholipids and lipoprotein. Tissue factor and factor VII in the presence of Ca^{++} ions act on factor X to form activated factor X. Activated factor X combines with tissue phospholipids, platelet phospholipids, and factor V to form the complex called **prothrombin activator**.

Intrinsic Pathway

This begins with damage to blood cells or exposure of blood to collagen in a traumatized vessel wall. It results in activation of factor XII to activated factor XII (XIIa). It also causes damage to platelets, and this releases platelet phospholipids. Activated factor XII acts on factor XI and activates it. Activated factor XI causes activation of factor IX. Activated factor IX along with activated factor VIII and traumatized platelets cause activation of factor X. Activated factor X combines with factor V and platelet or tissue phospholipids to form the complex called **prothrombin activator**.

After formation of the prothrombin activator, the second step in clotting is the conversion of prothrombin to thrombin.

The third step in the clotting mechanism is conversion of fibrinogen to fibrin.



Thrombin acts on fibrinogen and converts it to fibrin monomer by removing four low-molecular-weight peptides from each molecule of fibrinogen. Many fibrin monomers polymerize within seconds to form long fibrin fiber.

These fibers ultimately form a meshwork in which platelets, blood cells, and plasma get entangled. This is known as a **clot**. The fibers are strengthened by a substance known as fibrin-stabilizing factor.

Clot formation by the extrinsic pathway is rapid. The intrinsic pathway is much slower, requiring 1–6 minutes to produce clotting. Ca^{++} ions are absolutely necessary for both the pathways. Therefore, in the absence of Ca^{++} ions, clotting does not occur.

Once a blood clot is formed, it follows one of the two courses:

1. It can be invaded by fibroblasts and form fibrous tissue within about 1–2 weeks.
2. It can be dissolved by substances such as plasmin or fibrinolysin.

Plasmin is formed from a substance called plasminogen under the influence of the tissue plasminogen activator. Plasmin is a proteolytic enzyme which digests fibrin as well as other clotting substances in blood.

CLINICAL NOTES

Bleeding Disorders

Important bleeding disorders include the following:
- Hemophilia
- Vitamin K deficiency
- Afibrinogenemia
- Disseminated intravascular coagulation (DIC)
- Thrombocytopenia

Hemophilia

Hemophilia major is due to deficiency of factor VIII. It is a sex-linked hereditary disease which occurs exclusively in males. Females are the carriers. This disease is a genetically transmitted recessive disorder. Persons suffering from this disease have bleeding tendencies after a minor trauma. The clotting time is prolonged and the bleeding time is normal in hemophilia. Treatment is by injection of the purified factor VIII.

Absence of factor IX is termed **hemophilia minor** or **Christmas disease**.

Vitamin K Deficiency

Vitamin K is necessary for the formation of five clotting factors—prothrombin, factor VII, factor IX, factor X, and protein C—in the liver. Absence or deficiency of vitamin K leads to deficiency of these factors and defective clotting. Diseases of the liver such as hepatitis and cirrhosis can also cause impaired absorption of vitamin K leading to decreased production of clotting factors.

Afibrinogenemia

There is deficiency of fibrinogen in this condition. This can occur due to genetic defect, liver diseases, and prostatic cancer. Treatment is supplementation of fibrinogen through transfusion or fresh blood transfusion (fresh frozen plasma).

Disseminated Intravascular Coagulation (DIC)

This is a serious complication of septicemia. DIC is caused due to increased formation of thrombin. In this condition, fibrin is deposited in blood vessels causing thrombosis in small and medium-sized vessels. This utilizes a large number of platelets and coagulation factors resulting in bleeding.

Thrombocytopenia

Thrombocytopenia has been discussed earlier.

TESTS FOR COAGULATION

BLEEDING TIME

Bleeding time is the time interval from the onset of bleeding to its spontaneous arrest (cessation or stoppage).

The normal bleeding time is 2–4 minutes. It is prolonged in thrombocytopenic purpura.

CLOTTING TIME

Clotting time is the time lag between the onset of bleeding and the appearance of the first fibrin thread.

The normal duration is 2–8 minutes. It is prolonged in hemophilia.

PROTHROMBIN TIME

Prothrombin time is a blood test used to measure time taken by plasma, the fluid portion of the blood, to clot. The normal prothrombin time is 11–16 seconds. It varies with alteration in the prothrombin level in the blood. Prothrombin time gives an indication about the total amount of prothrombin present in the blood. Increased prothrombin time delays coagulation. It is increased in liver diseases and vitamin K deficiency.

ANTICOAGULATION

Anticoagulation is a process of limiting blood clotting within the body to optimum levels. This is brought about by the following:

- **Prostacyclin**: It is formed at the site of injury in the initial layer. This prevents extension of the clot.
- **Antithrombin III**: It is a protease inhibitor present in plasma. It prevents activity of factors IXa, Xa, XIa, and XIIa.
- **Thrombomodulin**: It is a protein present on the endothelial cells which bind to thrombin. The thrombin–thrombomodulin complex activates protein C. This inactivates factors V and VIII, thereby preventing coagulation.

FLUID STATE OF BLOOD/BLOOD IN CIRCULATION

Blood is kept in a fluid state mainly due to continuous motion.

Other factors helping this are

- smoothness of endothelium,
- negative charge of endothelium,
- natural anticoagulants such as heparin, and
- anticlotting mechanisms.

FIBRINOLYTIC SYSTEM

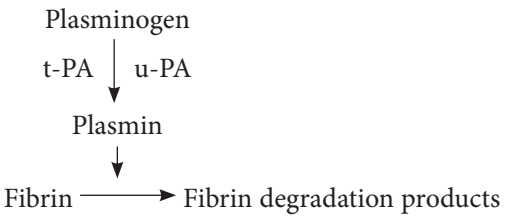
The fibrinolytic system dissolves clot and keeps the lumen of the blood vessel patent. Lysis (breakdown) of fibrin is brought about by plasmin.

Plasmin is produced from its inactive precursor plasminogen by plasminogen activators.

Plasminogen activators are of two types:

1. Tissue-type plasminogen activator (t-PA)
2. Urokinase-type plasminogen activator (u-PA)

Plasminogen activators are secreted by endothelial cells. Their plasma half-life is around 5 minutes. They are present in human plasma, milk, tears, saliva, and many other tissues. They act on plasminogen and hydrolyze the bond between arginine and valine resulting in the formation of plasmin. This plasmin will act on fibrin or fibrinogen to form fibrin degradation products.



Streptokinase and urokinase are used in lysis of clots in conditions of intravascular clotting, for example, management of the early stages of myocardial infarction.

ANTICOAGULANTS

Anticoagulants are substances which prevent or retard the coagulation of blood.

Heparin

Heparin is a naturally occurring anticoagulant found in basophils and mast cells. It is used both in vivo (inside the body) and in vitro (outside the body). It acts by neutralizing the action of thrombin by facilitating the binding of

antithrombin III with thrombin. It also inhibits factors IXa, Xa, XIa, and XIIa.

Vitamin K Antagonists

Vitamin K antagonists include warfarin sodium and dicumarol. They inhibit the formation of vitamin K–dependent clotting factors.

Calcium-Chelating Agents

Calcium-chelating agents include EDTA (ethylene diamine tetra-acetic acid), citrates, and oxalates of sodium and potassium. These substances form insoluble salts with calcium and precipitate them. Thus, calcium is not available for the process of clotting.

BLOOD GROUPS

Blood is categorized into different groups based on their antigenic properties. The antigenic and immunologic properties of blood have clinical, genetic, and medicolegal importance.

Karl Landsteiner discovered blood groups. There are around 23 blood group systems containing more than 400 antigens.

Of these 400 antigens, only about 30 occur commonly and most of them are weak antigens. These weak antigens do not cause agglutination reactions but are important for studying genetic inheritance to establish parentage.

Blood group systems include ABO system, Rh system, M and N system, Lewis system, P system, Kell system, and Duffy system. Most important are the ABO and Rh systems.

USES OF BLOOD GROUPING AND Rh TYPING

- Ensures safe blood transfusion
- Medicolegal importance—paternity testing and crime detection
- Genetic studies
- Studies the relationship between blood group and various diseases

ABO SYSTEM

Human blood is categorized into four major groups depending on the presence or absence of antigens.

Antigens are present on the surface of RBC. They are called **agglutinogens**.

There are two agglutinogens in the ABO system: A and B.

Further, A agglutinogen is of two types:

1. $\mathbf{A_1}$: Contains A and A_1 agglutinogens
2. $\mathbf{A_2}$: Contains only A agglutinogens

A and B antigens are complex oligosaccharides. All individuals possess H genes which form H antigens. In addition to H antigens, A and B group individuals have different transferases. O group individuals do not have transferases.

Group	Agglutinogen	Agglutinin
A	A	Anti-B (β)
B	B	Anti-A (α)
AB	Both A and B	Nil
O	Nil	Anti-A and anti-B (α and β)

Blood contains antibodies in plasma. These are called **agglutinins**. Most of them are IgM and IgG immunoglobulin molecules. They are absent at birth and develop within 2–8 months after birth, reaching a maximum by 8–10 years, and gradually decline thereafter for the remaining period of the life.

Antigens similar to A and B are present in the intestinal bacteria and food consumed by the infants. Therefore, infants develop antibodies to these antigens.

Type A individuals develop anti-B antibody, type B individuals develop anti-A antibody, type O individuals develop both anti-A and anti-B antibodies, and type AB individuals do not develop any antibodies.

LANDSTEINER'S LAW

1. If an agglutinogen is present on the RBCs of an individual, the corresponding agglutinin must be absent in plasma.
2. If the agglutinogen is absent on the RBC, the corresponding agglutinin must be present in the plasma.

Thus, group A individuals have A agglutinogen and β agglutinin.

Group B individuals have B agglutinogen and α agglutinin.

Group AB individuals have A and B agglutinogens and no agglutinin.

Group O individuals have no agglutinogen and α and β agglutinins.

The first law holds good for all types of blood grouping.

The second law is applicable to the ABO system of blood grouping.

BOMBAY BLOOD GROUP

The Bombay blood group was first discovered in Bombay, hence the name. Individuals with this rare group do not express H antigen and therefore do not form A and B antigens. So when their blood group is tested routinely, it is labeled as O group. However, their serum contains anti-A, anti-B, and anti-H antibodies.

These people can donate blood to any individual but cannot receive blood from any individual with the ABO blood group system other than individuals with the Bombay phenotype.

ABO Incompatibility

When mismatched blood is transfused to a person, serious reactions can occur resulting in death of the person.

The affected person develops hemolysis resulting in shock and renal failure.

Rh SYSTEM

The Rh system is also an important system of blood grouping. The term Rh is derived from the Rhesus factor since the original discovery was made in Rhesus monkeys.

There are six agglutinogens in the Rh system. They are C, D, E, c, d, e. Out of the six agglutinogens, only D agglutinogen is potent and therefore the Rh group is described only in relation to D agglutinogen.

Individuals having D agglutinogen are said to be Rh+ (positive) and individuals not having D agglutinogen are said to be Rh– (negative). About 85% of the population is Rh+ and 15% of the population is Rh–.

The Rh system is found only in blood and not detected in other tissues. Anti-D antibodies are not present in Rh– individuals unless the person is exposed to Rh+ blood. However, if they receive Rh+ blood, they develop anti-D antibodies.

Such individuals develop hemolytic reactions if they are transfused with Rh+ blood again. The anti-D antibodies are of IgG type and they can easily pass through the placenta.

CLINICAL NOTES

Rh Incompatibility

An Rh– individual transfused with Rh+ blood develops anti-Rh agglutinins slowly. If this person is later exposed to Rh+ blood, severe transfusion reactions occur.

Erythroblastosis Fetalis

Erythroblastosis fetalis is a disease of neonates with Rh incompatibility. There is agglutination and destruction of fetal red cells. In this condition, the mother is Rh– and the fetus is Rh+. There is no complication in the first pregnancy, but problem occurs in subsequent pregnancies.

If an Rh+ baby is born to an Rh– mother, some fetal erythrocytes pass to the mother during childbirth. This produces anti-D antibodies in the mother. In the next pregnancy, if the fetus is Rh+, these antibodies from the mother destroy fetal erythrocytes leading to hemolytic disease of the newborn.

(*Contd.*)

Clinical Features

The fetus is jaundiced and anemic; the liver and spleen are enlarged. Increased concentration of bilirubin in the brain tissue can damage the nerve cells leading to kernicterus. In a severe form, it presents as hydrops fetalis.

Prevention

Administration of anti-D antibodies to the mother soon after the delivery of the first child can help in the prevention of erythroblastosis fetalis. This causes destruction of Rh+ fetal cells in maternal blood.

Treatment

Erythroblastosis fetalis can be treated with replacement of blood of the newborn (exchange transfusion) with Rh– blood repeatedly during the first few weeks. About 400 mL of Rh– blood is transfused. During the procedure, blood is slowly removed from the newborn and replaced with an equal volume of Rh– blood from the donor.

Universal Donors

Individuals with O negative group are considered universal donors since their blood can be transfused to any individual as their blood does not contain any antigen.

Universal Recipient

Individuals with AB positive group are considered universal recipients since they can receive blood from any individual as their blood does not contain any antibodies.

However, this concept of universal donor and recipient can be used only in emergency situations and not as a routine. There are many minor blood group systems, and transfusion reactions can occur due to the differences in minor blood groups. Hence, proper blood grouping and cross-matching should be done before blood transfusion.

BLOOD TRANSFUSION

Blood transfusion is a procedure in which blood collected from the donor and preserved with the help of an anticoagulant is transfused to the recipient.

INDICATIONS

- Sudden blood loss due to accidents
- During major surgeries
- Patients with bleeding disorders
- Patients with severe burns
- Patients with severe anemia, thalassemia, and leukemia
- Hemolytic disease of newborn

COLLECTION AND STORAGE OF BLOOD

Blood is collected from a healthy donor free of all infectious diseases such as HIV, hepatitis, malaria, and syphilis.

It is collected under strict aseptic precautions and mixed with anticoagulant (acid citrate dextrose).

One unit of blood (420 mL) can be collected from a donor at a time. This is stored at 2–4°C in a blood bank.

The stored blood has to be used within 3 weeks from the time of its collection.

Leukocytes and platelets are absent after 24 hours of storing blood. Therefore, patients requiring leukocytes or platelets should be transfused fresh blood.

PRECAUTIONS DURING BLOOD TRANSFUSION

- The temperature of the blood to be transfused must be brought to room temperature.
- Transfusion should be done under strict aseptic precautions.

- Transfusion must be very slow since rapid infusion can lead to excessive load on the heart resulting in cardiac failure.

BLOOD GROUPING AND CROSS-MATCHING

Blood grouping and cross-matching have to be done to prevent complications of blood transfusion.

Blood Grouping

Saline suspension of RBC is mixed with anti-A, anti-B, and anti-D sera. Presence or absence of agglutination helps to identify the blood group.

Cross-Matching

The erythrocyte of the donor is matched with the serum of the recipient in **major cross-matching**.

In **minor cross-matching**, the erythrocyte of the recipient is matched with the serum of the donor.

HAZARDS OF BLOOD TRANSFUSION

Transfusion of blood may be hazardous if proper precautions are not taken. Sometimes, complications can occur even if all necessary precautions are taken (Flowchart 2.4). The hazards of blood transfusion include the following:

- Hazards of mismatched blood transfusion
- Other hazards of blood transfusion

Hazards of Mismatched Blood Transfusion

Immediate Effect

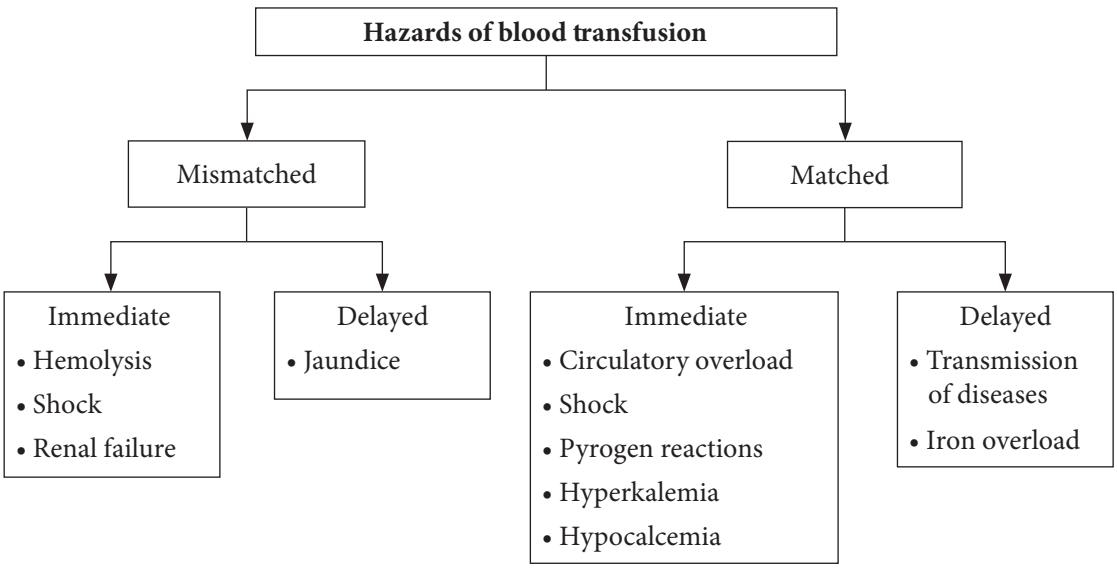
This includes hemolysis leading to shock and renal failure due to precipitation of Hb in the nephrons.

Hemolysis Mismatched blood transfusion results in antigen–antibody reaction inside the recipient's body causing massive destruction of red blood cells.

Shock Shock is caused due to loss of circulating RBCs and also production of toxic substances from the hemolysed cells.

The arterial pressure falls leading to decreased renal blood flow.

Renal Failure Renal failure occurs within few minutes to few hours of blood transfusion. It is due to



Flowchart 2.4 Hazards of blood transfusion.

- constriction of renal blood vessels by toxins released,
- reduced blood flow secondary to circulatory shock, and
- precipitation of Hb in the nephrons.

Delayed Effect

Jaundice occurs due to release of hemoglobin from hemolysed RBCs. Hemoglobin released is converted to bilirubin. The bilirubin concentration in the body fluids increases resulting in jaundice.

Other Hazards of Blood Transfusion

- **Immediate**: Pyrogen reactions, shock, circulatory overload, hyperkalemia, and hypocalcemia.
  - *Pyrogen reactions:* Fever with chills and rigors can develop during transfusion.
  - *Circulatory overload:* Rapid transfusion of blood can lead to hypervolemia resulting in circulatory overload.
  - *Hyperkalemia:* This occurs due to loss of K^+ ions from red cells into plasma in stored blood.
  - *Hypocalcemia:* Addition of citrate to blood results in lack of ionized calcium resulting in hypocalcemia.
- **Delayed:** Transmission of diseases and iron overload.
  - *Transmission of diseases:* Malaria, syphilis, and HIV can be transmitted through blood.
  - *Iron overload:* This occurs in patients receiving repeated blood transfusion.

AUTOLOGOUS BLOOD TRANSFUSION

This refers to transfusion of an individual's own blood which has been drawn earlier and stored. Around 1–1.5 L of blood can be withdrawn over a period of 3 weeks. This can be used in case of elective surgeries.

REVIEW QUESTIONS

Long Essay

1. Name the plasma proteins. Explain their chemical nature. Add a note on their functions.
2. What is erythropoiesis? Describe the stages and factors influencing it.
3. What is anemia? Describe the types of anemia. Give the blood picture in each of them.
4. Explain the structure, synthesis, functions, and breakdown of hemoglobin.
5. Classify leukocytes. Describe their morphology. Add a note on their functions.
6. Describe the various stages of leukopoiesis.
7. What is immunity? Explain its types.
8. Describe the mechanism of cell mediated immunity.
9. Explain intrinsic and extrinsic mechanisms of blood clotting.
10. Name the blood group systems. Explain the basis for its classification. Add a note on its clinical importance.

Short Essay

1. List the functions of blood.
2. List the functions of plasma proteins.
3. Erythropoietin
4. What is polycythemia? Explain its different types.
5. Describe any two abnormal types of hemoglobin.

6. Explain the absorption, storage, and functions of iron in the body.
7. Explain the role of lymphocytes in immunity.
8. What are immunoglobulins? What are their functions?
9. Describe the mechanism of humoral immunity.
10. Discuss the changes that occur during phagocytosis.
11. Explain the formation, composition, and functions of lymph.
12. What is reticuloendothelial (monocyte-macrophage) system? Outline its functions.
13. Explain the functions of platelets.
14. Explain the mechanism of hemostasis.
15. Give a brief account of hemophilia.
16. Explain in brief the thrombocytopenic purpura.
17. Name the clotting factors. Explain the properties of factor VIII.
18. What are anticoagulants? Explain their mechanism of action.
19. Explain the consequences of mismatched blood transfusion.

Short Answer

1. Name the plasma proteins.
2. What is albumin–globulin ratio? What is its clinical importance?
3. Explain plasmapheresis.
4. Give an account of the blood picture in pernicious anemia.
5. Give an account of the blood picture in iron-deficiency anemia.
6. What are reticulocytes? How are they demonstrated in the blood film?
7. What are the structural and functional differences between adult and fetal hemoglobin?
8. Sickle cell anemia
9. Hereditary spherocytosis
10. What is the normal ESR? Mention factors that influence it.
11. Give the normal value for MCV, MCH, MCHC, and color index.
12. What is normal PCV? When is it altered?
13. Leukocytosis
14. Leukopenia
15. Describe innate immunity.
16. Natural killer cells
17. What is a plasma cell? What is its function?
18. Define active immunity. Give examples.
19. Define passive immunity. Give examples.
20. List the biological effects of complement.
21. Autoimmune diseases
22. Afibrinogenemia
23. Describe the role of heparin as an anticoagulant.
24. Prothrombin time
25. What is the fibrinolytic system?
26. What is Landsteiner's law?
27. What is cross-matching? What are its types?
28. What is erythroblastosis fetalis?
29. How is blood stored in blood banks?
30. Autologous blood transfusion

CHAPTER

3 Nerve–Muscle Physiology

Outline

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Nerve Impulse 84
Nerve Injury 88
Neuroglia 91
Neuromuscular Junction 93
Muscle Physiology 96
Skeletal Muscle 97
Smooth Muscles 111

Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the structure of a neuron. Explain the process of myelination and neuronal transport.
- Classify neurons. Discuss their electrical properties.
- Describe the impulse transmission in myelinated and unmyelinated nerve fibers and factors influencing it.
- Explain the structure of neuromuscular junction. Discuss the transmission of impulse across it.
- Describe the changes after a nerve injury. Discuss the regeneration of nerve fibers.
- Classify neuroglia. Explain their structure and functions.
- Classify muscle fibers. Explain their structure.
- Discuss the molecular basis of skeletal muscle contraction.
- Explain the properties of skeletal muscle. Illustrate different types of muscle contraction with examples.
- Describe the structure and mechanism of smooth muscle contraction.
- Successfully answer the questions and MCQs at the end of this chapter.

The muscles and nerves are the excitable tissues. There are about 100 billion neurons in the human central nervous system (CNS). The neurons are the building blocks of the nervous system. They respond to various types of stimuli. The generation and transmission of impulse is the specialized function of a neuron. The neurons develop from the primitive neuroeffector cells.

Glial cells are present along with neurons in the nervous system. Their numbers range from 10 to 50 times the number of neurons. They were considered connective tissue cells. Glia means **glue** in Greek. Recent evidence shows that glial cells have a role in communication in the CNS. However, they do not generate or propagate action potentials.

Glial cells are capable of division and proliferation even in adulthood. Neuroglia multiplies and fills the space occupied by neurons following injury or disease.

Gliomas are highly malignant brain tumors derived from glial cells.

The human body contains three different types of muscles performing specialized functions. They are skeletal, cardiac and smooth muscles. Skeletal muscles are under voluntary control moving the bones. Cardiac muscle contracts with each heartbeat. Smooth muscle exhibit sustained contraction.

The muscle cells, in addition to the property of excitability, have the capacity to contract. The contractile mechanism of the muscle is activated by an action potential. Actin and myosin are the contractile proteins present in the muscle, which bring about contraction.

Development of the nervous system begins by division of undifferentiated **stem cells**. Stem cells can differentiate into neurons or glial cells.

Neurons send out a process which becomes axon and dendrites. The tip of the axon forms **growth cone** to reach the target cell/tissue of innervation. The growth of axon is guided by attracting, inhibiting, and supporting molecules such as neurotrophic factors.

Neural development is seen during pregnancy and early infancy. Exposure to radiation, malnutrition, and some drugs and viruses can permanently hamper neural growth. Half the numbers of axons formed in the CNS undergo programmed cell death termed **apoptosis**. This is believed to help in refining the connections.

This chapter deals with the excitation, the integration, and the activity of the excitable tissues of the body.

NEURON

Neuron is the structural and functional unit of the nervous system (**Fig. 3.1**). Neurons function as **integrators** because their output shows the balance of inputs received from multiple neurons.

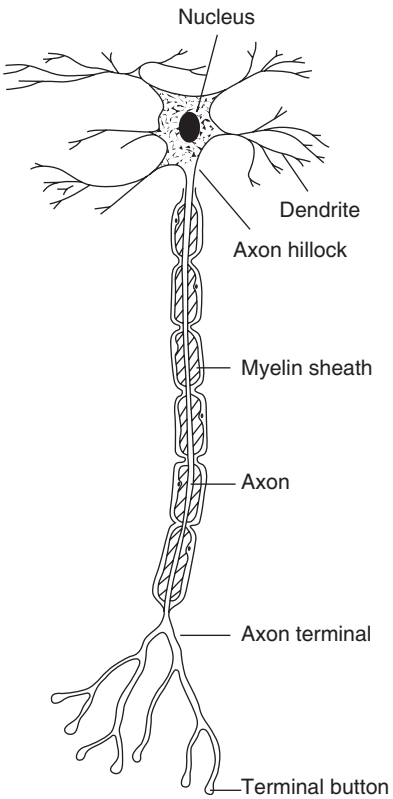


Figure 3.1 Structure of a neuron.

STRUCTURE

A neuron has the following structures:

- Cell body (soma)
- Nissl granules
- Dendrites
- Axon

Cell Body (Soma)

The cell body is also called **perikaryon**. It contains nucleus, endoplasmic reticulum, ribosome, and Golgi apparatus that have structure and function similar to other cells. It has genetic information and system required for protein synthesis. In addition, it has Nissl granules.

Nissl Granules

Nissl granules are also called tigroid bodies, named after a German psychiatrist Franz Nissl. They are present all over the cell except the axon hillock. They resemble ribosomes and help in the synthesis of proteins needed for the transmission of impulses from one neuron to another. The proteins produced by them are useful in the maintenance and regeneration of the nerve fibers. They disappear when the nerve is injured. This process is called *chromatolysis*. They reappear during the regeneration of neuron.

Axon

The axon (also called the nerve fiber) is the long process of a neuron. It carries information away from the cell body. It arises from the prominent portion of the cell body called the **axon hillock**. The portion of the axon close to the cell body (near the site of origin) is termed the **initial segment**. The initial segment is the trigger zone where the electrical signals are generated and then propagated away from the cell body. The axons vary in length and diameter. The length of the axon varies from a few millimeters to a meter. The diameter ranges from 1 to 20 μ. The cytoplasm of axon is called **axoplasm**. It is surrounded by a plasma membrane termed **axolemma**. The axon gives out lateral branches at right angles along its length called **axon collaterals**.

Axon Telodendria (Terminal Buttons)

Axon telodendria are the terminal portions of the axon which divides into branches. They contain vesicles filled with neurotransmitter.

Myelination of Axon

The axons of many neurons are covered by a myelin sheath. They are called **myelinated nerve fibers**. The cells of Schwann form the myelin sheath in the peripheral nervous system (PNS). The myelin sheath is a protein–lipid complex that wraps around the neuron. It is formed when the cells of Schwann wrap its membrane about 100 times around the axon. Later, the layers of the membrane are compacted to form the myelin sheath.

The process of formation of myelin sheath is termed **myelinogenesis** (**Fig. 3.2**). The myelin sheath acts as an insulator around the axon. It is interrupted at periodic intervals at the **nodes of Ranvier**. The cells of Schwann form the myelin sheath for a single neuron.

The oligodendrocytes form the myelin sheath for the neurons of the CNS. A single oligodendrocyte forms myelin sheath for multiple neurons. Majority of the mammalian neurons are myelinated. The neurons in invertebrates are unmyelinated.

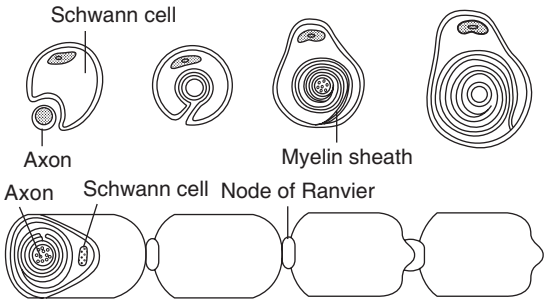


Figure 3.2 Formation of myelin sheath (myelinogenesis).

In the peripheral neuron, the *neurilemma* covers the nerve fiber. It is the basement membrane of the cells of Schwann. During nerve injury, if the neurilemmal tube is intact, the nerve can regenerate. The neurilemma is absent in the neurons of the CNS. Hence, regeneration of the nerve is not possible in the CNS.

The nerve fibers (axons) are covered by a connective tissue layer called the **endoneurium**. Several such fibers form a bundle and are enclosed in a sheath called the **perineurium**. These bundles are termed **fascicles**. Several bundles are enclosed by the outermost layer called the **epineurium**.

CLINICAL NOTES

Multiple Sclerosis

Multiple sclerosis is an autoimmune disease. In this disease, there is patchy destruction of the myelin sheath in the CNS. Loss of the myelin sheath is associated with a delay or block in the conduction of impulses. Antibodies destroy myelin sheath. Damage to myelin sheath results in leakage of K^+ reducing impulse transmission. Multiple sclerosis is more common in females. The disease presents with

- weakness in lower limbs,
- spasticity,
- brisk-to-exaggerated reflexes,
- numbness, and
- urinary incontinence

Other features include

- blurring of vision,

(*Contd.*)

- altered color perception,
- painful eye movements,
- defective field of vision,
- difficulty in speech, and
- difficulty during deglutition

The principles in the management of the disease include

- use of corticosteroids to reduce inflammation
- administration of drugs for immunosuppression

Transport in the Axon

The axon does not have the ability to synthesize proteins. Hence, the proteins formed in the cell body are transported through the axon by the *axoplasmic flow*. If the movement is from the cell body to the axon terminal, it is called the **orthograde transport**.

The substances and organelles to be moved are connected to the microtubules present in the cell body and the axon with the help of proteins. The microtubules serve as the pathway through which the substances are transported.

The linking proteins act as motors to move the substance, and ATPase enzymes help in the generation of energy.

The flow of substances in the opposite direction is called the **retrograde transport**. Growth factors and harmful substances, such as tetanus toxin and herpes and polio viruses, reach the CNS by the retrograde transport.

The axonal transport system carries material from the cell body to the axon terminal and back.

Dendrites

The term **dendrite** is derived from a Greek word *dendron* meaning a "tree." These are five to seven short branching processes. They carry information toward the cell body. Dendrites in the cerebral and cerebellar cortices have small projections, termed the **dendritic spines**. The branching dendrites increase the cell's receptive area and thereby increase its capacity to receive signals. Dendrites make synaptic connections with multiple neurons. The impaired function of the nervous system is often associated with defective formation of dendrites.

Neurofibrils and Neurofilaments

These are bundles of microtubules and microfilament. They form the cytoskeleton and provide structural support to the neuron. The neurofibrils form a pathway for the rapid transport of molecules from the far end of the neuron.

FUNCTIONAL ZONES OF A NEURON

Neurons exhibit four functional zones:

1. Receptor or dendritic zone
2. Initial segment
3. Axonal process
4. Nerve endings

The receptor zone integrates multiple potentials generated at synaptic connections and conveys them to the cell body. The cell body is located in this zone.

The initial segment is the site of generation of propagated action potential.

The axonal process conducts the action potential generated at the initial segment.

The action potential releases the neurotransmitter stored in vesicles in nerve endings.

CLASSIFICATION

1. **Based on the number of processes** (**Fig. 3.3**)
   - *Unipolar neuron:* The neuron has a single pole. The process arises from this pole. The unipolar neurons originate in the embryo as bipolar neurons. Later, the processes fuse into one for a short distance beyond the cell body. Then, they separate into the axon and the dendrite. The sensory neurons are unipolar.
   - *Bipolar neuron:* The neuron has two poles. The axon and dendrite arise from these poles. The bipolar neurons are present in the retina of the eye.

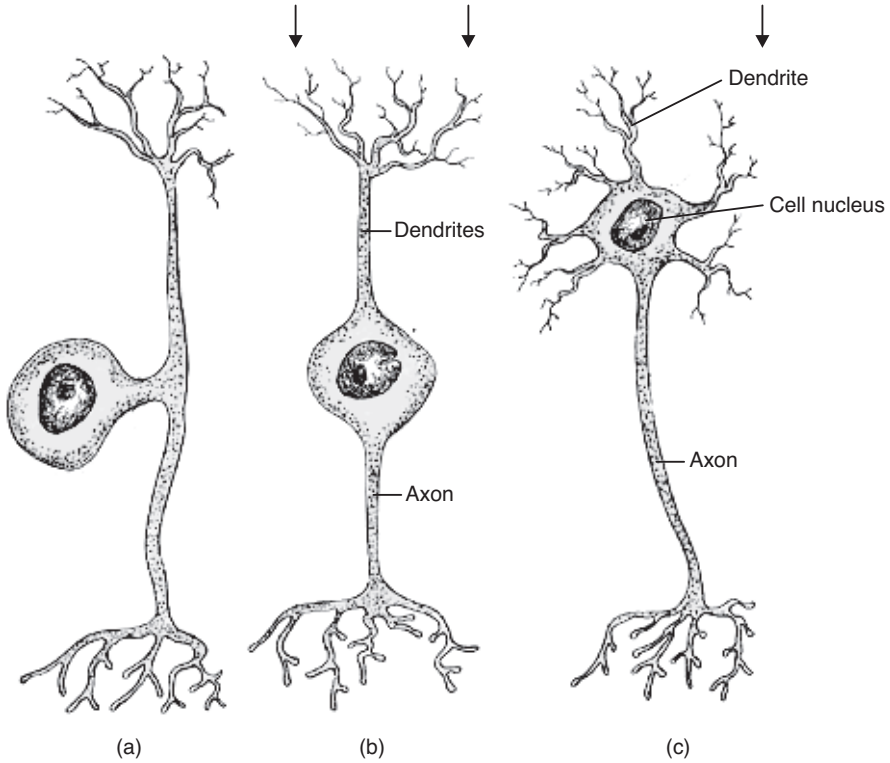


Figure 3.3 Types of nerve cells: (a) unipolar, (b) bipolar, and (c) multipolar. (*Source*: DR Singh, Essentials of Anatomy for Dentistry Students. Wolters Kluwer India, New Delhi; 2010.)

- *Multipolar neuron:* The neuron has multiple poles. The neuronal processes arise from these poles.

2. **Based on myelination**
   - *Myelinated nerve fiber:* The nerve fiber is covered by a myelin sheath. It insulates the axon and facilitates faster transmission of impulse by saltatory conduction. The myelin sheath is formed by the cells of Schwann for the peripheral neuron and oligodendrocytes for the neurons of the central nervous system.
   - *Nonmyelinated nerve fiber:* The nerve fiber lacks the covering of a myelin sheath. The velocity of impulse transmission is slower when compared to the myelinated nerve fibers of the same diameter.
3. **Based on functions**
   - *Sensory or afferent neurons:* They carry information from the periphery to the CNS. The sensory information to the brain and spinal cord is carried through cranial and spinal nerves.
   - *Motor or efferent neurons:* They carry motor impulses from the CNS to the effector organs. The information is carried from the brain toward the spinal cord or out of the brain and spinal cord to muscles and glands. Stimulation of the effector system by motor neuron results in muscle contraction or secretion from the gland.
   - *Interneurons:* They connect neurons within the CNS.
4. **Depending on the neurotransmitter secreted**
   - *Adrenergic neurons:* These neurons secrete adrenaline (epinephrine), norepinephrine, or dopamine at the nerve terminal. They are found in the neurons of the sympathetic nervous system.

Table 3.1 Erlanger and Gasser's Classification

Type	Function	Diameter (μm)	Conduction Velocity (m/s)
Aα	Proprioception	12–20	70–120
Aβ	Touch, pressure	5–12	30–70
Aγ	Motor to muscle spindle	3–6	15–30
Aδ	Pain, temperature	2–5	12–30
B	Preganglionic autonomic	<3	3–15
C	Dorsal root: pain, temperature	0.4–1.2	0.5–2.0
C	Sympathetic postganglionic	0.3–1.3	0.7–2.3

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

- *Cholinergic neurons:* These neurons secrete acetylcholine at the nerve terminal. They are present in the neuromuscular junction.
- *Dopaminergic neurons:* These are dopamine-secreting neurons present in the substantia nigra of the basal ganglia.
- *GABAergic neurons:* GABA is an inhibitory neurotransmitter secreted by these neurons. They are distributed in different parts of the brain.
- *Serotonergic neurons:* These neurons secrete serotonin which acts as either an excitatory or an inhibitory transmitter.

5. **Based on diameter and conduction velocity** (**Table 3.1**)

ELECTRICAL PROPERTIES OF A NERVE

The nerve is an excitable tissue. It is capable of generating rapidly changing electrical impulses at its membrane.

The electrical activity occurring in a nerve is better understood if the basic principles of electricity of nerve conduction are studied.

PRINCIPLES OF ELECTRICITY

The body fluid is distributed in the intracellular and extracellular compartments. The extracellular fluid (ECF) has greater concentration of sodium and chloride ions. The intracellular fluid has greater concentration of potassium ions and nondiffusible protein molecules. The distribution of these charged particles on either side of the cell membrane plays a major role in cell integration and communication.

Like charges repel each other and unlike charges attract each other. Opposite charges move toward each other when they are not separated.

Electrical charges of opposite signs separated by a membrane generate **electrical potential**. The difference in the number of charges across the membrane constitutes the **potential difference**. It is measured in living tissues as millivolts (mV).

The movement of electrical charges is called the **electrical current**. The electrical forces between the charges make them flow producing a current. The current depends on the difference in potential between the charged areas and the nature of the membrane through which they pass.

The opposition experienced by the electrical charge for its movement is known as **resistance**.

Ohm's law explains the relationship between flow of current and difference in voltage and resistance. Current flowing between two points is directly proportional to the voltage difference.

Current flow is inversely proportional to the resistance offered by the conductor. It decreases when the resistance is high and vice versa.

The materials having high resistance to the flow of current are termed **insulators** and those with low resistance are called **conductors**.

Lipids contain few charged particles. Hence, they cannot carry current. The lipid layers of the plasma membrane have a high electrical resistance.

Water containing dissolved ions is a good conductor of electricity. The body fluid is distributed in the intracellular and extracellular compartments. The extracellular fluid (ECF) has a greater concentration of sodium and chloride ions. The intracellular fluid has a greater concentration of potassium ions and nondiffusible protein molecules. The distribution of these charged particles on either side of the cell membrane plays a major role in cell integration and communication.

Ion Channels

The ion channels present in the membrane of excitable tissues are of different types.

They are as follows:

- **Ligand-gated channels** open in response to binding of signaling molecules called **ligands**. Binding of the ligand to the receptor brings about a conformational (structural) change in the channel permitting the passage of a specific ion.
- **Mechanically gated channels** open in response to stretching of the membrane (physical deformation).
- **Voltage-gated channels** open in response to application of potential difference across the membrane. Voltage-gated channels are present for sodium and calcium ions.
- **Nongated or leaky channels** are present in the nerve membrane. They permit the passage of small quantities of sodium, potassium, and chloride ions even at rest.

Nerve cells have an excitable membrane. They respond to different types of stimuli such as electrical, mechanical, chemical, and thermal.

Electrical stimulus is the preferred type as it can be measured precisely, regulated effectively, and delivered accurately at the designated location.

Electrochemical disturbance is created at the site of stimulation of excitable membrane. It can be as follows:

- Nonpropagated potential termed differently in different locations as **generator**, **synaptic**, **receptor**, or **electrotonic potential**.
- Propagated potentials are **action potentials**. Propagated potential is also termed **nerve impulse**. Action potentials are a mode of communication in the nervous system.

The time and voltage related to action potentials are measured as **milliseconds (ms)** and **millivolts (mV)** since the change is of small magnitude.

The passage of electricity through a conductor is passive and subject to loss during transmission. However, the transmission of impulse in a nerve is active and self-propagated.

Hence, there is no loss during transmission; the impulse moves at constant amplitude and velocity.

ELECTRICAL ACTIVITY IN A NEURON

Resting Membrane Potential

Resting membrane potential (RMP) is the potential difference existing across the cell membrane at rest. It keeps the cell in an excitable state. The interior of the cell is negatively charged in relation to the exterior. Sodium and potassium ions play an important role in the generation of RMP.

In a motor nerve, the RMP is about –70 mV. It means that the inside of the neuron is negative in relation to the outside, which is positive.

The potential difference across the membrane has a magnitude of 70 mV. In the muscle, RMP ranges from –80 to –90 mV.

The genesis and maintenance of RMP depend on the following:

- Unequal distribution of differently charged ions on either side of the excitable cell membrane
- Difference in permeability of membrane to few of the ions present on either side of the membrane

The movement of ions across the membrane is through specific and gated ion channels. RMP is a state of equilibrium between the two opposing forces, namely concentration and electrical gradients.

Molecular Basis for Resting Membrane Potential

- The concentration of sodium ions is greater outside the cell (150 mmol/L outside and 15 mmol/L inside the cell). The concentration of potassium ions is greater inside the cell (150 mmol/L inside and 5.5 mmol/L outside the cell). There is a natural concentration gradient for sodium ions directed inward and for potassium ions outward.
- In the resting state, the permeability of membrane is greater for potassium ions. (The plasma membrane has a 50–75 times greater number of potassium channels as compared to sodium channels.) Hence, potassium ions move out of the cell. This takes away the positive charges from within the cell.
- Sodium–potassium ATPase pump. It pumps three sodium ions to the exterior in exchange for two potassium ions pumped in. This differential pumping makes the inside of the cell more negative. A pump that moves net charges across the membrane and helps in the genesis of membrane potential is called the **electrogenic pump**.
- Large, nondiffusible, negatively charged protein molecules present within the cell add negativity to the inside of the cell.

Membrane Permeability

The ion channels present in the membrane are highly selective for a particular ion. This is due to the difference in size and shape of hydrated ions and channels matching the characters of ions. Permeability is influenced by the size of hydrated ions. Hydrated sodium ions are larger than hydrated potassium ions. Hence, the membrane is more permeable to potassium compared to sodium ions. The channels lined with positive or negative charge repel the ions of the same charge.

Graded Potential

A sudden change in the environment around the excitable tissue alters the permeability of the membrane to different ions. This changes membrane potential over a small area of the membrane. The response dies down exponentially at the site of stimulation. The magnitude of response depends on the intensity of stimulation. This type of local potential without the period of latency is termed the **graded potential (Fig. 3.4; Table 3.2**).

The graded potentials in different regions are named as the receptor potential, pacemaker potential, and synaptic potential. The graded

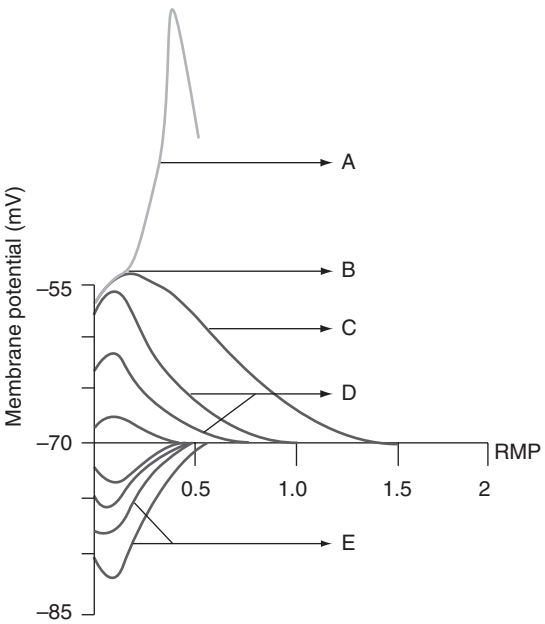


Figure 3.4 Electrotonic potential and local response. (A) Action potential. (B) Firing level. (C, D, and E) Graded local response. *RMP*, resting membrane potential. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Table 3.2 Differences Between Graded Potential and Action Potential

Graded Potential	Action Potential
Amplitude of response varies with the strength of the stimulus	Response shows an all-or-none pattern
It does not have a threshold	It has a threshold (15 mV less than the resting level)
The response can be summated	The response cannot be summated
There is no latent and refractory period	It has a latent and refractory period
It is a nonpropagated response	It is a propagated response
It can be depolarization or hyperpolarization	It is normally depolarization
Duration depends on the character of the stimulus	Duration is fixed for a particular cell type
It depends on ligand-gated channels	It depends on voltage-gated channels

potential and action potential are the important ways by which the nerve cells process and transmit the information. The graded potentials transmit the signals for a short distance, whereas the action potentials transmit them over long distances.

ACTION POTENTIAL

The action potential is an electrochemical change (**Table 3.2**) occurring in the excitable tissue in response to the threshold stimulus (**Fig. 3.5**). It has phases of depolarization and repolarization.

The action potentials are large, rapid alterations in the membrane potential showing a fluctuation of about 100 mV (from –70 mV to +30 mV).

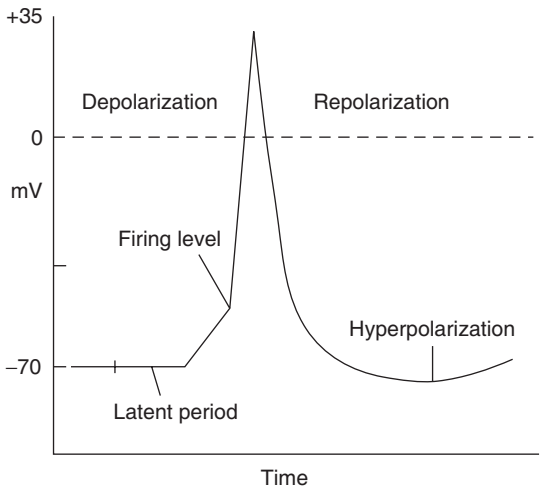


Figure 3.5 Action potential in a neuron.

The nerve, muscle, endocrine, immune, and reproductive cells have the plasma membrane capable of producing the action potential.

Ionic Basis for Action Potential

- Stimulation of the motor nerve with minimal stimulus increases permeability of the membrane to the sodium ions.
- The sodium ions start entering into the cell.
- The inside of the cell tends to move toward the positive side. (RMP which is –70 mV becomes less negative due to the entry of sodium ions.)
- At around –55 mV (firing level), the permeability of the membrane increases to sodium ions significantly resulting in its explosive entry.
- Sudden influx of sodium makes the inside of the cell relatively positive. There is reversal of polarity. This phase is termed **depolarization**.
- During depolarization, the potential difference across the membrane becomes zero. This is termed the **isoelectric potential**.
- Subsequently, it becomes positive inside.
- On reaching a maximum potential of +35 mV (spike potential), the sodium channels are inactivated and the potassium channels open.
- The potassium ions move out of the cell.

- There is restoration of potential. This phase is termed **repolarization**.
- The potassium ions continue to move out of the cell in spite of reaching the resting level. The inside of the cell becomes relatively more negative. This phase is termed **hyperpolarization**. Hyperpolarization reduces the excitability of the cell.

Activation and Inactivation of Ion Channels (Fig. 3.6)

Sodium Channels

A voltage-gated sodium channel has two gates.

The gate outside of the channel is **activation gate** and the gate near the inside is **inactivation gate**.

During the resting state, the activation gate is closed and hence sodium ions will not enter the cell. As the resting potential becomes less negative, the activation gate opens following conformational change.

The permeability of membrane increases significantly causing explosive entry of sodium ions resulting in depolarization.

Depolarization causes conformational change in the inactivation gate bringing it to a closed state.

The inactivation gate does not open till the membrane potential is restored to the resting state.

Inactivation of the sodium channel accounts for the absolute refractory period.

INFLUENCE OF IONS ON RESTING MEMBRANE POTENTIAL AND ACTION POTENTIAL

Sodium Ions

A decrease in the sodium ion concentration outside the cell reduces the size of the action potential. However, there is little influence on the RMP.

Potassium Ions

An increase in the potassium ion concentration outside the cell decreases the RMP moving it close to the firing level.

Calcium Ions

Reduction in the extracellular calcium ion concentration increases the excitability of the cell.

Low levels of ionized calcium in the extracellular fluid increase the permeability of neuronal membranes to sodium ion, causing a progressive depolarization. These changes increase the possibility of formation of action potentials spontaneously or with minimal stimulation.

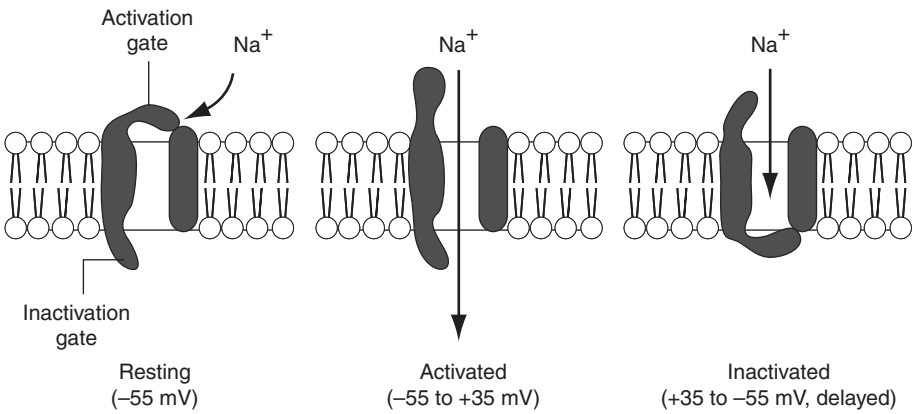


Figure 3.6 Activation and inactivation of ion channels. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

An increase in the calcium ion concentration decreases the excitability and stabilizes the membrane of the cell.

Local Response

When a subminimal stimulus is given to an excitable tissue, there is a depolarizing change. However, the number of ions entering the cell is unable to depolarize the cell up to the firing level. Hence, the response dies down exponentially at the site of stimulation. This is a **local response**.

The local response recorded at the anode is termed the **anelectrotonic potential**. The response recorded at the cathode is termed the **catelectrotonic potential**.

TYPES OF ACTION POTENTIAL

The threshold stimulus results in a fully formed action potential. Any increase in the strength of the stimulus does not change the magnitude of the action potential. This is the all-or-none character of action potential.

There are different types of action potentials which are as follows:

- **Monophasic action potential**: The action potential is recorded by placing one electrode within and the other electrode outside the cell. The recording is in one direction. This is called the monophasic action potential.
- **Biphasic action potential**: The biphasic action potential is recorded when both the recording electrodes are placed over the surface of the cell (**Fig. 3.7**).

When the nerve is stimulated, the electrode nearest to the point of stimulation becomes positive. An upward deflection is recorded. The impulse gets propagated and reaches a point in between the two recording electrodes. At this point, no potential is recorded by both the electrodes. Hence, the recording returns to zero potential, or *isoelectric potential.*

Later, the impulse moves toward the second electrode. The first electrode becomes positive with respect to the second electrode. The recording shows a negative deflection.

Thus, a biphasic action potential shows an upward deflection followed by an isoelectric line and then a downward deflection. The duration of the isoelectric potential depends on the speed of conduction.

The ionic basis for monophasic and biphasic action potentials is the same.

- **Compound action potential**: The action potential recorded from a group of nerve fibers results in compound action potential (**Fig. 3.8**).

The mixed nerve is made up of groups of fibers with different conduction velocities. When all the fibers are stimulated simultaneously, impulses reach the recording electrode at different times. Hence, the recording shows multiple peaks.

The number and size of peaks vary with the type of fiber stimulated in the nerve. The separation of peaks depends upon the conduction velocity and the distance of recording electrode from the point of stimulation.

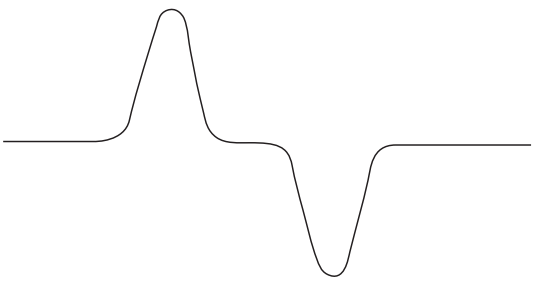


Figure 3.7 Biphasic action potential.

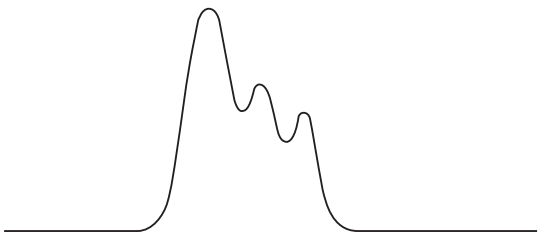


Figure 3.8 Compound action potential.

CLINICAL NOTES

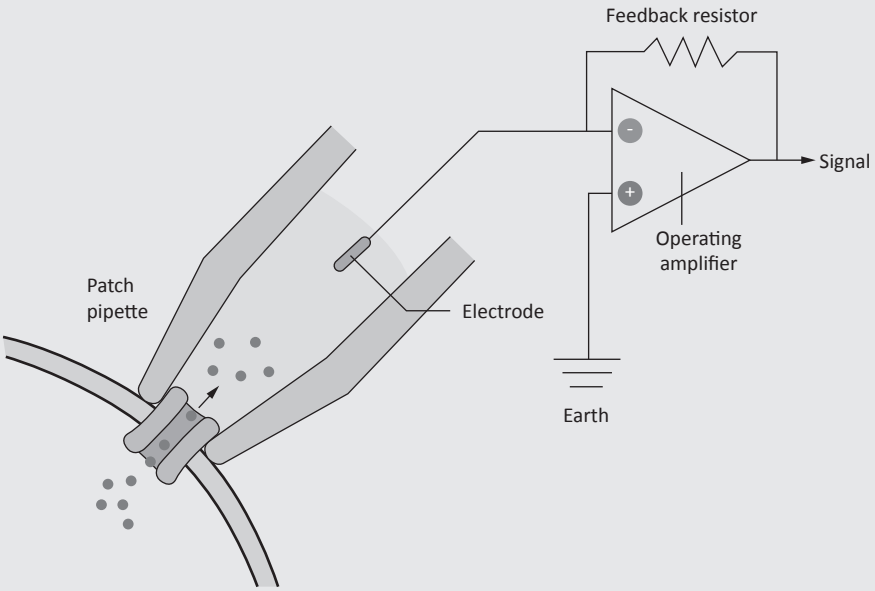
The movement of ions across the membrane during electrical activity is determined by patch-clamp and voltage-clamp techniques.

- **Patch-clamp technique**: This technique allows determination of the activity of a single membrane channel.

  A specially designed micropipette is placed over the membrane and a tight seal of the membrane is obtained.

  A small patch of the membrane covering the tip of the pipette is isolated. This patch of the membrane contains one to several ion channels.

  The membrane is later perfused with fluids with different ionic concentrations on the outer or inner surface. This technique allows recording of the current flow through an individual channel. It also provides facility to study the behavior of the ion channels not influenced by other regions of the cell.



- **Voltage-clamp technique**: This technique uses a feedback apparatus to deliver current across the membrane in order to clamp the membrane potential at a selected voltage. The current passed to clamp the voltage is continuously monitored.

  There is no flow of current when the voltage is clamped at resting potential. When the potential is changed toward the positive side, an action potential is produced.

  There is an initial inward flow of current followed by prolonged outward flow. The voltage-clamp technique helps to study the changes in the ionic conductance underlying an action potential.

NERVE IMPULSE

The nerve is in a polarized condition at rest. Positive charges are present on the outer surface of the cell membrane and negative charges are present along the inner side of the membrane. The action potential (electrochemical change) is generated at the site of stimulation. It travels along the nerve fiber (**Fig. 3.9**). The traveling action potential constitutes an impulse. Thus, an impulse is defined as a self-propagating physicochemical change.

TRANSMISSION

- Stimulation of the motor nerve results in depolarization at the site of stimulation.

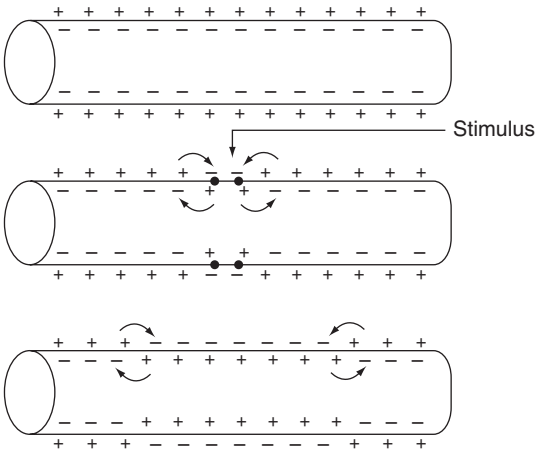


Figure 3.9 Propagation of action potential.

- The inside of the cell becomes positive in relation to the exterior.
- Positive charges move forward to the segment ahead within the cell.
- Positive charges are drawn backward from the segment ahead outside the cell.
- There is a drop in the positive charges outside the cell. It is termed the **current sink**.
- This results in depolarization of the next segment or the next node of Ranvier.
- Thus, the spread of depolarization wave results in transmission of impulse.

Saltatory Conduction

In a myelinated nerve fiber, the myelin sheath is interrupted at periodic intervals called the **nodes of Ranvier**. Voltage-gated sodium channels are found in large numbers in the initial segment of myelinated neuron and at the nodes of Ranvier. In myelinated neurons, potassium channels are present close to sodium channels.

The electrical current flows through extracellular fluid outside the myelin sheath and through axoplasm within the cell from one node to the next node of Ranvier. During the impulse transmission, depolarization jumps from one node to the next node. This type of conduction is called saltatory conduction (from the Latin word *saltare*, meaning to hop or jump) (**Fig. 3.10**).

Saltatory conduction has the following benefits:

- As the process of electrical activation (depolarization) occurs only at nodes of

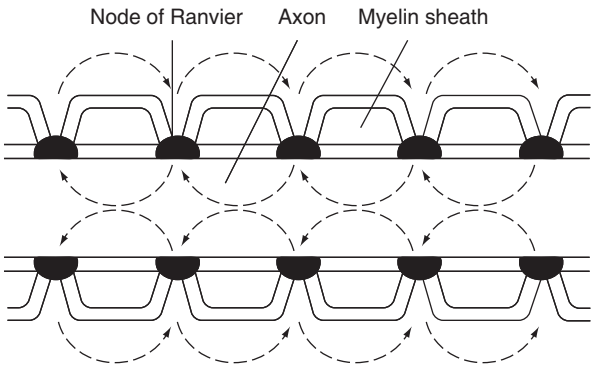


Figure 3.10 Saltatory conduction.

Ranvier, there is an increase in velocity of impulse transmission.

- Saltatory conduction helps in conservation of energy during impulse transmission. Reduced expenditure of energy is due to decreased ionic movement in and out of the cell. Depolarization occurring only at the nodes causes movement of ions which is 100 times less than what is needed otherwise.

Orthodromic Transmission

Orthodromic transmission is the conduction of impulse in a normal direction (from the cell body toward the nerve terminal).

Antidromic Transmission

Transmission of impulse in the opposite direction is antidromic transmission.

VELOCITY OF CONDUCTION

The factors influencing conduction velocity are as follows:

1. **Diameter of the nerve fiber**: An increase in the diameter increases the velocity of conduction.

   An increase in the diameter decreases the resistance to the flow of ions. The larger fibers have more space for the movement of ions to carry the current.

   The extracellular resistance does not influence the ionic movement because of a large volume of ECF.

2. **Myelination**: The velocity of conduction in the myelinated fibers is 50 times greater than that in the unmyelinated fibers. Myelination restricts the regeneration of action potential to the nodes of Ranvier. Conduction velocity increases as electrochemical changes take place at nodes of Ranvier. Multiple layers in the myelin sheath increase the effective membrane resistance. Less current is lost through the membrane during the transmission of signals through the axon. Hence, the effort in regenerating the signal at each node of Ranvier is also reduced.

   The benefits of myelination are
   - higher conduction velocity for rapid transmission of impulse,
   - smaller diameter of nerve fiber to conserve space, and
   - higher metabolic efficiency because of reduced movement of ions and expenditure of energy.

3. **Temperature**: Increased temperature increases the conduction velocity.

   The conduction velocity decreases by about 3% for a fall of 1°C.

   The conduction block occurs at 7°C in large myelinated nerve fibers and at 3°C in unmyelinated fibers.

4. **Pressure**: The application of pressure resulting in compression of nerve reduces the conduction velocity of impulse.

   The compression and anoxia selectively block the large myelinated fibers.

   Thus, painful stimuli transmitted by small unmyelinated fibers are still appreciated when the other modes of sensation are lost.

5. **Local anesthetics**: The local anesthetics reduce the rate of conduction of nerve impulse or may even block its transmission. They prevent the generation of action potential by inhibiting the voltage-dependent opening of sodium channels. Local anesthetics are used to perform surgical procedures. They reduce the perception of pain by the patient.

6. **pH**: The decrease of pH reduces the velocity of the nerve impulse.

7. **Degeneration and regeneration**: A change in the conduction velocity can occur as a result of a disease or accident. The neural degeneration followed by regeneration leads to the formation of thinner fiber with a lower conduction velocity.

   Diseases such as multiple sclerosis can reduce the thickness of the nerve fiber and localized loss of the myelin sheath.

   During the process of remyelination, the distance between the nodes of Ranvier is reduced. This reduces the conduction velocity.

PROPERTIES OF A NERVE FIBER

1. **Resting membrane potential**: The nerve fiber shows a potential difference across its membrane at rest. This is resting membrane potential. In a motor nerve, it is about –70 mV.
2. **Action potential**: It is an electrochemical change occurring in the excitable tissue in response to an adequate (threshold) stimulus.

   When a threshold stimulus is given, the membrane potential reaches the firing level, resulting in an action potential.

   However, a subthreshold stimulus fails to take the membrane potential up to the firing level. This results in a local response. In a given nerve, the size (amplitude) of the action potential remains constant in spite of a variation in the intensity of the stimulus.

   The difference in the intensity of the stimulus is appreciated by a varying number of action potentials transmitted per unit time and not by its magnitude.
3. **Latent period**: It is the time interval between the application of a stimulus and the beginning of a response. It is the time required for the occurrence of electrochemical changes in the nerve to form an action potential (in response to a stimulus).
4. **Excitability**: It is the responding property of the tissue to a stimulus. It is also termed **irritability**.

   A threshold stimulus can excite the tissue. It causes a drop in the membrane potential to take it to the critical level and produces an action potential.

   A subthreshold stimulus produces a local response.

   The nerve fibers with larger diameter are more excitable and fibers with smaller diameter are less excitable.
5. **Conductivity**: The action potential generated at the point of stimulation is conducted along the nerve fiber.

   The conduction velocity in a nerve fiber depends on its myelination and diameter. In a myelinated fiber, the impulse is transmitted by the saltatory conduction. Hence, the conduction velocity is greater in a myelinated nerve fiber.

   The conductivity of nerve impulse is influenced by anoxia, pressure, and local anesthetics.
6. **All-or-none law**: When a nerve is stimulated with a threshold stimulus (or above the threshold strength), it responds to its maximum by producing an action potential.

   However, if the stimulus is subthreshold, there is no recordable response. Hence, the action potential fails to occur.
7. **Refractory period (Fig. 3.11)**: The latent period is divided into absolute refractory period and relative refractory period.
   - *Absolute refractory period:* It is the period during which a second stimulus of any magnitude fails to produce a response.

     The cell is refractory because a large number of sodium channels are voltage inactivated. Hence, these channels cannot be reopened until the membrane is repolarized.
   - *Relative refractory period:* It is the phase during which a second stimulus of greater intensity produces a response. During this phase, some of the sodium channels remain in an inactive state. Hence, a stronger stimulus is required to open a critical number of sodium channels to produce a response.

     In a motor nerve, the entire phase of depolarization and the first one-third of repolarization are absolutely refractory. The last two-third of repolarization is relatively refractory.
8. **Accommodation**: When a low-intensity stimulus is given to an excitable tissue, it responds initially. As the stimulus is continued for a prolonged duration, the magnitude of response gradually declines

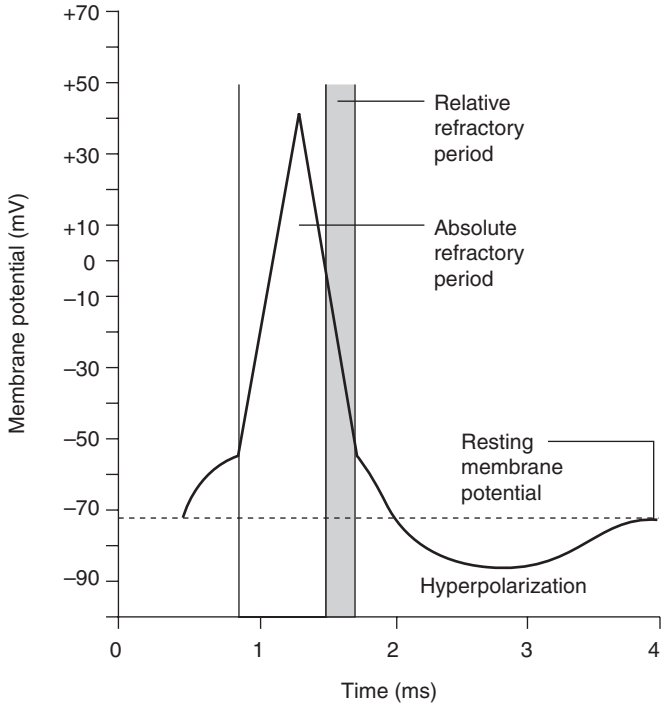


Figure 3.11 Refractory period. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

and may finally stop. This is termed accommodation.

Accommodation is due to slower opening and delayed closing of the potassium channels.

If the process of depolarization is rapid, the opening of the sodium channel overrides the repolarizing forces and an action potential is produced.

However, when the depolarization is produced slowly, the opening of the potassium channels balances gradual opening of the sodium channels. Hence, the action potential is not produced.

9. **Infatigability**: The metabolic activity is very low in a nerve fiber during the conduction of an impulse. Hence, the nerve is resistant to being fatigued.

NERVE INJURY

The neurons are liable to injury due to their cutting or crushing. The damage to the neurons is variable and it depends on the type and extent of injury. The neurons do not multiply during life. Fortunately, an injury to a peripheral nerve fiber (axon) does not destroy the neuron. The damaged neuron can undergo repair and become functional.

Nerve fibers can be damaged due to a number of causes. The common causes for nerve injury are as follows:

- **Trauma** resulting in crushing or transection of a nerve fiber
- Compression or stretching of a nerve fiber
- **Ischemia**—reduced blood supply damaging the nerve
- **Metabolic disorders** like diabetes mellitus
- **Exposure to toxic substances** like mercury, lead, and arsenic
- Use of anticancer drugs
- Vitamin deficiency
- Autoimmune diseases

The common manifestations of nerve injury are as follows:

- Sensory changes
  - Tingling sensation
  - Numbness/loss of sensation
  - Pins and needle feeling/burning sensation
  - Sharp and intense pain
  - Complete loss of sensation
- Motor changes
  - Muscle weakness/paralysis
  - Muscle atrophy
  - Poor bladder and bowel control

TYPES OF NERVE INJURY (Fig. 3.12)

Seddon in 1941 introduced classification for nerve injury. There are three types of injuries depending upon the nerve components affected, the loss of functionality, and the ability to recover spontaneously.

1. Neuropraxia
2. Axonotmesis
3. Neurotmesis

Neuropraxia (First-Degree Injury)

In this type of injury, there is only pressure on the axon causing local anoxia. Recovery is possible within a few hours to a few days. The functions are lost temporarily. However, the structures remain intact.

Axonotmesis (Second-Degree Injury)

In this injury, the axon is divided but the endoneural sheath is continuous. This is due to prolonged and severe pressure on a part of the neuron. It is caused due to a crushing injury. Regeneration is possible in this type of injury. Recovery from the injury is complete.

Neurotmesis (Third-, Fourth-, and Fifth-Degree Injury)

In this injury, the axon and endoneural tube are divided. Regeneration is more complex. It depends on the alignment of the endoneural tube. If the alignment is restored, regeneration is possible.

EFFECT OF INJURY TO THE NEURON

The manifestation of injury depends on the site of injury. The injury close to the cell body results in destruction of the neuron. If the injury occurs to the axon away from the cell body, it results in degeneration followed by regeneration.

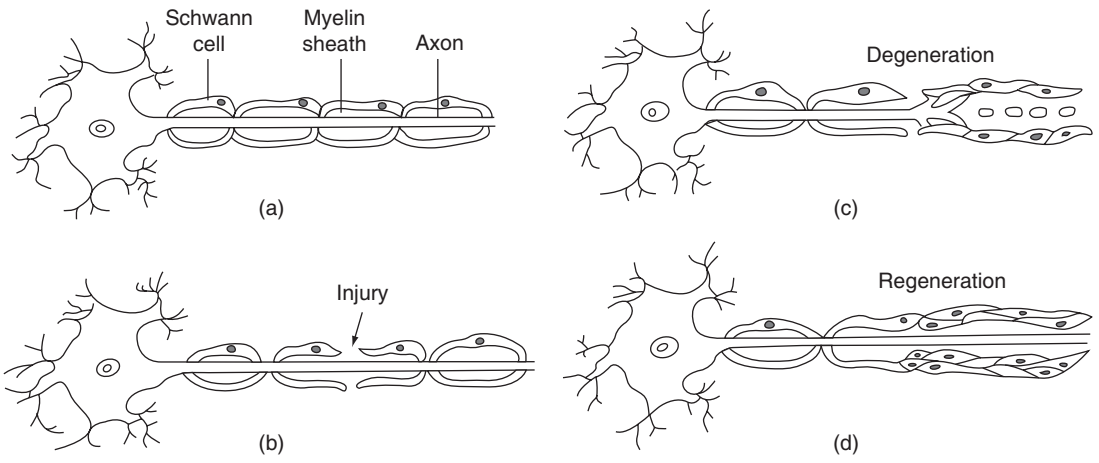


Figure 3.12 Changes after nerve injury.

Wallerian Degeneration

When a nerve fiber is injured, a part of the nerve fiber distal to the site of injury undergoes changes. This process is known as Wallerian degeneration. It is named after a British Physiologist, Augustus Volney Waller, who first described the following changes:

1. **Changes in nerve fiber distal to injury**
   - The peripheral part remains alive, conducting impulses up to 3 days from the day of injury.
   - The axis cylinder swells and breaks down into small rodlets.
   - The myelin sheath begins to disintegrate and is replaced by fatty droplets. This can be noted by about 8th day after injury and completed by 32nd day.
   - Sensing the injury to the axon, Schwann cells reduce the synthesis of lipid for the formation of myelin sheath.
   - Schwann cells attract phagocytes to the site of injury by releasing cytokines and chemokines.
   - The phagocytes invade the peripheral part and engulf the broken-down processes of the axis cylinder and fat droplets.
   - The myelin sheath is cleared faster in the peripheral nervous system due to increased permeability of blood vessels around the damaged nerve.
   - The hollow tube of the neurilemma with phagocytes is known as the **ghost tube**.
   - If the neurilemma remains intact, the cells of Schwann multiply rapidly. These cells can bridge a gap of about 3 mm.
   - If the gap at the site of injury is greater than 3 mm, repair occurs by the formation of scar tissue.
2. **Changes proximal to injury**
   - The part of axon between the site of injury and the cell body constitutes the proximal part.
   - Similar degenerative changes are seen in the proximal stump up to the nearest node of Ranvier. The changes are called **retrograde degeneration**.
   - The cell body undergoes swelling with degeneration of Nissl granules.

     The neurofibrils disappear associated with a reduction in the number of Golgi apparatus.

     The nucleus is pushed to the periphery. This is called **chromatolysis**.

REGENERATION OF A DAMAGED NERVE FIBER

If the cut end of the neurilemma is brought close to each other (less than 3 mm), the axis cylinder grows into the neurilemmal tube. Alignment of the neurilemmal tube is a critical factor for regeneration of the neuron.

The rate of growth is about 1 mm/day.

Schwann cells are stimulated by macrophages by producing interleukin-1.

Schwann cells and fibroblasts increase the production of **nerve growth factor** and mRNA.

The newly formed Schwann cells provide structural framework for the regeneration of an axon.

The cut end of the axis cylinder gives out fine branches called **regenerative sprouting**.

One of these branches reaches the cut end of the original tube and starts growing rapidly. The other branches disappear.

The newly formed fibers are thin and unmyelinated. Later, the cells of Schwann and the myelin sheath are formed. The regeneration and growth of the nerve fiber through the site of injury is a very slow process. The presence of a scar tissue retards the growth of fibers. It results in the formation of a **neuroma**, which is the swollen central portion of the nerve fiber.

During the process of regeneration, the cell regains its normal size. The Nissl granules reappear.

In reconstruction surgery (surgery done to repair the cut limb or fingers during an accident), care is taken to bring the cut ends of the neurilemmal tube as close as possible and to establish a good alignment.

NEUROTROPHINS

Neurotrophins are proteins required for the growth and survival of neurons. They are produced by muscle structures innervated by neurons and astrocytes. Neurotrophins reach the cell body by a retrograde transport and facilitate the production of proteins needed for the growth and survival of neurons. Neurotrophins produced in the cell body are transported to the nerve terminal, which maintains the integrity of the postsynaptic neuron.

Various neurotrophins are as follows:

- Nerve growth factor (NGF)
- Brain-derived neurotrophic factor (BDNF)
- Neurotrophin 3 (NT-3)
- Neurotrophin 4/5 (NT-4/5)

Nerve Growth Factor

The nerve growth factor (NGF) is a protein necessary for the growth and maintenance of the sympathetic neurons. NGFs are picked up by neurons and transported to the cell body in a retrograde manner. The NGF present in the brain is responsible for the growth and maintenance of the cholinergic fibers. Other factors affecting the neuronal growth are

- ciliary neurotrophic factor (CNTF),
- glial cell line–derived neurotrophic factor (GDNF),
- leukemia inhibitory factor (LIF),
- insulin-like growth factor I (IGF-I),
- transforming growth factor (TGF),
- fibroblast growth factor (FGF), and
- platelet-derived growth factor (PDGF).

Degeneration in the Central Nervous System

- The damage to neurons in the CNS results in its degeneration similar to that in the PNS. However, regeneration does not occur due to the absence of neurilemma. The site of injury is covered by neuroglia with the formation of the glial scar. However, there are efforts by researchers to devise methods to regenerate damaged nerve fibers in the central nervous system.

CLINICAL NOTES

Stem Cell Transplantation

- Efforts are made to implant stem cells to develop new neurons in place of damaged ones and replace the neurotransmitters and neurotrophic factors destroyed by the disease process. Stem cell transplantation has been tried in the treatment of degenerative diseases such as Parkinsonism with limited success.

NEUROGLIA

Neuroglia (**Fig. 3.13**) are supporting cells present in the CNS. Their number is about 10–50 times that of neurons.

TYPES OF NEUROGLIA

The glial cells in the CNS are as follows:

- Microglia
- Oligodendroglia
- Astrocytes
- Ependymal cells

The glial cells in the PNS are as follows:

- Schwann cells
- Satellite cells

Microglia

The microglia resembles tissue macrophages. It consists of small cells with branching protoplasmic processes. The cytoplasm is scanty. The nucleus is oval and deeply stained. The microglia is derived from the mesoderm. It comes from the bone marrow and enters the CNS through blood vessels. The microglia is usually found in the gray matter of the CNS close to the surface and ventricles of the brain.

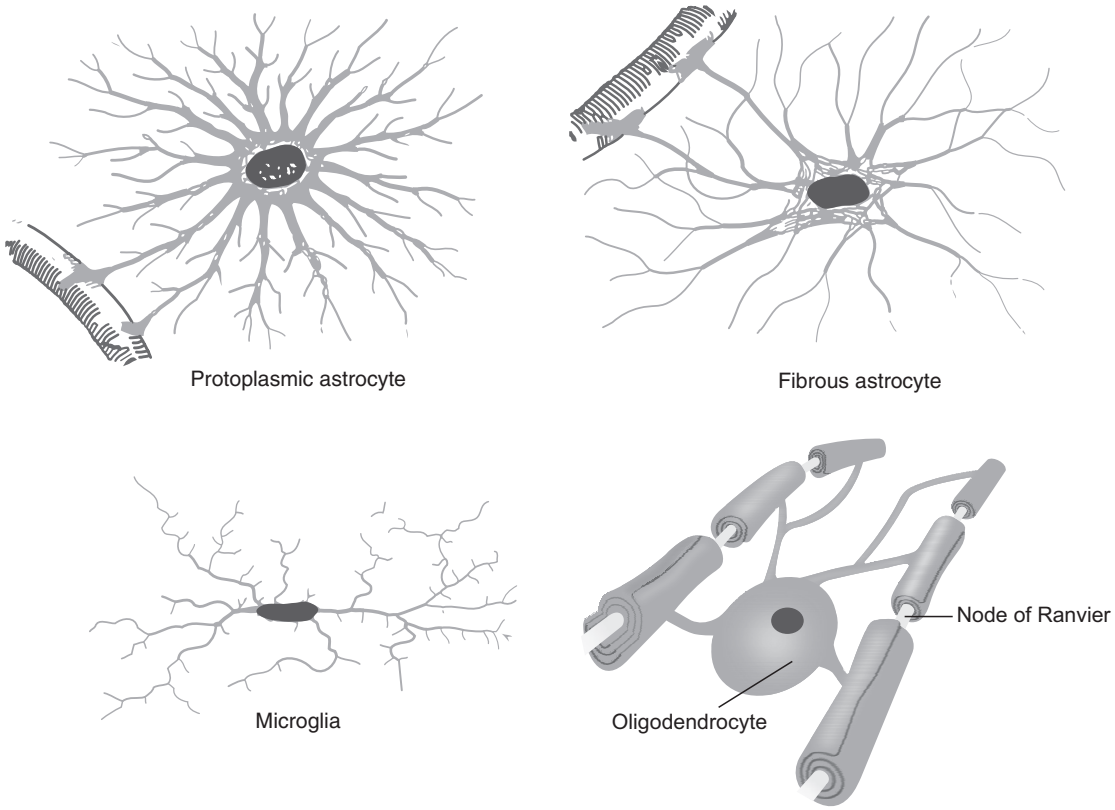


Figure 3.13 Different types of glial cells. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edn. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

Functions

- The microglia acts as scavenger cells.
- They remove debris and dead bacteria from the CNS by the process of phagocytosis.
- The microglia exhibit amoeboid movement and assemble in the region of damage from a considerable distance.
- It produces inflammation by activating the immune system at the site of injury in the brain.
- It removes damaged neurons, and synapses which are nonfunctional.
- It promotes neuronal regrowth by neuronal recruitment and production of anti-inflammatory cytokines.

Oligodendroglia

The oligodendrocytes are present in both the gray and the white matter, but more in the white matter. The cells have a darkly stained spherical nucleus. The cytoplasm is dense with rough endoplasmic reticulum. The dendrites are fewer in number.

Their RMP depends on the extracellular potassium ion concentration.

Functions

- They are helpful in the formation of myelin sheath around the axons. Each oligodendroglia cell forms myelin sheath for multiple neurons. Its function is similar to the cells of Schwann of the PNS.
- They insulate the axon and limit the flow of current around it.
- They facilitate effective transmission of electrical signals by providing insulation.

Astrocytes

Astrocytes are of two types:

1. Fibrous astrocytes
2. Protoplasmic astrocytes

The fibrous astrocytes are found in the white matter. They contain intermediate filaments. The protoplasmic astrocytes are present in the gray matter. They have the granular cytoplasm.

Functions

- They are responsible for the formation of the blood–brain barrier.
- Both the types of astrocytes send processes to blood vessels to form a tight junction.
- The processes also envelop synapses and the surface of nerve cells.
- The RMP of the cell depends on extracellular K^+ concentration.
- They do not produce propagated action potential.
- They maintain a constant level of K^+ ion concentration in the CNS.
- They are helpful in the resynthesis of neurotransmitter glutamate.
- They produce substances that are trophic to the neuron.

Ependymal Cells

Ependymal cells line the ventricles of the brain and the central canal of the spinal cord. Their processes fuse with the processes of the astrocytes to form brain–CSF and blood–CSF barriers.

Functions

- Help in the formation, circulation, regulation, and absorption of CSF

Schwann Cells

Schwann cells are responsible for the formation of a myelin sheath around the axon of the PNS. They are named after the physiologist Theodor Schwann.

Functions

- Help in the transmission of nerve impulse by saltatory conduction
- Assist the development and regeneration of nerve fibers
- Provide trophic support to neurons
- Modulate activity in the neuromuscular junction
- Produce extracellular matrix for nerve
- Secrete neurotrophins required for the maintenance of a healthy neuron

Satellite Cells

Satellite cells are flat cells surrounding neuronal cell bodies in ganglia. They provide structural support and regulate the exchange of material between the cell body of the neuron and the interstitial fluid.

Functions

- Provide structural support and regulate the exchange of substances between the neuronal cell body and the interstitial fluid
- Supply nutrients to the neurons surrounding it
- Provide cushioning support and protection to the cells

NEUROMUSCULAR JUNCTION

The neuromuscular junction is a specialized area where a motor nerve ends on the skeletal muscle fiber (**Fig. 3.14**). Thus, it is a junction between a motor nerve and the muscle fiber.

The junction between the autonomic neurons with smooth and cardiac muscle is not well formed. Therefore, the transmission of impulse across these junctions is diffuse.

The neuromuscular junction consists of the following:

- **Prejunctional membrane (presynaptic membrane)**
- **Synaptic cleft or synaptic gutter**
- **Postjunctional membrane**

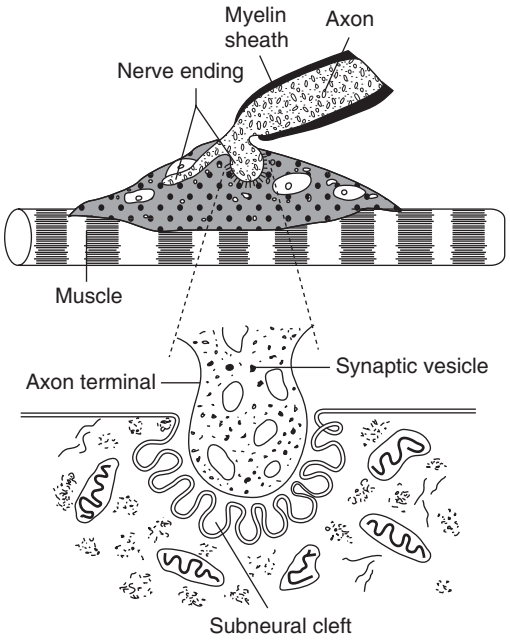


Figure 3.14 Neuromuscular junction.

- **Prejunctional membrane**
  This is the terminal part of the motor nerve with vesicles containing acetylcholine. The motor nerve supplying the muscle breaks into several branches called the **axon telodendria**. These terminals supply muscle fibers. The swollen part of the nerve terminal (terminal button) fits into depression on the muscle membrane.

  The terminal button contains vesicles filled with neurotransmitter and mitochondria.

  The number of mitochondria indicates the metabolic activity. It increases when the terminal is active.
- **Synaptic cleft or gutter**
  It is a potential space between the nerve terminal and the muscle. This cleft produces structural discontinuity. However, there is functional continuity due to the presence of the neurotransmitter, acetylcholine.

  The synaptic cleft contains the enzyme cholinesterase, which breaks down acetylcholine.

  Gap in the synaptic cleft prevents the direct transmission of impulses from the presynaptic to the postsynaptic terminal.
- **Postjunctional membrane (Motor end plate)**
  This is the muscle membrane containing the acetylcholine receptors. It forms the postjunctional membrane. The membrane is thrown into a number of folds termed the **subneural cleft**. The folding of membrane increases the surface area to accommodate more number of acetylcholine receptors.

TRANSMISSION OF IMPULSE ACROSS THE NEUROMUSCULAR JUNCTION

- Impulses arrive at the nerve terminal and increase the permeability of the membrane to calcium ions.
- Calcium ions enter the nerve terminal from the ECF.
- Calcium ions activate the calcium–calmodulin-dependent protein kinase.
- Calcium–calmodulin-dependent protein kinases phosphorylate the anchoring protein, synapsin, and release the vesicles containing acetylcholine.
- Vesicles move to the nerve terminal and release neurotransmitter by either rupture or exocytosis.
- Neurotransmitter crosses the cleft and binds to the nicotinic acetylcholine receptors present on the postjunctional membrane.
- This increases the permeability of the membrane to sodium ions.
- Entry of **sodium** ions results in **end-plate potential** (EPP).
- EPP on reaching the firing level produces an action potential.
- Generated action potential travels over sarcolemma and passes through to sarcoplasmic reticulum to activate the contractile process in the muscle.
- Acetylcholine is destroyed by cholinesterase after completion of its function.
- Rapid destruction of acetylcholine prevents re-excitation of the muscle.

The products of acetylcholine breakdown are taken up by the nerve terminal for the resynthesis of the neurotransmitter.

End-Plate Potential

The end-plate potential (EPP) is a potential generated at the motor end plate during transmission of impulse across the neuromuscular junction. It is a graded, nonpropagated response without a period of latency. The EPP is due to an increase in the permeability of the motor end plate to Na^+ ions.

When the EPP reaches the firing level, it forms an action potential.

Miniature End-Plate Potential

During rest, a small quantity of acetylcholine is released from the presynaptic terminal. This alters the permeability of the motor end plate to produce depolarizing change. This is called the miniature end plate potential (MEPP). It is incapable of producing an action potential.

NEUROMUSCULAR BLOCKING AGENTS

Chemicals and drugs modify the impulse transmission across the neuromuscular junction. They act by various mechanisms by:

- modifying the release of neurotransmitter (NT),
- binding to the receptor, and
- destruction of acetylcholine.

Few of the neuromuscular blocking agents are discussed in the following text.

- **Succinylcholine**: It binds to the acetylcholine receptors in the motor end plate. This produces prolonged depolarization as succinylcholine is destroyed slowly by the cholinesterase.
- **Botulinum toxin**: It is a bacterial toxin produced by the organism *Clostridium botulinum*. It prevents the release of acetylcholine from the presynaptic terminal.
- **D-tubocurare**: It blocks the acetylcholine receptors in the motor end plate by competitive binding and prevents action of acetylcholine.
- **Physostigmine and neostigmine**: They destroy the enzyme cholinesterase and prolong the action of acetylcholine. There is sustained depolarization at the motor end plate.
- **Organophosphorus compounds (insecticides)**: The mechanisms of action of these compounds are similar to the actions of physostigmine. They inhibit the action of acetylcholinesterase. The ion channels in the motor end plate remain open for a longer duration. Their effect is produced by sustained depolarization of the motor end plate.

CLINICAL NOTES

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease caused by the destruction of acetylcholine receptors on the postjunctional membrane. This destruction is due to the formation of circulating antibodies to the nicotinic acetylcholine receptors.

The disease is characterized by a failure in the neuromuscular transmission with repetitive nerve stimulation.

The symptoms are as follows:

- Weakness and fatigue of extraocular muscles
- Difficulty in speech (dysarthria)
- Difficulty in swallowing (dysphagia)
- Respiratory failure in advanced stages due to the weakness of muscles
- A reduction in the amplitude of EPP and MEPP in the intercostal muscles in patients with myasthenia gravis
- Severe weakness in eyelid and respiratory muscles

In this condition, the release of acetylcholine is normal, but the receptors are reduced in numbers. The disease is associated with hyperplasia of the thymus gland.

This condition can be managed by using anticholinesterase or cholinesterase inhibitors such as physostigmine or neostigmine.

The cholinesterase inhibitors delay the destruction of acetylcholine. The neurotransmitter remains in contact with the receptor for a longer time, resulting in the depolarization of the motor end plate. The removal of thymus gland has beneficial effect in some patients.

Lambert–Eaton Syndrome

The Lambert–Eaton syndrome is also a condition affecting the neuromuscular junction. The antibodies damage the calcium channels at the nerve terminal. The release of the neurotransmitter is defective and is associated with muscle weakness. However, the strength of the muscle increases with prolonged contraction due to greater release of the calcium ions.

MUSCLE PHYSIOLOGY

Muscle develops from the mesoderm of the embryonic germ cell. The formation of muscle is termed **myogenesis**.

Muscle is covered by a connective tissue layer made up of collagen and elastin. Blood vessels and nerves supplying the muscles are present in the connective tissue layer—perimysium. The muscle cell contains protein filaments, namely, actin and myosin.

The muscles are excitable tissues similar to nerves. They are capable of contracting in response to a stimulus.

They are classified as follows (**Table 3.3**):

- Skeletal muscle
- Smooth muscle
- Cardiac muscle

1. **Skeletal muscle**: It is a voluntary muscle, attached to the skeletal system. The muscle fibers show alternate dark and light bands called **striations**. They are supplied by the somatic nerves.
2. **Smooth muscle**: These are the involuntary muscles and do not have striation. They are supplied by the autonomic nervous system. The smooth muscles are present in the wall of the gastrointestinal tract (GIT) and the hollow internal organs. Hence, they are also called *visceral muscles*. Visceral smooth muscles function as syncytium and contain a pacemaker to drive the spontaneous contraction, but these pacemakers discharge at irregular intervals.
3. **Cardiac muscle**: They are striated muscles, but involuntary. They are regulated by input from the autonomic nervous system. These are muscles of the heart. Cardiac muscles contract in a rhythmic manner without the external stimulation because of the presence of pacemakers. The pacemakers have the

Table 3.3 Features of Different Types of Muscles

Features	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Microscopy			
Striations	Present	Present	Absent
Fiber type	Long, cylindrical	Branched, cylindrical	Spindle-shaped
Nucleus	Peripheral	Central	Central
Fiber size	Very large	Large	Small
Sarcomere	Well formed	Well formed	Not well formed
T tubules	Present at the junction of the A-I band	Present at Z line	Not present
Sarcoplasmic reticulum	Present in large numbers	Present, but less in number	Very few in number
Junction between fibers	No junctions	Intercalated discs, have gap junctions	Gap junctions in visceral smooth muscles
Regulatory protein	Troponin and tropomyosin	Troponin and tropomyosin	Calmodulin and myosin light chain kinase
Functions			
Control	Voluntary	Involuntary	Involuntary
Nerve supply	Somatic nervous system	Autonomic nervous system	Autonomic nervous system
Autorhythmicity	Absent	Present	Present
Speed of contraction	Fast	Moderate	Slow

ability to generate impulses spontaneously. However, the rate of discharge of such impulses can be influenced by stimulation of the autonomic nervous system.

Sympathetic stimulation increases and parasympathetic stimulation reduces the rate of impulse generation.

The contraction of all types of muscles results in movement. The skeletal muscle contraction moves the joints, the smooth muscle contraction moves the contents of the hollow viscera, and the contraction of cardiac muscle causes the movement of blood. Hence, the muscles are termed *biological motors.*

4. Other classifications
   (a) Histological appearance (based on striations)
      - Striated muscle
      - Nonstriated muscle
   (b) Depending on the control
      - Voluntary
      - Involuntary

SKELETAL MUSCLE

DEVELOPMENT

The skeletal muscle fibers develop from the cell of the embryonic mesoderm. These myogenic precursors (myoblasts) are formed from somites. The somites are tissue blocks adjacent to the developing brain and spinal cord. The myoblasts migrate from somites to different parts of the body. They fuse with other cells in the new location to form multinucleated muscle fiber. The number of fibers in skeletal muscle appears to be genetically determined. However, the expression of their full genetic capacity depends on the development of the nerve supply to the muscle. The specific messengers, the **myogenic regulatory factors**, released by the motor nerves influence the development of the muscle fibers innervated by them.

FUNCTIONS OF SKELETAL MUSCLES

The functions of skeletal muscles are as follows:

- Producing movements of the body
- Stabilizing the position of the body
- Generating heat during contraction
- Controlling breathing cycle by the contraction of diaphragm
- Functioning as a pump to return the blood to heart (venous return)

STRUCTURE OF SKELETAL MUSCLE (Fig. 3.15)

Skeletal muscles are so named because they move the bones of skeleton. Majority of skeletal muscles are controlled through the somatic division of the nervous system.

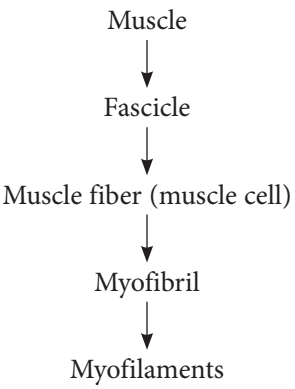
They are under voluntary or reflex control.

A typical skeletal muscle consists of the tendon at either end. The muscle belly is enclosed in a connective tissue covering called the **epimysium**.

The muscle belly is made up of a number of muscle bundles called the **fascicles**. A layer called the perimysium covers each fascicle.

Each muscle fascicle is made of a large number of muscle fibers arranged parallel to each other. A single bundle of muscle fibers is covered by the **endomysium**.

Each muscle fiber is a single cell, cylindrical, and multinucleated and is surrounded by a cell membrane called **sarcolemma**.



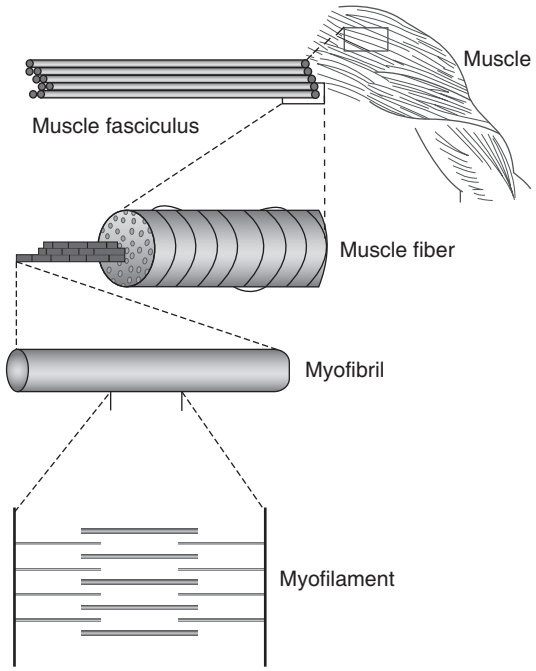


Figure 3.15 Structure of muscle. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The muscle fiber contains several thousand myofibrils.

Each myofibril is in turn made up of around 1500 myosin and 3000 actin filaments. These are large protein molecules which cause muscle contraction.

The cytoplasm of the muscle cell is called the **sarcoplasm**.

The endoplasmic reticulum is called the **sarcoplasmic reticulum**.

SARCOMERE

Sarcomere is the structural and functional unit of the muscle bounded by two Z-lines (**Fig. 3.16**). The muscle fiber shows alternate light and dark bands.

The A (anisotropic) band is formed by myosin filaments. The I (isotropic) band is formed by thin filaments made of troponin, tropomyosin, and actin. The Z-line bisects the I-band. The center of A-band where the thin filaments do not overlap the thick filament forms the H-zone. The center of H-zone has a globular prominence and it forms the M-line (**Fig. 3.17**).

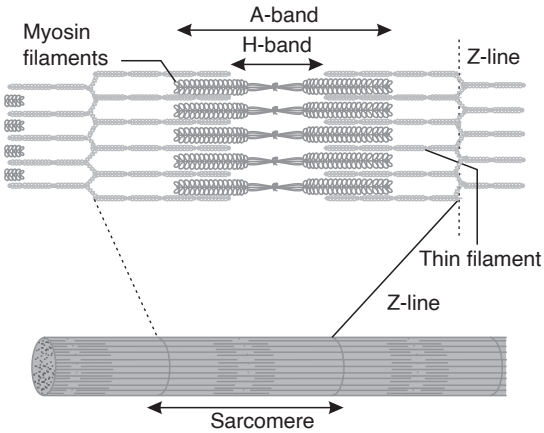


Figure 3.16 Diagrammatic representation of the arrangement of myofilaments. Sarcomere is seen as a segment of myofibril between two Z-lines. (*Source*: DR Singh, Essentials of Anatomy for Dentistry Students, 1st edn. Wolters Kluwer India, New Delhi; 2010.)

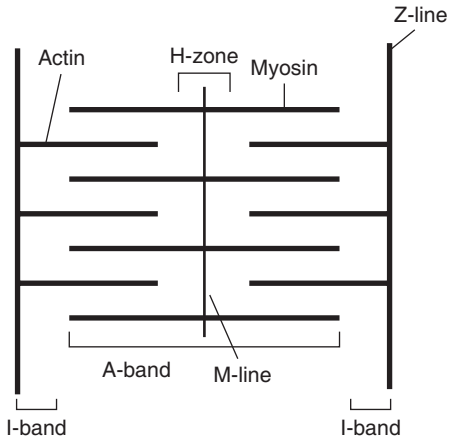


Figure 3.17 Sarcomere.

MUSCLE PROTEINS

The sarcomere is composed of thick and thin filaments made up of muscle proteins.

The various types of muscle proteins are as follows:

- Myosin
- Actin

- Troponin
- Tropomyosin (**Fig. 3.18**).

The thick filament is formed by myosin molecule, whereas the thin filament is formed by actin, troponin, and tropomyosin.

Myosin (Thick Filament)

Myosin 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. One end of each chain is folded into a globular head. The other portion forms the tail. The light chains are present near the myosin head.

The tails of the myosin molecules join together to form the body of the myosin filament. The head of myosin protrudes beyond the body. The portion of myosin connecting the head and body forms the arm. The head and arm together form the cross-bridges.

Thin Filament

The muscle proteins actin, troponin, and tropomyosin are present in the thin filament.

Actin

Each actin filament contains a double helix made of F-actin molecules. The F-actin molecules contain polymerized G-actin molecules. The adenosine diphosphate (ADP) molecules are present on the actin filaments.

The actin filament has active binding sites. Myosin interacts with these sites to form cross-bridges to cause the muscle contraction.

Tropomyosin

Tropomyosin has a double-helix structure. It lies in the groove between the two strands of F-actin filaments. In the resting state, tropomyosin covers the active binding sites on

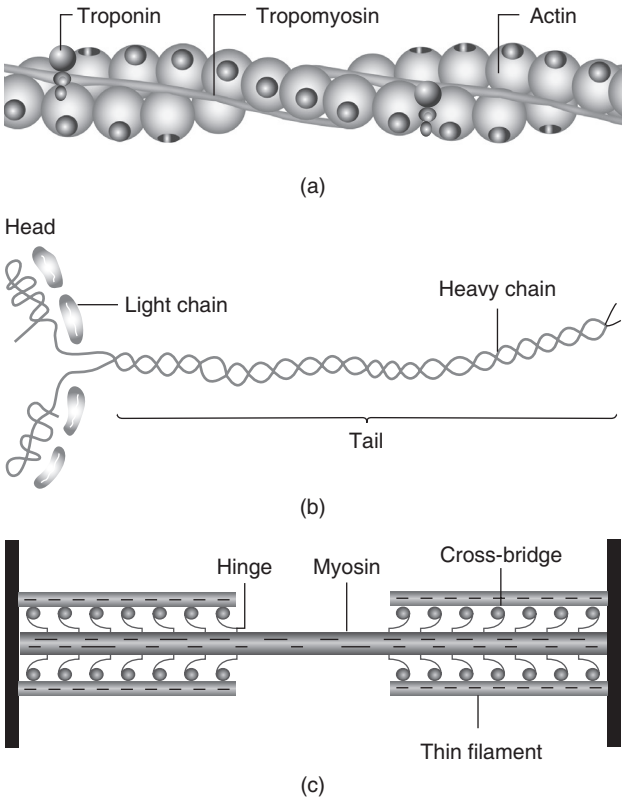


Figure 3.18 (a) Actin, troponin, tropomyosin, (b) myosin, and (c) arrangement of actin and myosin. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

the actin molecule. Tropomyosin is an integral part of actin regulating its interaction with myosin during muscle contraction.

Troponin

Troponin is a protein associated with thin filaments. It is a globular protein with three subunits: troponin I, troponin T, and troponin C.

Troponin I has affinity for actin.

Troponin T has affinity for tropomyosin.

Troponin C has affinity for calcium ions.

There are several other proteins which have an important role in the function of skeletal muscle. They are as follows:

- Actinin
- Titin
- Desmin
- Dystrophin

Actinin binds actin filament to Z lines in the skeletal muscle and dense bodies in the smooth muscle.

Titin (connectin) provides a structural framework for sarcomere and connects the Z line with the M line. It provides elasticity to the muscle. Titin offers little resistance to the initial stretch of muscle. However, the resistance increases with further stretch of muscle. These changes in resistance to stretch help to protect the muscle against any damage.

Structural changes in titin during passive stretch help the sarcomere in restoring its length after stretch.

Desmin binds the Z line to the plasma membrane and nuclear membrane.

It helps to maintain structural and mechanical integrity during contraction.

Dystrophin is a part of complex sarcolemmal protein binding to F-actin.

It provides support to the muscle fibers and strength for contraction.

Absence of dystrophin reduces stiffness of the muscle and mechanical stability.

Deficiency of dystrophin is the cause for muscular dystrophy.

CLINICAL NOTES

Muscular Dystrophy

Muscular dystrophy is a condition of progressive weakness in the skeletal muscle.

Duchenne Muscular Dystrophy

It is a genetic disorder common in males caused by a missing fragment in the X chromosome. The condition is also called **pseudohypertrophic muscular dystrophy**. In this condition, the muscle protein dystrophin is absent due to mutation of the gene that encodes it.

Duchenne muscular dystrophy is a degenerative disease that leads to progressive wasting of the muscle and loss of ability to contract. The age of onset is 3–5 years. The muscle is replaced by fat and fibrous tissue. It affects proximal limb muscles and neck flexors.

Becker Muscular Dystrophy

It is a less, severe form of X-linked recessive muscular dystrophy. The muscle protein, dystrophin, is present in an altered form and in reduced quantity.

SARCOTUBULAR SYSTEM

The sarcotubular system is the medium of communication between the outer sarcolemma (cell membrane of the muscle) and the interior of the muscle (**Fig. 3.19**).

The sarcolemma invaginates (enters) into the muscle to form the T-tubule (transverse tubule). On either side of the T-tubule, there are two systems of tubules called the **sarcoplasmic reticulum** (L-tubules). The enlarged terminal part of the L-tubule is called **terminal cistern (lateral sac)**. The terminal cistern stores calcium ions. Junctional feet (foot process) connect T-tubules to the terminal cistern.

T- and L-tubules together form the **sarcotubular system (triad)**.

Functions

- Helps in transmission of impulse from the surface of the muscle to its interior
- Stores calcium ions which are released during muscle contraction

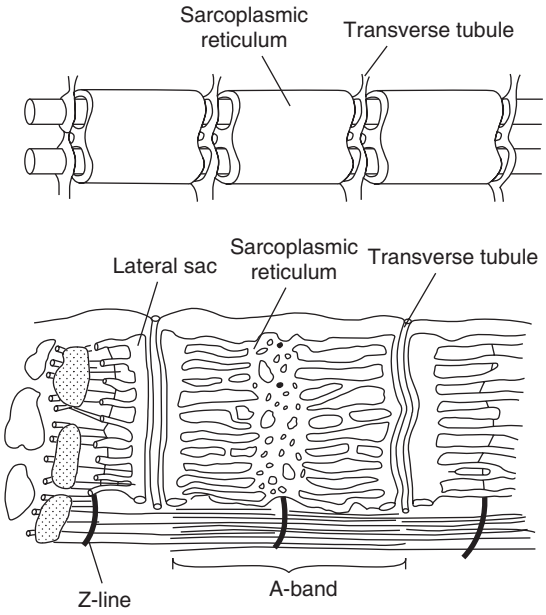


Figure 3.19 Sarcotubular system.

EXCITATION-CONTRACTION COUPLING

The excitation contraction coupling comprises the electrochemical changes occurring in the nerve, neuromuscular junction, and muscle in response to a stimulus.

During this process, the electrical activity gets transformed into the mechanical activity.

A threshold stimulus produces an action potential at the site of stimulation.

The impulse travels along the nerve fiber and crosses the neuromuscular junction.

This activates the motor end plate and generates the necessary signals to produce mechanical shortening of the muscle.

The action potential travels along the sarcolemma and enters the substance of the muscle through the T tubule.

The action potential reaches the terminal cistern and releases calcium ions.

Calcium ions act on the regulatory protein, troponin, and tropomyosin and expose the active binding site on the actin molecule.

The resultant cross-bridge formation causes mechanical shortening of the muscle.

Pumping back of calcium ions actively into the terminal cistern results in relaxation of the muscle.

MECHANISM OF MUSCLE CONTRACTION (Fig. 3.20)

- Stimulation of the motor nerve with adequate stimulus produces electrochemical change producing an impulse.
- This impulse travels through the nerve, crosses the neuromuscular junction, and activates the motor end plate. *(Refer to the section **Neuromuscular Junction**.)*
- Action potential is formed at the motor end plate.
- This action potential travels along the sarcolemma and enters the muscle through T-tubules.
- Action potential passes down the T-tubules producing conformational changes in dihydropyridine receptors (DHPR) present in the tubule.
- Conformational change triggers protein–protein interaction and opens ryanodine receptors (RYR) present in the sarcoplasmic reticulum.
- Activation of RYR releases calcium ions into the myoplasm.
- The action potential, on reaching the terminal vesicle of the sarcoplasmic reticulum, releases calcium ions from it.
- Calcium ions bind to the calcium-binding site on the troponin molecule.
- This bondage of calcium with troponin weakens the link between troponin and tropomyosin. The change causes the tropomyosin to move away exposing the active binding site on the actin molecule.
- The active site on the actin molecule attracts myosin.
- The ATP molecule binds to the head of myosin.
- The ATPase activity in the head of myosin cleaves ATP to ADP and phosphate with the release of energy.

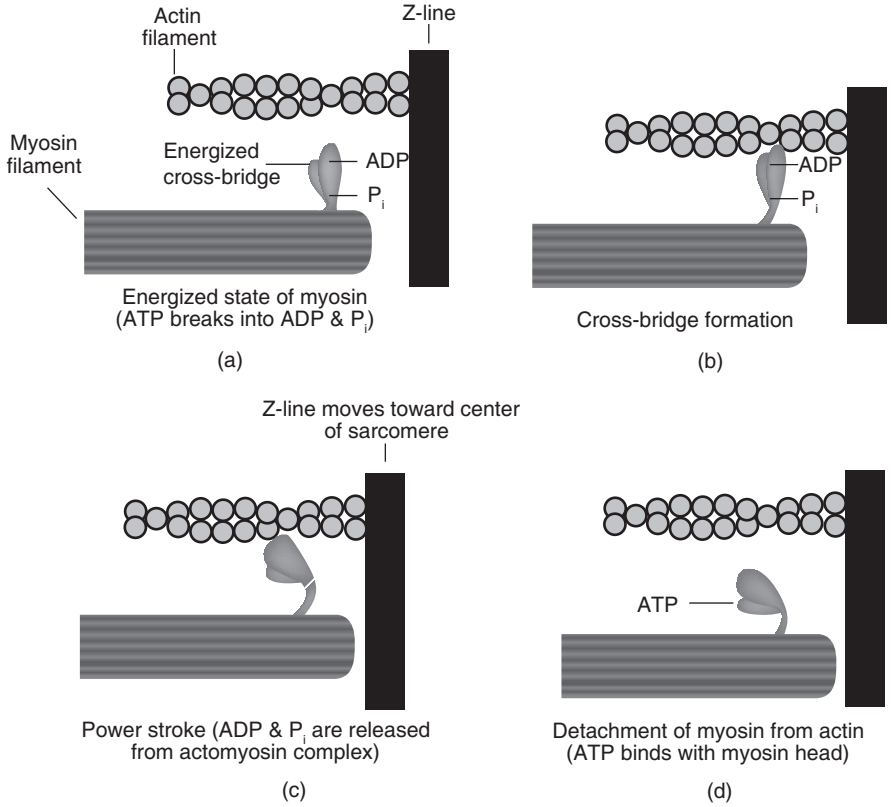


Figure 3.20 Molecular mechanism of muscle contraction.

- The energy liberated during chemical reaction helps in the sliding of thin filament over the myosin filament. This is called **power stroke**.
- Tilt of the head of myosin releases ADP and phosphate molecules from it.
- A new ATP molecule binds to the head of myosin causing detachment of myosin from the active site on the actin molecule.

  Cleavage of the ATP molecule begins the next cycle, leading to new power stroke. Gross muscle contraction occurs due to repeated myosin cross-bridge cycles and multiple myosin cycles at the same time.
- During relaxation, calcium ions are separated from the troponin molecule and pumped back into the terminal cistern. The changes that occur during contraction are reversed.

  Troponin without the calcium ions allows tropomyosin to cover the active binding site on the actin molecule.

The myosin reaching for the next active site on the actin molecule is blocked. Hence, the cross-bridges are not formed.

The muscle fiber remains at its contracted length. But the external forces restore the muscle to its resting length (**Fig. 3.21**).

When myosin gets attached to the active site of actin, there is a swiveling movement of the head of myosin that draws the actin filament toward the center of the sarcomere. This movement or tilt of the myosin head is called the **power stroke**. Immediately after tilting, a new ATP binds to the myosin head and the head automatically breaks away from the active site and returns to its original position. Here, it combines with a new binding site on actin and causes a new power stroke. Many such repeated power strokes produce successive shortening of the sarcomere resulting in muscle contraction.

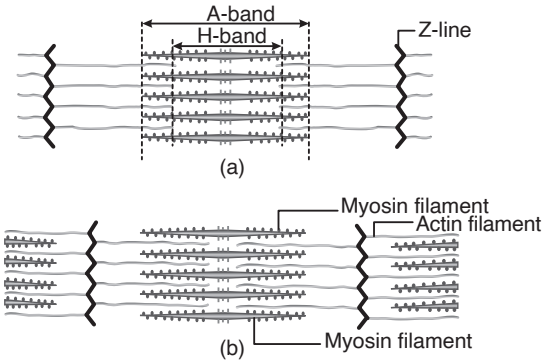


Figure 3.21 Diagrammatic representation of the phases of muscle contraction, depicting the sliding filament theory of contraction. The positions of thick and thin filaments during (a) relaxed and (b) contracted states. Note that the width of the H band decreases in a contracted state. (*Source*: DR Singh, Essentials of Anatomy for Dentistry Students, 1st edn. Wolters Kluwer India, New Delhi; 2010.)

Since this process involves sliding of the actin filament over myosin filaments, it is called **sliding filament theory** (Ratchet theory) (**Fig. 3.22a**).

Muscle Relaxation

- During relaxation, calcium ions are separated from the troponin molecule and pumped back into the terminal cistern.
- The calcium–ATPase pump moves the calcium ions from the muscle back to the terminal cistern using the energy derived from the hydrolysis of ATP.
- A decrease in calcium ion concentration in the muscle reduces the interaction between actin and myosin resulting in muscle relaxation.
- ATP provides energy for both contraction and relaxation.
- Troponin without the calcium ions allows tropomyosin to cover the active binding site on the actin molecule.

Inhibition to pumping back of calcium from the muscle to the terminal cistern results in sustained contraction of the muscle. This state of the muscle is termed **contracture**.

The muscle fiber remains at its contracted length. But the external forces restore the muscle to its resting length (**Fig. 3.22b**).

Skeletal muscle contraction

Generation of action potential in a motor nerve

↓

Transmission of impulse along the nerve

↓

Release of acetylcholine at nerve terminal

↓

Binding of acetylcholine to nicotinic receptors on the motor end plate

↓

Generation of end plate potential by changing conductance to sodium ion

↓

Formation of action potential

↓

Spread of action potential over sarcolemma and T tubule

↓

Release of calcium ions from terminal cistern

↓

Binding of calcium to its binding site on troponin

↓

Weakening of bondage between troponin and tropomyosin

↓

Sliding off tropomyosin exposing active binding site on actin

↓

Formation of actin–myosin complex

↓

Sliding of thin filament over thick filament resulting in mechanical shortening

Figure 3.22 (a) Changes during muscle contraction. (*Contd*.)

Skeletal muscle relaxation

Pumping of calcium ions back into terminal cistern

↓

Restoration of bondage between troponin and tropomyosin

↓

Tropomyosin covers active binding site on actin

↓

Dissociation of actin–myosin complex

↓

Restoration of original length

Figure 3.22 (b) Changes during muscle relaxation.

ENERGY SOURCES FOR MUSCLE CONTRACTION

The energy needed for muscle contraction is obtained by hydrolysis of ATP, glycogen, and creatine phosphate.

Glycogen is the storage form of glucose present intramuscularly. It is useful in generating energy quickly after intramuscular creatine stores are exhausted.

The energy is provided by breakdown of high-energy bonds present in ATP. The energy is necessary for the movement of thin filament over thick filament during contraction.

ATP is resynthesized regularly from another high-energy compound creatine phosphate as the muscle can store only a small quantity of ATP.

The energy for the synthesis of both ATP and creatine phosphate comes from catabolism of food.

The efficient metabolism of nutrients by muscle requires glucose and oxygen. Glucose is a nutrient molecule containing chemical bonds.

The energy contained in these chemical bonds is released during catabolic reaction and transferred to ATP and creatine phosphate.

The muscle fibers maintain uninterrupted supply of glucose by storing it in the form of glycogen.

The oxygen is needed for the metabolic process and aerobic respiration.

The oxygen is stored in the muscle bound to a large protein molecule myoglobin.

Myoglobin is an iron-containing pigment similar to hemoglobin. It readily releases oxygen when the oxygen concentration decreases in the muscle.

A gross reduction in the concentration of oxygen shifts the catabolic activity in the muscle to anaerobic respiration.

Anaerobic respiration rapidly forms ATP without the utilization of oxygen but it produces an incompletely catabolized molecule called **muscle lactic acid**.

The metabolic process of the cell is not 100% efficient. Some amount of energy is lost as heat.

PHYSIOLOGICAL PROPERTIES

Simple Muscle Twitch

Simple muscle twitch is the response of the muscle to a single stimulus (**Fig. 3.23**).

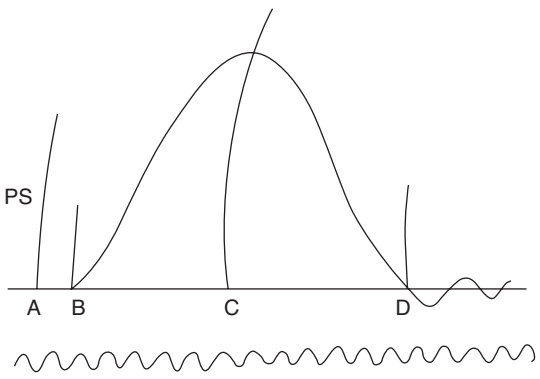


Figure 3.23 Simple muscle twitch with time-trace below the curve. PS: Point of stimulation; AB: latent period; BC: contraction period; CD: relaxation period.

Simple muscle twitch consists of the following phases:

1. **Latent period (0.01 second)**: It represents the time interval from the application of the stimulus to the actual commencement of the response. The electrical and mechanical changes occurring in the nerve and muscle after stimulation account for the latent period. The first half of the latent period corresponds to the absolute refractory period. The second half corresponds to the relative refractory period.
2. **Contraction period (0.04 second)**: It represents the time from the commencement of contraction to reach maximum contraction.
3. **Relaxation period (0.05 second)**: It is the period from the peak of contraction to the point of complete relaxation. In an ideal condition, the contraction period is shorter than the relaxation period. This is explained on the basis of release and reuptake of calcium ions.
4. During contraction, the calcium ions are released from the sarcoplasmic reticulum rapidly. But during relaxation, the calcium ions are pumped back into the sarcoplasmic reticulum. Pumping back of calcium takes a longer time. This accounts for a longer relaxation period.
5. **Total twitch period (0.10 second)**.

Excitability

It is the responding property of the tissue to a stimulus. It is also termed **irritability**.

1. **Stimulus**: It is a sudden and significant change in the environment brought about by release of energy.

   The types of stimuli are
   - electrical,
   - chemical,
   - mechanical, and
   - thermal.

   Electrical stimuli are normally preferred as they can be measured accurately and their quantum can be regulated.

   A stimulus has two variables: (i) strength and (ii) duration.

   The *strength–duration curve* is the relationship between the strength of the stimulus and the duration for which it is to be given to excite a tissue (**Fig. 3.24**).
2. **Rheobase**: It is the minimum strength of current delivered indefinitely to excite a tissue.
3. **Utilization time**: It is the minimum time required to excite a tissue with single rheobasic strength of current.
4. **Chronaxie**: It is the minimum time required to excite a tissue with twice the rheobasic strength of current.

Contractility

The muscle contracts when it is stimulated. The force generated during contraction is dependent on the initial length of the muscle.

1. **Length–tension relationship**

   Force exerted by the contracting muscle on an object is called **tension**. The protein titin binds the myosin filament to the Z line. It has a spring-like character. **Passive tension** is the elastic property in the muscle at rest. It is contributed by titin.

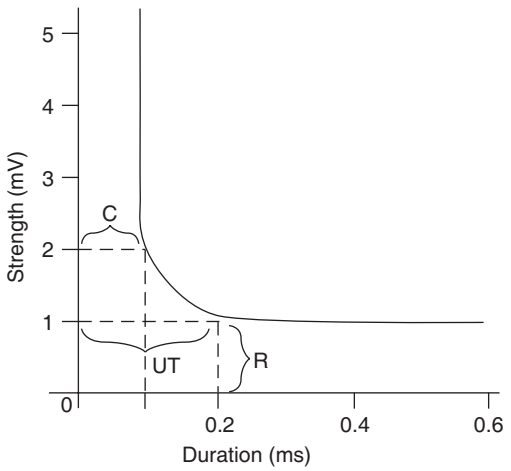


Figure 3.24 Strength–duration curve.
C, chronaxie; *R*, rheobase; *UT*, utilization time.

Tension developed in the muscle following stimulation is termed **active tension**.

The length of muscle fibers in different conditions is defined as follows:

- *Initial length:* It is the length of the muscle fiber just before the contraction.
- *Resting length:* It is the length of the muscle in a relaxed state with its attachment intact. The passive elastic property maintains the length.
- *Equilibrium length:* It is the length of the muscle in a relaxed state when it is cut off from its attachments.
- *Optimal length:* It is the length of the muscle at which maximum tension is generated during contraction.

2. **Length–force relationship (Fig. 3.25)**
   - *Starling's law:* The force of contraction is directly proportional to the initial length of the muscle fiber within physiological limits.

     Molecular basis for Starling's law:
     - When the muscle fiber is stretched, more and more active binding sites on the actin molecule are exposed. This helps in the formation of a greater number of cross-bridges.
     - Stretch of the muscle increases resting metabolism producing heat. Increased temperature brings about better enzymatic activity. Increase of enzymatic activity enhances the force of contraction.

All-or-None Law

When a single skeletal muscle fiber or the whole of the cardiac muscle is stimulated with an adequate stimulus, it responds to its maximum. If the stimulus is not adequate, it does not respond at all.

Latent Period

The latent period is the time interval between the application of stimulus and the onset of contraction. The muscle does not have any mechanical activity during this period. It is due to the time taken for the impulse to travel from the point of stimulation to the muscle, activities occurring at the neuromuscular junction, and

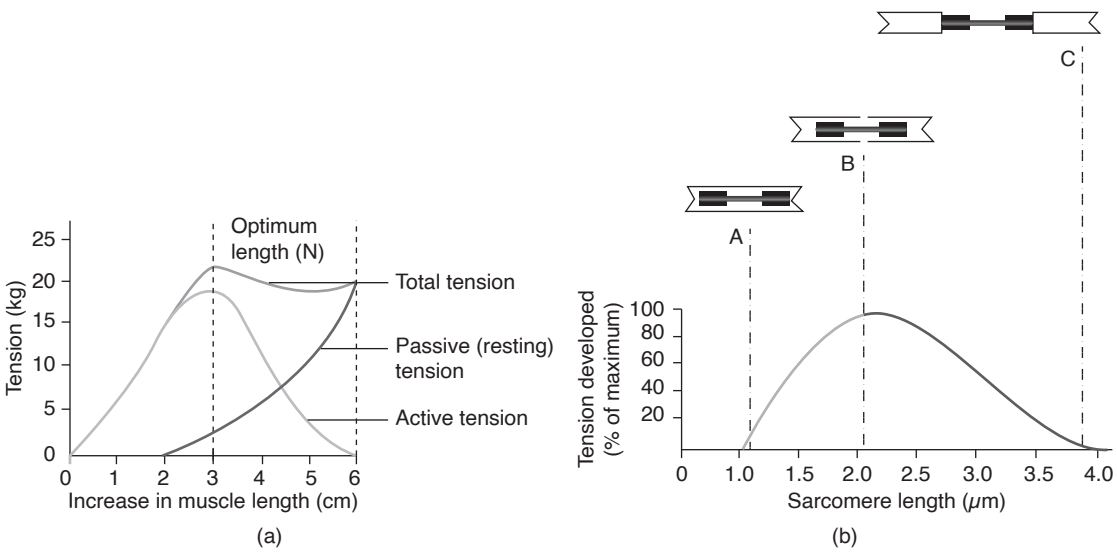


Figure 3.25 Length–tension relationship: change in force of contraction with alteration in the length of the muscle. (a) Length–tension relationship and (b) molecular basis of length–tension curve. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

chemical changes occurring in the muscle before contraction.

Refractory Period

The refractory period is the period during which the muscle does not show any response to a second stimulus. It is of two types:

1. **Absolute refractory period**: It is the period during which a second stimulus of any magnitude fails to produce a response. It corresponds to the first half of the latent period during muscle contraction.
2. **Relative refractory period**: It is the phase during which a second stimulus of greater intensity produces a response. It corresponds to the second half of the latent period during muscle contraction.

In the case of cardiac muscle, the entire phase of the cardiac contraction is in the absolute refractory period. Hence, the cardiac muscle cannot be tetanized.

Effect of Increasing Strength of Stimulus (Fig. 3.26)

The contractile response of the muscle depends on the intensity of stimulation.

Motor Unit

The motor unit is a single motor nerve innervating a group of muscle fibers. The number of muscle fibers in a motor unit depends upon the location and type of activity of the muscle.

In the muscles of hand and eye performing fine, graded, and precise movements, each motor unit will have three to six muscles fibers innervated by a motor nerve.

The motor units in the muscles of the lower limb can have up to about 600 muscle fibers innervated by a nerve.

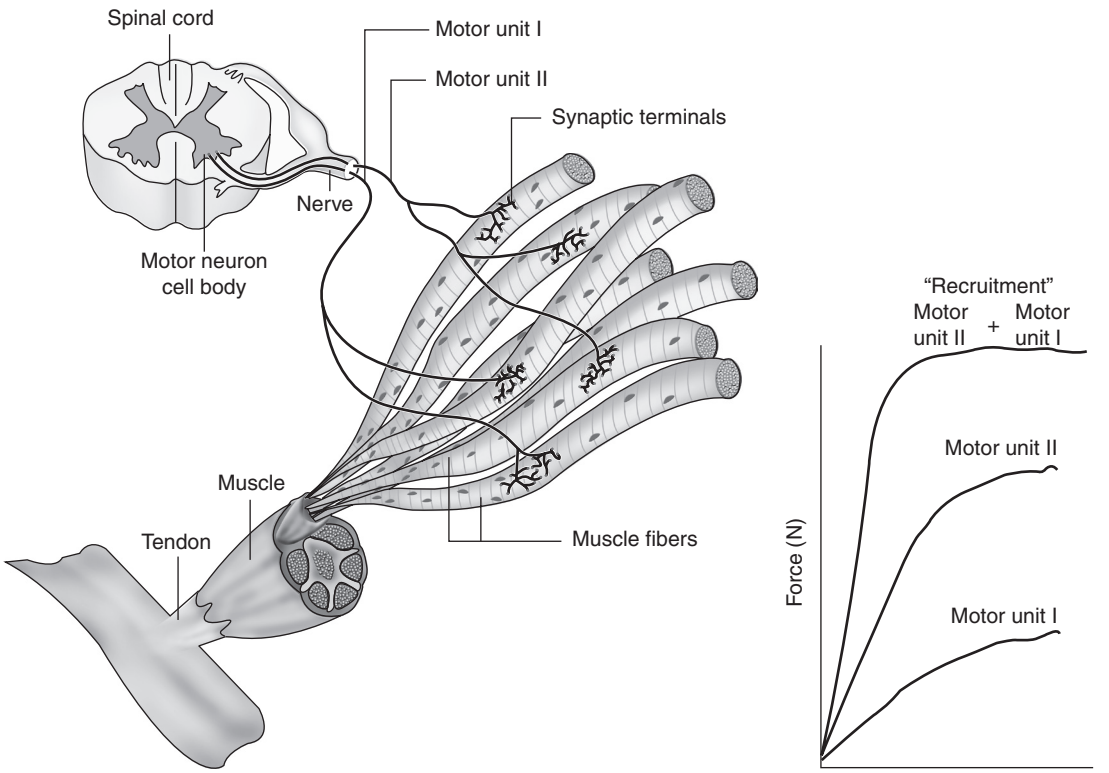


Figure 3.26 Motor unit and its recruitment during contraction. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Quantal Summation

A gradual increase in the strength of stimulus increases the force of contraction. It is due to the activation of more and more motor units. This phenomenon is termed the **recruitment of motor unit**. The summated response is the **quantal summation**.

Temporal Summation

When the frequency of stimulation is increased, the stimuli add up and therefore the total strength of contraction is increased. This is termed the **temporal summation**.

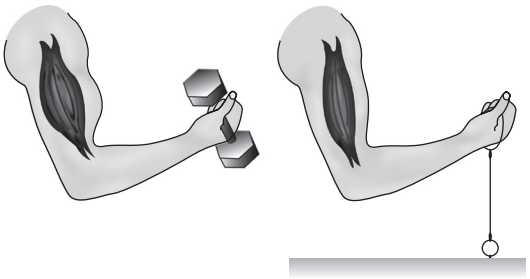


Figure 3.27 Types of muscle contractions: (a) isotonic and (b) isometric. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

TYPES OF MUSCLE CONTRACTIONS (Fig. 3.27)

Isotonic Contraction

In the isotonic contraction, tension in the muscle remains constant but the length of the muscle changes. Effective work is done in this type of contraction. A part of energy is converted to useful work and the remaining is converted to heat, for example, lifting a small weight from the ground.

Isometric Contraction

In this type of contraction, there is a change of tension in the muscle fiber but there is no change in the length. There is no effective work done. Energy is converted to heat, for example, trying to lift a heavy object, which cannot be moved.

The differences between isotonic and isometric contractions are enumerated in **Table 3.4**.

Table 3.4 Differences Between Isotonic and Isometric Contractions

Isotonic Contraction	Isometric Contraction
Tone (tension) remains constant (iso=same)	Tone (tension) increases
Length of muscle changes	Length remains constant
Useful for movements of the body	Does not produce any movement but useful for maintaining posture
Shorter latent, contraction and relaxation periods	Longer latent, contraction and relaxation period
Resistance offered by the object is less than the force generated by the muscle	Resistance offered by object is more than the force generated by contracting muscle
There is expenditure of energy and work is done	There is expenditure of energy, but no work is done. Heat is generated
Heat generation is greater and less energy efficient	Heat generation is less and more energy efficient
During contraction, thin filament moves over thick filament.	There is no movement of thin filaments over thick filament
Occurs in the middle of muscle contraction	Occurs at the beginning and end of muscle contractions
Examples: Walking, running, and lifting objects	*Example*: Pushing the wall

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

EFFECT OF LOAD ON MUSCLE CONTRACTION

The load acting on the muscle before or during contraction alters its contractile response.

1. **Free load**: If the weight is acting on the muscle before the commencement of contraction, it is said to be free-loaded. This increases the initial length of the muscle and hence the force of contraction.
2. **Afterload**: The muscle is said to be afterloaded if the weight is acting on the muscle during contraction.

EFFECT OF TWO SUCCESSIVE STIMULI

When a second stimulus is given immediately after the first, it potentiates the effect of the first stimulus.

The response varies depending on the timing of the second stimulus in relation to the first stimulus.

Beneficial Effect

A second stimulus is applied to the muscle immediately after its relaxation following the first contraction. The second contraction has greater amplitude. This is termed the **beneficial effect**.

It is due to

- calcium ions released during the first contraction add to calcium released during the second contraction to potentiate the effect;
- reduction in the viscosity of the muscle;
- increase in the temperature of the muscle, hence an enhanced enzyme activity and a better contraction.

SUMMATION OF CONTRACTIONS (Fig. 3.28)

Treppe

When a series of stimuli are given to the muscle in rapid succession, it increases the force of contraction gradually. This is **treppe** or **staircase phenomenon**.

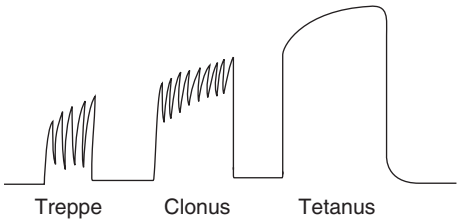


Figure 3.28 Summation of contractions.

Tetanus

A series of stimuli delivered to the muscle with a very short time interval in between them results in a state of sustained contraction. This is termed **tetanus**.

The tetanizing frequency for a frog's muscle is 30/s and for human muscle it is over 60/s.

Clonus

If the frequency of stimuli is less than the tetanizing frequency, it results in clonus. The clonus is an incomplete tetanus.

Fatigue

Fatigue is temporary inability of the muscle to respond satisfactorily after being repeatedly stimulated. (It is a temporary state of inexcitability of the muscle.) It is the decline in the ability of muscle to generate force.

Causes

- Depletion of acetylcholine at the nerve terminal
- Exhaustion of the source of energy, ATP
- Accumulation of metabolic end products such as lactic and pyruvic acid

Site

- In an isolated preparation, the site of fatigue is in neuromuscular junction.
- In an intact animal, the site of fatigue is in synapse.

Tone

Tone is a state of partial contraction of the muscle at rest. It is also defined as the resistance offered by the muscle to its passive movement.

Skeletal muscle tone is due to a low rate of nerve impulses originating at the spinal cord. These spinal nerve impulses are controlled by signals from the brain as well as from the muscle spindles.

CLINICAL NOTES

The tone of the muscle can be altered in different conditions.

Hypertonia

Hypertonia is a state of the muscle where the tone is increased. It is described as **rigidity** or **spasticity**.

Hypertonia is seen in upper motor neuron lesions and Parkinsonism.

Hypotonia

The reduction in the tone of the muscle is termed hypotonia. It is clinically identified as **flaccidity**. Total absence of tone is **atonia**.

Hypotonia is seen in lower motor neuron lesion.

Hyperplasia

Hyperplasia is a Greek term, derived from *hyper* which means "over" and *plasis* which means "formation." It is a condition in which the number of muscle fibers increases.

Hypertrophy

It is the increase in the size of cells or tissues in response to a stimulus. Exercise induces hypertrophy of the muscles. Exercise-induced hypertrophy increases the force of contraction and delays the onset of fatigue. This improves the performance of the muscle.

Disuse Atrophy

Atrophy is wasting or thinning of the muscle mass. Wasting of a muscle which is not used for a long time results in disuse atrophy.

Anabolic Steroids

Anabolic steroids are steroid hormones similar to testosterone used by athletes to increase the size and strength of the skeletal muscle.

To achieve the desired benefits, large doses of anabolic steroids have to be used.

Long-term use can produce dangerous side effects such as liver cancer, damage to kidney, and increased risk of heart diseases.

Muscle Cramps

Involuntary tetanic contractions of muscle produce muscle cramps. They are caused due to electrolyte imbalance surrounding the muscle.

Rigor Mortis

Rigor mortis is a state of rigidity or stiffness developed in the muscle after death. Rigor mortis begins within 3–4 hours and continues up to 24 hours. However, if the person or animal is killed in action, rigor mortis begins in about 30 minutes.

After death, there is exhaustion of ATP.

Actomyosin complex is formed in an abnormal, irreversible, and resistant way to produce the rigidity.

Changes During Rigor Mortis

- Muscle loses its excitability and shortens in length.
- It becomes more viscous.
- The glycogen stores disappear.
- It becomes acidic and liberates carbonic acid.

Importance: Helps to determine the time and cause of death.

Denervation Hypersensitivity

When a motor nerve supplying the muscle is cut, the muscle degenerates and undergoes atrophy. It exhibits abnormal excitability responding to circulating acetylcholine. This is denervation hypersensitivity.

Denervated skeletal muscle shows fine, irregular contractions of the individual fibers termed **fibrillation**. Fibrillation is due to the instability of membrane potential.

This response is due to the formation of more number of acetylcholine receptors on the surface of the muscle. The resting membrane potential decreases.

As a delayed response, the muscle loses its capacity to develop tension on stimulation, change in enzymatic composition, and decrease in the diameter of the fiber (**atrophy**).

Electromyogram

Electromyogram is recording of electrical activities of the muscle. Activation of motor units can be studied by this recording. Small metal electrodes are placed over the skin overlying the muscle. These electrodes are used for recording the electrical activity.

Alternatively, hypodermic needles can also be used for recording. By using the needle electrodes, it is possible to record the activity from a single muscle fiber.

RED AND WHITE MUSCLES

The muscles are classified based on the color. They have significant differences in morphology and composition.

The types of muscle are as follows:

- Red muscle
- White muscle

The major differences are listed in **Table 3.5**.

Table 3.5 Differences Between Red and White Muscles

Red (Slow) Muscle (Type I)	White (Fast) Muscle (Type II)
Muscle fibers are thin	Muscle fibers are thick
Capillary bed is more dense	Density of capillary bed is less
Myoglobin content is more, hence red color	Myoglobin content is less, hence white in color
Mitochondria are more in number	Mitochondria are less in number
Soluble proteins and glycogen are less	Soluble proteins and glycogen are more
Lipid content is higher	Lipid content is less
Has more sarcoplasm	Has less sarcoplasm
Contraction is sustained but with lower power	Rapid (fast) contraction with higher power
More resistant to fatigue	Gets easily fatigued
Develop tetanus at lower rate of stimulation	Develop tetanus at higher rate of stimulation
Depends on aerobic metabolism for energy	Depends on anaerobic metabolism (glycolysis)
ATPase activity is lower. Have higher oxidative enzymes and lesser glycolytic enzymes	ATPase activity is higher. Have higher glycolytic enzyme and lesser oxidative enzymes.
There is no accumulation of lactic acid	Lactic acid may accumulate
It is postural muscle, e.g., long muscles of back	Performs fine, skilled movements, e.g., extraocular muscles

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

SMOOTH MUSCLES

The smooth muscles are involuntary in function (**Fig. 3.29**). They do not exhibit the alternate light and dark bands. They are different from skeletal muscles by the following features:

- The Z-line is not well defined.
- Actin and myosin are attached to dense bodies which replace the Z-line.
- Sarcoplasmic reticulum is not well developed.
- Regulatory protein troponin is absent.
- Arrangement of actin and myosin does not follow a regular pattern.

Smooth muscles have an unstable membrane potential capable of contracting without nerve supply. They show continuous, irregular contractions. This partial contracted state is called **tonus** or **tone**.

TYPES OF SMOOTH MUSCLES

Smooth muscles are of two types:

1. Unitary or single-unit smooth muscle
2. Multiunit smooth muscle

1. **Unitary or single unit (visceral) smooth muscle**: It consists of thousands of muscle fibers. It has low-resistance gap junctions, and functions as a single unit. Gap junctions permit free passage of ions from one fiber to the next. Electrical activity arising in one muscle fiber will spread rapidly to the connected fibers. Thus, the entire muscle bundle contracts as a single unit. It is also called **syncytial smooth muscle**.

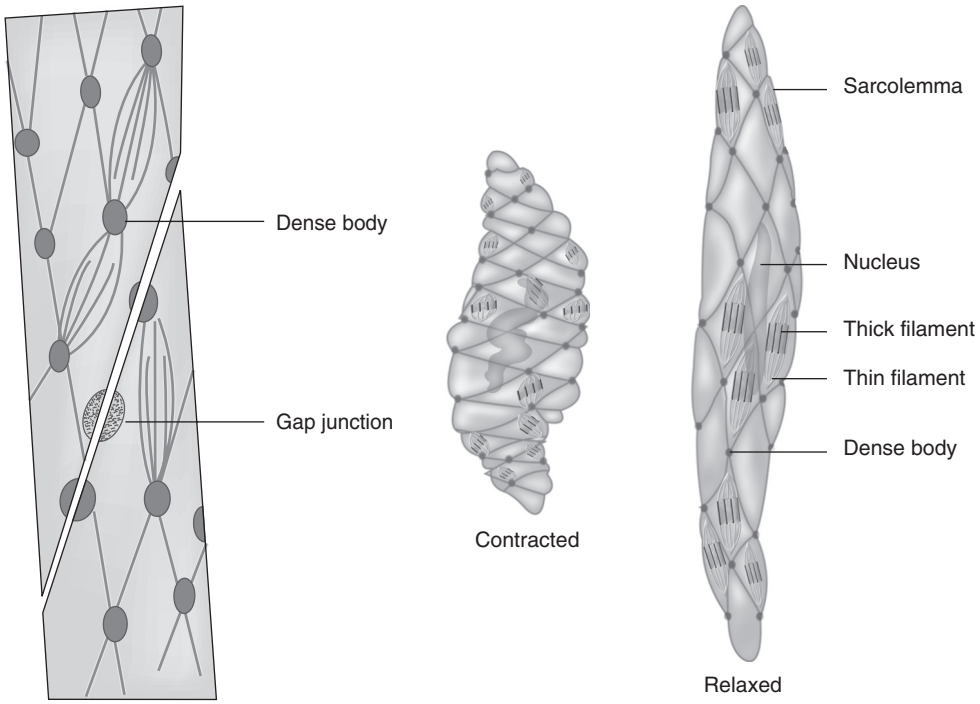


Figure 3.29 Smooth muscle. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Some cells in a single-unit smooth muscle are self-excitatory. They act as a pacemaker and generate impulses without external stimulation. Slow waves are generated due to a change in pumping and conductance of ions.

Mechanical stretch also triggers muscle contraction by activating calcium ion channels. Entry of calcium ions produces smooth muscle contraction.

It is present in the intestine, uterus, and ureter.

2. **Multiunit smooth muscle**: Muscle is made up of discrete individual fibers. Each fiber has a separate innervation. The individual fiber can contract independently. These muscles perform fine and graded contractions. The contractions are localized. The muscle cells respond to the hormones and circulating substances.

It is present in the iris, ciliary muscle of the eye, and large airways in the lungs (**Table 3.6**).

NERVE SUPPLY TO SMOOTH MUSCLES

The visceral smooth muscles are supplied by two divisions of the autonomic nervous system. The function of these nerves is to modify activity in the muscle rather than to initiate the action.

ELECTRICAL POTENTIAL IN SMOOTH MUSCLES

The **membrane potential** does not show a true resting value. It is low when the tissue is active and high when it is inhibited. During the period of quiescence, the average resting membrane potential is about –50 mV. However, it ranges

Table 3.6 Differences Between Single and Multiunit Smooth Muscles

Single-Unit Smooth Muscle	Multiunit Smooth Muscle
Muscle fibers are arranged as sheets or bundles	Muscle fibers are discrete (individual fibers)
All fibers contract as a single unit	Muscle fibers contract as a separate unit
Gap junctions are present	Very few or no gap junctions present
Exhibits pacemaker activity	Does not have pacemaker activity
Stretch of muscle results in contraction	Stretch does not produce any contraction
Shows all-or-none response	Shows graded contraction with recruitment of fibers
Present in hollow visceral organs (e.g. GIT, urinary bladder)	Present in ciliary muscle, iris, and wall of large blood vessels

from –20 to –65 mV in different phases of activity.

Smooth muscles show different types of electrical activities (**Fig. 3.30**)

- slow sine wave
- spikes potential
- Action potential

Slow Wave Potential

Slow waves are generated by pacemaker cells called interstitial cells of Cajal. The waves spread to the adjacent cells and regulate their motility. Motility is initiated by the influx of calcium ions.

Slow waves, on becoming strong, initiate the action potential. They are unable to produce muscle contraction.

Spike Potential

It occurs in unitary smooth muscles by electrical stimulation, mechanical stretch, and action of hormones. It has a duration of 10–50 milliseconds.

Action Potential

Action potential of smooth muscles is similar to that of skeletal muscles. There is also **action potential with a plateau**. The initial phase is similar to the spike potential. However, the repolarization is delayed as much

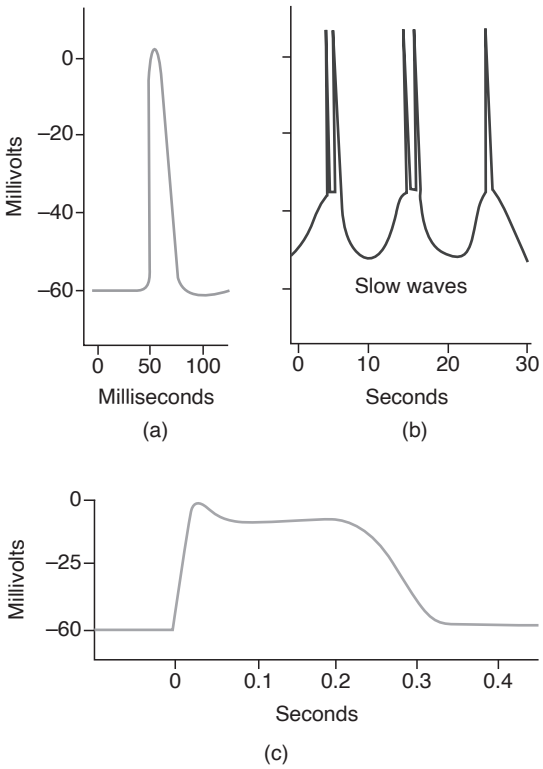


Figure 3.30 (a) Smooth muscle action potential (spike potential) produced by external stimulus. (b) Multiple spike potential seen in muscles of the intestinal wall produced by slow rhythmical electrical waves. (c) Action potential recorded from smooth muscle fibers of the uterus (has plateau). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

as 1000 milliseconds. This helps to prolong the duration of contraction.

The electrical activity in the smooth muscles is influenced by K^+, Na^+, and Ca^{2+}.

Some of the smooth muscles are capable of generating action potential without external stimulation (self-excitatory). This is attributed to the slow wave rhythm of the membrane potential.

Genesis of slow wave rhythm is due to

- increase and decrease in the outward pumping of sodium ions and
- rhythmic increase and decrease in the conductance of ion channels.

Stretch of smooth muscle results in its contraction due to

- generation of normal slow wave potential and
- decrease in the negativity of membrane potential.

MOLECULAR BASIS OF SMOOTH MUSCLE CONTRACTION

- Stimulation of smooth muscle causes entry of calcium ions from the ECF.
- Calcium binds to the calcium-binding protein calmodulin.
- The calcium–calmodulin complex activates the enzyme myosin light-chain kinase, phosphorylating myosin.
- Phosphorylation reaction activates myosin ATPase releasing energy for the process of contraction. Actin slides on the myosin producing contraction (shortening).
- During relaxation, myosin is dephosphorylated by myosin light-chain phosphatase.
- However, dephosphorylation does not lead to complete relaxation of the smooth muscle.

The initial length is not restored immediately due to the presence of **latch bridges**.

Smooth muscle contraction

Activating stimulus

↓

Entry of calcium into the muscle cell

↓

Binding of calcium to calmodulin forming complex

↓

Activation of calcium–calmodulin-dependent light chain kinase

↓

Phosphorylation of myosin

↓

Binding of actin and myosin, increased ATPase activity

↓

Shortening of muscle resulting in contraction

↓

Myosin light chain phosphatase—dephosphorylates myosin

↓

Relaxation of the muscle

PLASTICITY: LENGTH–TENSION RELATIONSHIP

The special character of smooth muscle is variability of the tension at a given length.

Stretch of the smooth muscle initially results in contraction. However if the muscle is stretched further, it relaxes. This is termed **plasticity**. The phenomenon is described as **stress relaxation**.

Plasticity of smooth muscle can be demonstrated by observing the response of bladder to its distension. Distension of the bladder by collection of urine stimulates the bladder muscle which contracts, creating an urge to pass urine. However, continued collection of urine relaxes the bladder muscle and more urine gets collected. When the bladder is filled up to its capacity, it finally contracts resulting in its evacuation.

NEUROTRANSMITTERS ACTING ON SMOOTH MUSCLES

Autonomic nerves innervating smooth muscles secrete acetylcholine and norepinephrine as neurotransmitters.

They are excitatory on smooth muscle in some locations and inhibitory in some other locations.

The action of a neurotransmitter is produced by binding to receptors. The receptors can be excitatory or inhibitory.

The action of the neurotransmitter is dependent on the type of receptor acted upon by the neurotransmitter in the given location.

However, if acetylcholine is excitatory in one location, norepinephrine will be inhibitory in the same location.

Norepinephrine stimulates the contraction of smooth muscle in blood vessels but inhibits the contraction in intestine.

Mechanism of Action of Neurotransmitter

The action of acetylcholine is mediated through phospholipase C. Phospholipase C produces inositol triphosphate (IP3), which facilitates passage of calcium ions through IP3 receptors.

Stimulation of the cholinergic nerve increases excitability and contraction of intestinal smooth muscles.

Smooth Muscle Relaxants

Nitric oxide (NO), initially identified as endothelium-derived relaxing factor (EDRF), is produced by endothelial cells of blood vessels. It relaxes the vascular smooth muscle.

REVIEW QUESTIONS

Long Essay

1. Describe the structure of neuromuscular junction (NMJ) with the help of a diagram and explain the mechanism of transmission of nerve impulse across it.
2. Describe the molecular basis for muscle contraction.
3. Discuss excitation–contraction coupling in a skeletal muscle.
4. Explain the properties of nerve fibers.

Short Essay

1. What is resting membrane potential? Explain its ionic basis.
2. Explain the classification of neurons based on different criteria.
3. Describe an action potential recorded from a nerve fiber. Explain its ionic basis.
4. What are the types of action potentials?
5. Tabulate the differences between graded potential and action potential.
6. Classify nerve fibers based on velocity and diameter. Explain the factors influencing the velocity of nerve impulse.
7. Explain the properties of nerve fibers.
8. Describe the transmission of impulse in myelinated and unmyelinated nerve fibers.
9. Explain the types of nerve injuries.
10. Describe Wallerian degeneration.
11. Explain the changes during regeneration of a damaged nerve.
12. List the types of neuroglia. Explain their structure and functions.

13. Describe the structure of neuromuscular junction.
14. Explain the transmission of impulse across neuromuscular junction.
15. What is myasthenia gravis? Explain its pathophysiology and clinical features. Add a note on its management.
16. List the neuromuscular blocking agents. Explain their mechanism of action.
17. Describe the structure of sarcomere.
18. Name the muscle proteins. Explain their chemical nature.
19. Define refractory period for an excitable tissue. Explain how it differs in cardiac and skeletal muscles.
20. Describe the sarcotubular system. What is its function?
21. Discuss the molecular basis of muscle contractions.
22. Define chronaxie and rheobase. Draw a strength–duration curve explaining its importance.
23. Discuss the properties of skeletal muscle.
24. Tabulate the differences between skeletal, cardiac, and smooth muscles.
25. Define fatigue. What is the site of fatigue? What are the causes for it?
26. What is beneficial effect? Explain the molecular basis for it.
27. What is rigor mortis? Describe the biochemical and physical changes associated with it. What is its medicolegal importance?
28. Explain denervation hypersensitivity.
29. Explain the molecular basis for smooth muscle contraction.

Short Answer

1. Describe the structure of a neuron.
2. Give the classification of neurons.
3. What is myelinogenesis?
4. Define a nerve impulse. What is saltatory conduction?
5. What is orthodromic and antidromic conduction?
6. What is compound action potential?
7. What is a nerve growth factor?
8. What is all-or-none law? How does it vary in different excitable tissues?
9. What is end-plate potential?
10. What is miniature end-plate potential?
11. What is Lambert–Eaton syndrome?
12. Give the classification of muscle fibers.
13. Name the muscle proteins.
14. Draw a labeled diagram of sarcomere.
15. Define latent period in a skeletal muscle. What are the factors influencing its duration?
16. Define the terms (a) resting length, (b) equilibrium length, and (c) optimal length.
17. What is "active tension" and "passive tension" in a muscle?
18. Define Starling's law of muscle contraction.
19. What is all-or-none law in an excitable tissue?
20. What is isometric and isotonic contraction?
21. Define motor unit.

22. What is simple muscle twitch?
23. What is effect of load on muscle contraction?
24. Explain the terms temporal, spatial, and quantal summation.
25. Define the terms (a) treppe, (b) clonus, and (c) tetanus.
26. List the differences between red and white muscles.
27. Define the terms (a) hypotonia, (b) hypertonia, and (c) atonia. Mention one condition of their occurrence.
28. Define muscle tone. What is its clinical importance?
29. What are the types of smooth muscles?

CHAPTER

4 Cardiovascular System

Outline

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the structure, blood and nerve supply for the heart.
- Explain the conducting system of the heart. Discuss the origin and spread of cardiac impulse.
- Describe the properties of cardiac muscle.
- Explain the method of recording, different waves of electrocardiogram. Mention its clinical application.
- Discuss the hemodynamics, and factors controlling blood flow.
- Explain the mechanism of heart rate regulation.
- Define blood pressure. Describe the short, intermediate and long term regulation of blood pressure.
- Explain the mechanical events during a cardiac cycle. Discuss the pressure and volume changes.
- List the differences between first and second heart sounds. Mention the cause for different heart sounds.
- Describe the factors influencing cardiac output.
- Explain the factors influencing and clinical importance of coronary, capillary, fetal and cutaneous circulation.
- Describe the autonomic functions test. Discuss the clinical application of these tests.
- Explain the pathophysiology of circulatory shock.
- Successfully answer the questions and MCQs at the end of this chapter.

Life started as a unicellular organism. The organisms became multicellular with evolution. The individual cells moved away from the environment; however, there was a need to supply oxygen and nutrients to individual cells and a need to carry metabolic waste to the organs of excretion. These changes in the organism prompted the development of a cardiovascular (circulatory) system.

The British physiologist William Harvey reported that the cardiovascular system is a closed system in which blood pumped out of the heart passes through one set of vessels and returns to the heart through the other set of vessels.

The cardiovascular system consists of heart and blood vessels. The heart acts as a pump and the blood vessels are channels carrying blood.

The functions of cardiovascular system are as follows:

- Distribution of respiratory gases and molecules of nutrition, and transportation of the material required for tissue repair
- Rapid movement of chemical signals for the cells such as hormones and neurotransmitters
- Dissipation of heat from the core to the surface of the body
- Mobilization of defense response against infections

STRUCTURE OF HEART (Fig. 4.1)

The human heart weighs about 300 grams. It is enclosed in the mediastinum, extending from the second rib to the fifth intercostal space in the left side of the thoracic cage. The heart is aligned obliquely with the base directed toward the right shoulder and the apex toward the left hip.

The heart is covered by an outer fibrous pericardium and inner serous pericardium. The space between these two layers is termed the **pericardial cavity**. The fluid present in the pericardial cavity ensures smooth movement of the heart by acting as a lubricant.

The human heart consists of four chambers—two atria and two ventricles (**Fig. 4.1**). The two atria are separated by interatrial septum. The two ventricles are separated by interventricular septum.

The right atrium receives deoxygenated blood from different tissues of the body through superior and inferior venae cavae.

The left atrium receives blood from lungs through pulmonary veins. The right ventricle pumps the blood to pulmonary circulation and the left ventricle pumps the blood to systemic circulation.

The opening between the right atrium and the right ventricle is guarded by the **tricuspid valve**. The opening between the left atrium and the left ventricle is guarded by the **bicuspid valve** (mitral valve). These valves

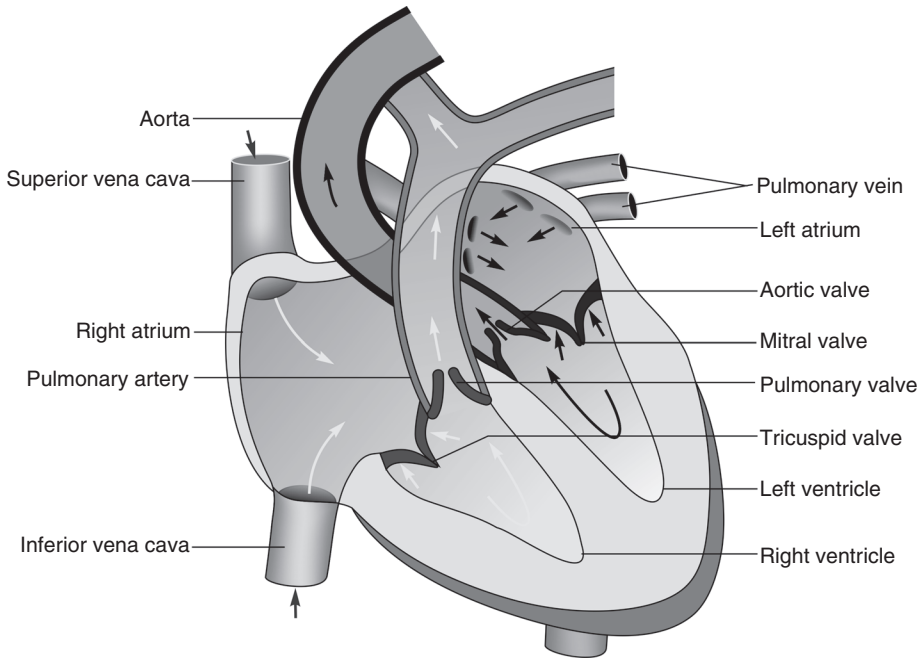


Figure 4.1 Structure of heart and direction of flow of blood. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

present between the atrium and the ventricle on both the sides are together called the **atrioventricular** (AV) valves. The AV valves permit the flow of blood from the atrium to the ventricle and prevent the blood from flowing in the opposite direction.

The opening and closing of the AV valves is passive. It depends on the pressure changes in the atrium and ventricle. When the pressure increases in the atrium, the valves are pushed open and the blood flows from the atrium to the ventricle.

The contraction of the ventricles increases the intraventricular pressure. This in turn closes the AV valves. The closure of the AV valves prevents the backward flow of blood from the ventricle to the atrium.

The AV valves are held in position by the **papillary muscles** arising from the walls of the ventricle.

The papillary muscles are attached to the free margins of AV valves with the help of fibrous strands termed **chordae tendinae**.

The papillary muscles prevent the bulging of AV valves into the atrium during ventricular contraction. These muscles do not help in opening or closing of the valves.

The **pulmonary artery** arises from the right ventricle and the **aorta** arises from the left ventricle.

The blood flow through these vessels is regulated by the pulmonary and aortic **semilunar valves**.

The arteries carry blood away from the heart and the veins carry blood toward the heart.

All the arteries carry oxygenated blood except the pulmonary artery.

All the veins except the pulmonary vein carry deoxygenated blood.

The wall of the heart has three layers:

1. Epicardium
2. Myocardium
3. Endocardium

Epicardium is a serous layer covering the heart.

Myocardium is made up of cardiac muscle cells which are involuntary in function.

Endocardium is a single layer of endothelial cells lining the inner surface of the heart.

CARDIAC MUSCLES

The cardiac muscles have branching fibers with a centrally located nucleus. The adjacent fibers are connected by intercalated disks. These are cell membranes that separate cardiac muscle cells from one another. The electrical resistance through the intercalated disk is 1/400th of the cardiac cell membrane.

The intercalated disks contain gap junctions. The gap junctions (specialized intercellular connections) between the adjacent fibers offer low resistance to the passage of ions. Because of the presence of low-resistance bridges, cardiac muscle fibers contract as a single unit. It is termed **functional syncytium**.

The desmosomes (a cell structure specialized for cell-to-cell adhesion) in the disk provide a site for adhesion between two cardiac muscle cells. These adhesions help to transmit the tension developed in one cell to the other during contraction.

The cardiac muscle has the contractile proteins actin and myosin arranged in a sarcomere (**Fig. 4.2**). It has the characteristic A-, I-, and H-bands with M- and Z-lines.

In the cardiac muscle, the sarcoplasmic reticulum is not well formed. The T-tubule is

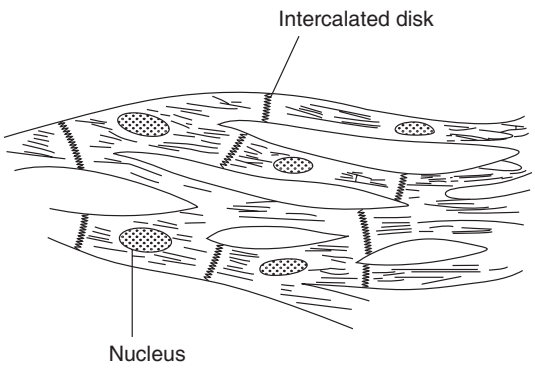


Figure 4.2 Cardiac muscle.

wider and located at the Z-line unlike the A–I junction in the skeletal muscle.

The properties of cardiac muscles are

- autorhythmicity,
- excitability,
- conductivity,
- contractility,
- all-or-none law,
- staircase phenomenon,
- refractory period, and
- tone.

AUTORHYTHMICITY

The junctional tissue of the heart is capable of generating its own impulses without external stimulation. The ability of the cardiac muscles to generate their own impulses is called **autorhythmicity**. This is due to unstable membrane potential in the junctional tissues.

Pacemaker Potential (Fig. 4.3)

- Pacemaker potential is the slow and positive increase in membrane potential occurring between the end of one action potential and the commencement of the next action potential. It is also called **prepotential**.
- Sodium and potassium ions move in and out of the cell through leak channels at rest in an excitable tissue.
- In the pacemaker tissue, the permeability of the membrane to potassium ions decreases spontaneously.

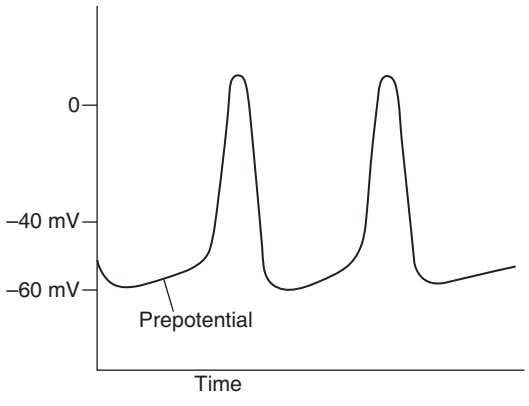


Figure 4.3 Pacemaker potential.

- The efflux (exit) of potassium ion is reduced resulting in a depolarizing change.
- This initial depolarizing change causes the opening of the **transient calcium channels** and entry of calcium ions. This produces the prepotential.
- Later, **long-lasting calcium channels** open, facilitating the rapid entry of calcium ions. This produces depolarization.
- At the end of depolarization, the calcium channels close and the potassium channels open.
- Efflux of the potassium ions result in repolarization. Thus, an impulse is generated.
- The impulse generated spreads over the cardiac muscle.

The action potentials produced in SA and AV nodes are due to the calcium ions with little contribution from the sodium ions.

The stimulation of the vagus nerve supplying the nodal tissue results in hyperpolarization of the membrane. The slope of prepotential decreases reducing the heart rate. The action is mediated through the muscarinic receptors.

The stimulation of the sympathetic fibers causes a rapid decline in the membrane potential increasing the rate of spontaneous discharge. This increases the slope of prepotential and hence the heart rate.

EXCITABILITY

Excitability is the responding property of the tissue to a stimulus.

Action Potential in Ventricular Muscle

Excitability is the responding property of the tissue to a stimulus. In the cardiac muscle, it occurs in the following phases:

- The resting membrane potential in a normal cardiac muscle is about –80 to –90 mV.
- The action potential in the ventricular muscle occurs in the following phases:
  - **Phase 0**: Excitation of cardiac muscle causes the entry of *sodium ions* resulting in depolarization.

- **Phase 1**: There is slight repolarization after a rapid depolarization. It is due to sudden closure of sodium channels associated with transient efflux of potassium ions.
- **Phase 2**: The state of depolarization is maintained by delayed and sustained entry of **calcium ions**. This phase is called *plateau.*
- **Phase 3**: The exit of *potassium ions* coupled with the closure of calcium channels results in the phase of repolarization.
- **Phase 4**: Restoration of the resting membrane potential constitutes Phase 4. The ionic balance is restored by sodium–potassium and sodium–calcium ATPase pumps.

The duration of the cardiac muscle action potential is about 200–250 ms (**Fig. 4.4**).

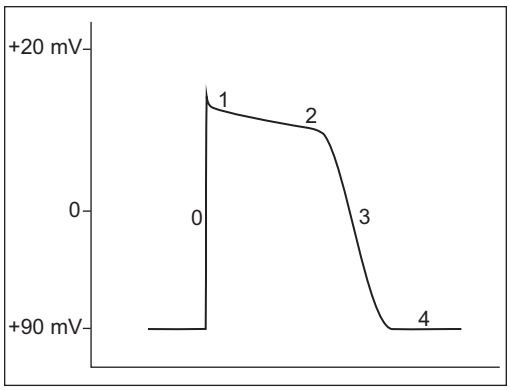


Figure 4.4 Cardiac muscle action potential. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Action Potential in Atrial Muscle

The ionic basis of action potential in the atrial muscle is the same as in the ventricular muscle. In atrial muscle action potential, the duration of plateau phase (Phase 2) is shorter. Therefore, the repolarization phase (Phase 3) is prolonged.

CONDUCTIVITY

The impulses generated by the pacemaker tissue spread to the entire cardiac muscle with the help of the **conducting system** or the **junctional tissue** of the heart.

The presence of gap junctions between the cardiac muscle fibers hastens the movement of ions. This helps in rapid spread of impulse in the cardiac muscle.

CONTRACTILITY

The chemical changes and mechanical shortening of the muscle in response to a stimulus is contractility. The molecular basis for the cardiac muscle contraction is similar to that of the skeletal muscle contraction.

Two atria or two ventricles contract simultaneously as a single unit. However, atrial and ventricular contractions never overlap. It occurs one after the other.

Starling's Law

The force of contraction is directly proportional to the initial length of the muscle fiber within physiological limits. With respect to the heart, it is stated as the greater the preload, the greater the force of contraction within physiological limits.

Importance

- The action potential helps to maintain the cardiac output equally on both the right and the left sides of the heart.
- In cases of heart failure, the heart pumps out excess blood which has accumulated during earlier contractions to reduce load on the heart.

Molecular Basis

- When the muscle is stretched, actin and myosin are separated exposing active binding sites on the actin molecule. This increases the number of cross-bridges formed. The greater the number of cross-bridges formed, the greater the force of contraction.
- The actin filament moves a longer distance in a stretched muscle during contraction. This increases the force of contraction.
- When the muscle is stretched, resting metabolism increases. There is increase in

the temperature of the muscle resulting in better enzymatic activity. This enhances the force of muscle contraction.

ALL-OR-NONE LAW

When the cardiac muscle is stimulated with the threshold stimulus, it responds to its maximum. However, if the stimulus is subthreshold, the muscle does not show any response.

The all-or-none law applies to the entire cardiac muscle.

STAIRCASE PHENOMENON

The heart is stopped by stimulation of the vagus nerve. Later, the heart is allowed to beat again by withdrawing the vagal stimulation. The initial few contractions show an increase in the amplitude of contractions. This is termed the **staircase phenomenon**.

It is due to

- accumulation of calcium ions released during the previous contraction potentiating the effect of subsequent contractions,
- decrease in the viscosity of the muscle, and
- increase in the temperature of the muscle, which enhances the enzymatic activity and hence improves contraction.

REFRACTORY PERIOD

Refractory period is a brief interval immediately after a response before it recovers to produce a second response in an excitable tissue.

The absolute refractory period is the period during which the second stimulus of any intensity fails to produce a response. It corresponds to a major part of the cardiac muscle action potential. The cardiac muscle cannot be tetanized because of a long absolute refractory period.

The relative refractory period is the period during which the second stimulus of greater intensity produces a response. It corresponds to the last part of repolarization.

TONE

Tone is a partial contracted state of myocardium without an external stimulus.

NERVE SUPPLY TO THE HEART

The heart is supplied by the sympathetic and parasympathetic nerves (**Fig. 4.5**).

SYMPATHETIC INNERVATION

The sympathetic nerves to the heart are from the first five thoracic segments of the spinal cord. The sympathetic preganglionic fibers arise from the thoracic segments.

They reach the superior, middle, and inferior cervical ganglia located in the sympathetic chain.

The postganglionic fibers arising from these ganglia innervate the heart. The sensations from the heart are also carried by the sympathetic nerves.

Stimulation of sympathetic nerves to the heart increases

- the heart rate (positive chronotropic effect),
- force of contraction (positive inotropic effect),
- rate of conduction (positive dromotropic effect), and
- excitability (positive bathmotropic effect).

The heart rate increases by the activation of β_1 receptors.

The force of contraction increases by enhancing the influx of calcium ions by opening the long-lasting calcium channel. This is done by the formation of cAMC by the activation of adenylyl cyclase.

PARASYMPATHETIC INNERVATION

The parasympathetic nerve supply is through the vagus nerve. The preganglionic parasympathetic fibers arise from the vagal nucleus. They pass through the cardiac nerve and end in the parasympathetic ganglion

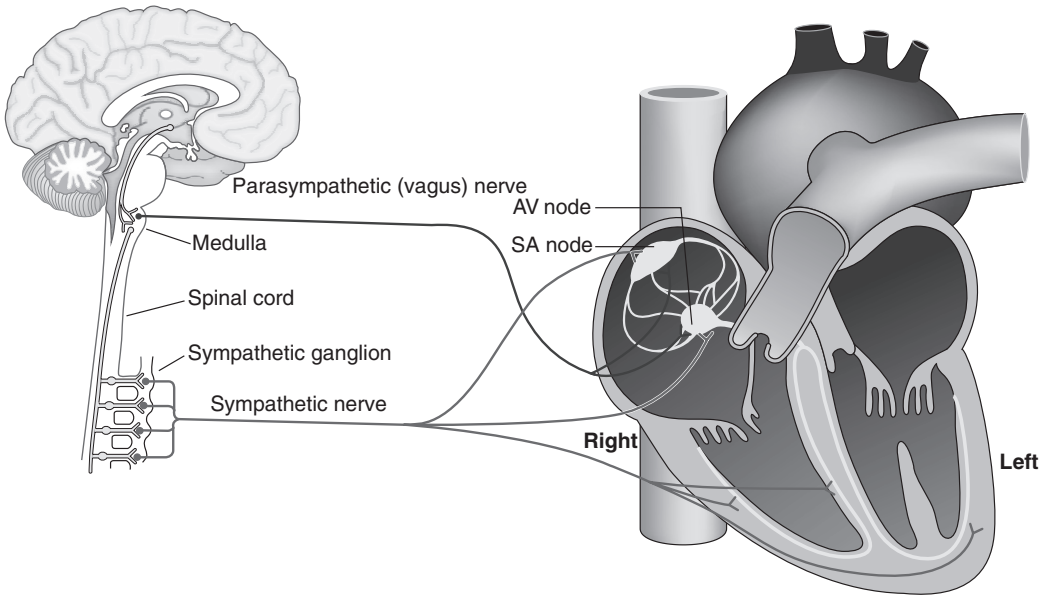


Figure 4.5 Nerve supply to the heart. *AV*, atrioventricular; *SA*, sinoatrial. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

in the heart. The postganglionic fibers arise from the ganglion to innervate the heart.

The right vagus supplies the sinoatrial (SA) node and the left vagus supplies the atrioventricular (AV) node. The stimulation of the parasympathetic nerve reduces the rate, force of contraction, and velocity of transmission of impulse.

The stimulation of the left vagus delays the conduction of the impulse through the AV node. The ventricles do not have parasympathetic supply.

Athletes have an increase in vagal tone which reduces the resting heart rate.

Parasympathetic stimulation reduces the heart rate by acting through G proteins. It promotes the efflux of potassium and decreases the slope of prepotential. This also causes hyperpolarization of the membrane and reduces the rate of impulse generation in the SA node.

It reduces the force of contraction by decreasing intracellular cAMP and delaying the opening of calcium channels.

BLOOD CIRCULATION

An artery is a blood vessel taking the blood from the heart to the different tissues of the body. Most of the arteries carry oxygenated blood except pulmonary and umbilical arteries.

The blood pumped out from the left side of the heart passes through the following:

- **Large-sized arteries**, e.g., aorta
- **Medium-sized arteries**, e.g., femoral artery
- **Small-sized arteries**
- **Arterioles** (resistance vessels)—the precapillary sphincter offers resistance to the flow of blood and hence they are termed resistance vessels
- **Capillaries** (exchange vessels)—the capillaries have a thin wall. They participate in exchange of substances and gas across its wall. The blood returns to the heart through the venous system
- **Venules** (capacitance vessels)—they are capable of storing a reasonable quantity of blood when it is not in circulation and release the same when it is needed most.

- **Major veins**, e.g., superior and inferior vena cava, return blood to the right side of the heart.

The circulation of blood through arterioles, capillaries, and venules is termed **microcirculation**.

STRUCTURE OF BLOOD VESSEL

The blood vessels except the capillaries have distinct layers in their wall. The layers from outside to inside are

- tunica adventitia (externa),
- tunica media, and
- tunica intima (interna) (**Fig. 4.6**).

The **tunica adventitia** is made up of elastic and collagen fibers. It has great tensile strength and maintains the integrity of the vessel.

The **tunica media** is made up of vascular smooth muscles and elastic fibers. The muscle fibers are arranged in concentric layers and they help to maintain the size of the blood vessel.

The **tunica intima** is further made up of three layers:

1. Internal elastic lamina
2. Lamina propria
3. Endothelial layer

Internal elastic lamina has pores. It allows the passage of various substances.

Lamina propria has elastic fibers, areolar tissue, and lipid deposits.

Endothelial lining is smooth. The smooth surface prevents clotting within the blood vessels.

The endothelial lining is considered the largest endocrine gland.

It secretes various hormones and physiologically useful substances.

Nitric oxide and endothelium-derived relaxing factor are produced by lining of the blood vessel.

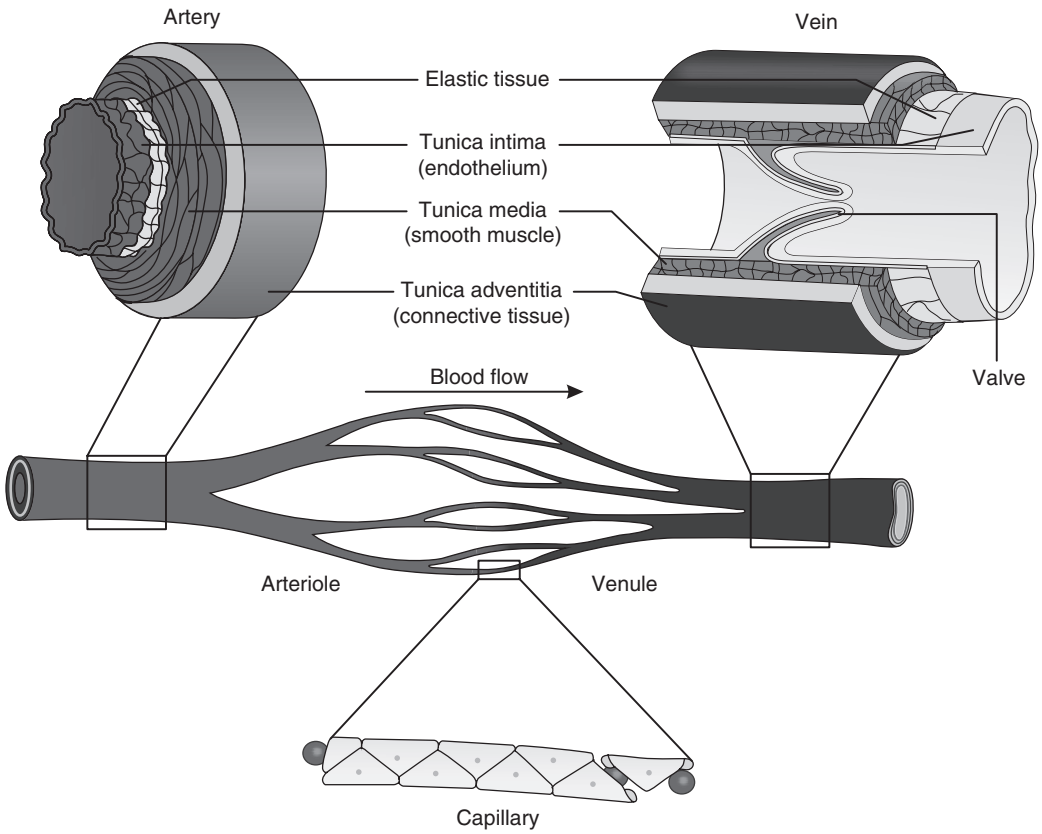


Figure 4.6 Structure of the blood vessel. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Vascular Smooth Muscle

The vascular smooth muscle responds to circulating vasoconstrictor, vasodilator substances, and stimulation of autonomic nerves.

Vasoconstrictor substances cause contraction of vascular smooth muscle. This results in narrowing of the blood vessel (vasoconstriction).

Vasodilator substances produce relaxation of the smooth muscle resulting in dilation of the blood vessel (vasodilation).

The normal size of the blood vessel is maintained by tone in the vascular smooth muscle.

Contraction of Vascular Smooth Muscle

Calcium ions are needed for contraction of the vascular smooth muscle. The sequence of events occurring in contraction of the vascular smooth muscle is similar to contraction of the smooth muscle elsewhere in the body.

Calcium ion channel blockers prevent contraction of the vascular smooth muscle resulting in relaxation. These blockers are used in the management of hypertension.

ARTERIES

The arteries carry blood away from the heart toward the various body tissues. They carry oxygenated blood, except the pulmonary artery which carries deoxygenated blood. They contain all the three layers seen in the blood vessels. The tunica media is well formed with vascular smooth muscle. The larger arteries exhibit Windkessel effect.

Windkessel Effect

Blood is pumped into the blood vessels during systole. When blood is pumped into large- and medium-sized arteries, they expand to accommodate the sudden rush of blood. The expansion of the blood vessel is possible due to the presence of plenty of elastic and collagen fibers in their walls.

During diastole, blood is not pumped from the heart. The walls of the blood vessel undergo elastic recoil and push the blood forward. The potential energy stored in the walls of the blood vessel during systole is converted to kinetic energy to propel the blood during diastole.

The Windkessel effect helps in converting intermittent pulsatile flow from the heart to continuous flow through arteries.

It prevents excessive increase in pressure during systole.

As the age advances, the walls of the blood vessel become harder due to the loss of elasticity. This causes an increase in systolic blood pressure, termed **systolic hypertension**.

ARTERIOLE

The arterioles are smaller sized blood vessels with narrower lumen. They have less of elastic fibers but are rich in vascular smooth muscles.

The arterioles offer maximum resistance to the flow of blood due to lack of elasticity. This high resistance reduces the blood pressure as blood flows through the arterioles. The pulsatile flow is converted into a continuous steady flow.

The vascular smooth muscles present in the arterioles respond to vasoconstrictor substances. The arteriolar constriction increases the systemic arterial blood pressure but reduces pressure in the capillaries.

An adjustment in the size of the arteriole regulates

- blood flow through the tissues and
- movement of fluid across the walls of capillaries.

CAPILLARIES

Arterioles divide into thin-walled blood vessels termed **metarterioles**. Metarterioles feed into capillaries. The opening of a capillary is surrounded by smooth muscles forming **precapillary sphincter**.

The capillaries (**Fig. 4.7**) are thin-walled blood vessels. They have a single layer of endothelial cells on the basement membrane. The capillary walls have pores.

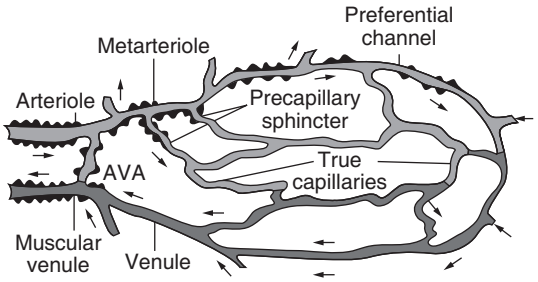


Figure 4.7 Arrangement of a capillary network. *AVA*, arteriovenous anastomosis. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edition. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

The capillary network provides a large cross-sectional area. The blood flows slowly through the capillaries. It provides an ideal condition for the exchange of gases and other substances between the blood and the interstitial fluid.

The fluid that leaks across the capillary wall is returned to systemic circulation through the lymphatic system.

The arterioles and venules are connected by short channels bypassing capillaries. These are termed **shunts or arteriovenous anastomoses**.

VEINS

The veins are thin-walled blood vessels; they are larger in size as compared to arteries. The veins also have three layers in their walls and respond to vasoactive substances. They can hold a large quantity of blood without a significant increase in pressure.

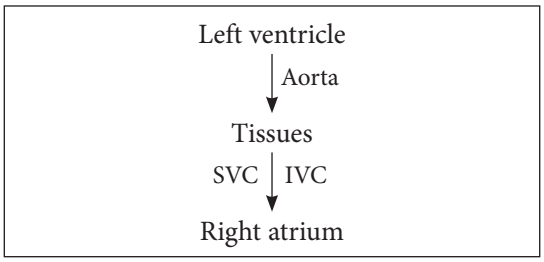
The veins have valves formed from the intima layer of the blood vessel. These valves permit the passage of blood only toward the heart. They transport blood at low pressures.

ANGIOGENESIS

Angiogenesis is the formation of new blood vessels. Formation of new blood vessels is essential during fetal and adult life. Growth of a new blood vessel is required for wound healing, formation of corpus luteum, and formation of endometrium. Growth of tumor is also associated with the development of new blood vessels. Vascular endothelial growth factor (VEGF) is required for angiogenesis.

SYSTEMIC CIRCULATION (MAJOR OR GREATER CIRCULATION)

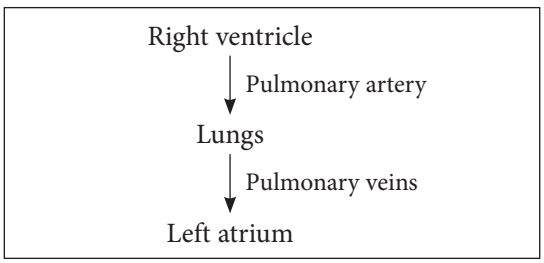
The oxygenated blood from the left ventricle reaches different tissues of the body passing through the aorta. The deoxygenated blood from these tissues reaches the right atrium through the superior and inferior vena cavae. This circulation is called **systemic circulation** (**Fig. 4.8**).



PULMONARY CIRCULATION (LESSER OR MINOR CIRCULATION)

The deoxygenated blood from the right ventricle reaches the lungs through the pulmonary artery.

The oxygenated blood comes back to the left atrium through the pulmonary vein. This is called **pulmonary circulation** (**Fig. 4.8**).



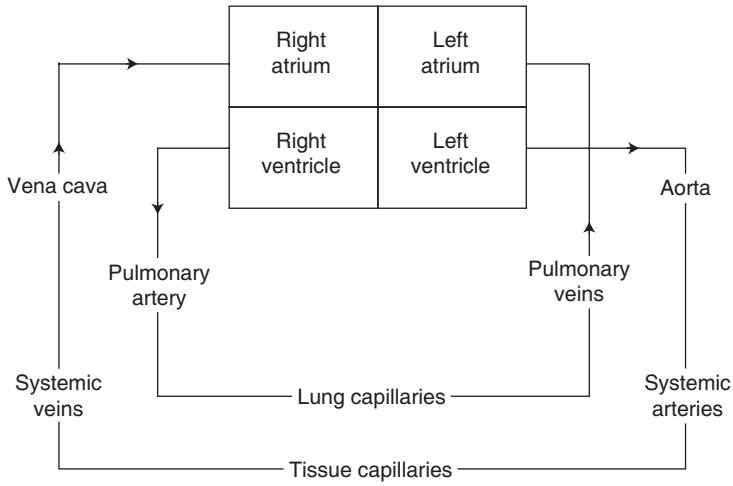


Figure 4.8 Systemic and pulmonary circulation.

CONDUCTING SYSTEM OF THE HEART (JUNCTIONAL TISSUE)

The heart has a special system that generates electrical impulses to cause rhythmic contractions.

It also has a specialized pathway that conducts these impulses. This allows the atria to contract before the ventricles. It ensures proper filling of the ventricles which will be later pumped into various parts of the body.

This special system is a combination of specialized excitable tissues and pathways which are collectively termed the **conducting** or **junctional tissue**.

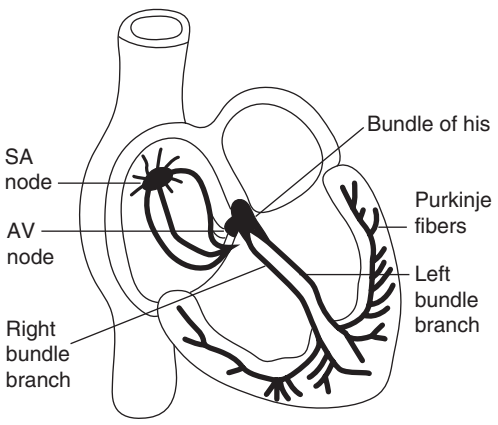


Figure 4.9 Conducting system of the heart.

The conducting system of the heart (**Fig. 4.9**) consists of

- sinoatrial node (SA node),
- atrioventricular node (AV node),
- bundle of His,
- right and left bundle branches, and
- Purkinje fibers.

SINOATRIAL NODE

The SA node is a specialized cardiac tissue present at the junction of the superior vena cava and the right atrium. It generates the maximum number of impulses (70–80/min) and sets the pace for the heart. Hence, it is called **pacemaker** of the heart. It is supplied by right vagus as it arises from right-sided embryonic structures.

ATRIOVENTRICULAR NODE

The AV node is present between the atrium and the ventricle close to the AV opening.

It develops from left-sided embryonic structures and is innervated by the left vagus.

It can produce 50–60 impulses/min. It is connected to the SA node by means of internodal pathways (anterior: Bachman, middle: Wenckebach, and posterior: Thorel).

It conducts the impulse generated by the SA node to AV node.

BUNDLE OF HIS

The AV node continues as the bundle of His. It gives out a left bundle branch and continues as the right bundle branch. The left bundle branch divides into anterior and posterior divisions. It supplies the left ventricle and interventricular septum. The right bundle branch supplies the right ventricle.

PURKINJE FIBERS

Purkinje fibers are specialized myocardial cells with gap junctions. They form a network in both the ventricles and transfer impulses from the bundle branches to the working myocardium. Purkinje fibers can generate about 15–40 impulses/min.

They are large in size and the gap junctions exhibit a high level of permeability. Hence, the velocity of impulse transmission is greatest in these fibers.

The Purkinje system facilitates spread of impulse to all portions of the ventricle within a short time. This results in contraction of all portions of both the ventricles in a synchronous manner to ensure effective pumping of blood.

Purkinje fibers directly supply papillary muscles. They help in contraction of papillary muscle and tighten chordae tendineae before the contraction of ventricle. This prevents prolapse of AV valves and regurgitation of blood.

ORIGIN AND SPREAD OF THE CARDIAC IMPULSE

The heart has the ability to generate its own impulses and set the pace for its beat (**Fig. 4.10**).

The cardiac impulse originates at the SA node.

It spreads over the atria through the atrial musculature. The depolarization of atria is completed in 0.1 second.

It passes through the internodal pathway to reach the AV node. The conduction through the AV node is slow.

There is a delay of 0.1 second (AV nodal delay). The delay is shortened by stimulation of the sympathetic nerves and lengthened by the parasympathetic stimulation (vagi).

Impulses from the AV node pass through the bundle of His, the left and right bundle branches, and the Purkinje fibers to activate the ventricles.

The wave of depolarization for the ventricles begins at the base of the septum and spreads to the other parts through Purkinje fibers in 0.08–0.1 seconds.

The wave of depolarization commencing on the left side of the interventricular septum moves to the right side across the midportion of the septum. Later, it spreads to the apex down the septum. It returns to the AV groove passing along the ventricular wall. The wave moves from the endocardial to the epicardial surface. The last portions to depolarize are the posterobasal part of the ventricles, pulmonary conus, and upper part of the septum.

ATRIOVENTRICULAR NODAL DELAY

The delay occurring at the AV node before excitation spreads to the ventricle is termed **AV nodal delay**. The normal delay is 0.1 second. This is due to the small size of the fibers, long refractory periods, and low resting membrane potential.

Importance

The AV nodal delay allows contraction of the atria to be completed before the ventricle starts contracting.

The AV nodal delay is reduced by the stimulation of the sympathetic nerve and increased by the stimulation of the parasympathetic nerve to the heart.

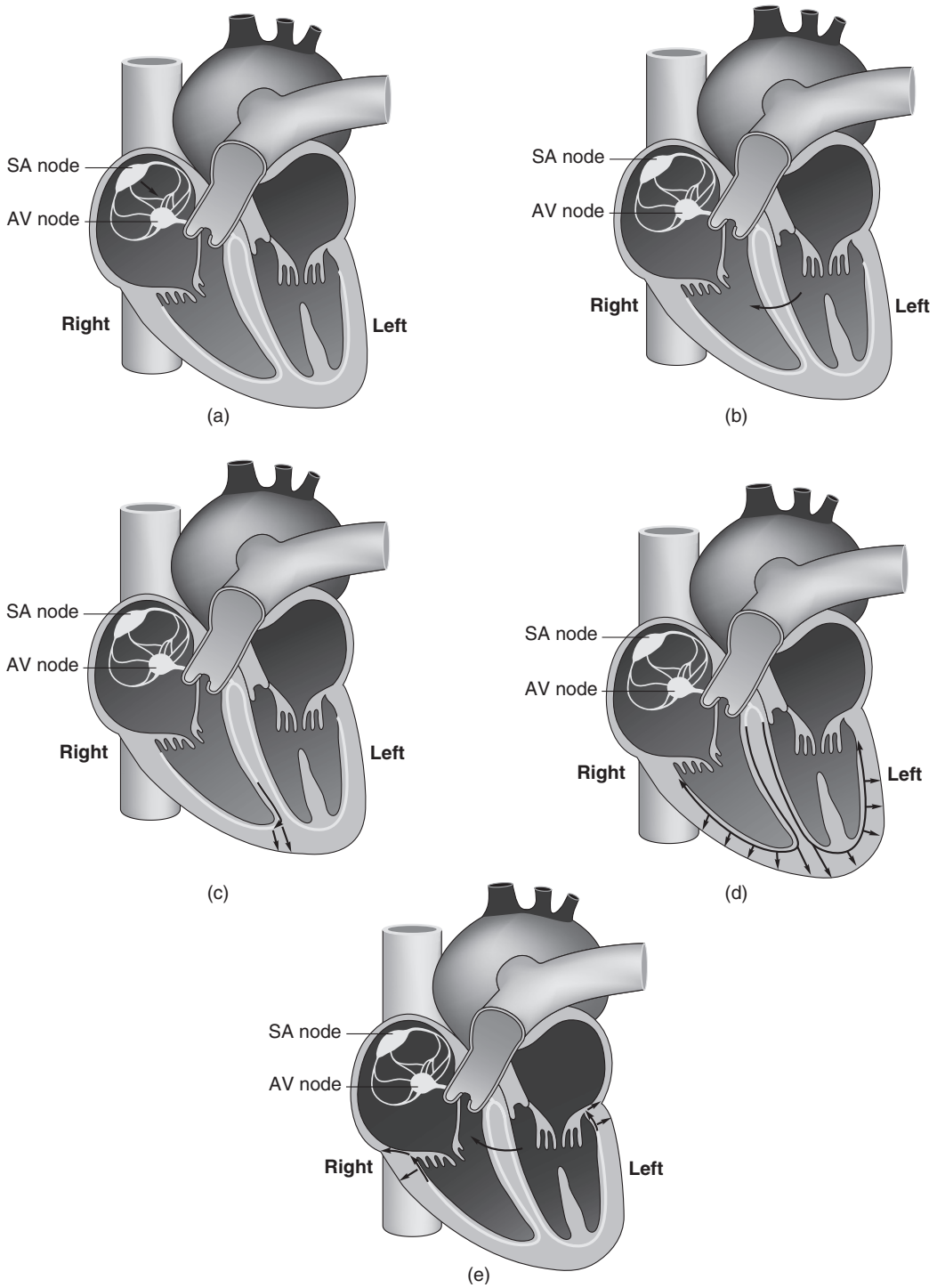


Figure 4.10 Spread of cardiac impulse. (a) Atrial activation, (b) septal activation from left to right, (c) activation of the anteroseptal region of the ventricular myocardium, and (d) activation of a major portion of ventricular myocardium from endocardial surfaces. (e) Late activation of the posterobasal portion of the left ventricle and the pulmonary conus. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Velocities of conduction in different cardiac tissues are as follows:

SA node	0.05 m/s
AV node	0.05 m/s
Atrial pathways	1.00 m/s
Bundle of His	1.00 m/s
Purkinje system	4.00 m/s
Ventricular muscle	1.00 m/s

CLINICAL NOTES

Abnormal Pacemakers

The AV node and other parts of the conducting system can generate impulses in abnormal conditions and function as cardiac pacemakers. Diseased atrial and ventricular muscle fibers can discharge impulses repeatedly due to reduction in their membrane potential (**ectopic focus**).

Heart Block

Damage to the conducting system of the heart hampers impulse transmission. This results in heart block. Depending on the site of damage, it is categorized as follows:

- Sinoatrial block
- Atrioventricular block

Depending on the extent of damage, it is categorized into first-, second-, and third-degree heart block. In **first-degree heart block**, the PR interval is prolonged beyond 0.2 second.

In **second-degree heart block**, all the atrial impulses do not reach the ventricle. Ventricular beat may follow second or third atrial beat. It is termed 2:1, 3:1 block.

The P wave is not regularly followed by the QRS complex.

In **complete** or **third-degree heart block**, the transmission of impulse from atria to ventricles is completely interrupted. Ventricles beat at a lower rate termed **idioventricular rhythm**.

Arrhythmias

Heart arrhythmia, also known as cardiac dysrhythmia, is a condition in which the heart beat is irregular. They include bradyarrhythmia, atrial and ventricular flutters and fibrillations.

The most common symptom of arrhythmia is awareness of heart beat called **palpitation**.

Arrhythmia can lead to decreased blood pressure resulting in dizziness fainting (syncope), and cardiac arrest.

An abnormal increase in the heart rate reduces the ventricular filling time. This causes cardiac output to decrease, resulting in heart failure.

The condition can be clinically managed by gentle massaging of the region of bifurcation of the carotid artery. This stimulates the baroreceptors and the vagus nerve. The heart rate is brought down by parasympathetic stimulation. This is termed **vagal maneuver**.

Defibrillation

Ventricular fibrillation results in ineffective pumping of blood from the heart. Normal sinus rhythm has to be restored by high-voltage electrical shocks. This process is termed **defibrillation** (**Fig. 4.11**).

This is done by passing high-voltage alternate current through large electrodes placed on either side of the heart for a very short duration.

The intense current stops fibrillation by forcing the ventricular muscle into refractoriness.

All the action potentials stop for about 3–5 seconds; the heart starts beating with rhythm of sinus or any other part of heart functioning as a pacemaker.

Small-sized defibrillators can be implanted surgically in patients prone to developing ventricular fibrillation.

Defibrillators are programmed to discharge within 5–10 seconds on detecting ventricular fibrillation.

Artificial Pacemakers (Implanted Pacemakers)

Artificial pacemakers are external electronic devices implanted when the patient has severe bradycardia due to defective functioning of a natural pacemaker or the conducting system of the heart.

Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) is a procedure performed during emergency. It is a combination of chest compression and

(*Contd.*)

artificial ventilation (commonly mouth-to-mouth respiration). The procedure is undertaken to preserve the function of the brain till remedial measures are administered as in cases of cardiac arrest. Closed chest cardiac massage is given to maintain the cardiac output and coronary circulation. Pressure is applied by placing both hands, one over the other, on the lower part of sternum above the xiphoid process. Sternum is depressed 4–5 cm toward the spine.

The process is repeated 80–100 times a minute.

Mouth-to-mouth breathing should be started if the breathing has stopped.

One ventilation should be followed by a cycle of five chest compressions.

This cycle is repeated till the restoration of cardiopulmonary function or at least for duration of 30 minutes.

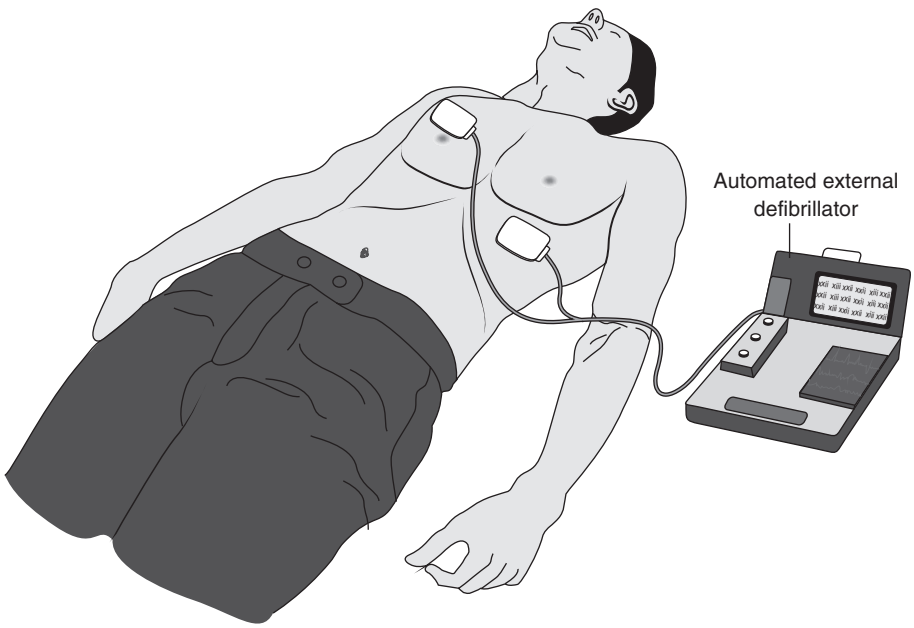


Figure 4.11 External defibrillator in use. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

ELECTROCARDIOGRAM

Electrocardiogram (ECG) is the electrical activity of the heart recorded from the surface of the body. ECG is recorded by using different electrodes.

The body acts as a volume conductor. The body fluids are good conductors of electricity. The summated effect of action potentials from the cardiac muscle can be recorded from the surface. The record of fluctuations in potential during a cardiac cycle is the electrocardiogram.

ECG is recorded by using an **active** or **exploring electrode** and an **indifferent electrode** at zero potential (as in unipolar recording) or by using two active electrodes (as in bipolar recording).

1. **Bipolar limb leads** (**Fig. 4.12**)
   - *Lead I*: Between the right arm (–ve) and the left arm (+ve)
   - *Lead II*: Between the right arm (–ve) and the left leg (+ve)
   - *Lead III*: Between the left arm (–ve) and the left leg (+ve)

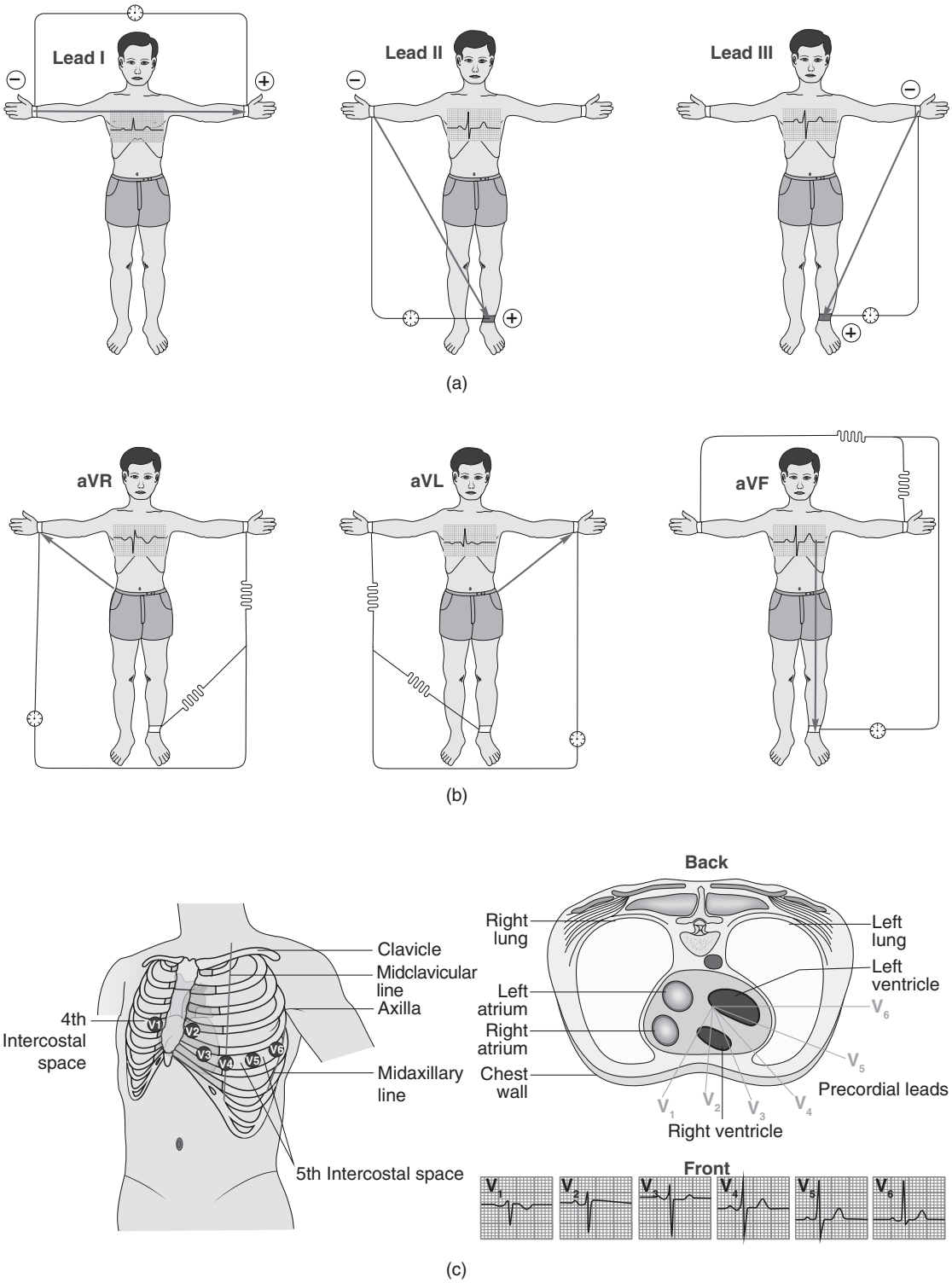


Figure 4.12 ECG recording. (a) Bipolar limb leads. (b) Augmented unipolar limb leads. (c) Chest leads. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

2. **Augmented unipolar limb leads**
   - *aVR:* Exploring electrode connected to the right arm
   - *aVL:* Exploring electrode connected to the left arm
   - *aVF:* Exploring electrode connected to the left leg

   The indifferent electrode is kept at zero potential.
3. **Chest leads**
   - V_1: Fourth intercostal space at the right margin of sternum
   - V_2: Fourth intercostal space at the left margin of sternum
   - V_3: In between V_2 and V_4
   - V_4: Fifth intercostal space in the midclavicular line
   - V_5: Fifth intercostal space in the anterior axillary line
   - V_6: Fifth intercostal space in the midaxillary line

ECG RECORDING

ECG is recorded on a heat-sensitive paper. Time (duration) is measured on the *X*-axis and voltage is measured on the *Y*-axis. The paper has small boxes of 1 mm^2. Five small squares are demarcated by a thick line. Each small square on the *X*-axis corresponds to 0.04 second. A block of five small squares is equal to 0.2 second (0.04 × 5). Each of the small squares on the *Y*-axis corresponds to 0.1 mV.

CALIBRATION

The instrument has to be calibrated before recording the ECG. For normal recording, the instrument has to be calibrated to show a displacement of 10 mm for 1 mV. Thus, each mm corresponds to 0.1 mV.

SPEED

The ECG paper can be moved at two different speeds depending on the type of recording. Normally, a speed of 25 mm/s is used. The paper moves a distance of 1500 mm (25 × 60) in 1 minute. A speed of 50 mm/s is used when the heart rate is high and a better view of different waves is required. At this speed, 3000 mm of the paper moves in 1 minute.

CLINICAL NOTES

The heart rate can be calculated by using the ECG in a regularly beating heart. The heart rate will be 1500/RR interval. This method cannot be used to calculate the heart rate when the beats are irregular.

EINTHOVEN'S LAW

Einthoven's law states that the voltage recorded in standard limb lead II is equal to the sum of voltages recorded in the other two leads:

Lead II = Lead I + Lead III.

This equation helps to check the proper placement of leads. Einthoven's law holds good for ECG recording done by using standard bipolar limb leads.

EINTHOVEN'S TRIANGLE

Einthoven's triangle is an equilateral triangle with the upper corners corresponding to the right and left shoulders. The lower corner corresponds to pubic symphysis. The heart which is oriented downward and to the left is considered to be situated in the center of this triangle. The recording electrodes (leads) placed on the right arm, left arm, and left leg is considered to be placed at the corners of this equilateral triangle.

In standard bipolar limb leads, the recordings are obtained between any two corners of the triangle. The fourth lead connected to the right leg serves as an earth (ground terminal).

In augmented limb leads, unipolar recording is obtained from one of the three corners of the triangle. The exploring electrode is placed

at one corner and the other two corners are connected through a high resistance to function as an indifferent electrode.

In augmented electrodes, recording shows an enhanced voltage (about 50% more) when compared to the voltage in standard limb leads.

In chest leads, a unipolar exploring electrode is placed in one of the six locations on the chest. The left arm, right arm, and left leg are connected together through a high resistance to form the indifferent electrode.

NORMAL ECG

The waves recorded in ECG depend on the pattern of depolarization and on the position of the heart in relation to the recording electrodes. The recording done in limb lead II is used for studying different waves of ECG (**Fig. 4.13**).

P-Wave

P-wave is produced due to atrial depolarization. Its normal duration is 0.1 second and voltage 0.1–0.12 mV.

It is an upright wave in all the leads except aVR. In this lead, a P-wave is inverted.

The P-wave is inverted in nodal rhythm. In this condition, impulses travel in the opposite direction, from the AV node toward the SA node.

The P-wave is absent when the SA node does not generate the impulses as in SA block.

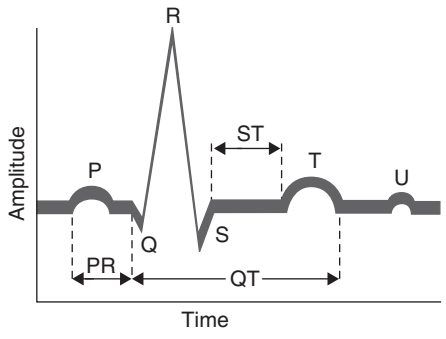


Figure 4.13 Electrocardiogram.

QRS Complex

QRS complex is produced due to ventricular depolarization. Its duration is 0.08–0.1 second and voltage varies from 0.5 to 2 mV.

The QRS complex in limb lead helps to determine the electrical axis of the heart.

T-Wave

T-wave is produced due to ventricular repolarization. Its normal duration is 0.15 seconds and voltage 0.3 mV.

It is a positive wave in all the leads except aVR. An inverted T-wave in lead III is considered normal. Inversion of T-wave in other leads is considered abnormal. An inverted T-wave is seen in myocardial ischemia, infarction, and ventricular hypertrophy.

U-Wave

U-wave is due to repolarization of the septum of ventricle and papillary muscle.

Atrial Repolarization Wave

The repolarization wave of atrium is submerged in QRS complex.

PR Interval

The PR interval is measured from the beginning of the P-wave to the beginning of the QRS complex. It measures about 0.12–0.16 seconds with a maximum of 0.2 seconds. It indicates the time for atrial depolarization and conduction of impulse through the AV node.

The PR interval increases gradually beat after beat in the Wenckebach phenomenon.

It is very short in the Wolff–Parkinson–White syndrome.

QT Interval

The QT interval is from the beginning of the Q-wave to the end of the T-wave. It is the measure of ventricular electrical events (depolarization and repolarization). Its normal duration is 0.40–0.43 seconds.

The QT interval is altered by drugs such as quinidine.

ST Segment

The ST segment is a segment between the end of the S-wave and the beginning of the T-wave. This segment is present on the isoelectric line. As the ventricle is completely depolarized, no potential difference is recorded in this segment.

Ischemia of ventricular muscle causes the depression of the ST segment.

Myocardial infarction results in elevation of the ST segment.

In cases of ischemia or infarction, ventricular muscles are not completely depolarized. Hence, a potential difference is recorded. This potential difference causes the shift of the ST segment from the isoelectric line.

HIS BUNDLE ELECTROCARDIOGRAM

His bundle electrocardiogram (HBE) is the record of electrical activity from the AV node, bundle of His, and Purkinje system. This can be recorded by placing the electrode close to the tricuspid valve with the help of a catheter and simultaneously recording activity with three or more leads.

ELECTRICAL AXIS OF THE HEART

The mean electrical axis is the direction of the largest vector in limb leads. It correlates with the long axis of the heart. The mean electrical axis can be used to determine the orientation of heart.

The normal mean electrical axis is about +55° (range –30° to +110°). If the heart is rotated in the anticlockwise direction, it is termed **left axis deviation**.

Hypertrophy of the left ventricle results in left axis deviation.

Rotation of heart in a clockwise direction beyond +110° is called **right axis deviation**.

Hypertrophy of the right ventricle produces right axis deviation.

Tall and thin people with narrow thorax have a vertical electrical axis.

A tall R-wave in lead II indicates a normal electrical axis of the heart.

In left axis deviation, the R-wave becomes prominent in lead I.

When the R-wave is taller in lead III, it is suggestive of right axis deviation.

CARDIAC VECTORS

Cardiac muscle cells show electrical activity with waves of depolarization and repolarization. At any given time, these waves having different magnitudes are moving in different directions. The resultant electrical activity having both magnitude and direction constitutes the **cardiac vector**.

Depolarization of atria commences at the SA node and spreads through atrial muscles to the AV node.

The resultant vector is directed downward and toward left (P-wave).

Later, the wave of depolarization spreads through the ventricular muscle from inside to outside.

Since the wall of the left ventricle is thick, the direction of vector is downward and left (QRS complex).

Activation of the last part of the ventricle (basal part) results in the vector directed upward and toward right (QRS complex).

The wave of ventricular repolarization spreads from the outer to the inner surface of ventricular myocardium. Since it is opposite in direction to the wave of ventricular depolarization, it produces a vector in the same direction as that of ventricular depolarization, directed downward and toward left (T-wave).

When the vector is directed toward a positive electrode (exploring electrode), a positive wave is recorded. When the vector moves away from the positive electrode, a negative wave is recorded in ECG.

USES OF ECG

- Useful in calculating the heart rate in a regularly beating heart
- Detecting functional abnormalities of heart such as heart blocks, arrhythmias, and myocardial infarction

CLINICAL NOTES

Stress ECG

- ECG recorded at rest in some individuals does not give an indication about ischemia. If there are symptoms suggestive of ischemia, ECG is recorded during graded physical activity. The changes in stress ECG recording provide evidence for ischemia of cardiac muscle.
- The subject is asked to run on a treadmill. Speed and gradient are gradually increased till the subject can no longer continue the exercise due to exhaustion or reaches the predicted heart rate, whichever occurs earlier.
- ECG is continuously recorded during the activity. Any demonstrable change in ECG with special reference to the ST segment confirms the presence of ischemia.
- Failure to achieve a desired increase in BP is suggestive of ventricular decompensation secondary to extensive ischemia.

Ambulatory ECG (Holter Monitoring)

ECG from one or more leads is recorded continuously by using a small portable device for duration of 24–48 hours. These recordings are later transmitted to the cardiac center for evaluation.

Recording of ECG signals over a prolonged period during the routine activities of the subject/patient will help to detect abnormal rhythms. Holter monitoring is useful in detecting the episodes of ischemia or arrhythmia which occur occasionally.

CARDIAC CYCLE

The cardiac cycle is the cyclical repetition of various changes in the heart from beat to beat (**Fig. 4.14**).

The contraction of the heart is called **systole**. During systole, blood is ejected from the contracting chamber of the heart.

The relaxation of heart is termed **diastole**. During diastole, blood collects in chambers of the heart.

The normal duration of a cardiac cycle is 0.8 second when the heart rate is 75 beats/min (60 sec/75 beats = 0.8 sec).

The duration of each cardiac cycle depends on the heart rate. An increase in the heart rate decreases the duration of the cardiac cycle.

Two atria or two ventricles contract simultaneously, but the atrial and ventricular contractions never overlap.

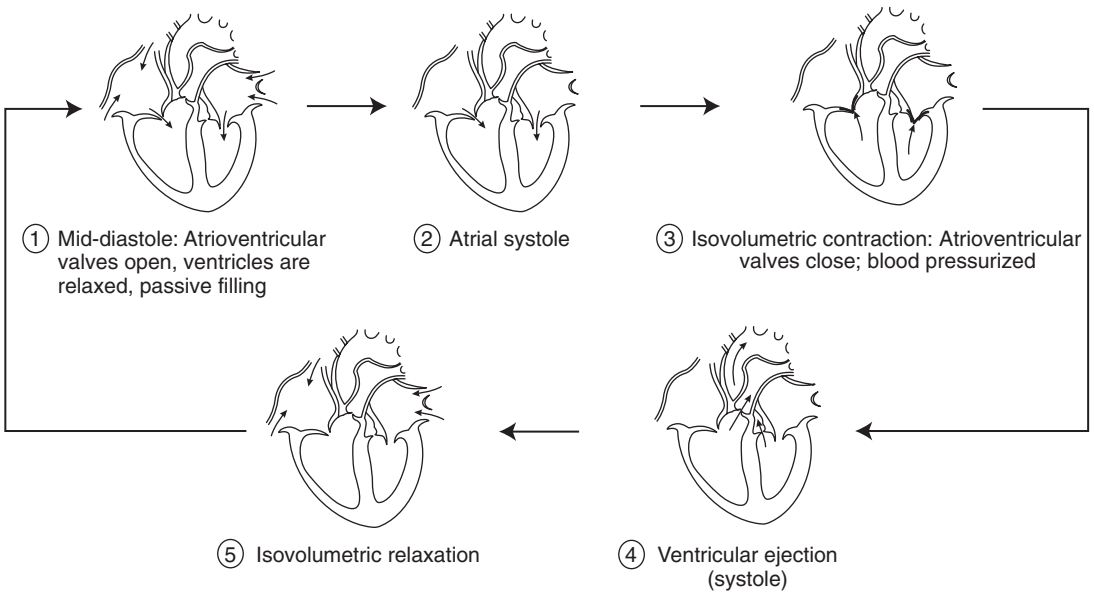


Figure 4.14 Major phases of the cardiac cycle.

Depolarization activates a wave of contraction through the myocardium. Atrial contraction commences after the P wave of ECG. Ventricular systole starts at the end of the R wave and ends after the completion of the T wave. These contractions change the pressure in a particular sequence resulting in flow of blood through the chambers of the heart and blood vessels.

MECHANICAL EVENTS DURING CARDIAC CYCLE

The mechanical events during the cardiac cycle are divided into atrial and ventricular events.

ATRIAL SYSTOLE AND DIASTOLE

During major part of the cardiac cycle, the atrium is relaxing. Atrial systole lasts for 0.1 second and its diastole for 0.7 seconds. It may be noted that atria contracts for a short duration and relaxes during major part of the cardiac cycle.

Mechanical Events (Fig. 4.15)	
Atrial Events	
Atrial systole	0.1 s
Atrial diastole	0.7 s
Ventricular Events	
Ventricular systole	0.3 s
Ventricular diastole	0.5 s
Ventricular Systole	
Isovolumetric contraction phase	0.05 s
Rapid ejection phase	0.10 s
Reduced ejection phase	0.15 s
Ventricular Diastole	
Protodiastolic phase	0.04 s
Isovolumetric relaxation phase	0.06 s
First rapid-filling phase	0.10 s
Slow-filling phase or diastasis	0.20 s
Last rapid-filling phase	0.10 s

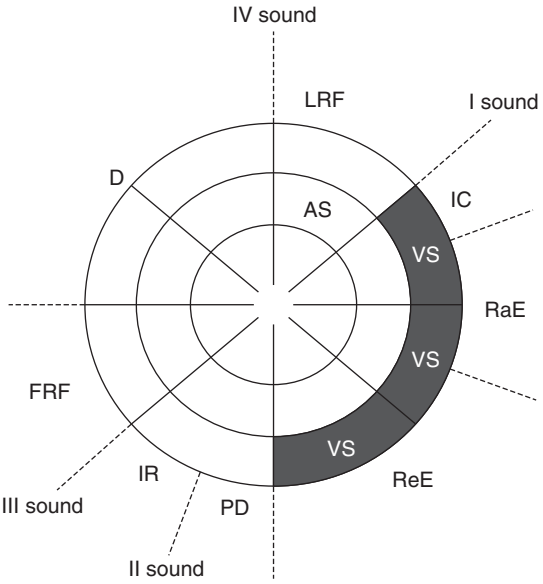


Figure 4.15 Mechanical events during a cardiac cycle. *IC*, isovolumetric contraction; *RaE*, rapid ejection; *ReE*, reduced ejection; *PD*, protodiastole; *IR*, isovolumetric relaxation; *FRF*, first rapid filling; *D*, diastasis; *LRF*, last rapid filling; *AS*, atrial systole; *VS*, ventricular systole.

Ventricular Systole

- **Isovolumetric contraction phase**: At the beginning of ventricular systole, the AV valve is open and the semilunar valve is closed. Due to ventricular contraction, the intraventricular pressure increases and the blood tries to enter the atrium. This is prevented by closure of the AV valve producing the **first heart sound**. Now, the ventricle becomes a closed cavity containing blood. It continues to contract. As the volume of ventricle does not change, this phase is called isovolumetric contraction phase. However, the intraventricular pressure increases due to continued ventricular contraction.
- **Rapid ejection phase**: When the intraventricular pressure increases above the pressure in the aorta (80 mm Hg) and pulmonary artery (10 mm Hg), the aortic and pulmonary semilunar valves open. This forces the blood into these vessels rapidly. The intraventricular pressure rises to a maximum and declines gradually till

the end of systole. The peak right ventricular pressure is 25 mm Hg and the left ventricular pressure is about 120 mm Hg

- **Reduced ejection phase**: The continued contraction of the ventricles pushes the remaining blood into the pulmonary artery and the aorta slowly. At the end of this phase, the ventricles begin to relax. About 70–90 mL of blood is pumped out of the ventricle during each ventricular systole. This is called **stroke volume**. At the end of systole, the ventricle contains 50 mL of blood (**end-systolic ventricular volume**).

Ventricular Diastole

- **Protodiastolic phase**: During this phase, the ventricles begin to relax. The AV valves are closed and the semilunar valve is still open. As the intraventricular pressure decreases below the pressure in the aorta and pulmonary artery, blood tries to come back into the ventricle. This is prevented by closure of the semilunar valve producing the **second heart sound**.
- **Isovolumetric relaxation phase**: Now, the ventricle is again a closed cavity, which is relaxing. During this phase, the intraventricular pressure goes below the atrial pressure.
- **First rapid-filling phase**: The reduced intraventricular pressure causes the opening of AV valves and there is sudden rush of blood. Turbulence to the flow of blood through narrow opening produces the **third heart sound**.
- **Slow-filling phase or diastasis**: During this phase, both atria and ventricles are relaxing. The AV valve is open. Blood entering the atria fills the ventricles passively.
- **Last rapid-filling phase**: This phase coincides with atrial contraction. The atrial systole forces the blood from the atria into the ventricle. Turbulence produced due to a rapid rush of blood produces the **fourth heart sound**. At the end of diastole, the ventricle contains about 130 mL of blood. This is the **end-diastolic ventricular volume**. The percentage of end-diastolic ventricular volume pumped during each stroke is **ejection fraction**. It is about 65%.

The events occurring in the right and left sides of the heart are similar. However, there is a slight difference in the timings of the activities.

PRESSURE CHANGES (Fig. 4.16)

The chambers of the heart show different pressures during different phases of the cardiac cycle. Generally, both atria and right ventricle have low pressure when compared to the left ventricle, which has a high pressure.

Ventricular Pressure Changes

In a normal individual, the pressure in the left ventricle reaches a maximum of 120–140 mm Hg during the rapid ejection phase. The pressure in the right ventricle during the corresponding period is about 25–30 mm Hg. During diastole, the left ventricular pressure drops to about 15–20 mm Hg and the right ventricular pressure reaches 0 mm Hg.

Aortic Pressure Changes

The aortic pressure change is around 120 mm Hg at the beginning of the rapid ejection phase of the ventricle and about 80 mm Hg at the beginning of the ventricular diastole.

Pulmonary Artery Pressure Changes

The pulmonary artery pressure reaches a maximum of 25–30 mm Hg during ventricular systole and reduces to 0 mm Hg during ventricular diastole.

Atrial Pressure Changes

The atrial pressure varies between 0 mm Hg when it is relaxing and a maximum of 15–20 mm Hg during its contraction.

The atrial systole starts after the P-wave of ECG; the ventricular systole starts near the end of R-wave and is completed after the T-wave.

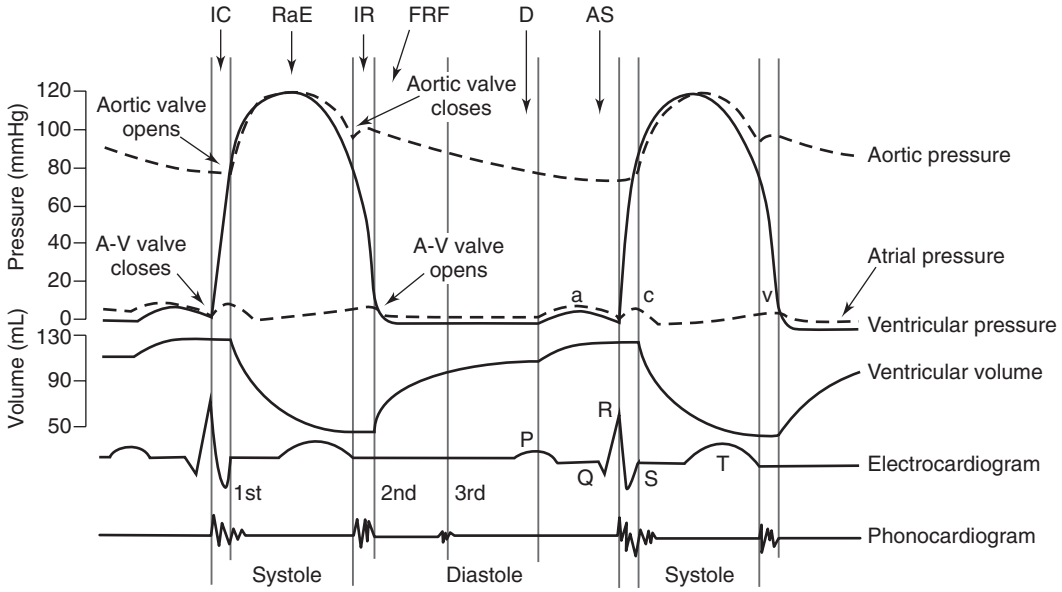


Figure 4.16 Pressure and volume changes during a cardiac cycle, ECG, and phonocardiogram (Wigger's diagram). *IC*, isovolumetric contraction; *RaE*, rapid ejection; *IR*, isovolumetric relaxation; *FRF*, first rapid filling; *D*, diastasis; *AS*, atrial systole.

VOLUME CHANGES (Fig. 4.16)

The ventricular volume changes are studied during different phases of the cardiac cycle.

- During atrial contraction, blood enters the ventricles. As a result of the entry of blood, there is a slight increase in the ventricular volume.
- Atrial contraction is followed by commencement of the ventricular contraction.
- Beginning of ventricular contraction is marked by the closure of AV valves.
- The ventricle is now a closed cavity that is contracting. There is no change in the volume of the ventricle which is under the isovolumetric contraction phase.

The atrial systole starts after the P-wave of ECG; the ventricular systole starts near the end of R-wave and is completed after the T-wave.

- The isovolumetric contraction phase is terminated by the opening of the semilunar valves.
- It is followed by the rapid ejection phase. As a substantial quantity of blood contained in the ventricle is ejected out rapidly during this phase, there is a sharp fall in the ventricular volume.
- The ventricles continue to contract ejecting the blood relatively slowly. This is reduced ejection phase. During this phase, the ventricular volume decreases slowly.
- Reduced ejection phase is followed by the ventricular diastole.
- During the protodiastolic phase, there is no change in the ventricular volume.
- The protodiastolic phase ends with the closure of semilunar valves.
- Now ventricles are closed cavities, relaxing.
- During the isovolumetric relaxation phase, there is no change in the ventricular volume.
- Decrease in the intraventricular pressure causes the opening of the AV valves.
- Opening of the AV valves marks the beginning of the first rapid-filling phase. During this phase, there is a significant increase in the ventricular volume due to a sudden rush of blood from the atrium.

- There is a slow increase in the ventricular volume during diastasis (slow-filling phase) which follows the first rapid-filling phase.
- The slow-filling phase is followed by the last rapid-filling phase due to contraction of the atrium.

HEART SOUNDS

There are four heart sounds. These sounds are produced due to the closure of valves or turbulence to the flow of blood during different phases of the cardiac cycle.

The heart sounds are produced due to vibrations set up by the closure of valves and vibrations of the walls of the heart, blood vessel, and column of blood in the vessel.

The first and second heart sounds are heard by using a stethoscope. The other sounds are demonstrated by the **phonocardiogram**.

The heart sounds are auscultated in the following areas (**Fig. 4.17**):

- **Mitral area**: It is located in the left fifth intercostal space, half an inch medial to the mid-clavicular line.
- **Tricuspid area**: It is located at the left border of sternum in the fifth intercostal space.
- **Aortic area**: It is located in the second intercostal space at the right border of sternum.
- **Pulmonary area**: It is located in the second intercostal space at the left border of sternum.

Both first and second heart sounds are heard in all the four areas (**Table 4.1**). However, the first heart sound is heard better in the mitral and tricuspid areas; the second heart sound is better heard in the aortic and pulmonary areas.

During prolonged inspiration, the second heart sound is split due to asynchronous closure of the aortic and pulmonary semilunar valves.

The **third heart sound (S_3)** is produced by a sudden rush of blood during the first rapid filling phase.

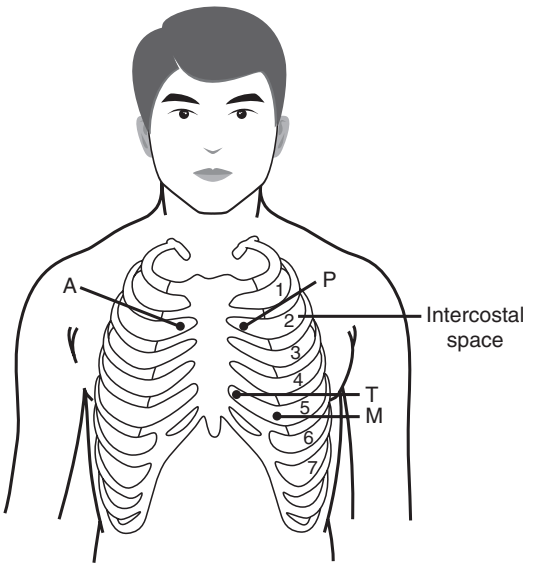


Figure 4.17 Areas of auscultation. *A*, aortic area; *P*, pulmonary area; *M*, mitral area; *T*, tricuspid area.

Table 4.1 Difference Between the First and Second Heart Sounds

Features	First Heart Sound	Second Heart sound
Cause	Closure of AV valves	Closure of semilunar valves
Duration	0.09–0.15 seconds	0.12 seconds
Frequency	25–45 Hz	50 Hz
Character	Prolonged, loud	Short, sharp (high pitch)
Heard as	Syllable LUBB	Syllable DUP
Heard best in	Mitral and tricuspid areas	Aortic and pulmonary areas
ECG	Coincides with R wave	Coincides with the end of T wave

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

It is low in frequency and intensity and can be heard in normal children and young adults.

The third heart sound in middle and old age is considered abnormal. It is produced by conditions that increase ventricular filling during early diastole, such as mitral regurgitation.

The **fourth heart sound (S_4)** is produced by rush of blood during the last rapid filling phase due to atrial contraction. It is a low-frequency sound produced by failing the left ventricle and in restrictive cardiomyopathies. It is also heard in left ventricular hypertrophy and severe aortic stenosis.

MURMURS

Murmurs are abnormal sounds produced due to turbulence in the flow of blood. They are appreciated when blood flows through a narrow opening as in mitral stenosis or through a defective valve as in aortic regurgitation.

The murmur heard between the first and second heart sounds is **systolic murmur**.

Systolic murmur is heard in aortic stenosis and mitral regurgitation.

Diastolic murmur is heard between the second and first heart sounds of the next cardiac cycle. It is heard in mitral stenosis and aortic regurgitation.

PULSE

The pulse is an expansile impulse arising from the base of the heart traveling along the walls of the blood vessel.

The pulse is also defined as the expansion and elongation of the arterial wall traveling along the walls of the blood vessel.

Types of pulsations are as follows:

- Arterial
- Venous

The radial artery is commonly used to examine the arterial pulse.

Venous pulsations are observed in the jugular vein.

Arterial pulsations are felt better and venous pulsations are seen better.

ARTERIAL PULSE

The arterial pulse tracing (**Fig. 4.18**) is called the **sphygmogram**. It is recorded by using the instrument **sphygmograph**. The normal pulse is a catacrotic pulse. (Dicrotic notch is in the descending limb of pulse tracing.) The normal pulse rate is 60–90 beats/min. A decrease in the pulse rate is **bradysphygmia** and an increase is **tachysphygmia**. The heart rate and pulse rate are equal in a normal individual. In some pathological conditions, the pulse rate is less than the heart rate. It is called **pulse deficit**.

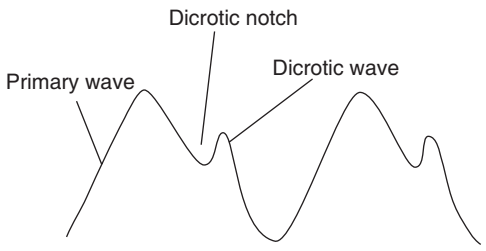


Figure 4.18 Arterial pulse tracing.

Pulse tracing has the following:

- **Primary wave**, or a percussion wave, is produced due to ventricular systole.
- **Dicrotic notch** is present in the descending limb of the pulse tracing. It is produced due to the rolling back of blood in aorta at the beginning of ventricular diastole.
- **Dicrotic wave** follows the dicrotic notch. It is due to the sudden closure of semilunar valves.

The arterial pulse is examined under the following headings by palpating the superficial artery like the radial artery (**Fig. 4.19**):

- **Rate**: Number of beats per minute counted for one complete minute
- **Rhythm**: Regularity of the occurrence of pulse wave (regular/irregular)
- **Volume**: Extent of displacement of the palpating finger (normal/high/low volume)
- **Character of the vessel wall**: Thickened and palpable/soft and not palpable

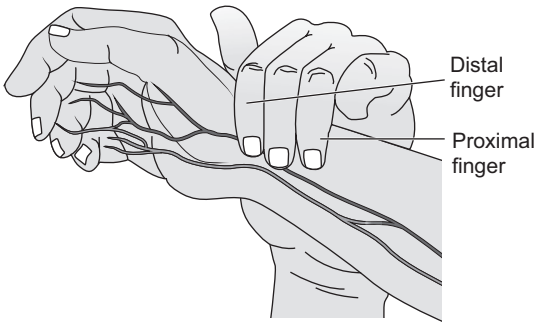


Figure 4.19 Palpation of arterial pulse. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- **Character of the pulse**: Anacrotic/catacrotic
- **Equality of the pulse**: Equal/unequal in volume in both the upper limbs
- **Comparison of volume**: Comparison of the volume of upper and lower limb pulse

JUGULAR VENOUS PULSE (JVP)

The examination of venous pulse gives an indication about the functioning of the right side of the heart. A recording of venous pulsation (**Fig. 4.20**) has the following waves:

1. **Positive waves**
   - *a-wave*: It is produced due to atrial systole.
   - *c-wave*: It is produced due to ventricular contraction (isovolumetric contraction) causing the AV valve to bulge into the atrium.
   - *v-wave*: It is produced due to increased intra-atrial pressure during the filling of atrium.
2. **Negative waves**
   - *x-wave*: It is caused due to fall in intra-atrial pressure during diastole.

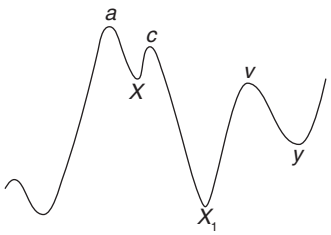


Figure 4.20 Jugular venous pulse tracing.

- *x_1 wave*: It is caused due to distension of atria as the AV ring is pulled down by ventricular contraction.
- *y-wave*: It is caused due to fall in intra-atrial pressure owing to the opening of the AV valve.

CLINICAL NOTES

Tachycardia (Tachysphygmia)

Tachycardia is an increase in pulse rate above 90 beats/min. Physiologically, it occurs during muscular exercise. Pathologically, it is seen in fever, circulatory shock, and thyrotoxicosis.

Bradycardia (Bradysphygmia)

Bradycardia is a decrease in pulse rate below 60 beats/min. Physiologically, it is seen in athletes and during sleep. Pathologically, it is observed in myxedema and heart blocks.

High-Volume Pulse

Physiologically, high-volume pulse is seen during exercise. Pathologically, it is seen in hyperdynamic states such as fever, thyrotoxicosis, and aortic regurgitation (water hammer pulse or Corrigan's pulse or collapsing pulse).

Low-Volume Pulse

Physiologically, low-volume pulse is seen during sleep, and pathologically, it is observed during shock.

Pulsus Paradoxus

Blood pressure varies with inspiration and expiration. It declines during inspiration and increases during expiration. In pulsus paradoxus, the amplitude of pulse wave decreases markedly during deep inspiration. The normal drop in pressure is about 10 mm Hg. When the drop is more than 10 mm Hg, it results in pulsus paradoxus.

Pulsus Alternans

In this condition, there are alternate strong and weak pulsations. It is due to alteration in the stroke volume in successive beats. It is seen in severe myocardial infarction and cardiac failure.

Pulse Deficit

Pulse deficit is a condition in which the pulse rate is less than the heart rate.

HEMODYNAMICS OF CIRCULATION

The arteries transport blood under high pressure and velocity to the tissues. Veins transport blood back to the heart and function as reservoirs. Blood flows in veins under low pressure. Hence, arteries have a strong vascular wall and veins have a thin wall. The heart pumps blood into aorta. The mean pressure in aorta is about 100 mm Hg. The pressure reduces to 0 mm Hg in venae cavae before the blood empties into the right atrium. The mean pulmonary artery pressure is about 16 mm Hg.

Blood flow through the vessel is influenced by

- pressure difference between the ends of the vessel and
- resistance to the flow of blood (vascular resistance).

$$\text{Flow} = \frac{\text{Perfusion pressure}}{\text{Resistance}}$$

Effective filtration pressure is the difference between intraluminal pressure at the arterial and the venous end.

Blood flow is the quantity of blood passing through a given point in circulation in a given duration of time. It is about 5000 mL/min which is equal to cardiac output at rest.

Blood flow is measured by

- electromagnetic flowmeter and
- ultrasonic Doppler flowmeter.

TYPES OF BLOOD FLOW (Fig. 4.21)

Blood flow is of the following two types:

1. Laminar or streamline flow
2. Turbulent flow

Laminar Flow

The normal flow of fluid in a tube is **laminar** or **streamline**. The movement of blood in blood vessels follows the same pattern. The blood cells move in the same direction in concentric layers. The velocities of motion of these layers are different. The central lamina has maximum velocity. It is lowest in the outermost lamina which is in contact with the vessel wall. When the fluid follows a laminar flow pattern, it does not produce any sound. Hence, no sound is heard when a normal artery is auscultated.

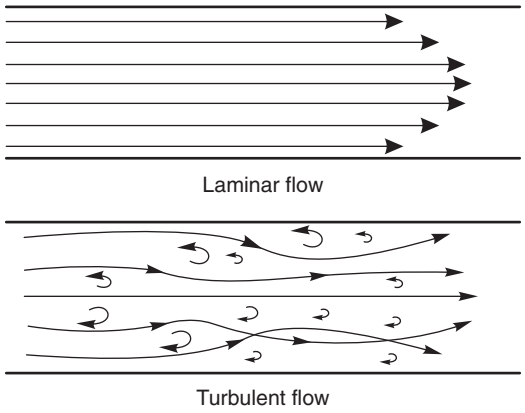


Figure 4.21 Pattern of laminar and turbulent flow. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Turbulent Flow

The loss of the laminar pattern of flow results in turbulence. The molecules move randomly in different directions and collide with each other. When the flow pattern is turbulent, it becomes noisy.

The following conditions produce turbulent flow:

- Significant increase in the rate of blood flow
- Passage of blood through an obstructed vessel
- Blood passing over a rough surface
- Path of blood taking a sharp turn

REYNOLD'S NUMBER

Reynold's number is a number to evaluate whether the flow pattern is turbulent or laminar.

It is calculated by using the formula

$$Re = \frac{\rho V D}{\eta}$$

where ρ is density of fluid, *V* velocity of flow, *D* diameter of the tube, and η viscosity of the fluid.

Reynold's number above 2000 produces turbulent flow in straight and smooth vessels. The velocity at which the flow becomes turbulent is called **critical velocity**. However, when Reynold's number rises above 200–400, turbulent blood flow will be seen in some branches of the vessel. It disappears as blood flows along the blood vessel.

Korotkoff sounds heard during measurement of blood pressure are also due to the turbulence of blood flow.

RESISTANCE TO BLOOD FLOW

It is the hindrance offered to the flow of blood through the vessel. It is measured as peripheral resistance unit (PRU). The resistance of the entire systemic circulation, termed **total peripheral resistance** is 1 PRU. It can increase up to 4 PRU when the blood vessels throughout the body are strongly constricted. It can be as low as 0.2 PRU when the blood vessels are grossly dilated. The total pulmonary vascular resistance is about 0.14 PRU which is on seventh of the resistance in systemic circulation.

The measure of blood flow through the vessel for a given pressure difference is termed **conductance**.

Conductance of blood depends on

- diameter (varies directly as the fourth power of diameter; the greater the diameter, the greater the blood flow);
- viscosity (varies inversely with viscosity; the greater the hematocrit, the greater the viscosity);
- pressure (blood flow increases with an increase in pressure. Doubling of pressure increases flow by four to six times. This is due to the increase in force that pushes the blood and distension of the vessels).

Shear Stress

Blood flowing through the vessel creates a force on the endothelium termed **shear force**. It is proportional to the product of viscosity and shear rate.

Capacitance (Compliance)

Capacitance describes the distensibility of the blood vessel. It is inversely related to stiffness or elastance. Increase in elastance decreases compliance.

Viscosity

Viscosity is the internal property of a fluid to offer resistance to flow. It is produced due to collision of particles in a fluid flowing at different velocities.

The viscosity of plasma is 1.8 times that of water and of whole blood is three to four times as viscous as water. Hematocrit influences the viscosity of blood. An increase in hematocrit produces a proportionate increase in viscosity.

In severe anemia, the peripheral resistance is decreased due to reduction in viscosity. In anemia, the oxygen-carrying capacity is decreased which is compensated by improved blood flow due to decreased viscosity.

Critical Closing Pressure

The blood vessels collapse when the intraluminal pressure falls below the tissue pressure. The intraluminal pressure at which the flow stops is termed **critical closing pressure**.

Poiseuille–Hagen Formula

The mathematical relationship between flow in a long tube, viscosity of fluid, and radius of tube is expressed by

$$F = (P\text{A} - P\text{B}) \times (\pi/8) \times (1/\eta) \times (r^4/L),$$

where F is flow, $P\text{A} - P\text{B}$ is pressure difference between the two ends of the tube, η is viscosity, r is radius, and L is the length of the tube.

Resistance to the flow of blood is calculated by using

$$R = 8\eta L/\pi r^4.$$

It is clear from the equations that flow varies directly and resistance varies inversely as the fourth power of radius. A small change in the size of the blood vessel significantly alters the flow and resistance.

Laplace Law

Laplace law states that tension in the wall of a cylinder (T) is equal to the product of transmural pressure (P) and radius (r) divided by the thickness of the wall (w):

$$T = Pr/w.$$

Transmural pressure is the difference between pressure within and outside the cylinder.

In a human body, tissue pressure is very low. Hence, transmural pressure will be equal to pressure within the hollow viscus.

LOCAL CONTROL OF BLOOD FLOW

The blood flow to the tissue depends on the need and its metabolic activity. It should alter with the changing needs of the tissue.

The mechanism of blood flow control is divided into two phases:

1. **Acute control:** Change in blood flow occurring within seconds to minutes to meet the local needs by rapid vasodilation or vasoconstriction
2. **Long-term control:** A slow and controlled change in blood flow occurring over days, weeks, or months

Mechanism of Acute Control of Local Blood Flow

Tissue metabolism has a significant impact on regulating the local blood flow. The mechanisms proposed to control the local blood flow are as follows:

- Vasodilator theory
- Oxygen lack theory
- Metabolic mechanism
- Myogenic mechanism
- Reactive hyperemia
- Active hyperemia
- Endothelium-derived factors

Mechanism of Long-Term Control of Local Blood Flow

The mechanisms proposed for long-term control of the local blood flow are as follows:

- Tissue vascularity
- Angiogenic factors
- Vascularity and blood flow

Humoral Regulation of Blood Flow

Blood flow is influenced by local factors that can constrict or dilate the blood vessel. They are called vasoconstrictors or vasodilators, respectively.

Vasoconstrictors are as follows:

- Angiotensin II
- Vasopressin
- Norepinephrine
- Prostaglandins
- Endothelin
- Neuropeptide Y

Vasodilators are as follows:

- Bradykinin
- Histamine
- Prostacyclin
- VIP (vasoactive intestinal peptide)
- Endothelium-derived relaxing factor

REGULATION OF THE HEART RATE

The normal heart rate ranges from 60 to 90 beats/min. The average heart rate is 72 beats/min.

The heart rate is regulated by the neural and chemical mechanisms. The vasomotor center plays a key role in the neural regulation. The chemical regulation is brought about by general, local hormones, and metabolites.

VASOMOTOR CENTER

The vasomotor center (VMC) is present in the ventrolateral part of the medulla. The neurons regulating heart rate and blood pressure project directly to the preganglionic sympathetic fibers. VMC has the intrinsic ability to generate impulses without external stimulation.

VMC has the following areas:

- Vasodilator area
- Vasoconstrictor area
- Sensory area

Vasodilator Area

The vasodilator area is present in the medial portion of VMC. It decreases the heart rate acting through the vagus nerve.

Vasoconstrictor Area

The vasoconstrictor area is present in the lateral portion of VMC. It increases the heart rate through sympathetic stimulation.

Sensory Area

The sensory area lies in the nucleus of tractus solitarius. It receives sensory information from periphery through IX and X cranial nerves.

The heart rate is regulated by

- stimulation of the autonomic nervous system,
- reflexes arising from outside the heart,
- reflexes from within the heart, and
- other reflexes.

STIMULATION OF THE AUTONOMIC NERVOUS SYSTEM

Stimulation of the sympathetic nerve fibers increases the heart rate and produces vasoconstriction.

Stimulation of the parasympathetic fibers decreases the heart rate and produces vasodilation.

REFLEXES FROM OUTSIDE THE HEART

Baroreceptor Mechanism

The baroreceptors are specialized cells capable of sensing changes in the blood pressure.

Increase of blood pressure stimulates baroreceptors.

This inhibits VMC and stimulates vagal nucleus.

These changes decrease the heart rate (also produce vasodilation, reduced cardiac output, and blood pressure).

Chemoreceptor Mechanism

The chemoreceptors are capable of recognizing changes in the chemical nature of blood.

- Reduction in the blood flow causes local accumulation of carbon dioxide and lack of oxygen at the chemoreceptors.
- These changes stimulate the chemoreceptors. This in turn activates VMC and inhibits vagal nucleus.
- These changes increase the heart rate (also produce vasoconstriction).

Vasomotor Center Ischemic Response

Ischemia (reduced blood flow) of the vasomotor center

- stimulates vasomotor center,
- increases heart rate by intrinsic activation, and
- produces vasoconstriction.

REFLEXES ARISING FROM WITHIN THE HEART

Bainbridge Reflex

Accumulation of blood in superior and inferior vena cavae causes stretch of these vessels and activation of receptors in them. This increases the heart rate. The reflex response is called **Bainbridge reflex**.

Increased blood volume leads to an increase in the rate of firing from low-pressure B fibers. Efferent impulses pass through the divisions of the autonomic nervous system to the SA node. Hence, there is a significant change in the heart rate but no demonstrable change in the force of contraction.

Right Atrial Stimulation

Stretch of right atrium stimulates A and B receptors. Impulses from these receptors pass through the vagus nerves. The efferent pathway is through both sympathetic and parasympathetic nerves. This reflex results in increased heart rate. It helps to reduce the load on the right side of the heart by removal of blood.

Bezold–Jarisch Reflex

The Bezold–Jarisch reflex originates in cardiac sensory receptors with a nonmyelinated vagal afferent pathway. The receptors for this reflex are present in the left ventricle. Stimulation of these receptors by stretch, chemical substances, and drugs increases parasympathetic activity and decreases sympathetic activity. These effects result in bradycardia, vasodilation, hypotension, apnea followed by rapid shallow breathing.

Role of Atrial Natriuretic Peptide

Distension of atrium causes the release of hormone atrial natriuretic peptide (ANP). It reduces cardiac congestion by increasing the sodium and water excretion. This hormone also produces vasodilation.

Left Ventricular Stimulation

The left ventricle has stretch receptors. Stimulation of these receptors decreases the heart rate and produces vasodilation.

OTHER REFLEXES REGULATING HEART RATE

- Stimulation of limbic system, hypothalamus, and cerebral cortex increases the heart rate.
- In **sinus arrhythmia**, the heart rate increases during inspiration and decreases during expiration. During inspiration, the intrathoracic pressure decreases. This increases the venous return. Activation of Bainbridge reflex increases the heart rate.
- An increase of body temperature as in fever increases the heart rate by enhancing the activity of the pacemaker. For every degree Fahrenheit rise in body temperature, the heart rate increases by about 10 beats/min.
- Muscular exercise increases the heart rate by stimulation of the sympathetic system.
- Advanced stages of pregnancy are associated with an increase in the heart rate.
- Hormones such as epinephrine and thyroxine increase the heart rate. (Thyroxine increases the metabolism of the SA node.)
- The heart rate increases in heart failure and circulatory shock.
- Sleep decreases the heart rate due to reduced metabolism.
- Athletes have a low heart rate due to increased vagal tone.
- Heart blocks and myxedema produce bradycardia (decreased heart rate).
- Pain increases the heart rate by sympathetic stimulation. However, pain produced by a blow to abdomen or testis reduces the heart rate by intense vagal stimulation.

CLINICAL NOTES

Tachycardia

Tachycardia is an increase in heart rate >90 beats/min.

- Physiological causes include exercise, anxiety, and emotional disturbances.
- Pathological causes include fever and thyrotoxicosis.

Bradycardia

Bradycardia is a decrease in heart rate <60 beats/min.

- Physiologically, it is seen in athletes and during sleep.
- Pathologically, it is observed in myxedema and heart blocks.

BLOOD PRESSURE

Blood pressure is the lateral pressure exerted by a column of blood on the walls of the blood vessel through which it flows.

SYSTOLIC BLOOD PRESSURE

Systolic blood pressure (SBP) is the maximum pressure exerted during ventricular systole.

It ranges from 100 to 140 mm Hg with an average of 120 mm Hg.

DIASTOLIC BLOOD PRESSURE

Diastolic blood pressure (DBP) is the minimum pressure during ventricular diastole. It ranges from 60 to 90 mm Hg with an average of 80 mm Hg. It is the measure of peripheral resistance.

PULSE PRESSURE

Pulse pressure (PP) is the difference between systolic and diastolic blood pressure:

Pulse pressure = Systolic BP — Diastolic BP.

MEAN ARTERIAL PRESSURE

Mean arterial pressure (MAP) is the average pressure present throughout the cardiac cycle.

It is around 93 mm Hg.

It is equal to diastolic pressure plus one-third of pulse pressure:

$$MAP = DBP + \frac{1}{3} PP.$$

METHODS OF RECORDING BLOOD PRESSURE (Fig. 4.22)

Blood pressure is recorded by

- direct method and
- indirect method.

In the direct method, the artery is cannulated and pressure is recorded by using a manometer. This type of recording is done in experimental animals.

In human beings, blood pressure is recorded by the indirect method. The instrument used for recording is called sphygmomanometer.

The parts of a sphygmomanometer are

- arm cuff,
- rubber bulb, and
- mercury/aneroid manometer.

The methods for recording blood pressure are as follows:

- Palpatory method
- Auscultatory method
- Oscillatory method

Palpatory Method

The arm cuff is tied around the arm, 1 inch above the cubital fossa. The sphygmomanometer is kept at the level of the subject's heart. The radial artery pulsations are felt. The arm cuff is inflated by pressing the rubber bulb. The pressure at which the pulse disappears is systolic pressure. This is confirmed by noting the reappearance of pulse when the pressure is decreased in the arm cuff.

The palpatory method gives an approximate idea about SBP.

Auscultatory Method

The pressure in the arm cuff is increased 20 mm Hg above the systolic pressure recorded by the palpatory method. The pressure is gradually reduced. The brachial artery is auscultated for any sound.

The pressure at which the first sound is heard corresponds to the SBP. As the pressure is decreased, the character of the sound changes and finally disappears.

The pressure corresponding to the disappearance of sound is DBP.

These are **Korotkoff sounds** named after a Russian scientist who described them. The sounds are produced due to turbulence in the flow of blood.

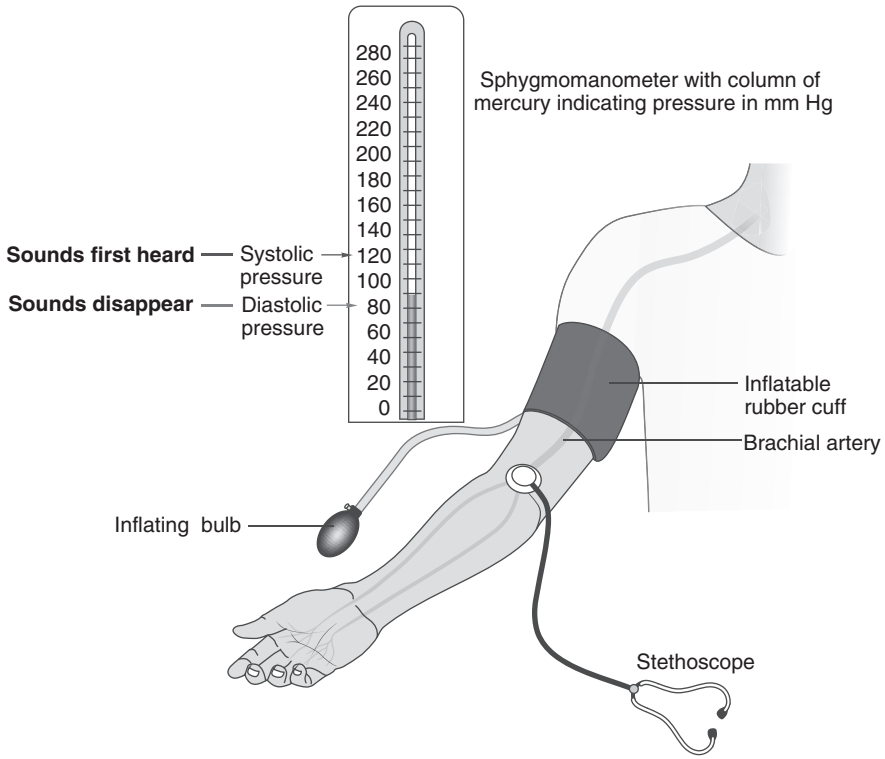


Figure 4.22 Recording blood pressure using a sphygmomanometer. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Silent Gap (Auscultatory Gap)

Silent gap is observed sometimes in people with high blood pressure.

During blood pressure recording, following the initial tapping sound, there is a period of silence during which no sounds are heard.

The sounds reappear after sometime. This gap is called **silent gap**. Because of the silent gap, the systolic pressure recorded will be lower than the actual blood pressure.

FACTORS INFLUENCING BLOOD PRESSURE

- **Age**: Blood pressure increases with age. In infants, BP is around 70/50 mm Hg. In a young healthy adult, it is around 120/80 mm Hg. Blood pressure of 140/90 mm Hg or more at any age is considered abnormal.
- **Sex**: Females (before menopause) have slightly lower BP than males.
- **Sleep**: There is a decrease in BP during sleep.
- **Meals**: Blood pressure rises after meals.
- **Emotions**: Fear or anger increases BP.
- **Exercise**: Systolic blood pressure increases during exercise.
- **Build**: Obese persons have higher BP.
- **Posture**: Blood pressure varies with posture. It is least in lying-down posture.
- **Respiration**: It varies with different phases of respiration. Systolic decreases by 4–6 mm Hg (up to 10 mm Hg) during inspiration.
- **Diurnal variation**: It is lowest in the mornings; it is higher in late afternoon and evenings.

FACTORS CONTROLLING BLOOD PRESSURE

The systemic arterial blood pressure depends on the stroke volume, heart rate, and peripheral resistance. The blood pressure is controlled by alteration in the following variables:

- **Cardiac output**: Cardiac output depends on stroke volume and heart rate. Systolic blood pressure increases as the stroke volume increases. An increase in heart rate increases the DBP.
- **Heart rate**: A mild-to-moderate increase in the heart rate does not significantly alter the BP. However, a marked increase in heart rate decreases the BP by reducing the diastolic filling time and stroke volume.
- **Peripheral resistance (PR) and elasticity of blood vessel**: Peripheral resistance varies inversely as the elasticity of the vessel wall. Further, DBP varies directly as the PR. Vasodilation reduces the PR and hence the diastolic pressure decreases. Diastolic pressure increases due to enhanced PR following vasoconstriction.
- **Viscosity of blood**: Viscosity of blood increases frictional resistance. An increase in viscosity increases the arterial blood pressure.
- **Velocity of blood flow**: An increase in the velocity of the blood flow increases the resistance and in turn enhances blood pressure.
- **Diameter of blood vessel**: Blood pressure is inversely proportional to the diameter of the blood vessel.

Marey's Law

Marey's law states that heart rate and blood pressure are inversely related:

$$\text{Heart rate } \alpha \frac{1}{\text{Blood pressure}}.$$

Exception: During exercise, both heart rate and blood pressure are increased.

REGULATION OF BLOOD PRESSURE

Short-Term Regulation

This type of regulation works for a few seconds to few minutes. Different mechanisms for short-term regulation are

1. Baroreceptor mechanism
2. Chemoreceptor mechanism
3. Vasomotor center mechanism

1. **Baroreceptor mechanism (sinoaortic mechanism; Fig. 4.23)**:

Baroreceptors are stretch receptors located in the wall of the heart and the blood vessels.

Whenever the blood pressure increases, baroreceptors present in carotid sinus (at the bifurcation of the carotid artery) and the arch of aorta are stimulated. This inhibits the VMC and stimulates the vagal nucleus. As a result, the heart rate decreases associated with vasodilation (decrease of peripheral resistance). These changes reduce the BP.

IX and X cranial nerves help in the regulation of blood pressure. Hence, they are called **buffer nerves**.

Pathway

Impulses are carried through the baroreceptors

↓

Glossopharyngeal nerve and vagus nerve

↓

Nucleus of tractus solitarius

↓

VMC, dorsal nucleus of vagus, and nucleus ambiguus

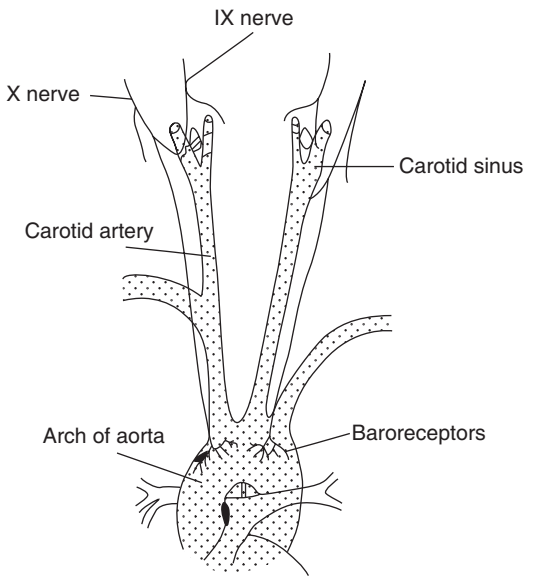


Figure 4.23 Arterial baroreceptors.

Baroreceptor mechanism

↑ Arterial blood pressure

↓

Stimulation of baroreceptors

↓

Inhibition of VMC and stimulation of vagal nucleus

↓

↓ Heart rate and vasodilation
(↓ Peripheral resistance)

↓

↓ Arterial blood pressure

Posture and Baroreceptors: Change of posture from lying down to sitting/standing reduces arterial blood pressure and blood flow to the upper parts of the body.

Discharge of impulses decreases from baroreceptors triggering spontaneous discharges from VMC. This restores blood pressure by an increase in heart rate and peripheral resistance.

2. **Chemoreceptor mechanism (Fig. 4.24)**: A decrease in BP reduces blood flow to chemoreceptors present in the carotid body and the arch of aorta.

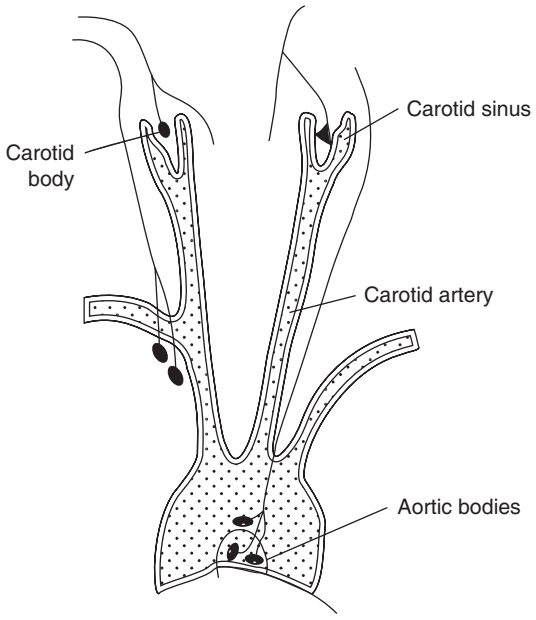


Figure 4.24 Arterial chemoreceptors.

Reduced oxygen supply stimulates the chemoreceptors. This stimulates the VMC increasing the heart rate and peripheral resistance by vasoconstriction. These changes result in increase of blood pressure.

Chemoreceptor Mechanism

↓ Arterial blood pressure

↓

Reduced blood flow to chemoreceptors

↓

Hypoxia and hypercapnia of chemoreceptors

↓

Stimulation of chemoreceptors

↓

Stimulation of VMC and inhibition of vagal nucleus

↓

↑ Heart rate and vasoconstriction
(↑ Peripheral resistance)

↓

↑ Arterial blood pressure

3. **Vasomotor center mechanism**: The reduced blood flow to VMC causes its ischemia. This stimulates the VMC causing an increase in heart rate and peripheral resistance. The net effect of these changes is an increase in BP.

Vasomotor center mechanism

Ischemic of VMC

↓

Stimulation of VMC

↓

Increased discharge from VMC

↓

↑ Heart rate and vasoconstriction
(↑ Peripheral resistance)

↓

↑ Arterial blood pressure

Abdominal Compression Reflex

Baroreceptor and chemoreceptor reflexes are associated with stimulation of abdominal muscles. Contraction of abdominal muscles mobilizes blood from the vascular reservoirs of the abdomen toward the heart. These changes increase cardiac output and blood pressure.

Skeletal Muscle Contraction and Blood Pressure

Contraction of skeletal muscle all over the body during exercise moves the blood from the peripheral blood vessels toward the heart and lungs. Increased venous return enhances cardiac output and blood pressure.

Influence of Respiration on Blood Pressure

Arterial pressure shows a change of 4–6 mm Hg with different phases of respiration. Signals arising from the respiratory center spread to the vasomotor center and influence blood pressure. The pressure in thoracic cavity becomes more negative during inspiration. The blood vessels in the chest expand, reducing blood coming to the left side of the heart. This reduces cardiac output and blood pressure.

Cushing Reflex

An increase in the intracranial pressure decreases blood flow to the VMC. Hypoxia and hypercapnia at the VMC increase the discharge from it. This enhances BP. Increased BP overcomes the raised intracranial pressure. Thus, blood flow to the intracranial structures is restored. An increase in systemic arterial BP reduces the heart rate by acting through baroreceptors.

Intermediate-Term Regulation

This mechanism works from few minutes to few hours.

- **Stress relaxation**: Increased BP exerts a greater force on the walls of blood vessel. This stretch of blood vessel causes initial contraction of the smooth muscle in its walls followed by relaxation. The relaxation of the vessel wall brings down the BP.
- **Fluid shift mechanism**: Increased BP increases the hydrostatic pressure. This pushes fluid out of blood vessel into the interstitial space. Loss of fluid from the blood vessel reduces the blood volume. There is a reduced venous return and hence a decrease in BP.
- **Renin angiotensin mechanism**: Reduced BP decreases blood flow to the kidney. This causes the juxtaglomerular apparatus of the kidney to produce renin.

  Renin acts on the plasma substrate, angiotensinogen, to form angiotensin I.

  Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE) present in the lungs. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II. Angiotensin II causes peripheral vasoconstriction and increases peripheral resistance. An increase in peripheral resistance restores the blood pressure.

Long-Term Mechanism

This mechanism helps in regulation of blood pressure over a prolonged period of time. Long-term regulation begins in a few hours after change in blood pressure and continues for days to weeks.

Renin-Angiotensin-Aldosterone Mechanism

Angiotensin II produced during the intermediate-term regulation stimulates the adrenal cortex to produce aldosterone as a delayed effect.

Aldosterone increases sodium reabsorption. Water is retained along with sodium. This helps to increase fluid volume. Increased fluid volume increases venous return to the heart and therefore the blood pressure increases.

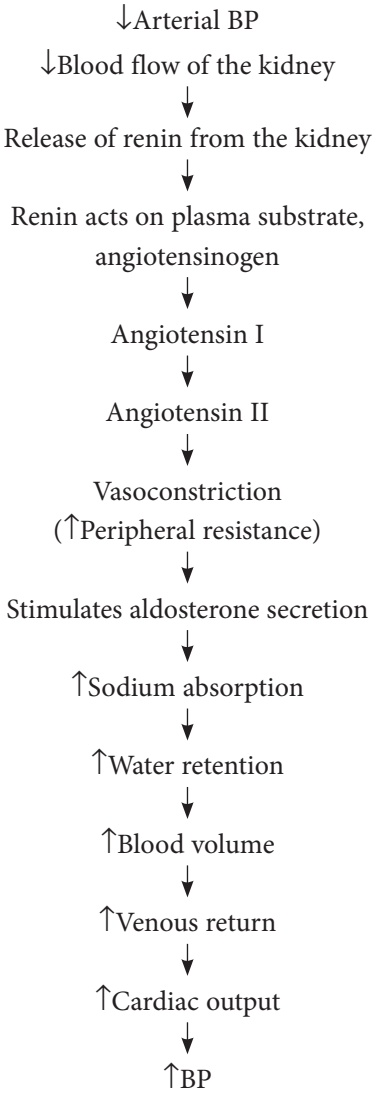
It stimulates hypothalamus and posterior pituitary to release antidiuretic hormone (ADH). ADH helps in water retention.

This mechanism also activates thirst, enhancing the fluid intake.

Retention of salt and water increases systemic arterial pressure. This in turn will increase

hydrostatic pressure facilitating the formation of a larger volume of filtrate. Increased salt and water promoting the formation of a larger volume of filtrate rich in salt is termed **pressure natriuresis and diuresis**.

Renin-angiotensin-aldosterone mechanism



EFFECT OF POSTURE ON BLOOD PRESSURE

A change of posture from lying (horizontal) to standing (vertical) position decreases the effective circulating blood volume.

In the horizontal position, all blood vessels are at the level of the heart. The weight of blood produces negligible pressure. In the vertical position, the pressure will be equal to the sum of pressures generated by cardiac contraction and weight of column of blood.

Increased pressure in the column of blood in the lower limbs will distend the veins causing peripheral pooling of blood.

An increase in capillary pressure due to gravitational forces pushes the fluid out of the blood vessel into interstitial space. The combined effect of venous pooling and increased capillary filtration reduces the effective circulating volume of blood.

The effect of posture on blood pressure is as follows:

- There is a decrease in venous return
- Transient drop in end-diastolic volume
- Stretch of ventricle is reduced (reduces the preload or reduces the initial length of muscle)
- Reduced cardiac output and hence blood pressure
- This will stimulate the baroreceptor-mediated compensatory response to restore blood pressure.

CLINICAL NOTES

Hypertension

Hypertension is a condition in which BP increases above the normal value of 140/90 mm Hg.

1. **Primary hypertension**: It is also termed essential hypertension. In about 90% of the patients with elevated BP, the cause for hypertension is not known. Essential hypertension is treatable but not curable. Effective lowering of BP can be achieved by the use of conventional antihypertensive drugs.
2. **Secondary hypertension**: Hypertension is secondary to a disease affecting the other systems. For example, pheochromocytoma, tumor of the adrenal medulla, or catecholamine-secreting tissue in other parts of the body can produce hypertension.
   - *Renal hypertension*: Constriction of the renal artery or compression of the kidney increases the blood pressure. Decreased ability of the

(*Contd.*)

kidney to excrete sodium ions can contribute to renal hypertension.

- *Cushing's syndrome*: Hypertension is due to increased secretion of deoxycorticosterone and angiotensin.

3. **Malignant hypertension**: Chronic hypertension can show necrotic arterial lesion. The condition is associated with papilledema, cerebral manifestation, and renal failure. This syndrome is termed malignant hypertension. The condition can be reversed by suitable antihypertensive therapy.

Management

A persistent increase in BP can damage the internal organs. There is a greater risk of cerebrovascular accidents.

Hence, it is advisable to maintain the BP within a normal range to reduce the risk of complication and improve survival.

Hypertension is managed by

- pharmacological methods and
- nonpharmacological methods.

Pharmacological Methods

Pharmacological methods use various drugs to manage hypertension.

The principal drugs used are

- diuretics,
- β-adrenergic receptor antagonists,
- calcium channel blocker,
- ACE inhibitors,
- angiotensin II receptor blocker, and
- vasodilators.

Diuretics reduce the fluid volume. This reduces the venous return and cardiac output, thus reducing the BP.

The cardiac muscles have β-adrenergic receptors. Blocking these receptors results in reduced cardiac output and hence reduces the BP.

The calcium channel blockers reduce the availability of calcium ions to myocardial cell. This reduces the myocardial contractility, cardiac output, and blood pressure.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II. This drug reduces BP by blocking the vasoconstrictor effect of angiotensin II.

Angiotensin receptor antagonists have action similar to that of ACE inhibitors. But they are free of side effects that are seen with the use of ACE inhibitors.

Vasodilators act directly on the smooth muscles of blood vessels. They produce vasodilation and reduce the blood pressure by decreasing the peripheral resistance.

Nonpharmacological Methods

Nonpharmacological methods for the management of hypertension include the following:

- **Diet**: Correction of obesity by regulated intake of food. Reduce the consumption of alcohol. Decrease salt intake. Salt sensitizes the receptors to circulating norepinephrine.
- **Modification of risk factors**
  - Stop/reduce smoking.
  - Effectively manage hyperlipidemia.
- **Relaxation and exercise**: Relaxation and regular exercise can lower the BP by improving physical fitness and reaction to stressful stimulus. Nonpharmacological management can be used as an adjuvant for pharmacological management.

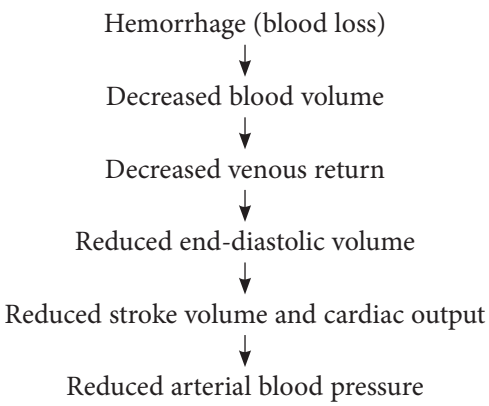
Hypotension

Hypotension is a decrease in BP below the normal value of 90/60 mm Hg. It can be caused due to low blood volume, myocardial infarction, excessive vasodilation, and chronic use of beta blockers.

Orthostatic hypotension (postural hypotension) is a common form of hypotension seen when a person suddenly stands up from a sitting or lying-down position.

HEMORRHAGE AND HYPOTENSION

Low blood pressure is termed **hypotension**. Loss of blood or significant volume of fluid causes hypotension. A serious consequence of hypotension is reduced blood flow to vital organs such as brain and heart resulting in irreversible damage.



CARDIAC OUTPUT

Cardiac output is the volume of blood ejected out from each ventricle per minute. It is about 5–6 L/min.

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$
$$= 70 \text{ mL} \times 72 \text{ beats/min}$$

Physiologically, cardiac output increases during muscular exercise. Cardiac output decreases in heart failure.

RELATED TERMS

Stroke Volume

Stroke volume is the volume of blood ejected per ventricle per beat. It is about 70–80 mL.

Cardiac Index

Cardiac index is the cardiac output per meter square of the body surface area:

$$\text{Cardiac index} = \frac{\text{Cardiac output}}{\text{Body surface area}}.$$

The normal cardiac index is 3.1–3.3 L/m^2.

It is a better indicator to evaluate the efficiency of the heart.

End Systolic Volume

End systolic volume is the volume of blood present in each ventricle at the end of systole. It is about 50 mL.

End Diastolic Volume

End diastolic volume is the volume of blood accumulated in the ventricle at the end of diastole. It is about 130 mL.

Ejection Fraction

Ejection fraction is that part (percentage) of blood which is ejected from the ventricle out of the end diastolic volume. The normal ejection fraction is about 65%.

Cardiac Reserve

Cardiac reserve is the maximum volume of blood that can be pumped out of the heart in excess of the normal cardiac output. In a normal healthy person, the cardiac reserve is about 300–400%. In athletes, it can go up to 500–600%. Cardiac reserve decreases in diseases affecting the pumping ability of the heart. The common causes are myocardial ischemia, infarction, damage to myocardium, and valvular heart diseases.

FACTORS REGULATING CARDIAC OUTPUT

Cardiac output depends on multiple factors. The factors regulating cardiac output are as follows:

1. **Venous return**: Venous return is the flow of blood back to the heart. It influences the initial length of the cardiac muscle. Whenever the venous return increases, the cardiac muscle gets stretched resulting in increased cardiac output.

   Venous return depends on the following factors:

   - *Respiration*: During inspiration, the intra-thoracic pressure decreases and becomes negative, but there is an increase in the intra-abdominal pressure.

     These changes cause an increase in the blood flow to right atrium from the lower parts of the body.
   - *Muscle pump*: When the skeletal muscles are contracting, they squeeze or compress the veins.

     This results in movement of blood toward the heart. (The flow of blood in the opposite direction is prevented by valves present in the veins; **Fig. 4.25**.)
   - *Venomotor tone*: Veins are supplied by sympathetic nerves. When they are stimulated, the veins undergo constriction mobilizing blood toward the heart.

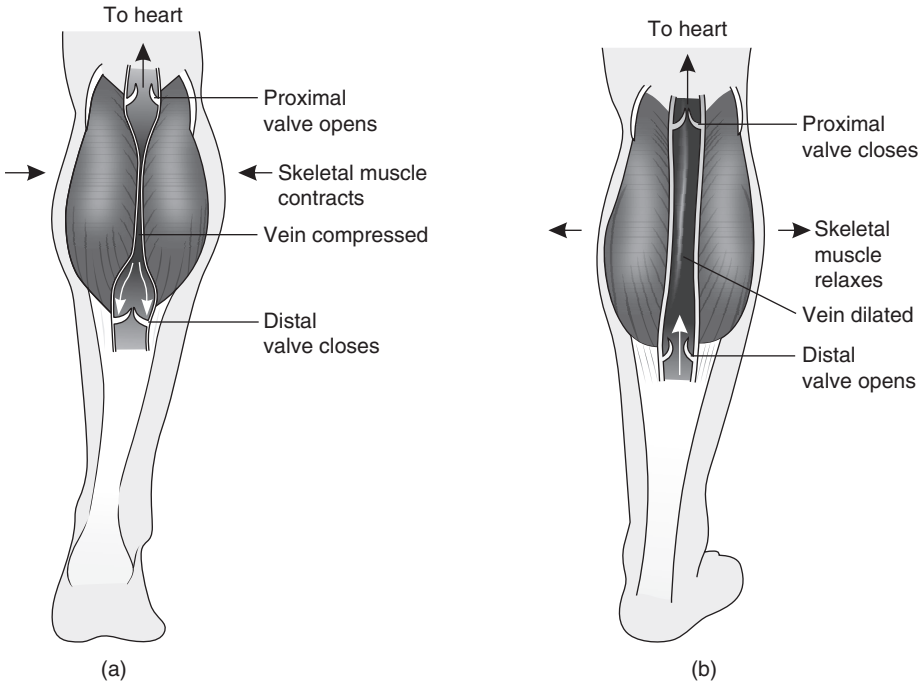


Figure 4.25 (a) Skeletal muscle contraction: compresses the vein, distal valve closes preventing backward flow of blood. (b) Muscle relaxes: proximal valve closes, distal valve opens facilitating flow of blood from lower parts of the leg. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- *Gravity*: Standing or sitting increases blood flow from the upper parts of the body toward the heart due to the effect of gravity.
- *Force of pumping of the blood*: When the force of cardiac contraction increases, it improves cardiac output and velocity of circulation. This causes greater venous return. The force exerted by the column of blood from behind to move blood toward the heart is termed **vis-a-tergo**. At the right atrium, the negative pressure created during diastole draws the blood toward it. This is termed **vis-a-fronte**.
- Reduced blood volume and peripheral pooling of blood reduces the venous return. This in turn reduces the end-diastolic volume and hence the cardiac output.

2. **Contractility of the heart**: The cardiac output is directly proportional to the force of contraction. The force of contraction depends on diastolic filling time. The longer the diastolic period, the greater the end diastolic volume. An increase in the initial length of cardiac muscle fiber enhances the force of the contraction.

   Stimulation of the sympathetic nerve or injection of epinephrine increases the contraction of the cardiac muscle. Hence, the cardiac output increases.

3. **Nutrition of the heart muscle**: Whenever the cardiac activity increases, there is a greater demand for oxygen and supply of nutrients. This demand is met by increasing the blood flow.

   If the cardiac activity increases without an increase in oxygen and nutrition supply, the heart muscles get damaged reducing the cardiac output.

4. **Heart rate**: A moderate increase in heart rate (up to about 180 beats/min) shows an

increase in the cardiac output. However if the heart rate increases to about 250–300 beats/min, the cardiac output decreases.

An increase in heart rate decreases the diastolic filling time. There is reduction in the volume of blood collected in the ventricle at the end of diastole.

Reduced end diastolic volume decreases the initial length of the ventricular muscle. This reduces the force of contraction.

Heart rate and cardiac output are increased during exercise. The venous return is increased due to muscle and respiratory pump. Hence, a shorter diastolic time is sufficient to ensure a good ventricular filling and a better cardiac output.

CONDITIONS INFLUENCING CARDIAC OUTPUT

Cardiac output increases

- after food,
- after exposure to high environmental temperature,
- during pregnancy,
- under the influence of epinephrine,
- during anxiety, and
- emotional disturbance

Cardiac output decreases during

- change of position from lying down to sitting or standing and
- ineffective pumping of the heart as in arrhythmias.

Cardiac output does not change significantly during sleep.

ESTIMATION OF CARDIAC OUTPUT

Cardiac output is estimated by the following methods:

- Fick principle
- Hamilton dye dilution method
- Thermodilution method
- Ballistocardiography
- Doppler with echocardiography

Fick Principle

According to Fick's principle, the amount of substance taken up by an organ is equal to the arteriovenous difference of the substance multiplied by the blood flow.

Cardiac output can be determined by measuring the O_2 consumed by the body in 1 minute and dividing this value by *A — V* difference of oxygen.

$$\text{Oxygen consumption} = \text{Blood flow} \times \text{AV difference of } O_2.$$

$$\text{Cardiac output} = \frac{O_2 \text{ consumption (mL/min)}}{\text{Arterial } O_2 - \text{Venous } O_2} \times 100.$$

Hamilton Dye Dilution Method

A known amount of the dye or radioactive isotope is injected into the arm vein.

The concentration of the indicator is estimated in serial samples from the arterial blood.

Cardiac output is equal to the amount of dye injected divided by its average (mean) concentration in the arterial blood after a single circulation through the heart.

$$\text{Cardiac output} = \frac{d \times 60}{ct}$$

d = Amount of dye injected
c = Mean concentration of the dye
t = Time for the first circulation

Thermodilution Method

Cold saline (indicator) is injected into the right atrium. Change in temperature of blood is recorded in the pulmonary artery.

The temperature change is inversely proportional to the volume of blood flowing through the pulmonary artery.

The advantages of this technique are as follows:

- Saline is nontoxic and tolerated well.
- Cold is distributed in the tissue and does not pose problems for circulation.

CLINICAL NOTES

Cardiac Failure

In this condition, the heart fails to pump out adequate quantity of blood to meet the need of the tissues. Sudden failure results in death; however, chronic failure can reduce the functioning capacity of the individual. Heart failure may involve right ventricle (cor pulmonale), left ventricle, or both.

Cardiac failure is of two types:

1. Systolic failure
2. Diastolic failure

In systolic failure, there is reduction in stroke volume due to weak ventricular contraction.

Diastolic failure is seen in conditions with reduced elasticity of myocardium. There is reduced filling during diastole. This leads to inadequate stroke volume.

In high output failure, the cardiac output is increased but unable to meet the increased needs of the tissue. It is seen in thyrotoxicosis and thiamine deficiency.

Cardiac Catheterization

Cardiac catheterization is a technique in which a multichannel catheter is passed into a chamber of the heart through the antecubital vein or femoral artery.

It is useful to

- study pressure changes in the chambers of the heart,
- measure electrical activities of the heart,
- detect the source of normal and abnormal cardiac sounds,
- perform coronary angiography, and
- analyze the gas content of the blood in different chambers.

Echocardiography

Echocardiography is a noninvasive technique to evaluate the cardiac function.

It uses the reflected ultrasound to study

- blood flow,
- structure of the heart,
- movement of valves, and
- cardiac muscle.

It is also used to measure the velocity and volume of blood flow.

Ultrasound is reflected at interfaces between blood and solid tissues. This is helpful in measuring the anatomic dimensions.

CIRCULATORY SHOCK

Shock is a state of circulatory failure. It is a condition characterized by insufficient cardiac output. The circulatory system fails to meet the oxygen and nutritional requirement of the tissues.

Types of shock are

- hypovolemic shock,
- distributive shock,
- cardiogenic shock, and
- obstructive shock.

TYPES OF SHOCK

Hypovolemic Shock

Hypovolemic shock occurs in cases of hemorrhage, trauma, burns, vomiting, and diarrhea. The condition is caused due to a reduction in blood volume.

It is characterized by

- rapid thready pulse,
- hypotension,
- cold clammy skin,
- restlessness,
- rapid respiration, and
- excessive thirst.
- In hypovolemic shock, inadequate supply of blood to the tissues leads to an increase in anaerobic glycolysis. It results in the production of large amounts of lactic acid. Lactic acidosis depresses the myocardium and responsiveness of the blood vessels to catecholamines.

Distributive Shock

Distributive shock comprises **anaphylactic shock**, **septic shock**, and **neurogenic shock**.

In this type of shock, the blood volume is normal but the capacity of circulation is increased due to intense vasodilation. It is also termed **warm shock**.

Anaphylactic Shock

The hypersensitivity reaction releases histamine. Histamine causes vasodilation and increased permeability of blood vessels. There is loss of fluid resulting in decreased venous return and cardiac output. These changes produce shock.

Septic Shock

Septic shock is produced due to uncontrolled infection. The bacterial toxins released cause generalized vasodilation and increased permeability of blood vessels. This reduces the circulating blood volume resulting in shock.

Neurogenic Shock

Neurogenic shock is produced due to sudden autonomic activity resulting in marked vasodilation. There is peripheral pooling of blood associated with fainting. It is also called vasovagal syncope. It lasts for a short duration and is reversible.

Other forms of syncope include the following:

- **Postural syncope**: Change in position results in fainting due to pooling of blood in the dependent parts of the body.
- **Micturition syncope**: This is commonly seen in subjects with orthostatic hypotension. Fainting occurs during urination due to orthostasis and reflex bradycardia.
- **Carotid sinus syncope**: Pressure on the carotid sinus causes marked bradycardia and vasodilation resulting in syncopal attacks.

Cardiogenic Shock

Cardiogenic shock is seen in conditions of myocardial infarction, congestive cardiac failure, and arrhythmias. In this type of shock, the heart fails to pump a sufficient quantity of blood to maintain normal tissue perfusion. It is due to extensive infarction of the left ventricle or diseases that depress the ventricular function. This is also called **congested shock** as the lungs and viscera get congested due to ineffective pumping of heart.

Obstructive Shock

Obstructive shock is seen in conditions such as cardiac tamponade, cardiac tumors, pulmonary embolism, and tension pneumothorax.

STAGES OF SHOCK

The outcome in circulatory shock depends on its severity.

The stages of shock are as follows:

1. **Non-progressive or compensated stage**: The normal circulatory compensatory mechanisms restore the normal function without any treatment.
2. **Progressive stage**: External therapy is necessary. Shock will steadily worsen and result in death without treatment.
3. **Irreversible stage**: All the known modes of treatment fail to arrest the deterioration in condition of shock, thus resulting in death.

COMPENSATORY MECHANISMS

Compensatory mechanisms are aimed at restoring blood pressure. They come into play within few seconds from the onset of shock.

Immediate Mechanism

- Baroreceptor mechanism
- Chemoreceptor mechanism
- VMC ischemic response (Refer to the section *Regulation of Blood Pressure*.)

Long-Term Mechanism

Reverse Fluid Shift Mechanism

In normal circulation, the hydrostatic pressure (which depends on the blood pressure) at the arterial end of the capillary exceeds the tissue pressure and colloidal osmotic pressure. Hence, fluid comes out of the capillary. But it re-enters

at the venous end. When the SBP decreases as in the case of shock, the hydrostatic pressure is less than the other two pressures put together. This causes the entry of fluid into the blood vessel from extravascular space. These changes enhance the blood volume and venous return and therefore increase the BP.

Water Conservation

ADH is released in a state of shock. It helps in reabsorption of water from the kidney. In large doses, ADH produces vasoconstriction and increases the peripheral resistance increasing BP. Reduced blood flow to kidney causes the release of renin.

Sodium and water are retained by the renin–angiotensin–aldosterone mechanism. This increases the blood volume and hence increases BP.

IRREVERSIBLE SHOCK

If prompt treatment is not given during a state of shock, it becomes irreversible. Death can be caused due to the following:

- Ischemic cardiac damage resulting in failure of the heart to pump blood.
- Accumulation of metabolic end products due to poor perfusion of the tissues causes acidosis. Acidosis results in peripheral vasodilation and peripheral pooling of blood. There is decreased venous return and reduced cardiac output producing irreversible cardiac damage.
- Hypoxia and hypercapnia due to poor perfusion of the tissues promote growth of microorganisms. These organisms produce toxins, which cause the paralysis of vascular smooth muscle and peripheral pooling of blood.
- Ischemia of the VMC results in its paralysis and failure of the sympathetic system to restore the blood pressure.

MANAGEMENT OF SHOCK

The general principles in management of shock are

- restoration of fluid volume by blood or plasma transfusion,
- administration of plasma substitutes and plasma expanders,
- maintenance of oxygen concentration in the blood by administering oxygen,
- correction of acidosis,
- maintenance of functions of vital organs, and
- use of sympathomimetic drugs and steroids to restore blood pressure.

REGIONAL CIRCULATION

Regional circulation deals with flow of blood in the regions which are clinically important, with respect to their special anatomical arrangements, functional variations, factors regulating, and clinical conditions related to impairment in circulation.

CORONARY CIRCULATION (Fig. 4.26)

The heart is supplied by the right and left coronary arteries. Coronary arteries arise from sinuses at the root of the aorta.

The right coronary artery is dominant in 50% and the left coronary artery in 20% of the individuals. In the remaining 30%, the flow in the right and left coronary arteries is equal.

The right coronary artery supplies the right ventricle and the posterior part of the left ventricle. The left coronary artery supplies the anterior and lateral portions of the left ventricle. The normal coronary blood flow in human beings at rest is 250 mL/min.

The capillary density of coronary arteries is very high when compared to other sites in the body.

The venous blood is drained into the right atrium through the coronary sinus and the anterior cardiac veins.

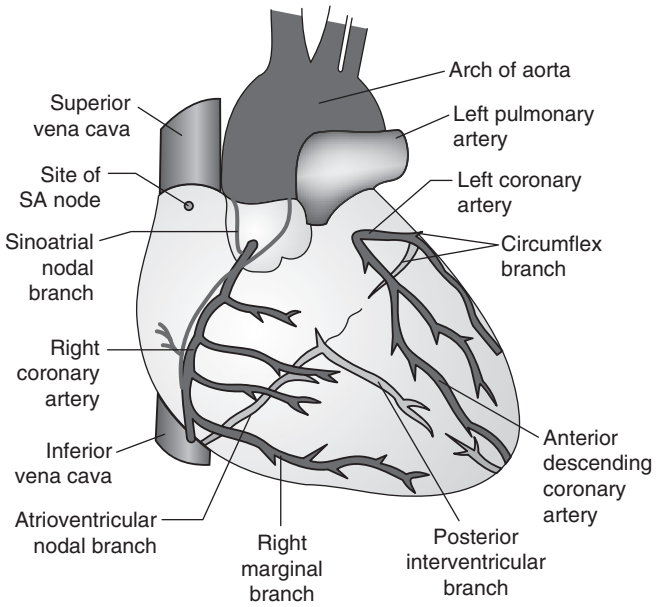


Figure 4.26 Simplified scheme of the coronary arteries. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edition. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

In addition, blood is drained directly into the chambers through

- thebesian veins,
- arteriosinusoidal vessels, and
- arterioluminal vessels.

Coronary arteries are end arteries with little anastomosis.

However, in patients with coronary artery disease, these blood vessels increase in number and size.

The normal coronary blood flow in human beings at rest is 250 mL/min (5% of the cardiac output). In the resting condition, the coronary blood flow is about 70 mL/min/100 g of the weight of heart. During exercise, the coronary blood flow increases three- to fourfolds as against cardiac output which increases four- to seven folds.

EVALUATION OF MYOCARDIAL BLOOD FLOW

The coronary blood flow is evaluated by using radioactive tracers. Radionucleotide such as thallium-201 is introduced by intravenous injection. It is pumped into the cardiac muscle by the sodium–potassium ATPase. After a lapse of about 10–15 minutes, the concentration of radioactive tracers is estimated by using radiation detectors placed over the chest. The distribution of thallium-201 is proportional to myocardial blood flow.

Uptake of radionucleotide is reduced in areas of ischemia.

Exertion-induced compromise in blood flow can be detected by measuring the uptake of radioactive isotope immediately after exercise and after few hours of rest.

FACTORS INFLUENCING CORONARY CIRCULATION

1. **Phases of cardiac cycle**: The blood vessels supplying the myocardium and endocardium pass through layers of the heart, arising perpendicular to the main artery. Hence, the blood vessels are compressed during the cardiac systole.

   The myocardium and endocardium do not get the blood supply during systole but get major part of the blood supply during diastole.

During diastole, the cardiac muscle relaxes and the blood vessels are no longer compressed. Hence, blood flows through the capillaries of ventricles.

2. **Chemical factors**: Metabolic activity results in the accumulation of end products such as lactates and hydrogen ions. During anaerobic metabolism, there is formation of adenosine from ATP and prostaglandins in the cardiac tissue. These substances cause increased blood flow due to local vasodilation. Cardiac muscle is capable of extracting about 70% of oxygen from the coronary arterial blood.

   The other factors known to produce local coronary vasodilation are
   - oxygen lack,
   - carbon dioxide excess,
   - increased potassium ion concentration,
   - adenine nucleotide accumulation, and
   - intracoronary injection of cyanide.

   The coronary artery occlusion followed by release of occlusion increases the blood flow through it due to the release of adenosine. This is termed **reactive hyperemia**.
3. **Autoregulation**: It is the ability of vital organs such as heart, brain, and kidney to regulate its own blood flow within a narrow range of fluctuation. This operates between arterial blood pressures of 60 and 160 mm Hg.
4. **Neural factor**: Stimulation of sympathetic nerves to the heart increases the heart rate and produces initial vasoconstriction. The accumulation of metabolic end products and adenosine finally produces vasodilation by its local action.

   Parasympathetic stimulation releases acetylcholine, which reduces the rate and force of cardiac contractility. This decreases oxygen consumption and constricts coronary arteries. Acetylcholine acting directly causes dilatation of coronary blood vessels.

CLINICAL NOTES

Ischemic Heart Disease

Ischemic heart disease is due to insufficient coronary blood flow. The most common cause for reduced blood flow in the coronary arteries is atherosclerosis.

Acute coronary occlusion can occur due to the formation of local blood clot over the pre-existing atherosclerotic plaque. Plaque acts as a site for platelet aggregation, fibrin deposition, and formation of clot by trapping of RBCs. The blood clot (thrombus) formed elsewhere can get dislodged and block the coronary artery as embolus.

Angina Pectoris

Angina pectoris is a severe constricting pain in the chest radiating from precardium due to ischemia of cardiac muscles. In this condition, pain is produced due to hypoxia of myocardial tissue. An obstruction of about 75% to the coronary artery produces angina pectoris. Reduction in blood flow causes local accumulation of pain-producing factors.

Nitroglycerin (nitrates) is used in the management of pain during angina pectoris.

Nitroglycerin generates nitric oxide (NO) and dilates the normal arteries.

Nitrates dilate the capacitance vessels and reduce the venous return.

This reduces myocardial oxygen consumption due to decreased stroke volume.

Nitric oxide (NO) production is defective in atherosclerotic vessels.

Myocardial Infarction

Myocardial infarction is the death of the myocardial tissue. It is caused due to sudden stoppage of blood supply to an area of the myocardium. Blood flow to the myocardium is stopped due to

- formation of thrombus in an already narrowed coronary blood vessel,
- spasm of the coronary artery,
- platelet aggregation in a severely sclerotic artery,
- rupture of atherosclerotic plaque, and
- hemorrhage into atherosclerotic plaque.

The patient presents with intense retrosternal pain, radiating to the inner aspect of the left upper limb associated with sweating.

(*Contd.*)

ECG Changes

In **myocardial infarction**, the ST segment is elevated and T-wave is inverted. Isolated T-wave inversion in limb lead III is considered normal (**Fig. 4.27**).

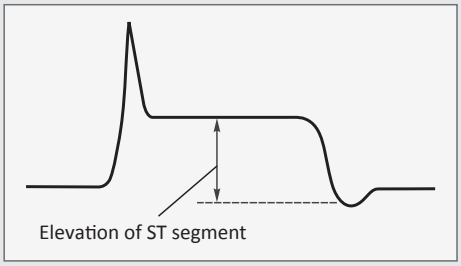


Figure 4.27 ECG changes in myocardial infarction (elevation of ST segment with T wave inversion). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Management

- Intracoronary clots are lysed by thrombolytic agents to restore the blood flow.
- Streptokinase is a lytic agent obtained from the bacteria hemolytic streptococci. It converts plasminogen to plasmin in the clot.
- Tissue-type plasminogen activator (t-PA) activates plasminogen bound to fibrin. It brings about fibrinolysis in the clots.
- Thrombolytic agents are very effective if they are used within a few hours after the onset of pain.

Angiography

Angiography is a procedure to detect the presence of block in the blood vessels due to a clot.

A radio-opaque dye is injected into the artery, and demonstration of filling defect radiographically confirms the presence of a block.

Angioplasty

Angioplasty is the procedure by which the clot obstructing the coronary artery is removed by catheterization.

Stent

Stent is a metal or plastic, mesh-like device placed in the coronary artery after the removal of the clot. This is done to keep the passageway open and to prevent the reocclusion of the blood vessels due to its spasm.

Coronary Bypass

Coronary bypass is a surgical procedure in which the proximal and distal parts of the coronary artery are connected bypassing the areas of obstruction due to a clot.

A healthy blood vessel taken from different parts of the body is used in this procedure to restore the blood flow to the cardiac tissue.

CEREBRAL CIRCULATION

In human beings, two internal carotid and two vertebral arteries supply the brain.

The normal cerebral blood flow is 750 mL/min or 54 mL/100 g of the tissue.

Factors Influencing Cerebral Circulation

- **Autoregulation**: The brain maintains its blood flow in spite of variation in the arterial blood pressure.
- **Hypoxia**: Hypoxia to the brain increases blood flow by vasodilation.
- **Oxygen excess**: High oxygen concentration produces vasoconstriction. This reduces the blood flow to the brain to prevent its damage.
- **Hypercapnia**: Increased carbon dioxide concentration in the blood causes cerebral vasodilation due to local effect enhancing the blood flow.
- **Intracranial pressure**: An increase in the intracranial pressure decreases cerebral blood flow. However if the intracranial pressure is reduced, the blood flow is restored.
- **Perfusion pressure**: The pressure difference between the arterial and venous systems to the brain plays an important role in the regulation of blood flow to the brain. Perfusion pressure helps to maintain a constant flow of blood.
- **Autonomic stimulation**: Sympathetic stimulation does not significantly alter the blood flow to the brain.
- **Anesthetics**: They reduce the flow of blood to the brain.

Blood flow to the brain can be monitored by

- positron emission tomography and
- functional magnetic resonance imaging.

CLINICAL NOTES

Stroke

Stroke is a condition of paralysis produced due to lack of oxygen supply to the brain.

Neurons in the brain are sensitive to the supply of oxygen. Anoxia of 3–4 minutes results in death of these neurons. When blood supply to a part of brain is interrupted, it produces signs and symptoms of stroke.

The types of stroke are

- hemorrhagic stroke and
- ischemic stroke.

Hemorrhagic stroke occurs when the blood vessels to the brain rupture.

Ischemic stroke occurs when the flow of blood in the vessels is reduced or stopped by thrombus or atherosclerotic plaques. Thrombus may also be formed elsewhere and reach the brain as emboli.

CUTANEOUS CIRCULATION

Cutaneous circulation is circulation through the skin (**Fig. 4.28**).

Blood flow to the skin is about 400–450 mL/min. It can vary from 50 to 4500 mL/min.

Features of Cutaneous Circulation

Cutaneous circulation plays an important role in the regulation of body temperature.

It acts as a reservoir for blood.

Blood flow to the skin is highly variable. There are plenty of arteriovenous anastomosis in cutaneous circulation.

Factors Influencing Cutaneous Circulation

- Sympathetic stimulation decreases blood flow to the skin.
- Increased body temperature causes vasodilation and hence increases blood flow.
- Epinephrine and norepinephrine cause vasoconstriction reducing the blood flow, Bradykinin and histamine cause vasodilation increasing the blood flow.

WHITE REACTION

When the skin is stroked lightly, the skin appears pale due to reduced blood flow. This response is due to the contraction of the precapillary sphincter. It is called **white reaction**.

TRIPLE RESPONSE

When the skin is stroked (scratched) firmly, it shows three reactions. They are as follows:

1. **Red reaction**: A red line appears when the stroke is made. This is due to relaxation of the precapillary sphincter and engorgement of the capillary under the influence of histamine. The line appears in about 10 seconds and becomes well developed in 1 minute.

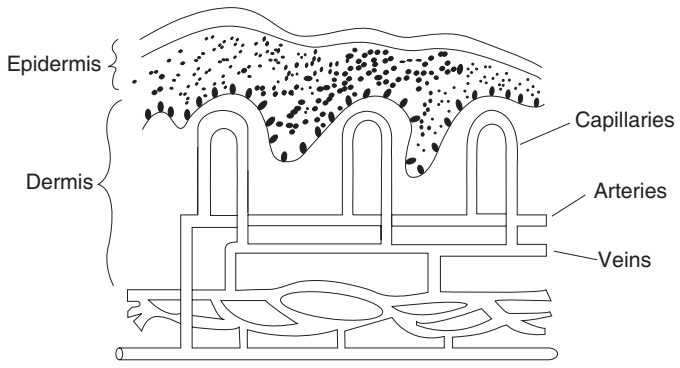


Figure 4.28 Cutaneous circulation.

2. **Flare or flush**: When stroking is firm, an area of redness develops surrounding the site of stroking. This is caused due to arteriolar dilation as a result of axon reflex. The area has increased temperature.
3. **Wheal**: In this stage, fluid collects around the area of stroking resulting in edema. Fluid is a transudate produced due to increased hydrostatic pressure in the dilated capillaries. Triple response is largely due to local release of histamine.

FETAL CIRCULATION (Fig. 4.29)

The fetal oxygen and nutritional requirements during the intrauterine period are obtained from maternal circulation through the placenta.

The placenta has a maternal portion and fetal portion.

The **maternal portion** consists of uterine spiral arteries which open into intervillous space.

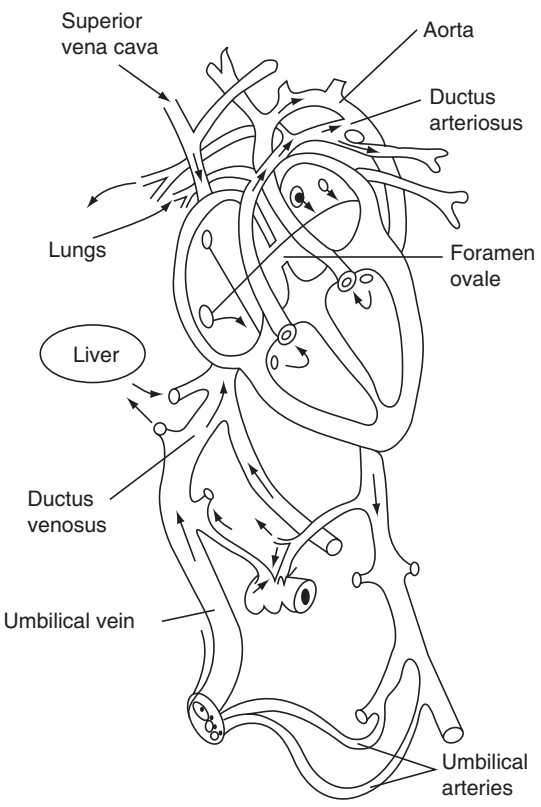


Figure 4.29 Fetal circulation.

The **fetal portion** consists of umbilical arteries and umbilical vein.

The umbilical vein carries blood from the placenta. One-third of the blood passes through the inferior vena cava and reaches the right atrium.

The remaining part of the blood enters the liver through the branch of the umbilical vein. Later, the blood moves through the portal vein to reach the right atrium.

There is an opening between the right atrium and the left atrium. This opening is called **foramen ovale**. The blood reaching the right atrium flows to the left atrium through this opening. The flow of blood from the right atrium to the left atrium bypasses pulmonary circulation (the lungs).

Blood from the superior vena cava enters the right atrium and then to the right ventricle. It later passes through the pulmonary trunk and gets shunted via ductus arteriosus to aorta. From the aorta, blood goes to the placenta through the internal iliac artery and umbilical arteries.

Changes at Birth

The placental circulation is cut off immediately after birth and peripheral resistance rises suddenly. Pressure in the aorta rises till it exceeds pressure in the pulmonary artery. The infant gasps because of asphyxia and the lungs expand. Once the lungs expand, pulmonary vascular resistance falls to less than 20% of intrauterine levels and hence pulmonary blood flow increases markedly. Blood returning from the lungs raises the pressure in the left atrium closing the foramen ovale. The ductus arteriosus constricts within a few minutes after birth and finally it is shut off completely.

Capillary Circulation (Fig. 4.30)

The capillary is the connection between the arterial and venous ends of the vascular tree.

The capillaries contain about 250 mL of blood (5% of circulating blood).

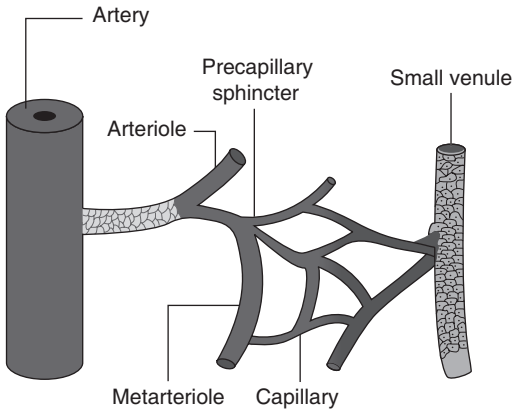


Figure 4.30 Capillary circulation.

The capillary circulation helps in the exchange of gases, supply of nutrients, and removal of waste from the tissues.

The types of capillaries are

- continuous capillary,
- fenestrated capillary, and
- sinusoidal capillary.

Continuous Capillaries (Nonfenestrated)

The majority of the capillaries are of this type. They have a single layer of continuous endothelial lining. They permit the exchange of fluid and water-soluble substances.

Fenestrated Capillaries

Fenestrated capillaries are found in glomerulus of the kidney, intestinal villi, and endocrine glands. They have fenestrations or pores which allow rapid movement of molecules.

Sinusoidal Capillaries

Sinusoidal capillaries are found in liver, spleen, and bone marrow. They are lined by a single layer of endothelial cells. There are large gaps in between the cells. They help in the passage of bigger molecules.

The filtration across the capillary wall depends on Starling's forces. These forces are acting in opposite directions. The resultant pressure influences the movement of fluid across the blood vessel.

Starling's forces are as follows:

- Capillary hydrostatic pressure
- Plasma colloid osmotic pressure
- Interstitial fluid hydrostatic pressure
- Interstitial fluid colloid osmotic pressure

At the arterial end of capillary, the net pressure is directed outward. Hence, fluid moves out of the capillary.

At the venous end, the resultant pressure is negative. Hence, fluid is drawn back into the capillary.

REVIEW QUESTIONS

Long Essay

1. Explain the properties of cardiac muscle.
2. Define cardiac cycle. Explain with the help of a diagram the mechanical and pressure changes during cardiac cycle.
3. Draw a labeled diagram showing the innervations of heart. Describe the regulation of heart rate.
4. Define blood pressure. Give its normal value. Explain short-term and long-term mechanisms of its regulation.
5. Define cardiac output and cardiac index. Give its normal values. Describe the factors regulating cardiac output.
6. What is shock? What are its types? Discuss the cardiovascular compensatory changes that occur during shock.

Short Essay

1. Describe the conducting system of heart.
2. Explain the effect of sympathetic and parasympathetic stimulation on heart.

3. Explain origin and spread of cardiac impulse.
4. Discuss briefly the pacemaker potential.
5. Explain cardiac muscle action potential.
6. Define Starling's law. Explain its molecular basis and clinical importance.
7. Explain all-or-none law and staircase phenomenon.
8. Mention the placement of standard limb leads.
9. List the differences between first and second heart sounds.
10. Define pulse. Describe a normal arterial pulse tracing.
11. Describe the waves in a normal jugular venous pulse.
12. Explain sinoaortic mechanism.
13. Explain the factors influencing blood pressure.
14. Explain the intermediate-term regulation of blood pressure.
15. Define cardiac output. Explain one method to measure it.
16. Explain the auscultatory method of recording blood pressure
17. Discuss the role of atrial natriuretic peptide on cardiovascular function.
18. Explain the factors influencing venous return.
19. Draw a normal ECG. Explain the cause for different waves.
20. Describe the circulatory changes during muscular exercise.
21. Explain the effect of hemorrhage on blood pressure.
22. Explain the factors influencing coronary circulation.
23. Describe the changes during irreversible shock.
24. Explain triple response.
25. Explain fetal circulation. Add a note on changes at births.

Short Answer

1. What is pulmonary and systemic circulation?
2. What is AV nodal delay? What is its clinical significance?
3. What is heart block and what are its types?
4. Define refractory period in a cardiac muscle. What is its importance?
5. What is staircase phenomenon? What is the molecular basis for it?
6. What is echocardiography?
7. How is different heart sounds produced?
8. What is pulse deficit?
9. What is Marey's law? Mention one condition that is an exception to this.
10. Explain briefly Bainbridge reflex.
11. What is sinus arrhythmia?
12. What is Bezold–Jarisch reflex?
13. What is Cushing's reaction?
14. What are Korotkoff's sounds? How are they produced?
15. What is laminar and turbulent blood flow? What is its clinical implication?
16. What is auscultatory gap?
17. What is end systolic and end diastolic volumes?
18. Mention four factors influencing the cardiac output.
19. Draw a labeled diagram of ECG.
20. What is PR interval? What is its significance?
21. Mention two ECG changes in myocardial infarction.

22. What are cardiac murmurs? How are they produced?
23. What are artificial pacemakers? When are they used?
24. Mention the role of thoracic pump in venous return.
25. What is autoregulation? Mention three theories that explain it.
26. What is heart block? What is the ECG change in first-degree heart block?
27. What are (a) resistance vessels and (b) capacitance vessels?
28. List the factors influencing cerebral circulation.
29. Mention four methods of measuring cardiac output.
30. List special features of capillary circulation.

CHAPTER

5 Respiratory System

Outline

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the anatomy, histology, and functions of the respiratory system.
- List the various pulmonary function tests and interpret their clinical significance.
- Explain the salient features of pulmonary circulation and summarize the concept of ventilation–perfusion ratio.
- List the muscles of respiration and explain their mechanism of action. Discuss the mechanics of breathing.
- Define compliance and explain its types. Discuss the role of surfactant in reducing surface tension.
- Describe the neural and chemical regulation of respiration. Explain periodic breathing.
- Describe the mechanism of transport of blood gases—oxygen and carbon dioxide. Illustrate oxygen and carbon dioxide dissociation curves.
- Explain the various disorders of breathing such as hypoxia, cyanosis, asphyxia, and apnea. Discuss oxygen therapy and oxygen toxicity.
- Illustrate the methods of providing artificial respiration and the procedure of performing cardiopulmonary resuscitation. Explain its indications.
- Explain the concept of high-altitude physiology and deep sea diving. Identify its clinical importance.
- Successfully answer the questions and MCQs at the end of this chapter.

Respiration is a process of uptake of oxygen and removal of carbon dioxide from tissues of the body.

The cells in the body derive energy mainly by utilizing oxygen. Carbon dioxide (CO_2) is produced as a byproduct. Carbon dioxide has to be eliminated from the cell as its accumulation leads to toxicity.

Unicellular organisms exchange oxygen and CO_2 directly with the external environment.

Multicellular organisms require a specialized system to exchange O_2 and CO_2 with the

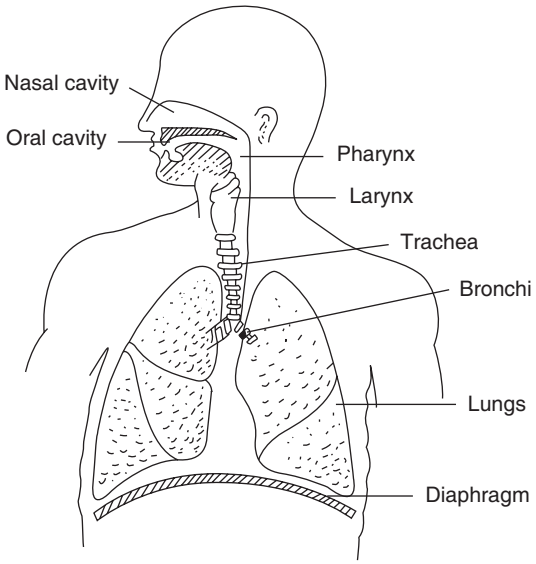


Figure 5.1 Respiratory tract.

external environment. This complex function is performed by the respiratory system (**Fig. 5.1**).

Exchange of gases between the atmosphere and lungs is called **external respiration**.

Exchange of gases between blood and tissues is called **internal respiration**.

Respiration involves two processes:

1. **Inspiration**: During this phase, air is taken into the lungs from the atmosphere.
2. **Expiration**: During this phase, air is expelled out of the lungs.

The process of inspiration followed by expiration is called **one respiratory cycle**. The normal respiratory rate is 12–18 cycles/min.

The process of respiration occurs in three steps:

1. The first step involves exchange of gases in the lungs.
2. The second step involves transport of gases through the blood.
3. The third step is exchange of gases at the tissues.

The main function of the respiratory system is to provide oxygen to the cells and remove carbon dioxide from them. It is also involved in many nonrespiratory functions. The respiratory system consists of lungs, conducting airways, ribcage, respiratory muscles, and respiratory centers in the central nervous system.

FUNCTIONAL ANATOMY

LUNGS

Lungs are the organs of respiration. The human respiratory system contains two lungs: (i) right and (ii) left. They are covered by a membrane called **pleura**.

The pleura has two layers:

1. Parietal (outer) pleura
2. Visceral (inner) pleura

The lungs are divided into lobes. The left lung has two lobes and the right lung has three lobes.

AIRWAYS

The respiratory tract includes nasal cavities, paranasal sinuses, pharynx, larynx, trachea, bronchi, bronchioles, and alveoli. The air passes from the nose to the nasal cavities and later into the pharynx. The pharynx is a common passage for air and food. It continues into larynx. The larynx contains vocal cords.

The larynx opens into a long tube called the **trachea**. The trachea divides into two bronchi. Each bronchus enters the lungs. Within the lungs, they branch further into bronchioles. The terminal parts of the bronchioles are termed **respiratory bronchioles**. The respiratory bronchioles end in the alveoli after a series of divisions.

Upper Respiratory Tract

The part of the respiratory passage from the nostrils up to the vocal cords is called the upper respiratory tract. It performs Four important functions:

1. Filters large particulates present in the inhaled air
2. Adjusts the temperature of inhaled air close to body temperature
3. Humidifies air as it enters the body
4. Helps in appreciation of smell (olfaction)

Lower Respiratory Tract

The respiratory passage below the vocal cords is called the lower respiratory tract.

The lower respiratory tract begins with the trachea and divides into two bronchi, which subdivide repeatedly to form bronchioles, which end as the alveoli.

The respiratory tract has 23 divisions (**Fig. 5.2**). The first 16 generations form the **conducting zone**. The seventeenth to nineteenth generations form the **transition zone**. The twentieth to twenty-third generations form the **exchange zone**. Exchange of gases can take place from the seventeenth to twenty-third generations. These divisions were numbered and designated as **generations** by a Swiss anatomist, E.R. Weibel. According to this model, the trachea is designated as **generation zero**.

Alveoli

The alveoli are the sites for gas exchange. These are tiny hollow sacs which continue with the lumen of the bronchioles.

The cells are flattened and form a single layer.

The alveoli contain two types of cells: (i) Type I and (ii) Type II.

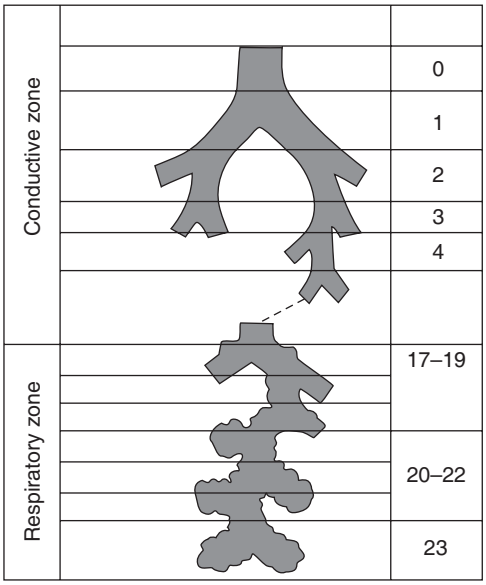


Figure 5.2 Weibel model of the respiratory tract.

Type I Cells

Type I cells are the main lining cells of the alveoli. Gas exchange occurs through these cells.

Type II Cells

Type II cells are specialized thicker cells that produce a substance called **surfactant**.

Other cells present are alveolar macrophages, mast cells, plasma cell, and amine precursor uptake and decarboxylation (APUD) cells.

Alveolar macrophages are phagocytic in nature. Mast cells contain heparin and histamine. APUD cells manufacture polypeptides and amines.

HISTOLOGY OF THE RESPIRATORY TRACT

The respiratory tract is made up of three layers:

1. Outer fibrous layer
2. Middle muscular layer
3. Inner epithelial layer

OUTER FIBROUS LAYER

The outer fibrous layer is made up of C-shaped cartilage in the trachea. As the respiratory tree divides, the cartilage decreases and ultimately there is no cartilage in the terminal bronchiole and further subdivisions including the alveoli.

MIDDLE MUSCULAR LAYER

The middle muscular layer is made up of smooth muscles. When these muscles contract, there is narrowing of bronchial lumen producing bronchoconstriction. Relaxation of muscles results in bronchodilation.

INNER EPITHELIAL LAYER

The inner epithelial layer is formed by the mucus membrane. It is made up of ciliated columnar cells in the upper respiratory tract. The cilia help to clear dust particles. The epithelium in the respiratory bronchiole is cuboidal and has no cilia.

This layer also contains glands that secrete mucus. Dust particles and particulate matter stick to the mucus. This is slowly moved upward toward the pharynx by the movement of cilia.

NERVE SUPPLY

The respiratory tract is supplied by the autonomic nervous system.

The sympathetic stimulation causes dilation of bronchioles by relaxation of smooth muscles. This action is mediated through β_2 receptors.

The parasympathetic stimulation increases the bronchial secretion and causes narrowing of the respiratory passage (bronchoconstriction).

Functions of the Respiratory System

The functions of the respiratory system are divided into two broad categories:

1. Respiratory functions
2. Nonrespiratory functions

Respiratory Functions

Nasal Cavity

- **Filtration of dust particles**: Larger dust particles of 5–10 μ size settle in the mucous membrane of the nasopharynx and do not enter the respiratory passage.
- **Humidification**: The atmospheric air is humidified as it enters the body.
- **Olfaction**: Movement of air delivers the odorant substances to the olfactory epithelium, helping the perception of smell.
- **Modification of temperature of inspired air**: The air entering the lungs is warmed/cooled to bring them close to the body temperature.

Lungs

- **Uptake of O_2 from the atmosphere**: Oxygen is taken from the inspired air. It is transported through the blood to the tissues where it is utilized.
- **Expulsion of CO_2 from the body**: Carbon dioxide in the tissues is taken up by the blood and delivered to the lungs from where it is expelled.

Nonrespiratory Functions

1. Defensive action
   - The mucosa of the lungs produces a secretory antibody, IgA, which protects the body against infection.
   - Alveolar macrophages are phagocytic; they engulf foreign particles and bacteria. They also help in processing of the inhaled antigens. They also secrete chemical substances that attract other leukocytes into the lungs.
   - Cilia present in the lungs trap microbes. These microbes get attached to mucus secreted in the respiratory tract. The beating of the cilia directed upward moves the microbes along with mucus which is later swallowed/voluntarily removed from the respiratory passage.
2. Surfactant secreted by type II alveolar cells lowers the surface tension, thereby reducing the work of breathing. Collagen and elastic fibers synthesized in the lungs help in maintaining the structural framework.
3. Fibrinolytic mechanism of the lungs helps in the lysis of clots. These fragments of broken clots are filtered in the pulmonary circulation and removed.

4. Conversion of angiotensin I to angiotensin II by ACE (angiotensin-converting enzyme) occurs in the pulmonary capillary endothelium.
5. APUD cells of the alveoli store biologically active substances such as VIP, substance P, hormones like CCK-PZ, and somatostatin.
6. Temperature regulation—excess heat is lost from the body along with water during expiration.
7. Acid–base balance—lungs regulate CO_2 content of blood, thereby helping in acid–base balance.
8. Excretory function—volatile substances such as alcohol are removed from the body through expiration.
9. Voice production—movement of air in the respiratory tract and through the vocal cords helps in speech.

RESPIRATORY MEMBRANE

The respiratory membrane is a thin membrane separating blood in the pulmonary capillaries and air in the alveoli (**Fig. 5.3**).

The diameter of pulmonary capillary is about 10 μm which is just enough for the RBC to pass through.

The RBC remains for about three-fourth of a second in the pulmonary capillary network. The gas exchange between the alveolar air and the RBC occurs within this short period.

The gas exchange occurs between the alveolar air and the blood in the pulmonary capillaries through the **respiratory membrane**.

The respiratory membrane consists of

- layer of surfactant lining the alveolus,
- alveolar epithelium,
- basement membrane of the alveolar epithelium,
- interstitial space between the alveolar epithelium and the capillary membrane,
- capillary basement membrane, and
- capillary endothelium.

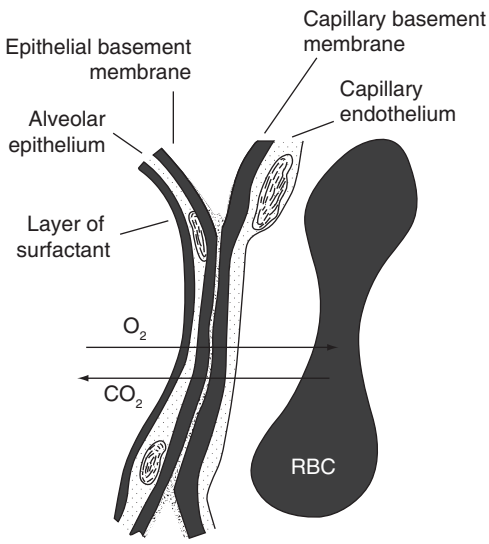


Figure 5.3 Respiratory membrane.

The thickness of the respiratory membrane is around 0.6 μm.

The total surface area of the respiratory membrane is about 70 m^2 in normal adults. The amount of blood present in the lung capillaries is around 150 mL.

About 150 mL of blood present in the pulmonary capillaries is spread over this large area. The diameter of the capillary is very small. There is hardly any gap between the surface of RBC and the capillary membrane. Hence, the diffusion of gases is very rapid across the respiratory membrane.

DIFFUSION ACROSS THE RESPIRATORY MEMBRANE

The following factors affect this process:

- **Thickness of the membrane**: The rate of diffusion through the respiratory membrane is inversely proportional to the thickness of the membrane. When the thickness is doubled, the rate of diffusion is reduced by 50%.
- **Surface area of the membrane**: The rate of diffusion is directly proportional to the

surface area of the membrane. The surface area of the membrane increases during exercise as more number of capillaries open up.

- **Diffusion coefficient**: The rate of diffusion is directly proportional to the diffusion coefficient of the gas. The diffusion coefficient of a gas is directly proportional to its solubility and inversely proportional to the square root of its molecular weight. Therefore, a small molecule with high solubility diffuses easily.
- **Pressure gradient across the respiratory membrane**: The rate of diffusion is directly proportional to the pressure difference between the gas in the alveoli and the pulmonary capillary. The diffusion gradient across the respiratory membrane is about 60 mm Hg for oxygen and about 6 mm Hg for carbon dioxide.

PULMONARY VENTILATION

Pulmonary ventilation is the process of flow of air into the lungs during inspiration (inhalation) and out of the lungs during expiration (exhalation).

RESPIRATORY MINUTE VOLUME

Respiratory minute volume (RMV) is the volume of air that can be breathed in and out of the lungs every minute under resting condition. It is equal to the tidal volume times the respiratory rate:

RMV = TV (Tidal volume) × RR (respiratory rate).

The normal tidal volume is around 500 mL and the respiratory rate is around 12/min. Thus, the normal RMV is 6 L/min.

A person can manage with an RMV as low as 1.5 L/min or as high as 200 L/min for a short duration.

ALVEOLAR VENTILATION

Alveolar ventilation is the volume of air entering the alveoli in 1 minute, which is used for the exchange of gases.

Alveolar ventilation = (Tidal volume − Dead space) × 12
= (500 − 150) × 12
= 350 × 12
= 4200 mL/min.

Alveolar ventilation determines the amount of oxygen and carbon dioxide in the alveoli. Alveolar ventilation decreases in rapid shallow breathing and increases in slow deep breathing.

DEAD SPACE

The part of the respiratory passage where there is no exchange of gases is called dead space.

Types

Dead space is of two types:

1. **Anatomical dead space (ADS)**: It is that part of the respiratory passage which is not involved in the exchange of gases. This includes air in the nose, pharynx, larynx, trachea, and bronchi up to terminal bronchioles.

   The gas exchange does not occur in these areas because the walls of the respiratory passages are too thick for the gas exchange.

   The normal value is 150 mL.

   It is measured by the single breath nitrogen analyzer method.
2. **Physiological dead space (PDS)**: It includes anatomical dead space and the part of lungs where the exchange of gases does not take place.

   Physiological dead space = Anatomical dead space + Alveolar dead space.

   Alveolar dead space is the volume of air present in the alveoli which does not participate in gaseous exchange. This can occur because of a mismatch in the ventilation and perfusion.

In healthy individuals, ADS = PDS.

PDS is more significant than ADS. It is increased in case of arteriovenous shunts and pulmonary embolism.

Measurement

Anatomical dead space is measured by analysis of the single breath N_2 curve (Fowler's method). The subject is asked to inhale 100% pure O_2 and then exhale into a nitrogen meter. The initial air exhaled corresponds to the ADS. This air contains only oxygen and no nitrogen. Later when the alveolar air reaches the nitrogen meter, the N_2 concentration increases steadily and reaches a plateau level.

The dead space volume will be equal to the volume of gas exchanged from the peak inspiration to the midportion of phase II as shown in **Figure 5.4**.

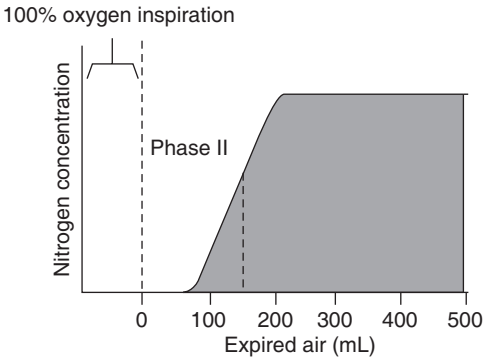


Figure 5.4 Dead space.

PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) are a series of tests performed to assess the lung functions in an individual.

PFTs include the following:

- Static lung volumes and capacities
- Dynamic lung volumes and capacities

STATIC LUNG VOLUMES AND CAPACITIES

Lung Volumes

Lung volumes are the volume of air breathed by an individual under a specific condition. The lung volumes are as mentioned in the following text.

Tidal Volume

Tidal volume (TV) is the volume of air inhaled or exhaled during normal breathing at rest.

The normal value is 500 mL.

Tidal volume is increased during exercise. It is decreased in conditions due to weakness of respiratory muscles and depression of the respiratory center.

Inspiratory Reserve Volume

Inspiratory reserve volume (IRV) is the volume of air inhaled with maximum effort over and above the normal tidal volume.

The normal value is 3000 mL.

Expiratory Reserve Volume

Expiratory reserve volume (ERV) is the volume of air exhaled forcefully after a normal expiration.

The normal value is 1100 mL.

Residual Volume

Residual volume (RV) is the volume of air remaining in the lungs after a forceful expiration.

The normal value is 1200 mL.

Lung Capacities

Inspiratory Capacity

Inspiratory capacity (IC) is the volume of air a person can inspire forcefully after a normal expiration:

$$IC = TV + IRV.$$

The normal value is 3500 mL.

Functional Residual Capacity

Functional residual capacity (FRC) is the volume of air that remains in the lungs at the end of normal expiration:

FRC = ERV + RV.

The normal value is 2300 mL.

FRC is increased in old age, bronchial asthma, and emphysema.

Significance of Functional Residual Capacity FRC is very important for continuous exchange of gases even during expiration. If FRC was not present, then PO_2 would have fallen to zero during expiration and increased to 150 mm Hg during inspiration. FRC maintains the average PO_2 at around 100 mm Hg.

Vital Capacity

Vital capacity (VC) is the maximum volume of air exhaled forcefully from the lungs after a maximum inspiration:

VC = TV + IRV + ERV.

The normal value is 4600 mL.

Significance of Vital Capacity Estimation of vital capacity provides information about the strength of the respiratory muscles. This helps to assess the maximum inspiratory and expiratory effort. It also provides information about other pulmonary functions through forced expiratory volume (FEV). Vital capacity is reduced in lung diseases such as fibrosis, pleural effusion, emphysema, and pneumothorax. It is also reduced in old age and during pregnancy.

Total Lung Capacity

Total lung capacity (TLC) is the volume of air present in the lungs after maximum inspiration:

TLC = VC + RV.

The normal value is 5800–6000 mL.

Measurement of Static Lung Volumes and Capacities

Lung volumes and capacities are measured by an instrument called **spirometer**.

The graph obtained is called **spirogram** (**Fig. 5.5**).

All the lung volumes and capacities are approximately 20–25% less in females as compared to males.

Spirometer (Fig. 5.6)

A simple spirometer consists of two concentric drums. Water is filled between the outer and the inner drum. A lightweight drum (bell) is placed inverted between the two drums so that it dips into water. The top of the inverted drum

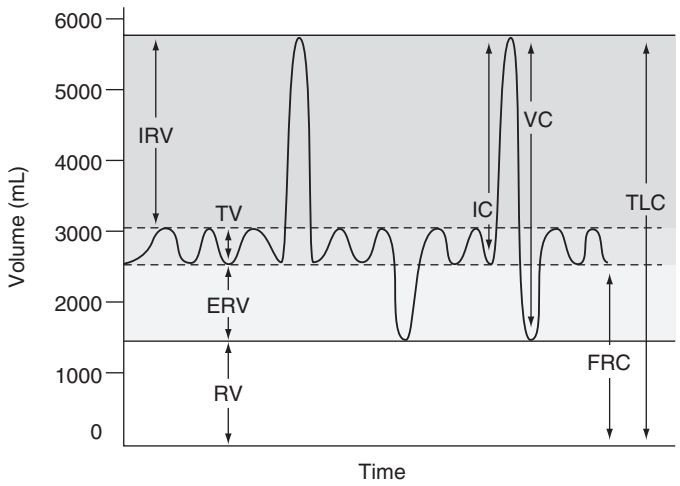


Figure 5.5 Spirogram. *ERV*, expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *IRV*, inspiratory reserve volume; *RV*, reserve volume; *TLC*, total lung capacity; *TV*, tidal volume.

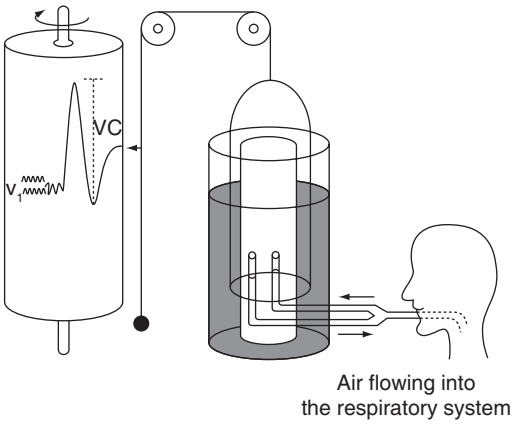


Figure 5.6 Spirometer.

is attached to a chain. This chain passes over a pulley and is connected to a counterweight and a writing pen. As the air in the bell is altered, the pen moves up and down. The pen records the graph on a drum which can be adjusted to rotate at different speeds.

A simple spirometer can record all volumes and capacities except FRC, RV, and TLC.

FRC, RV, and TLC are determined by two methods:

1. Helium dilution method
2. Nitrogen washout method

Helium Dilution Method The spirometer is filled with air mixed with a known concentration of helium. The subject inhales air from the spirometer commencing from the end of normal expiration. FRC can be determined by the degree of dilution of helium.

Nitrogen Washout Method The subject is asked to breathe normally. At the end of normal expiration, the subject inspires pure oxygen and later exhales into a Douglas bag. This procedure is repeated for 7 minutes till the nitrogen in the lungs is displaced by oxygen. FRC can be calculated by knowing the volume of air in the Douglas bag, N_2 concentration in the atmosphere, and air sample in the Douglas bag.

Once FRC is determined, RV and TLC can be calculated by

$$RV = FRC - ERV,$$
$$TLC = FRC + IC.$$

DYNAMIC LUNG VOLUMES AND CAPACITIES

Timed Vital Capacity (FEV)

Timed vital capacity is the measurement of vital capacity in relation to time. Forced expiratory volume (FEV) is the volume of air exhaled forcefully in unit time.

- FEV_1: Volume of air expired forcefully in 1 second. The normal value is 83%.
- FEV_2: Volume of air expired forcefully in 2 seconds. The normal value is 94%.
- FEV_3: Volume of air expired forcefully in 3 seconds. The normal value is 97–100%.

FEV values are decreased significantly in obstructive airway diseases such as asthma and emphysema.

In restrictive airway diseases, vital capacity is reduced but FEV can be normal.

FEV values are helpful to distinguish between obstructive and restrictive lung disorders.

Maximum Voluntary Ventilation/ Maximum Breathing Capacity

The maximum volume of air that can be breathed in and out of the lungs by maximum respiratory effort in 1 minute is called maximum voluntary ventilation (MVV) or maximum breathing capacity (MBC).

The normal value is 125–170 L/min in males and 80–100 L/min in females.

The subject is asked to breathe forcefully and rapidly into the spirometer for 15 seconds. The amount of air inspired and expired is measured. MVV is calculated by multiplying the measured volume by 4.

Peak Expiratory Flow Rate

The maximum rate at which air can be exhaled forcefully after a deep inspiration is known as peak expiratory flow rate (PEFR).

The normal value is 300–400 L/min.

PEFR is measured by using an instrument called Wright's peak flow meter. This is useful in assessing obstructive airway diseases such as asthma, cystic fibrosis, and emphysema.

PULMONARY CIRCULATION

Pulmonary circulation is the flow of blood between the right ventricle and the left atrium, i.e., passing through the pulmonary capillaries (**Fig. 5.7**). The pulmonary artery arises from the right ventricle and divides into right and left branches. These branches subdivide and form pulmonary capillaries. The pulmonary capillaries are lined by a single layer of epithelium and form a dense network around the alveoli (**Fig. 5.8**).

The pulmonary arteries and their branches are thin walled and distensible. The total resistance in pulmonary circulation is about one-tenth of systemic circulation. This is because the pulmonary vessels offer far less resistance compared to systemic vessels.

FEATURES OF PULMONARY CIRCULATION

- Pulmonary circulation is a low-pressure, low-resistance, and high-capacitance system.
- The pulmonary vessels are thin walled and can be easily distended.
- The pulmonary capillaries are larger than the systemic capillaries. They also have rich anastomoses.
- The pulmonary capillaries surround the alveoli, and thereby completely enclose them.
- The thickness of the pulmonary artery and the right ventricle is one-third that of the aorta and the left ventricle.

FUNCTIONS OF PULMONARY CIRCULATION

Gas Exchange

Oxygen is transferred from the alveoli to the blood in the pulmonary capillaries and carbon dioxide moves from the blood to the alveoli.

Metabolic Functions

Pulmonary capillary endothelium secretes angiotensin-converting enzyme which converts angiotensin I to angiotensin II.

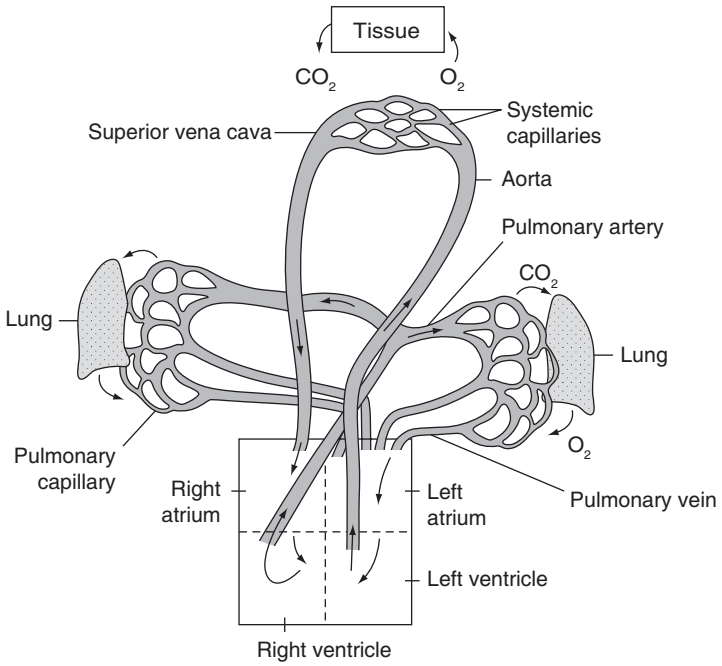


Figure 5.7 Circulation in the pulmonary system.

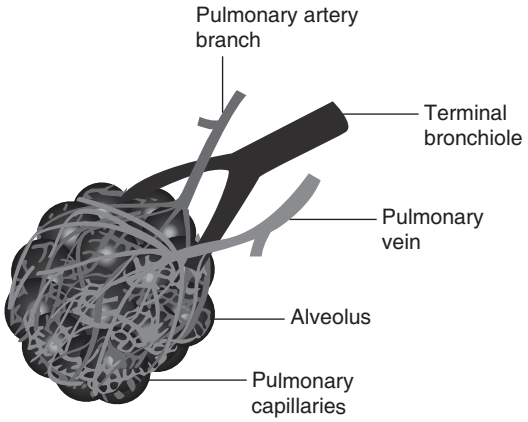


Figure 5.8 Alveolar blood supply.

Filtration and Dissolution of Clots

Small clots and emboli formed on the right side of the heart are filtered in the pulmonary vessels. These clots are dissolved by fibrinolytic agents released by pulmonary endothelial cells.

Blood Reservoir

Pulmonary circulation holds around 450 mL of blood, thereby functioning as a reservoir.

PRESSURES IN THE PULMONARY SYSTEM

The right ventricular pressure reaches a peak of 25 mm Hg during systole and falls to 0 mm Hg during diastole.

The pressure in the pulmonary artery during systole is 25 mm Hg and during diastole is 8 mm Hg. The mean pulmonary arterial pressure is 15 mm Hg.

The pressure in the pulmonary veins is around 5 mm Hg. Therefore, the pressure gradient in the pulmonary system is around 10 mm Hg.

The pulmonary capillary pressure is about 10 mm Hg. This low pressure causes a suction force drawing fluid from the alveolar interstitial space, thereby helping to keep the alveoli dry. If the pulmonary capillary pressure rises above 25 mm Hg (colloid osmotic pressure), it causes pulmonary edema.

The left atrial pressure is around 5 mm Hg. This is indirectly measured by pulmonary wedge pressure.

The pulmonary vascular resistance is about 10 times lower than the systemic vascular resistance. It is around 1.7 mm Hg/L/min. An increase in either pulmonary arterial or venous pressure reduces pulmonary vascular resistance. This is due to opening up of dormant capillaries and capillary distension.

Blood flow is not uniform throughout the lungs. When the subject is in upright position, the blood flow is maximum at the base of the lungs and minimum at the apex. However, when the subject is in supine position, blood flow to the apex increases and becomes equal to that of the base.

BLOOD VOLUME OF LUNGS

Lungs contain around 450 mL of blood. Out of this blood, around 70 mL is in the pulmonary capillaries and the remaining is equally distributed among pulmonary arteries and veins.

CLINICAL NOTES

Pulmonary Hypertension

Pulmonary hypertension is sustained elevation of pulmonary arterial pressure. There is an increase in pulmonary vascular resistance leading to right heart failure.

Oxygen therapy, vasodilators, and calcium channel blockers are used in the treatment of this condition.

Pulmonary Edema

Pulmonary edema occurs due to an increase in pulmonary interstitial fluid pressure. It causes accumulation of fluid in the pulmonary interstitial space and alveoli.

It is caused due to

- left-sided heart failure,
- infections such as pneumonia,
- oxygen toxicity, and
- high altitude.

VENTILATION–PERFUSION RATIO

The ventilation–perfusion ratio is the ratio of the alveolar ventilation to the volume of blood flowing through the pulmonary capillaries (perfusing) surrounding the alveoli.

It is expressed as

$$\frac{\text{Alveolar ventilation}}{\text{Perfusion}} = \frac{V_A}{Q}.$$

The normal value is 0.8.

It is more at the apex (up to 3) than at the base (0.6) of lungs.

Hydrostatic pressure in the lungs determines the blood flow to different zones of the lungs. Ventilation is more at the base than at the apex. The blood flow is also greater at the base than at the apex. However, change in the blood flow from the apex to the base is greater than the change in ventilation. Overall, perfusion increases more than ventilation at the base. Therefore, the ventilation–perfusion ratio is more at the apex and low at the base of the lungs.

This uneven V_A/Q ratio causes some diseases to be localized to a particular part of the lung. Tuberculosis of the lung is more common in the apex than in the base because the tubercle bacilli grow better in regions where oxygen availability is better.

Whenever alveolar ventilation becomes more and pulmonary blood flow is less, the V_A/Q ratio becomes greater. In this condition, the ventilation of the alveoli gets wasted leading to an increase in physiological dead space.

When alveolar ventilation is less and pulmonary blood flow is more, the V_A/Q ratio will be less than normal. The ventilation is inadequate to oxygenate all the blood flowing through the capillaries. This results in a portion of venous blood not being oxygenated. This is called a **physiological shunt**.

EFFECTS OF ALTERING THE V_A/Q RATIO (Fig. 5.9)

When ventilation is reduced relative to its perfusion, the V_A/Q ratio becomes less. This causes a fall in the alveolar PO_2 level and a rise in the PCO_2 level. When ventilation is increased relative to its perfusion, the V_A/Q ratio becomes more. This causes rise in the alveolar PO_2 level and fall in the PCO_2 level.

ABNORMAL VENTILATION–PERFUSION RATIO

V_A/Q is increased in conditions of anatomical shunts wherein blood bypasses the lungs through an anatomical defect. This occurs in conditions such as ventricular septal defect and Fallot's tetralogy.

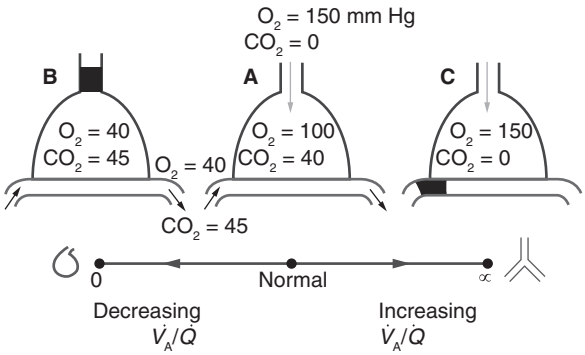


Figure 5.9 Effect of alterations of the ventilation–perfusion ratio on the PO_2 and PCO_2 in a lung unit. *V_A/Q, ventilation–perfusion ratio*. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edition. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

V_A/Q is decreased in conditions where portions of lungs are not oxygenated due to low alveolar ventilation. This occurs in conditions such as pneumonia and pulmonary embolism.

MECHANICS OF BREATHING

Respiration is a process in which air moves into the lungs during inspiration and moves out of the lungs during expiration. Inspiration is an active process due to contraction of inspiratory muscles and expiration in the resting state is a passive process occurring due to the elastic recoil of the lungs.

The mechanics of breathing deals with various physical forces that are involved in it.

This involves

- change in the size of thoracic cavity brought about by muscles of respiration and
- changes in the intrapleural and intrapulmonary pressures.

MUSCLES OF RESPIRATION

Muscles of respiration are necessary for the processes of inspiration and expiration.

Inspiratory Muscles (Fig. 5.10a)

Diaphragm

Diaphragm is a dome-shaped muscle with convexity upward. It separates the thorax and abdomen. It is supplied by the phrenic nerve.

It moves 1–1.5 cm during normal breathing. During deep breathing, it moves by 10 cm.

Normal quiet breathing is due to the action of the diaphragm (**Fig. 5.11**).

Contraction of the diaphragm causes the following:

- Flattening of the diaphragm (it moves down 1–1.5 cm during normal breathing and moves down by 10 cm during deep breathing)
- Rise in intra-abdominal pressure which is compensated by relaxation of abdominal muscles

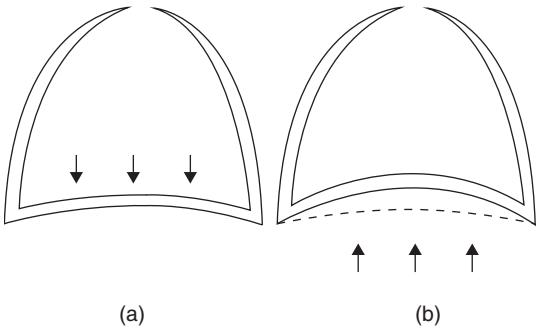


Figure 5.11 Position of diaphragm during (a) inspiration and (b) expiration.

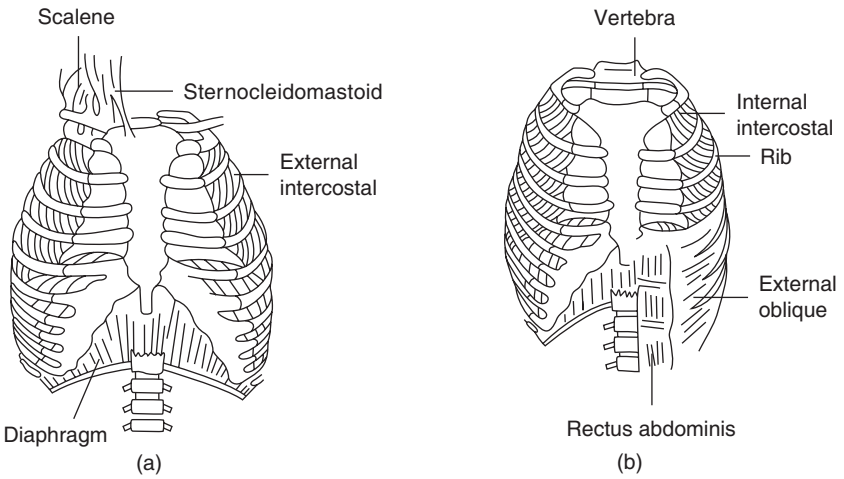


Figure 5.10 Muscles of (a) inspiration and (b) expiration.

- Increases the volume of the thoracic cavity in the anteroposterior axis

External Intercostals

These muscles are present between the ribs. The fibers are directed downward and medially.

Contraction of the external intercostal muscles causes

- increase in the transverse diameter of rib cage and
- increase in the anteroposterior diameter of rib cage.

When the external intercostal muscles contract, the ribs are elevated due to the lever effect at the pivot-like joint **(Fig. 5.12)**. This causes an increase of both anteroposterior and transverse diameters of the thoracic cavity. The increase of the anteroposterior diameter is similar to the operations of a pump handle; hence, it is termed a **pump-handle effect (Fig. 5.12a)**. The increase of transverse diameter is compared to the action of a bucket handle and hence termed **bucket-handle effect (Fig. 5.12b)**.

Expiratory Muscles (Fig. 5.10b)

Muscles of the Anterior Abdominal Wall

They include rectus abdominis, internal and external oblique, and transversus abdominis.

Contraction of muscles of the anterior abdominal wall causes increased intra-abdominal pressure resulting in elevation of diaphragm.

Internal Intercostals

Internal intercostals are present in between the ribs. They pull the ribs downward, thereby reducing both the anteroposterior and the transverse diameters of the thorax. This causes a reduction in the volume of the thoracic cage.

Internal intercostals are particularly important during coughing.

Accessory Muscles of Respiration

These muscles normally do not take part in inspiration but are active during forceful inspiration such as during exercise and conditions such as asthma.

The accessory muscles are as follows:

- **Scaleni**: Cause elevation of the thoracic cage
- **Sternocleidomastoid (SCM)**: Cause elevation of the thoracic cage
- **Serratus anterior**: Help in fixing the thoracic cage so that ribs can move efficiently

INSPIRATION (Fig. 5.13a)

The discharge from the inspiratory center through the phrenic nerve results in the descent of diaphragm and increase in the vertical diameter.

Contractions of the external intercostals increase the transverse diameter by the bucket

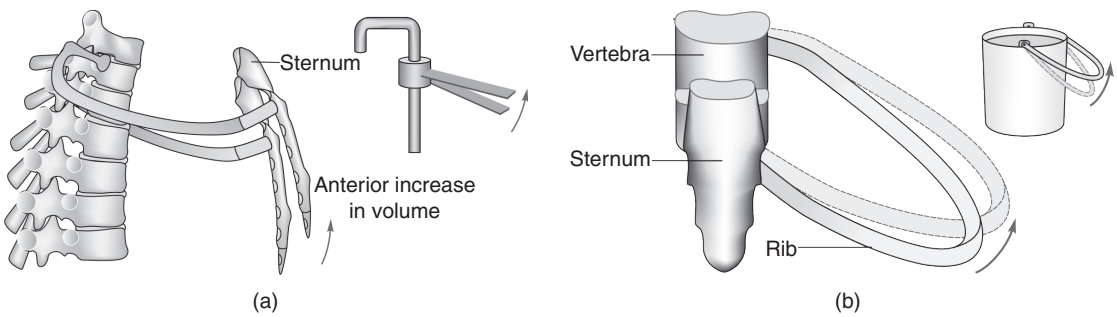


Figure 5.12 Action of external intercostals. (a) Pump-handle movement; increased anteroposterior diameter. (b) Bucket-handle movement; increased transverse diameter. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

handle movement. The anteroposterior diameter is increased by the pump handle movement.

This occurs by elevation of the anterior portion of the ribs. The second to fifth ribs assume horizontal position due to the contraction of external intercostal muscles. The sternum moves forward and upward.

Expansion of the thoracic cage makes intrapleural pressure more negative. Later, it creates negative pressure within the lungs.

Air enters the lungs from atmosphere to equalize the difference in pressure.

During forced expiration, neck muscles such as sternocleidomastoid and scaleni are used. The exercise-induced increase in the respiratory effort involves all the accessory muscles of respiration.

Inspiration

Contraction of diaphragm/external intercostal muscles

↓

Decreased intrapleural pressure

↓

Expansion of thoracic cage

↓

Negative pressure in the alveoli

↓

Air flows into the lungs

EXPIRATION (Fig. 5.13b)

In quiet breathing, expiration is a passive process.

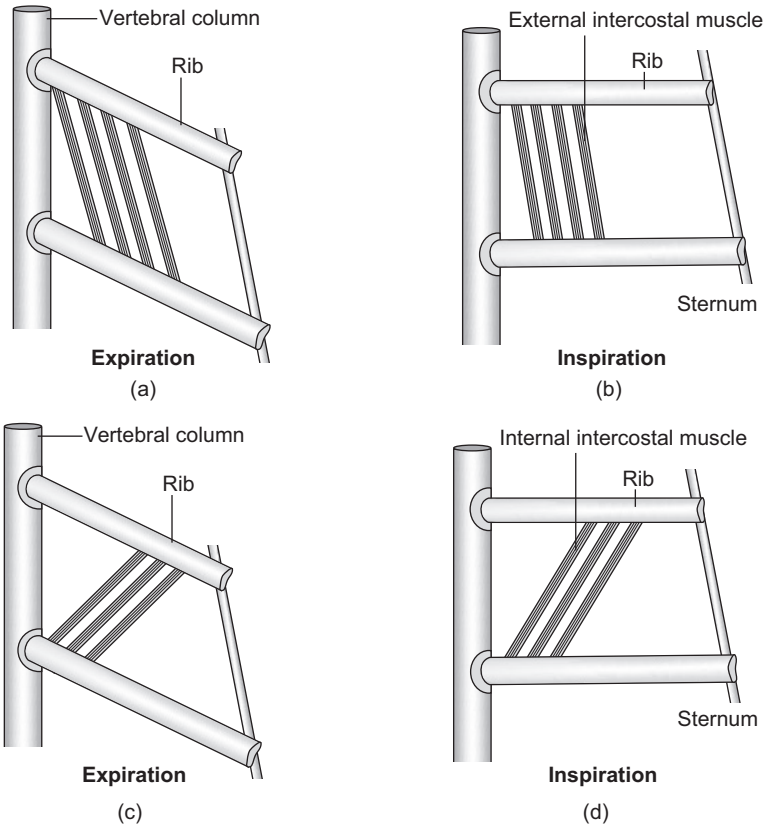


Figure 5.13 (a and b) Position of ribs due to action of external intercostal muscles during expiration and inspiration. (c and d) Position of ribs due to action of internal intercostal muscles during expiration and inspiration. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

It is produced by relaxation of inspiratory muscles assisted by elastic recoil of the thoracic cage.

Expiratory muscles are active during forced expiration.

Expiration

Relaxation of diaphragm/intercostal muscles

↓

Elastic recoil of thoracic cage

↓

Positive pressure inside alveoli

↓

Air flows out of the lungs

TYPES OF BREATHING

Breathing is of two types:

1. Abdominothoracic
2. Thoracoabdominal

Abdominothoracic breathing is seen predominantly in males and thoracoabdominal breathing is seen in females and children. The cause for this difference is not definitely known; however, it is attributed to stronger abdominal muscles in males. The term is based on the predominant component participating in the process of respiration. In males, the contribution of abdominal component predominates over the thoracic component.

BREATH SOUNDS

These are sounds caused by the movement of the air through the respiratory passage. They are heard by placing a stethoscope over the chest wall.

Breath sounds are of two types:

1. Vesicular
2. Bronchial

Vesicular breath sounds are produced due to flow of air in the larger airways and alveoli. It is caused due to opening and closing of alveoli.

Bronchial breath sounds are produced due to turbulent flow of air in the bronchi and larger airways (**Table 5.1**).

Table 5.1 Differences Between Vesicular and Bronchial Breath Sounds

Characteristics	Vesicular	Bronchial
Place heard	All over the chest wall	Over the trachea
Pitch	Low pitched	High pitched
Character	Rustling	Harsh
Duration of inspiration and expiration	Inspiration is prolonged	Equal
Gap between inspiration and expiration	No gap, continuous	Present

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

RESPIRATORY PRESSURE CHANGES

The lungs are present within the thoracic cavity. The visceral pleura cover the outer surface of the lungs. The parietal pleura line the inner surface of the thoracic cavity (**Fig. 5.14**). The space between the parietal and the visceral pleura forms the **pleural cavity**.

Four to eight milliliters of fluid (pleural fluid) is present in this cavity. It lubricates movement of the lungs.

INTRAPLEURAL PRESSURE (Fig. 5.15)

The pressure within the pleural cavity is termed *intrapleural pressure*. This pressure is normally negative. However, during forced expiration it can be positive. The normal intrapleural pressure varies between –2.5 and –6 mm Hg (–5 and –8 cm H_2O). At the beginning of

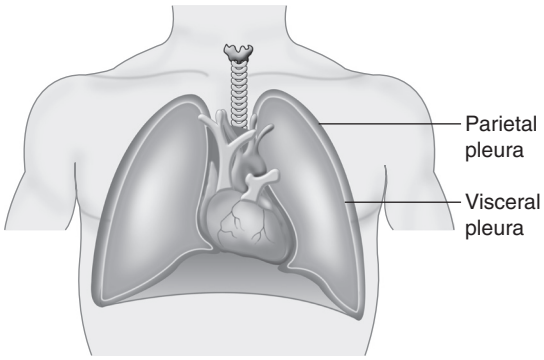


Figure 5.14 Visceral and parietal pleura. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

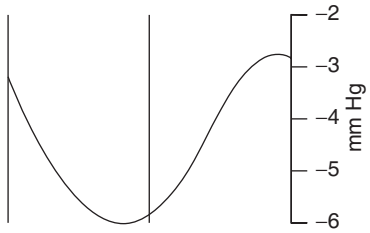


Figure 5.15 Intrapleural pressure.

inspiration it is –2.5 mm Hg and at the peak of normal inspiration it is –6 mm Hg. At the end of expiration, it comes back to –2.5 mm Hg.

INTRA-ALVEOLAR PRESSURE (INTRAPULMONARY PRESSURE; Fig. 5.16)

The pressure within the lungs is termed *intra-alveolar pressure*. During inspiration, it becomes negative (–1.5 mm Hg). During expiration, it becomes positive (+1 mm Hg). At the end of inspiration and expiration, the intra-alveolar pressure is zero.

TRANSPULMONARY PRESSURE (Fig. 5.17)

The pressure difference between the intrapleural and the intra-alveolar pressure is called **transpulmonary pressure**. Transpulmonary pressure is a measure of the elastic forces in the lungs.

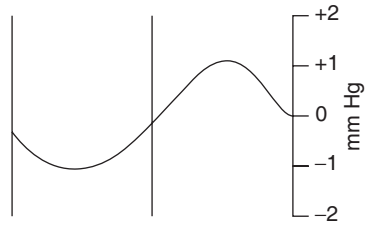


Figure 5.16 Intra-alveolar pressure.

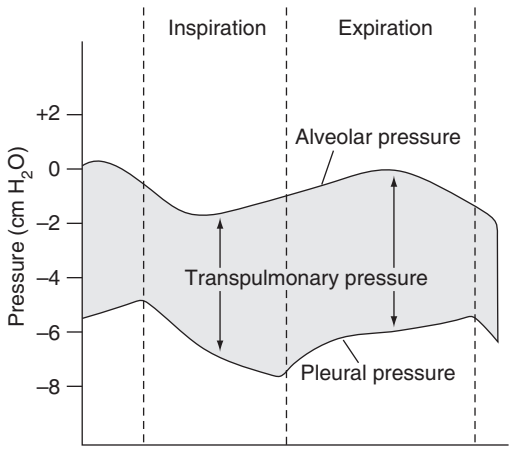


Figure 5.17 Pressure changes during respiration.

CLINICAL NOTES

Pleural Effusion

Accumulation of fluid in the pleural cavity is termed pleural effusion. The commonest cause of pleural effusion is **tuberculosis**.

The accumulation of pus is called pyothorax, accumulation of fluid is hydrothorax, and accumulation of blood is hemothorax. This diminishes expansion of the lungs and leads to difficulty in breathing.

Pneumothorax

Accumulation of air in the pleural cavity is called pneumothorax. This leads to collapse of the lungs. It is caused due to

- perforating injury of the chest wall by a sharp object or gunshots and
- rupture of the lung, opening into the pleural cavity (e.g., rupture of a lung abscess).

In pneumothorax (presence of air inside the pleural cavity), the normal negative intrapleural pressure is lost. It results in collapse of the lungs.

COMPLIANCE

Compliance is stretchability of the lungs.

It is the extent to which lungs expand for each unit increase in the transpulmonary pressure. The normal compliance is 200 mL/cm H_2O. This means every time the transpulmonary pressure increases by 1 cm H_2O, the lungs expand by 200 mL. Compliance is due to elasticity of the lungs and the thoracic cage.

$$\text{Compliance} = \frac{\text{Change in volume}}{\text{Change in pressure}} = \frac{\Delta V}{\Delta P}.$$

TYPES

Lung compliance is of two types:

i. static and
ii. dynamic.

Static Compliance

Static compliance is the change in the volume of the lungs for the application of a particular pressure. A more accurate measure of static compliance is specific compliance.

Specific Compliance

The compliance expressed as a function of FRC is termed specific compliance.

$$\text{Specific compliance} = \frac{\text{Compliance}}{\text{FRC}}.$$

This is a more specific measure of compliance, especially in persons having only one lung and in children.

Dynamic Compliance

The compliance measured with respect to time is called dynamic compliance. The measurement of dynamic compliance is useful in conditions such as bronchial asthma in which static compliance is normal but dynamic compliance is reduced.

COMPLIANCE CURVE (Fig. 5.18)

The pleural pressure is plotted along the *X*-axis and the lung volumes are plotted on the *Y*-axis.

The transpulmonary pressure is changed in small steps. The record of lung volumes shows two curves: one inspiratory and another expiratory curve separately. These are called **compliance curves**. The inspiratory and expiratory curves do not overlap but form a hysteresis loop. The curves obtained are due to the elastic forces of the lungs.

The line midway between the two curves represents the average compliance of lungs.

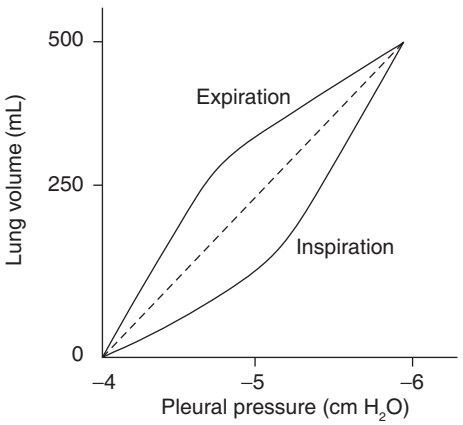


Figure 5.18 Compliance.

FACTORS AFFECTING LUNG COMPLIANCE

Lung compliance is mainly determined by the elastic forces:

- Elastic forces of the lung tissue
- Elastic forces caused by surface tension within the alveoli

Elastic forces of the lung tissue are due to elastic and collagen fibers. They contribute little to the elasticity.

Elastic forces produced by surface tension within the alveoli contribute about two-third of the total elastic forces in the lungs.

ABNORMAL LUNG COMPLIANCE

A decrease in lung compliance is seen in lung diseases which cause fibrosis of lungs, e.g., tuberculosis and silicosis.

An increase in lung compliance is seen in conditions such as emphysema.

SURFACE TENSION

Surface tension is the force caused due to intermolecular attraction (attraction between the molecules) on the surface.

The surface tension has to be kept low in the alveoli. Otherwise according to Laplace law, the alveoli tend to collapse during expiration.

According to Laplace law, the force or pressure on the wall of a hollow structure is equal to twice the tension divided by the radius:

$$P = \frac{2T}{R},$$

where P is pressure, T surface tension, and R radius.

Whenever the radius is reduced without a reduction in tension, the tension on the wall exceeds the distending pressure causing collapse of the alveoli. The surfactant reduces this surface tension and prevents collapse of alveoli whenever the radius is reduced.

SURFACTANT

Surfactant is a surface-active agent that reduces the surface tension when it is spread over a surface. It is secreted by Type II alveolar cells that occupy 10% of the surface area of the alveoli. These cells are granular and contain lipid inclusions. They secrete tubes of lipid called *tubular myelin*. This tubular myelin forms a thin film over the surface and helps to reduce the surface tension.

Composition

- Dipalmitoyl phosphatidylcholine (62%)
- Phosphatidyl glycine (5%)
- Other phospholipids (10%)
- Neutral lipids (13%)
- Proteins (8%)
- Carbohydrates (2%)

Functions

- **Prevents collapse of the alveoli**: The surfactant reduces the surface tension at the air–fluid interface of the alveoli, thereby preventing lung collapse.
- **Increases lung compliance and reduces the work of breathing**: The surfactant reduces the effort required for the expansion of alveoli. As the alveoli expand easily, the work of breathing is reduced.
- **Keeps the alveoli dry by preventing the tissue fluid formation**: Surface tension is an inward force which tends to decrease the interstitial pressure. This pulls fluid out of the capillaries and tends to cause pulmonary edema. The surfactant reduces the surface tension, thereby preventing pulmonary edema.
- **Increases alveolar stability**: The surfactant causes stability of the alveoli by maintaining a uniform size of the alveoli. It also reduces the surface tension of smaller alveoli to a greater degree, thereby preventing collapse of smaller alveoli.
- **Provide immunity**: IgA and apoproteins provide immunity by acting as opsonins.

Production of the surfactant starts by the seventh month of the intrauterine life. The thyroid hormone and glucocorticoids enhance the production of the surfactant.

CLINICAL NOTES

Infant Respiratory Distress Syndrome (Hyaline Membrane Disease)

Respiratory effort by a baby at birth expands the alveoli. The surfactant prevents the collapse of alveoli. In premature babies, the production of surfactant is reduced. Small diameter of alveoli along with reduced surfactant increases the tendency for alveoli to collapse. This is called **infant respiratory distress syndrome**, or hyaline membrane disease. This condition can be fatal if proper treatment is not given at the right time.

Treatment

- Continuous positive pressure breathing
- Administration of bovine surfactant

Adult Respiratory Distress Syndrome

This occurs due to an abnormal secretion of surfactant. This occurs in severe chest injuries, severe respiratory infections, and burns.

Differences Between Obstructive Lung Disease and Restrictive Lung Disease

	Obstructive Lung Disease	Restrictive Lung Disease
Characteristics	Limitation of airflow due to obstruction	Reduced lung expansion
Type of breathing	Slow and deep breaths	Rapid and shallow breaths
Total lung capacity	Normal	Decreased
Forced vital capacity	Normal	Decreased
FEV1/FVC ratio	Decreased	Normal
PEFR	Decreased	Normal
Example	Asthma, emphysema	Interstitial pneumonia, pulmonary fibrosis, obesity, kyphoscoliosis

REGULATION OF RESPIRATION

Respiration involves the process of inspiration and expiration. It is controlled by

- neural regulation and
- chemical regulation.

NEURAL REGULATION (Fig. 5.19)

Neural regulation is by the involvement of

- respiratory centers,
- peripheral receptors, and
- higher centers.

Respiratory Centers

The respiratory centers are a group of neurons present in the brainstem (**Fig. 5.20**). They are paired. These centers are as follows:

- Dorsal respiratory group
- Ventral respiratory group
- Apneustic center
- Pneumotaxic center

Dorsal Respiratory Group

The dorsal respiratory group (DRG) is situated in the dorsal portion of the medulla around the nucleus of tractus solitarius.

DRG receives sensory inputs from different parts of the respiratory system and peripheral chemoreceptors via IX and X cranial nerves. It integrates the received sensory information, and the neurons from DRG project to the cell bodies of the phrenic nerve in the spinal cord.

Ventral Respiratory Group

The ventral respiratory group (VRG) is present in the ventral aspect of the medulla. The neurons of this group remain inactive during

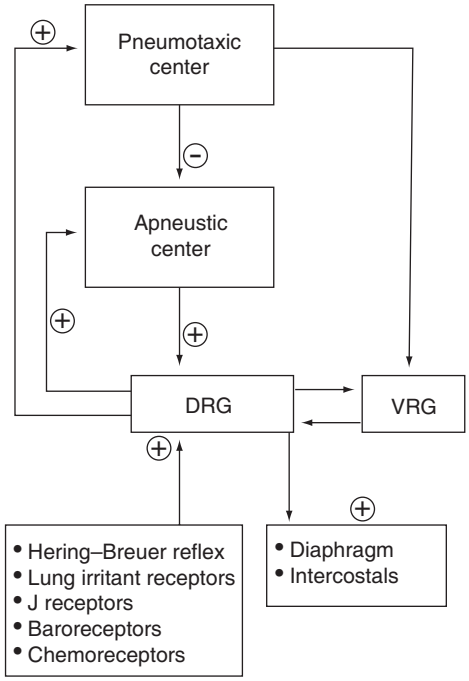


Figure 5.19 Neural regulation of respiration. *DRG*, dorsal respiratory group; *VRG*, ventral respiratory group.

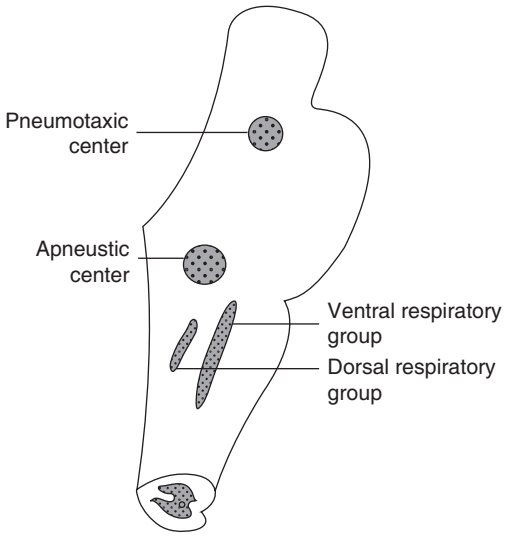


Figure 5.20 Respiratory centers.

normal respiration. When the respiratory drive becomes greater than normal, they participate in respiration.

Pre-Botzinger Complex This is a small group of cells present on either side of the medulla between nucleus ambiguus and lateral reticular nucleus. These neurons produce rhythmic discharges in phrenic motor neurons. The neurons of the pre-Botzinger complex are considered to be the pacemaker cells of the respiratory system. The dorsal and ventral groups of neurons project to pre-Botzinger pacemaker neurons.

Apneustic Center

The apneustic center is present in the lower pons. It gets feedback from the vagus nerve and other respiratory centers. It acts with the pneumotaxic center to control the depth of inspiration. Stimulation of the apneustic center produces deep inspiration.

Pneumotaxic Center

The pneumotaxic center is located in the upper part of the pons in the nucleus parabrachialis medialis. It controls the duration of inspiration by regulating the switch-off point of inspiratory ramp signals. Strong stimulation of the pneumotaxic center decreases the duration of inspiration and hence increases the rate of respiration. Damage to pneumotaxic center causes slower respiration and increases tidal volume.

Genesis of the Respiratory Rhythm

The normal respiratory rhythm is generated by the central pattern generator present in the medulla. The pacemaker cells of the pre-Botzinger complex discharge rhythmically to activate inspiratory signals. The signals are weak in the beginning, but rise rapidly to reach a peak in a **ramp** fashion for about 2 seconds and stop abruptly. This is called the **inspiratory ramp**. After 3 seconds, the inspiratory neurons start discharging the impulses again. This cycle gets repeated. A negative feedback loop in the medulla regulates the cyclical discharges from the inspiratory neurons.

The pneumotaxic center also plays an important role in regulating the switch-off point of inspiratory

(*Contd.*)

ramp signals. It controls the duration of inspiration. Strong signals from the pneumotaxic center reduce the duration of inspiration. There is an increase in the rate of respiration.

In addition, signals from stretch receptors in the lungs control the duration of inspiration similar to the pneumotaxic center. The apneustic center has a limited role in the normal respiration.

The reflexes from within and outside the lungs influence respiration.

Peripheral Receptors

Reflexes Arising Within Lungs

1. **Hering–Breuer reflex**: Inflation of the lungs inhibits inspiration and initiates expiration. This is termed *Hering–Breuer inflation reflex*. Deflation of the lungs inhibits expiration and initiates inspiration. This is *Hering–Breuer deflation reflex*. This reflex is abolished by vagotomy. The reflex has a limited role in quiet breathing in adults. The receptors for this reflex are located in airway smooth muscles, in the walls of the bronchioles, and in the alveolar duct. Afferent impulses travel through the myelinated vagal nerve fibers.
2. **Lung irritant receptors**: These receptors are located in between the epithelial lining of the airways. Myelinated vagal fibers carry afferent impulses. These receptors adapt rapidly. The receptors respond to chemical and mechanical irritants (inhalation of dust, irritant gases, cigarette smoke, and cold air). They also respond to sudden inflation and deflation of the lungs and pulmonary congestion. The response is hyperpnea, bronchoconstriction, and bradycardia. Unpleasant sensation produced in asthma is due to activation of this reflex.
3. **J (juxtacapillary) receptors**: These are located close to pulmonary capillaries. The afferent impulses travel in the unmyelinated vagal fibers. They are stimulated by an increase in the volume of interstitial fluid, pulmonary congestion, edema, and microemboli. There is reflex apnea followed by rapid shallow breathing, bronchoconstriction, bradycardia, and hypotension. J receptors are responsible for dyspnea produced during left-sided heart failure.
4. **Effect of vagotomy**: The respiration becomes slower and deeper (with prolonged inspiration) after bilateral vagotomy. This response is due to the abolition of the Hering–Breuer inflation reflex. However, the pneumotaxic center maintains rhythmic breathing.
5. **Effect of vagal stimulation**: The stimulation of the cut end of vagus produces varying results. The response depends on the type of fibers stimulated in the vagal trunk. The stimulation of the vagus can result in arrest of breathing or an increase in the rate and depth of respiration.

Reflexes Arising Outside Lungs

1. Reflexes from baroreceptors—a sudden and significant increase in the arterial blood pressure stimulates the baroreceptors. There is reflex inhibition of respiration resulting in reduced rate and depth of breathing.
2. Reflexes from chemoreceptors—the peripheral chemoreceptors present in the aortic and carotid bodies are sensitive to changes in partial pressure of oxygen and carbon dioxide. The reduction in PO_2 or an increase in PCO_2 stimulates the chemoreceptors. This increases the rate and depth of respiration.
3. There is reflex inhibition of respiration during the second stage of swallowing. This is termed **deglutition apnea**. It is a protective reflex to prevent the entry of food into the larynx. This reflex is produced by stimulation of the glossopharyngeal nerve.
4. The somatic pain sensation causes respiratory stimulation. It increases the rate and depth of respiration. The pain sensations arising from the internal organs and hollow viscus due to traction or distension inhibit the respiration.

5. The afferent proprioceptive impulses from the receptors of muscles and joints stimulate respiration. Hyperventilation observed during exercise is due to this reflex mechanism.
6. The stimulation of thermoreceptors in the skin by increased environmental temperature increases the rate and depth of respiration. This mechanism helps to regulate the body temperature in lower animals.

Influence Of Higher Centers

Respiration is mainly an involuntary act. The respiratory muscles are skeletal muscles. Therefore, voluntary control of respiration is possible, but to a limited extent. Breathing can be voluntarily stopped for about a minute. This is termed **breath holding time**. The rate and depth of respiration can also be increased by voluntary effort for a short duration.

The voluntary breath holding builds up the carbon dioxide concentration. When it reaches a critical level, it stimulates the respiratory center to restart respiration. This is termed **breaking point**.

The cerebral cortex, limbic system, hypothalamus, and reticular activating system influence respiration.

The cerebral cortex helps to exercise voluntary control over respiration.

Emotional disturbances influence the rate and depth of respiration by acting through the limbic system.

Higher centers are not essential for normal respiration. However, they have a modifying effect on the pattern of breathing.

CHEMICAL REGULATION (Flowchart 5.1)

There are three factors responsible for the chemical regulation of respiration. They influence the rate and depth of respiration by acting through the chemoreceptor. There are two types of chemoreceptors:

1. Central chemoreceptors
2. Peripheral chemoreceptors

Central Chemoreceptors

Central chemoreceptors are located in the medulla oblongata and are therefore also called medullary chemoreceptors. These receptors monitor the H^+ concentration of the CSF and the brain interstitial fluid.

Peripheral Chemoreceptors

Peripheral chemoreceptors are present in the carotid and aortic bodies. These bodies contain two types of cells: Type I and Type II. Type I cells (glomus cells) are closely associated with the endings of the afferent nerves. These cells have K^+ channels which are sensitive to hypoxia. Type II cells are glia-like cells. They surround the glomus cells. They are supportive in function.

The factors influencing respiration are

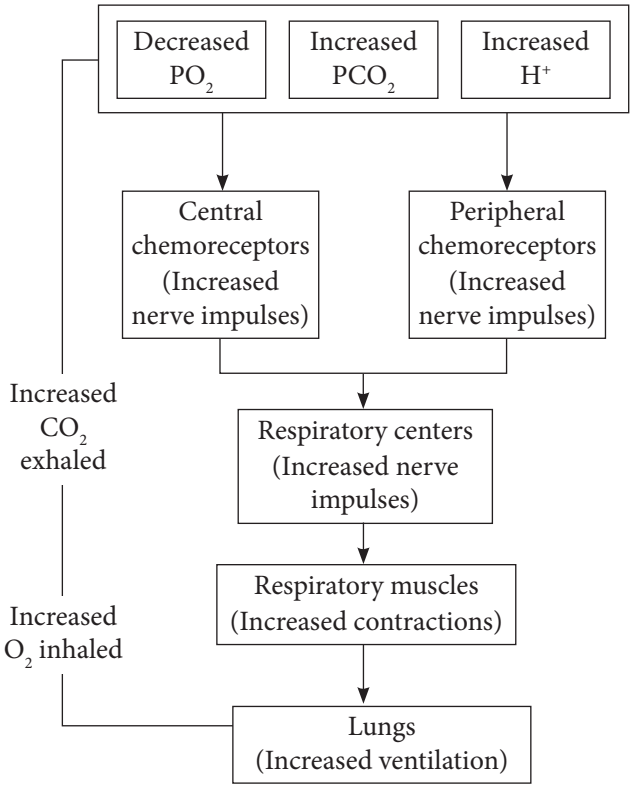
- PCO_2,
- H^+ ion concentration, and
- PO_2.

Role of Carbon Dioxide

The respiratory changes depend on CO_2 concentration in the blood. Carbon dioxide acts by influencing the central and peripheral chemoreceptors. A mild-to-moderate increase in the concentration of CO_2 increases the rate and depth of respiration. A severe increase in the concentration of CO_2 leads to loss of consciousness and respiratory depression.

Mode of Action Carbon dioxide stimulates respiration by acting on the central chemoreceptor and reflexly through the peripheral chemoreceptor.

It crosses the blood–brain barrier and combines with water in the presence of an enzyme carbonic anhydrase to form carbonic acid. Carbonic acid being a weak acid dissociates into H^+ ions and HCO_3^- ions. The H^+ ions formed stimulates the central chemoreceptor to increase the rate and depth



Flowchart 5.1 Chemical regulation of respiration. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

of respiration. The central effect of CO_2 is more dominant when compared to its influence on the peripheral chemoreceptor.

Role of Hydrogen Ions

An increase in the hydrogen ion concentration stimulates respiration and increases the rate and depth of respiration. A decrease in the hydrogen ion concentration decreases respiration and reduces the pulmonary ventilation. H^+ acts mainly through the peripheral chemoreceptors. Its influence on the central chemoreceptor is limited, as the hydrogen ion does not cross the blood–brain barrier. The respiratory response to H^+ ion concentration is to adjust the pulmonary ventilation to restore the pH of blood.

Role of Oxygen

Lack of oxygen stimulates respiration, by increasing the rate and depth of breathing. The stimulant effect is produced as a reflex by stimulation of the peripheral chemoreceptor located at the carotid body and the arch of aorta. The direct effect of lack of oxygen is a depressant on the respiratory center. However, the depressant effect is overcome by the stimulatory effect on the peripheral chemoreceptor.

A mild reduction in the oxygen concentration has little influence on the respiration. A moderate decrease in the oxygen concentration stimulates respiration, resulting in increased rate and depth of respiration. A severe decrease in the oxygen concentration depresses respiration resulting in respiratory paralysis.

PERIODIC BREATHING

When a normal person hyperventilates for a few minutes, there is a period of apnea alternating with shallow breathing following hyperventilation. This is termed *periodic breathing*. Periodic breathing is due to lack of stimulation of the respiratory center by CO_2.

CHEYNE–STOKES BREATHING (Fig. 5.21b)

Cheyne–Stokes breathing occurs in patients with congestive cardiac failure, uremia, brain diseases, and during deep sleep.

Breathing is characterized by alternate apnea and hyperventilation.

It is due to the sluggish chemical regulation of respiration.

BIOT'S BREATHING (Fig. 5.21c)

In this condition, there is alternate eupnea (normal breathing) and apnea.

This is seen in meningitis and severe brain damage.

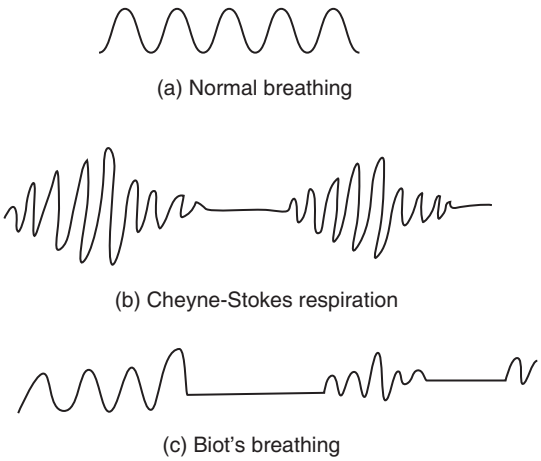


Figure 5.21 Breathing patterns. (a) Normal breathing; (b and c) periodic breathing.

KUSSMAUL'S BREATHING

Kussmaul's breathing occurs in metabolic acidosis like diabetic ketoacidosis or renal failure. There is rapid and deep breathing due to respiratory stimulation by increased hydrogen ion concentration.

PRINCIPLES OF GAS EXCHANGE

Atmospheric air contains gases such as N_2, O_2, and CO_2. At the sea level, it contains 79% of N_2 and 21% of O_2. The total pressure of gases at the sea level is 760 mm Hg. Partial pressure of a gas *(P)* is the pressure exerted by that gas in a mixture of gases. Partial pressure of oxygen is denoted as PO_2, nitrogen as PN_2, and carbon dioxide as PCO_2.

MOLECULAR BASIS OF DIFFUSION OF GAS

The gas molecules move freely among each other in random motion. The pressure exerted by the gas depends upon three factors. They are as follows:

1. Concentration of the molecules
2. Volume
3. Temperature

Concentration of the Molecules

As the concentration of molecules increases, the force exerted by them also increases. Therefore, the pressure exerted by the gas is directly proportional to its concentration.

Volume

According to **Boyle's law**, under constant temperature, the volume of a fixed mass of gas is inversely proportional to the pressure exerted on it.

Temperature

According to **Charles' law**, the volume of a fixed mass of gas at a constant pressure is directly proportional to the absolute temperature.

Transfer of gases from the alveoli to the pulmonary blood occurs by diffusion. Diffusion through tissue is described by Fick's law.

Fick's law states that the rate of transfer of a gas through a tissue is directly proportional to

- surface area,
- difference in partial pressure of the gases between two sides, and
- solubility of gas in the fluid.

It is inversely proportional to

- thickness of the tissue (distance) and
- molecular weight of the gas.

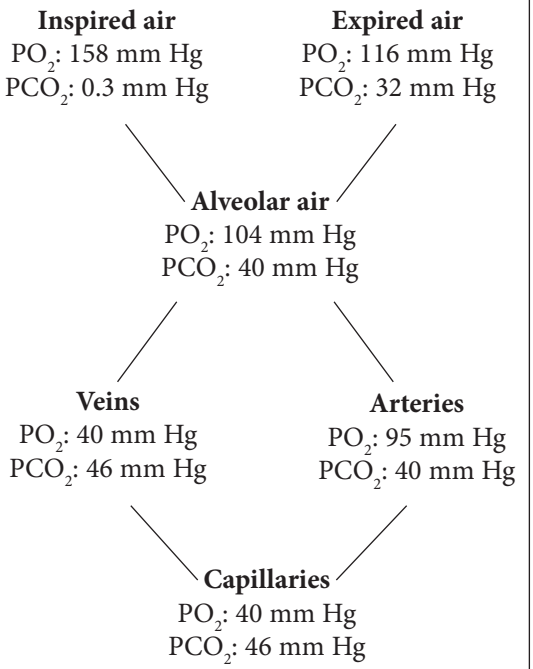
$$D \propto \frac{\Delta P \times A \times S}{d \times \text{MW}},$$

where ΔP is pressure difference between the two sides, A cross-sectional area of tissue, S solubility of the gas, d distance of diffusion, and MW molecular weight of the gas.

Alveolar air does not have the same concentration of gases as atmospheric air. This is because

- O_2 is constantly absorbed from alveolar air,
- CO_2 is diffusing from blood into the alveolar air,
- alveolar air is partially replaced by atmospheric air with each breath, and
- water vapor is added to alveolar air.

Partial Pressures of O_2 and CO_2 in mm Hg in Different Parts of the Body



TRANSPORT OF BLOOD GASES

Tissues require oxygen for their metabolic activity. Atmospheric oxygen is taken up by the lungs. The oxygen is transported from the lungs to the tissues through blood. Tissues liberate carbon dioxide during metabolism. It is transported to the lungs through blood for expulsion to the atmosphere.

OXYGEN TRANSPORT

O_2 is transported in the blood in two forms:

1. Physical solution
2. Combination with hemoglobin

Physical Solution

Oxygen in physical solution is the amount of oxygen carried in a dissolved state in plasma.

Normal arterial blood with PO_2 of 100 mm Hg contains 0.3 mL of O_2/100 mL in a dissolved form. This is because the solubility of oxygen in water is very much limited.

The normal cardiac output is 5 L/min and the oxygen transported in the dissolved state is only 15 mL/min. This accounts for only 3% of total O_2 transport and it is grossly inadequate to meet the oxygen needs of the body.

Combination with Hemoglobin

About 97% of oxygen is transported from the lungs to the tissues in combination with hemoglobin.

Oxygen molecules combine loosely and reversibly with the heme portion of Hb. This process is termed **oxygenation**.

Hemoglobin is made up of four subunits. Each subunit consists of heme and polypeptide. Each heme contains one atom of iron. Each atom of iron combines with one molecule of oxygen. Therefore, a single Hb molecule can bind to four molecules of oxygen. This combination of iron with oxygen occurs only when it is in a ferrous state.

When PO_2 is high, O_2 binds with Hb, and when PO_2 is low, O_2 is released from hemoglobin.

$$O_2 + Hb \leftrightarrow Hb\ O_2.$$

The combination of O_2 with Hb is better understood by studying the oxygen dissociation curve.

The curve is obtained by plotting the partial pressure of O_2 against the percentage saturation of Hb. The curve shows a progressive increase in the percentage saturation of Hb as the PO_2 increases.

Arterial Blood	
PO_2	95 mm Hg
O_2 saturation	97%
Venous Blood	
PO_2	40 mm Hg
O_2 saturation	75%

The O_2 dissociation curve is **sigmoid shaped** (**Fig. 5.22**). This sigmoid shape is physiologically significant. The curve is divided into two phases:

1. Middle steep phase
2. Plateau phase

The steep middle part of the curve shows that a small change in PO_2 leads to a significant change in the percentage saturation of Hb.

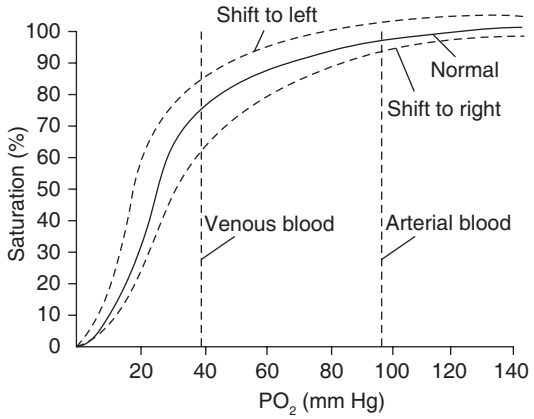


Figure 5.22 O_2 dissociation curve.

This helps in easy delivery of O_2 to the tissues and also uptake of O_2 in the lungs.

The top portion of this curve is flat. A considerable change in PO_2 results in a slight change of percentage saturation. The advantage is that a slight fall in alveolar PO_2 does not significantly alter the oxygenation of Hb.

P_{50} This is the partial pressure of O_2 at which Hb is 50% saturated.

P_{50} is an index of affinity of Hb with O_2. The higher the P_{50} value, the lower the affinity.

Normal P_{50} is about 26 mm Hg at sea level in adults.

Fetal hemoglobin and myoglobin have lower P_{50} values compared to adult hemoglobin.

A normal person has 15 grams of Hb/100 mL of blood. Each gram of Hb can combine with 1.34 mL of O_2. Therefore, 100 mL of blood can carry 19.8 mL of O_2 when Hb is fully saturated.

Since Hb is usually saturated to about 95%, the O_2 carrying capacity is 19 mL of O_2/100 mL of blood.

Venous blood contains 14 mL of O_2/100 mL of blood. Therefore, the net utilization of O_2 by tissues is around 5 mL/100 mL of blood flow.

FACTORS AFFECTING THE O_2 DISSOCIATION CURVE

If the affinity of Hb toward O_2 decreases, the O_2 dissociation curve shifts to the right.

The shift to the right occurs in conditions of

- ↑PCO_2,
- ↑H^+ ion concentration (decreased pH),
- ↑temperature, and
- ↑2,3-DPG (diphosphoglycerate)/2,3-BPG (biphosphoglycerate).

Effect of CO_2 and H^+ Ions (Bohr's Effect)

Bohr's effect is the influence of CO_2 on the release and uptake of oxygen by hemoglobin.

Increased CO_2 content of the blood helps to release more O_2 from Hb. This is called **Bohr's effect**.

Application of Bohr's Effect

- **In the tissues**: CO_2 is produced in the tissues. This increases H^+ ion concentration and decreases pH. These changes cause an alteration in the configuration of the Hb molecule. Hence, its affinity to O_2 is reduced. Therefore, more amount of O_2 is delivered to the tissues.
- **In the lungs**: CO_2 diffuses from blood into the alveoli. This reduces CO_2 and H^+ ion concentration in blood. The affinity of Hb to O_2 is increased. Therefore, more oxygen binds to Hb.

Effect of DPG (BPG)

2,3-DPG is formed inside the RBC during glucose metabolism. It has an affinity for Hb. It causes release of O_2 from Hb. Therefore, when 2,3-DPG is increased in RBC, more O_2 is released and delivered to the tissues. This is very helpful during chronic hypoxic conditions.

Effect of Exercise

Exercise causes a shift of the O_2 dissociation curve to the right. During exercise, there is an increase in temperature and release of large quantities of CO_2 and acid metabolites. It enhances the release of O_2 to the muscle from Hb. Increased release of O_2 satisfies enhanced O_2 need of the muscle.

Shift to the left occurs in conditions of

- effect of fetal hemoglobin and
- carbon monoxide poisoning.

Effect of Fetal Hemoglobin

The O_2 dissociation curve in fetal hemoglobin is shifted to the left when compared to the curve of adult hemoglobin. This is because the γ chains present in the fetal hemoglobin have less affinity for 2,3-DPG as compared to the β chain of adult hemoglobin.

This is advantageous for the fetus since it can take up more oxygen even though fetal blood is exposed to low PO_2 values of maternal blood inside the placenta.

Effect of Carbon Monoxide

Carbon monoxide has about 200 times more affinity to hemoglobin than oxygen. Carbon monoxide combines with Hb at the same site as that of oxygen to form carboxyhemoglobin. Therefore, it replaces oxygen from hemoglobin and causes severe tissue hypoxia. In healthy individuals, carbon monoxide occupies only 1% of the binding sites of Hb. In chronic smokers and people living in polluted areas, it may occupy 10% of the Hb.

DIFFUSION OF O_2 TO TISSUES

O_2 is continuously used by the tissues. Therefore, the intracellular PO_2 remains lower than PO_2 in the blood. The normal intracellular PO_2 is 5–40 mm Hg. Therefore, O_2 diffuses easily from the blood into the tissues.

Cells require PO_2 between 1 and 3 mm Hg for their function. PO_2 of 23 mm Hg in tissues, therefore, provides a wide safety factor for its diffusion.

CARBON DIOXIDE TRANSPORT

The tissues during metabolic activity utilize oxygen and produce carbon dioxide. Carbon dioxide is taken up from the tissues by blood

in the capillaries. It is transported through the venous system and expelled from the lungs.

Carbon dioxide is transported by the blood in three forms:

1. As bicarbonate
2. In combination with Hb and plasma proteins as carbamino compounds
3. In physical solution

As Bicarbonate Ions

This is the major mechanism of CO_2 transport. About 70% of CO_2 is transported in this form. RBC plays a major role in this mechanism.

The carbon dioxide produced in the tissues diffuses into the plasma and from plasma into the RBC. Inside the RBC, the dissolved CO_2 reacts with water to form carbonic acid. This occurs very rapidly due to the presence of the enzyme carbonic anhydrase. Carbonic anhydrase enzyme accelerates the reaction 5000 times.

$$H_2O + CO_2 \rightleftarrows H_2CO_3.$$

Subsequently, carbonic acid dissociates into H^+ ions and HCO_3^- ions. H^+ ions combine with Hb to form HHb in the red cells. Bicarbonate ions diffuse from red cells into plasma in exchange for chloride ions. This exchange is possible due to the presence of bicarbonate–chloride carrier protein present in the RBC membrane. The movement of chloride ions from plasma into RBC is termed **chloride shift** (Hamburger's phenomenon; **Fig. 5.23**). Chloride shift occurs at the tissues. Thus, the chloride content of RBC in venous blood is greater than that in arterial blood.

When blood reaches the lungs, there is reversal of changes that occurred at the tissues. Hemoglobin is oxygenated releasing H^+ ions from hemoglobin. H^+ ion combines with HCO_3^- ion to form CO_2 and H_2O. CO_2 diffuses out of RBC into the alveoli. The HCO_3^- ion is supplied from the plasma in exchange for the chloride ions. This is termed **reverse chloride shift** (**Fig. 5.24**).

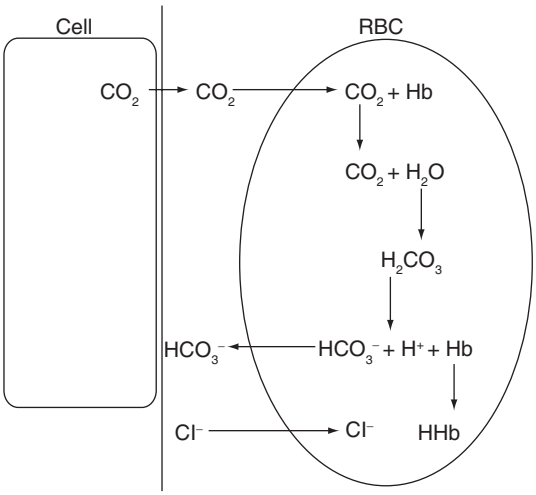


Figure 5.23 Chloride shift.

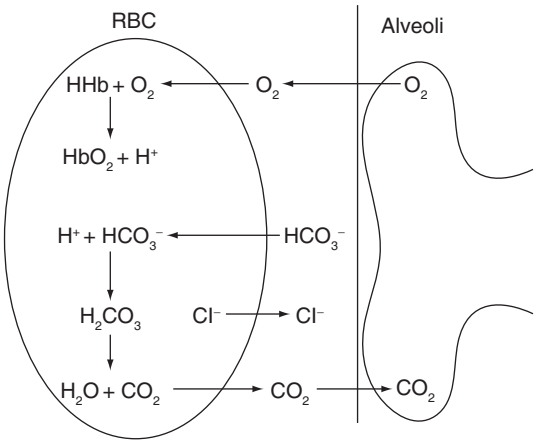


Figure 5.24 Reverse chloride shift.

As Carbamino Compounds

CO_2 combines chemically with Hb and plasma proteins to form carbamino compounds. Since Hb is the most abundant protein in blood, CO_2 combines mainly with Hb. It is carried as carbamino hemoglobin. About 20% of the total CO_2 transport occurs in this form.

In Dissolved Form

About 7% of the CO_2 is transported in a dissolved state to the lungs.

PCO_2 of venous blood is 45 mm Hg. Hence, the dissolved CO_2 is 2.7 mL/dL.

PCO_2 of arterial blood is 40 mm Hg. Therefore, dissolved CO_2 is 2.4 mL/dL.

About 0.3 mL/dL of CO_2 is transported in a dissolved state.

CO_2 DISSOCIATION CURVE (Fig. 5.25)

The relationship between PCO_2 and volume of CO_2 carried by blood is depicted by the CO_2 dissociation curve.

CO_2 present in arterial blood is 48 mL/100 mL at PCO_2 of 40 mm Hg.

CO_2 present in venous blood is 52 mL/100 mL at PCO_2 of 45 mm Hg.

For every 100 mL of blood, 4 mL of carbon dioxide is transported from the tissues to the lungs. Therefore at rest, about 200 mL of CO_2 is transported from the tissues to the lungs every minute.

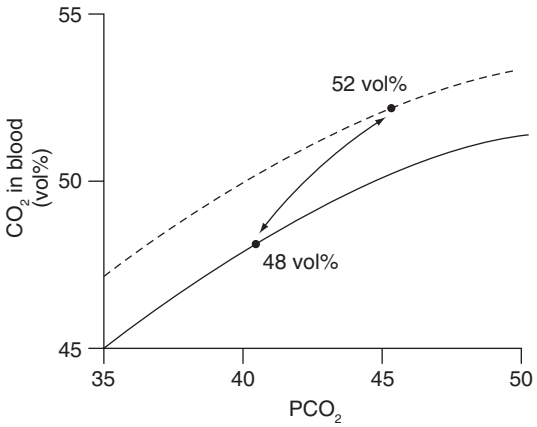


Figure 5.25 CO_2 dissociation curve.

HALDANE EFFECT

The influence of O_2 on the release and uptake of CO_2 by Hb is termed **Haldane effect**.

Combination of Hb with O_2 causes Hb to become a stronger acid. The highly acidic Hb has a lesser tendency to combine with CO_2. Therefore, CO_2 present in the carbamino form is displaced from the blood.

Increased affinity of Hb with oxygen releases excess of H^+ ions. H^+ ions bind with HCO_3^- to form carbonic acid. This dissociates into CO_2 and water. CO_2 is released from the blood into alveoli.

$$HHb + O_2 \rightarrow HbO_2 + H^+$$
$$H^+ + HCO_3^- \rightarrow H_2CO_3$$
$$H_2CO_3 \rightarrow CO_2 + H_2O$$

In Tissue Capillaries

The Haldane effect increases the uptake of CO_2 due to the removal of O_2 from Hb.

In The Lungs

The Haldane effect causes increased release of CO_2 due to O_2 uptake by Hb. The volume of CO_2 eliminated is doubled by the Haldane effect.

DISORDERS OF BREATHING

Respiratory disorders vary widely from mild deficiency of oxygen, which will be compensated by the body itself, to severe oxygen deficiency, which can be life threatening. Similarly, there can be abnormal accumulation of CO_2 which is even more dangerous than oxygen deficiency. Symptoms and signs of common respiratory disorders include hypoxia, asphyxia, cyanosis, dyspnea, and apnea.

HYPOXIA

Hypoxia is a condition characterized by deficiency of O_2 at the tissue level.

Types

Types of hypoxia are as follows:

- Hypoxic hypoxia
- Anemic hypoxia

- Stagnant hypoxia
- Histotoxic hypoxia

Hypoxic Hypoxia

In this type of hypoxia, PO_2 decreases in the blood. The O_2 saturation of Hb is reduced. However, the Hb content is normal.

It occurs

- at high altitude,
- in ill-ventilated rooms, and
- in conditions such as pneumonia, respiratory paralysis, arteriovenous shunts, and collapse of lungs.

Anemic Hypoxia

The hemoglobin content is reduced but PO_2 is normal. There is a decrease in the O_2 carrying capacity of blood.

It is seen in severe anemia and carbon monoxide poisoning.

Stagnant Hypoxia

Stagnant hypoxia is seen when the blood flow through a tissue is sluggish.

It occurs in cardiac failure, circulatory shock, and hemorrhage.

Histotoxic Hypoxia

The tissues are unable to use oxygen present in the blood due to damage of the cytochrome oxidase enzyme system. Cytochrome oxidase is involved in energy production of aerobic cell.

Histotoxic hypoxia is seen in cyanide poisoning.

Symptoms

Hypoxia initially causes

- impaired judgment,
- drowsiness and excitement,
- disorientation,
- loss of time sense, and
- headache.

Other symptoms include anorexia, nausea, vomiting, and tachycardia.

Hypoxia affects the brain. A sudden drop in PO_2 to 20 mm Hg causes unconsciousness in 10–15 seconds and death in about 4–5 minutes.

Compensatory Changes

- Hyperventilation (increased rate and depth of respiration)
- Increased blood pressure and cardiac output
- Polycythemia
- Increased 2,3-DPG in RBC
- Excretion of alkaline urine

CYANOSIS

Cyanosis is the bluish discoloration of skin and mucus membrane.

It is observed in lips, nail bed, earlobes, and cheeks.

It occurs when the amount of reduced Hb in blood is more than 5 g/dL.

It is of two types:

1. Central
2. Peripheral

Central cyanosis occurs in hypoxic hypoxia, e.g., right-to-left shunts (mixing of oxygenated and deoxygenated blood).

Peripheral cyanosis occurs due to reduced peripheral circulation, e.g., exposure to severe cold and frostbite.

ASPHYXIA

Asphyxia is a condition characterized by decreased O_2 and increased CO_2 in the body.

It is of two types:

1. Generalized asphyxia
2. Local asphyxia

Generalized Asphyxia

Generalized asphyxia is produced by occlusion of airway, e.g., strangulation and drowning.

Local Asphyxia

Local asphyxia is produced due to obstruction of blood supply to a particular region, e.g., accidental ligature of blood vessel during surgery.

DYSPNEA

Abnormal awareness of breathing is termed dyspnea. This condition is characterized by distress and discomfort during breathing. A person generally feels dyspneic if his/her breathing reserve falls below 70% of normal.

Its causes are bronchial asthma, severe anemia, and cardiac failure.

Orthopnea

Dyspnea in lying-down position is orthopnea.

Dyspneic Index

Dyspneic index (DI) is an index to evaluate if a person has dyspnea:

$$DI = \frac{MVV - RMV}{MVV} \times 100.$$

A value less than 70% indicates that the person is dyspneic.

APNEA

Apnea is temporary cessation of breathing.

Types

Types of apnea are as follows:

- Sleep apnea
- Deglutition apnea
- Voluntary apnea
- Hyperventilation apnea
- Sudden infant death syndrome

Sleep Apnea

Sleep apnea is a temporary cessation of breathing during sleep. It occurs due to failure of respiratory centers to discharge impulses or due to airway obstruction. Sleep apnea is common during REM sleep since muscles are hypotonic. This condition can occur in any age group.

If sleep apnea becomes severe, there are recurrent periods of hypoxia and hypercapnia, which leads to polycythemia, right-sided heart failure, and pulmonary hypertension.

Deglutition Apnea

Deglutition apnea is a temporary stoppage of respiration during swallowing. This prevents the entry of food into the respiratory passage.

Voluntary Apnea

Voluntary apnea is the temporary cessation of respiration by voluntary effort. Higher centers override the respiratory control by medullary and pontine centers.

Hyperventilation Apnea

Hyperventilation apnea is a phase of apnea following hyperventilation due to the removal of CO_2. There is lack of stimulation of respiration due to excessive CO_2 washout.

Sudden Infant Death Syndrome

The death of an apparently healthy infant in the crib (cot) for no detectable reason is termed sudden infant death syndrome (SIDS). It is common in premature infants due to repeated apneic spells.

COUGHING

Coughing is a respiratory act wherein forced expiration occurs after a deep inspiration. This is produced due to stimulation of irritant receptors in air passages. It helps to keep the airways clear.

- First, there is deep inspiration
- Closure of glottis and building up of intrapleural pressure
- Sudden opening of glottis
- Air rushes out at maximum coughing velocities of 13.2 m/s in males and 10.2 m/s in females.

Sneezing is a similar respiratory effort which occurs with a continuously open glottis.

Hiccup

Spasmodic contraction of diaphragm and other inspiratory muscles during inspiration produces hiccup. Sound is produced due to a sudden closure of glottis.

OXYGEN THERAPY

Oxygen therapy is required in conditions of respiratory failure due to lung diseases or poisoning.

Oxygen is administered through nasal catheters. Usually, pure oxygen is not administered; it is mixed with air. Masks are used for giving oxygen in higher concentrations.

Oxygen therapy is useful in

- Atmospheric hypoxia—O_2 therapy can correct depressed O_2 levels in inspired air. It provides 100% effective therapy.
- Hypoventilation hypoxia as seen in neuromuscular disorders.
- Hypoxia caused by impaired diffusion through the alveolar membrane.

Oxygen therapy is **not useful** in hypoxia caused by anemia, abnormal transport of oxygen, circulatory deficiency, and physiological shunt.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy is administration of 100% oxygen at 2–3 atmosphere pressure. This is helpful in the treatment of carbon monoxide poisoning, radiation-induced tissue injury, gas gangrene, severe blood loss anemia, and diabetic leg ulcers. It is also used in the treatment of decompression sickness and air embolism.

OXYGEN TOXICITY

Inhalation of 100% oxygen causes toxicity due to the production of superoxides. Infants administered with oxygen continuously develop lung cysts and densities.

Withdrawal of O_2 therapy produces corneal opacities due to vascularization (retrolental fibroplasia).

Eupnea: It is normal respiration.

Dyspnea: It is the abnormal awareness of one's own breathing (labored breathing).

Orthopnea: It is dyspnea in lying-down position.

Tachypnea: It is increased rate of respiration.

Hyperventilation: This is a condition wherein both the rate and depth of respiration are increased.

Hypoventilation: This is a condition where alveolar ventilation is less than normal.

ARTIFICIAL RESPIRATION

Artificial respiration is a process of restoring the respiratory activity which has stopped suddenly. Respiratory arrest can occur as a result of drowning, poisoning, suffocation, electrocution, myocardial infarction, or cerebrovascular accidents. This can lead to death unless the oxygen supply to vital organs is restored within 2–3 minutes.

Therefore, it is important to restart respiration artificially as a life-saving measure.

INDICATIONS

- Drowning
- Poisoning
- Suffocation
- Electrocution
- Myocardial infarction
- Cerebrovascular accidents
- Poliomyelitis

METHODS

1. Manual methods
   - Mouth-to-mouth breathing
   - Schafer's method
   - Holger–Nielsen's method
2. Mechanical methods

Manual Methods

1. **Mouth-to-mouth breathing**
   - The subject is placed in supine position; the airway is cleared, neck extended, and nose closed.
   - The resuscitator blows air twice the tidal volume into the subject's mouth.
   - The procedure is repeated 12 times a minute.
2. **Schafer's method**
   - The subject is placed in prone position and the head is turned to one side.
   - The operator kneels down and presses the loin for 2–3 seconds and then releases the pressure.
   - On application of pressure, there is expiration and release of pressure causes inspiration.
3. **Holger–Nielsen's method**
   - The subject is placed in prone position and arms are kept in folded position in front of the head.
   - The operator kneels down near the head of the patient, places his hand on the back, and compresses the chest. This effort forces the air out of the lungs.
   - After 3 seconds, the operator lifts the arms of the subject to produce inspiration.
   - Inspiration occurs due to elastic recoil of the lungs.

Mechanical Methods

Mechanical methods are used to treat chronic respiratory insufficiency due to inadequate ventilation.

1. **Drinker's method**: In this method, the subject is placed in an airtight metal or plastic container and the head is kept outside. Now, portable respirators are available that cover only the chest. Negative pressure is created around the chest at regular intervals with the help of a motor. The chest wall is moved in a way that resembles normal breathing. Air moves in and out of the lungs with the movement of chest.
2. **Positive pressure breathing**: In this method, inspiration is produced by forcing air into the lungs by application of positive pressure. Release of pressure results in expiration.
3. **Intermittent positive pressure ventilation (IPPV)**: This is a technique used in most of the respirators. Positive pressure is applied intermittently to introduce air into the respiratory passage.

CARDIOPULMONARY RESUSCITATION

Cardiopulmonary resuscitation (CPR) is a life-saving technique performed on individuals in whom the cardiac and respiratory activity has suddenly stopped.

The main objectives of CPR are to restore adequate ventilation and to restart the pumping action of the heart.

Indications

The indications for CPR are as follows:

- Cardiac arrhythmias
- Myocardial infarction
- Electric shock
- Drowning
- Poisoning
- Anaphylactic shock

CPR involves the following three components:

1. Compression of the chest (external cardiac massage)
2. Airway clearance
3. Breathing (artificial respiration)

Compression of the Chest

- This is done if the carotid pulse is not felt. The subject is put on his or her back on a firm surface.
- The resuscitator kneels next to the subject's neck and shoulders.
- The heel of one hand is placed over the precordial area and the other hand is placed on top of the first hand.

- The elbows are kept straight and the shoulders are positioned directly above the hands.
- The chest of the subject is compressed about 5 cm at a rate of 100 times a minute till the pulse reappears.

Airway Clearance

- This is very essential in an unconscious subject.
- The subject is positioned on a firm, flat surface. His or her mouth is opened and any substance such as blood, vomitus, or mucus is removed.
- The neck of the subject is extended by placing the palm of one hand on the forehead and by applying firm pressure to tilt the head backward. With the other hand, the chin is lifted forward to open the airway.
- The subject is then checked for normal breathing, and mouth-to-mouth respiration is started if the breathing is not normal.

Breathing

Breathing is restored by the manual method of artificial respiration. The most commonly used method is mouth-to-mouth respiration (explained earlier).

HIGH-ALTITUDE PHYSIOLOGY

As we ascend to higher altitudes, the barometric pressure starts falling. However, the percentage composition of air remains the same as that of the sea level. The decrease in barometric pressure due to high altitude causes a proportionate decrease of PO_2 and PN_2.

However, the partial pressures of H_2O and CO_2 do not undergo much change.

HIGH ALTITUDE SICKNESS

Ascent to high altitude causes a lot of pathological changes in the body. The symptoms of pathological changes can be of sudden onset or can occur slowly over days and weeks.

Acute Mountain Sickness

Acute mountain sickness is a condition that develops in a person who rapidly ascends to high altitudes. It is caused due to decreased alveolar PO_2. This occurs due to a fall in barometric pressure at high altitude and also partial pressure of O_2.

Symptoms

- Headache, dizziness, insomnia
- Nausea, vomiting
- Breathlessness, hyperventilation
- Palpitation
- Severe conditions result in cerebral edema, convulsions, and unconsciousness.

The symptoms start at heights above 12,000 ft. They begin 8–12 hours after arrival at high altitude and last for 4–8 days. Convulsions occur at heights of 18,000 ft and coma followed by death occurs at 23,000 ft.

Treatment

- Descent to lower altitude
- Acetazolamide (diuretic)
- Oxygen therapy

Chronic Mountain Sickness

Chronic mountain sickness is seen in persons staying at high altitudes for longer durations.

Features

- Easy fatigability
- Polycythemia
- Pulmonary hypertension

ACCLIMATIZATION TO HIGH ALTITUDE

Acclimatization is the ability of the body to adjust to an altered environmental condition.

Changes Occurring During Acclimatization

- Hyperventilation
- Polycythemia (physiological)
- ↑ Diffusion capacity of lungs
- ↑ Vascularity of tissues
- ↑ Ability of cells to use oxygen despite low PO_2
- ↑ Cardiac output
- Excretion of alkaline urine. This helps to combat respiratory alkalosis caused by excessive removal of CO_2

Acclimatization in natives of high altitudes occurs during infancy itself.

They are short statured; the chest becomes broader (barrel shaped); and there is hypertrophy of the right heart. They have polycythemia.

PHYSIOLOGY OF DEEP SEA DIVING

The atmospheric pressure at sea level is 760 mm Hg and the pressure inside the lungs is equal to the atmospheric pressure. When an individual descends down the sea, the pressure around him or her increases depending on the depth.

For every increase of depth of 33 ft. (nearly 10 m), the pressure increases by 1 atm and volume of air is reduced by half.

DYSBARISM (DECOMPRESSION SICKNESS, CAISSON'S DISEASE)

Dysbarism is a condition occurring in persons who move to the region of low barometric pressure from a region of high barometric pressure.

This occurs in deep sea divers staying underwater for prolonged periods and rapidly ascending to sea surface. Similarly, rapid ascent from sea level to about 10,000 ft. above sea level in an unpressurized airplane can also cause decompression sickness.

Deep sea divers usually breathe a mixture of gases containing 80% nitrogen. Under a high barometric pressure, gases, especially N_2, are dissolved in blood. When such persons are suddenly exposed to a lower barometric pressure, the gases tend to escape. N_2 bubbles are formed in blood and there is pain due to local ischemia.

Symptoms

- **Bends**: Severe pain in the joints and muscles
- **Chokes**: Dyspnea caused due to blockage of capillaries in the lungs
- **Strokes**: Abnormality in brain function such as sensory and motor deficits, temporary paralysis, dizziness, and unconsciousness.

Treatment

- **Slow ascent**: The diver should be brought to the surface slowly so that dissolved nitrogen can be eliminated by expiration through lungs.
- **Decompression chambers**: The diver is put into a pressurized tank and slow decompression is done.

Prevention

Dysbarism can be prevented by slow decompression. The diver should be brought to the surface slowly so that dissolved nitrogen can be eliminated by expiration through lungs.

REVIEW QUESTIONS

Long Essay

1. Describe the mechanics of breathing.
2. Explain the neural regulation of respiration. Add a note of periodic breathing.

3. Discuss the transport of carbon dioxide in the blood.
4. Explain oxygen transport in the blood. Add a note on the oxygen dissociation curve.
5. Classify hypoxia. Describe them with suitable examples.

Short Essay

1. Explain the structure and functions of the respiratory membrane.
2. Explain the functions of lungs.
3. Draw a spirogram indicating various lung volumes and capacities.
4. Define lung volumes and give their normal values.
5. Define lung capacities and give their normal values.
6. What is timed vital capacity? How is it measured? Give its clinical importance.
7. What is dead space? What are its types? How is it measured?
8. Explain the chemical nature and the role of surfactant in pulmonary function.
9. Describe the muscles of respiration.
10. What is the ventilation–perfusion ratio? Explain its significance.
11. Explain the intrapleural and intrapulmonary pressure changes during different phases of respiration.
12. Give an account of the Hering–Breuer reflex.
13. Define lung compliance. Mention the factors affecting it. How does it vary in health and disease?
14. Discuss the chemical regulation of respiration.
15. Explain briefly Hamburger's (chloride shift) phenomenon.
16. Classify hypoxia. Explain any two of them.
17. Explain the types of periodic breathing.
18. Name the methods of artificial respiration. Explain any one of them.
19. Discuss the changes that occur during acclimatization to high altitude.
20. What is decompression sickness? Add a note on its management.
21. What are the non-respiratory functions of lungs?

Short Answer

1. List the functions of nasal cavity.
2. Name the muscles of respiration.
3. Define the following giving their normal values: (a) inspiratory reserve volume and (b) vital capacity.
4. Define the following giving their normal values: (a) inspiratory capacity and (b) expiratory reserve volume.
5. Define the following giving their normal values: (a) tidal volume and (b) total lung capacity.
6. Define the following giving their normal values: (a) residual volume and (b) functional residual capacity.
7. What is maximum breathing capacity?
8. Peak expiratory flow rate
9. Physiological dead space
10. What is hyaline membrane disease?
11. What is dyspneic index?
12. Draw an oxygen dissociation curve. List the factors influencing it.
13. What is P_{50}?
14. What is Bohr effect?
15. What is Haldane effect?

16. Give the normal partial pressures of oxygen and carbon dioxide in the arterial and venous blood.
17. List the types of hypoxia.
18. What is cyanosis? What are its types?
19. What is asphyxia? When is it produced?
20. Define the terms (a) dyspnea, (b) apnea, and (c) orthopnea.
21. Explain mouth-to-mouth breathing.
22. Write briefly about oxygen therapy in clinical practice.
23. Hyperbaric oxygen therapy
24. What is oxygen toxicity? What are its effects?
25. Explain Drinker's method of artificial respiration.

CHAPTER

6 Gastrointestinal System

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Outline the functions of the gastrointestinal system.
- Describe the histology, blood supply, and nerve supply of the gastrointestinal system.
- Discuss the general movements of the gastrointestinal tract.
- Describe the process of mastication and muscles involved in mastication.
- Describe the phases, mechanism, and control of deglutition. Underline the disorders of deglutition.
- Describe the movements of the stomach. Identify the function of the pyloric pump. Discuss the factors regulating gastric emptying.
- Explain the movements of the small intestine and large intestine. Describe defecation reflex.
- Describe the functional anatomy of salivary glands. Describe the composition, functions, mechanism of secretion, and regulation of saliva.
- Discuss the gastric glands and secretion of HCl. Describe the phases and regulation of gastric secretion.
- List the composition and functions of gastric juice. Explain the experiments to study gastric secretion. List the gastric function tests.
- Describe the histology, blood supply, and functions of the liver. Distinguish the different types of jaundice. List the liver function tests.
- Describe the composition, functions, secretion, storage, and concentration of bile.
- Describe the composition, mechanism of secretion, functions, and importance of pancreatic secretion.
- Describe the functional anatomy of small intestinal mucosa. Explain the composition and functions of succus entericus.
- List the gastrointestinal hormones and their functions. Describe the regulation of gastrin, secretin, and cholecystokinin pancreozymin.
- Discuss the process of digestion and absorption of carbohydrates, proteins, and lipids.
- Successfully answer the questions and MCQs at the end of this chapter.

The gastrointestinal (GI) system is the route through which the nutritive substances, vitamins, minerals, and fluids enter the body. The food consumed cannot be utilized by the body directly. It is broken down into simpler substances such as glucose, amino acids, and fatty acids. The process of conversion of complex substances into simple chemical substances that can be absorbed is termed **digestion**.

The GI tract (**Fig. 6.1**) consists of the following parts:

Mouth → Pharynx → Esophagus → Stomach → Duodenum → Jejunum → Ileum → Cecum → Ascending colon → Transverse colon → Descending colon → Sigmoid colon → Rectum → Anal canal.

It also includes accessory structures like salivary glands, liver, gallbladder, and pancreas.

The gastrointestinal tract begins with the mouth and the oral cavity. It consists of teeth and the tongue which help in chewing and swallowing of food.

Pharynx is a passage common to GI and respiratory tracts. It is composed of three parts: (i) nasopharynx, (ii) oropharynx, and (iii) laryngopharynx. The anterior portion of the laryngopharynx is continuous with the larynx and the posterior portion opens into the esophagus.

The esophagus is a muscular tube with a length of about 25 cm. It opens into the stomach.

The stomach is a hollow muscular bag which stores, grinds, and mixes the food with gastric juice to form a semisolid substance called **chyme**.

The small intestine is a long, tubular structure consisting of three parts: (i) duodenum, (ii) jejunum, and (iii) ileum. Duodenum is the first part of the small intestine. It measures about 25 cm in length. The middle part, jejunum, is around 2.5 m long. It continues as ileum which is around 3.5 m in length.

The large intestine is wider and shorter than the small intestine. It measures about 1.5 m in length.

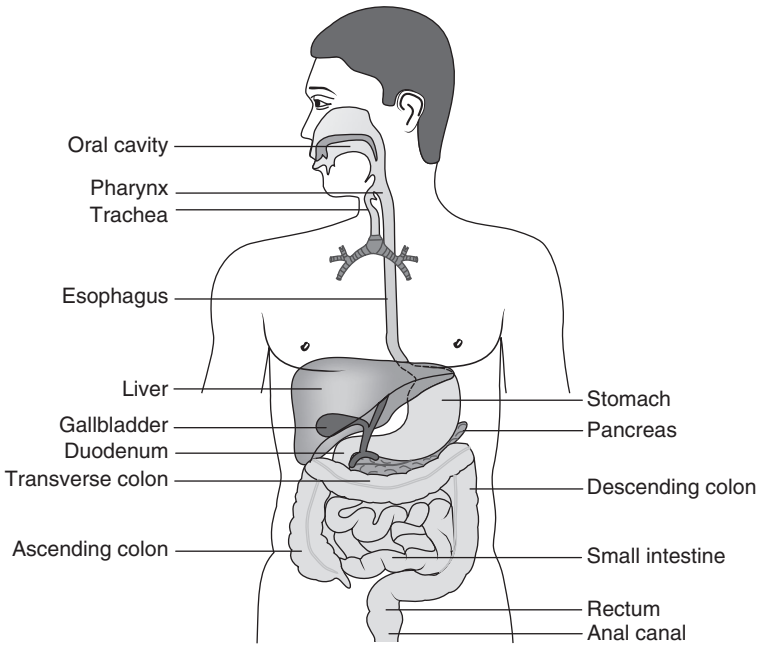


Figure 6.1 Gastrointestinal tract. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

It consists of cecum, appendix, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anal canal.

FUNCTIONS

The GI system has the following functions:

- **Secretion of digestive juices**: Hydrochloric acid (HCl) is secreted by the stomach, bile is secreted by the liver, and various digestive juices are secreted by the salivary glands, pancreas, and intestinal epithelial cells.
- **Digestion of food**: The churning and mixing action of the GI tract causes breakdown of the large food particles into smaller size; thereafter, the enzymes secreted in the digestive juices cause the breakdown of various components of the food into smaller molecules.
- **Absorption of digested food products, water, and electrolytes**: The digested food particles are absorbed from the lumen of the small intestine (SI) into the blood.
- **Movement of food from the mouth toward the anus**: While the processes of digestion, secretion, and absorption are going on in the GI tract, the smooth muscles mix the contents in the lumen of the GI tract with various juices and enzymes and move them from the mouth toward the anus.
- **Protection of gut against harmful and toxic substances in the food**: The HCl secreted in the stomach causes destruction of harmful bacteria and toxins.
- **Elimination of waste products**: The GI tract plays an important role in the elimination of solid waste products. Saliva has antibacterial properties.
- **Intestinal bacterial flora**: They are nonpathogenic bacteria that inhabit the intestine. They help in synthesis and absorption of vitamins, and in detoxification of harmful substances in the food.

HISTOLOGY

The GI tract is made up of three layers (**Fig. 6.2**):

1. Outer serosa
2. Middle muscular layer
3. Inner mucosa

The serosa is the outermost serous layer of the GI tract. It is formed by the peritoneum.

The middle muscular layer is made up of smooth muscles. It consists of outer longitudinal and inner circular muscle layers. The contraction of circular muscles causes narrowing of the lumen and the contraction of longitudinal muscles causes shortening of the gut. The muscle fibers are electrically connected with one another through a large number of gap junctions. The bundle fuses with one another at many points and therefore the muscle layer functions as syncytium.

The inner mucosa has the submucus layer which is composed of areolar tissue, blood vessels, lymphatics, and nerves. It is lined by a single layer of columnar cells called the **mucosa**. It also has a thin layer of muscle called the **muscularis mucosae**.

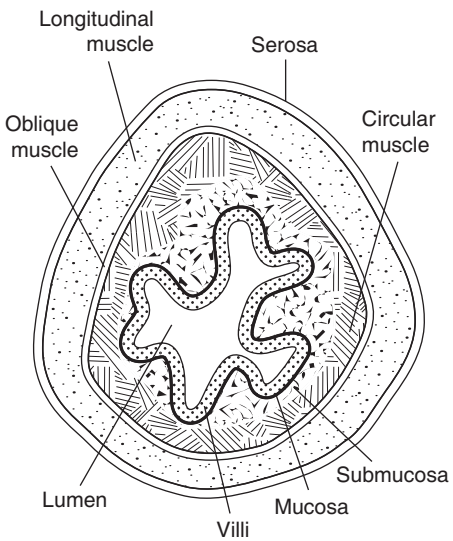


Figure 6.2 Layers of the gastrointestinal tract.

BLOOD SUPPLY

The blood supply to the GI tract is from the following branches of the aorta:

- Celiac plexus
- Superior and inferior mesenteric arteries

The blood leaving the GI tract is drained by the portal vein to the liver.

The GI tract receives nearly 30% of the cardiac output. The blood flow to the GIT is proportional to its activity. The **splanchnic circulation** supplies the stomach, pancreas, SI, colon, liver, spleen, omentum, and mesenteric tissues. The splanchnic circulation is arranged both in parallel and in series.

NERVE SUPPLY

The GI tract is supplied by an intrinsic as well as an extrinsic nerve supply.

INTRINSIC NERVE SUPPLY

The intrinsic nerve supply is by the enteric nervous system.

Enteric Nervous System

There are two major networks in the GI tract:

1. **Myenteric plexus of Auerbach**: This is present in between the outer longitudinal and the inner circular layers of muscles.
2. **Submucus plexus of Meissner**: This is present in between the circular muscle layer and the mucosa.

The enteric nervous system is connected to the central nervous system (CNS) by the sympathetic and parasympathetic fibers, but they can function independently without these connections.

EXTRINSIC NERVE SUPPLY

The extrinsic nerve supply has afferent and efferent nerves from both the sympathetic and the parasympathetic nervous systems:

1. **Afferent nerves**: These nerves transmit information from the GI tract to the CNS. They pass through the spinal cord and the vagus nerve.
2. **Efferent nerves**: These are of two types:
   - *Parasympathetic:* The parasympathetic supply to the GI tract is mainly through the vagus nerve. The parasympathetic stimulation increases secretion and motility.
   - *Sympathetic:* The sympathetic nerve supply to the GI tract arises from the fifth thoracic segment to the second lumbar segment of the spinal cord. It inhibits the GI smooth muscles except the sphincters. It reduces GI motility and secretions.

Influence of a Higher Center

The autonomic output is modified by influences from higher centers, particularly from the limbic system and the cerebral cortex.

ELECTRICAL ACTIVITY OF THE GASTROINTESTINAL SMOOTH MUSCLE

The GI smooth muscle shows two types of electrical waves (**Fig. 6.3**):

1. Slow waves
2. Spikes

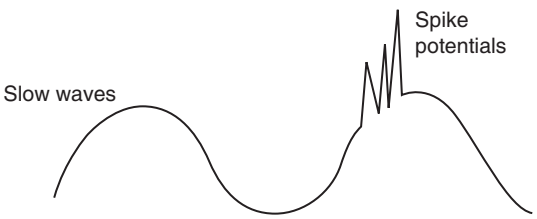


Figure 6.3 Slow waves and spike potential.

Slow Waves

The spontaneous rhythmic fluctuations in the membrane potential (between –65 and –45 mV) are termed the **basal electrical rhythm** (BER). These fluctuations produce slow waves.

The BER is initiated by the stellate muscle cells called **interstitial cells of Cajal**. These cells are the **pacemaker cells**. They are present between the smooth muscle layers and form a network with one another.

The slow waves are not action potentials but are slow undulating changes in the resting membrane potential. Their intensity ranges from 5 to 15 mV. The frequency ranges from 3 to 12/min.

In the stomach, their frequency is about 4/min. In the duodenum, it rises to 12/min and falls to around 8/min in the terminal ileum.

The slow waves arise due to slow undulation of the sodium–potassium pump. These slow waves do not cause muscle contraction but control the appearance of intermittent spike potentials. These spike potentials cause muscle contraction.

Spike Potentials

Spike potentials are true action potentials. They occur when the potential rises above –40 mV. Their frequency increases if the spike potential value increases.

The frequency of spike potentials ranges from 1 to 10 spikes/s. Spike potentials last for a duration of about 10–20 ms. This is about 10–40 times longer when compared to nerve action potentials.

These spike potentials occur due to the entry of a large number of calcium ions along with a small number of sodium ions.

Spike potentials do not propagate for more than a few millimeters in the intestinal muscles.

Acetylcholine increases the number of spikes and epinephrine decreases the number of spikes.

Migrating Motor Complex

The migrating motor complex (MMC) occurs between the periods of digestion. This migration of motor activity occurs from the stomach to the distal ileum.

Each cycle of MMC has three phases:

- **Phase I**: It is also termed quiescent phase.
- **Phase II**: This phase continues with a period of irregular electrical and mechanical activity.
- **Phase III**: This phase is characterized by a burst of regular electrical activity.
- MMCs occur at intervals of approximately 90 minutes. They migrate at a rate of about 5 cm/min.

Function

The MMC clears the contents of the GI lumen to prepare for the next meal.

GASTROINTESTINAL REFLEXES

Three types of reflexes operate in the GI tract. They are as follows:

1. Short reflexes or local reflexes
2. Long reflexes
3. Central reflexes

Short reflexes operate within the enteric nervous system. Receptors sensitive to chemicals or stretch of GI wall are present in the mucosal walls.

Stimulation of these receptors mediates a local reflex involving the myenteric plexus and the intestinal smooth muscles or glands, e.g., enterogastric reflex.

Long reflexes carry signals for long distances in the GIT. These reflexes usually travel from the GIT to the prevertebral sympathetic ganglia and back, e.g., gastrocolic reflex in which signals from the stomach cause evacuation of colon.

Central reflexes have long reflex arcs involving the brain or the spinal cord as the center.

For example, defecation reflex travels from the colon and rectum to the spinal cord and back. It causes powerful contractions of colon, rectum, and abdominal muscles necessary for the act of defecation.

GASTROINTESTINAL MOVEMENTS

The food consumed needs to move continuously in the gastrointestinal (GI) tract. The rate of movement is different at different parts of the GI tract and depends on various neural and chemical factors.

GENERAL MOVEMENTS OF THE GASTROINTESTINAL TRACT

The movements of the gastrointestinal (GI) tract are regulated by the autonomic nervous system. The parasympathetic stimulation causes release of acetylcholine, which increases the movement. The sympathetic stimulation causes release of norepinephrine, which inhibits movements.

The GI hormones such as gastrin stimulate movements while secretin and gastric inhibitory polypeptide (GIP) inhibit movements.

Two basic types of movements occur in the GI tract:

1. Propulsive movements
2. Mixing movements

PROPULSIVE MOVEMENTS

Propulsive movements propel the food along the GI tract. This causes proper digestion and absorption of food. The basic propulsive movement is **peristalsis**.

Peristalsis (Fig. 6.4)

Peristalsis is a reflex response that begins when the GI wall is stretched by the food present in the lumen. It occurs throughout the GI tract from the esophagus to the rectum. Peristalsis occurs at the rate of 2–25 cm/min.

Peristalsis consists of a ring of contraction in one segment and receptive relaxation in the immediate distal segment. Apart from the GI tract, peristalsis occurs in the bile ducts and ureters.

The stimulus for peristalsis is distension of the gut. Distension stimulates the gut wall and a contractile ring appears which initiates peristalsis.

Peristalsis is influenced by neural and hormonal mechanisms. Sympathetic stimulation

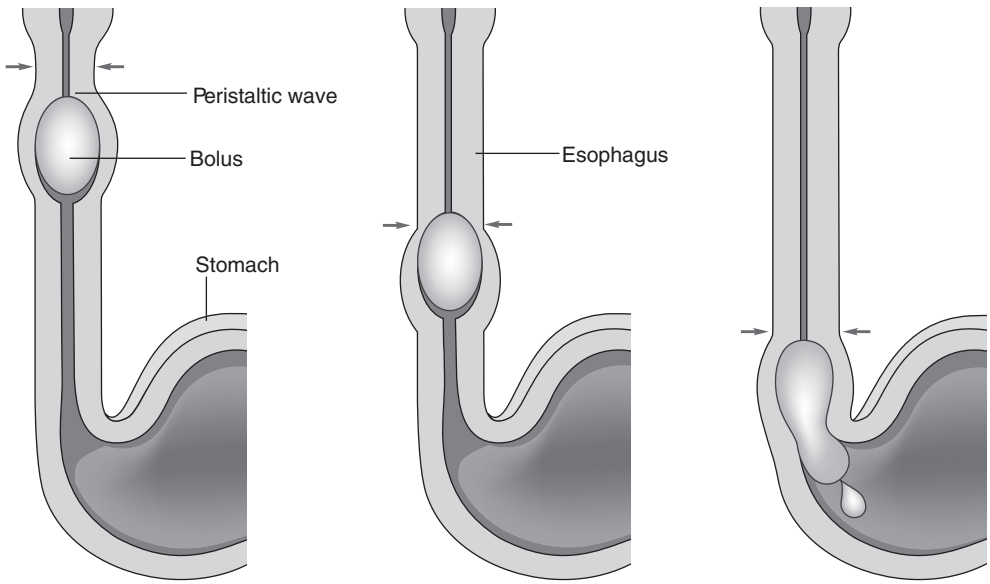


Figure 6.4 Peristalsis. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

inhibits peristalsis and parasympathetic stimulation enhances it. Local hormones also influence peristalsis.

Peristalsis is brought about by the myenteric plexus. It occurs only in one direction, i.e., from the esophagus toward the rectum.

The occurrence of peristalsis and its movement toward the anus is termed the **law of the gut**.

MIXING MOVEMENTS

The mixing movements are caused by either the peristaltic contractions or the local constrictions of a small segment of the GI tract. These constrictions last for a few seconds and new contractions occur at other points of the gut.

Mixing movements are of two types:

1. Segmentation contraction
2. Pendular movement

Segmentation contractions help to chop the chyme 8–12 times a minute. Pendular movement helps in mixing of intestinal contents.

Mixing movements help in mixing of chyme with pancreatic and intestinal secretions. They also help in bringing fresh chyme into contact with the intestinal surface.

MASTICATION (CHEWING)

Mastication is a process by which food taken in the mouth is crushed into small particles by the grinding action of the teeth. The anterior teeth (incisors and canines) provide cutting action and the posterior teeth (premolars and molars) provide the grinding action. The muscles of mastication are innervated by various branches of the trigeminal nerve.

The process of mastication is controlled by the nuclei in brainstem.

CHEWING REFLEX

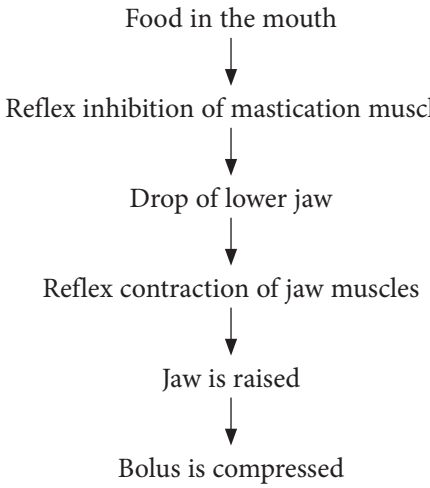
The presence of food in the mouth causes reflex inhibition of the muscles of mastication, causing the lower jaw to drop. This activates a stretch reflex of muscles resulting in their contraction. The jaw is raised to cause apposition of the teeth and compression of the bolus. The compression of the bolus inhibits contraction of the jaw muscles and the process is repeated.

FUNCTIONS

- Mastication increases the surface area of the food by breaking it into small particles for better digestion.
- The grinding action prevents excoriation of the GI tract and increases the rate of emptying of food from the stomach.

Muscles of Mastication

Muscles of mastication include masseter, temporalis, pterygoids, and buccinator. Masseter causes elevation of the mandible. Temporalis causes retraction of the mandible. Pterygoids help in opening the mouth and grinding movements. Buccinator helps in prevention of accumulation of food in the mouth.



DEGLUTITION (SWALLOWING)

Deglutition is the process of transfer of food from the mouth to the stomach. It has both voluntary and involuntary phases. It is called **deglutition reflex** since a major part of the deglutition process is under involuntary control.

PHASES

The phases of deglutition are as follows (**Fig. 6.5**):

- Buccal (oral) phase
- Pharyngeal phase
- Esophageal phase

Buccal Phase

Buccal phase is also called **oral phase**. It is a voluntary phase. The food present in the mouth is converted to a bolus by the process of mastication and mixing with saliva. Later, the food is pushed backward by pressure of the tongue against the palate. Once the food touches the pharyngeal opening, the receptors are stimulated and the swallowing reflex is initiated.

Pharyngeal Phase

Pharyngeal phase is partly an involuntary phase. As the food enters the pharynx, stimulation of receptors around the pharyngeal opening initiates impulses that pass to the brainstem. This initiates a series of complex changes that allows the food to pass through the pharynx.

- The soft palate is raised to close the posterior nares so that the food does not enter the nasal cavity.
- The palatopharyngeal folds are pulled medially to form a sagittal slit which allows the masticated food to pass through it.
- The vocal cords come close to each other. The hyoid bone and larynx are pulled upward and anteriorly by the neck muscles causing the epiglottis to swing back over the laryngeal opening. This prevents the entry of food into the trachea.
- The opening of the esophagus stretches and the upper esophageal sphincter relaxes, allowing the food to pass down into the esophagus.
- At the same time, the superior constrictor muscle of the pharynx contracts, giving rise to a rapid peristaltic wave which passes down into the esophagus.

The entire process occurs in 1–2 seconds. During this period, the respiratory centers of the medulla are inhibited causing cessation of respiration (**deglutition apnea**).

Esophageal Phase

The esophagus conducts the food from the pharynx to the stomach. It is about 25 cm in length. It has two sphincters:

1. Upper esophageal sphincter
2. Lower esophageal sphincter

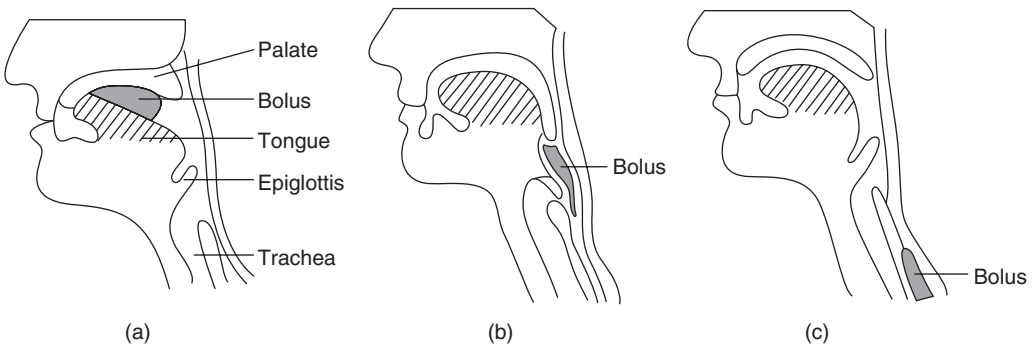


Figure 6.5 Phases of deglutition: (a) buccal phase, (b) pharyngeal phase, and (c) esophageal phase.

The esophagus exhibits two types of peristaltic movements:

1. Primary peristalsis
2. Secondary peristalsis

Primary Peristalsis

Primary peristalsis is continuation of peristalsis from the pharynx.

As soon as the food enters the esophagus, the upper esophageal sphincter contracts preventing regurgitation of food into the mouth.

The wave of peristalsis moves at a speed of 2–4 cm/s. Gravity does not play a major role in this process.

As the wave enters the lower esophageal sphincter, it relaxes and allows the bolus to easily enter the stomach.

Secondary Peristalsis

Some amount of food may remain in the esophagus even after primary peristalsis is completed. This stretches the mechanical receptors present in the esophagus, which initiates another peristaltic wave. This is called secondary peristalsis.

It is coordinated by the intrinsic nervous system of the esophagus. The secondary peristaltic wave continues till all the food in the esophagus is emptied into the stomach.

As the food reaches the lower esophageal sphincter, there is relaxation of the stomach and sphincter to receive the food. This is termed **receptive relaxation**.

The esophageal phase lasts for 8–10 seconds for solids and 1–2 seconds for liquids. It ends with the entry of food into the stomach.

CONTROL OF DEGLUTITION

The presence of food in the mouth causes stimulation of the tractus solitarius of the medulla through V (trigeminal), IX (glossopharyngeal), and X (vagus) cranial nerves. The afferent impulses from these nerves are integrated at the nucleus of tractus solitarius and the nucleus ambiguus present in the medulla.

DEGLUTITION CENTER

The deglutition center is present in the reticular areas of the upper medulla and lower pons. It consists of the nucleus of tractus solitarius and nucleus ambiguus.

CLINICAL NOTES

Achalasia Cardia

In this condition, the lower esophageal sphincter fails to relax during swallowing. It is caused due to deficiency of myenteric plexus at lower esophagus. There is excessive dilation of the esophagus proximal to the sphincter. Treatment is by mechanical dilation of the sphincter.

Gastroesophageal Reflux Disorder

Gastroesophageal reflux disorder is caused due to incompetence of the lower esophageal sphincter. This causes reflux of acidic gastric contents into the esophagus leading to heartburn and esophagitis. It is the most frequent gastrointestinal disorder. It may lead to ulceration and stricture of esophagus if the condition is not treated. This condition can be treated by H_2 receptor blockers or proton pump inhibitors.

Aerophagia

Aerophagia is swallowing of air along with food and water. It is caused due to reduced tone of the upper esophageal sphincter. Majority of the swallowed air passes to the colon and is expelled as flatus. The remaining air gets either regurgitated (belching) or absorbed.

Bulbar Paralysis (Bulbar Polio)

Bulbar paralysis is caused due to infection by the poliovirus. In this condition, food regurgitates through the nose.

Paralysis of Laryngeal Muscles

In this condition, food enters the respiratory tract, leading to suffocation and death.

The motor impulses arise from this area and bring about swallowing by constriction of the pharyngeal muscles.

The efferent fibers pass through V (trigeminal), VII (facial), and XII (hypoglossal) cranial nerves.

MOVEMENTS OF STOMACH

The movements of the stomach are responsible for the motor functions of the stomach. These functions include the following:

- Storage of food
- Mixing of food with gastric secretions
- Emptying of food

The movements observed in the stomach are of three types:

1. Movements in an empty stomach
2. Receptive relaxation
3. Digestive peristalsis

MOVEMENTS IN AN EMPTY STOMACH

The various movements of an empty stomach are as follows:

- **Type I movements**: They are mild movements occurring at a rate of 3/min. These are discrete movements.
- **Type II movements**: They are stronger movements, called *hunger contractions*. They are rhythmic, tetanic peristaltic contractions lasting for 2–3 minutes. They are more intense in healthy adults. The hunger contractions are increased by low blood sugar levels.
- **Type III movements**: They occur in conditions of extreme hunger, termed *hunger pangs*. They begin 12–24 hours after the last meal and reach the greatest intensity in 3–4 days. They gradually weaken in the succeeding days. It produces pain in the pit of the stomach.

RECEPTIVE RELAXATION

Receptive relaxation occurs after a meal. There is active relaxation of the stomach which causes increase in the volume of the stomach. It is caused by the vagovagal reflex originating in the pharynx and esophagus. The neurotransmitters involved are vasoactive intestinal polypeptide (VIP), nucleotides, and dopamine.

DIGESTIVE PERISTALSIS

Digestive peristalsis begins as soon as the food enters the stomach (**Fig. 6.6**). It starts in the form of small indentation on the wall and encircles the middle part of the stomach in the form of a ring. Later, it proceeds toward the pylorus.

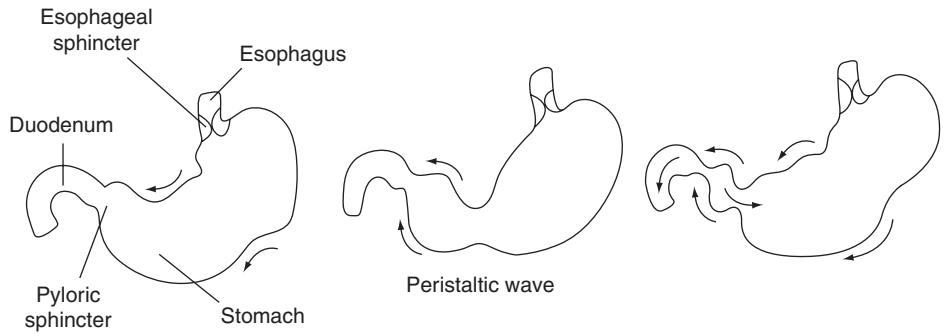


Figure 6.6 Movements of stomach: digestive peristalsis.

The contractions are initially weak, but gradually increase in strength. Each time the peristaltic waves pass down the wall of the gastric antrum, the contractions dig deeply into the food contents in the antrum. As each peristaltic wave reaches the pyloric region, the pyloric muscles contract and the contents are pushed upward. These two mechanisms help in mixing the food particles and secretions.

GASTRIC EMPTYING

Gastric emptying is a process by which the stomach empties its contents into the duodenum. Normally, the pylorus remains closed, partially allowing only fluids to pass through it. Whenever food is present in the stomach as chyme, the contractions become intense and cause gastric emptying. It occurs till the stomach is totally emptied and this pumping action is called the **pyloric pump**.

PYLORIC PUMP

The presence of food in the stomach causes contractions of the stomach to become intense. These contractions are strong ring-like constrictions that begin in the region of the midstomach and then progress distally. These strong contractions push the contents toward the duodenum.

As the stomach becomes empty, these constrictions begin further up on the body of the stomach and push the contents toward the duodenum.

Each peristaltic wave pushes several milliliters of chyme into the duodenum.

The degree of constrictions of pylorus can be controlled by various neural and hormonal factors. These factors regulate emptying of the stomach contents into the duodenum.

FACTORS REGULATING GASTRIC EMPTYING

Gastric emptying takes about 2–3 hours. It is regulated by various factors which are as follows:

- **Consistency of chyme**: Smaller particles and liquids empty faster compared to larger food particles.
- **Volume of food**: Increased volume of food in the stomach leads to increased pyloric pump activity.
- **Hormones**: Gastrin, cholecystokinin, secretin, and GIP affect gastric emptying.

Gastrin is released from antral mucosa in response to the presence of food. It enhances the activity of the pyloric pump, thereby promoting gastric emptying.

Cholecystokinin is released from the duodenum due to the presence of products of protein and fat digestion. It inhibits gastric emptying by increasing the tone of pyloric sphincter.

Secretin is released from duodenum due to the presence of acid. It inhibits gastric emptying.

GIP is released from the small intestine. It reduces gastric motility.

- **Osmolality of duodenum**: Hyperosmolar chyme in the duodenum inhibits gastric emptying.
- **Neural factors**: Vagal stimulation promotes gastric emptying and sympathetic stimulation inhibits gastric emptying.

CLINICAL NOTES

Vomiting

Vomiting is a process by which the upper GI tract empties its contents when it is excessively irritated or overdistended. The process of vomiting occurs by antiperistalsis.

The impulses are transmitted by both sympathetic and parasympathetic nerves to the vomiting center. The efferent impulses from the vomiting center reach the upper GI tract to induce vomiting.

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Vomiting Center

The vomiting center is present bilaterally in the medulla. It lies near the tractus solitarius at the level of the dorsal motor nucleus of the vagus.

Chemoreceptor Trigger Zone

This is a small area located bilaterally on the floor of the fourth ventricle near the area postrema. Drugs such as morphine and apomorphine can stimulate the chemoreceptor trigger zone (CTZ) to initiate vomiting. Motion sickness causes vomiting by stimulation of the CTZ.

Total Gastrectomy

Total gastrectomy is the removal of the whole stomach. It leads to various effects that include

- ineffective control of blood glucose levels,
- deficiency of intrinsic factor producing pernicious anemia,
- predisposition to iron-deficiency anemia, and
- dumping syndrome.

Dumping Syndrome

Dumping syndrome is a condition seen in individuals who have undergone partial or total gastrectomy. It is characterized by weakness, dizziness, and sweating after meals. It is commonly seen in obese individuals undergoing bariatric surgery.

MOVEMENTS OF THE SMALL INTESTINE

Movements of the small intestine (SI) are required for proper mixing of chyme with the digestive juices, for propulsion of food, and for absorption of the products of digestion.

The various movements of the SI are

- mixing movements,
- propulsive movements, and
- antiperistalsis.

MIXING MOVEMENTS

Mixing movements of the SI cause proper mixing of food with digestive juices secreted into the lumen of SI.

These movements include the following.

Segmentation Contraction (Fig. 6.7)

When a portion of the SI gets distended with the entry of chyme, the stretch of the intestinal wall elicits localized constrictions spaced at periodic intervals along the intestine. As one set of segmentation contraction relaxes, a new set begins between the previous contractions. These segmentation contractions chop the chyme 8–12 times a minute.

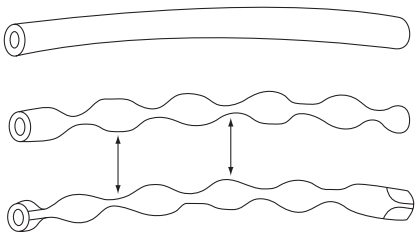

Figure 6.7 Segmentation contraction of the intestine.

Pendular Movements

This type of movement helps in mixing of intestinal contents. A long segment of intestine moves over its contents to and fro like a pendulum and hence it is called pendular movement.

PROPULSIVE MOVEMENTS

Peristalsis

The chyme is propelled through the small intestine by peristaltic waves. Normally, 3–5 hours are required for the passage of chyme through the SI.

Antiperistalsis is the peristaltic movement in the opposite direction (anal to oral direction).

It occurs normally in the region of duodenum. It results in vomiting.

MOVEMENTS OF VILLI

Movements of villi are due to alternate contraction and relaxation of muscles present in them. These movements cause repeated shortening and elongation of the villi and milk the villi, facilitating free flow of the lymph.

Contraction of Muscularis Mucosae

The muscularis mucosae can cause short or long folds to appear in the intestinal mucosa. They occur at a frequency of 3/min. This increases the surface area exposed to chyme, thereby increasing the rate of absorption.

Ileocecal Valve

The ileocecal valve is located at the junction of ileum and cecum. The main function of this valve is to prevent the movement of fecal contents from the colon back to the SI. The lips of the ileocecal valve protrude when the cecum gets filled.

The wall of the ileum for a short distance preceding the ileocecal valve has a thickened muscular coat called the **ileocecal sphincter**. This normally remains mildly constricted. The gastroileal reflex and the hormone gastrin have a relaxant effect on this sphincter. Abdominal tuberculosis commonly occurs at the ileocecal region.

CLINICAL NOTES

Paralytic Ileus

Paralytic ileus is a disruption in the normal propulsive ability of the intestine. A decrease in intestinal activity causes irregular distension of the intestine with the accumulation of gas and fluid. Usually, intestinal peristalsis returns after a few hours.

Temporary paralytic ileus is commonly seen after abdominal surgeries. It is called **postsurgical ileus**.

Peristaltic Rush

Peristaltic rush occurs due to intense irritation of the intestinal mucosa. It causes powerful and rapid peristalsis as in severe cases of intestinal infections resulting in diarrhea.

Intestinal Colic

Localized obstruction in the intestine produces intense peristaltic waves which cause accumulation of fluid and gas proximal to the obstruction. This results in distention of the intestine, leading to compression of blood vessels of the intestinal wall. This leads to local ischemia, causing severe pain termed intestinal colic.

MOVEMENTS OF THE LARGE INTESTINE

The large intestine is wider and shorter than the small intestine. It measures about 1.5 m in length. It consists of cecum, appendix, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anal canal. The movements of the large intestine are sluggish in nature. These movements are necessary for mixing, propulsion, and absorption.

MIXING MOVEMENTS (HAUSTRATIONS)

Large circular constrictions appear in the large intestine narrowing the lumen of the colon, sometimes leading to complete occlusion. At the same time, the longitudinal muscles of the colon contract. The combined contractions of the longitudinal and circular smooth muscles cause the unstimulated portion of the large intestine to bulge outward like a sac called **haustration**. Thus, the fecal matter is gradually exposed to the surface of the large intestine and a major part of the fluid is absorbed.

PROPULSIVE MOVEMENTS (MASS MOVEMENTS)

Propulsive movements occur only a few times each day.

First, a constrictive ring appears at the distended or irritated point in the colon, usually in the transverse colon. Then about 20 cm of the colon distal to the constriction contracts almost as a single unit, forcing the fecal matter to move down the colon.

When the fecal matter enters the rectum, the subject gets the urge to defecate.

COLONIC REFLEXES

The important reflexes of colon are as follows:
- Gastrocolic reflex
- Colonocolic reflex

Gastrocolic Reflex

This reflex is initiated due to accumulation of food in the stomach. Distension of the stomach causes movement of the colon. This pushes the fecal contents into the rectum causing a desire for defecation. This reflex is more active in children than in adults.

Colonocolic Reflex

Distension of one part of the colon causes relaxation of the remaining parts of the colon.

FUNCTIONS OF COLON

The colon helps in
- absorption of water and electrolytes from the chyme and
- storage of fecal matter until it is excreted.

The proximal half of the colon is concerned with the absorption and the distal half with the storage of fecal matter.

DEFECATION

The rectum is empty most of the time. When a mass movement forces the feces into the rectum, a desire for defecation is initiated. Defecation occurs if the conditions are favorable.

The dribbling of fecal matter is prevented by the tonic contraction of the following:
- **Internal anal sphincter**: Composed of smooth muscles
- **External anal sphincter**: Composed of striated muscles

The internal sphincter is supplied by the autonomic nervous system; the external anal sphincter is supplied by the pudendal nerve. The external anal sphincter is under voluntary control.

DEFECATION REFLEX (Fig. 6.8)

The defecation reflex occurs in the following steps:
- The entry of feces into the rectum causes its distension.
- The afferent signals are initiated in the myenteric plexus. It results in the formation of peristaltic waves in the descending colon, sigmoid colon, and rectum.
- The movement of feces toward the anal canal relaxes the internal sphincter.
- Defecation occurs if the external anal sphincter is also relaxed.

The contraction of the abdominal muscles helps in the process of defecation.

If the circumstances are not favorable, defecation is inhibited by voluntary contraction of the external anal sphincter. Soon, the internal anal sphincter and the rectum also relax. The reflex disappears but reappears a few minutes later.

CLINICAL NOTES

Diarrhea

Diarrhea is produced due to rapid movement of the fecal matter through the intestine. This is accompanied by loss of large quantities of fluid and electrolytes from the body.

Causes

- **Enteritis**: It is the infection of the GI tract caused by either virus or bacteria. The mucosa becomes

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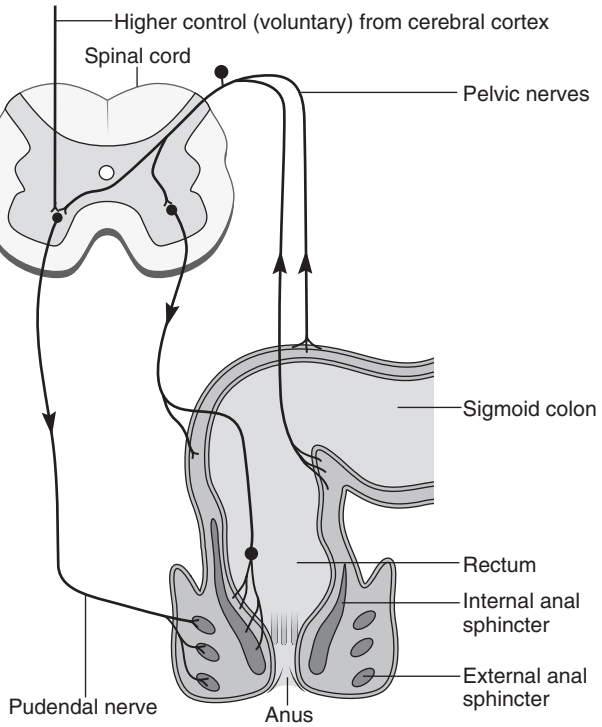


Figure 6.8 Defecation reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

extensively irritated and secretion becomes greatly enhanced. There is passage of loose stools.

The toxins secreted by pathogens cause secretion of large quantities of fluid and electrolytes.

- **Psychogenic diarrhea**: It is caused by excessive stimulation of the parasympathetic nervous system, which increases both motility and secretion of mucus in the distal colon. This results in the passage of frequent loose stools.
- **Intestinal bacterial flora**: Intestinal bacteria supply vitamin K and vitamin B complex. They have an important role in preventing infection. Destruction of intestinal flora can result in loose stools, commonly seen following the administration of broad-spectrum antibiotics.

Ulcerative Colitis

Ulcerative colitis is a disease in which extensive areas of the large intestine become inflamed and ulcerated. The motility of the ulcerated colon increases significantly. As a result, the patient has repeated loose motions.

Megacolon

Megacolon is a congenital condition characterized by the absence of intrinsic nerve plexus (Auerbach plexus). It results in the accumulation of fecal matter, resulting in distension of sigmoid colon (a segment of colon) with improper defecation.

Constipation

Constipation occurs mainly due to decreased bowel movements. Symptoms include anorexia, abdominal discomfort, and distension. Chyme stays for a longer duration in the large intestine causing increased absorption of water. This causes hardening of feces and difficulty in defecation.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional disorder of the intestine characterized by changes in the bowel habits and abdominal pain without an underlying organic cause.

It is more common in women and subjects younger than 45 years. Symptoms include diarrhea, constipation, or both. Treatment is symptomatic in nature.

GASTROINTESTINAL SECRETIONS

The major function of the gastrointestinal tract is digestion of food. This is brought about by secretions of glands present in the GIT. These glands together produce around 7 L of secretions per day. Most of these secretions are produced only in the presence of food in the GIT and the amount produced matches with the amount required for digestion.

Gastrointestinal secretions are produced from the exocrine glands of GIT.

The important GI secretions include

- salivary secretion from salivary glands,
- gastric secretion from gastric glands,
- succus entericus from intestinal epithelial cells,
- bile secretion from the liver, and
- pancreatic secretion from the exocrine pancreas.

FUNCTIONS

- **Digestion of food**: The enzymes produced in the GI secretions break down the food into smaller absorbable particles. Starch is broken down into monosaccharides, proteins into peptides and amino acids, and fat into fatty acids.
- **Mixing**: The fluid part of secretions causes mixing of food with enzymes and chemical substances. Adequate exposure of food with chemical substances is essential for proper digestion of food particles.
- **Lubrication of food**: Mucus produced by the GI secretions facilitates the smooth passage of food through the GI tract. It also protects the mucosa from the harmful effect of HCl and toxins present in the food.
- **Protection**: The chemicals such as HCl, IgA, and lysozymes which are present in the GI secretions protect the body from infections that may enter the body through food.

PHASES

Gastrointestinal secretions occur in three phases:

1. Cephalic phase
2. Gastric phase
3. Intestinal phase

Cephalic Phase

In this phase, the GI secretions are influenced by impulses from the brain. Thought, sight, smell, and taste of food initiate the cephalic phase of GI secretion. This phase is also activated by various emotional factors.

The cephalic phase prepares the GIT before the food reaches the stomach and intestines. This phase is mediated by the vagus nerve. Stimulation of the vagus nerve activates the enteric nervous system which in turn influences gastric secretion and motility.

Gastric Phase

The gastric phase begins when food enters the stomach.

Distension of stomach is the main stimulus for this phase. This distension activates various reflexes that cause alteration in gastric, intestinal, biliary, and pancreatic secretions.

The chemical composition of food, pH of the gastric contents, and hormone gastrin also influence gastric secretion.

Intestinal Phase

The intestinal phase begins when food in the form of chyme enters the duodenum. Products of digestion, osmolality of the contents, and distension of the intestine form the stimuli in this phase. They cause activation of reflexes and secretion of hormones which cause digestion of food into its simplest form.

Gastrointestinal secretions are regulated by both neural and hormonal factors. However, the degree of influence by these factors varies depending on the phase of GI secretion.

The cephalic phase is predominantly regulated by neural mechanisms. Gastric and intestinal phases are regulated by both neural and hormonal mechanisms.

SALIVARY SECRETION

Saliva is the secretion from salivary glands. It is secreted by a number of salivary glands that are present around the mouth and open into the oral cavity.

SALIVARY GLANDS (Fig. 6.9)

There are three pairs of salivary glands:

1. Parotid glands
2. Submandibular glands
3. Sublingual gland

The parotid glands are the largest salivary glands. They open on the inner surface of the cheek opposite the second molar tooth, by the **duct of Stenson**. They are serous glands which produce watery secretions.

The submandibular glands are present below the inner ramus of the mandible. They open by **Wharton's duct** in the floor of the mouth by the side of the frenulum of the tongue. The secretions from these glands are of mixed type containing both serous and mucus secretions.

The sublingual glands are present below the tongue in the floor of the mouth. They open by several fine ducts in the floor of the mouth on either side of the frenulum of the tongue. These are called the **ducts of Rivinus**. These glands are predominantly of the mucus type.

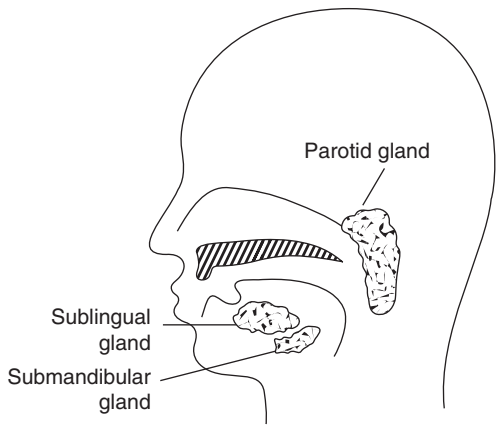


Figure 6.9 Salivary glands.

SALIVA

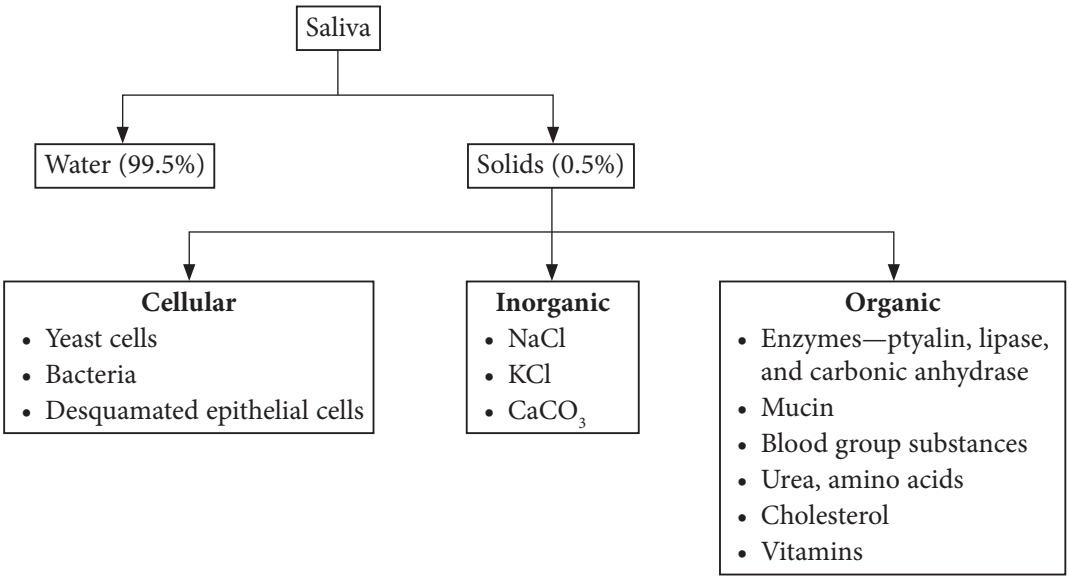
Composition (Flowchart 6.1)

Total volume	1200–1500 mL/24 h
Appearance	Slightly cloudy
Reaction	Slightly acidic
Specific gravity	1.002–1.012
Solids	0.5%

Functions

The various functions of saliva are summarized as follows:

1. **Mechanical functions**
   - Keeps the mouth moist and helps in speech (articulation)
   - Acts as a lubricant for the formation of the bolus of food
   - Dilutes hot and irritant substances, thereby preventing injury to the mucus membrane
   - Washes down the food debris and prevents bacterial growth
2. **Digestive functions**
   - The enzyme ptyalin secreted in the saliva splits cooked starch into maltose. Maltase converts maltose to glucose.
3. **Excretory functions**
   - Excretes urea, drugs, heavy metals, and thiocyanates.
4. **Taste**
   - Helps in sensation of taste. Saliva dissolves the food and taste is perceived by the taste buds.



Flowchart 6.1 Composition of saliva.

5. **Water balance**
   - Helps in water balance. Saliva keeps the mouth moist. When body water is lost, saliva is reduced and sensation of thirst is felt.
6. **Heat loss**
   - Helps in heat loss from the body.
7. **Buffering action**
   - Bicarbonate in saliva acts as a buffer for the acid produced in stomach.
8. **Bacteriolytic action**
   - Lysozyme, the enzyme present in the saliva, dissolves the cell wall of many bacteria and destroys them.

Mechanism of Secretion

The salivary secretion occurs in two stages: the first stage involves changes in the acini and the second stage involves secretion from the ducts.

The acini secrete ptyalin and mucin.

As the secretion passes through the ducts, Na^+ is reabsorbed and K^+ is secreted.

Cl^- is passively absorbed. HCO_3^- is secreted by the ductal epithelium into the lumen.

Saliva is continuously secreted even when there is no food in the mouth. This secretion helps to keep the mouth moist. This is called **basal secretion**.

Reflex Secretion Saliva is secreted due to the presence of food in the mouth. This is present since birth and is an unconditioned reflex. Saliva is also secreted due to thought, smell, or sight of food. This is acquired later in life and is a conditioned reflex.

Salivary secretion is purely due to neural mechanisms and no hormones are involved in its secretion.

Regulation

The salivary secretion is predominantly under the neural control from the superior

CLINICAL NOTES

Mumps

Mumps is a viral infection affecting the parotid gland.

Xerostomia

Xerostomia is a condition due to reduced salivary secretion resulting in dryness of mouth. This predisposes to infection of the oral cavity.

and inferior salivary nuclei present in the brainstem.

Salivary secretion increases by

- parasympathetic stimulation,
- smelling or eating favorite foods, and
- presence of irritating food in the stomach.

Salivary secretion decreases by

- atropine and other cholinergic blockers.

Stimulation of the sympathetic nerve causes secretion of small amounts of saliva rich in organic constituents.

STOMACH

The stomach is a J-shaped, hollow structure connected to the esophagus at the upper end and duodenum at the lower end. Its capacity ranges from 50 mL to 5 L and the average is 1.2–1.7 L.

It is divided into three parts: (i) fundus, (ii) body, and (iii) pylorus (**Fig. 6.10**).

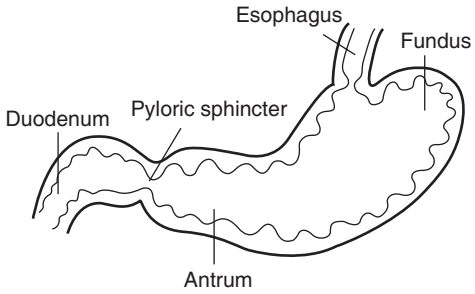


Figure 6.10 Stomach.

Unlike other parts of the GI tract, the muscular layer of the stomach contains outer longitudinal, middle circular, and inner oblique layers.

The inlet of the stomach is guarded by esophageal sphincter and the outlet by pyloric sphincter.

Gastric mucosa is thick, thrown into folds called *rugae*, and has a number of gastric glands.

FUNCTIONS

The functions of the stomach are as follows:

- Helps in storage of food. The food is stored in the stomach for 3–4 hours and slowly emptied into the duodenum.
- Helps in proper mixing of food and converts it into semisolid substance called chyme.
- Helps in digestion of food by secretion of gastric juice.
- HCl secreted by the stomach destroys microorganisms and other harmful substances present in the food.
- Secretes intrinsic factor which helps in the absorption of vitamin B_{12}.

GASTRIC GLANDS (Fig. 6.11)

The mucosa of the stomach has mucus-secreting cells and tubular glands.

A typical gastric gland is tubular and straight. The gland is divided into three parts:

1. neck,
2. body, and
3. base.

The opening of the gland to the surface is called **gastric pit**. The cells lining these glands are of different types—neck cells, oxyntic cells, and chief cells. These cells continuously form and desquamate at regular intervals. Each cell develops, matures in 2–3 days, performs its function, and then desquamates. Thus, about half a million cells are replaced every hour.

The gastric glands are of three types:

1. Cardiac glands
2. Oxyntic glands
3. Pyloric glands

Cardiac Glands

Cardiac glands are present in the mucosa of cardia of the stomach around the distal end of esophagus. They mainly contain mucus-secreting cells.

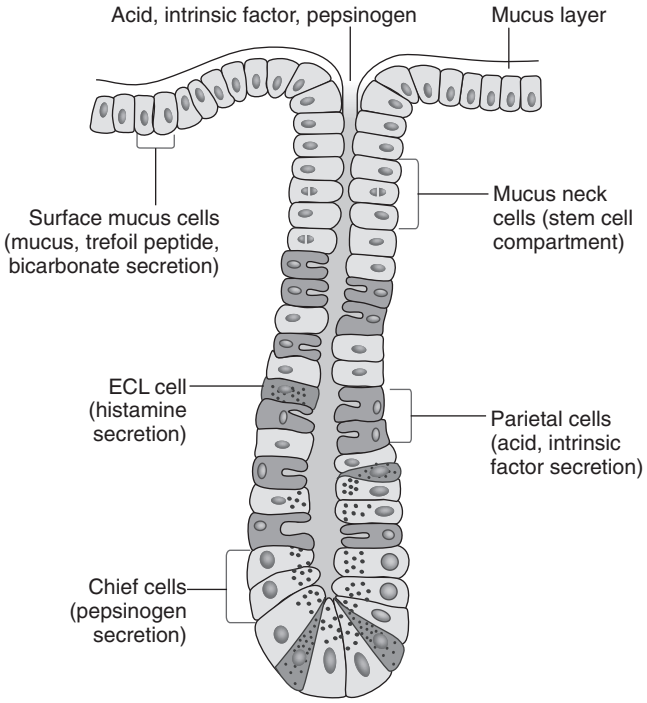


Figure 6.11 Gastric glands. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Mucus Cells

Mucus cells are columnar in shape. They absorb carbohydrates from the bloodstream and convert them into mucin. Hydration of mucin forms mucus.

Functions of Mucus

- Forms a protective barrier against acid and prevents peptic damage
- Lubricates the food particles as they pass through the gut

Oxyntic Glands

Oxyntic glands are present on the inner surface of the body and fundus of the stomach which constitutes the proximal 80% of the stomach. The oxyntic gland is composed of three types of cells:

1. Peptic cells (chief cells)
2. Parietal cells (oxyntic cells)
3. Mucus neck cells

Peptic Cells (Chief Cells)

Peptic cells are primarily found at the base of the oxyntic glands in the body of the stomach.

They produce pepsinogen. Pepsinogen is an inactive form which gets converted to the active form pepsin when it comes in contact with the HCl.

Further, pepsin activates the remaining pepsinogen to pepsin.

$$\text{Pepsinogen} \xrightarrow{\text{HCl}} \text{Pepsin}$$

Pepsin digests proteins to proteases, peptones, and polypeptides by hydrolyzing the peptide bonds.

Parietal Cells (Fig. 6.12)

Parietal cells are also called **oxyntic cells**. They are present in the neck and the body of oxyntic glands. The parietal cells contain many large branching microcanaliculi and

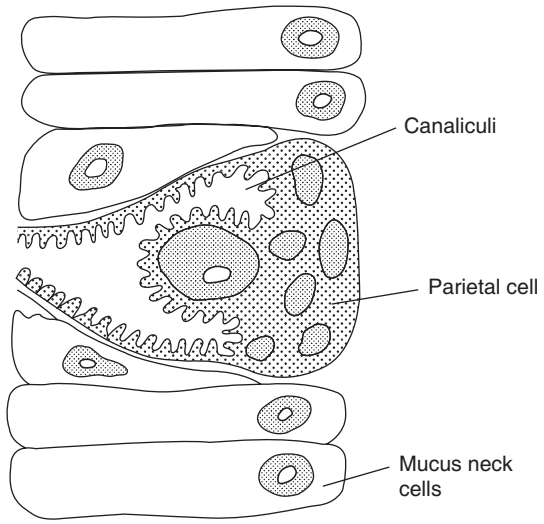


Figure 6.12 Parietal cell.

a tubulovesicular system. The membrane of these tubulovesicular structures contains H^+–K^+ ATPase. Whenever the cell is active, these tubulovesicular structures fuse with the microvilli that project into the canaliculi. This increases the surface area of the inner portion of the cell membrane which is in contact with the gastric lumen.

HCl Secretion (Fig. 6.13) HCl is formed from the parietal cells present in the fundus and the body of the stomach. The inner cell membrane of the parietal cell has a number of H^+–K^+ ATPase. This pumps H^+ into the lumen. Chloride ions are also secreted into the lumen. HCl is therefore formed in the lumen of the parietal cell.

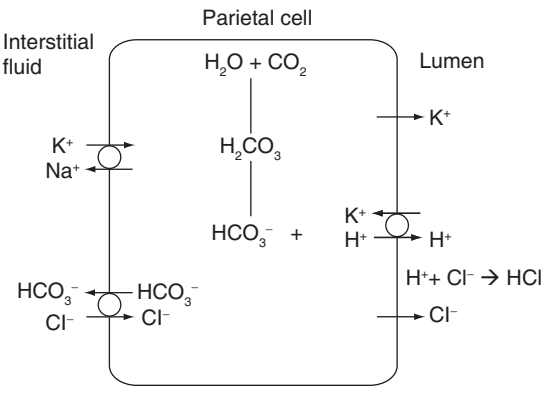


Figure 6.13 HCl secretion.

Steps in HCl Synthesis

1. The water present inside the parietal cell is ionized into hydrogen ions and hydroxyl ions. Hydrogen ions are actively secreted into canaliculi.
   $$H_2O \longrightarrow H^+ \text{ and } OH^-.$$
2. CO_2 combines with H_2O in the presence of carbonic anhydrase to form carbonic acid.
   $$CO_2 + H_2O \longrightarrow H_2CO_3.$$
3. Carbonic acid dissociates to form hydrogen ions and bicarbonates
   $$H_2CO_3 \longrightarrow H^+ + HCO_3^-.$$
4. Chloride enters the parietal cell in exchange for bicarbonate ions. This chloride is secreted into canaliculi.
5. The H^+ ion is pumped into canaliculi. It combines with Cl^- to form HCl.

Thus for each H^+ secreted into the gastric lumen, one HCO_3^- is produced. This bicarbonate ion is reabsorbed into the plasma. Therefore, as the rate of HCl secretion increases, the plasma bicarbonate increases proportionately. After a meal, H^+ secretion sharply increases causing increased HCO_3^- levels of blood. This causes an increase in the excretion of alkaline urine. This condition is called **postprandial alkaline tide**.

K^+ that enters the cell in exchange of H^+ is transported back to the gastric lumen which is reutilized for secretion of further amounts of H^+.

Intrinsic Factor The intrinsic factor is a glycoprotein with a molecular weight of 45,000.

It is synthesized and secreted by the parietal cells. It is required for the absorption of vitamin B_{12}. It forms a complex with vitamin B_{12} which is transported to the terminal ileum from where vitamin B_{12} is absorbed. Deficiency of vitamin B_{12} causes failure of maturation of red blood cells. This leads to a condition called *megaloblastic anemia*.

Pyloric Glands

Pyloric glands are located in the antral portion of the stomach, which constitutes the distal 20% of the stomach. They contain mucus-secreting cells which secrete mucus and G cells which secrete the hormone gastrin.

GASTRIC SECRETION

The secretion of gastric juice occurs continuously. However, the volume of secretion is variable.

PHASES

Gastric secretion occurs in the following phases:

- Cephalic phase
- Gastric phase
- Intestinal phase
- Interdigestive phase

Cephalic Phase

Gastric secretion in this phase occurs even before the food enters the stomach. It is due to sight, smell, thought, or taste of the food.

The signals originate in the cerebral cortex and reach the stomach through the vagus.

It accounts for 20% of the total gastric secretion.

Gastric secretion is due to both conditioned and unconditioned reflexes.

The conditioned reflexes are sight, smell, and thought of food.

The unconditioned reflex is food in the mouth, chewing, and swallowing.

The secretion of gastric juice starts in about 5 minutes and continues for 20–30 minutes.

Gastric Phase

It is initiated by the presence of food in the stomach. The secretion continues as long as the food remains in the stomach.

This phase accounts for 70% of the total gastric secretion. The rate of secretion is 50–70 mL/h.

This phase is controlled by both neural and hormonal mechanisms. The neural control is through long vagovagal reflexes. The main hormone involved in this phase is **gastrin**.

Intestinal Phase

The presence of food in the upper portion of the SI causes the stomach to produce small amounts of gastric juice.

The hormones responsible are gastrin and bombesin. This phase begins 2–3 hours after a meal and may continue for 7–8 hours.

Interdigestive Phase

The interdigestive phase is also called *basal secretion*. The secretion contains mucus and pepsin and no acid. This type of secretion is found in between consumption of the food.

REGULATION

Gastric secretion is regulated by both neural and chemical mechanisms.

Parasympathetic stimulation (vagus) causes increased acid and pepsinogen secretion, increased contraction of stomach, and relaxation of fundus. It also increases gastrin secretion. Sympathetic stimulation inhibits gastric secretion and motility.

The intrinsic nerve plexuses are either adrenergic or cholinergic in nature. The cholinergic neurons stimulate secretion of acid, pepsinogen, and intrinsic factor. The adrenergic neurons have an opposite effect.

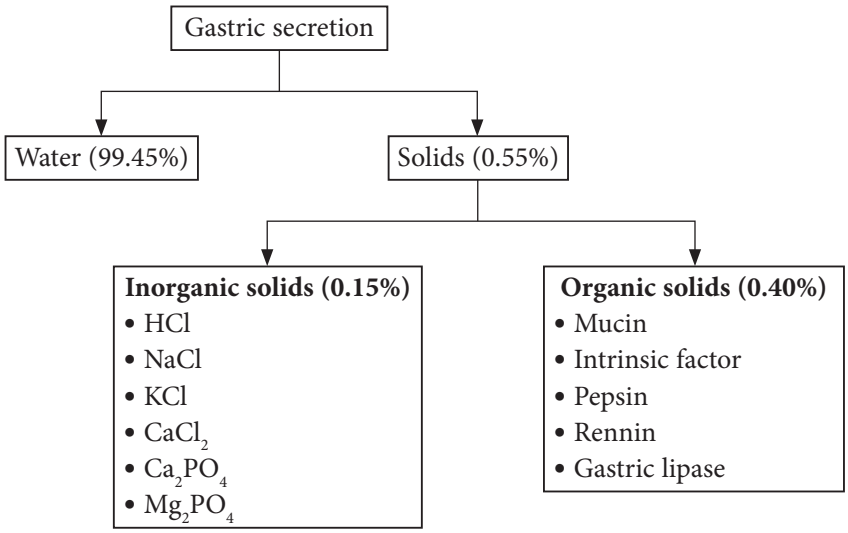
The chemicals involved in the regulation include various general and local hormones. General hormones such as cortisol, parathormone, and insulin increase gastric secretion. Local hormones such as gastrin, bombesin, histamine, Ca^{2+} ions, and products of protein digestion increase the gastric secretion. CCK-PZ, secretin, VIP, and somatostatin reduce the gastric secretion.

GASTRIC JUICE

Gastric juice is the secretion from different gastric glands.

Composition (Flowchart 6.2)

Volume	1200–1500 mL/day
pH	0.9–1.5
Specific gravity	1.002–1.004



Flowchart 6.2 Composition of gastric juice. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Functions

The enzyme pepsin digests proteins up to the stage of peptones.

Rennin coagulates caseinogen of milk. (It is present in infants.)

Gastric lipase digests fat.

HCl acts as an antibacterial and hydrolyzes foodstuff.

It converts pepsinogen to pepsin.

Toxins, heavy metals, and certain alkaloids are excreted through the gastric juice.

EXPERIMENTS TO STUDY GASTRIC SECRETION

1. **Sham feeding (false feeding; Fig. 6.14a)**: The esophagus of a dog is exposed in the neck, divided in the middle. Both the cut

CLINICAL NOTES

Gastritis

Gastritis is the inflammation of gastric mucosa. It is of two types: (i) acute and (ii) chronic. It is caused by nonsteroidal anti-inflammatory drugs, alcohol, and smoking. It can also be caused due to infection by *Helicobacter pylori*.

Peptic Ulcer

Peptic ulcer is an excoriated area of mucosa caused by the digestive action of gastric juice. It occurs in the stomach (gastric ulcer) or duodenum (duodenal ulcer).

It is caused by an imbalance between the rate of secretion of gastric juice and the degree of protection offered by the gastroduodenal mucosal barrier.

H. pylori infection is said to be the cause for peptic ulcer.

Anti-inflammatory drugs, alcohol, and smoking also cause gastric ulcers.

Management

Gastritis and peptic ulcer are treated with antacids, H_2 receptor antagonists (ranitidine), and proton–pump inhibitor (omeprazole/pantoprazol).

Combinations of antibacterials are used to treat *H. pylori* infection in patients not responding to conventional treatment.

Achlorhydria

Achlorhydria is a condition wherein the stomach fails to secrete HCl as in atrophic gastritis (it is a condition with chronic inflammation associated with thinning of the lining of the stomach).

It is associated with pernicious anemia due to reduced secretion of the intrinsic factor and hence decreased absorption of vitamin B_{12}.

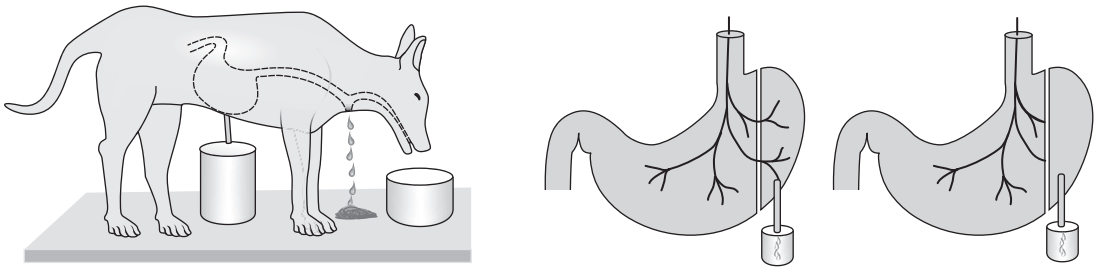


Figure 6.14 (a) Sham feeding and (b) Pavlov's pouch. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

ends are kept open to the exterior. A canula is introduced into the stomach to drain the gastric juice. The food given to the animal comes out through the cut end of the esophagus without reaching the stomach. There will be gastric secretion even without food reaching the stomach. This experiment is helpful to prove the cephalic phase of gastric secretion.

2. **Pavlov's pouch (Fig. 6.14b)**: It is a small diverticulum prepared from the body of the stomach, representing about one-eighth of the whole stomach. A pouch is prepared in such a way that one end is shut off from the main cavity of the stomach by two layers of the mucus membrane while the other end communicates with the exterior through an opening in the abdominal wall. Vagus nerve supply is kept intact for the pouch.

   Its advantage is that uncontaminated gastric juice can be collected.
3. **Heidenhain's pouch**: This is a denervated pouch made of the gastric mucus membrane. Secretion from this pouch occurs only under the influence of blood-borne chemicals. This experiment helps to study the hormonal control of gastric secretion.

GASTRIC FUNCTION TESTS

HCL Secretion

Gastric juice is collected by a Ryle's tube introduced through the nose and different types of HCl secretions are assessed.

Basal Acid Output

Basal acid output is the acid output in the interdigestive phase. The normal value is 0.5–2 mEq/h. It is increased in duodenal ulcer and Zollinger–Ellison syndrome.

Peak Acid Output

Peak acid output is measured from the gastric juice collected after the stimulation of gastric glands by the food or other agents. The normal value is 40–60 mEq/h. It is measured by

- histamine test,
- pentagastrin test, and
- insulin test.

Fractional Test Meal

Fractional test meal gives an indication about the acid output and also other functions of the stomach.

Barium Meal X-Ray

Barium meal X-ray is helpful in evaluating the movements of the stomach and gastric emptying. It is also helpful in the diagnosis of peptic ulcer.

Endoscopy

It is a procedure of inserting a long, flexible tube called endoscope into the esophagus through the mouth and throat. A small camera helps to visualize the esophagus, stomach, and beginning of the small intestine. Endoscopy is helpful in diagnosing various

conditions such as gastritis, peptic ulcer, and study of gastric emptying. Biopsy can be taken from different areas of the upper GIT for histological study.

Biopsy

Biopsy is helpful in diagnosing gastric malignancy and atrophic gastritis.

BILIARY SECRETION

Bile is secreted by cells of the liver. It is stored in the gallbladder and emptied into the duodenum.

LIVER

The liver is the largest gland in the body (**Fig. 6.15**). It is present in the right upper part of the abdominal cavity. It weighs around 1.5 kg.

The liver is both an exocrine and an endocrine gland since part of its secretions directly drains into the blood and the remaining is drained through the ducts.

The liver is made up of cells termed **hepatocytes**. In between the layers of hepatocytes are the sinusoids.

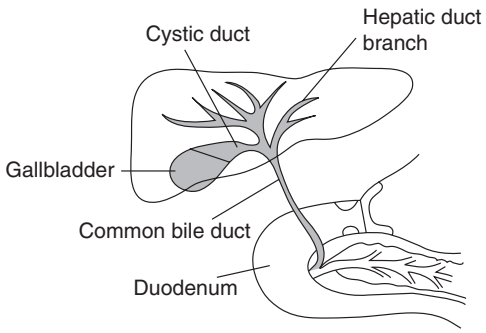


Figure 6.15 Liver with gallbladder.

Histology of Liver

The liver is made up of a large number of hexagonal structures termed **hepatic lobules** (**Fig. 6.16**). Each lobule consists of a central vein in the middle and columns of hepatic cells radiating from the center forming a plate. These plates are only one cell thick and separated by liver sinusoids. The sinusoids open into the central vein. The sinusoids are lined by endothelial cells which have large fenestrations. Tissue macrophages called **Kupffer cells** are present at regular intervals between the endothelial cells.

Portal triads are present at the angles of hepatic lobule. They consist of a branch of portal vein, branch of hepatic artery, and tributary of the bile duct. Blood from the

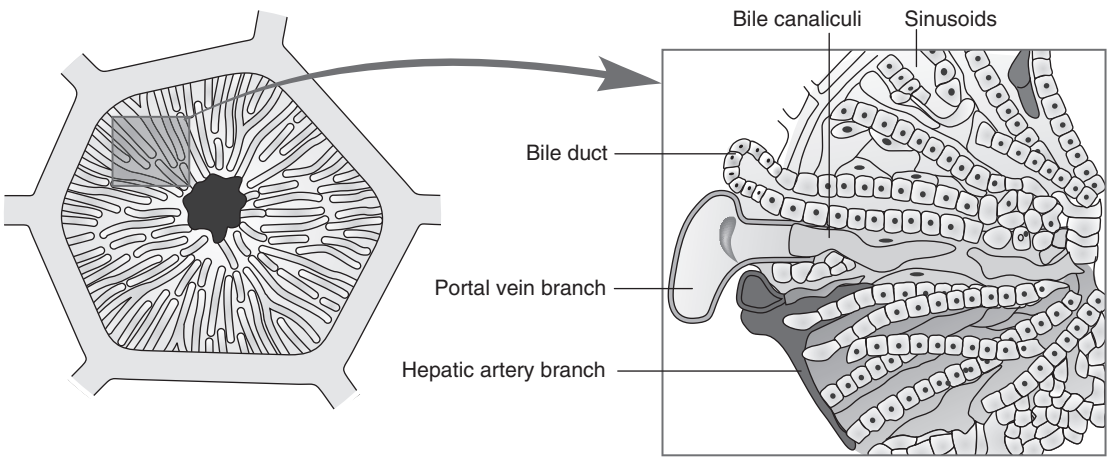


Figure 6.16 Hepatic lobule. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

hepatic artery and portal vein enters the hepatic sinusoids and drain into the central vein.

Blood Supply to Liver

The liver receives blood supply from the hepatic artery and portal vein. The hepatic artery contains arterial blood rich in oxygen. Blood from the portal vein is rich in end products of digestion and various gastrointestinal (GI) hormones. The hepatic artery and portal vein branch repeatedly and finally enter the sinusoids. Oxygen and nutrients are delivered to the hepatic cells through the sinusoids. Substances produced in the liver, waste products, CO_2, and products of metabolism are emptied into the sinusoids. These are drained into the central vein which ultimately drains into the inferior vena cava through the hepatic vein.

Functions of Liver

The functions of liver are as follows:

- **Formation and secretion of bile**: Bile is continuously produced in the liver cells. About 500 mL of bile is produced each day.
- **Metabolism of nutrients and vitamins**: The liver is essential for the metabolism of glucose, amino acids, lipids, and vitamins.
- **Inactivation of various substances**: Various toxins and hormones are inactivated in the liver.
- **Synthesis of plasma proteins**: Albumin, globulins, and clotting factors are synthesized in the liver.
- **Immunity**: Kupffer cells present in the liver are protective in function.
- **Hemopoiesis**: The liver is a major site for hemopoiesis during the first few weeks of intrauterine life.
- **Storage**: The liver stores vitamins A, D, B_{12}, iron, and glycogen in significant quantities.

Liver Function Tests

- **Serum bilirubin**: The normal plasma bilirubin is 0.2–0.8 mg%. Plasma bilirubin is increased in jaundice.
- **Estimation of plasma proteins**: The normal albumin/globulin ratio (1.7:1) is reversed in liver diseases. Albumin production in the liver is reduced due to the disease process.
- **Serum fibrinogen and prothrombin levels**: The levels of these two substances are decreased in liver diseases.
- **Serum enzyme estimation**: Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) increase in liver disorders. Serum alkaline phosphatase is markedly increased in biliary obstruction.
- **Hippuric acid excretion and bromsulphalein excretion test**: These tests are done to assess the detoxifying capacity of the liver by measuring the excretion rate of these substances from the liver.
- **Ultrasound scan of liver**: It helps in the detection of an abscess, a cyst, or any malignant growth. It also gives information about the size of the liver.
- **CAT scan**: It helps in detecting any malignancy in the liver.
- **Liver biopsy**: Ultrasound scan of the liver, CAT scan, and liver biopsy give an indication about the structural and functional changes in the liver.

CLINICAL NOTES

Cirrhosis of Liver

Cirrhosis of the liver is a chronic condition in which the liver is irreversibly damaged. There is extensive fibrosis with the formation of regenerative nodules.

Causes

Chronic alcoholism is a major cause for cirrhosis. Other causes include viral infections, biliary causes, and metabolic abnormalities.

Clinical Features

Cirrhosis leads to jaundice, edema, portal hypertension, ascites, and hepatic encephalopathy.

Hepatitis

Hepatitis is the inflammation of the liver. It is commonly caused due to the hepatitis virus. The common types of hepatitis virus include hepatitis A and B.

BILE

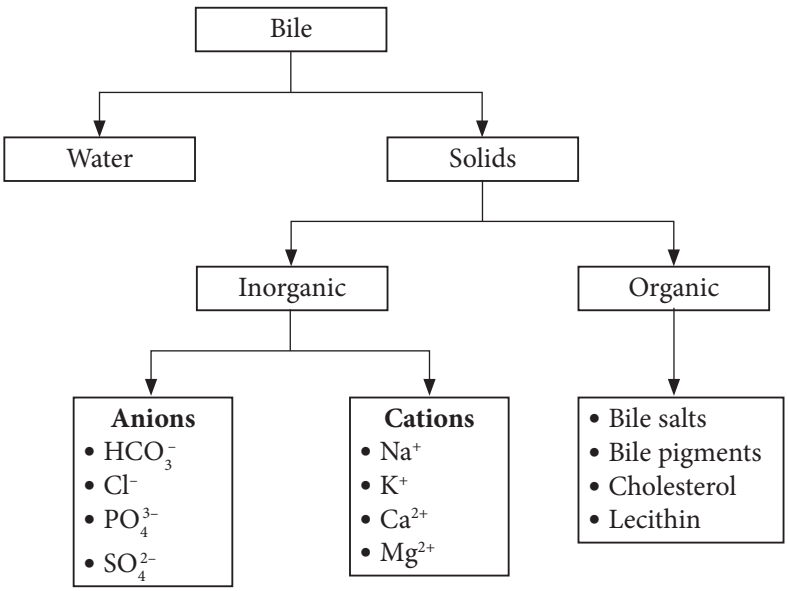
Bile is secreted by the cells of the liver into the bile duct. Later, it drains into the duodenum. The bile is actually a product of secretion as well as excretion.

Composition (Flowchart 6.3)

Total quantity	500–1000 mL/day
Specific gravity	1.010–1.011
Color	Yellowish green
Taste	Bitter
Reaction	Alkaline
pH	7–7.6
Solids	2–11%

Functions

1. **Digestion**: Bile helps in digestion and emulsification of fats by
   - *Reducing the surface tension:* Fats are converted to emulsion.
   - *Activating lipases:* Bile salts act as a specific activator for different lipases.
   - *Solvent action:* Bile acts as a solvent.
2. **Absorption**
   - Bile is necessary for fat absorption by hydrotropic action.
   - Insoluble fatty acids and cholesterol are made readily soluble in the watery contents of the intestine.
   - Absorption of iron, calcium, and fat-soluble vitamins is facilitated by bile.
3. **Excretion**
   - Metals, toxins, bile pigments, and cholesterol are excreted through bile.
4. **Laxative action**
   - The bile salts stimulate peristalsis and act as laxative.
5. **Choleretic action**
   - Bile acts as its own stimulant for further secretion. This is brought about by bile salts present in the bile.
6. **pH**
   - Bile helps to *maintain a suitable pH* of duodenum.
7. **Emulsification**
   - Lecithin and cholesterol present in bile act as an *adjuvant* to bile salts during the process of *fat emulsification.*
8. **Cholagogue action**
   - The bile salts present in bile cause contraction of gallbladder resulting in expulsion of bile.



Flowchart 6.3 Composition of bile. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Secretion

Bile is secreted in two stages by the liver. The initial portion containing bile acids and cholesterol is secreted by the liver cells.

Sodium, bicarbonate, and water are added as it passes through the canaliculi.

Bilirubin, the metabolic end product of Hb breakdown, is actively secreted into the bile canaliculi. Cholesterol and lecithin are also secreted into the bile canaliculi.

Storage and Concentration

Bile is secreted by the liver and stored in the gallbladder. It is normally concentrated five times. The capacity of the gallbladder is 30–60 mL.

Emptying of Gallbladder

The gallbladder empties its contents by rhythmic contractions as the food begins to get digested. The main stimulus for the contraction of gallbladder is the hormone **cholecystokinin**.

Gallbladder

The gallbladder is a sac present underneath the liver. The capacity of the gallbladder is around 50 mL. It is connected to the common hepatic duct through the cystic duct.

Function

- Stores bile
- Concentrates bile

Shortly after the consumption of food, the smooth muscles of the gallbladder contract rhythmically and empty gradually. The stimulus for its contraction is mainly hormonal. CCK is the most important hormone causing contraction of the gallbladder.

Bile Salts

Bile salts are sodium and potassium tauro and glycocholates. These are salts of bile acids.

Three to four grams of bile salts are present in the body. Bile salts recycle six to eight times per day.

Functions

- Bile salts have a detergent action on fat. This decreases the surface tension of particles and allows breakdown of fat globules into smaller particles. This is called the emulsifying or detergent function of bile salts (**Fig. 6.17**).
- They help in the absorption of fatty acids, monoglycerides, cholesterol, and other lipids from the intestinal tract.
- They stimulate the peristaltic action of the intestine and thereby have laxative effect.
- They prevent the formation of gallstones by keeping cholesterol and lecithin in solution.
- Choleretic action—bile salts stimulate the secretion of bile.

Bile salts form minute complexes with lipids and these complexes are called **micelles**.

Lipids collect in the form of micelles. The micelles play an important role in keeping lipids in solution and transporting them to the brush border of the intestinal epithelial cells, where they are absorbed.

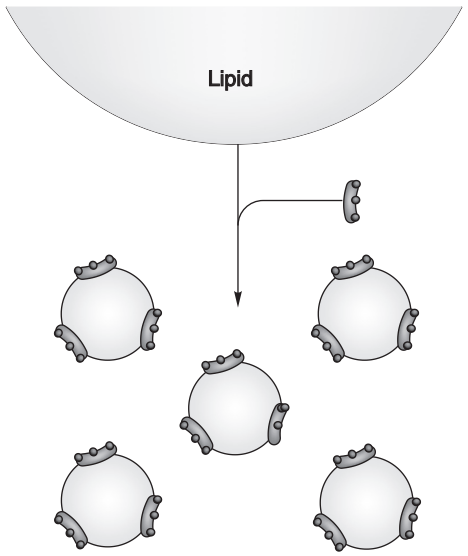


Figure 6.17 Emulsification of fat by bile salts. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Bile Pigments

Bile pigments are degradation products of hemoglobin. They include bilirubin and biliverdin. They are excretion products and do not have specific function to perform. They are responsible for the color of bile.

Regulation of Biliary Secretion

Biliary secretion is increased by

- vagal stimulation,
- cholecystokinin, and
- secretin.

When the food enters the mouth, the sphincter of Oddi relaxes. Fatty acids and amino acids in the duodenum cause the release of CCK. CCK causes the gallbladder contraction. Stimulation of vagus and hormone secretin increases the water and HCO_3^- content of the bile.

Choleretics

Choleretics are the substances that increase the secretion of bile. Bile salts themselves act as choleretics.

Cholagogues

Cholagogues are substances that cause contraction of the gallbladder, e.g., cholecystokinin.

Composition of Bile		
	Liver	**Gallbladder**
Water	97%	91%
Bile salts	1.1 g/dL	6 g/dL
Bilirubin	0.04 g/dL	0.3 g/dL
pH	7.8–8.6	7.0–7.4
Cholesterol	0.1 g/dL	0.3–0.9 g/dL
Na^+	145 mEq/L	130 mEq/L
Cl^-	100 mEq/L	25 mEq/L

Enterohepatic Circulation (Fig. 6.18)

Enterohepatic circulation is a process of absorption of bile salts from the intestine and re-secretion in the bile. About 94% of the bile salts are reabsorbed from the intestine into the blood. Of this 94%, about 50% are absorbed in the proximal portions of the small intestine by diffusion while the remaining is absorbed in the distal ileum by active transport.

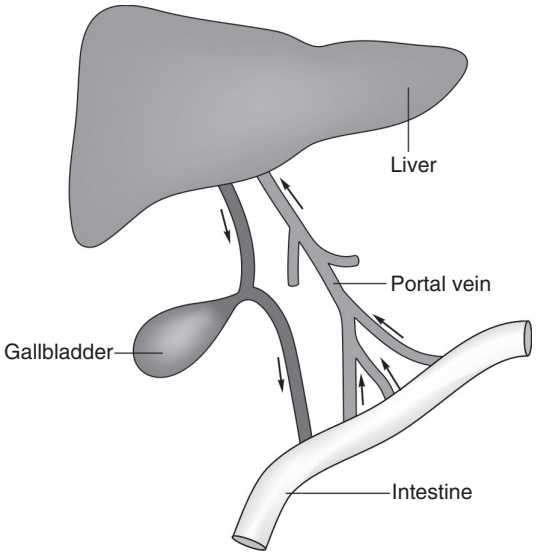


Figure 6.18 Enterohepatic circulation. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The bile salts enter the portal circulation and are then taken up by the hepatic cells.

The remaining 6% of bile salts are excreted into the feces. This small quantity of bile salts lost into the feces is replaced by the formation of new bile salts by the liver cells. The rate of formation of new bile salts is determined by the quantity of bile salts lost by excretion.

Other substances passing through enterohepatic circulation include thyroxine, vitamin B_{12}, and vitamin D.

Importance

Enterohepatic circulation ensures that substances are preserved and reutilized so that a small quantity of substance is enough to maintain adequate levels of the substance in the body.

Jaundice

Jaundice is yellowish discoloration of the skin and mucus membrane. It is caused due to excessive deposition of bile pigments.

Clinically, jaundice occurs when plasma bilirubin exceeds 2 mg/dL.

Physiological Jaundice

Physiological jaundice occurs in newborn babies on the second or third day after birth and disappears before 10 days.

Cause Physiological jaundice is caused by rapid hemolysis leading to increased bilirubin production and reduced conjugation due to deficiency of the enzyme glucuronyl transferase. This condition is self-limiting and requires no treatment. However, the globulin production is normal.

Pathological Jaundice

There are three types of jaundice:

1. Prehepatic (hemolytic)
2. Hepatic
3. Posthepatic (obstructive)

Prehepatic Jaundice This is caused due to excessive breakdown of RBCs. Therefore, it is also called **hemolytic jaundice**. The liver cannot conjugate bilirubin and therefore the concentration of unconjugated bilirubin increases in the blood. There is increased excretion of stercobilinogen and urobilinogen.

Hepatic Jaundice This is caused due to infection or toxic damage to the liver. There is increase in both unconjugated and conjugated bilirubin in the blood. The stercobilinogen and urobilinogen are reduced. Conjugated bilirubin gets excreted in urine giving a deep yellow color to urine.

Obstructive Jaundice This is caused by obstruction to bile ducts either by tumors or by stones. In this condition, conjugated bilirubin increases in the blood. Fecal stercobilinogen is not formed leading to clay-colored stools. Urobilinogen is absent in urine. Conjugated bilirubin gets excreted in urine giving a deep yellow color to urine.

Differences between hemolytic, hepatic, and obstructive jaundice are listed in **Table 6.1**.

Van den Bergh Test

Van den Bergh test helps to identify the type of jaundice. The serum of a patient is mixed with a diazo reagent. If a red color develops immediately, it is called **direct positive**. It happens if conjugated bilirubin is present.

Table 6.1 Differences Between Hemolytic, Hepatic, and Obstructive Jaundice

	Hemolytic	Hepatic	Obstructive
Increase in bilirubin	Mild	Moderate	Severe
Type of bilirubin	Unconjugated	Both unconjugated and conjugated	Conjugated
Urobilinogen in urine	Increased	Decreased	Absent
Bilirubin in urine	Absent	Present	Present
Stercobilinogen in feces	Increased	Decreased	Absent
Van den Bergh test	Indirect positive	Biphasic	Direct positive
Liver function	Normal	Impaired	Normal or Impaired

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

CLINICAL NOTES

Gallstones (Cholelithiasis)

This is a condition in which stones are formed in the gallbladder. Its incidence increases with age.

Gallstones are of two types:

1. Calcium bilirubinate stones
2. Cholesterol stones

Cholecystitis

Cholecystitis is inflammation of the gallbladder. It is more common in fatty, fertile females who are in their forties.

Cholecystography

Cholecystography is an investigation in which radio-opaque substances are administered either orally or intravenously. This is excreted by the liver and gets concentrated in the bile. X-rays are taken after a few hours to visualize the gallbladder.

Cholecystectomy

Removal of gallbladder is termed cholecystectomy. It is indicated in conditions of chronic cholecystitis and symptomatic cholelithiasis.

In an **indirect positive** test, the patient's serum is first treated with alcohol and later mixed with the diazo reagent. This causes development of the red color. It is seen if unconjugated bilirubin is present.

If both conjugated and unconjugated bilirubins are present, the reaction is termed **biphasic reaction**.

In hemolytic jaundice, the unconjugated bilirubin is increased. The Van den Bergh reaction is indirect positive. Urobilinogen levels are increased.

In obstructive jaundice, bilirubin is of the conjugated type. The Van den Bergh reaction is direct positive. The serum alkaline phosphatase levels are increased. Bile salts are present in urine.

PANCREATIC SECRETION

The pancreas is both an exocrine and an endocrine gland (**Fig. 6.19**). The endocrine secretion is from the islet of Langerhans. The exocrine secretion is necessary for digesting carbohydrates, proteins, and fats and for neutralizing the acidity of the duodenal contents.

ANATOMY

The exocrine pancreatic gland is a compound alveolar gland resembling the salivary gland.

The secretory units are called **acini**. The acini secrete enzymes of the pancreatic juice.

The secretions pass through

Intercalated duct → Interlobular duct → Extralobular duct → Larger duct → Main collecting duct (duct of Wirsung).

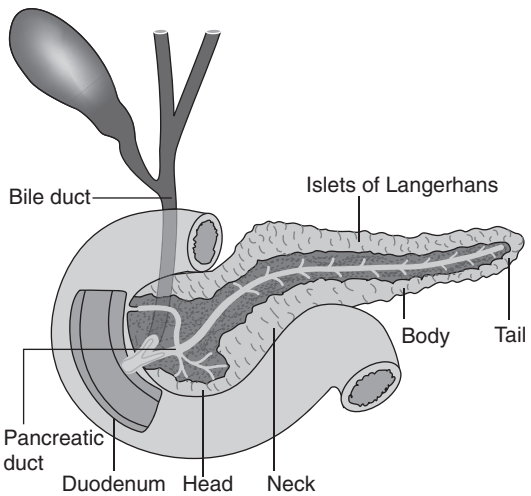


Figure 6.19 Structure of pancreas. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The pancreatic duct joins the common bile duct to form the ampulla of Vater, which drains into the duodenum.

NERVE SUPPLY

The pancreas is supplied by both sympathetic and parasympathetic nerves.

Sympathetic

This is from celiac plexus and superior mesenteric plexus.

Sympathetic stimulation inhibits the pancreatic secretion.

Parasympathetic

It is through the vagus. The stimulation of the vagus increases the pancreatic secretion.

COMPOSITION (Flowchart 6.4)

The secretion of pancreas is a colorless fluid isotonic to plasma.

It is alkaline in nature (pH of 8–8.3) due to the presence of a large number of bicarbonate ions.

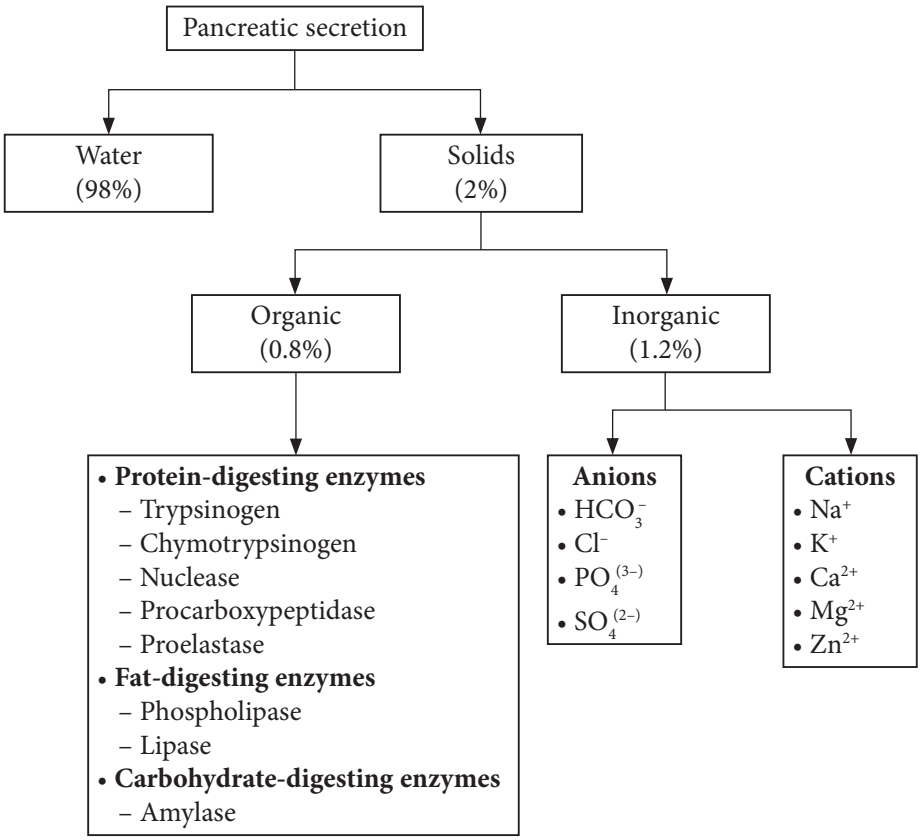
The quantity is 1500 mL/day.

Specific gravity varies from 1.010 to 1.018.

MECHANISM OF SECRETION

The enzymes are secreted by the acinar cells. They are stored as zymogen granules in the acinar cells. The stimulation of these cells leads to exocytosis of the zymogen granules and release of enzymes.

The fluid and electrolytes of the pancreatic juice are secreted by centroacinar cells and



Flowchart 6.4 Composition of pancreatic secretion. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

intercalated and interlobular ducts. HCO_3^- ions are secreted in plenty.

STEPS IN HCO_3^- SYNTHESIS

- CO_2 present in blood diffuses into the ductal cells. It combines with H_2O in the presence of enzyme carbonic anhydrase to form H_2CO_3.
- H_2CO_3 dissociates into H^+ and HCO_3^-.
- HCO_3^- is exchanged with Cl^- through the HCO_3^-–Cl^- exchanger.
- Cl^- is transported back to the lumen through chloride channels present on the luminal membrane.

REGULATION

Pancreatic secretion is regulated in relation to the food intake. Both hormonal and neural factors are involved in its regulation.

Neural regulation is by parasympathetic stimulation through the vagus nerve. It increases the pancreatic secretion by releasing acetylcholine.

Hormonal regulation is through secretin and CCK which increase the secretion of pancreatic juice.

There are three phases of pancreatic secretion:

1. Cephalic phase
2. Gastric phase
3. Intestinal phase

Cephalic Phase

In this phase, sight, smell, and taste of food stimulate the brain to send efferent impulses through the vagus nerve to the pancreas. This causes secretion of enzymes. The acidic contents from the stomach on reaching the intestine cause the secretion of bicarbonate-rich pancreatic juice.

Gastric Phase

The presence of food in the stomach is responsible for this phase. It is regulated by the neural mechanism through the vagovagal reflex and hormonal mechanism through gastrin. Vagovagal reflexes result in secretion of low volumes of pancreatic juice rich in bicarbonate and enzymes. The gastric phase is mediated by acetylcholine.

The hormone gastrin released into the blood reaches the pancreas and stimulates the acinar cells producing enzyme-rich pancreatic secretion.

Intestinal Phase

The intestinal phase is the most important phase. It begins when the chyme enters the duodenum. It is characterized by markedly increased secretion of both enzymes and the fluid component of pancreatic juice. It is mainly regulated by the hormones **secretin** and **cholecystokinin**.

Acid in the intestine stimulates the bicarbonate-rich pancreatic secretion by the action of secretin. The alkaline pancreatic secretion neutralizes the acid in the food and provides the required pH for the activity of pancreatic enzymes.

Products of lipid and protein digestion, i.e., peptides and amino acids, stimulate cholecystokinin secretion. Cholecystokinin stimulates the formation of enzyme-rich pancreatic juice. This in turn enhances the secretion of digestive products by a positive feedback mechanism.

FUNCTIONS

- **Digestion of proteins**: Trypsin, chymotrypsin, and carboxypeptidase hydrolyze proteins to amino acids.

  Proteolytic enzymes are present in the inactive form as trypsinogen, chymotrypsinogen, and procarboxypeptidase. They are activated on being secreted into the intestinal lumen.

  $$\text{Trypsinogen} \xrightarrow{\text{Enterokinase}} \text{Trypsin}.$$

  $$\text{Chymotrypsiongen} \xrightarrow{\text{Trypsin}} \text{Chymotrypsin}.$$

  $$\text{Procarboxypeptidase} \xrightarrow{\text{Trypsin}} \text{Carboxypeptidase}.$$

CLINICAL NOTES

Steatorrhea

Deficiency of pancreatic enzymes leads to indigestion of fats. This produces fatty, foul-smelling feces, termed steatorrhea. This can occur in pancreatitis, blockage of pancreatic duct by gallstones, or pancreatic malignancy.

Acute Pancreatitis

Acute pancreatitis is a serious disease, often fatal, caused by acute inflammation of the gland.

In this condition, pancreatic enzymes are activated within the pancreas. This damages the pancreas and the contents are released into the abdomen causing acute peritonitis.

Symptoms include severe pain in the upper abdomen, nausea, and vomiting. Blood investigations show markedly elevated levels of serum amylase.

Chronic Pancreatitis

Chronic pancreatitis is a condition resulting in slow destruction of pancreatic tissue. It is caused by the consumption of alcohol and presence of gallstones. It causes digestive disturbances due to deficiency of pancreatic enzymes, especially affecting fat metabolism resulting in steatorrhea.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder caused due to mutation of the *CFTR* gene located on chromosome 7. It affects not only the lungs but also the pancreas, liver, kidneys, and intestine.

Inside the pancreas, the action of proteolytic enzymes is inhibited by the presence of the trypsin inhibitor in pancreatic juice. The trypsin inhibitor does not prevent the action of proteolytic enzymes in the intestine since they are activated by enterokinase.

- **Digestion of carbohydrates**: Pancreatic amylase splits starch to maltose and α-dextrins.

$$\text{Starch} \xrightarrow{\text{Amylase}} \text{Maltose} + \alpha\text{-Dextrin}$$

- **Digestion of fats**: Pancreatic lipase splits fats into fatty acids and monoglycerides.

  The other enzymes present are colipase, phospholipase, and bile salt-activated lipase.

$$\text{Fats} \xrightarrow{\text{Lipase}} \text{Fatty acids}$$

- **Neutralization of acidic food**: This is brought about by HCO_3^- secreted in pancreatic juice.

  Maintenance of alkaline pH is necessary for the activity of digestive enzymes.

SECRETIONS OF SMALL INTESTINE

The small intestine (SI) is the longest segment of the gastrointestinal tract. It extends from the pylorus to the ileocecal valve. It consists of duodenum, jejunum, and ileum.

INTESTINAL MUCOSA

The intestinal mucosa is spread over an area of 250 sq. m. This is due to

- valve-like folds of the intestinal mucosa called *valvulae conniventes*,
- finger-like projections called *villi*, and
- microvilli that project from the intestinal cells

VALVULAE CONNIVENTES

Valvulae conniventes are circular folds present throughout the length of the small intestine. They do not get obliterated when the intestine is distended.

They increase the surface area available for absorption and also slow down the passage of food through the intestine.

INTESTINAL VILLI (Fig. 6.20)

Intestinal villi are finger-like projections present in the mucus membrane of the small intestine.

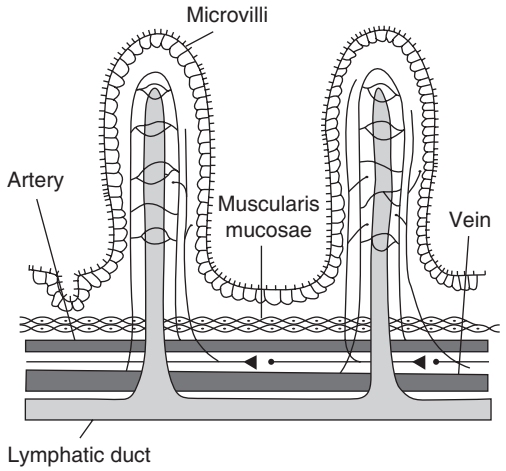


Figure 6.20 Intestinal villi.

Each villus is about 0.5–1 mm in length. There are an estimated 5 million villi distributed throughout the length of the intestine.

Each villus is covered by a single of layer of columnar cells called **enterocytes**. The core central part of a villus contains an arteriole, venule, and lymphatic vessel. The arteriole and venule are connected by the capillary plexus. It also has a fine network of nerves that connect to the intrinsic nerve plexus.

Large numbers of mucus-secreting cells termed **goblet cells** are present among the enterocytes.

MICROVILLI

Microvilli are present on the luminal surface of the enterocyte. Each enterocyte has around 1000 microvilli. They increase the surface area 30 times.

The combination of valvulae conniventes, villi, and microvilli increases the surface area about 600 times.

CRYPTS OF LIEBERKUHN

Crypts of Lieberkuhn are small pits located on the entire surface of the SI. These crypts are formed in between the intestinal villi. They are tubular glands formed by a single layer of epithelium. They also contain goblet cells, Paneth cells, and argentaffin cells.

The cells of crypts of Lieberkuhn are formed by active mitosis at the lower end. Later, they differentiate and migrate toward the tips of the villi from where they are shed off. This happens in about 5 days. Therefore, the epithelium of the intestine is constantly replaced. Thirty grams of protein is lost due to shedding of these intestinal cells.

Secretion of the small intestine is called **succus entericus**. It contains many enzymes required for digestion of carbohydrate, protein, and fat.

SUCCUS ENTERICUS

The total quantity of succus entericus is 1–2 L/day. Its specific gravity is 1.010 and pH ranges between 6.3 and 9.

Composition (Flowchart 6.5)

Intestinal secretion is mainly composed of water. Enzymes and ions which make up for the solid component are present in lesser quantity.

Mechanism of Secretion

The important components of succus entericus such as mucus, enzymes, and water are secreted by different mechanisms.

Secretion of Enzymes

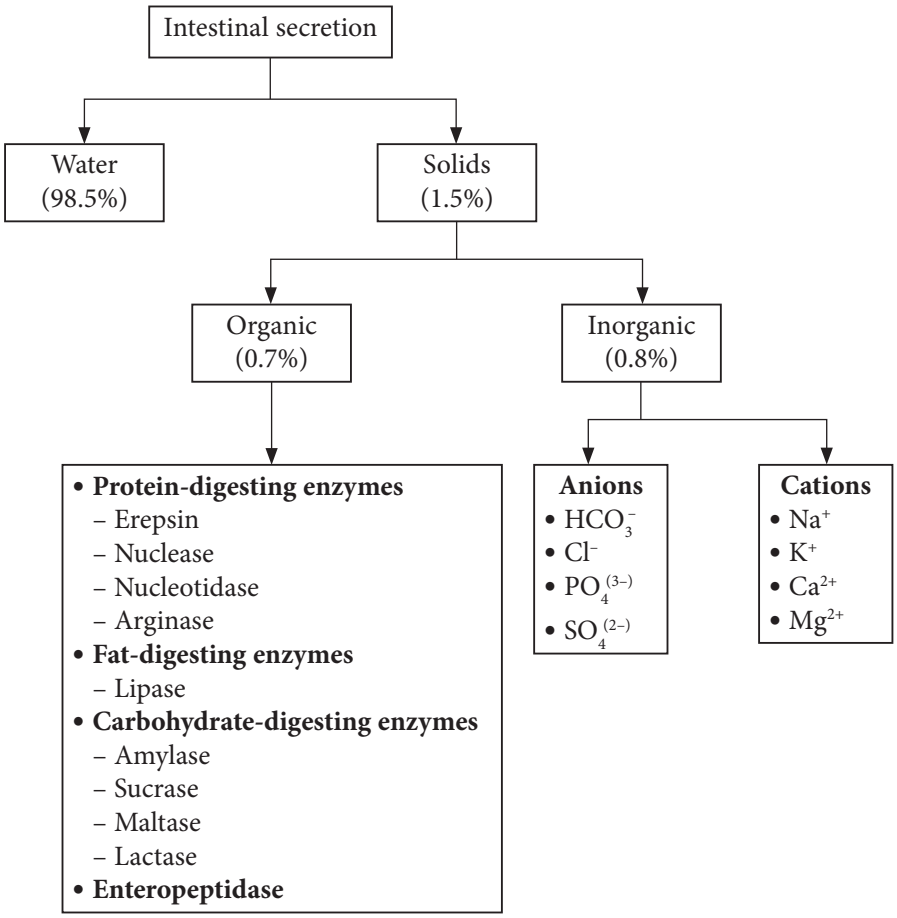
The epithelial cells of the villi contain a large quantity of digestive enzymes in their luminal surface. When the epithelium desquamates, these digestive enzymes are released into the intestinal secretion.

Secretion of Mucus

Mucus is produced by Brunner's glands located in the first few centimeters of the duodenum.

Mucus protects the duodenal wall from digestion by gastric juice.

Large amounts of mucus are secreted due to tactile stimulation of the mucosa, vagal



Flowchart 6.5 Composition of intestinal secretion. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

stimulation, and secretion of hormones such as secretin.

Secretion of Water

The enterocytes secrete large quantity of water and electrolytes along with the end products of digestion.

Secretion of watery fluid is due to

- active secretion of chloride ions into the crypts,
- active secretion of bicarbonate ions,
- chloride ions drag sodium ions through the membrane, and
- all these ions together cause osmotic movement of water.

Enzymes of the Small Intestine

The enzymes in the intestinal juice help in the conversion of a partially digested food particle to simpler chemicals suitable for absorption.

Peptidase splits small peptides into amino acids:

$$\text{Peptides} \longrightarrow \text{Amino acids.}$$

Sucrase, maltase, isomaltase, and lactase split disaccharides into monosaccharides:

$$\text{Disaccharides} \longrightarrow \text{Monosaccharides.}$$

Intestinal lipase splits neutral fats into glycerol and fatty acids:

$$\text{Fats} \longrightarrow \text{Glycerol} + \text{Fatty acid.}$$

Enzymes hydrolyze the food at the outer surface of the microvilli. The digested products are later absorbed through the intestinal mucosa into the blood.

REGULATION OF INTESTINAL SECRETION

- **Local stimulus**: It occurs through mechanical and chemical forms. Chyme in the intestine increases the secretion of intestinal juice by causing mechanical distension of the intestine as well as irritation caused by chemical substances present in the food.
- **Hormonal regulation**: Secretin and cholecystokinin increase the secretion.

SECRETIONS OF THE LARGE INTESTINE

Large intestinal secretion is not considered physiologically important as it does not help in digestion.

It is mainly concerned with absorption of water and electrolytes.

The mucosa of the large intestine has many crypts of Lieberkuhn which secrete fluid which is isotonic in nature.

There are no villi in the large intestinal mucosa.

The epithelial cells do not contain enzymes; instead, they have numerous goblet cells that secrete only mucus.

COMPOSITION

Large intestinal secretion mainly contains mucus. It contains large amounts of HCO_3^- and K^+. It also has small amounts of Na^+ and water.

REGULATION

Mucus secretion is regulated by the following:

- Direct tactile stimulation of mucus cells on the surface of the mucosa increases mucus secretion.
- Stimulation of local nervous reflexes to the mucus cells in the crypts of Lieberkuhn increases mucus secretion.
- Stimulation of pelvic nerves also causes marked increase in the secretion of mucus.

FUNCTIONS

Mucus in the large intestine

- protects its wall against excoriation,
- provides the adherent medium for holding fecal matter together, and
- protects the intestinal wall from bacterial activity.

GASTROINTESTINAL HORMONES

The gastrointestinal (GI) hormones are polypeptides secreted by glandular cells and nerve cells present in the mucosa. The cells secreting these hormones are called **enteroendocrine cells**. More than 15 cell types have been identified in the mucosa of stomach, small intestine, and colon.

The gastrointestinal (GI) hormones play a major role in the regulation of GI secretion and motility.

The GI hormones are classified into two groups:

1. **Gastrin family**: Gastrin and cholecystokinin
2. **Secretin family**: Secretin, glucagon, vasoactive intestinal polypeptide (VIP), and gastric inhibitory peptide (GIP)

The cells secreting these hormones are called **enteroendocrine cells**.

GASTRIN

Gastrin is produced by G cells present in the pyloric glands. These glands are present in the antral wall of the gastric mucosa. The cells are flask shaped with the apex projecting toward the lumen. The apical surface of G cells contains numerous microvilli.

It is found in the pancreatic islets in fetal life. Gastrin-secreting tumors, gastrinomas, occur in the pancreas.

Gastrin is a polypeptide hormone found in various forms. The physiologically important forms are G34, G17, and G14.

G17 is the principal form of hormone connected with the gastric acid secretion.

Gastrins are inactivated primarily in the kidney and small intestine.

Functions

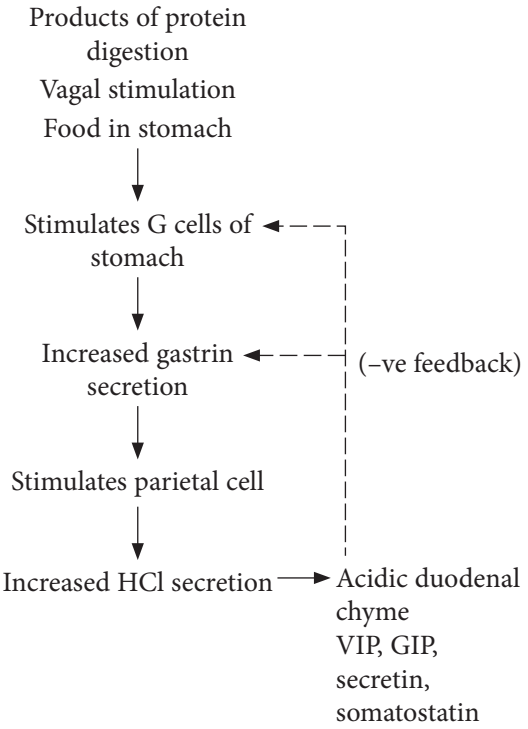
- Stimulates gastric acid and pepsin secretion
- Stimulates mucosal growth of stomach, small intestine, and large intestine
- Enhances gastric motility
- Stimulates insulin secretion after protein intake
- Causes contraction of the gastroesophageal sphincter

The chief function of gastrin is stimulation of HCl secretion. It binds to CCK receptors present on the parietal cells and opens Ca^{2+} channels to increase intracellular calcium. An increase in Ca^{2+} activates protein kinase which stimulates H^+–K^+ ATPase and promotes acid secretion.

Regulation of Gastrin Secretion

The products of protein digestion, vagal stimulation, acetylcholine, Ca^{++} ions, and bombesin stimulate gastrin secretion.

Increased acidity in stomach, somatostatin, VIP, GIP, secretin, and glucagon inhibit gastrin secretion.



CHOLECYSTOKININ PANCREOZYMIN (CCK-PZ)

This is a single hormone secreted by I cells of the upper small intestine. It is also present in the cerebral cortex, nerves of distal ileum, colon, and somatic nerves.

It is a polypeptide hormone found in various forms.

The half-life of circulating CCK is about 5 minutes.

Functions

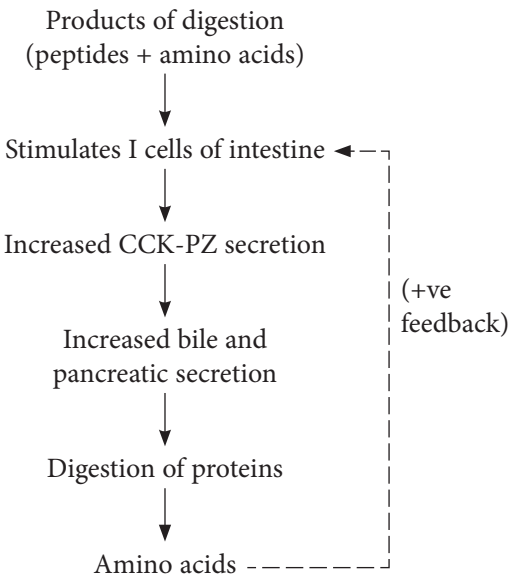
- Causes contraction of gallbladder and expulsion of bile
- Causes secretion of pancreatic juice rich in enzymes
- Increases the action of secretin in producing alkaline juice
- Inhibits gastric emptying
- Enhances the motility of the small intestine and colon

- Increases the secretion of enterokinase
- Stimulates the secretion of calcitonin and glucagon

In the brain, CCK-PZ may be involved in the regulation of food intake and is related to the production of anxiety and analgesia.

Regulation of CCK-PZ Secretion

CCK secretion is increased by contact of intestinal mucosa with the products of digestion, particularly peptides and amino acids. Its effect on pancreatic enzyme secretion is potentiated by secretin.



SECRETIN

Secretin was the first hormone to be discovered in 1902 by Bayliss and Starling. Starling coined the word *hormone*.

Secretin is produced by S cells located in the mucosa of the upper small intestine.

It is a polypeptide containing 27 amino acids.

The half-life of secretin is 5 minutes.

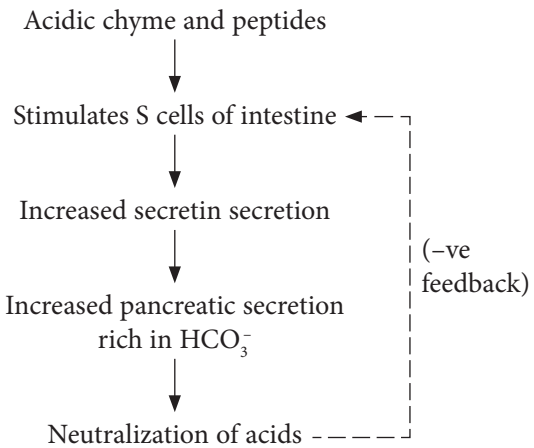
Functions

- Increases the secretion of bicarbonate by the duct cells of pancreas and biliary tract
- Causes secretion of a watery and alkaline pancreatic juice
- Potentiates the action of CCK to produce enzyme-rich pancreatic secretion
- Decreases gastric acid secretion and may cause contraction of the pyloric sphincter

Regulation

The products of protein digestion and acid bathing the mucosa of the upper small intestine increase the secretion of secretin.

The bile salts in the intestine also stimulate secretin production.



SOMATOSTATIN

Somatostatin is a growth hormone–inhibiting hormone, isolated originally from the hypothalamus. It is secreted into circulation by D cells in the pancreatic islets and by similar D cells in the gastrointestinal mucosa.

It exists in two forms: (i) somatostatin-14 and (ii) somatostatin-28.

Somatostatin inhibits the secretion of gastrin, VIP, GIP, secretin, and motilin.

It also inhibits the exocrine pancreas, gastric acid secretion, GI motility, contraction of gallbladder, and absorption of glucose, amino acids, and triglycerides.

Its secretion is stimulated by the acid in the lumen.

GASTRIC INHIBITORY POLYPEPTIDE

Gastric inhibitory polypeptide (GIP) is a polypeptide containing 42 amino acid residues. It is produced by K cells in the mucosa of duodenum and jejunum. Large quantities of GIP inhibit gastric motility and secretion. It stimulates insulin secretion. The presence of glucose and fat in the duodenum stimulates secretion of GIP.

VASOACTIVE INTESTINAL POLYPEPTIDE

Vasoactive intestinal polypeptide (VIP) contains 28 amino acid residues. It is secreted from cells all along the GIT but predominantly from the colon. It is found in the nerves of the GI tract. VIP is also found in blood.

- Stimulates intestinal secretion of electrolytes and water
- Relaxes the intestinal smooth muscle including sphincters
- Causes dilation of peripheral blood vessels
- Inhibits gastric acid secretion

GUANYLIN

Guanylin is a paracrine hormone secreted by the mucosa of the small intestine.

It is a polypeptide containing 15 amino acids. Guanylin functions as an agonist of guanylyl cyclase receptor. Binding of guanylin to the receptor increases the concentration of cGMP. This increases secretion of Cl^- into the intestinal lumen and reduces absorption of fluid. These changes can result in diarrhea.

GHRELIN

Ghrelin is secreted by the mucosal cells of the stomach.

It plays an important role in the control of food intake. It is called **hunger hormone** as it increases the desire to eat. It helps in food intake by increasing gastric motility and gastric acid secretion.

It stimulates growth hormone secretion. It has a role in learning, memory, sleep–wakefulness cycle, taste sensation, behavior, and carbohydrate metabolism.

MOTILIN

Motilin is a polypeptide containing 22 amino acids.

It is secreted by the enterochromaffin cells and Mo (M) cells in the GIT (duodenum and jejunum).

It produces contraction of smooth muscles of the stomach and small intestine in the interdigestive phase. It stimulates the secretion from the endocrine pancreas. Motilin increases the migrating motor complex, enhancing GI motility, and stimulates the production of pepsin. It increases peristalsis of the small intestine, clearing it to prepare for subsequent meal. High levels of motilin promote contraction of the fundus and antrum, accelerating gastric emptying. Motilin helps emptying the gallbladder and increases the release of pancreatic polypeptide and somatostatin.

GASTRIN-RELEASING PEPTIDE

Gastrin-releasing peptide (GRP) contains 27 amino acids.

It is a neuropeptide present in the vagal nerve endings that terminate on G cells.

It produces a vagally mediated increase in gastric secretion. It also regulates enteric motor function. GRP influences the circadian rhythm and mediates certain aspects of stress.

SUBSTANCE P

Substance P is found in the endocrine and nerve cells of the GIT. It increases the motility of the small intestine.

It is a neuropeptide functioning as neuromodulators and neurotransmitter. Substance P is found in brain and spinal cord having a strong association with perception of pain and the process of inflammation.

It is a potent vasodilator mediated through nitric oxide.

PEPTIDE YY (PEPTIDE TYROSINE TYROSINE)

Peptide YY contains 36 amino acids. Its release is stimulated by the presence of fat in the food.

It is released from cells in the ileum and colon. It is shown to reduce appetite.

It inhibits gastric and pancreatic secretion and motility. It increases nutrient absorption by improving the efficiency of digestion.

DIGESTION AND ABSORPTION

Digestion is the chemical breakdown of food by the enzymes of the GI tract. The food that we consume contains carbohydrates, fats, proteins, vitamins, and minerals. These substances cannot be absorbed in their natural form and therefore have to be broken down into smaller particles.

Digestion of foodstuff involves action of enzymes secreted at different levels in the GI tract. Various enzymes along with HCl and bile break down larger food substances into small absorbable particles. The absorption of broken-down products of all major food substances takes place in the small intestine. The substances pass from the intestinal lumen into the enterocyte. From the enterocyte, it enters the interstitial fluid from where it enters the blood.

DIGESTION OF CARBOHYDRATES

Diet contains carbohydrates in disaccharide (sucrose and lactose), polysaccharide (starch), and monosaccharide (glucose and fructose) forms. All the carbohydrates are ultimately converted into monosaccharides.

Diet also contains large amounts of cellulose. However, there are no enzymes in the human GI tract capable of hydrolyzing cellulose.

In the Mouth

Carbohydrate digestion starts in the mouth. The saliva contains an enzyme ptyalin (salivary amylase). This enzyme hydrolyzes starch into maltose and other glucose polymers. Since the food stays for a very short period in mouth, only 5% of the starch is hydrolyzed before the food is swallowed. The action of salivary amylase continues in the stomach.

In the Stomach

Acidic gastric juice inhibits the action of salivary amylase, but before this action, about 30–40% of the starch is hydrolyzed.

In the Small Intestine

Pancreatic secretion contains pancreatic amylase. This enzyme digests starch into maltose completely in 15–30 minutes after the chyme enters the duodenum. The enterocytes lining the villi of SI contain lactase, sucrase, maltase, and α-dextrinase. These enzymes split disaccharides into their constituent monosaccharides:

Lactose ⟶ Glucose + Galactose
Maltose ⟶ Glucose + Glucose
Sucrose ⟶ Fructose + Glucose

These final products of digestion are water soluble. They are immediately absorbed into portal circulation.

ABSORPTION OF CARBOHYDRATES

Carbohydrates are absorbed in the form of monosaccharides, especially glucose.

Transport of glucose is by cotransport with sodium. Sodium-dependent glucose transporter

(SGLT) is the cotransporter responsible for this transport. Glucose moves with sodium into the intestinal cell. Sodium is then transported to the lateral intercellular spaces. Glucose is transported by GLUT-2 into the interstitium and later into the capillaries.

Galactose is transported by a similar mechanism. Fructose is transported by facilitated diffusion through intestinal epithelium by GLUT-5 and GLUT-2.

CLINICAL NOTES

Lactose Intolerance

Lactose intolerance occurs in individuals who have lactase deficiency at the brush border of enterocytes. When such individuals consume milk and other dairy products, they exhibit lactose intolerance. They are unable to digest lactose completely. This condition is associated with diarrhea, abdominal bloating, and production of gas after consuming dairy products.

DIGESTION OF PROTEINS

Diet contains simple proteins such as albumin and complex proteins such as collagen and glycoproteins. These dietary proteins are long chains of amino acids connected by peptide linkages.

About 10–30 grams of proteins are added daily from GI secretions and exfoliated cells.

In the Stomach

Digestion of proteins begins in stomach. The pepsin secreted in the gastric juice is responsible for protein digestion. It is most active at a pH of 2–3.

Pepsin is produced as inactive pepsinogen. It is later activated to pepsin by HCl.

Ten to twenty percent of the protein digestion is by pepsin.

Pepsin hydrolyzes bonds between amino acids. Pepsin converts protein to proteoses, peptones, and a few amino acids.

In the Small Intestine

Majority of protein digestion occurs in SI. Pancreatic proteolytic enzymes such as trypsin, chymotrypsin, carboxypeptidase, and elastase help in the digestion of proteins.

Trypsin and chymotrypsin convert protein molecules to small polypeptides by breaking the internal peptide bonds. Therefore, they are called **endopeptidases**.

Carboxypeptidase cleaves individual amino acids from these polypeptides. They are called **exopeptidases**.

In the intestinal lumen, the peptidase present in the brush border of enterocytes splits larger polypeptides into tripeptides, dipeptides, and amino acids. These substances are transported through the microvilli into enterocyte.

Inside the enterocyte, dipeptides and tripeptides are broken down to amino acids. These amino acids are later absorbed into the bloodstream.

Therefore, digestion of proteins occurs at three places: (i) in the lumen of the small intestine, (ii) along the brush border of enterocyte, and (iii) inside the enterocyte.

Nucleic acids are broken down into nucleotides by pancreatic nucleases. The nucleotides are split into nucleosides and phosphoric acid. The nucleosides are broken down into nitrogenous bases and sugar. The bases are absorbed by active transport.

ABSORPTION OF PROTEINS

Proteins are absorbed in the intestine as dipeptides, tripeptides, and amino acids.

Amino acids and peptides are transported by seven different types of transport systems. Five of these systems require Na^+ ions. Transport of amino acids is by cotransport with Na^+. In two systems, transport is independent of Na^+.

The dipeptides and tripeptides are transported into the enterocytes by peptide transporter 1. This system requires H^+ instead of Na^+.

Absorption of amino acids occurs predominantly in the duodenum and jejunum. Very little is absorbed in the ileum. These amino acids are later transported into the blood by facilitated diffusion.

In infants, proteins which are intact can be absorbed from the intestine by endocytosis. IgA is absorbed in this way providing immunity to the infant.

In adults, the absorption of intact proteins occurs only in small quantities. This mechanism is responsible for the development of allergy to certain foods.

CLINICAL NOTES

Hartnup Disease

Hartnup disease is a congenital defect (autosomal recessive metabolic disorder) in the transport of neutral amino acids like tryptophan in the intestine and renal tubules.

Cystinuria

Cystinuria is a congenital defect in the transport of basic amino acids in the intestine and renal tubules. In this condition, the amino acid cystine appears in urine.

DIGESTION OF FATS

In the Mouth

A small quantity of lingual lipase is secreted in the mouth. The amount of fat digested by this enzyme is very small (<10%). Majority of fat digestion takes place in the intestine.

In the Small Intestine

The first step in the digestion of fats is breakdown of fat globules into smaller particles. This process is termed **emulsification**. It is partly achieved by movements of the stomach and by bile in the duodenum. Bile salts and lecithin are extremely important in emulsification of fat.

Pancreatic lipase present in the pancreatic juice splits triglycerides into free fatty acids and monoglycerides. Enteric lipase present in the enterocytes also helps in the digestion of triglycerides.

Accumulation of monoglycerides and free fatty acids causes interaction of bile salts to form micelles.

Micelles are small, spherical globules 3–6 nm in diameter containing 20–40 bile salt molecules. Micelles transport monoglycerides and free fatty acids to the brush border of intestinal epithelium for absorption.

ABSORPTION OF FATS

Fats are absorbed in the form of free fatty acids and monoglycerides. Transport of fatty acids and monoglycerides in SI occurs by diffusion across the membrane of microvilli into the intestinal cell. From the intestinal cell, small fatty acids directly enter the portal blood and larger fatty acids are re-esterified to triglycerides. Triglycerides are coated with protein, cholesterol, and phospholipids to form chylomicrons. These chylomicrons leave the enterocyte and enter the lymphatics.

CLINICAL NOTES

Steatorrhea

Steatorrhea is a condition characterized by excretion of fatty, bulky, clay-colored stools. It is caused due to deficiency of pancreatic lipase. This leads to impairment of digestion and absorption of fat. Hypersecretion of gastric acid can cause steatorrhea. It can also be caused due to defective reabsorption of bile salts in the distal ileum.

ABSORPTION OF WATER

Every day, about 9 L of water is presented to the gut. Ninety-eight percent of the water is reabsorbed and only about 200 mL passes out of the gut in the stools.

Absorption of water starts from the stomach. Maximum water is absorbed from the small intestine. The large intestine also absorbs significant quantity of water.

ABSORPTION OF ELECTROLYTES

Sodium is absorbed from the lumen through diffusion and active transport. Chloride enters the enterocytes by diffusion. Chloride is secreted into the lumen of intestine.

HCO_3^- is absorbed indirectly. It is secreted into the intestine in exchange for chloride ions. Calcium ions are actively absorbed from the duodenum.

ABSORPTION OF VITAMINS

Water-soluble vitamins are rapidly absorbed from the intestinal lumen by simple diffusion. However, the absorption of vitamin B_{12} is little complex.

Vitamin B_{12} binds with the intrinsic factor in the small intestine and forms a complex. This complex is recognized by specific receptors present in the brush border of intestinal cells and absorbed by endocytosis.

Vitamins A, D, E, and K are the fat-soluble vitamins. Absorption of fat-soluble vitamins occurs in the upper part of the small intestine. It depends on fat absorption which in turn depends on normal bile and pancreatic secretion.

REVIEW QUESTIONS

Long Essay

1. Describe the phases and control of deglutition. Add a note on its applied importance
2. What is the composition of saliva? What are its functions?
3. Describe the phases of gastric secretion. Give suitable experimental evidences to prove it.
4. Describe the phases of pancreatic secretion.

Short Essay

1. Name the phases of deglutition. Explain any one of them.
2. Describe the gastrointestinal reflexes.
3. Explain the movements of stomach.
4. Describe the factors regulating gastric emptying.
5. Explain the movements of small intestine.
6. Describe briefly the defecation reflex.
7. Explain the mechanism of salivary secretion.
8. Describe the functions of saliva.
9. Explain the composition and functions of gastric juice.
10. Explain the gastric function tests.
11. Explain the mechanism of secretion of HCl in the stomach.
12. What is the normal gastric emptying time? Explain the factors that alter it.
13. What is jaundice? What are its types?
14. Give the composition and functions of pancreatic juice.
15. Explain liver function tests.
16. Give the composition and function of succus entericus.
17. Explain the chemistry, action, and regulation of secretion of gastrin.
18. Explain the chemistry, action, and regulation of secretion of secretin.
19. Describe the digestion and absorption of carbohydrates.
20. Describe the digestion and absorption of fats.
21. Describe the digestion and absorption of proteins.

Short Answer

1. Migrating motor complex
2. Chewing reflex
3. Deglutition center
4. Achalasia cardia
5. What is antiperistalsis?
6. What is Pavlov's pouch? What is its importance?
7. What is sham feeding?
8. Explain the movements of the large intestine.
9. Name any four gastrointestinal hormones.
10. List four important functions of saliva.
11. List four functions of stomach.
12. Give the composition of gastric juice.
13. Name the different cell types of gastric mucosa. Mention their functions.
14. Enumerate the functions of HCl present in gastric juice.
15. What is Heidenhain's pouch? What is its importance?
16. What is achlorhydria? What is its effect?
17. List any four functions of bile.
18. List four functions of liver.
19. What is enterohepatic circulation?
20. Name the bile salts and bile pigments.
21. Physiological jaundice
22. Explain the functions of colon.
23. Lactose intolerance
24. Steatorrhea

CHAPTER

7 Excretory System

Outline

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Formation of Urine 261
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Specific Learning Objectives

After studying this chapter, you should be able to:

- Discuss the functional anatomy of the kidney.
- Explain the types, structure and functions of nephron.
- Describe the features of renal circulation.
- Discuss the theories of autoregulation.
- Explain the structure and functions of juxtaglomerular apparatus.
- Describe the factors influencing glomerular filtration.
- Explain the renal function tests.
- Discuss the process of tubular reabsorption.
- Describe the process of tubular secretion.
- Discuss the normal and abnormal constituents of urine.
- Explain the counter-current mechanism in the formation of urine.
- Describe the innervation of bladder and micturition reflex.
- Successfully answer the questions and MCQs at the end of this chapter.

The metabolic activities of the body result in the formation of waste products. These are excreted through the kidneys, lungs, skin, and digestive tract.

The kidney removes unwanted substances and retains physiologically useful substances in the body. It eliminates the end products of metabolism, which are not useful to the body such as urea, uric acid, creatinine, metabolites of hormones, and drugs.

The consumption of water and electrolytes is greater than the quantity required by the body. The kidneys excrete this excess intake. Thus, they maintain fluid and electrolyte balance. They have a major role in the maintenance of acid–base balance.

The kidneys are essential for life. There are two kidneys present retroperitoneally in the posterior part of the abdominal cavity, one on either side of the vertebral column.

They extend from T12 to L3 vertebra. The right kidney is relatively lower than the left kidney as it is pushed by the liver. Kidneys are protected by the lower part of the rib cage.

STRUCTURE OF KIDNEY

Each kidney weighs about 150 grams. The kidneys are bean shaped (**Fig. 7.1**). The medial side of each kidney is indented and is called the **hilum**. Blood vessels, nerves, and ureter enter or leave the kidney through the hilum. The kidney is covered by renal capsule, adipose capsule, and renal fascia.

The renal capsule made up of fibrous tissue prevents the spread of infection.

The adipose capsule anchors the kidney and provides cushioning effect.

Adrenal or suprarenal glands are present over the upper pole of the kidney.

A cut section of the kidney shows the outer cortex and the inner medulla. The medulla has a number of cone-shaped structures called **renal pyramids**. The apex of the pyramid is directed toward the central portion of the kidney.

The central portion of the kidney is called the **pelvis**. The pelvis has branching extension termed **major and minor calyces**.

The pelvis narrows down to continue as a tube-like structure called the **ureter**. The ureter leaves the kidney from the medial side and continues as a tube to open into the urinary bladder. Urine is temporarily stored in the urinary bladder till it is emptied by the process of micturition.

The urinary bladder communicates with the exterior through the **urethra**.

NERVE SUPPLY TO THE KIDNEY

The kidney is supplied by the sympathetic fibers from T11 to L1 segments of the spinal cord through the celiac ganglion. The parasympathetic nerve supply is through the vagus nerve. The pain-mediating fibers pass through the sympathetic trunk. The sympathetic stimulation causes vasoconstriction and secretion of renin; it enhances the reabsorption of water and sodium ions.

FUNCTIONS OF THE KIDNEY

The kidney helps to maintain a stable internal environment by performing the functions given next.

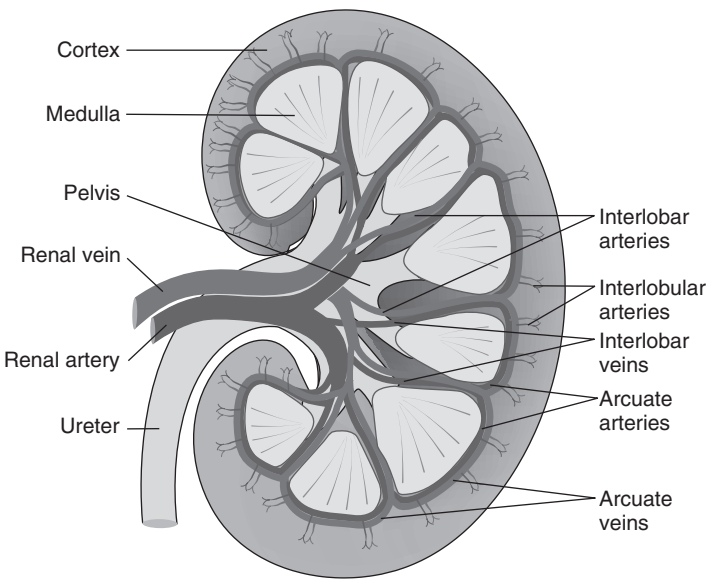


Figure 7.1 Section of kidney. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Excretory Functions

The excretory functions of the kidney are

- formation of urine,
- metabolism and excretion of hormones,
- excretion of waste products of metabolism,
- maintenance of water and electrolyte balance,
- maintenance of composition of body fluids, and
- regulation of osmolality of body fluids and electrolyte concentration.

Non-Excretory Functions

The nonexcretory functions of the kidney are

- regulation of acid–base balance,
- regulation of blood pressure,
- secretion of renin and erythropoietin,
- formation of the active form of vitamin D, and
- secretion of prostaglandins.

Water and Electrolyte Balance

Precise regulation of water and electrolyte balance is necessary for the maintenance of homeostasis. Consumption of water and electrolytes is governed by the eating and drinking behavior of the individual. The kidneys will adjust their excretory function to maintain the fluid and electrolytes within a narrow range of fluctuation. The phenomenal ability of the kidney to adjust its excretory function can be illustrated by taking the example of sodium.

A 10-fold increase in sodium intake causes retention of sodium and water for a few days. An increase in extracellular fluid volume stimulates hormonal changes and other compensatory mechanisms. There is increased excretion of sodium and water to restore the balance.

CLINICAL NOTES

Pyelonephritis

Infection of the renal pelvis and calyces produces a condition termed **pyelitis**. Infection and inflammation of the entire kidney is called **pyelonephritis**.

Clinical features include fever, burning micturition, frequent urination, and abdominal pain. These are treated by administering antibiotics based on culture and sensitivity reports.

Hydronephrosis

Hydronephrosis is swelling of the kidney due to the retention of urine in the kidney and part of the ureter. It is due to obstruction of the ureter by renal calculi or obstruction to the urethra preventing evacuation of the bladder (prostatic hypertrophy).

Treatment is aimed at removing the obstruction by addressing the cause for it.

NEPHRON

Nephron is the functional unit of the kidney (**Fig. 7.2**). There are about 1 million nephrons in each kidney. About 80–85% of the nephrons are located in the cortex, and they are called **cortical nephrons**.

The remaining 15% are located more toward the medulla and are designated as **juxtamedullary nephrons**.

Blood flow to the nephron is through the afferent arteriole that opens into the glomerular capillary bed. Blood from the glomerular capillary drains into the efferent arteriole. The efferent arterioles redivide to form the peritubular capillary or vasa recta.

CORTICAL NEPHRON (Fig. 7.3)

The cortical nephrons are superficial nephrons having a short loop of Henle reaching only to the outer medullary zone. The loop of Henle is surrounded by the **peritubular capillaries**.

JUXTAMEDULLARY NEPHRON (Fig. 7.3)

The juxtamedullary nephrons are present in the medullary portion of the kidney. They have a long loop of Henle surrounded by **vasa recta**. Renal blood flow and glomerular filtration

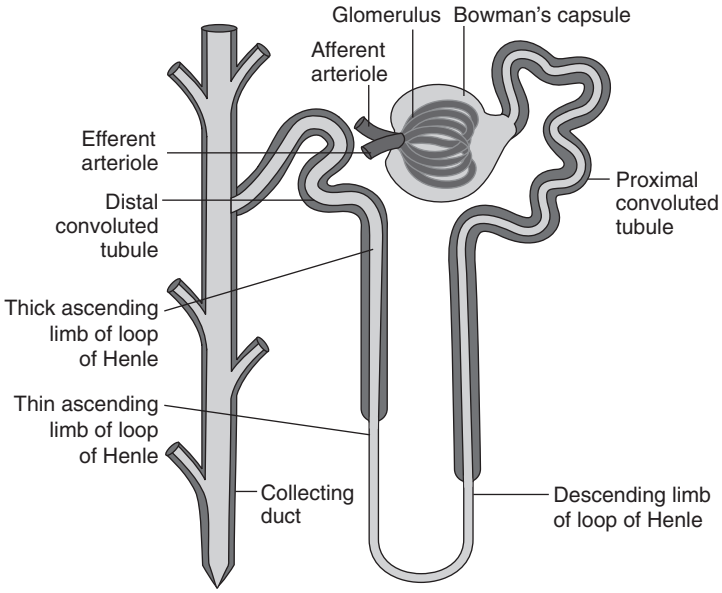


Figure 7.2 Structure of nephron. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

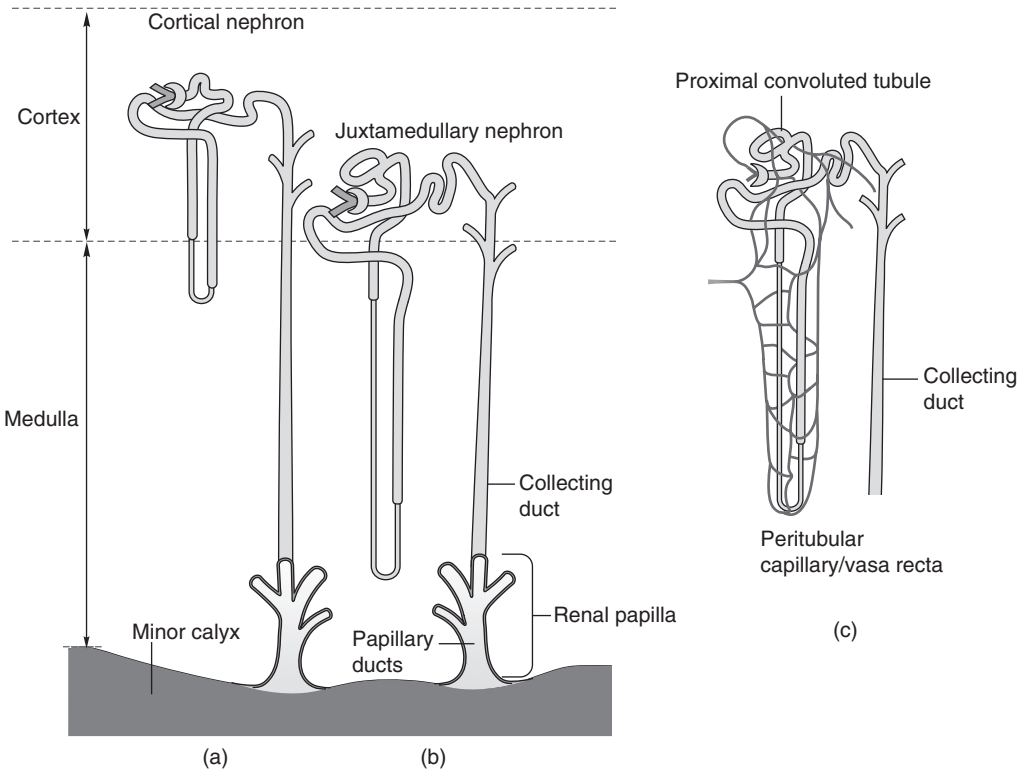


Figure 7.3 Types of nephrons. (a) Cortical, (b) juxtamedullary, and (c) nephron with a capillary network. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Table 7.1 Comparison Between Cortical and Juxtamedullary Nephrons

Cortical Nephrons	Juxtamedullary Nephrons
80–85% of total nephrons, present in cortex	15–20% of total nephrons, present in medulla
Have rich sympathetic innervation	Have poor sympathetic innervation
Have a short loop of Henle, extending into the outer renal medulla	Have a long loop of Henle, extending into deeper parts of the renal medulla
Glomeruli are present in the outer renal cortex	Glomeruli are present in the corticomedullary junction
Glomeruli are small	Glomeruli are large
Diameter of afferent arteriole is larger than efferent arteriole	Diameter of afferent and efferent arterioles is equal
Have a low glomerular filtration rate	Have a high glomerular filtration rate
Surrounded by a peritubular capillary network	Surrounded by vasa recta
Help in the formation of urine and perform excretory and regulatory functions	Help in concentrating or diluting urine

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

rate are greater in these nephrons. They have a greater capacity to absorb water and salt than the cortical nephrons. The juxtamedullary nephrons play a major role in concentrating the urine. The differences between cortical and juxtamedullary nephrons are summarized in Table 7.1.

PARTS OF NEPHRON

Malphighian Corpuscle

The Malphighian corpuscle is a flattened, spheroidal structure consisting of **glomerulus** and **Bowman's capsule**. It helps in filtration, which is the first step in the formation of urine. The Malphighian corpuscle is also called renal corpuscle.

Glomerulus

The glomerulus is formed by a tuft of capillaries arising from the afferent arteriole. The glomerular capillaries join to form the efferent arteriole.

Filtrate is formed from the blood passing through the glomerular capillaries with the help of the **filtration membrane**.

Bowman's Capsule

Bowman's capsule is the blind end of the nephron, which is funnel shaped. It encloses the glomerulus. It has an inner visceral layer covering the glomerulus and an outer parietal layer.

The parietal layer is made up of simple squamous epithelial cells.

The inner visceral layer covering the glomerulus has highly modified, branching epithelial cells called **podocytes**. Podocytes terminate in foot processes.

The foot processes (pedicels) of the podocytes are in contact with the other surface of the basement membrane.

The **slit pores** or **filtration slits** present between the foot processes of podocytes provide passage for the flow of plasma into Bowman's space.

Proximal Convoluted Tubule

The proximal convoluted tubule (PCT) is the continuation of Bowman's capsule measuring about 15 mm.

It is made up of a proximal convoluted portion called **pars convoluta** and a straight part called **pars recta**. The pars recta form the first part of the descending limb of the loop of Henle. The PCT is lined by a single layer of epithelial cells that are columnar in pars convoluta and cuboidal in pars recta.

The luminal surfaces of the lining cells have microvilli that give it a brush-border appearance.

The microvilli increase the surface area of the cells. The cytoplasm of the cells is granular and the nucleus is situated toward the base.

Functionally useful substances are absorbed from this part of the nephron.

Loop of Henle

The loop of Henle is a continuation of the PCT. It is short in cortical nephrons and long in juxtamedullary nephrons.

The loop of Henle has the following parts:

- Descending loop
- Hair pin bend
- Ascending loop

The descending loop is thin walled and permeable to water. It is the continuation of pars recta of the PCT. The thin descending limb of the loop of Henle after a variable length turns back to form the thin ascending limb. The thin descending and short ascending loops are lined by the squamous epithelium.

The thick ascending loop is the continuation of the thin ascending loop of Henle. The thick ascending loop is thick walled and impermeable to water. It ends at the macula densa. It is lined by columnar epithelium with few microvilli without a brush border. The nucleus is closer to the lumen and the cell contains numerous mitochondria.

Distal Convoluted Tubule

Distal convoluted tubule (DCT) is the distal coiled part of the nephron measuring about 5 mm. It is lined by cuboidal cells. The cells lining the DCT resemble the cells of the thick ascending limb with few microvilli and mitochondria.

Collecting Duct

The DCT continues as the collecting duct. The DCT and the collecting duct are made up of P cells (principal cells) and I cells (intercalated cells). These cells contain an enzyme called carbonic anhydrase. In addition, the collecting duct has simple columnar cells. The collecting ducts receive the filtrate from the DCT and open into the renal pelvis. Two hormones, namely, ADH and aldosterone, act on this part of the nephron.

Renal Medullary Interstitial Cells (RMIC)

These cells resemble fibroblasts. They are an important site for the production of cyclooxygenase 2 (COX 2) and prostaglandin synthase. PGE2 produced by the kidney regulates salt and water balance.

RENAL CIRCULATION

Blood supply to the kidney is from the renal artery, a branch of the abdominal aorta (**Fig. 7.4**). The normal renal blood flow is 1100–1200 mL/min. Renal arteries arise at right angles from the abdominal aorta. The renal artery divides into segmental arteries.

The segmental artery divides into several interlobar arteries which further divide into arcuate, interlobular arteries. Afferent arterioles are formed from interlobular arteries. Branching of afferent arteriole forms glomerular capillaries. This is the first capillary bed.

Glomerular capillaries fuse to form an efferent arteriole. These efferent arterioles branch again to form the second bed of capillaries surrounding the nephron.

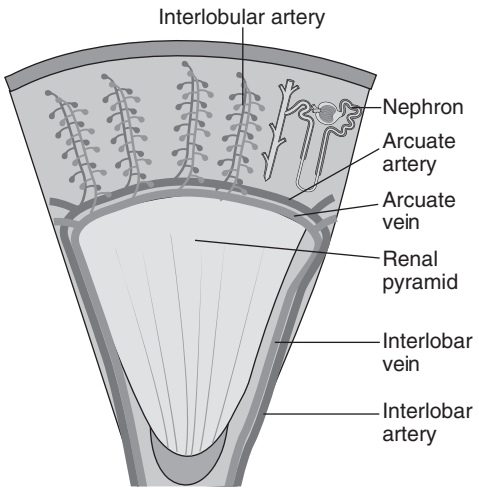
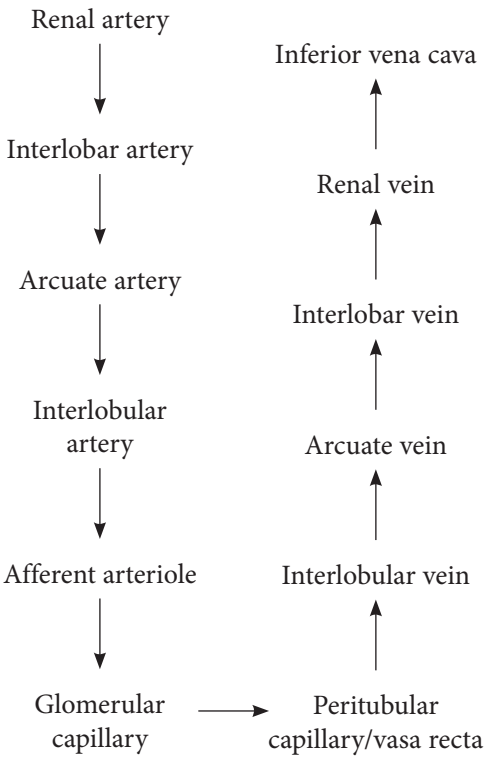


Figure 7.4 Renal circulation. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

These capillaries around the cortical nephron are called **peritubular capillaries** and those around the juxtamedullary nephrons are termed **vasa recta**.

The second bed of capillaries fuses to form the interlobular vein. Veins follow the path of the arteries to finally drain into inferior vena cava.



SPECIAL FEATURES OF RENAL CIRCULATION

- The kidneys receive a large quantity of blood in relation to their size. They receive more than 25% of the cardiac output.
- The renal artery arises as a direct branch of the aorta. Hence, it is a high-pressure system.
- The renal blood vessels form a portal system. They have two capillary networks.
- The kidneys have a system of autoregulation.
- The glomerular capillaries are a high-pressure bed, and peritubular capillaries form a low-pressure bed.

MEASUREMENT OF RENAL BLOOD FLOW

Renal plasma flow (RPF) is measured by the PAH (para-amino hippuric acid) clearance test. Renal blood flow is calculated using renal plasma flow and hematocrit value.

$$\text{Renal blood flow} = \text{RPF} \times \frac{100}{100 - \text{Hematocrit}}.$$

Regulation of Blood Flow

The nerves supplying the renal blood vessels do not significantly influence the blood supply to the kidneys. The sympathetic vasoconstrictor activity is minimal at rest. However, it increases with change of posture, pain, emotion, and exercise. Hence, the renal blood flow decreases.

The reduction of renal blood flow with erect posture and exercise is exaggerated in patients with cardiac failure.

Severe reduction of arterial blood pressure as in shock depresses the renal blood flow; this may precipitate renal failure.

Chronic diseases that destroy the nephrons also reduce the renal blood flow.

The kidney maintains its own blood supply by the mechanism of autoregulation.

AUTOREGULATION

Autoregulation is the ability of the kidney to maintain a constant flow of blood despite a variation in the systemic arterial blood pressure from 60 to 160 mm Hg. It occurs in denervated and isolated kidneys. Vital organs such as the brain and heart also have autoregulation.

Theories

Myogenic Theory

Myogenic theory is based on the intrinsic contractile response of the smooth muscle to stretch. The smooth muscles contract in response to increase of tension on the walls of

the blood vessel. An increase in blood pressure enhances the flow of blood to an organ.

Sudden rush of blood into a segment of blood vessel causes it to stretch. The stretching of the smooth muscle in the wall of the blood vessel results in its reflex contraction. Contraction of the muscle produces vasoconstriction and hence reductions in the blood flow to the organ. Vasoconstriction increases resistance to the flow of blood.

The fall in blood pressure reduces the flow of blood into the blood vessel. Lack of stretching relaxes the smooth muscle in the wall of the blood vessel. The blood vessel dilates, reducing resistance to the flow of blood. The blood flow improves through that blood vessel.

Interstitial Tissue Pressure Theory

This theory states that increased blood pressure will cause an increase in the flow of blood. As a result, more fluid comes out of the blood vessel and accumulates in the area surrounding the blood vessel. A progressive increase in the volume of accumulated fluid will exert pressure on the blood vessel making it narrow. This mechanical obstruction to the flow of blood will regulate the entry of blood to the organ.

Metabolite Theory

According to this theory, reduced blood flow to a vital organ due to decreased arterial pressure results in hypercapnia associated with hypoxia; this will lead to accumulation of metabolic end products locally.

These end products of metabolism such as lactic acid and pyruvic acid will produce local vasodilation and restore the flow of blood.

Conversely, an increase in blood flow washes away the accumulated metabolites. The blood vessels constrict, restricting the flow of blood through the blood vessel.

Cell Separation Theory

When blood is flowing through the blood vessels, the blood cells are arranged centrally and plasma is arranged in the periphery surrounding the blood cells. If the branch arises perpendicular to the main artery, the fluid portion of the blood separates out easily and flows into the branch leaving behind the cellular portion in the main artery.

An increase in cellular component associated with a reduction in fluid portion will increase the viscosity of blood. This delays further entry of blood into that segment of the vessel.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus (JGA; **Fig. 7.5**) is a specialized structure with vascular and tubular components. The ascending limb of the loop of Henle (beginning of DCT) passes close to its own glomerulus and comes in contact with the afferent and efferent arterioles. The modified cells of the afferent arteriole and the DCT along with the interstitial cells form the **juxtaglomerular apparatus**.

The JGA consists of

- macula densa,
- juxtaglomerular cells, and
- interstitial cells of Lacis.

MACULA DENSA

Macula densa are the modified cells of the DCT present close to the afferent arteriole. The cells of the tubule become narrower and taller. The cells of macula densa send cytoplasmic projections to the juxtaglomerular cells. The cells of macula densa contain a number of secretory granules which sense ionic changes in the filtrate.

Macula densa responds to changes in the concentration of sodium ions in the DCT through tubuloglomerular feedback. The elevated level of sodium reduces GFR by causing the constriction of the afferent arteriole.

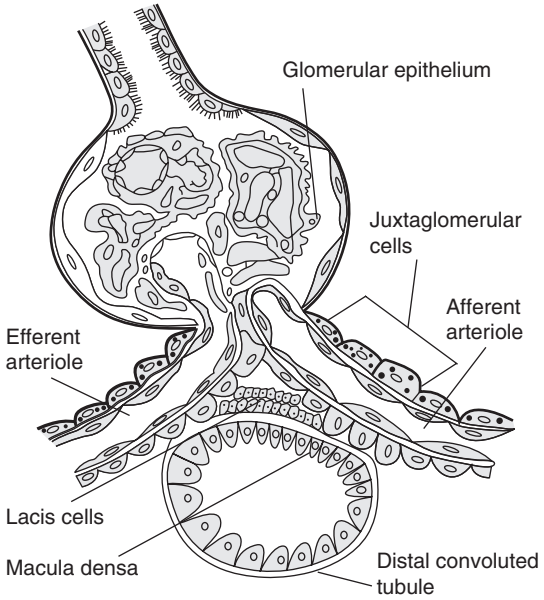


Figure 7.5 Juxtaglomerular apparatus.

Macula densa stimulates the production of nitric oxide and prostaglandins in response to decreased sodium ion concentration. This results in dilatation of afferent arterioles and release of renin.

JUXTAGLOMERULAR CELLS

The cells of tunica media of the afferent arteriole undergo modification to form the juxtaglomerular cells. The cells thicken containing a large number of granules.

The granules are made up of precursors of renin. The juxtaglomerular cells secrete renin.

JG cells are capable of sensing changes in blood pressure in the afferent arteriole.

INTERSTITIAL LACIS CELLS (MESANGIAL CELLS)

The Lacis cells are present in the region between the afferent and the efferent arterioles; these cells are in contact with the macula densa and the juxtaglomerular cells. They resemble the glomerular mesangial cells. Few of the cells contain granules and secrete renin.

JGA is richly supplied by sympathetic nerve fibers.

FUNCTIONS OF THE JUXTAGLOMERULAR APPARATUS

- The JGA secretes renin in response to a drop in blood pressure and thus helps to regulate the blood pressure. The juxtaglomerular cells produce a glycoprotein hormone renin.
- Renin is a proteolytic enzyme that acts on the renin substrate present in the plasma (angiotensinogen). It converts angiotensinogen to a decapeptide angiotensin I. Angiotensin I gets converted to angiotensin II in lungs by angiotensin converting enzyme (ACE). Angiotensin II is a vasoconstrictor. It also stimulates the release of aldosterone.
- The juxtaglomerular cells detect changes in the blood volume from the degree of stretch of the walls of the afferent arteriole.
- The macula densa detects changes in the ionic concentration of the filtrate.
- The JGA controls glomerular blood flow and glomerular filtration rate.

FORMATION OF URINE

About 1.5–2 L of urine is formed per day by both the kidneys. Approximately 180 L of filtrate is formed per day. Almost 99% of the filtrate is reabsorbed as it passes through the nephron.

Urine is formed by the processes of

- glomerular filtration (ultrafiltration),
- tubular reabsorption, and
- tubular secretion.

GLOMERULAR FILTRATION

Glomerular filtration is a passive process of formation of protein-free filtrate containing water and solutes.

Filtration takes place in the glomerulus and Bowman's capsule. It is influenced by various forces acting in opposite directions.

- **Hydrostatic pressure** is the pressure exerted by fluid on the walls of the blood vessel. It depends on the systemic arterial blood pressure and helps to push fluid out of the glomerular capillaries.
- The outward movement of the fluid is opposed by **colloidal osmotic pressure** exerted by the plasma proteins. The colloidal osmotic pressure retains the fluid within the blood vessel. It is the force that draws fluid due to the presence of plasma protein, especially albumin and colloids.
- **Bowman's capsular pressure** resists the movement of fluid from the blood vessel to the exterior.

In a normal individual, the hydrostatic pressure is about 45 mm Hg, colloidal osmotic pressure is 25 mm Hg, and Bowman's capsular pressure is 10 mm Hg.

As the hydrostatic pressure is more than the other two pressures combined, fluid is pushed out of the blood vessel with an effective filtration pressure of 10 mm Hg (Fig. 7.6).

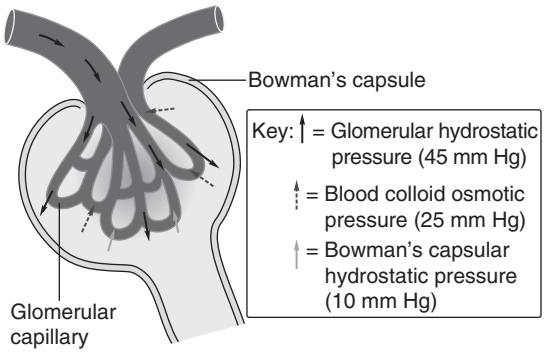


Figure 7.6 Forces influencing glomerular filtration. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Effective Filtration Pressure

= Hydrostatic pressure — (Colloidal osmotic pressure + Bowman's capsular pressure)

= 45 – (25 + 10) = 10 mm Hg.

During the process of filtration, a protein-free filtrate is formed in the PCT. Hence, it is termed **ultrafiltration**. Filtration occurs through the filtration membrane.

Filtration Membrane

The filtration membrane (**Fig. 7.7**) is made up of

- endothelium of the glomerular capillary,
- basement membrane of the capillary endothelium,
- interstitial layer,
- epithelial lining of Bowman's capsule, and
- basement membrane of the epithelial lining.

These structures form a barrier for the process of filtration.

The glomerular capillaries form the first capillary bed. The endothelial lining of the capillary is porous containing numerous openings termed **fenestrae**. The lining has negative charge. Though the membrane is porous, the passage of plasma protein is restricted by the presence of negative charge. It allows solute-rich, protein-free filtrate to pass from blood to the glomerular capsule.

The basement membrane is composed of loose, fibrillar glycoprotein and collagen fibers with negative charge.

It has large spaces through which the water and solutes can easily pass. Strong negative charges associated with proteoglycans prevent the passage of proteins through them.

The epithelial cells of Bowman's capsule are called **podocytes**. Podocytes terminate in foot processes. The **slit pores** or **filtration slits**, present between the foot processes of podocytes, provide passage for the flow of plasma into Bowman's space.

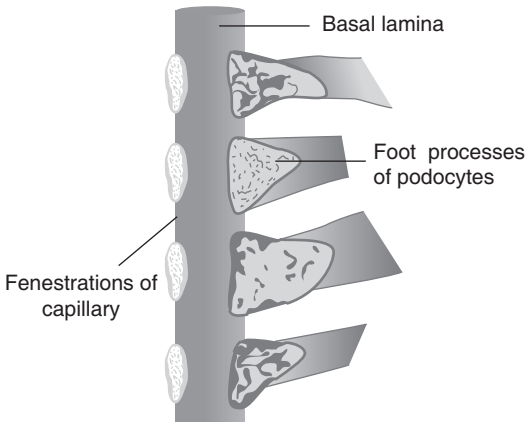


Figure 7.7 Filtration membrane.

Glomerular Filtration Rate

The glomerular filtration rate (GFR) is the rate at which filtrate is formed in all the nephrons in a minute.

GFR is 125 mL/min and amounts to 180 L/ day. It is estimated by inulin clearance.

Factors Influencing Glomerular Filtration

- **Capillary hydrostatic pressure**: Filtration is favored by the capillary hydrostatic pressure. An increase in the capillary hydrostatic pressure enhances the effective filtration pressure and hence the filtration.

  Constriction of the afferent arteriole reduces glomerular filtration.

  A marked decrease in blood pressure as in hemorrhage or shock reduces glomerular filtration.
- **Colloidal osmotic pressure**: It is the pressure exerted by plasma proteins and colloids in the blood. Effective filtration at the glomerulus is opposed by colloidal osmotic pressure.

  An increase in the colloidal osmotic pressure in the afferent arteriole or glomerulus decreases GFR.

  Dilution of blood or hypoproteinemia reduces colloidal osmotic pressure. There is an increase in effective filtration pressure and GFR.
- **Bowman's capsular pressure**: It is the hydrostatic pressure exerted by the fluid present in Bowman's space. This will also oppose filtration of fluid at the glomerulus.

  An increase in the Bowman's capsular pressure as seen in an obstruction to the urinary tract by renal calculi reduces GFR.
- **Thickness of the filtration membrane**: The rate of filtration varies inversely to the thickness of the filtration membrane. The greater the thickness of the membrane, the lesser the filtration.
- **Surface area of the filtration membrane**: The rate of filtration depends on the surface area of the membrane. An increase in the surface area enhances the filtration. A reduction in the size of the glomerular capillary bed due to renal diseases or partial nephrectomy reduces glomerular filtration.
- **Size of the afferent and efferent arterioles**: The relative sizes of the afferent and efferent arterioles determine the glomerular capillary hydrostatic pressure. Normally, the efferent arteriole is narrower and longer as compared to the afferent arteriole. This anatomical character offers greater resistance to outward flow of blood from the glomerular capillaries. Hence, the hydrostatic pressure generated at the glomerular capillary is increased.

  Constriction of the efferent arteriole associated with dilation of the afferent arteriole can further enhance the glomerular capillary hydrostatic pressure and hence GFR.
  - **Size of solute:** Electrolytes like sodium and organic substances such as glucose are freely filtered. The rate of filtration decreases as the size of the molecule increases. Thus, filtration is inversely proportional to the size of the molecule.
- **Sympathetic stimulation**: Mild-to-moderate stimulation of the sympathetic nervous system has little influence on renal blood flow and hence GFR. However, a strong stimulation of the sympathetic system constricts renal arterioles reducing the blood supply and GFR. The sympathetic system is instrumental in reducing GFR during severe autonomic disturbances produced due to acute hemorrhage and ischemia of brain.
- **Protein intake and blood glucose levels**: High protein intake and increased blood glucose level increase renal blood flow and hence GFR.
- **Hormonal control**: A significant increase in the levels of epinephrine and norepinephrine constricts afferent and efferent arterioles. This in turn reduces renal blood flow

and GFR. **Endothelium**-derived nitric oxide reduces renal vascular resistance, thus increasing renal blood flow and GFR. **Atrial natriuretic peptide (ANP):** ANP is released from the cardiac muscle. It increases GFR by causing constriction of the efferent arteriole and dilatation of the afferent arteriole.

Barriers for Filtration

There are two major barriers for the process of filtration:

1. **Mechanical or structural barrier**
2. **Electrical barrier**

Mechanical Barrier

The glomerular basement membrane is the main mechanical barrier. The pores in the epithelial lining of the capsule and the endothelium of the blood vessel restrict the movement of large-sized particles. However, particles with a smaller size are filtered freely.

Electrical Barrier

Bowman's capsular cells and basement membrane have negative charge. They repel negatively charged particles in blood.

Albumin is a large negatively charged protein repelled by this barrier. Hence, a minimum amount of albumin enters the filtrate. Due to these two barriers, molecules measuring more than 4 nm do not enter the filtrate.

Abolition of negative charge occurs in a number of renal diseases and advanced stage of diabetic nephropathy. Large amounts of protein (mainly albumin) get filtered resulting in **proteinuria**.

Measurement of GFR

Inulin clearance is used to measure GFR.

The substance used for the measurement of GFR should have the following properties:

- It should be filtered freely.
- It should be neither secreted nor absorbed.
- It should be nontoxic.
- It should not alter the function of kidneys.
- It should not be metabolized in the body.
- There should be an accurate and easy method to estimate it.

Inulin Clearance and Glomerular Filtration Rate

Inulin is introduced through the intravenous route and the plasma level is maintained by continuous infusion. When the inulin attains equilibrium concentration with the body fluids, urine specimen and plasma samples are collected. The urine collected over a specified time and the plasma samples are analyzed for inulin concentration. Inulin clearance gives an estimate of GFR.

Principle

$$\begin{matrix}\text{Amount of inulin} \\ \text{filtered } (P \times \text{GFR})\end{matrix} = \begin{matrix}\text{Amount of inulin} \\ \text{excreted } (U \times V)\end{matrix}$$

$$P \times GFR = U \times V$$

Where P is the concentration of inulin in plasma, GFR the glomerular filtration rate, U the concentration of inulin in urine, and V the volume of urine produced in unit time.

GFR is calculated using the formula

$$\text{GFR} = \frac{U \times V}{P}.$$

Creatinine Clearance

Creatinine is produced by the metabolism of muscle creatine and creatine phosphate. Urinary creatinine is derived from endogenous creatinine.

It is not absorbed in the renal tubule.

However, a small quantity of creatinine is secreted in the tubule.

Hence, creatinine clearance is marginally higher than inulin clearance.

Creatinine clearance is routinely used for the measurement of GFR as it is produced in the body and its estimation is easy.

Creatinine clearance may exceed actual GFR due to its secretion in the nephron.

$$\text{Filtered load} = \text{GFR} \times \begin{matrix}\text{Plasma concentration} \\ \text{of the solute.}\end{matrix}$$

Measurement of GFR Using Radioactive Tracers

GFR can be accurately measured using radioactive substances, such as chromium-51 and technetium-99m.

Variations in GFR

The GFR is reduced due to

- fall of blood pressure below 60 mm Hg as in circulatory shock,
- erect posture,
- emotion,
- pain,
- exercise,
- cold,
- loss of blood, and
- pathological processes that destroy the nephron.

The GFR is increased when the extracellular fluid and blood volume are increased. It happens during the administration of saline. Infusion of saline dilutes the plasma and decreases the colloidal osmotic pressure.

Filtration Fraction

Filtration fraction is the ratio of the glomerular filtration rate to renal plasma flow (RPF). The normal value is about 20%.

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}}.$$

Filtered Load

Filtered load is the amount of any solute filtered per minute.

Renal (Plasma) Clearance

Renal clearance of any substance is the volume of plasma from which that substance is completely removed by both kidneys in unit time. (It is the volume of plasma cleared off the substance in unit time.)

$$\text{Clearance of a substance} = \frac{\text{Mass of the substance excreted in unit time}}{\text{Plasma concentration of the substance}}.$$

Urea Clearance

Urea clearance is the volume of plasma from which urea is removed in 1 minute. Depending on the urine output, it can be

1. **Maximal urea clearance**: The urine output is more than 2 mL/min. It is calculated by using the formula

$$\text{Maximal urea clearance} = \frac{U \times V}{P}.$$

The normal maximum urea clearance is 75 mL/min.

2. **Standard urea clearance**: The urine output is less than or equal to 2 mL/min.

$$\text{Standard urea clearance} = \frac{U \times \sqrt{V}}{P}.$$

The normal standard urea clearance is 54 mL/min.

Para-Amino Hippuric Acid Clearance

Para-amino hippuric acid (PAH) clearance is used to measure the renal plasma flow. It is freely filtered and completely excreted in the tubules.

A known amount of PAH is infused intravenously; its concentration in plasma and urine is measured. About 90% of PAH is cleared.

Clearance of PAH is calculated, which gives effective renal plasma flow. The extraction ratio for PAH is 90% or 0.9. The actual renal plasma flow is calculated.

$$\text{Actual renal plasma flow} = \frac{\text{Effective renal plasma flow}}{\text{Extraction ratio}}.$$

Renal Blood Flow

Based on the actual renal plasma flow and the hematocrit value, renal blood flow is calculated by using the formula

$$\text{Renal blood flow} = \text{RPF} \times \frac{100}{100 - \text{Hematocrit}}.$$

The normal renal plasma flow is about 600–650 mL/min.

The normal renal blood flow is about 1100–1200 mL/min.

TUBULAR REABSORPTION

The filtrate contains physiologically useful substances, namely, glucose, sodium, amino acids, chloride, bicarbonates, phosphates, potassium, and water, which are absorbed in different parts of the nephron.

Substance excreted in urine = Filtered load – Tubular reabsorption + Tubular secretion.

Tubular reabsorption is quantitatively very high but very selective. Useful substances like glucose and amino acids are completely reabsorbed. Metabolic wastes such as urea and creatinine are poorly absorbed. Sodium, potassium, and hydrogen ions are absorbed based on body's requirements.

During the process of reabsorption, the substances have to pass from

- tubular lumen into the cell lining the lumen,
- cells to lateral intercellular space (interstitial space), and
- interstitial space back into blood through peritubular capillaries.

Reabsorption of different substances can be by means of active transport and different types of passive transport.

It can take the transcellular (through the cell membrane) route or the paracellular (spaces between cell junctions) path.

Tubular Load and Transport Maximum. The substance which is actively absorbed in the nephron has a **transport maximum** for that specific substance. The limit is determined by saturation of the transport system. The amount of substance/solute delivered to the tubule is called the **tubular load**.

The glucose present in the filtrate is completely reabsorbed in the PCT. However, when the tubular load of glucose exceeds its transport maximum, it appears in urine.

Sodium

- Sodium is actively pumped out into the lateral intercellular space in the proximal convoluted tubule (space between the two adjacent cells lining the lumen of the nephron). This creates a concentration gradient between the lumen and the cell. Therefore, sodium ions move from the lumen into the cell (**Fig. 7.8**).
- Sodium is transported along with glucose by cotransport. Sodium and glucose share a common carrier.
- Sodium is also absorbed by countertransport. For every sodium ion absorbed, one hydrogen ion is transferred to the lumen of nephron.
- Sodium, chloride, and potassium are pumped out actively in the thick ascending loop of Henle.

  Absorption of sodium in the thick ascending loop of Henle is influenced by the sodium–potassium ATPase pump present in the basolateral portion of the epithelial cell.

  Sodium is transported across the luminal membrane with the help of 1-sodium, 2-chloride, 1-potassium co-transporter. This transporter derives energy generated by the passive movement of sodium ions along its concentration gradient.
- Absorption is also influenced by chloride. Movement of chloride creates more positivity inside the lumen. This repels the positively charged sodium ions which move from the lumen into the cell.

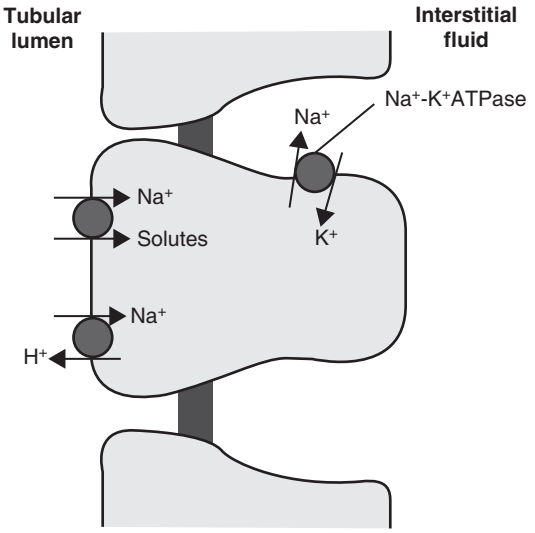


Figure 7.8 Mechanism of sodium reabsorption.

In the distal convoluted tubule, sodium is reabsorbed by the sodium–chloride cotransporter.

- Aldosterone, hormone of the adrenal cortex, increases sodium reabsorption from the DCT and cortical collecting duct. It promotes the secretion of potassium.

Potassium

Extracellular potassium concentration has to be maintained within a narrow range of fluctuation. A major part of the filtered potassium is absorbed in the PCT and the loop of Henle. Potassium is reabsorbed passively in the PCT following the absorption of NaCl and other solutes along with water.

In the thick ascending limb of the loop of Henle, potassium is actively pumped out along with sodium and chloride. Late distal tubule and cortical collecting duct regulate excretion of potassium.

About one-third of the total excreted potassium is secreted in the distal tubule and collecting duct. Increased intake of potassium enhances its secretion and reduced intake decreases its secretion.

The principal cells of the distal tubule and collecting duct secrete potassium from blood into the tubular lumen. Cells take up potassium from the interstitium with the help of the sodium–potassium ATPase pump. Later, potassium diffuses into the tubular lumen from the cell along the concentration gradient. Potassium secretion by the principal cell is influenced by the activity of the sodium–potassium pump, concentration gradient, and permeability of the luminal membrane for potassium.

During severe potassium depletion, there is cessation of potassium secretion. Instead, there is potassium absorption by the intercalated cells in the distal tubule and the collecting duct. The hydrogen–potassium ATPase transport system is known to facilitate absorption of potassium in exchange for hydrogen ions.

Extracellular fluid has about 2% of the total potassium content. Ingestion of potassium can cause severe hyperkalemia and a small loss of it can cause hypokalemia in the absence of appropriate handling of potassium by the kidney.

Insulin, aldosterone, metabolic alkalosis, and β adrenergic stimulation decrease the extracellular potassium level by promoting its uptake by the cell. Breakdown of cell and strenuous exercise increase extracellular potassium concentration.

Acute acidosis decreases the excretion of potassium. However, chronic acidosis increases its excretion.

An increase in hydrogen ion concentration reduces potassium secretion by inhibiting the sodium–potassium ATPase pump.

An increase in the plasma potassium can cause cardiac arrhythmias, fibrillation, and arrest.

Calcium

Calcium ions bound to plasma proteins are not filtered by the kidneys. Ionized calcium is filtered. About 60% of the filtered calcium is absorbed in the PCT through the paracellular path. The calcium dissolved in water is absorbed through the transcellular route. Calcium moves out of the cell by the pumping action of the calcium ATPase pump, sodium and calcium countertransport.

The remaining part is absorbed in the ascending limb of the loop of Henle, DCT, and collecting duct. Parathormone regulates calcium reabsorption from ascending limb of loop of Henle.

Calcium absorption in the distal tubule is by active transport. It is pumped out of the cell at the basolateral region by the calcium ATPase pump. Parathormone, calcitriol, and calcitonin stimulate calcium reabsorption from the distal tubule.

Calcium excretion depends on the dietary intake and the requirement of the body. An increase in the intake of calcium increases its excretion from the kidney and GIT. Less than 5% of the filtered load of calcium is excreted.

Magnesium

The kidneys filter ionic magnesium. Approximately 25% of filtered load is reabsorbed in the PCT, 65% in the thick ascending limb of the loop of Henle, and about 5% in the DCT. Parathormone, glucagon, calcitonin, and ADH stimulate magnesium absorption in the thick ascending limb.

Reabsorption of magnesium in the loop of Henle is passive and it depends on paracellular permeability.

Glucose

All the glucose that is filtered gets reabsorbed by cotransport or secondary active transport with sodium ions (**Fig. 7.9**). The energy for transport is provided by the sodium—potassium ATPase pump. Absorption of sodium and glucose takes place in the PCT.

Pumping of sodium into the lateral intercellular space creates a concentration gradient between the lumen and the cells lining it. Transport of sodium along its concentration gradient provides energy for the movement of glucose against the concentration gradient.

Ninety percent of glucose is transported by SGLT2 in the initial part of PCT against the concentration gradient. SGLT1 transports the remaining 10% in the later part of PCT.

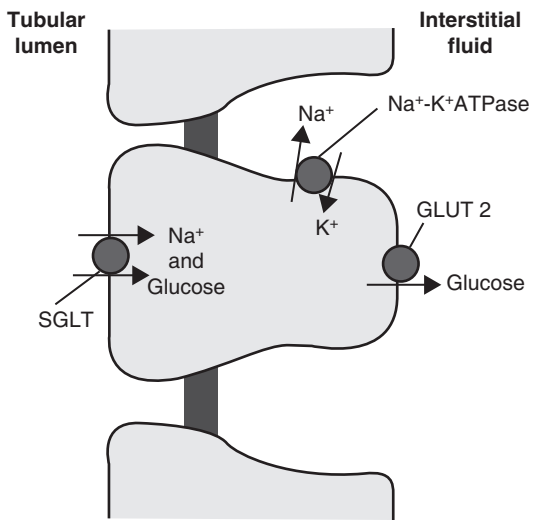


Figure 7.9 Glucose reabsorption.

Transporter GLUT2 carries glucose to the lateral intercellular space in the initial part of PCT, and in the later part glucose is carried by GLUT1.

Renal Threshold for Glucose

It is the concentration of glucose in the blood above which it starts appearing in the urine. It is 180 mg/dL of blood.

Tubular Maximum for Glucose

It is the maximum capacity of all the nephrons together to reabsorb glucose from the filtrate in an ideal condition.

It ranges from 325 to 375 mg/min.

Although the maximum capacity of reabsorption of glucose is reported to be 325–375 mg/min, actual reabsorption is far below the expected level. This deviation of actual absorption compared to maximum capacity is called **splay** (**Fig. 7.10**).

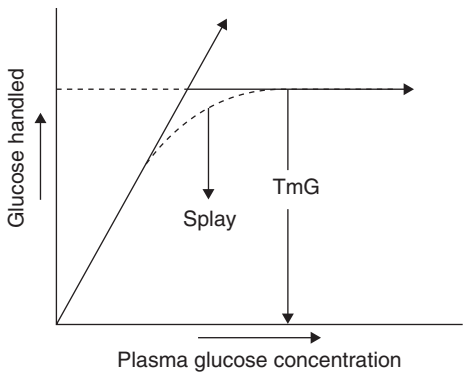


Figure 7.10 Renal splay.

The variation is seen because

- all the nephrons do not have the same capacity of reabsorption as the ideal nephron, and
- all the nephrons are not active and absorbing to their maximum at any given point of time.

Water

The PCT is highly permeable to water. About 85% of water filtered is reabsorbed passively (**Fig. 7.10**). It depends on the reabsorption

of other osmotically active substances. As the water absorption is obliged to absorption of other substances, it is called **obligatory water reabsorption**. Absorption of water in the PCT is greatly influenced by sodium.

The solutes are transported from the lumen to the renal interstitium by primary or secondary active transport. The concentration of solutes decreases and that of water increases. The interstitium becomes hypertonic. Hence, water moves from lumen to renal interstitium by the process of osmosis.

Water reabsorption depends not only on the osmotic gradient but also on the permeability of the membrane. In the ascending loop of Henle, the membrane is impermeable to water. Hence, there is no water reabsorption in spite of an osmotic gradient.

A major portion of the remaining 15% of water is reabsorbed in the DCT and collecting duct under the influence of ADH (antidiuretic hormone or vasopressin). This process is called **facultative reabsorption of water**. Water channel proteins, termed **aquaporins**, help in the process of water reabsorption (**Fig. 7.11**).

As the filtrate passes through the descending limb of the loop of Henle, water gets reabsorbed and the filtrate gets concentrated. In the ascending limb of the loop of Henle, ions such as sodium, potassium, and chloride are pumped out actively. The filtrate becomes dilute again.

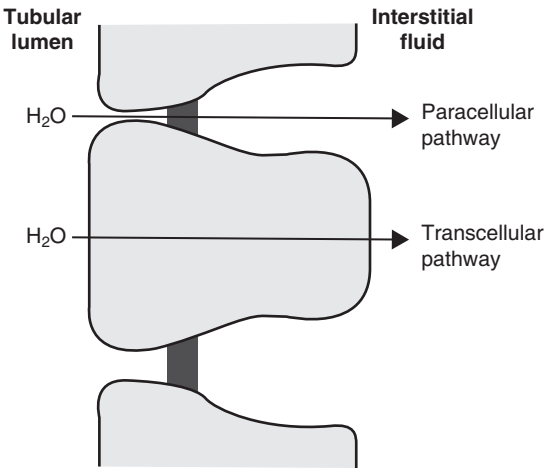


Figure 7.11 Water reabsorption.

However, there is gross reduction in the volume of the filtrate.

CLINICAL NOTES

Water Intoxication

Ingestion of water at a high rate dilutes the ECF. Water moves from the hypotonic ECF into the cell resulting in its swelling. This is termed water intoxication. Swelling of cells in the brain causes convulsion, coma, and death. Water intoxication can occur when there is an imbalance between the intake and the output of water.

Proteins and Peptides

Small-molecular-weight proteins and peptides are filtered in the kidneys to a little extent. Proteins are absorbed in the PCT by pinocytosis. The protein in the vesicle is digested to form amino acids. Amino acids reach the intercellular fluid passing through the basolateral portion of the cell. This mode of absorption of proteins is also categorized as active transport because pinocytosis requires expenditure of energy.

The filtered proteins are taken up by endocytosis and degraded. The constituent amino acids are transferred to the plasma. The rate of reabsorption is dependent on the concentration of proteins in the plasma.

Release of myoglobin from the damaged muscle and release of hemoglobin during excessive breakdown of the red blood cell increase the concentration of small-molecular-weight proteins in the plasma. When the filtered load exceeds the maximum capacity of reabsorption, the concentration of protein increases in tubules. This precipitates proteins causing blockage of lumen resulting in renal failure.

Amino Acids

Approximately 98% of filtered load of amino acids is reabsorbed in the PCT. The neutral and acidic amino acids are transported along with sodium ions across the luminal membrane. Normally, about 0.5–2.0% of the filtered amino acids are excreted in urine.

Bicarbonate

Carbon dioxide is produced by the brush border of the epithelial cell lining the lumen of the nephron. It combines with water in the presence of the enzyme carbonic anhydrase to form carbonic acid (within the cell). Carbonic acid dissociates into hydrogen ions and bicarbonate ions. The hydrogen ion is extruded into the lumen.

In the lumen of the nephron, filtered sodium bicarbonate splits into sodium ions and bicarbonate ions. The bicarbonate ions combine with the hydrogen ions extruded from the luminal cell to form carbonic acid. This again breaks down into water and carbon dioxide. Carbon dioxide from the lumen diffuses into the cell to form bicarbonate ion.

Within the cells lining the lumen, the following reaction takes place:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

$$NaHCO_3 \rightarrow Na^+ + HCO_3^-$$

$$H^+ + HCO_3^- \rightarrow H_2CO_3$$

$$H_2CO_3 \rightarrow H_2O + CO_2$$

Phosphate

Filtered phosphate is actively reabsorbed in the proximal tubule. Reabsorption involves cotransport with sodium ions.

Phosphate acts as an important buffer in the urine.

Absorption is inhibited by parathormone.

Prolonged deprivation of phosphate in diet increases the reabsorptive capacity of the kidney.

Sulfate

Most of the filtered sulfate is reabsorbed in the PCT by sodium cotransport. A small quantity of sulfate is excreted in urine. Sulfate excretion depends on its concentration in the plasma. There is no hormonal control for sulfate reabsorption.

Chloride

About 99% of filtered chloride is reabsorbed in the nephron. A major part of chloride is passively reabsorbed secondary to absorption of sodium ions. It is also countertransported in exchange for OH^- ions. Chloride is also cotransported with sodium ions.

Reabsorption of sodium from the lumen increases the concentration of chloride ions in the lumen. Thus, a concentration gradient is created between the lumen and the renal interstitial space. Chloride ion diffuses passively from the lumen to the interstitial space through the paracellular pathway.

Urea

Urea is reabsorbed passively from the collecting duct. Water is absorbed from the tubule secondary to reabsorption of sodium. Hence, the urea concentration in the tubular lumen increases. This creates a concentration gradient for urea. Urea moves along the concentration gradient out of the lumen. However, absorption of urea is less due to lower permeability of the tubular membrane to urea.

In the inner part of the medullary collecting duct, passive absorption of urea is facilitated by **urea transporter**. The remainder of urea in the nephron is excreted through the urine.

The urea absorbed from the nephron contributes for creation of the medullary interstitial concentration gradient.

Creatinine

Creatinine is another metabolic waste excreted by the kidney. It is a breakdown product of creatine phosphate present in the muscle. Filtered load of creatinine is entirely excreted by the kidney as it is not reabsorbed due to its large molecular size.

A small quantity of creatinine is secreted by the renal tubules.

A rise in the serum creatinine level indicates damage to the nephron.

Uric Acid

Uric acid is the end product of purine metabolism. It is reabsorbed and secreted by the renal tubules. Uricosuric drugs such as phenylbutazone used to treat **gout** prevent its reabsorption.

A high concentration of uric acid in the serum predisposes to the formation of renal stones (urate).

Organic Acids

Metabolic substrates such as lactates, acetates, oxalates, and ketoacids are filtered in small quantities and reabsorbed in the PCT. They are cotransported with sodium ions.

In ketoacidosis, the plasma concentration of these acids increases beyond the tubular maximum. Hence, the ketoacids escape reabsorption and get excreted in urine. The excreted ketoacids act as additional urinary buffers.

Organic acids and bases such as bile salts, oxalates, and catecholamines are secreted in the PCT.

Tubuloglomerular Feedback

The rate of flow of filtrate in the ascending limb of the loop of Henle and the DCT will regulate the rate of filtration in the glomerulus.

Macula densa of the DCT will sense the ionic concentration of the filtrate and the rate of flow of the filtrate. Consequently, the filtration rate is altered by suitable changes in the size of the afferent arteriole and arteriolar resistance.

This feedback will maintain a constant load of filtrate to the DCT. The possible mediators regulating tubuloglomerular feedback are the renin–angiotensin system, adenosine, cAMP, and prostaglandins.

Each nephron regulates its own blood flow by this mechanism. Tubuloglomerular feedback operates through the juxtaglomerular apparatus. A change in the afferent arteriole alters the resistance and regulates the flow of blood.

Tubuloglomerular feedback functions on two mechanisms:

1. Afferent arteriolar feedback
2. Efferent arteriolar feedback

Macula densa sense the changes in the level of sodium ions in the filtrate. A decrease in GFR reduces the filtered load of sodium ions. A decrease in sodium ion concentration at macula densa triggers signals resulting in dilation of afferent arterioles and release of renin.

(*Contd.*)

Dilation of the afferent arteriole reduces the vascular resistance. Renin forms angiotensin II, which constricts the efferent arteriole. This increases glomerular capillary hydrostatic pressure helping to restore GFR.

Renal vasoconstrictors such as prostaglandins (thromboxane) also play an important role in autoregulation in the kidney.

TUBULAR SECRETION

The renal tubules not only absorb physiologically useful substances but also secrete a few substances through the tubular epithelial cells.

The substances secreted in the DCT are

- ammonium ions,
- potassium ions, and
- hydrogen ions.

Ammonium Ions

The tubular cells form ammonium ions by the action of the enzyme glutaminase on glutamine. Glutamine enters the cell by sodium-dependent cotransport. It is supplied to the kidney by the liver. The breakdown of glutamine yields ammonium and α-ketoglutarate. Metabolism of α-ketoglutarate consumes hydrogen ions.

Under normal conditions, the proximal tubular cells produce most of the ammonium ions. In the thick ascending loop of Henle, the ammonium ion is reabsorbed in exchange for the potassium ions. The reabsorbed ammonium ions accumulate in the medulla.

As the filtrate passes through the collecting duct, the epithelial cells secrete hydrogen ions. This lowers luminal pH favoring diffusion of ammonia. The ammonium ions formed in the lumen are excreted through the urine.

When the reaction of urine is more acidic, excess of ammonium ions are produced to regulate the acid–base balance.

Potassium Ions

Potassium is secreted in exchange for sodium ions. However, when the hydrogen ion secretion increases, the potassium ion secretion decreases.

It is secreted in the thin descending loop of Henle.

The principal cells present in the distal tubule and collecting duct also secrete potassium ions. Thus, in a normal individual, potassium excretion depends on the intake and need of the ion.

Hydrogen Ions

Hydrogen ions are also secreted in exchange for sodium ions. They help in retention of sodium ion, which is physiologically important and useful to the body.

Secretion of hydrogen ions is by a form of secondary active transport, which is termed **counter-transport**.

During counter-transport, the energy liberated by the movement of one substance along its concentration gradient helps to transport other substances against the concentration gradient. The transport is mediated by a specific protein, **sodium–hydrogen exchanger**.

Drugs

Some of the drugs are secreted in the PCT and eliminated rapidly from the body. This poses a challenge to maintain the plasma concentration of the drug for a long duration. Penicillin and salicylates are cleared by the kidney rapidly.

CLINICAL NOTES

Renal Glycosuria

Renal glycosuria is the inability of the kidney to reabsorb glucose in spite of a normal blood glucose level. This is because of reduced tubular maximum for glucose.

Diabetes Insipidus (Insipid = Tasteless Urine)

Deficiency of ADH results in excretion of large quantities of dilute urine (polyuria). Other features of the disease are polydipsia (excessive intake of water) and dehydration. Dehydration is due to excessive loss of water.

The inability to produce ADH and release from the posterior pituitary is called **central diabetes insipidus**. About 15 L/day of dilute urine can be formed in these cases.

Nephrogenic Diabetes Insipidus

It is a condition in which the kidney fails to respond to ADH. Secretion of ADH is normal. There is excretion of a large quantity of dilute urine.

The loss of water increases sodium retention, resulting in **hypernatremia**.

Renal Tubular Acidosis

In this condition, renal tubules fail to secrete hydrogen ions and there is continuous loss of bicarbonate ions leading to metabolic acidosis.

It is caused due to the failure of bicarbonate absorption from PCT or adequate secretion of hydrogen ions from DCT.

Aminoaciduria

In this condition, a large quantity of amino acids is excreted in the urine. This condition is due to the deficiency of some specific enzyme or transport process associated with abnormal metabolism of the amino acid. Aminoaciduria is a genetic defect.

UNHEALTHY KIDNEY AND ITS ALTERED FUNCTIONS

Kidney diseases are divided into two main categories. They are as follows:

1. Acute renal failure
2. Chronic renal failure

In either of the above conditions, the glomerular and tubular functions are compromised.

Altered Glomerular Functions

In **nephrotic syndrome**, the glomerular basement membrane is destroyed. This results in the leakage of protein into the filtrate. The patient has proteinuria. Urinary protein loss is not compensated by its production in liver. This reduces the plasma proteins and, hence, the colloidal osmotic pressure decreases. Reduced colloidal osmotic pressure produces generalized edema and retention of sodium ions.

In **chronic renal failure**, the glomeruli are destroyed. Urea and creatinine are retained in the body due to decreased GFR.

Altered Tubular Function

In chronic glomerular diseases, the glomerular capillaries are destroyed. The associated peritubular capillaries and nephrons are also destroyed. The remaining nephrons have to handle greater filtered load. The nephrons operate in a state of osmotic diuresis. Hence, the ability of the nephron to concentrate or dilute the urine is lost progressively.

An early sign of renal failure is nocturia. This is produced by the inability of the kidney to concentrate urine.

Loss of nephrons reduces the excretion of potassium ions resulting in their retention.

The kidney is unable to synthesize bicarbonate ions in sufficient quantities. This results in metabolic (renal) acidosis.

RENAL HYPERTENSION

Renal hypertension was induced experimentally by partially occluding the renal artery of the remaining kidney, and the other kidney was removed.

This reduces the perfusion pressure to the kidney. The procedure stimulates the release of renin, resulting in the formation of angiotensin II. There is peripheral vasoconstriction and sustained rise of systemic arterial pressure.

The initial increase in systemic arterial blood pressure is due to the renin-angiotensin mechanism. The sustained increase is due to the release of aldosterone with retention of salt and water.

Partial clamping of one of the renal arteries in a healthy animal also produces hypertension. This procedure also increases secretion of renin with formation of angiotensin II. The other normal kidney retains salt and water. These experiments throw light on the possible options for management of hypertension in human beings.

The commonest forms of renal hypertension are produced due to arteriosclerotic stenosis of the renal artery. It is also seen in stenosis of preglomerular arteries and arterioles due to inflammation and fibrotic lesions. Administration of ACE inhibitors is beneficial as they lower the levels of angiotensin II.

COUNTERCURRENT MECHANISM (Fig. 7.12)

The countercurrent mechanism is a system of U-shaped tubules. In this system, flow of fluid occurs in an opposite direction in the two limbs of the tubule. The countercurrent mechanism helps in concentrating the urine.

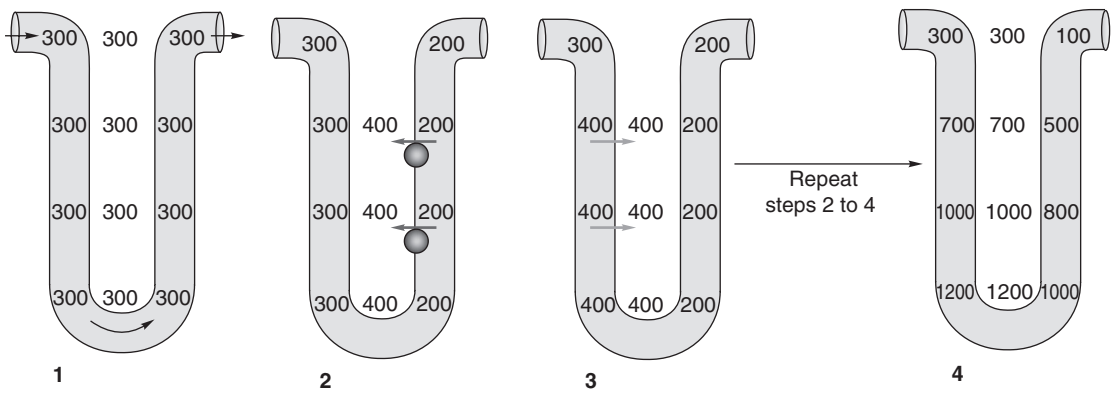


Figure 7.12 Countercurrent multiplier system producing a medullary gradient. 1. Loop of Henle filled with fluid with the concentration being the same as that coming from proximal convoluted tubule. 2. Ions actively pumped out of the thick ascending limb. 3. Osmosis of water from the descending limb. 4. Repetition of steps 2 and 3 creates a gradually increasing medullary gradient to a maximum of 1,200–1,400 mOsm/L. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

In the kidney, the countercurrent mechanism involves the movement of fluid through the long loop of Henle of the juxtamedullary nephron and passage of blood through the adjacent blood vessel. The countercurrent mechanism creates a gradually increasing osmotic gradient extending from the cortex to the medulla.

The loop of Henle functions as a **countercurrent multiplier system (Fig. 7.13)**.

Vasa recta operate as a **countercurrent exchanger**.

Two important factors that help in the process of concentration of urine are

1. flow of fluid in the opposite direction in both nephron and vasa recta and
2. increasing medullary concentration gradient (300–1200 mOsm/L).

The osmolarity of plasma is 300 mOsm/L.

The osmolarity of interstitial fluid in the medulla of the kidney shows a gradual increase from 300 to 1200 mOsm/L.

FACTORS INFLUENCING THE GENESIS OF THE MEDULLARY GRADIENT

The factors influencing the genesis of the medullary gradient are as follows:

- Active transport of ions such as sodium, potassium, and chloride from the thick limb of the loop of Henle into the interstitium
- Diffusion of urea from the medullary collecting duct into the interstitium

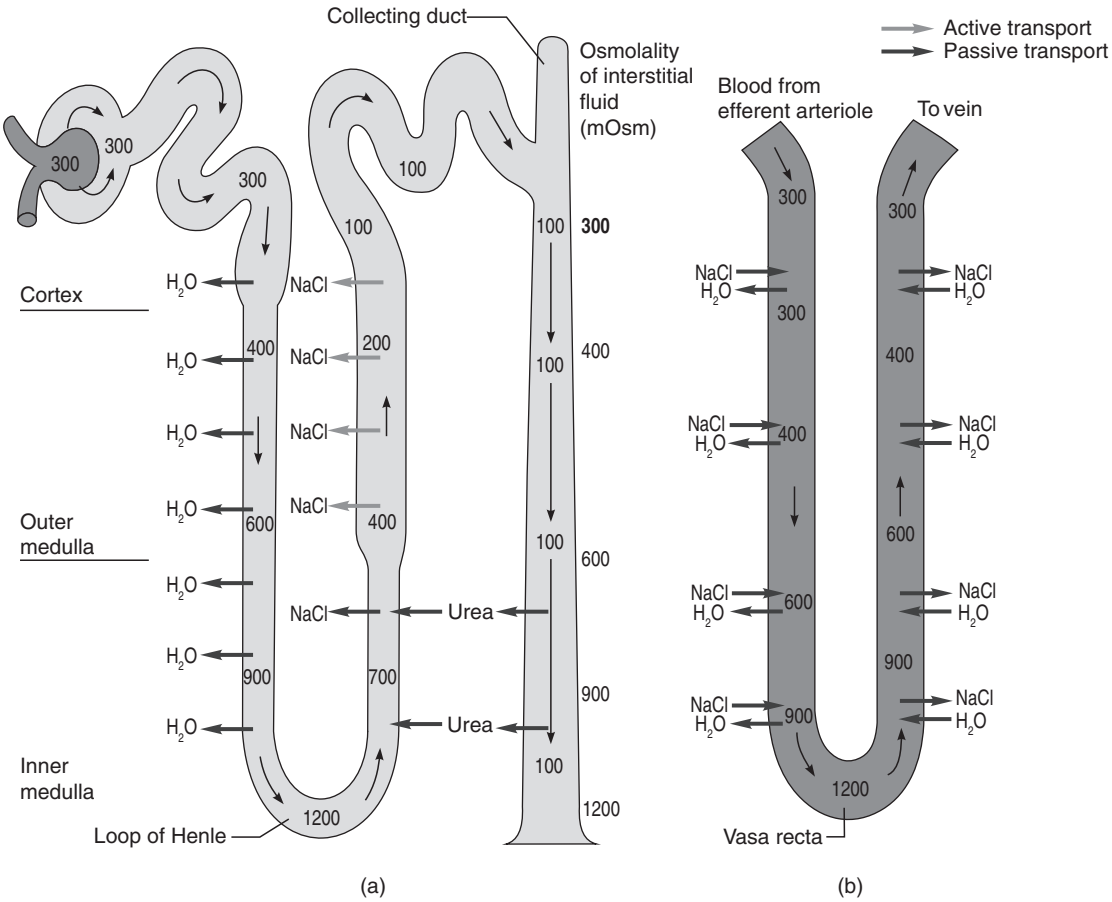


Figure 7.13 (a) Countercurrent multiplier system and (b) countercurrent exchange system. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- Reduced water reabsorption in relation to solute reabsorption into the medullary interstitium

CHANGES TO THE FILTRATE IN THE JUXTAMEDULLARY NEPHRON

The countercurrent multiplier is formed by the loop of Henle. It is responsible for generation of gradually increasing the medullary concentration gradient. The maximum solute concentration is about 1200–1400 mOsm/L. This indicates that the medullary interstitium has accumulated more solutes than water. The following changes take place as the filtrate passes through the nephron:

- The osmolality of filtrate entering the PCT is identical to that of plasma (about 300 mOsm/L).
- As the filtrate passes through the PCT, physiologically useful substances are reabsorbed.
- In the descending limb of the loop of Henle, water moves out of the lumen into the interstitium by the process of osmosis. This change reduces the volume of filtrate and increases its osmolarity.
- The filtrate formed in the PCT has an osmolarity of 300 mOsm/L. The osmotic reabsorption of water increases osmolarity gradually to reach a maximum of 1200 mOsm/L at the tip of the loop of Henle.
- As the filtrate moves up the ascending limb of the loop of Henle, sodium, potassium, and chloride ions are actively pumped out of the lumen. Water is retained in the lumen, as a thick limb is impermeable to water. The ions pumped out to interstitium increase the medullary concentration gradient.
- At the beginning of the ascending limb of loop of Henle, osmolarity is around 1200 mOsm/L. As the filtrate passes through the ascending limb, the osmolarity gradually decreases to about 150 mOsm/L due to pumping of ions and retention of water.
- As the fluid leaves the ascending limb of the loop of Henle, it is dilute with an osmolarity of about 150 mOsm/L.
- In the early part of the distal tubule, the fluid gets further diluted due to the active pumping of ions.
- In the remaining part of the distal tubule and the collecting duct, the filtrate gets concentrated due to reabsorption of water under the influence of ADH. In the absence of ADH, this segment is impermeable to water.

Urea that is passively absorbed from the tubule contributes significantly in creating the medullary concentration gradient. Renal tubules in the deep medullary region are highly permeable to urea. Urea diffuses from the lumen into the medullary interstitium.

Diffusion of urea is facilitated by urea transporters UT-A1 and UT-A3. ADH activates UT-A3 increasing the diffusion of urea. Urea contributes about 40–50% osmolarity (500–600 mOsm/L) for the interstitial gradient.

An increase in the fluid content in the body reduces ADH secretion and diffusion of urea into the renal medullary interstitium. This facilitates the formation of a large quantity of dilute urine. Low levels of body fluids increase ADH secretion and diffusion of more of urea into the renal medullary interstitium. These changes help to reabsorb and conserve water resulting in the formation of a small quantity of concentrated urine.

CHANGES IN VASA RECTA

The medullary blood flow is low and constitutes about 1–2% of renal blood flow. The countercurrent exchange system of vasa recta regulates the removal of solute from medullary interstitium to maintain the concentration gradient.

- Blood enters the vasa recta and descends down slowly through the long loop.
- The wall of vasa recta is highly permeable. Blood in the descending loop picks up the solute from the medulla and becomes progressively more concentrated.

- There is water loss in this part of the vasa recta by the process of osmosis.
- By the time blood reaches the tip, it has a solute concentration of about 1200 mOsm/L.
- As the blood moves up the ascending part of the vasa recta, it becomes progressively diluted as the solutes diffuse back into the medullary interstitium and water moves into the vasa recta.
- Flow of blood through the vasa recta does not drain the solutes from the medullary interstitium.
- Thus, the vasa recta helps to maintain a gradually increasing medullary concentration gradient.

URINARY BLADDER

The urinary bladder is a sac made up of smooth muscle. It has two parts:

1. Body
2. Neck

The smooth muscle of the bladder is called the **detrusor muscle**. A small triangular area above the bladder neck is called the **trigone**. The mucosa lining the bladder is thrown into a number of folds termed **rugae**.

The ureter enters the bladder posteriorly at the upper angle of the trigone. The ureter passes through the wall of bladder before opening into it. It is kept compressed by the normal tone of the bladder muscle. This prevents the backflow (reflux) of urine when the pressure increases in the bladder.

Ureters are lined by the transitional epithelium and the wall has longitudinal and circular smooth muscle fibers. Contraction of smooth muscle fibers resembles the contraction in the other regions of the body. Entry of calcium ion triggers the contraction. Peristaltic waves are set up in the ureter with an electrical pacemaker in the proximal part of the renal pelvis. These peristaltic waves propel the urine along the ureter into the bladder.

The bladder neck has detrusor muscle with the elastic tissue forming the **internal sphincter**.

The urethra passes through the urogenital diaphragm. It has a layer of skeletal muscle constituting the **external sphincter**. The external sphincter is voluntary and can be used to control micturition.

The contraction of the detrusor muscle results in emptying of the bladder and the pressure within it increases to 40–60 mm Hg.

The bladder can hold about 300–400 mL of urine with little increase in tension. An increase in the volume of urine beyond this level increases tension. It is appreciated as sensation of fullness of the bladder. If the conditions are suitable, the micturition reflex is triggered and urination occurs. The first urge to empty the bladder is felt when it contains about 150 mL of urine. Accumulation of urine beyond 600 mL becomes painful.

Urine enters the bladder without a significant increase in pressure (intravesical pressure) within it. The pressure increases only when the bladder is filled up. The bladder muscles exhibit the property of **plasticity**. When the hollow viscus is stretched, initially the tension increases. However, the tension reduces immediately thereafter.

NERVE SUPPLY TO THE URINARY BLADDER

Urinary bladder receives both sympathetic and parasympathetic nerve supply (**Fig. 7.14**).

Parasympathetic Innervation

Parasympathetic innervation to the bladder arises from the sacral segment of the spinal cord (S_2, S_3).

It passes through the pelvic nerves and supplies the detrusor muscles of the bladder and the internal sphincter.

Stimulation of nerve causes the contraction of bladder muscles and relaxation of the internal sphincter resulting in emptying of the bladder. Hence, it is called the **nerve of emptying**.

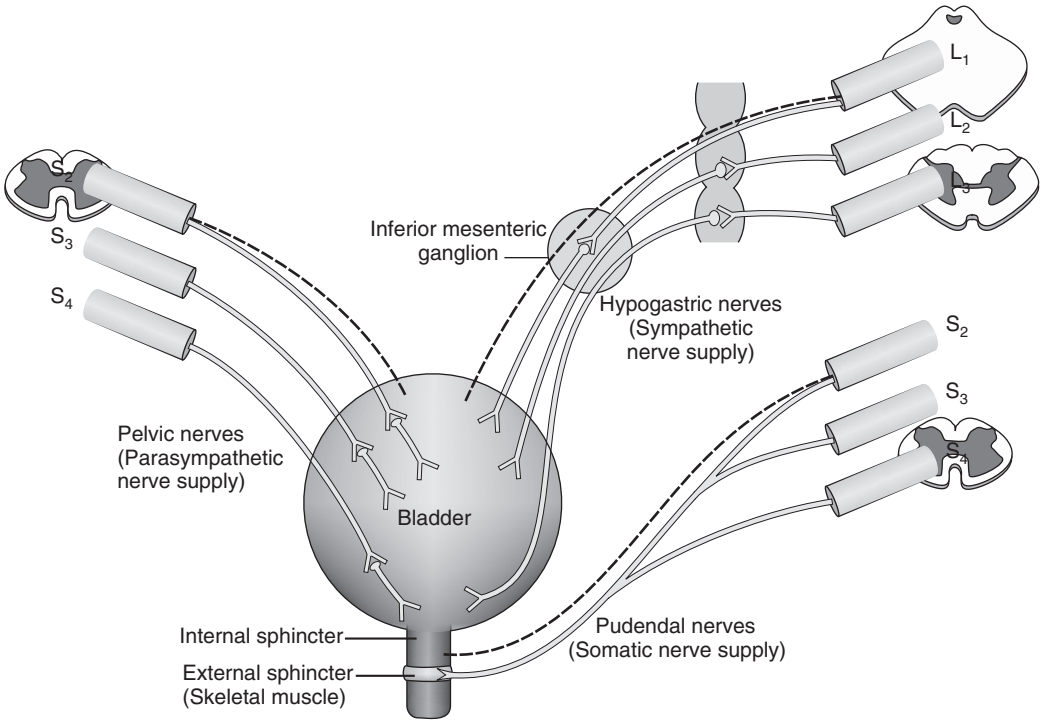


Figure 7.14 Innervation of the urinary bladder.

Sympathetic Innervation

Sympathetic innervation to the bladder arises from the first, second, and third lumbar segments of the spinal cord. It relays in the hypogastric ganglion. Postganglionic fibers supply the bladder muscle and internal sphincter.

Stimulation of sympathetic fibers influences the blood vessels and alters the blood flow, but has very little role in the bladder muscle contraction.

Pudendal Nerve

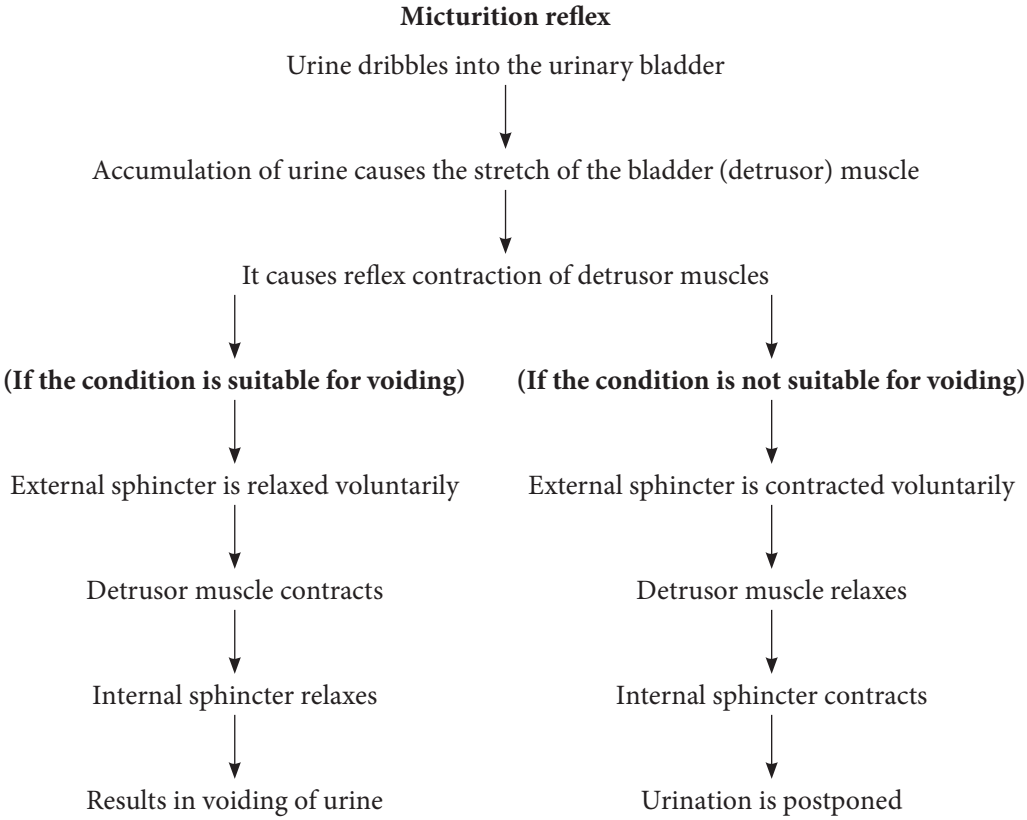
The pudendal nerve carries motor fibers to the external sphincter of the urinary bladder controlling its voluntary activity.

MICTURITION REFLEX

Micturition is the process of voiding of urine. It is a spinal reflex influenced by the higher centers.

- Urine formed in the kidneys dribbles into the bladder continuously.
- Urge to empty the bladder arises with accumulation of about 150 mL of urine.
- If the bladder is partly filled, detrusor muscles relax spontaneously (up to 300–400 mL).
- Accumulation of a sufficient quantity of urine causes the stimulation of sensory stretch receptors in the bladder.
- Sensory signals reach the sacral segment of the spinal cord through the pelvic nerve.
- Motor response reaches the bladder through the parasympathetic nerve fibers. This causes contraction of the detrusor muscle resulting in micturition reflex.
- As the bladder gets filled up gradually, the micturition reflex becomes frequent.
- When the micturition reflex begins, the initial contraction of bladder further stimulates the stretch receptors to strengthen the contraction of the detrusor muscles.
- Once the micturition reflex becomes powerful, it reflexly inhibits the external sphincter through the pudendal nerve.

- This causes relaxation of perineal muscles, and urine passes through the urethra.
- However, if the condition is not suitable for voiding urine, higher centers exercise an inhibitory control over the lower centers to temporarily postpone micturition.



INFLUENCE OF HIGHER CENTERS

These centers are mainly located in the pons and certain areas of the cerebral cortex.

1. Higher centers exert inhibitory control over the bladder except when micturition is desired.
2. If micturition is desired, the higher centers can facilitate the sacral micturition center to initiate the reflex.

VOLUNTARY CONTROL OF URINATION

Urination can be commenced, withheld, or postponed by voluntary effort.

During voluntary emptying of the bladder, the muscles of the pelvic floor relax. This causes downward tug of the detrusor muscle to initiate its contraction.

The contraction of perineal muscles and external sphincter can interrupt the flow and stop urination.

Urination can be postponed by voluntarily contracting the external sphincter.

After urination, the female urethra empties due to the influence of gravity whereas the male urethra is emptied by repeated contraction of the bulbocavernous muscles.

Voluntary urination can be initiated by contracting the abdominal muscles.

This forces more urine into the neck of the bladder activating the micturition reflex.

Relaxation of the external sphincter by voluntary effort completes the process of urination.

ABNORMAL FUNCTIONING

Urinary bladder plays an important role in storing and eliminating urine from the body. Intact nerve supply and control from the higher centers are necessary for the normal functioning of the bladder. Any damage to the nerves innervating the bladder or loss of control from the higher centers results in abnormal function of the urinary bladder.

Atonic Bladder

In the atonic bladder, the tone of the bladder muscle is lost. It occurs due to damage to the sensory nerve from the bladder to the spinal cord or crush injury to the sacral segment of the spinal cord. Periodic emptying of bladder becomes difficult. There is overflow of urine when the bladder is full, resulting in **overflow incontinence**.

In **tabes dorsalis**, the dorsal roots of sacral nerves are interrupted. Hence, the reflex contraction of bladder is abolished. The bladder becomes thin walled, hypotonic, and distended.

Automatic Bladder

Damage to the spinal cord above the regions of the sacral segment results in automatic bladder. During recovery from spinal shock, the micturition reflex is regained but without voluntary control.

There is automatic voiding of urine when small quantities of urine accumulate in the bladder. It is also called *spastic neurogenic bladder*.

Neurogenic Bladder

Partial damage to the spinal cord or the brainstem produces frequent, uncontrolled urination due to loss of inhibitory control. Accumulation of a small quantity of urine triggers the micturition reflex and voiding of urine.

CLINICAL NOTES

Cystometrogram

Cystometrogram is the graphical representation of the relationship between the volume of the urinary bladder and the pressure within it (intravesical pressure) (**Fig. 7.15**). It helps to demonstrate the plasticity of the urinary bladder.

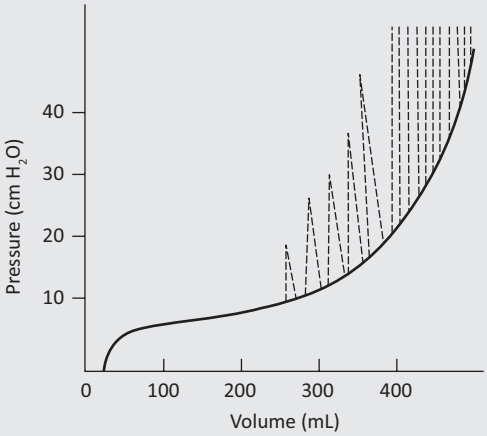


Figure 7.15 Cystometrogram.

A double-barrel catheter is introduced into the urinary bladder. The bladder is emptied and the pressure is measured.

Later, the bladder is filled with 50 mL of water or air each time. The corresponding bladder pressure is recorded when the fluid or air is introduced into the bladder. The plot of intravesical pressure against the corresponding volume of the bladder is called **cystometrogram**.

The curve shows three components:

1. Slight increase in the intravesical pressure with an initial increase in the volume
2. Long, but flat, segment with a further increase in the volume
3. Sudden and sharp increase in pressure as the micturition reflex is triggered

DIURESIS

Discharge of a large volume of urine is termed **diuresis**. The presence of osmotically active particles in the filtrate can increase the urine output. Reduced secretion and the release of ADH are other causes for diuresis.

The types of diuresis are
- osmotic diuresis and
- water diuresis

Osmotic Diuresis

In this condition, the urine output is increased due to the presence of osmotically active particles in the filtrate. *Reducing sugars* in diabetes mellitus produce osmotic diuresis.

Water Diuresis

Increased water intake increases the urine output due to reduced secretion of ADH.

DIURETICS

Diuretics are substances which increase the output of urine by modifying the functions of nephrons. They are used to get rid of excess fluid which has accumulated in the body.

- **Osmotic diuretics** reduce the water reabsorption by increasing the osmotic pressure in the tubular fluid. In diabetes mellitus, the tubular load of glucose exceeds its transport maximum. The glucose in the filtrate acts as an osmotically active particle preventing reabsorption of water. This osmotic diuresis is the cause for polyuria in diabetes mellitus.
- **Loop diuretics** reduce active sodium, potassium, and chloride absorption in the thick ascending loop of Henle. These diuretics block the action of the sodium–chloride–potassium transporter located in the luminal surface of epithelial cells.
- **Thiazide diuretics** inhibit sodium–chloride reabsorption in the distal tubule by blocking the sodium–chloride cotransporter.
- **Carbonic anhydrase inhibitors** (acetazolamide) block sodium–bicarbonate reabsorption in the proximal tubule.
- **Competitive inhibitors** of aldosterone decrease sodium reabsorption and promote potassium secretion into the collecting duct.
- **Potassium-sparing diuretics** like spironolactone reduce the excretion of potassium.

CLINICAL NOTES

Renal Failure

Renal failure is a condition in which the kidneys stop the normal functioning.

Types of Renal Failure

Renal failure is of two types:

i. acute renal failure and
ii. chronic renal failure.

Acute Renal Failure

In this condition, the kidneys stop functioning suddenly. The loss of function could be partial or complete. The renal functions may be restored subsequently.

Initial damage to the kidney which is not effectively treated leads to extensive destruction of the functioning nephrons. The patient needs dialysis or renal transplant for survival. This is called end-stage renal disease (ESRD).

Chronic Renal Failure

There is progressive loss of renal function with damage to an increasing number of nephrons.

Causes

Renal failure can occur because of reduced blood supply to the kidney (**prerenal cause**), abnormalities of the kidney (**renal cause**), or defective function of the collecting system of the kidney (**postrenal cause**).

Renal failure results in
- fluid and electrolyte disturbances,
- accumulation of toxic metabolic waste,
- anemia due to reduced formation of erythropoietin,
- metabolic acidosis, due to reduced ability of the kidney to excrete hydrogen ions, an
- death, if not treated properly.

Management

Acute renal failure can be reversed with early treatment. The kidney resists damages due to reduced blood flow for a longer duration compared to other tissues in the body.

Chronic renal failure is managed by
- dialysis and
- renal transplantation.

Dialysis with an Artificial Kidney (Fig. 7.16) It is a process by which the normal composition of blood is restored. Dialysis is indicated in patients with severe loss of kidney functions.

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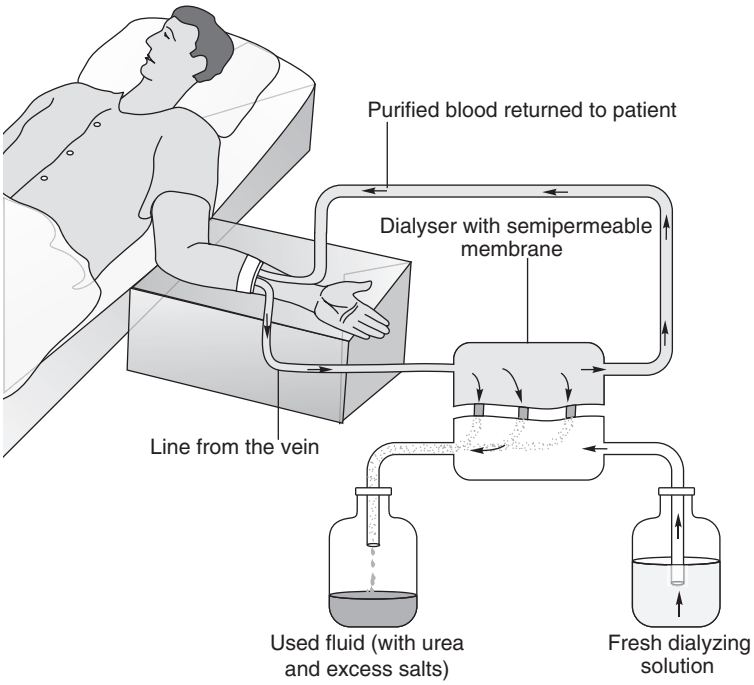

Figure 7.16 Dialysis with an artificial kidney. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Blood from the patient and dialyzing fluid (fluid having composition similar to that of plasma) are passed on either side of a semipermeable membrane. The metabolic wastes from the blood move into the dialyzing fluid and the physiologically useful substances move from the fluid to the blood.

Later, the blood is reintroduced back into the patient. The process of dialysis has to be repeated periodically if the loss of kidney function is irreversible.

Renal Transplantation

Renal transplantation is a method of long-term management of chronic renal failure. The kidney of the matched donor is transplanted to the recipient. If the organ is well accepted, the renal function is restored. However, the common complication is rejection of the transplanted kidney. There is need to use immunosuppressants on a regular basis to prevent rejection of the transplanted kidney.

Polyuria

Polyuria is a condition of increased urine output with reduced solute concentration.

Nocturia

Nocturia is excessive voiding of urine during night. It is a common symptom of diabetes mellitus.

Oliguria

Oliguria is reduction in the urine output less than 400 mL/day; it is commonly seen in renal failure.

Anuria

Anuria is the absence of urine output commonly seen in shock and renal shutdown.

RENAL FUNCTION TESTS

Normally functioning kidneys are essential for life. There is a need to objectively assess the functioning ability of the kidney in health and disease. Deranged renal function provides vital clues to the potential damage to the kidney.

PHYSICAL TEST

Volume	1000–1500 mL/day
Color	Pale yellow
Specific gravity	1.003–1.030
pH	Acidic, 4.5–6
Odor	Aromatic odor in a fresh sample

ROUTINE BLOOD TEST

An estimation of serum urea, uric acid, and creatinine gives an indication about the excretory function of the kidney.

GLOMERULAR FUNCTION

Glomerular function is assessed by the evaluation of urea, creatinine, and inulin clearance. Creatinine clearance is a more specific test for renal function.

TUBULAR FUNCTION

The concentrating capacity of the kidney gives an idea about the tubular function. Varying quantities of fluid are given to the subject and the urine output is estimated. Variation in the urine volume and specific gravity corresponding to changes in the fluid intake indicates normal tubular function.

MEASUREMENT OF RENAL PLASMA FLOW AND RENAL BLOOD FLOW

Clearance of a substance is used to estimate renal function.

Creatinine clearance is used to measure GFR. Para-amino hippuric acid clearance measures renal plasma flow.

Renal blood volume is calculated by using renal plasma flow and hematocrit.

RADIOLOGICAL INVESTIGATIONS

- Ultrasonography
- X-ray
- Intravenous pyelography
- CT and MRI scanning

They help to detect the structural and functional abnormalities in the kidneys.

Constituents of Urine

Normal Constituents

- **Inorganic**: Sodium, potassium, calcium, and phosphate
- **Organic**: Urea, uric acid, and creatinine
- **Others**: Ammonium chloride, oxalates, and minerals

Abnormal Constituents

- **Proteins**: Presence of protein in urine is proteinuria. Appearance of albumin in urine is albuminuria. Albuminuria is seen in pregnancy and kidney diseases such as nephrotic syndrome.
- **Glucose**: Presence of reducing sugars in urine is glycosuria. It is seen in diabetes mellitus and renal glycosuria.
- **Ketone bodies**: Acetone, acetoacetic acid, and beta-hydroxybutyric acid are called ketone bodies. They are present in the urine in uncontrolled diabetes mellitus and during prolonged fasting.
- **Bilirubin**: It appears in the urine in cases of jaundice.
- **Blood**: In diseases of kidney such as nephritis, RBC appears in the urine. Hemoglobin appears in the urine in conditions with excessive breakdown of RBC.
- **Creatinine**: Creatinine appears in the urine whenever there is muscle wasting as in myopathies and starvation.

ACID–BASE BALANCE

Metabolic activities in the body generate acids and bases. Addition of these will disturb the acid–base balance. The imbalances are effectively managed by the buffer systems in the body.

There is a delicate balance between the intake and the output of the fluid. Maintenance of the fluid at the optimal level is required for normal functioning. Acid–base and fluid–electrolyte balance is discussed in this section.

The maintenance of a stable hydrogen ion concentration is necessary for life. The molecules that donate hydrogen ions are called **acids** while those that remove the hydrogen ions from solution are called **bases**.

The pH is the negative logarithm of hydrogen ion concentration.

An increase in hydrogen ion concentration reduces the pH of blood. The condition is called **acidosis**.

A decrease in hydrogen ion concentration is termed **alkalosis**. The pH increases in alkalosis.

The pH of arterial plasma is 7.40. In a normal healthy individual, the pH of plasma is slightly alkaline, ranging from 7.35 to 7.45. It is slightly less in venous blood. The pH of water at 25°C is 7.0. The pH of gastric juice is highly acidic (up to 2) and the pancreatic juice is alkaline (up to 8).

HCl is a strong acid and NaOH is a strong base. Strong acids and bases can dissociate completely in water. Most acids and bases in the body are **weak**; hence, they release or take up few hydrogen ions.

The pH of body fluid is stabilized by its **buffering capacity**. **Buffer** is a substance that can bind or release hydrogen ions in a solution. It keeps the pH relatively constant even when a considerable quantity of acids or bases is added.

$$\text{Buffer} + H^+ \leftrightarrow H\ \text{Buffer}$$

An increase in the concentration of H^+ shifts the reaction to right, promoting binding of H^+ to the buffer. A decrease in the concentration of H^+ forces the reaction to left, releasing H^+.

There are different buffers working in a biological fluid. More than one buffer system act in the body at any given time.

The buffers in the body are

- bicarbonate buffer system,
- phosphate buffer system,
- proteins, and
- hemoglobin

BICARBONATE BUFFER SYSTEM

The bicarbonate buffer system is an acid–base homeostatic mechanism regulating the balance of carbonic acid, bicarbonate ion, and carbon dioxide to maintain the pH of blood. This system consists of two components, a weak acid and a salt, namely,

1. Carbonic acid (H_2CO_3), a weak acid
2. Sodium bicarbonate ($NaHCO_3$), a salt

Carbonic acid is formed in the body by the combination of carbon dioxide with water in the presence of an enzyme *carbonic anhydrase.*

$$CO_2 + H_2O \xleftrightarrow{\text{Carbonic anhydrase}} H_2CO_3\ \text{(Carbonic acid)}$$

H_2CO_3 ionizes to form H^+.

$$H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

Sodium bicarbonate present in the extracellular fluid dissociates into sodium ion and bicarbonate ion.

$$NaHCO_3 \leftrightarrow Na^+ + HCO_3^-$$

Addition of strong acids such as HCl results in the formation of H^+, which will be buffered by HCO_3^-.

$$H^- + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

It is clear from these reactions that H^+ from a strong acid HCl reacts with the bicarbonate ion to form a weak acid, carbonic acid. Carbonic acid dissociates, thereby producing carbon dioxide and water.

Addition of a strong base such as sodium hydroxide (NaOH) produces opposite reaction.

$$NaOH + H_2CO_3 \leftrightarrow NaHCO_3 + H_2O$$

In this reaction, a weak base ($NaHCO_3$) is formed from a strong base (NaOH). Additionally, HCO_3^- is formed. The increase in blood HCO_3^- is compensated by excretion of HCO_3^- by the kidney.

PHOSPHATE BUFFER SYSTEM

The phosphate buffer system plays an important role in the tubular fluid of the kidney and intracellular fluid.

The components of the phosphate buffer system remain in the renal tubule due to their poor reabsorption.

The phosphate buffer system has

- $H_2PO_4^-$ and
- HPO_4^{2-}.

On addition of a strong acid, HCl, to this mixture, hydrogen ion is released from the acid which is accepted by HPO_4^{2-} to form $H_2PO_4^-$. A strong acid, HCl, is replaced by a weak acid NaH_2PO_4.

$$HCl + Na_2HPO_4 \leftrightarrow NaH_2PO_4 + NaCl$$

On addition of a strong base NaOH, OH^- is buffered by $H_2PO_4^-$ to form HPO_4^{2-}.

$$NaOH + NaH_2PO_4 \leftrightarrow Na_2HPO_4 + H_2O$$

The strong base NaOH is converted to a weak base causing a slight increase in pH.

PROTEINS

Plasma proteins are very effective buffers as their carboxyl and amino groups dissociate. They are important buffering systems as their concentrations are very high within the cells.

$$RCOOH \leftrightarrow RCOO^- + H^+$$

$$RNH_3 \leftrightarrow RNH_2^- + H^+$$

HEMOGLOBIN

Buffering is provided by hemoglobin by the dissociation of the imidazole group of histidine residues.

The buffering capacity of hemoglobin is six times greater than that of plasma proteins. Deoxyhemoglobin is a weaker acid and has better buffer than oxyhemoglobin because of its dissociation capacity.

$$H^+ + Hb \leftrightarrow HHb$$

RENAL CONTROL OF ACID–BASE BALANCE

The acid–base balance is maintained by kidneys by secreting acidic or basic urine. The pH of urine depends on the content of the acid and base in the extracellular fluid.

A large number of H^+ and HCO_3^- are filtered into the tubules. However, the number of H^+ is more than HCO_3^-. This excess of H^+ helps to get rid of nonvolatile acid produced by metabolism of proteins from the body.

In metabolic alkalosis, HCO_3^- excretion increases in urine as it is not completely reabsorbed and remains in the tubule.

In metabolic acidosis, H^+ excretion increases and there is complete reabsorption of HCO_3^-. Thus, the kidney regulates H^+ concentration in extracellular fluid by secreting H^+ or by absorbing HCO_3^-.

Excess of H^+ in the filtrate is neutralized by phosphate buffer or ammonia and it is excreted as a compound of sodium.

Uncontrolled (commonly in type I) diabetes mellitus, consumption of methyl alcohol (which forms formic acid on metabolism), and chronic renal failure produce metabolic acidosis.

Acid–base disorders are of four types:

1. Respiratory acidosis
2. Respiratory alkalosis
3. Metabolic acidosis
4. Metabolic alkalosis

Respiratory acidosis results from accumulation of carbon dioxide due to hypoventilation.

Respiratory alkalosis is seen during hyperventilation.

Metabolic acidosis can occur either due to increased production of metabolic acids such as lactic acid or due to the reduced ability of kidney to excrete acids.

Metabolic alkalosis is seen with loss of hydrogen ions through vomiting or renal excretion.

Different biological systems compensate for acid–base imbalance.

Metabolic acidosis is compensated by the respiratory system by hyperventilation (increase in the rate and depth of respiration). In respiratory alkalosis, the rate and depth of respiration decreases the building up of carbon dioxide concentration.

The kidney conserves bicarbonates in acidosis and excretes bicarbonates in alkalosis.

FLUID–ELECTROLYTE BALANCE

Body fluid constitutes about 60% of the total body weight of a normal healthy male. It is distributed between the extracellular and the intracellular compartments.

A delicate balance between the intake of fluid and its excretion is required to maintain normal body functions.

Hormones and thirst play an important role in the maintenance of fluid balance.

When there is excess fluid in the body, plasma osmolarity decreases and dilute urine is excreted. However, reduction in fluid volume will influence the kidney to excrete a small quantity of concentrated urine. **Thirst** is one of the important mechanisms promoting intake of fluids.

Increased extracellular fluid osmolarity
↓
Intracellular dehydration in thirst center
↓
Stimulation of thirst center
↓
Increased fluid intake
↓
Restoration of extracellular fluid volume

Decrease in extracellular fluid volume
↓
Reduction in arterial pressure
↓
Activation of the renin-angiotensin-aldosterone system (kidney)
↓
Stimulation of thirst center
↓
Increased fluid intake
↓
Restoration of extracellular fluid volume

Powerful feedback systems mediated by several hormones play an important role in the maintenance of fluid balance.

Increased plasma osmolarity
↓
Reduced blood volume
↓
Decreased blood pressure
↓
Release of renin from the kidney
↓
Formation of angiotensin II
↓
Feeling of dryness of mouth
↓
Stimulation of thirst center
↓
Increased intake of water
↓
Reduction of plasma osmolarity
↓
Restoration of normal blood pressure

ROLE OF ADH

Antidiuretic hormone (ADH) has an important role in regulation of fluid balance.

Increased intake of fluid reduces the secretion of ADH resulting in excretion of dilute urine.

Decreased intake of fluid increases the production of release of ADH.

Antidiuretic hormone acts on the distal convoluted tubule and collecting duct of the nephron.

ADH helps in the formation of water channels by insertion of aquaporin-2 in the apical membrane of the collecting duct.

Aquaporins allow water to move down their osmotic gradient out of the nephrons. This increases water reabsorption.

Increase in osmolarity of body fluids
↓
Shrinkage of osmoreceptors in hypothalamus due to exosmosis
↓
Secretion of ADH (vasopressin) from hypothalamus and release from posterior pituitary
↓
Increase in permeability of DCT and collecting duct of nephron
↓
Reabsorption of a large volume of water
↓
Excretion of concentrated urine

Increase in fluid volume
↓
Decrease in osmolarity of body fluids
↓
Swelling of osmoreceptors in hypothalamus due to endosmosis
↓
Reduced secretion and release of ADH
↓
Decreased in permeability of distal tubule and collecting duct to water
↓
Excretion of a large quantity of dilute urine

ROLE OF ALDOSTERONE

The hormone aldosterone secreted from the adrenal cortex regulates electrolyte balance. It facilitates reabsorption of sodium ions and excretion of potassium ions.

Aldosterone produces the effect by acting on the mineralocorticoid receptors in the distal tubule and collecting ducts of the nephron.

The drugs that reduce secretion and action of aldosterone are used as antihypertensives.

Decreased blood flow to the kidney due to reduced blood pressure
↓
Release renin from the kidney
↓
Formation of angiotensin II
↓
Stimulation of adrenal cortex to produce aldosterone
↓
Increased absorption of sodium under the influence of aldosterone
↓
Enhanced water retention by the kidney
↓
Increased fluid volume

ROLE OF ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) reduces the extracellular volume by increasing renal excretion of sodium. ANP promotes excretion of sodium by increasing pressure in glomerular capillaries, increasing GFR, and by reducing its absorption in DCT.

Increase in fluid and electrolytes
↓
Increase in blood volume
↓
Distension of atria
↓
Release of ANP from atrial myocytes (muscle cells)
↓
Increased GFR and reduced sodium absorption by the kidney
↓
Increased excretion of salt and water
↓
Reduced blood volume

REVIEW QUESTIONS

Long Essay

1. Describe the mechanism of urine formation.
2. Draw a labeled diagram showing nerve supply to the urinary bladder. Explain the mechanism of micturition. What is a neurogenic bladder?
3. Describe the role of countercurrent multiplier and exchange system in concentrating urine.

Short Essay

1. Describe the structure of a nephron.
2. Describe the functions of proximal convoluted tubules of the kidney.
3. Explain the structure of juxtaglomerular apparatus. What are its functions?
4. List peculiarities of renal circulation.
5. Explain the theories of autoregulation.
6. What is GFR? What is its normal value? How is it measured?
7. What is effective filtration pressure in the kidney? List the factors influencing it.
8. What is the normal renal blood flow? How is it measured?
9. Define renal clearance. Explain standard and maximal urea clearance.
10. Explain tubuloglomerular feedback
11. Describe the renal tubular handling of sodium.
12. Describe the reabsorption of water in renal tubules.
13. Describe the glucose reabsorption in the kidney. Give the normal value for renal threshold and tubular maximum for glucose.
14. Explain the mechanism of bicarbonate absorption.
15. Explain the mechanism of potassium handling by the kidney.
16. Explain the nerve supply to urinary bladder. Add a note on micturition reflex.
17. Write briefly about artificial kidney.
18. Explain renal function tests.
19. Explain two types of an abnormally functioning bladder.
20. Discuss the mechanism of action of diuretic

Short Answer

1. Draw a labeled diagram of a nephron.
2. Mention types of nephrons and one function for each.
3. List the functions of kidney.
4. Mention nonexcretory functions of kidney
5. What are the peculiarities of renal circulation?
6. List the factors influencing GFR.
7. What is PAH clearance? What is its clinical application?
8. Mention the components of filtration membrane.
9. What is filtration fraction? What is its normal value?
10. What is renal glycosuria?
11. What is splay?
12. What is tubuloglomerular feedback?
13. What is osmotic and water diuresis?

14. Mention substances secreted and reabsorbed in the distal convoluted tubule of the kidney.
15. How do you distinguish between diabetes mellitus and diabetes insipidus by examination of urine?
16. What is automatic urinary bladder?
17. What is atonic bladder?
18. What is cystometrogram?
19. What is renal failure? What are its types?
20. Enumerate the pathological constituents of urine.
21. What is the normal body temperature? Describe the role of hypothalamus in its regulation.
22. What are the physiological changes that occur in the body when exposed to high temperature?
23. What are the physiological changes that occur when the body is exposed to low temperature?
24. What is fever? Describe the mechanism of its causation.
25. Explain the mechanisms for heat loss and gain by the body.

CHAPTER

8 Central Nervous System

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Enumerate the division of nervous system. List the parts of the brain and its functions.
- Describe the structure of a chemical synapse. Discuss the properties and impulse transmission across it.
- Explain the components of a reflex arc. Discuss the properties of it.
- Classify the receptors. Describe the properties of it.
- Explain the organization and functions of sensory and motor system.
- Discuss the pathophysiology of pain and its clinical importance.
- Explain origin, course and termination of important sensory and motor tracts.
- Describe the effect of hemisection and complete transection of spinal cord.
- List the nuclei and discuss the functions of hypothalamus.
- List the divisions of thalamus. Explain its functions. Discuss the features of thalamic syndrome.
- List the divisions of basal ganglia. Describe its functions.
- Enumerate the division of cerebellum. Explain its functions.
- Explain the physiological basis of sleep.
- Explain the formation and functions of reticular activating system. Discuss the waves of EEG.
- Explain the formation and functions of CSF and blood brain barrier.
- Describe the mechanism of regulation of tone, posture and equilibrium.
- Explain the evolution and higher functions in human beings.
- Describe the formation of autonomic nervous system. Tabulate effect of its stimulation on different systems.
- Successfully answer the questions and MCQs at the end of this chapter.

The living beings respond to changes in the external environment. The constantly changing surrounding poses a great threat to homeostasis. Internally, there will be changes to suit the alteration in the exterior. The various systems of the body are controlled by the **nervous** and **endocrine** systems. The regulatory mechanisms are together called **neuroendocrine control**.

Solving a complex mathematical problem, responding to a painful stimulus, reacting to emotional disturbance, feeling hungry, and getting satisfaction on consuming food need neural processing.

Different regions of the central nervous system react under varying circumstances to produce an optimal response.

The general pattern of functioning of the nervous system has three major components, namely:

1. Input
2. Processing
3. Output

The information received by the receptors is transmitted to the site of processing like the brain and spinal cord through the afferent nerve. Complex processing of information happens at the level of the brain, whereas subconscious, life-saving responses are produced at the spinal level. There may not be involvement of higher centers of the brain during this processing. However, the information about the processing at the spinal level is sent later to the cortex for information and further processing. Later, the output generated passes through the effector nerve. The final effect is produced by the activation of the effector organ.

DEVELOPMENT OF BRAIN

The earliest phase of brain development starts in a 3-week-old embryo. The ectoderm along the dorsal midline axis of embryo forms the **neural plate**. This plate invaginates to form a neural groove with **neural folds** on either side. The superior edge of the neural folds fuses to form the **neural tube**.

The neural tube formed in the fourth week of pregnancy differentiates into the CNS. The anterior part of the neural tube forms the brain and the posterior part forms the spinal cord.

DIVISIONS OF THE NERVOUS SYSTEM

The nervous system is divided into

i. central,
ii. peripheral, and
iii. autonomic nervous systems.

1. The **central nervous system** consists of
   - brain and
   - spinal cord.
2. The **peripheral nervous system** consists of
   - 12 pairs of cranial nerves and
   - 31 pairs of spinal nerves.
3. The **autonomic nervous system**, consists of
   - sympathetic division and
   - parasympathetic division.

The central nervous system is enclosed by a protective covering termed **meninges**.

The layers of meninges are as follows:

- Outer **dura mater**
- Middle **arachnoid mater**
- Inner **pia mater**

BRAIN

The human brain is divided into three main divisions.

These divisions are as follows:

1. Prosencephalon or forebrain
2. Mesencephalon or midbrain
3. Rhombencephalon or hindbrain

The **prosencephalon** (forebrain) is divided into **telencephalon** and **diencephalon**.

The **telencephalon** includes cerebral hemispheres, basal ganglia, hippocampus, and amygdala.

The **diencephalon** comprises thalamus, hypothalamus, metathalamus, and subthalamus.

Mesencephalon (midbrain) comprises the tectum, tegmentum, cerebral aqueduct, and cerebral peduncles (crus cerebri).

The **rhombencephalon** (hindbrain) is made up of cerebellum, pons, and medulla oblongata.

CEREBRAL HEMISPHERES

The cerebral hemispheres occupy a major part of the cranial cavity (**Fig. 8.1**). They are divided into right and left hemispheres by the longitudinal fissure. The two cerebral hemispheres are connected by a bundle of nerve fibers called the **corpus callosum**. The cerebral hemispheres have an outer shell of gray matter, termed the **cerebral cortex**.

The cerebral cortex has three kinds of functional areas:

1. Motor areas
2. Sensory areas
3. Association areas

The cells of the cerebral cortex are arranged in six layers.

The cortical neurons are made up of pyramidal and nonpyramidal types of cells. The pyramidal cells give major output from the cortex.

The myelinated nerve fibers of tracts form the white matter.

The basal nuclei are the gray matter present deep within the white matter. The subcortical nuclei are called the **basal ganglia** or **basal nuclei**.

CEREBRAL VENTRICLES

The ventricles arise from the expansion of lumen of the embryonic neural tube. The brain contains four interconnected cavities lined by ependymal cells (type of neuroglia) called **cerebral ventricles** (**Fig. 8.2**). They are paired lateral ventricles, third and fourth ventricles. They are filled with circulating cerebrospinal fluid.

DIENCEPHALON

The diencephalon forms the central core of the forebrain, surrounded by the cerebral hemispheres.

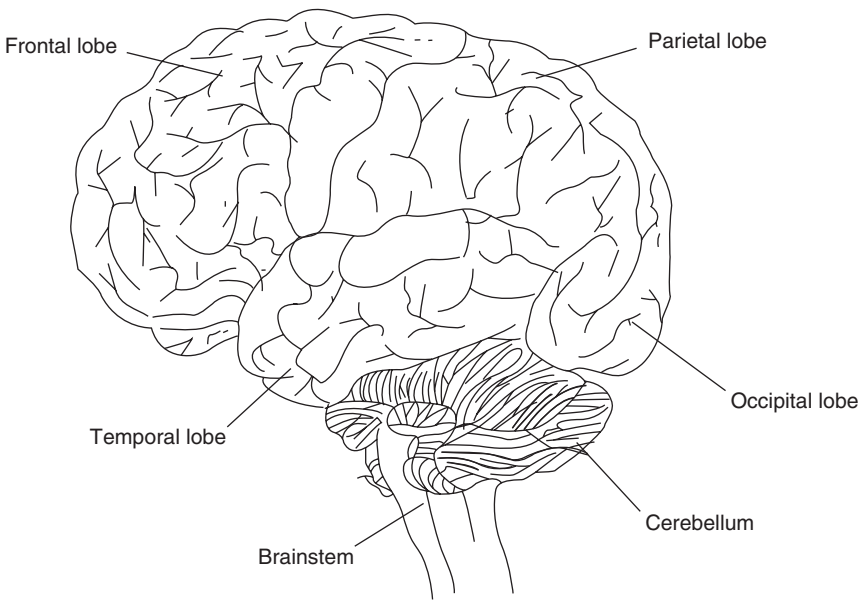


Figure 8.1 Lateral view of the brain.

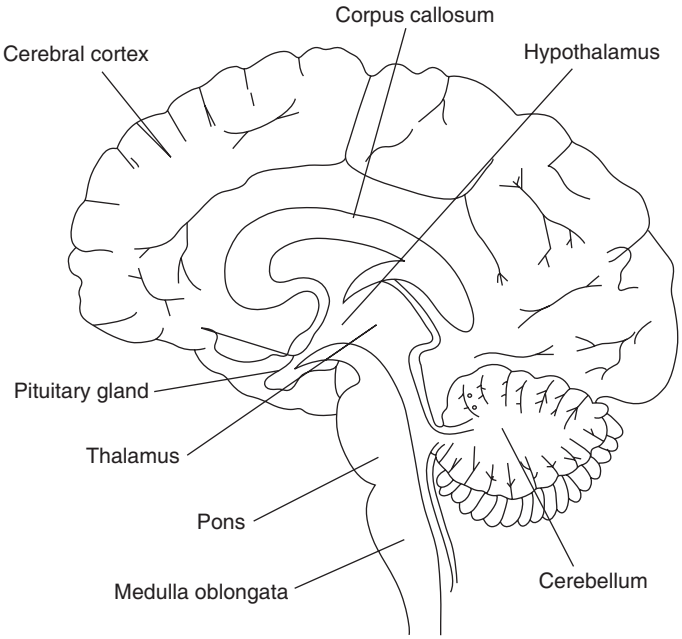


Figure 8.2 Sagittal section of the brain.

It contains three paired structures:

1. Thalamus
2. Hypothalamus
3. Epithalamus

The epithalamus is the most dorsal part of diencephalon and forms the roof of the third ventricle. The pineal gland is seen as an extension from its posterior border.

BRAINSTEM

The brainstem consists of midbrain, pons, and medulla oblongata. The core of the brainstem consists of loosely arranged neuronal cells with bundles of axons termed **reticular formation**.

The reticular formation is absolutely essential for life. It is involved in the control of motor functions and cardiovascular and respiratory activities. It regulates the sleep and wakefulness cycle.

CEREBELLUM

The cerebellum is located posterior and inferior to the cerebrum. It has two cerebellar hemispheres. It is an important center for coordinating movements, controlling posture, and maintaining equilibrium.

It receives information from the muscles, joints, eyes, ears, viscera, and parts of brain involved in the control of movements. The cerebellum not only performs motor functions but is also involved in the process of learning.

SPINAL CORD (Fig. 8.3)

The spinal cord is an extension of the medulla oblongata and is located in the bony vertebral column. It has an outer white matter and an inner gray matter. The central canal which is a continuation of the cerebral ventricles passes through the spinal cord.

The cell bodies of the neurons group together in the CNS to form the **gray matter** and the fibers form the **white matter**. In the brain, the gray matter is outside and the white matter is inside.

The cell bodies of the neurons collect together to constitute the **nuclei** and the fibers join to form the **tract**.

The inputs reach the brain through sensory receptors and sensory division of

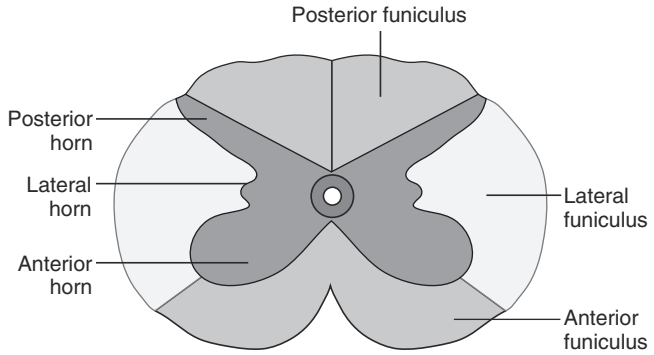


Figure 8.3 Cross-section of the spinal cord. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

the nervous system. The brain acts as an information-gathering, data-analyzing, and decision-making device. The useful information is stored as memory. The desired response is produced with the help of motor division of the nervous system. It results in the contraction of the muscle or secretion from the gland.

The spinal cord gives out segmental nerves. There are 31 spinal segments with 31 pairs of nerves, which are as follows:

- Cervical 8
- Thoracic 12
- Lumbar 5
- Sacral 5
- Coccygeal 1

A typical spinal nerve is a mixed nerve. It has a sensory division located in the dorsal root. The cell body of the afferent nerve is in the dorsal root ganglion. The ventral division is motor and carries somatic efferent to the muscles. The anterior root of the spinal nerve from T_1 to L_2 segments carries sympathetic efferents. The parasympathetic fibers are carried by the spinal nerves from the S_2 to S_4 segments.

In addition to the neurons, the nervous system has the supporting cells called the **neuroglia**.

The neuron is the structural and functional unit of the nervous system. It is also called **nerve fiber**. A group of neurons together in the peripheral nervous system forms a **nerve**. A group of neurons in the central nervous system constitutes a **pathway or a tract**.

Groups of cell bodies of neurons in the peripheral nervous system are termed **ganglia** (singular: ganglion). They are called **nuclei** (singular: nucleus) in the central nervous system.

There are about 100 billion neurons in the CNS.

SYNAPSE

The synapse (Greek word meaning clasp or join) is a junction between two neurons. The information from the nerve terminal of one neuron is relayed to the other neuron.

There are about 10^{14} synapses in the CNS.

The organization of the synapse depends on the protein bound to the presynaptic membrane called **neurexin**. Neurexin holds the synapse together and provides synaptic specificity.

The neuron which ends at the synapse is termed the **presynaptic neuron**. The neuron which receives the information is termed the **postsynaptic neuron**.

The electrical activity of the presynaptic neuron influences the activity in the postsynaptic neuron. The response in the postsynaptic terminal can be excitatory or inhibitory depending on the type of neurotransmitter.

TYPES OF SYNAPSE

The anatomical types of synapses are

- **Axoaxonic**—axon of one neuron makes synaptic connection with the axon of another neuron
- **Axodendritic**—axon of one neuron makes connection with the dendrite of the other neuron
- **Axosomatic**—axon of one neuron makes connection with the cell body or soma of the other neuron
- **Dendrodendritic**—dendrites of two neurons make connection with each other

The functional types of synapses are

- electrical,
- chemical, and
- conjoint.

The **electrical synapses** have open fluid channels that conduct electricity between the adjacent cells. They have gap junctions and the ions pass through low-resistance bridges. The communication in these synapses can be unidirectional or bidirectional depending on their nature. The synaptic cleft is absent in an electrical synapse.

In the **chemical synapse**, the synaptic cleft separates pre- and postsynaptic terminals. There is functional continuity but no structural continuity. The chemical mediator (neurotransmitter) released from the presynaptic terminal conveys the signals to the postsynaptic terminal.

Conjoint synapse: The transmission of impulse in these types of synapse is both chemical and electrical.

STRUCTURE OF A SYNAPSE (Fig. 8.4)

A typical chemical synapse has the following parts:

- Presynaptic terminal
- Synaptic cleft or synaptic gutter
- Postsynaptic terminal

The **presynaptic terminal** is a distended portion of the nerve terminal forming the

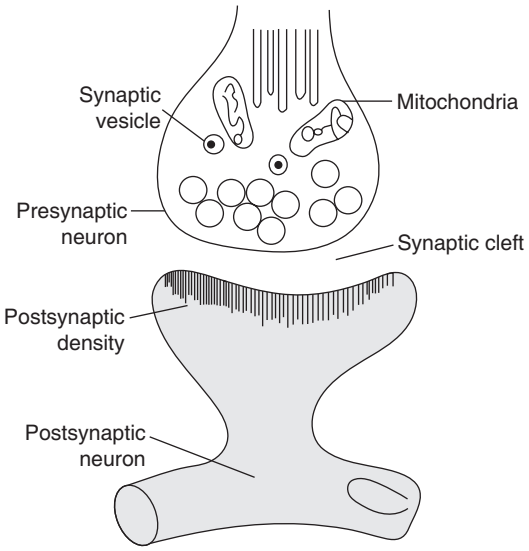


Figure 8.4 Structure of synapse.

terminal button or **synaptic knob**. The terminal has mitochondria and vesicles with a neurotransmitter. The vesicles fuse with the presynaptic membrane and release the content to the synaptic cleft at the thickened area of membrane termed **active zone**.

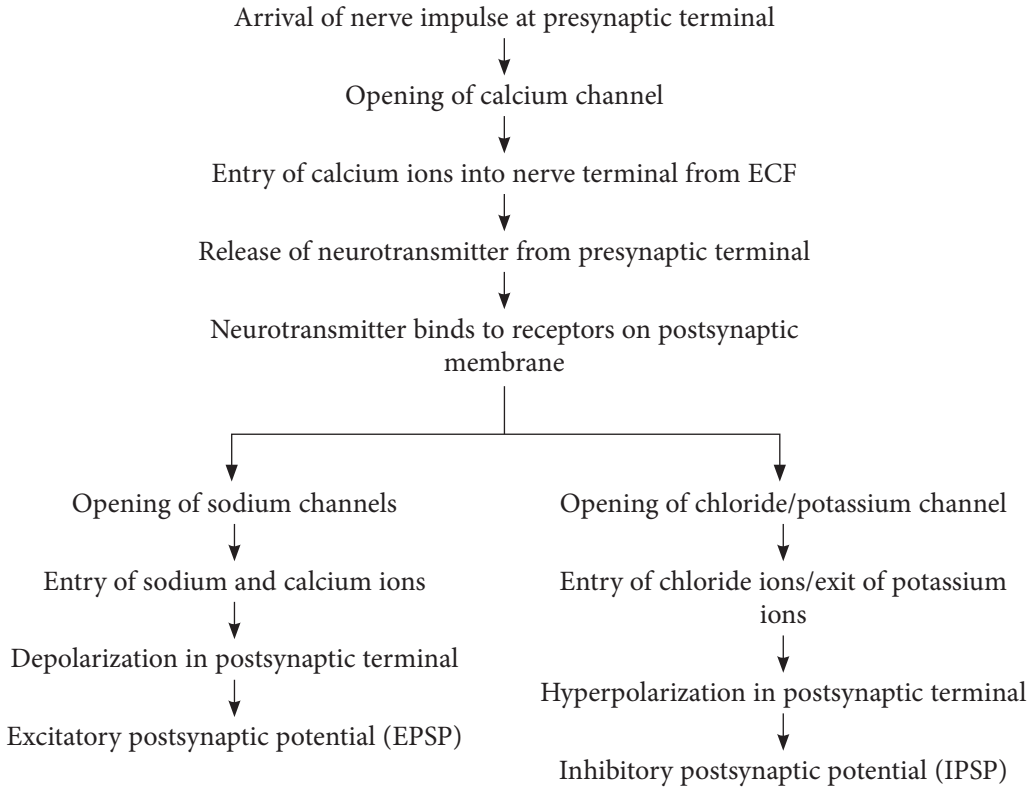
Majority of neurotransmitters are synthesized in the cell body and transported to the nerve terminal by axoplasmic transport. The neurotransmitters are recycled at the nerve terminal.

The **synaptic cleft** or **synaptic gutter** separates the pre- and postsynaptic terminals. It is about 20–40 nm wide.

The **postsynaptic terminal** contains receptors for the neurotransmitter secreted from the presynaptic terminal. The neurotransmitter binds to these receptors and conveys the signals from the presynaptic terminal.

TRANSMISSION OF IMPULSE ACROSS A SYNAPSE

- The impulse (action potential) comes to the nerve terminal. This increases the permeability of the membrane to the calcium ions.
- The calcium ions enter the nerve terminal from the extracellular compartment.



- The calcium ions bind to the protein anchoring the vesicles.
- The release of vesicles from the anchoring protein causes its movement to the presynaptic membrane.
- Synaptobrevin (a protein) present on the membrane of the vesicle binds to syntaxin on the presynaptic membrane.
- The vesicles rupture, releasing the neurotransmitter into the synaptic cleft. Alternatively, during the release of a neurotransmitter, the vesicles fuse with the presynaptic membrane and discharge the neurotransmitter through a small hole. The hole gets sealed off immediately and the vesicle remains inside the terminal.
- The neurotransmitter crosses the synaptic cleft and binds to the receptor on the post-synaptic membrane.
- The neurotransmitter binding to the receptor increases the permeability of the membrane to the sodium ions.
- The entry of sodium ions forms the action potential in the postsynaptic terminal. Alternatively, opening of chloride or potassium ion channel results in hyperpolarization.
- After the impulse transmission is completed, the neurotransmitter is broken down.
- The broken-down products are taken up by the nerve terminal for the resynthesis of the neurotransmitter.

Excitatory Postsynaptic Potential

A single stimulus applied to a sensory nerve results in partial depolarization in the postsynaptic neuron. During this process, the excitability of the neuron is increased to a second stimulus.

Ionic Basis

The excitatory neurotransmitter at the synapse binds to the receptors on the postsynaptic membrane. This triggers opening of the sodium/calcium channels. The sodium/calcium moves along its concentration gradient.

It produces partial depolarization resulting in excitatory postsynaptic potential (EPSP).

The summation of EPSP results in the formation of propagated action potential.

Inhibitory Postsynaptic Potential

A stimulus applied to a sensory nerve can result in hyperpolarization in the postsynaptic neuron. During this potential, the excitability of the neuron to a second stimulus is decreased.

Ionic Basis

The stimulation of the inhibitory synaptic knob at the synapse releases the neurotransmitter. This triggers the opening of the chloride channels on the postsynaptic membrane. The chloride moves along the concentration gradient. This results in hyperpolarization producing inhibitory postsynaptic potential (IPSP).

During IPSP, the membrane potential moves away from the firing level. IPSP can also be produced by opening the potassium channel, resulting in its efflux (efflux of positive charges), or by closing sodium and calcium channels, thus preventing the entry of positive charges.

PROPERTIES OF SYNAPSE

Synaptic Delay

There is a delay in between the application of stimulus in the presynaptic terminal and the onset of response in the postsynaptic terminal. This time interval is called the **synaptic delay**. A normal synaptic delay is about 0.5 ms. This delay is due to the time needed for changes at the synapse during the impulse transmission. It is possible to estimate the number of synapses in a pathway by measuring the synaptic delay.

Convergence and Divergence

Convergence is the ending of a number of presynaptic terminals on a single postsynaptic terminal. Divergence is a single presynaptic terminal establishing connection with multiple postsynaptic terminals. Convergence and divergence are structural requirements for properties such as facilitation, occlusion, and reverberation.

One-Way Conduction

The impulse transmission occurs from the pre- to the postsynaptic terminal. This is due to the structure of the pre- and postsynaptic terminals, which is different from each other. It must be noted that the transmission of impulse cannot occur in the opposite direction.

The presynaptic terminal has the neurotransmitter. The postsynaptic membrane has the receptor for binding of the neurotransmitter. This unique structure of synapse facilitates transmission of impulse from the presynaptic terminal to the postsynaptic membrane.

Fatigue

The partial depletion or exhaustion of the neurotransmitter reduces or stops the transmission of impulse at the synapse temporarily. This phenomenon is called **fatigue**. Fatigue can also be produced due to poor responsiveness of postsynaptic receptors (receptor desensitization).

Summation

Two stimuli applied to the excitable tissue in relation to time or space add up to give the effect of summation. They are termed **temporal** and **spatial** summation, respectively. The second stimulus potentiates the effect of the first stimulus. **Figure 8.5** shows neurons A and B converging on X. Stimulus applied to A or B produces EPSP at X. However, when A and B are stimulated simultaneously, two areas of depolarization are produced in X. Summation of these depolarizing changes produces an action potential.

Occlusion

The stimulation of two neurons sharing a common neuronal pool produces a response. The response obtained is less than the sum of

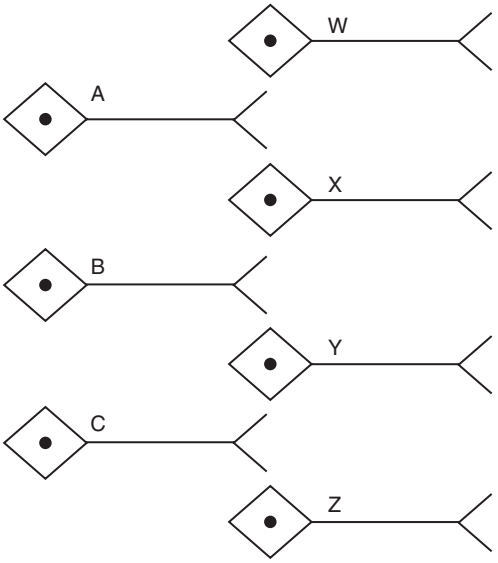


Figure 8.5 Summation and occlusion.

the responses produced by an individual neuron when they are stimulated separately. This effect is called **occlusion**. It is due to the overlap of neurons. **Figure 8.5** shows presynaptic fibers from B and C sharing postsynaptic neuron Y. Stimulation of B and C simultaneously produces a response in Y, which is less than the sum of responses produced by stimulation of B and C separately.

Habituation and Sensitization

When noninjurious stimuli are repeated, the intensity of response decreases or may even stop. This is **habituation**. When the injurious stimuli are given along with the noninjurious stimulus, it causes an increase in the response. This is called **sensitization**. Habituation is due to reduced calcium ions at the presynaptic terminal. Increased entry of the calcium ions at the presynaptic terminal produces sensitization.

Post-Tetanic Potentiation

It is an example of plasticity of the neuron. Repeated or continuous use of synapse enhances the ability of the presynaptic terminal to excite the postsynaptic neuron. There is enhanced postsynaptic potential in response to stimulation. It is also called **synaptic potentiation**. It is produced due to the presynaptic accumulation of the calcium ions in response to the tetanizing stimulation. The change lasts for about 60 seconds.

It is a mechanism underlying the process of learning. Post-tetanic potentiation increases the efficiency of neurotransmission along a particular pathway. Hippocampus, which plays a vital role in learning and memory, exhibits post-tetanic potentiation.

Synaptic Plasticity

Synaptic plasticity is the ability of the synapse to change its function in response to alteration in the activity. Increase or decrease of activity strengthens or weakens the synaptic function. Learning and memory is based on the property of synaptic plasticity. Synaptic plasticity depends on

- change in the number of receptors,
- alteration in the quantity of neurotransmitter release,
- responsiveness of the cell to the released neurotransmitter, and
- release and concentration of calcium ions.

Synaptic Development

The axons during the formation of synapse exhibit growth cones at their tips, which pass through the tissues. The specialized proteins termed *semaphorins* influence the migrations of these cones. During the process of development, a large number of synapses are formed. The nonfunctional synapses disappear subsequently.

SYNAPTIC INHIBITION

Presynaptic Inhibition (Fig. 8.6)

In this type of inhibition, the inhibitory neuron ends on the presynaptic terminal. The stimulation of presynaptic and inhibitory neurons simultaneously results in a decreased response at the postsynaptic terminal. This is accomplished by reducing the amplitude

of the action potential. The mechanisms for presynaptic inhibitions are as follows:

- Hyperpolarization is produced due to the increased efflux of potassium or influx of chloride at the presynaptic terminal.
- Hyperpolarization at the presynaptic terminal reduces the calcium influx. This in turn reduces the neurotransmitter release.
- Inhibitory neurotransmitters act through G proteins.
- There occurs direct reduction in the release of the neurotransmitter which is independent of the ionic mechanism.

The first neurotransmitter which has been demonstrated to produce presynaptic inhibition is **gamma-aminobutyric acid** (GABA).

The gate control mechanism of inhibition of pain perception is an example of presynaptic inhibition. The descending pathway inhibits the pain impulses coming through the afferent nerve.

Presynaptic facilitation is produced due to prolongation of the duration of action potential and opening of calcium channels for a longer duration.

Postsynaptic Inhibition (Fig. 8.6)

The voluntary or reflex contraction of a muscle is accompanied by simultaneous relaxation of the antagonistic group of muscles. This is known as **reciprocal inhibition**. This occurs as a result of the reciprocal innervation.

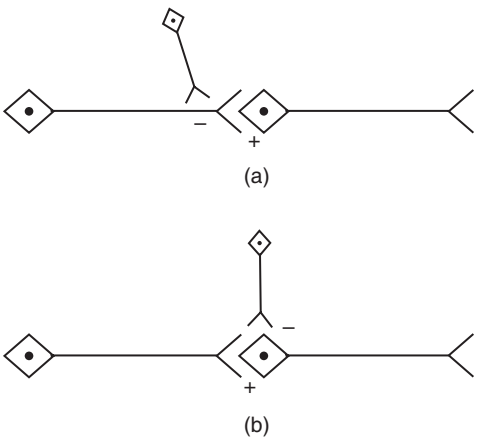


Figure 8.6 Synaptic inhibition. (a) Pre- and (b) postsynaptic inhibitions.

The afferent impulses from the agonist muscle cause **postsynaptic inhibition** of the motor neuron to the antagonistic muscle. The pathway mediating this effect is bisynaptic.

Postsynaptic inhibition occurs when an inhibitory neurotransmitter such as glycine or GABA is released from the presynaptic terminal.

For example, the contraction of biceps muscle relaxes the triceps muscle, resulting in smooth flexion at the elbow joint.

Reciprocal Innervation (Fig. 8.7)

The sensory nerve arising from a group of muscles (biceps) makes excitatory connection with the motor neuron for the same muscle. The sensory nerve makes connection with the inhibitory neuron, which ends on the motor nerve to the antagonistic muscle (triceps).

This type of innervation helps the contraction of one (agonist) group of muscles by relaxing the opposing (antagonist) group of muscles to the same extent.

Renshaw Cell Inhibition (Negative Feedback Inhibition)

The axons of the motor neurons give off collaterals as they emerge through the anterior horn of the spinal cord. These collaterals make an excitatory synaptic connection with a special group of neurons called the **Renshaw cells**, present in the anterior horn.

The Renshaw cells send short axons, making inhibitory synaptic connection with the same motor neuron. These cells are activated when the motor neurons are excited. They have a feedback effect on the same motor neuron,

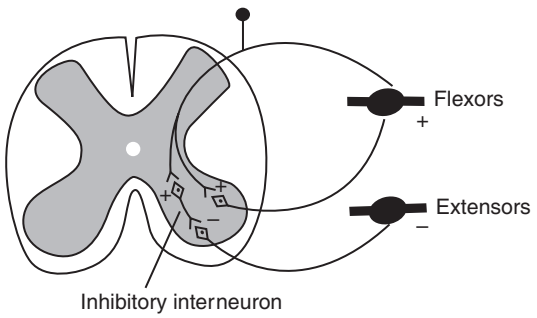


Figure 8.7 Reciprocal Innervation.

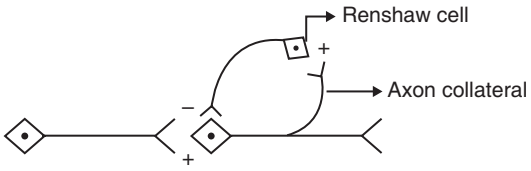


Figure 8.8 Renshaw cell inhibition.

inhibiting their discharge. This is known as **Renshaw cell inhibition** (**Fig. 8.8**).

RECEPTORS OF SYNAPSE

Receptors of synapse are modified proteins which act as the binding site for hormones and neurotransmitters.

The receptors can be **postsynaptic** or **presynaptic**.

Postsynaptic Receptors

The postsynaptic receptors regulate the activity in the postsynaptic neuron in response to the presynaptic stimulation and release of neurotransmitter.

Presynaptic Receptors

The presynaptic receptors or **autoreceptors** inhibit further secretion of the neurotransmitter, thus providing a feedback control.

The **heteroreceptor** is also a type of presynaptic receptor. It responds to a chemical mediator different from the neurotransmitter released from the same nerve terminal.

Norepinephrine acts on the heteroreceptor present on the cholinergic terminal to regulate the release of acetylcholine.

NEUROTRANSMITTERS

Neurotransmitters are the substances that help in the transmission of impulses across the synaptic cleft in a chemical synapse. Otto Loewi, a German pharmacologist, introduced the concept of a chemical neurotransmitter. The proteins needed for the synthesis of neurotransmitter are formed in the cell body and transported to the nerve terminal by the **axoplasmic flow**.

The neurotransmitters are as follows:

- **Acetylcholine**
- **Amines**: Epinephrine, norepinephrine, serotonin, dopamine, and histamine
- **Excitatory amino acids**: Aspartate and glutamate
- **Inhibitory amino acids**: Glycine and GABA
- **Polypeptides**: Opioid peptides like enkephalin, endorphin, dynorphin, and substance P
- **Gases**: Nitric oxide
- **Lipids**: Cannabinoids such as anandamide
- **Others**: Purines, pyrimidines, and prostaglandins

FATE OF NEUROTRANSMITTERS

A neurotransmitter after completing the transmission of impulse undergoes change at the synapse. The fate of neurotransmitter is as follows:

- Reuptake by the presynaptic terminal
- Degradation by enzymatic action
- Diffusion out of the synaptic cleft

NEUROMODULATORS

Neuromodulators are substances having nonsynaptic action on the neurons. They alter the sensitivity of the neuron to synaptic stimulation or inhibition. Neuromodulators are secreted by the neurons having very little action of their own, but modify the action of neurotransmitter.

Dopamine, histamine, and serotonin function as neuromodulators. The neuromodulators work for a long duration as they are not metabolized immediately.

NEUROTROPHINS

Neurotrophins are proteins required for the growth, development, and survival of the neurons. They are produced by the muscles, astrocytes, and structures innervated by the neurons. Neurotrophins help in differentiation of progenitor cells to form neurons.

REFLEX ACTION

The reflex action is an involuntary response to a sensory stimulus. Many of the body control mechanisms belong to the category termed **reflexes**. The hand is withdrawn on touching a hot object. This response is integrated at the level of spinal cord without any help from the higher centers of the brain.

Noxious stimulus produces a response even before the conscious realization in order to protect the body against potential damage. There are constant changes within and outside the body. These changes have to be perceived and necessary modifications done to counter them to maintain a stable state.

Examination of somatic reflexes is clinically important to assess the condition of the nervous system. It is helpful in locating the site and identifying the type of lesion.

The reflex action is produced with the help of a reflex arc (**Fig. 8.9**).

The **reflex arc** consists of

- **receptor**—a modified nerve terminal with a group of special cells capable of receiving different types of stimuli,
- sensory or **afferent nerve**, transmitting signals to the center,
- synapse or the **center** present in the spinal cord (sensory input is converted to motor response),
- motor or **efferent nerve**, conducting motor response to effector organs, and
- **effector organ**—muscle or gland.

Bell–Magendie Law

This law states that the dorsal or posterior root entering the spinal cord is sensory and the ventral or anterior root emerging from the spinal cord is motor.

CLASSIFICATION OF REFLEXES

1. **Based on the number of synapses**
   - *Monosynaptic reflex:* There is a single synapse in the reflex arc, e.g., stretch reflex.
   - *Polysynaptic reflex:* This reflex involves group of muscles. There is more than one synapse in the reflex arc, e.g., withdrawal reflex.
2. **Based on the development**
   - *Unconditioned reflex:* It is an inborn reflex or a reflex present since birth; e.g., taste of the food produces salivation.

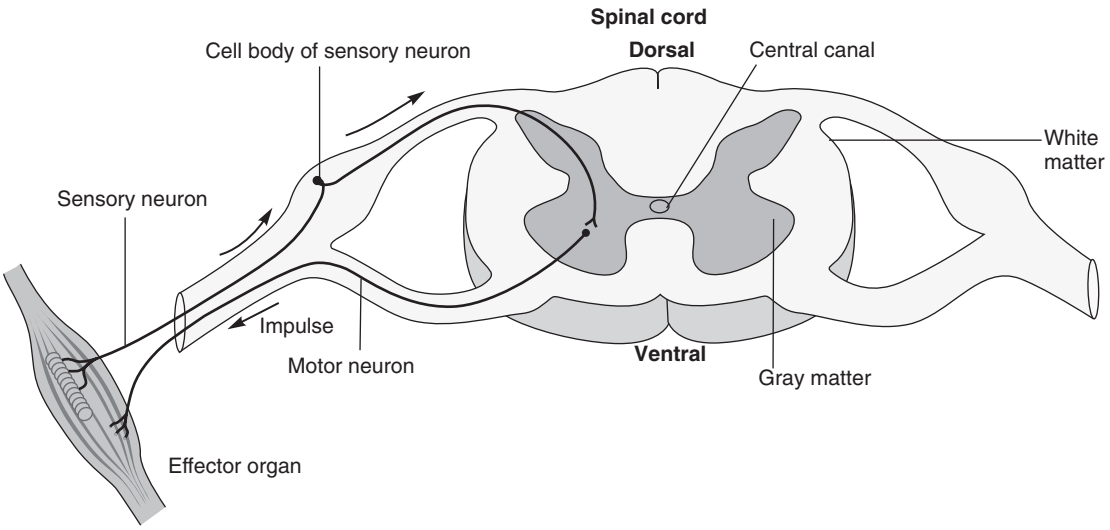


Figure 8.9 Reflex arc. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- *Conditioned reflex:* It is an acquired reflex or a reflex produced by learning. The conditioned reflex can be produced over an unconditioned response; e.g., thought of favorite food produces salivation.

3. **Clinical classification**
   - *Superficial reflex:* Examples include conjunctival, corneal, and plantar reflexes.
   - *Deep reflex:* Tendon reflexes such as biceps jerk and triceps jerk.
   - *Visceral reflex:* Examples include micturition and defecation reflex.
4. **Functional classification**
   - Somatic reflexes: They activate skeletal muscles. The somatic reflexes mediated by the spinal cord are called spinal reflexes.
   - Autonomic (visceral) reflexes: They activate visceral effectors such as glands or smooth and cardiac muscles.

PROPERTIES OF REFLEXES

- **Delay**: The time interval between the application of stimulus and the onset of response is known as delay. This delay is due to the passage of impulse through components of the reflex arc.
- **One-way conduction**: The conduction of impulse occurs in one direction. The conduction is toward the center (centripetal) in the afferent limb and it is away from the center (centrifugal) in the efferent limb.
- **Summation**: A reflex action is capable of being summated. When the summation is related to time, it is known as **temporal summation**. In this condition, successive stimuli are given one after the other with a short time interval in between them at the same point. The effect of the second stimulus potentiates the action of the first stimulus to produce a better response.

  If the summation is related to space, it is called **spatial summation**. Two stimuli are given simultaneously close to each other. The local response produced by each of the stimulus adds up to give a summated response. (Summation means to add up.)
- **Occlusion**: Simultaneous stimulation of two nerves sharing a common neuronal pool produces a response. The response obtained would be less than the sum of two individual responses. This occurs as a result of the overlap of two neurons.
- **Facilitation**: Repeated elicitation of the reflex increases the response. This is termed facilitation. Facilitation is due to increased presynaptic calcium ion concentration leading to release of a greater quantity of neurotransmitter.
- **Subliminal fringe (subminimal fringe)**: The stimulation of a reflex pathway increases the excitability of the associated pathways. As the associated pathway is partially stimulated, it can be activated easily. This increased excitability of the associated pathway is the subliminal fringe.
- **Irradiation**: When the strength of the stimulus is gradually increased, the central excitatory state spreads. (Impulses in the spinal cord spread to the segments above and below the level of activation.) Hence, a greater number of nerve fibers and additional groups of muscles take part in reflex response. This is called irradiation.
- **Habituation and sensitization**: When a noninjurious stimulus is applied repeatedly, the intensity of response decreases or may even stop. This is known as **habituation**. During habituation, synaptic transmission is depressed. It is attributed to prolonged inactivation of calcium ion channels in a presynaptic terminal.

  On the other hand, injurious stimulus applied repeatedly causes intensification of the response. This is known as **sensitization**. Sensitization is due to increased responsiveness of calcium ion channels in the presynaptic terminal. There will be increased calcium influx and release of a larger amount of neurotransmitter from the nerve terminal.

TYPES OF REFLEXES

Conditioned Reflex

The conditioned reflex is a learned or acquired reflex set up by experience. The characteristic features of the conditioned reflex are as follows:

- Conditioned reflex always develops on the basis of the unconditioned reflex.
- The speed of development is fairly quick.
- Unconditioned stimulus must accompany or precede the conditioned stimulus.
- Conditioned reflex can be established or abolished.
- It is not transmitted by heredity.

Example

The normal response for presentation of food to an animal is salivation. The conditioned stimulus (ringing the bell) is given along with or immediately before the unconditioned stimulus (presentation of food). When the same procedure is repeated several times, mere ringing the bell (conditioned stimulus) results in salivation. This acquired behavior is a **conditioned reflex**.

Stretch Reflex (Fig. 8.10)

The stretch reflex is an example of a monosynaptic reflex. The stretch of skeletal muscle with intact nerve supply responds by reflex contraction. In this reflex, stimulus is stretch of the muscle. The receptor is muscle spindle. Type Ia and II fibers carry afferent information to the spinal cord. The sensory signals are converted into the motor response at the spinal cord and the neurotransmitter is glutamate. The motor neurons from the center in the spinal cord end on the contractile element (extrafusal fibers) of the same muscle.

A branch of the afferent (sensory) neuron also makes synaptic connection with the interneuron which inhibits the motor neuron controlling the antagonistic muscle. The resulting inhibition is termed **reciprocal inhibition**.

Thus, the stretch stimulus causes the contraction of agonists and relaxation of antagonists facilitating smooth shortening of the contracting muscle.

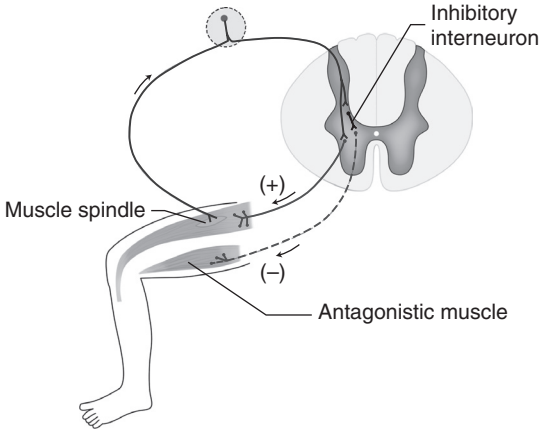


Figure 8.10 Pathway for stretch reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Inverse Stretch Reflex (Golgi Tendon Reflex)

A sudden stretch of the muscle results in its reflex contraction. However, when the tension becomes great enough, the contraction suddenly stops and the muscle relaxes. This relaxation in response to a strong stretch is known as **inverse stretch reflex** or **autogenic inhibition** (**Fig. 8.11**).

The receptor for this reflex is the Golgi tendon organ (GTO).

GTO regulates the force of muscle contraction.

Golgi tendon organs are in series with muscle fibers. They respond to both active

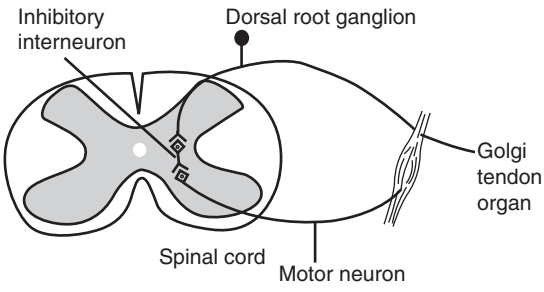


Figure 8.11 Inverse stretch reflex.

contraction and passive stretch. They have a low threshold.

Withdrawal Reflex

The withdrawal reflex is an example of the polysynaptic reflex. The efferent limb has a varying number of synapses. The polysynaptic path causes prolonged bombardment of the motor neurons supplying the muscle. Hence, a single stimulus produces a prolonged motor response and a sustained contraction of the muscle. There is reflex contraction of the flexor group of muscles and inhibition of the extensor muscles. Thus, the limb is withdrawn from the painful stimulus (**Fig. 8.12**).

Crossed Extensor Reflex (Fig. 8.13)

When a strong painful stimulus is given to the animal, there is flexion and withdrawal of the same limb with extension of the opposite limb.

This response is due to **irradiation of the impulses** and **recruitment of the motor units**. The crossed extensor response is a complex spinal reflex consisting of ipsilateral withdrawal reflex and contralateral extensor reflex. The afferent fibers make synaptic connection with interneurons controlling the flexor withdrawal reflex of the same side and the contralateral extensor reflex.

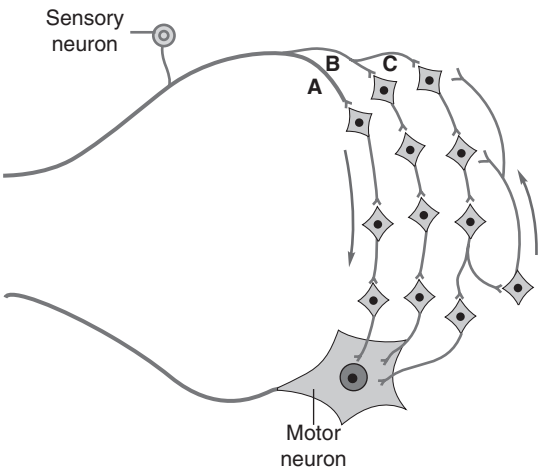


Figure 8.12 Withdrawal reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

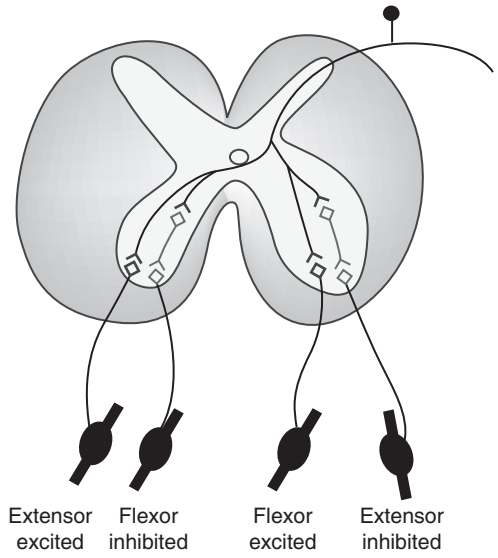


Figure 8.13 Crossed extensor reflex.

The cross-extensor reflex is important for maintenance of balance.

Axon Reflex (Fig. 8.14)

In this reflex, a branch of the sensory nerve returns back to the same area of skin. It innervates the cutaneous arteriole without reaching the spinal cord. Whenever the skin is stroked, it results in arteriolar dilation manifesting as redness at the site of injury (flare). This is known as axon reflex. It is an **asynaptic reflex**.

The conduction of nerve impulse occurs antidromically causing release of vasodilators.

The axon reflex–mediated responses include itching, pain, inflammation, and asthma.

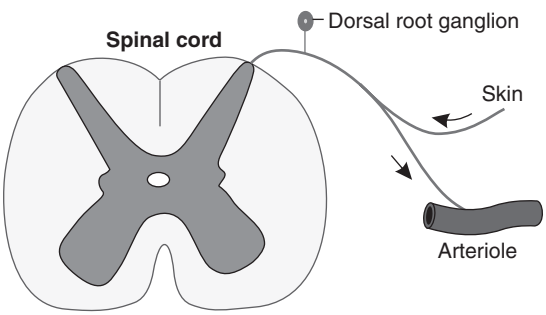


Figure 8.14 Axon reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

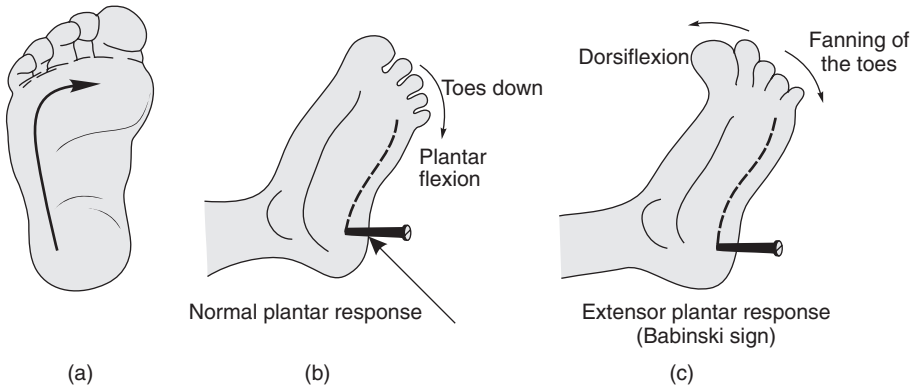


Figure 8.15 Plantar reflex. (a) Direction of stroking the sole of foot. (b) Normal plantar reflex. (c) Babinski's sign. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Plantar Reflex (Fig. 8.15)

When the lateral aspect of the sole of the foot is scratched, it results in plantar flexion and adduction of all the toes. This is the normal flexor response. However, it can be extensor in the upper motor neuron lesion. Then it is termed **positive Babinski's sign**.

In this condition, scratching the lateral aspect of the sole of the foot results in fanning of all the toes, dorsiflexion of the great toe, dorsiflexion at the ankle joint, and flexion at knee and hip joints.

An examination of the plantar reflex helps to recognize the upper motor neuron lesion.

In a normal individual, Babinski's sign can be positive

- in a child below the age of 18 months due to incomplete myelination and
- during deep sleep due to temporary removal of inhibition from higher centers.

RECEPTORS (Fig. 8.16)

The receptors are modified nerve terminals capable of converting different forms of energy into electrical signals.

The external and internal environment is changing constantly. The changes around and within us have to be conveyed to the central nervous system. These changes are perceived by **sensory receptors**.

Awareness of the stimulus is termed **sensation**. Interpretation of the meaning of the stimulus is **perception.**

CLASSIFICATION BASED ON LOCATION

- **Exteroceptors**: These receptors are capable of recognizing changes in the external environment. (E.g., receptors for touch, pain, and temperature).
- **Interoceptors**: These receptors respond to alterations in the internal environment. (E.g., baroreceptors and chemoreceptors).
- **Telereceptors**: These receptors perceive changes in the surroundings from a distance. (E.g., receptors for vision and audition).
- **Proprioceptors**: These receptors provide information about the orientation of different parts of the body in space. (E.g., muscle spindle and Golgi tendon organ).

CLASSIFICATION BASED ON THE STIMULUS TYPE

- **Mechanoreceptors** for perceiving mechanical changes such as touch and pressure
- **Proprioceptors** for detecting muscle length and tension

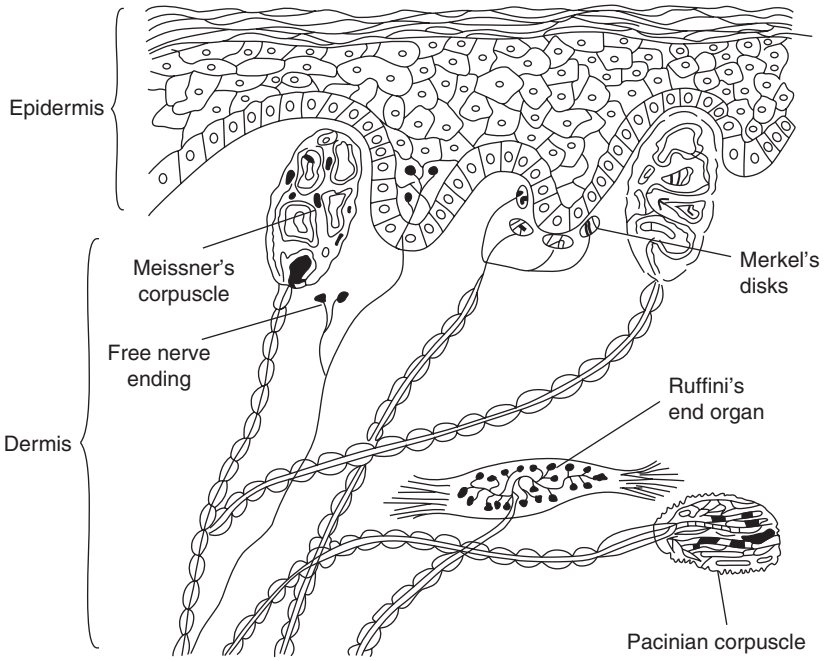


Figure 8.16 Cutaneous receptors.

- **Thermoreceptors** for temperature sense
- **Nociceptors** for pain perception
- **Chemoreceptors** for detecting changes in the chemical nature of body fluids
- **Photoreceptors** for responding to light

TYPES OF SENSATION

General Sensations

1. **Touch and pressure**
   - *Rapidly adapting*: Meissner's corpuscles and Pacinian corpuscles
   - *Slowly adapting*: Merkel's disk
2. **Pain**: Free nerve endings
3. **Temperature**: Thermoreceptors for cold and warm sensations
4. **Joint sense**
   - *Muscle length*: Muscle spindle
   - *Muscle tension*: Golgi tendon organ

Special Sensations

- **Vision**: Rods and cones
- **Audition**: Hair cells of the organ of Corti
- **Taste**: Taste receptor cells of taste buds
- **Smell**: Olfactory neurons
- **Linear and rotational acceleration**: Hair cells of vestibular apparatus

RECEPTOR (GENERATOR) POTENTIAL

A low-intensity stimulus to a receptor produces a nonpropagated, depolarizing potential resembling the EPSP. This is called the **generator potential** or the **receptor potential**.

It is produced due to the distortion of the receptor and activation of the unmyelinated part of the sensory nerve. As the intensity of the stimulus increases, the magnitude of the response also increases (**Fig. 8.17**). The receptor converts mechanical energy to electrical response. In the initial phase, the magnitude of the response depends on the intensity of the stimulus. Thus, the response is a **graded potential**.

On reaching the firing level, it produces a propagated **action potential**.

The frequency of the action potential is proportional to the magnitude of the stimulus applied.

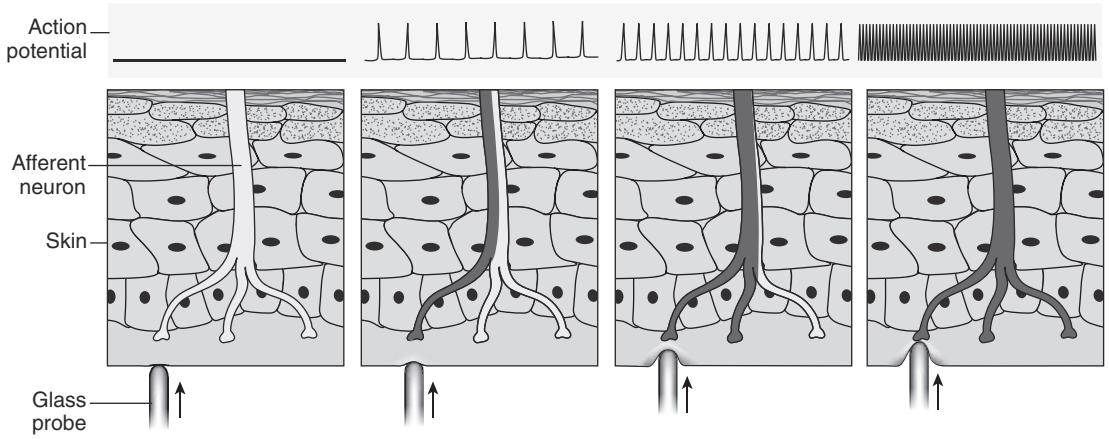


Figure 8.17 Influence of stimulus intensity on the frequency of impulse generation. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The rate of generation of action potential in response to stimulus helps to discriminate the intensity of various stimuli.

PROPERTIES OF RECEPTORS

1. **Specificity**: The sensory receptors respond to a specific type of energy for its stimulation.

   Four different receptor types have been identified, which are as follows:
   - Mechanical
   - Thermal
   - Chemical
   - Electromagnetic

   For example, the chemoreceptors respond to changes in the chemical nature of the blood.
2. **Adaptation**: The stimulation of a receptor with a nonpainful, low-intensity stimulus results in a gradual decline in the response. The receptor may finally stop responding. This is termed **adaptation** or **desensitization**.

   Rapidly adapting receptors are phasic receptors, e.g., touch receptors.

   Prolonged stimulation of the touch receptor can be irritating and distracting. This is overcome by rapid adaptation of the touch receptor to low-intensity stimulation over a long duration.

   Slowly adapting receptors are tonic receptors, e.g., muscle spindle and pain receptors.
3. **Law of specific nerve energies**: This principle was proposed by Johannes Muller in the year 1835. It is also called Muller's doctrine of specific nerve energies. Stimulation of the receptor or the sensory pathway anywhere along its course produces the same sensation as normally perceived by the stimulation of the receptor.
4. **Law of projection**: The stimulation of the sensory pathway from the receptor to its termination in the cortex gives the sensation as if it is arising from the location of the receptor. If the limb is amputated, stimulation of the sensory pathway gives the impression as if the sensation is coming from the receptor of the nonexistent limb (**phantom limb**). Changes in the thalamus and somatosensory cortex following limb amputation are a phenomenon of **cortical plasticity**.
5. **Discrimination of intensity**: The intensity of stimulation is appreciated by the brain through
   - changes in the number of action potential produced by the active receptors or
   - number of receptors activated by the stimuli.

Magnitude of the sensation felt depends on the intensity of stimulus.

Weber–Fechner Law

Weber–Fechner law states that the sensation felt is proportional to the log of the stimulus intensity:

$$R \propto \log S.$$

However, a more accurate relationship appears to be the power function:

$$R = KS^A,$$

where R is the sensation felt, S is the intensity of stimulus, and K and A are constants.

6. **Recruitment of sensory units**: A stimulus activates the receptors which are in close contact with it. If the intensity of stimulation is increased, the effect spreads to the surrounding areas activating the receptors in that region. This is termed **recruitment of sensory unit**. The weaker stimulus activates a less number of receptors and those with a lower threshold. However, a stronger stimulus activates a greater number of receptors including those with a higher threshold for stimulation.

LOCALIZATION AND TWO-POINT DISCRIMINATION

The skin has discrete sensory units. The area of the skin producing a single response or sensation on stimulation is termed the **receptive field** of that sensory unit.

An important mechanism for localization of the site of stimulation is lateral inhibition. On application of the stimulus, receptors located at the edge of receptive field are inhibited. This mechanism helps the brain to localize the area of stimulation.

Two-Point Discrimination

Two-point discrimination is the ability to identify two independent points when they are stimulated simultaneously. It depends on the touch sensation and the cortical component to identify two different stimuli.

The distance of separation for two-point discrimination varies from place to place.

A separation of 2–4 mm can be appreciated at the tip of the tongue and the fingers. On the back, the distance of separation has to be 5–7 cm to appreciate two distinct points. The distance of separation is the least where the touch receptors are present in large numbers and has a greater representation in the cerebral cortex.

Two-point discrimination is tested by using Weber's compass or compass aesthesiometer. This test helps to evaluate the integrity of the dorsal column tract which is the central pathway for perception of touch and proprioception.

SENSORY SYSTEM

The sensory system is responsible for carrying different sensations from all over the body to the CNS. Different types of sensations are perceived by the sensory receptors.

The receptors convert these sensations to electrical signals. The impulses generated at the receptors are transmitted through the sensory tract present in the spinal cord. The sensory tracts finally terminate in the somatosensory cortex (Brodmann areas 3, 1, 2). The somatosensory area is located in the postcentral gyrus. Understanding the meaning of sensation is termed **perception**. Perception is a result of the neural processing of the sensory information.

SENSORY HOMUNCULUS (Fig. 8.18)

The representation of body in the somatosensory cortex is termed sensory homunculus. The body is represented upside down in the sensory cortex except for face which is represented upright. The representation of body is contralateral except for face which has bilateral representation.

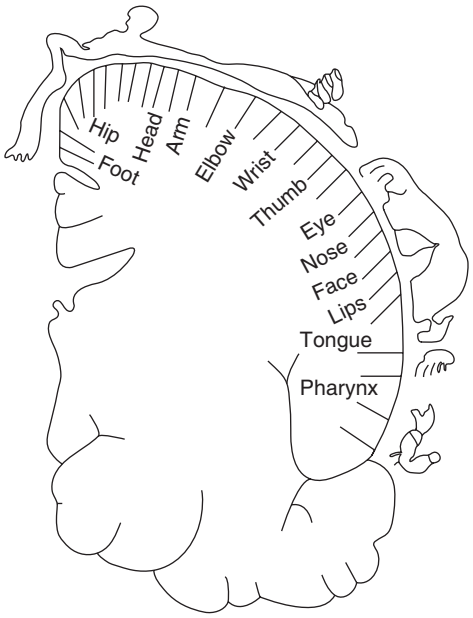


Figure 8.18 Sensory homunculus.

The representation from the medial surface to the lateral surface are toe, ankle, knee, hip, trunk, head, arm, elbow, wrist, hand, fingers, eyes, nose, face, lips, tongue, jaw, and pharynx.

The peripheral parts of the body such as hand and finger that perform finer movements have a larger area of representation. These areas have more number of receptors. However, the trunk has a smaller area of representation when compared to its size.

The representation follows a dermatomal pattern instead of a regional distribution.

SENSORY TRACTS

The neural pathway in the sensory system consists of three or more neurons connected end to end by synapses. The bundles of parallel nerve fibers form the **tract**.

The sensory tracts are present in the spinal cord. These tracts are formed by the sensory fibers from the receptors and reach the higher centers in the CNS. They are also called the **ascending tracts** as they go up to the brain. The sensory inputs pass through the spinal cord, medulla, and thalamus. These are called **relay stations**.

The sensory inputs reach the thalamus and cerebral cortex. The crude form of sensations and pain are appreciated at the thalamus. This type of sensation is called **protopathic sensation**.

The finer details of the sensations are perceived by the cerebral cortex. This sensation is termed **epicritic sensation**.

SENSORY UNIT

A single afferent neuron with all its receptors forms the **sensory unit**. Generally, a single neuron has multiple receptors. Sometimes, each neuron can have a single receptor.

SPINAL CORD

The spinal cord is a part of the central nervous system along with the brain. It houses the pathways carrying information to and from the brain from different parts of the body. Sensory information is carried by the **ascending tracts**.

The information about the action to be carried out is sent through the **descending tracts**.

The spinal cord is present within the vertebral column extending from the foramen magnum in the skull to the first or second lumbar vertebra. It is covered by single layer of dura mater termed **spinal dural sheath**. The space between the bony vertebra and the dural sheath is the **epidural space**.

A section of the spinal cord shows outer white matter and inner gray matter (**Fig. 8.19**). The central canal passes through the center of the spinal cord.

The **white matter** has anterior, lateral, and posterior compartments called the **funiculus**.

The **anterior funiculus** contains the anterior spinothalamic tract.

The **lateral funiculus** contains the lateral spinothalamic tract.

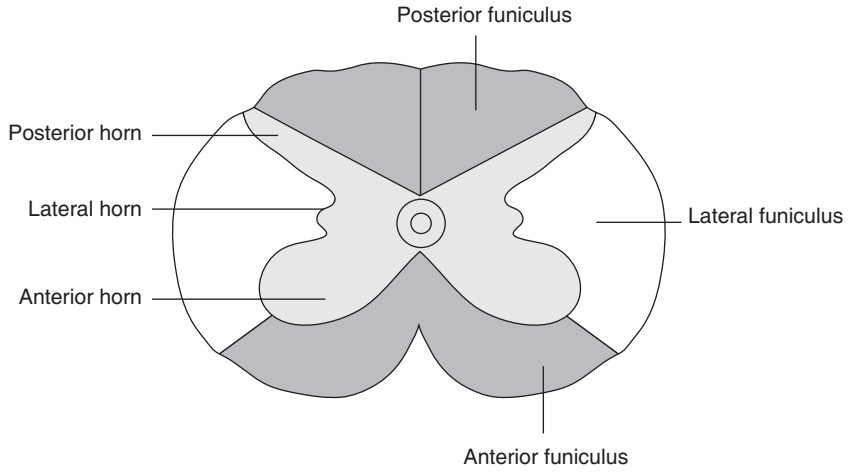


Figure 8.19 Cross-section of the spinal cord.

The **posterior funiculus** contains the fasciculus gracilis and fasciculus cuneatus.

The **gray matter** has anterior, lateral, and posterior horns.

The **anterior (ventral) horn** contains

- alpha motor neurons supplying the skeletal muscles,
- gamma motor neurons supplying proprioceptors in the muscle (muscle spindles), and
- interneurons modifying the activity of alpha motor neurons.

The **lateral horn** contains preganglionic fibers of the autonomic nervous system. The lateral horns are prominent in the thoracic, lumbar, and sacral segments of the spinal cord.

The **posterior (dorsal) horn** contains the cell bodies of the neurons forming the afferent tract.

The posterior column has several layers of cells. The layers from the outer to the innermost are

- substantia gelatinosa of Rolando,
- nucleus of proprius,
- Clarke's column, and
- visceral afferent nucleus.

REXED LAMINA (Fig. 8.20)

Rexed has identified 10 layers in the spinal cord based on the histological features of the spinal cord. They are numbered from I to X and are called Rexed lamina. The posterior horn of the spinal cord has laminae from I to VI; lamina VII is present in between the anterior and the posterior horns. The VIII and IX laminae are present in the anterior horn. Lamina X is present around the central canal.

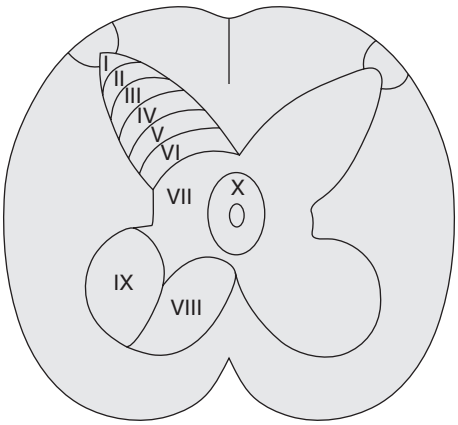


Figure 8.20 Rexed lamina.

SPINAL NERVE

The spinal cord gives out the spinal nerve in each of its segments. The spinal nerves have anterior and posterior roots.

The posterior or dorsal roots contain the sensory fibers entering the CNS. The cell bodies

of these sensory neurons are located in the dorsal root ganglion (DRG). The fibers from the ganglion on entering the spinal cord divide into the medial and lateral divisions.

The medial division has thicker fibers and carries sensations of fine touch, proprioception, and vibration.

The lateral division has thinner fibers carrying pain and temperature sensations.

The anterior root of the spinal nerve has motor fibers. It carries alpha and gamma motor neurons.

ASCENDING TRACTS (Fig. 8.21)

The ascending tracts are sensory tracts. They carry sensation from different receptors all over the body to the CNS.

The major spinal tracts are multineuronal pathways connecting the brain and the peripheral parts of the body.

Most pathways cross from one side to the other (decussate) at some point along their route.

They contain two or three neurons contributing successive tracts of the pathway.

Tracts exhibit a precise spatial relationship representing orderly mapping of the body.

In the uncrossed tracts, the sensory fibers carrying information from the upper part of the body are located laterally and those carrying sensation from the lower parts are more medial.

In the crossed tracts, the sensory fibers from the lower limbs are lateral and those from the upper limbs are medial.

The ascending tracts are paired tracts.

The important sensory tracts are

1. **In the dorsal (posterior) column**
   - Tract of Goll (fasciculus gracilis)
   - Tract of Burdach (fasciculus cuneatus)
2. **In the lateral column**
   - Lateral spinothalamic tracts
   - Dorsal spinocerebellar tract
   - Ventral spinocerebellar tract
   - Spinotectal tract
   - Spino-olivary tract
   - Spinovestibular tract
   - Spinopontine tract
   - Spinoreticular tract
3. **In the ventral (anterior) column**
   - Anterior spinothalamic tract

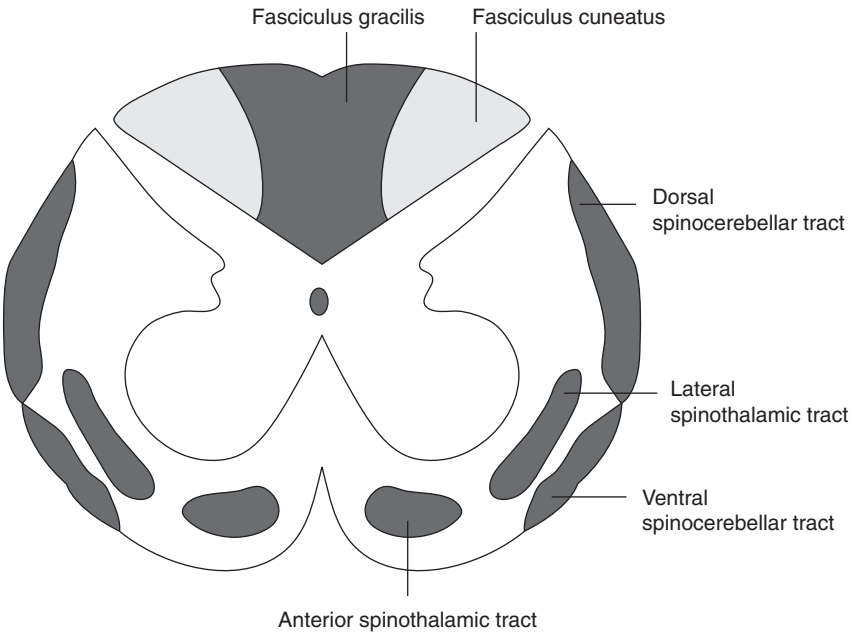


Figure 8.21 Ascending tracts.

Tracts of Goll and Burdach (Fig. 8.22)

Sensations Carried

- Fine touch
- Proprioception
- Vibration
- Pressure

Pathway

The ascending tracts carry sensory impulses through a chain of three successive neurons (first-, second-, and third-order neurons).

- The **first-order neurons** arise from the respective receptors and enter the spinal cord through the posterior root.

  They ascend on the same side of the spinal cord to end (relay) in the nucleus gracilis and cuneatus present in the medulla.

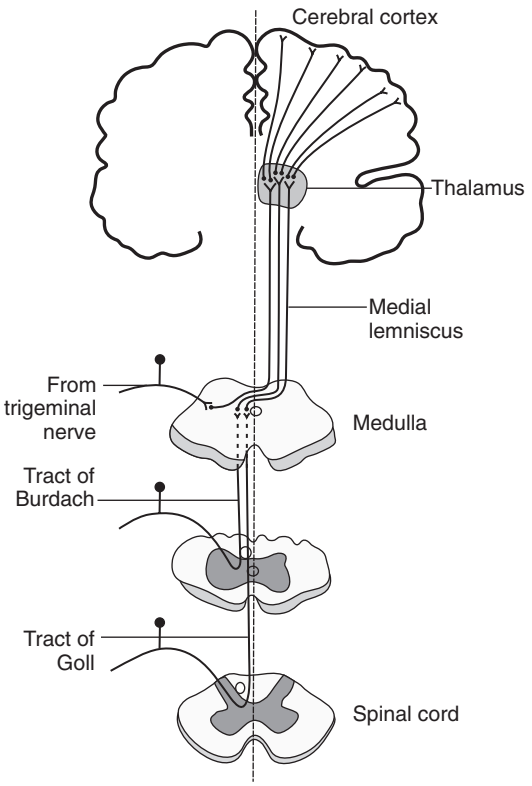


Figure 8.22 Pathway for fine touch. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The fasciculus gracilis contains fibers from the lower parts of the body (sacral and lower thoracic segments).

The fasciculus cuneatus contains fibers from the upper part of the body (upper thoracic and cervical segments).

In the spinal cord, the fibers close to midline are from the lower parts of the body and lateral fibers are from the upper part.

- The **second-order neurons** arising from these two nuclei cross to the opposite side.

  These crossing fibers are called the **internal arcuate fibers**.

  The fibers ascend close to the midline forming medial lemniscus (bundle).

  The second-order neurons end in the ventral posterolateral nucleus of the thalamus.
- The **third-order neurons** arising from the thalamic nucleus end in the sensory cortex (areas 3, 1, 2) present in the postcentral gyrus of the cerebral cortex.

  The tracts of Goll and Burdach do not cross the midline or have a relay at the spinal level. The relay occurs at the medulla and thalamus.

Anterolateral (Ventrolateral) Spinothalamic Tract (Fig. 8.23)

Sensations Carried

- Pain and temperature (lateral tract)
- Crude touch (ventral tract)

Pathway

- The fibers arising from the receptors enter the spinal cord through the posterior or dorsal horn and end in the dorsal horn cells. This forms the **first-order neurons**.
- The **second-order neurons** arise from the dorsal horn cells and cross to the opposite side in front of the central canal. They occupy the lateral or anterior part of the spinal cord.

  The axons of second-order neurons from sacral and lumbar segments are pushed laterally after crossing the midline.

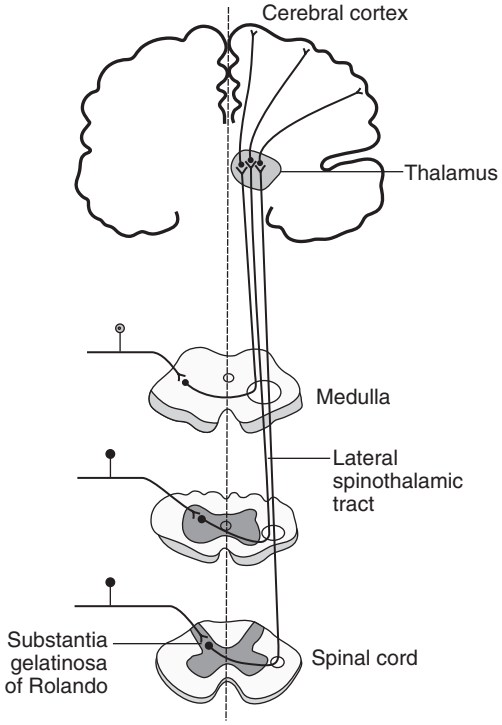


Figure 8.23 Pathway for pain. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

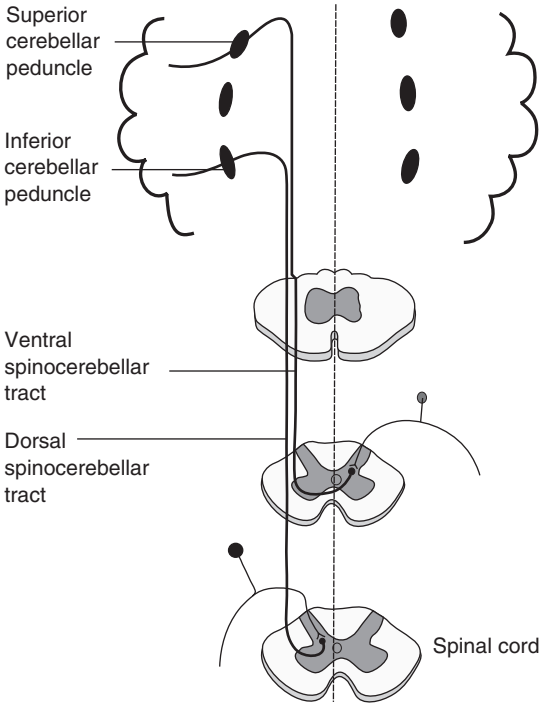


Figure 8.24 Dorsal and ventral spinocerebellar tracts. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

In the spinal cord, cervical fibers are medial and sacral fibers are lateral.

- The fibers ascend through the segments of the spinal cord, medulla, pons, and midbrain to end in the ventral posterolateral nucleus of the thalamus.
- As the tract ascends through the midbrain, it gives out branches to the reticular formation of the brainstem. Hence, the number of fibers is reduced.
- The **third-order neurons** from the thalamic nucleus reach the sensory cortex (areas 3, 1, 2).

Dorsal Spinocerebellar Tract (Flechsig's Tract; Fig. 8.24)

Sensations Carried

- Unconscious kinesthetic impulses to the cerebellum

Pathway

- The **first-order neurons** arise from the muscle spindle, joints, and skin and enter the spinal cord through the DRG.
- They terminate in Clarke's column situated at the base of the dorsal horn.
- The **second-order neurons** arise from Clarke's column and ascend on the same side to the medulla.
- They turn posteriorly to enter the cerebellum through the inferior cerebellar peduncle.

Ventral Spinocerebellar Tract (Gower's Tract; Fig. 8.24)

Sensations Carried

- Unconscious kinesthetic impulses to the cerebellum

Pathway

- The **first-order neurons** arise from the muscle spindle, joint, and skin.
- They enter the spinal cord through the DRG and relay in the dorsal horn. The second-order neuron arises from Rexed laminae V–VII.
- The **second-order neurons** cross to the opposite side and proceed through the medulla, pons, and midbrain.
- In the midbrain, the fibers turn posteriorly to enter the cerebellum through the superior cerebellar peduncle.

The spinocerebellar tracts carry impulses from the muscles, joints, and skin like the nonconscious proprioceptive and cutaneous sensations.

SYNTHETIC SENSE

Synthetic sense is produced due to the combination of two types of basic sensations:

1. Stereognosis
2. Vibration sense

Stereognosis

Stereognosis is the ability to appreciate the size, shape, texture, and weight of the objects by past experience without actually looking at them. It is a complex perception which depends on the synthesis of several somatic sensations.

Stereognosis is a combination of touch and pressure sensations. It is one of the most sophisticated sensations. An impaired stereognosis is an early sign of damage to the cerebral cortex and a lesion in the parietal lobe posterior to the postcentral gyrus.

The inability to identify the commonly used objects by touching them is termed **tactile agnosia**.

Other types of agnosia are as follows:

- **Visual agnosia**: Inability to identify the objects by looking at them
- **Auditory agnosia**: Loss of ability to detect sound and words
- **Position agnosia**: Inability to localize the position of extremities

Vibration Sense

Vibration sense is also a type of synthetic sensation produced by a combination of touch and pressure sensations.

The ability to appreciate the sense of mechanical vibration is called **pallesthesia or vibratory sense**.

Vibration sense is lost under the following conditions:

- Damage to dorsal column tracts
- Uncontrolled/poorly controlled diabetes mellitus
- Vitamin B_{12} deficiency
- Pernicious anemia
- Tabes dorsalis

PATHOPHYSIOLOGY OF PAIN

Pain is an unpleasant, subjective sensation produced due to nerve damage.

It warns the organism about the possible damage to the tissue.

Sherrington described pain as "the physical adjunct of an imperative protective reflex."

The crude sensation of pain can be appreciated at the thalamic level whereas the finer aspects of it can be perceived at the cortical level.

The sense organs for pain are the free nerve endings present in all the tissues.

Pain is of two major types:

1. A sharp, localized **fast pain** carried by Aδ fibers. These nerve fibers have a diameter of 2–5 μ and conduct impulses at the rate of 15–30 m/s.
2. A poorly localized, dull-aching **slow pain** carried by C fibers. These are unmyelinated fibers having a diameter

of 0.4–1.2 μ. They carry impulses at the rate of 0.5–2 m/s.

Depending on the duration, pain is of two types:

- Acute pain
- Chronic pain

Acute pain has a short duration of onset, reduces with the normal healing process, and serves as a protective mechanism.

Chronic pain is considered "bad pain" as it persists even after the healing process for the injury is complete. It is due to damage to the nerve. It does not respond to conventional painkillers.

The sensation of pain is produced by substances such as

- prostaglandins,
- bradykinin,
- serotonin,
- potassium ions,
- adenosine, and
- substance P.

Pain is produced due to the following changes in the body:

- Inflammation
- Obstruction
- Ischemia
- Distension of hollow viscus
- Muscle spasm
- Dilation of blood vessels

HYPERALGESIA AND ALLODYNIA

Pain is associated with two features:

1. Hyperalgesia
2. Allodynia

Hyperalgesia is increased response to a painful stimulus.

Allodynia is perception of pain in response to an insignificant stimulus.

Bradykinin, prostaglandins, histamine, and serotonin are produced by the injured cells. They increase the sensitivity of nociceptive neurons and enhance the intensity of pain perception.

Aspirin and nonsteroidal anti-inflammatory drugs reduce the pain by inhibiting cyclooxygenase.

DEEP PAIN

Deep pain is poorly localized associated with nausea, sweating, and change in blood pressure. Muscle spasm leading to ischemia produces deep pain.

REFERRED PAIN (Fig. 8.25)

Referred pain is the pain sensation from an internal organ felt in an area of skin away from the site of its production.

Theories of Referred Pain

Dermatomal Rule

Pain is referred to the region of the skin which has developed from the same segment or dermatome from which the internal organ has developed. The organ and region of the skin get nerve supply from the same segment of the spinal cord.

Convergence and Facilitation

The sensory nerve fibers from the skin and the internal organ end on the same dorsal horn cell of the spinal cord. Any irritation in the internal organ causes stimulation of the sensory nerve. The pain gets projected to the region of skin, which has the common nerve supply.

Facilitation Visceral pain fibers make synaptic connection with the second-order neuron in the spinal cord. The pain fibers from the region of skin also make synaptic connection with the same second-order neuron.

Irritation of the internal organ reduces the threshold for pain sensation. A minor stimulation over skin, which normally goes without notice, is experienced as pain due to lowered threshold. This is called the **subminimal fringe effect**.

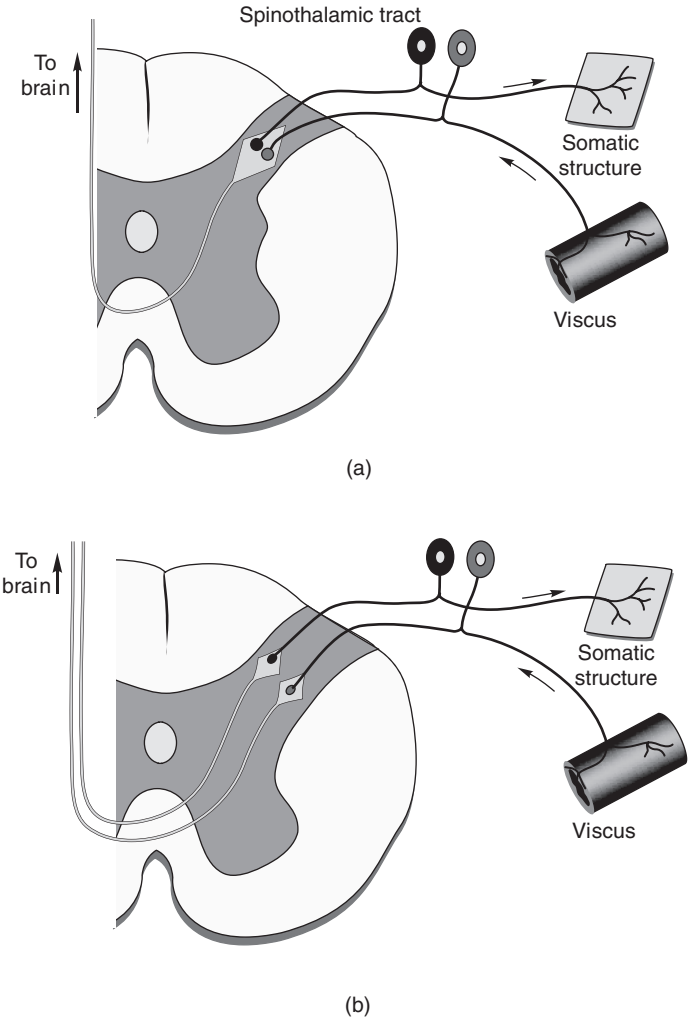


Figure 8.25 Referred pain. (a) Convergence theory and (b) facilitation theory. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Examples:

1. Pain produced due to myocardial damage is referred to the left shoulder and the ulnar aspect of the left upper limb.
2. Pain produced due to the inflammation of liver and gallbladder is felt in the right shoulder.
3. Pain produced due to the inflammation of appendix is initially felt around the umbilicus.

Importance: Some diseases such as appendicitis, early myocardial infarction, and cholecystitis can be diagnosed early by knowing the relationship between the site of origin of pain and the region to which it gets referred.

CLINICAL NOTES

Pain Inhibition

The somatic nerve from the skin and the visceral nerve from the hollow viscus end on the same dorsal horn of the spinal cord. Pain signals from the hollow viscus can be blocked by increasing the impulse traffic in the somatic nerve by irritating that region of skin, e.g., application of counterirritant balms to get relief from headaches. The perception of pain is reduced but the basic cause for pain remains untreated.

(*Contd.*)

Gate Control Theory

Transmission of pain impulses can be modified or gated at the posterior horn of the spinal cord. This is achieved by stimulating the inhibitory interneuron in that region.

The counterirritants reduce pain perception by the gate control mechanism.

Acupuncture-induced analgesia is also due to this mechanism.

Anesthetics

Anesthetics are substances used to block the perception of pain. They act on GABA and glycine receptors. The effect is produced by increasing the conductance of chloride ions.

Local anesthetics stabilize the activation gates of the sodium channel making it difficult to open the gate. This reduces the excitability of the membrane.

ENDOGENOUS OPIOID ANALGESIC SYSTEM

It is a pain-inhibiting system present in the body. The pathway contains receptors which can bind to morphine (opioid) and endogenously produced opioids such as enkephalins, endorphins, and dynorphins.

The opioids can act at the following sites to inhibit the pain:

- At the site of injury
- In the dorsal horn where pain fibers synapse with DRG
- At rostral sites in the brainstem

Opioids reduce the nociceptive transmission. The dorsal horn contains interneurons having opioid peptides such as enkephalin and dynorphin. These interneurons end in the dorsal horn where the nociceptive afferents end. Opioid receptors are present on the nociceptor fibers and dorsal horn. Opioids can act presynaptically and postsynaptically.

Activation of the presynaptic opioid receptor reduces the influx of calcium and subsequent release of glutamate and substance P.

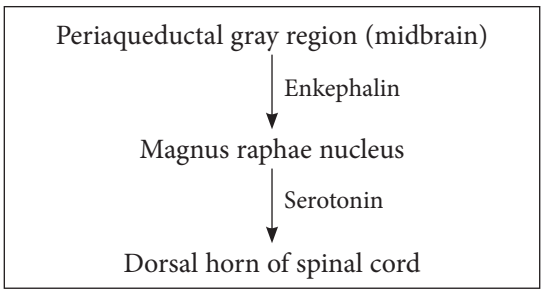
Activation of the postsynaptic opioid receptor hyperpolarizes the terminal by increasing potassium conductance.

PATHWAY FOR ENDOGENOUS PAIN INHIBITION

Morphine (opioid analgesic) and endogenous opioids act on the mesencephalic periaqueductal gray (PAG) region. Periaqueductal gray region is a part of the descending pathway which inhibits transmission of impulses in afferents of dorsal horn influencing pain perception.

The PAG neurons activate serotonergic magnus raphe nucleus and catecholaminergic neurons in the rostral ventromedial medulla. These neurons project to the dorsal horn of the spinal cord. Serotonin and norepinephrine produced from these neurons inhibit inputs from nociceptive afferent fibers in the dorsal horn.

Locus coeruleus is also a part of the descending endogenous opioid analgesic system present in brainstem. It produces analgesic response by producing norepinephrine in the dorsal horn.



STRESS-INDUCED ANALGESIA

Pain sensitivity is reduced under stressful conditions. A soldier wounded in war does not feel severe pain till the battle is completed. An animal attacked by a predator has reduced pain perception. Stress-induced analgesia is due to release of norepinephrine from amygdala and endogenous cannabinoids such as anandamide. These chemicals act on G protein-coupled receptors. Binding of agonists to these receptors reduces inflammation and has analgesic effect.

MOTOR SYSTEM

The motor system is responsible for the transfer of information from the center to the periphery. The information from the center is finally passed on to the glands or muscles called effector organs.

The descending pathways are motor tracts. They are broadly divided into pyramidal and extrapyramidal systems.

PYRAMIDAL SYSTEM

The corticospinal tract is the main tract of the pyramidal system (**Fig. 8.26**).

Pyramidal (Corticospinal) Tract

Origin

The pyramidal tract arises from the pyramidal cells in the motor area (4), premotor area (6), and frontal eye field (8). It also gets fibers from the sensory areas (3, 1, 2).

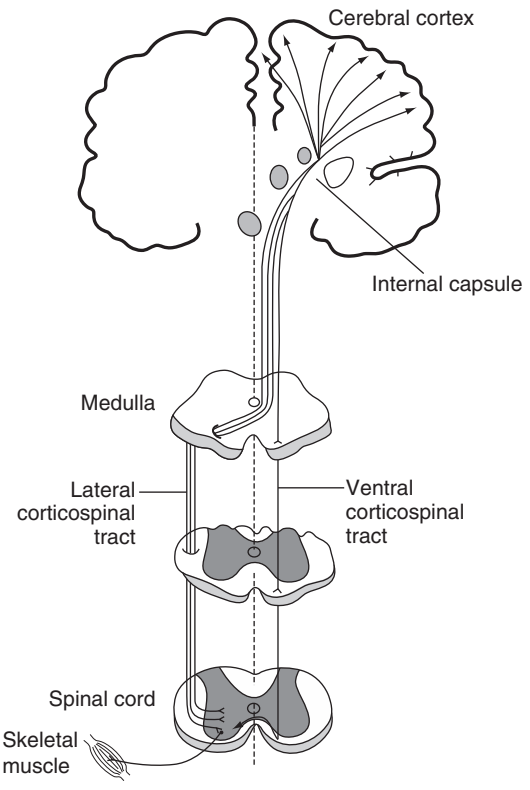


Figure 8.26 Pyramidal tract.

Course

- From the cerebral cortex, the fibers descend as the corona radiata.
- The pyramidal tract passes through genu and anterior two-third of the posterior limb of the internal capsule. (In this region, the fibers are closely packed and hence liable for extensive damage.)
- Then the fibers pass through crus cerebri of the midbrain to enter pons. In pons, the fibers get scattered.
- After leaving the pons, the fibers again become compact in the medulla assuming a pyramidal shape.
- At the lower border of the medulla, the majority of fibers (about 80%) cross to the opposite side forming the crossed pyramidal tract or the **lateral corticospinal tract**.
- The remaining fibers form the uncrossed pyramidal tract, also termed the **ventral corticospinal tract**. These uncrossed fibers cross to the opposite side before they end on the anterior horn cell of the spinal cord.

The tract is termed **pyramidal tract** because of the pyramidal shape assumed by it during its course through the medulla. It is also suggested that the name pyramidal tract was due to the idea that the origin of the tract was solely from the pyramidal cells of the cortex.

Termination

The fibers of the pyramidal tract finally end on the anterior horn cell of the spinal cord.

Some fibers of the pyramidal tract while traveling from the cortex to the spinal cord give branches to the cranial nerve nucleus. These are called the **corticonuclear fibers**.

As the corticospinal fibers descend through the brain from the cerebral cortex, they are accompanied by the **corticobulbar pathway**.

The corticobulbar pathway begins in the sensorimotor cortex and ends in brainstem. The corticobulbar fibers control the motor neurons, innervating the muscles of the eye,

face, tongue, and throat. They are the main source of voluntary control for the muscles of the head and neck.

The pyramidal tract from its origin in cerebral cortex to its termination in the anterior horn cell of the spinal cord forms the **upper motor neuron**.

The fibers from the anterior horn cell of the spinal cord to its termination on the muscle constitute the **lower motor neuron**.

Functions

- The pyramidal tract carries impulses for voluntary movements from the brain to the spinal cord.
- It helps to maintain posture by regulating the action of the trunk muscles.
- It has an influence on the stretch reflex.

EXTRAPYRAMIDAL SYSTEM (Fig. 8.27)

The extrapyramidal system consists of fibers descending through the brainstem and spinal cord without passing through the pyramids. These fibers control the gross and synergistic movements involving a large group of muscles and are concerned with the control of posture.

Conventionally, the fibers in the extrapyramidal system are grouped into the following tracts:

- Tectospinal tract
- Rubrospinal tract
- Reticulospinal tract
- Vestibulospinal tract
- Olivospinal tract

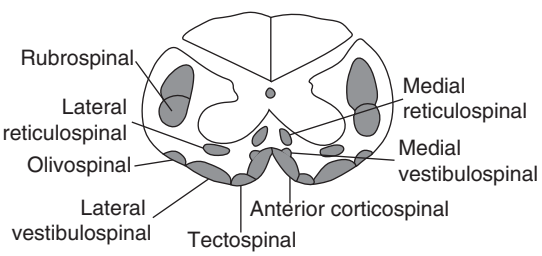


Figure 8.27 Descending tracts.

Functions

- Helps in regulation of muscle tone
- Influences the activity in postural (extensor) muscles
- Helps in maintenance of posture and equilibrium
- Facilitates gross postural movements
- Controls the movement of eyeballs

UPPER MOTOR NEURON LESION

The damage to the pyramidal tract from its origin in the cerebral cortex to the anterior horn cell is termed **upper motor neuron lesion**.

It has the following features:

- Voluntary movements are lost.
- Muscle tone is increased—spasticity.
- Deep reflexes exaggerated; ankle and patellar clonus present.
- Superficial reflexes are lost.
- Babinski's sign becomes positive.
- In long-standing cases, there is atrophy of muscle due to disuse, for example, hemiplegia.

LOWER MOTOR NEURON LESION

A lesion in the anterior horn cell or the nerve from the anterior horn cell to its termination results in **lower motor neuron lesion**.

It shows the following features:

- Loss of voluntary motor activity
- Hypotonia—flaccid paralysis
- Absence of superficial and deep reflexes in the affected segment
- Muscles supplied by the affected nerves progressively atrophy
- Fibrillation potential seen in electromyogram
- Reaction of degeneration present, for example, poliomyelitis

Stroke

Stroke is caused by rupture of the blood vessel associated with hemorrhage or obstruction to

the flow of blood due to thrombosis in major arteries supplying brain. It results in damage to the motor control system involving the cortex or corticospinal tract.

Hemiplegia

Hemiplegia is paralysis of one-half of the body. Hemiplegia is the term used to explain the loss of muscle strength on one side of the body, often including the face. This occurs as a result of damage to the pyramidal tract, usually at the internal capsule. Hemiplegia has features of the upper motor neuron type of lesion.

Paraplegia

Paraplegia is paralysis of both the lower limbs. It usually occurs due to spinal cord injury.

Monoplegia

Monoplegia is paralysis of any one limb. It occurs due to a defect in the cerebral cortex.

Quadriplegia

Quadriplegia is paralysis of all the four limbs. It occurs due to damage to spinal cord at the upper cervical segment.

EFFECTS OF COMPLETE TRANSECTION OF THE SPINAL CORD

This can occur in spinal injuries due to accidents. They exhibit the following features:

- Immediate and permanent loss of all voluntary movements below the level of lesion
- Immediate loss of all reflexes below the level of lesion
- Permanent loss of all sensations below the lesion

Clinically, it has three stages:

1. **Stage of spinal shock**
   - Loss of reflexes due to the removal of supraspinal influences.
   - Loss of voluntary muscle power.
   - All sensations below the level of lesion are lost.
   - There is a sharp fall in the blood pressure due to vasomotor paralysis. Circulation becomes sluggish.
   - The overlying skin and subcutaneous tissue suffer lack of nutrition and are prone to develop bedsores.
   - Urinary bladder muscles become hypotonic or atonic.
   - Bowel becomes hypotonic.
2. **Stage of reflex activity**
   - After a lapse of about 2 weeks, the tone of flexor muscle returns giving rise to paraplegia in flexion.
   - Babinski's sign becomes positive.
   - Tendon jerk begins to appear.
   - Mass reflex may appear. (When the medial surface of the thigh is stroked, there is flexor spasm of the lower limb, evacuation of the bladder and bowel associated with sweating. All these changes together constitute **mass reflex**.) This reflex is clinically used to periodically evacuate bladder and bowel.
   - The bladder becomes automatic.
3. **Stage of reflex failure**

   Degeneration of the spinal cord and intercurrent infection causes failure of reflex activities. Once again the muscles become hypotonic, mass reflexes disappear, and the patient dies.

EFFECTS OF HEMISECTION OF THE SPINAL CORD (BROWN SEQUARD SYNDROME)

Above the Level of Lesion

In this lesion, the zone of hyperesthesia is limited to one segment.

At the Level of Lesion on the Same Side

1. **Sensory changes**
   - Loss of all sensations (fine touch, pressure, pain, temperature, and vibration)

2. **Motor changes**
   - Lower motor neuron type of paralysis

Below the Level of Lesion

1. **Sensory changes**
   - Pain and temperature sensations lost on the opposite side
   - Position sense, fine touch, and vibration sense lost on the same side
2. **Motor changes**
   - The upper motor neuron type of paralysis on the same side because of damage to the corticospinal tract.
   - On the opposite side, there is minimal motor paralysis following damage to the anterior corticospinal tract.

CLINICAL NOTES

Tabes Dorsalis

Tabes dorsalis is a condition seen in neurosyphilis. The disease is characterized by progressive degeneration of the posterior nerve root up to the dorsal root ganglia (DRG). However, the DRG is not affected.

In this condition, one side of the dorsal column is affected. It also occurs in diabetes.

Manifestations

- Loss of pain, position, and vibration sense
- Loss of passive movements due to defective kinesthetic sensations
- Loss of superficial and deep reflexes due to extensive sensory loss
- Lack of coordination of movements (ataxia)
- Involvement of sacral segments results in loss of micturition reflex and atonic bladder

Syringomyelia

Syringomyelia is characterized by the enlargement of the central canal with destruction of the gray matter around the canal. It commonly affects the cervical and thoracic segments.

Manifestations

- Loss of pain, temperature, and crude touch sensation because of damage to the fibers crossing in front of the central canal.
- If the anterior gray horn is affected, it results in flaccid paralysis of the muscles.
- Pain sensation is lost in this condition. The withdrawal reflex gets affected. Hence, the subject is more prone to injuries.

Poliomyelitis

Poliomyelitis is an acute infectious disease characterized by local or widespread muscular paralysis. It is produced by specific neurotrophic virus causing destruction of the anterior horn cell of the spinal cord or the corresponding cell in medulla.

Facial Palsy

Facial palsy is produced because of damage to the facial nerve. It can be one of the following three types:

1. Supranuclear
2. Nuclear
3. Infranuclear

In the supranuclear type of facial palsy, one side of the face is affected (unilateral). However, the upper part of the face is spared (due to bilateral innervation).

Voluntary movements of facial muscles are affected, but emotional expressions are intact.

In nuclear and infranuclear types, one-half of the face is affected. It may be unilateral or bilateral. There is no impairment of taste sensation.

Features

- Facial muscles are paralyzed on the affected side.
- The eye cannot be closed completely and palpebral fissure is widened. Tears collect in the eye and tend to overflow (epiphora).
- Whenever the individual tries to close the eye, the eyeball rolls upward under the partly covered eyelid. This is termed **Bell's phenomenon**.
- One angle of mouth droops on the affected side and the other angle gets deviated to the normal side.
- The nasolabial fold is lost on the affected side.

HYPOTHALAMUS

The hypothalamus (**Fig. 8.28**) is present on the undersurface of brain. It is situated below the thalamus. It is composed of a group of nuclei regulating important bodily functions.

The hypothalamus extends from the optic chiasma anteriorly to the mammillary body posteriorly. It weighs about 4 grams. A stalk of hypothalamic tissue connects it with the pituitary gland.

The hypothalamus has two-way communications with reticular formation, pons, medulla, anterior thalamus, limbic system, and cerebral cortex.

It has the following nuclei.

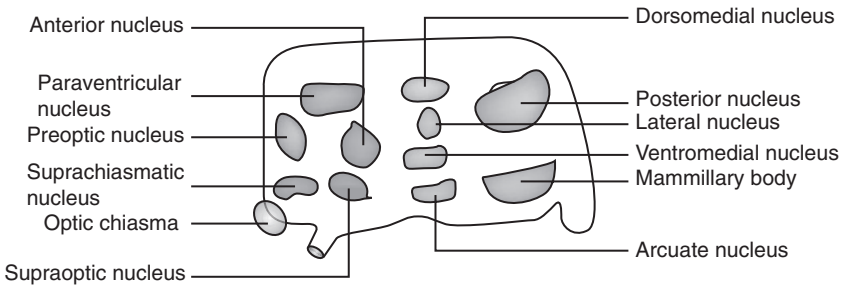


Figure 8.28 Hypothalamus.

ANTERIOR HYPOTHALAMUS

- Preoptic nucleus
- Paraventricular nucleus
- Supraoptic nucleus
- Suprachiasmatic nucleus
- Anterior hypothalamic nucleus

MEDIAL HYPOTHALAMUS

- Dorsomedial nucleus
- Ventromedial nucleus
- Arcuate nucleus

LATERAL HYPOTHALAMUS

- Lateral hypothalamic nucleus

POSTERIOR HYPOTHALAMUS

- Posterior hypothalamic nucleus
- Mammillary nucleus

CONNECTIONS

Afferent Connections

The hypothalamus receives afferent connections from the following areas:

- Cerebral cortex
- Globus pallidus
- Olfactory area
- Amygdala
- Limbic system
- Hippocampus
- Midbrain
- Reticular formation

Efferent Connections

The hypothalamus has efferent connections to the following areas:

- Anterior thalamic nucleus
- Tegmentum of midbrain
- Brainstem reticular formation
- Frontal lobe of cerebral cortex
- Posterior pituitary
- Limbic system
- Lateral horn of the spinal cord

FUNCTIONS

1. **Control of food intake**: The hypothalamus has a feeding center in its lateral part and a satiety center (satisfaction) in the ventromedial part. The coordinated activity

of these centers determines the feeding behavior of the animal.

The stimulation of the feeding center produces the desire to eat. The stimulation of the satiety center produces a sense of satisfaction.

Destruction of the feeding center causes severe anorexia and death. Lesion of the satiety center results in excessive eating producing *hypothalamic obesity*.

Mammillary bodies regulate feeding reflexes, such as licking and swallowing.

The mechanisms for the control of food intake are as follows:

- *Glucostatic hypothesis*: The satiety center has glucostatic cells. The entry of glucose under the influence of insulin stimulates these cells producing a sense of satiety.

  Relative or absolute deficiency of insulin reduces the entry of glucose into these cells. Hence, in diabetes mellitus, the patient has a desire to consume excess food (polyphagia) as he/she does not get a sense of satisfaction (satiety).
- *Lipostatic hypothesis*: It suggests that the signals are generated in proportion to fat present in the body. These signals influence the hypothalamus to decrease the food intake and increase the energy output.
- *Gut peptide hypothesis*: It proposes that the polypeptides are produced in the GIT by the presence of food. These polypeptides inhibit further intake of food.
- *Thermostatic hypothesis*: According to this theory, a drop in the body temperature below a critical level stimulates the desire to consume food. A rise in temperature above the set point reduces the appetite.

In addition, the hypothalamus receives sensory information about the filling of stomach and chemical signals from blood about the presence of glucose, amino acids, and fatty acids that can produce a sense of satisfaction.

The signals from the cerebral cortex about the smell and taste of food can also influence the feeding behavior.

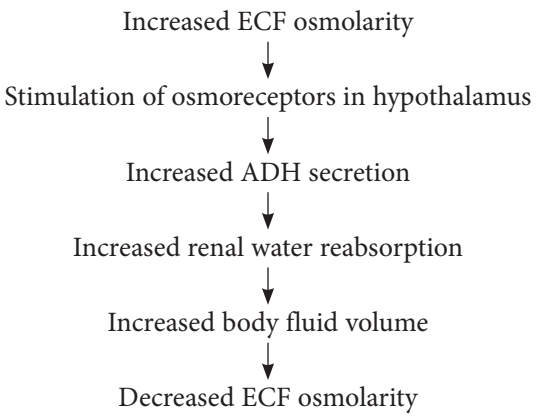
Orexigenic substances such as neuropeptide Y, orexins A and B, cortisol, ghrelin, and endorphins increase the intake of food.

2. **Regulation of water balance**: The hypothalamus controls body water by
   - controlling water excretion from the body and
   - fluid intake by the thirst mechanism.

   The supraoptic nucleus of hypothalamus controls renal excretion of water. Hypothalamus has got osmoreceptors. These are capable of detecting osmolarity of the blood. When there is hemoconcentration (decrease in the fluid content of the blood), the fluid moves out of the osmoreceptor into the blood. This stimulates the nerve cells. Nerve fibers project through the infundibulum of hypothalamus into the posterior pituitary. The nerve endings increase the production of the hormone ADH (antidiuretic hormone), also called **vasopressin**.

   ADH enhances water reabsorption and conserves (retain) water by reducing urine output. However it allows the excretion of electrolytes, thus reducing the concentration of solutes in the body fluids and restoring back to normal. Hemodilution inhibits ADH secretion and increases urine output.

   ADH also stimulates the thirst center and increases the desire to drink water.



3. **Control of the anterior pituitary**: The hypothalamus produces releasing and inhibiting factors, which regulate the secretion from the anterior pituitary.

   The releasing and inhibiting factors produced in hypothalamus pass through the bloodstream to reach the anterior pituitary. This in turn controls the secretion of various anterior pituitary hormones. The channel of blood vessels connecting the hypothalamus and anterior pituitary is termed the **hypothalamo-hypophyseal portal system**.

   For example, TSH-releasing hormone causes secretion of the thyroid-stimulating hormone (TSH).

4. **Control of the posterior pituitary**: The hypothalamus regulates the formation and release of oxytocin and ADH.

   Stimulation of paraventricular nuclei causes the neuronal cells to secrete the hormone oxytocin. This causes contraction of gravid uterus, thus resulting in **parturition**.

   Oxytocin causes the contraction of myoepithelial cells surrounding the alveoli of breast, thus resulting in ejection of milk.

5. **Regulation of body temperature**: The hypothalamus maintains the body temperature within a narrow range of fluctuation.

   Stimulation of lateral hypothalamus produces vasoconstriction and shivering. These changes increase the body temperature.

   Stimulation of the anterior hypothalamus causes loss of heat by vasodilation and sweating.

   The hypothalamus acts as a thermostat to maintain the normal body temperature.

   Hypothalamic control of body temperature and fever: Bacterial and viral infections result in production of toxins in the body. These toxins reset the thermostat present in the hypothalamus.

   The normal body temperature is perceived to be at a lower level as the hypothalamic thermostat is set at a higher level.

   Body temperature is increased within a short period of time by shivering. Violent muscle contraction generates heat and the body temperature increases significantly.

6. **Control of autonomic functions**: The stimulation of the anterior hypothalamus decreases the heart rate, produces vasodilation, and increases movement and secretion of the digestive system. These are the effects of parasympathetic stimulation.

   The stimulation of lateral hypothalamus produces vasoconstriction, pupillary dilation, and increase in heart rate.

7. **Control of sleep and wakefulness**: The posterior hypothalamus forms a part of the reticular activating system. The stimulation of this system produces wakefulness.

   Activity of the anterior hypothalamus produces electrical changes in the brain similar to those seen during sleep.

8. **Control of the circadian rhythm**: The body functions exhibit cyclical variation over a period of 24 hours.

   The sleep–wakefulness cycle and the secretion of hormones such as cortisol follow the circadian rhythm. This rhythm is maintained by the ventromedial nucleus of hypothalamus.

9. **Control of behavior**: Stimulation of the lateral hypothalamus produces fight-flight reactions and overt rage.

   Stimulation of the ventromedial hypothalamus reduces rage resulting in avoidance reaction. Further, it reduces eating and bestows a sense of tranquility.

   Stimulation of periventricular nuclei leads to fear and punishment reactions.

   Stimulation of the most anterior and posterior parts of the hypothalamus increases sex drive. Stimulation of the ventromedial nucleus reduces sex drive.

THALAMUS (Fig. 8.29)

The thalamus is an oval mass containing groups of nuclei forming the lateral boundary of the third ventricle. It partly forms the floor of the lateral ventricle. Thalamus is a Greek word meaning "inner room."

The desire to carry out voluntary motor activity is generated in the cerebral cortex. The subcortical structures such as basal ganglia, thalamus, and cerebellum assist the cerebral cortex in producing the intended movement in the most effective manner.

The appreciation of sensation in a crude form occurs at the thalamic level. However, the finer details of sensation are appreciated at the level of cerebral cortex.

The thalamus is involved in the perception of sensory information, integration of motor activity, learning, memory, and cortical arousal.

The thalamus contains groups of nuclei arranged as mentioned next.

NUCLEI

- Anterior nucleus (A)
- Midline nucleus (ML)
- Intralaminar nucleus (IL)

Dorsal Group

- Medial dorsal nucleus (MD)
- Lateral dorsal nucleus (LD)
- Lateral posterior nucleus (LP)

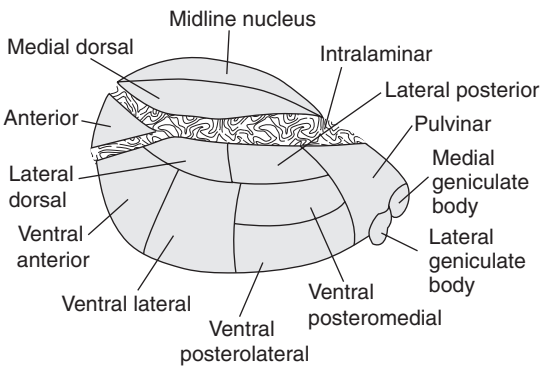


Figure 8.29 Thalamus.

Ventral Group

- Ventral anterior nucleus (VA)
- Ventral lateral nucleus (VL)
- Ventral posterolateral nucleus (VPL)
- Ventral posteromedial nucleus (VPM)

Posterior Group

- Pulvinar (P)
- Medial geniculate body (MGB)
- Lateral geniculate body (LGB)

AFFERENT CONNECTIONS

1. **Medial lemniscus**: It is the continuation of fasciculus gracilis and cuneatus. It conveys fine touch, pressure, vibration, and proprioceptive sensations to the ventral posterolateral nucleus.
2. **Spinal lemniscus**: It carries pain, temperature, and crude touch senses to the ventral posterolateral nucleus.
3. **Trigeminal lemniscus**: It carries all sensations from the trigeminal area to the ventral posteromedial group.
4. **Sensory visceral fibers from the hypothalamus**: They terminate on the medial part of thalamus.
5. **Cerebellar efferents from the opposite side**: They terminate in the ventrolateral nucleus.
6. **Rubrothalamic tract**: The fibers from red nucleus of the same side terminate on the ventrolateral nucleus.
7. **Corticothalamic fibers from different areas of cortex**: They terminate in different nuclei of thalamus.

EFFERENT CONNECTIONS

1. Thalamocortical fibers: They are widely distributed to different parts of the cerebral cortex.
2. Efferent fibers to caudate nucleus

3. Efferent fibers to globus pallidus
4. Efferent intrathalamic connections
5. Efferents to hypothalamus and midbrain

FUNCTIONS

- Thalamus is a sensory relay station; relays general and special sensations except smell sensation
- Functions as a subcortical center for perception of pain sensation
- Helps in information storage and short-term memory
- Forms a functional part of the reticular activating system responsible for consciousness, sleep, and wakefulness
- Forms a part of the neural circuit (Papez) for emotional experience, personality, and social behavior
- Regulates autonomic functions associated with emotions
- Forms a part of the posture-adjusting system; helps the motor cortex to modify and update signals to perform voluntary motor activity
- Integrates cortical and subcortical areas for execution of speech
- Plays an important role in the genesis and synchronization of waves of EEG
- Forms a link between the cerebellum, basal ganglia, and cerebral cortex

In short, the thalamus plays a key role in mediating sensations, motor activities, cortical arousal, learning, and memory acting as a gateway for cerebral cortex.

Thalamic Syndrome

Ischemic damage to the posteroventral part of thalamus due to a blockage in the feeding artery produces thalamic syndrome. This condition is characterized by

- loss or alteration in different sensations,
- ataxia—incoordination of voluntary movements due to loss of joint sense,
- astereognosis—it is the inability to identify commonly used objects by the feel of it,
- hypotonia and muscular weakness,
- emotional disturbance, and
- increased pain perception.

The medial nucleus of thalamus is not damaged in the thalamic syndrome. The pain fibers reach this nucleus. Hence, there is dominance of pain sensation over the other sensations.

BASAL GANGLIA (Fig. 8.30)

The basal ganglia are paired subcortical structures located lateral to the thalamus, below the lateral ventricle. They are located lateral to the third ventricle, consisting of the following nuclear groups:

1. Caudate nucleus
2. Putamen
3. Globus pallidus
   - External segment
   - Internal segment
4. Substantia nigra
   - Pars compacta
   - Pars reticulata
5. Subthalamic nucleus (red nucleus)

Caudate nucleus and putamen are together called the **striatum**.

Putamen and globus pallidus are termed the **lenticular nucleus**.

The important neurotransmitters in the basal ganglia are

- dopamine,
- GABA,
- acetylcholine, and
- norepinephrine

Dopamine pathway: This pathway is from substantia nigra to caudate nucleus and putamen.

GABA pathway: This pathway is from caudate nucleus and putamen to globus pallidus and substantia nigra.

Acetylcholine pathway: This pathway is from cortex to caudate nucleus and putamen.

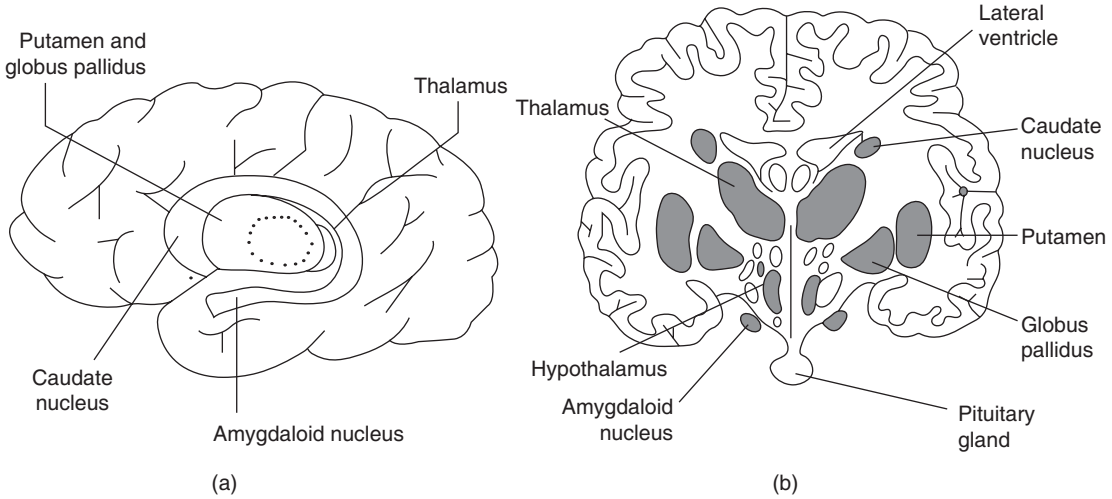


Figure 8.30 Basal ganglia.

Norepinephrine pathway: There are multiple pathways from brainstem secreting norepinephrine, serotonin, and enkephalins.

CONNECTIONS OF BASAL GANGLIA

Afferent Connections

Corticostriate projection—from all parts of the cerebral cortex to the striatum.

Connections Within Basal Ganglia (Fig. 8.31)

- Nigrostriatal (dopaminergic) projection from pars compacta of substantia nigra to striatum
- Projection from striatum to pars reticulata (GABAergic) of substantia nigra
- Projection from caudate nucleus and putamen (GABAergic) to both segments of globus pallidus

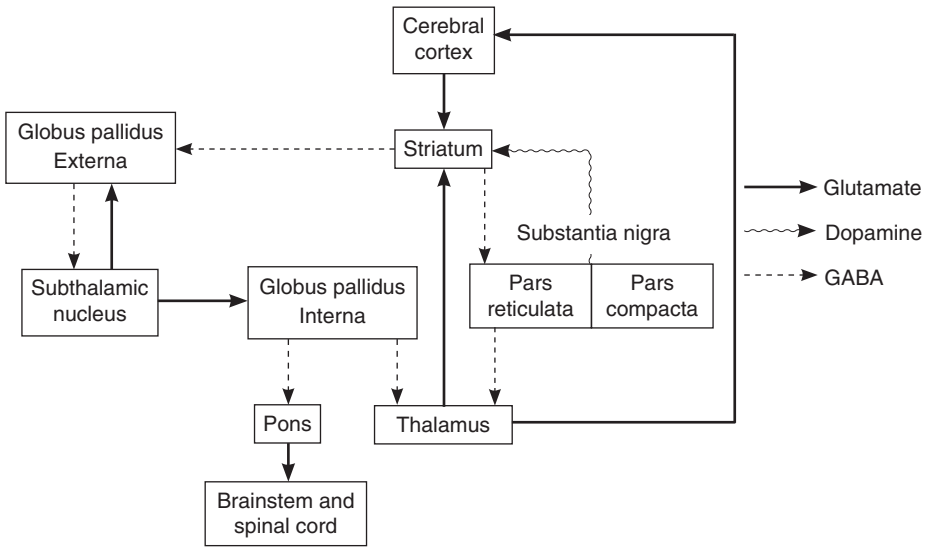


Figure 8.31 Connections of basal ganglia.

- Connection from the external segment of globus pallidus to subthalamic nucleus
- Connection from the subthalamic nucleus to substantia nigra and both segments of globus pallidus (opposite direction)

Efferent Connections

- Output from the internal segment of globus pallidus through thalamic fasciculus to thalamus.
- From thalamus, the fibers project to the prefrontal and premotor cortices.

FUNCTIONS

- Responsible for planning and programming the voluntary motor activity. The thinking process starts in the brain from sensory inputs, stored memory, and intended activity.
- Regulates stretch reflex throughout the body
- Controls the transfer of information from sensory and association areas to motor cortex
- Essential for initiation, control, and cessation of muscular activity
- Provides the necessary muscle tone for skilled movements
- Coordinates the impulses for skilled motor activity
- Controls the normal automatic associated movements
- Regulates the subconscious gross associated movements
- Intact basal ganglia are necessary for a normal degree of tone and posture
- Controls the activity of muscle group for emotional expression

CLINICAL NOTES

Parkinson Disease (Paralysis Agitans)

The lesion of the basal ganglia results in Parkinson disease.

In this condition, the dopaminergic pathway is damaged. The interplay of facilitatory and inhibitory signals is unbalanced. It has both hypokinetic and hyperkinetic features.

Akinesia (grossly reduced movements) and bradykinesia (slow movements) are the hypokinetic features.

Rigidity and tremor are the hyperkinetic features. There is an imbalance between facilitatory and inhibitory circuits controlling the movements.

Parkinson disease has the following features:

- Rigidity of muscle—lead pipe type/cogwheel type; damage to the dopaminergic pathway allows caudate nucleus and putamen to send excitatory signals continuously to the corticospinal motor control system.
- Resting tremors (pill-rolling tremors); loss of inhibition in oscillation of feedback circuits. This results in tremors at rest.
- Flexed attitude due to increased tone in the flexor muscles; difficulty in commencing the movements (akinesia); reduction of dopamine in the limbic system is believed to reduce the psychic drive for motor activity resulting in akinesia.
- Difficulty in execution of movements and slowness of movements (bradykinesia); poverty of movements. Poverty of movement and difficulty in execution of movement are attributed to rigidity in the muscles and reduced motivation to perform motor activity.
- Loss of associated movements
- Short shuffling gait (festinant gait)
- Autonomic disturbances
- Loss of facial expression—mask-like face
- Cognitive decline: Cognitive dysfunction in Parkinson's disease includes dementia and changes in personality, mood, and behavior.

Disease associated with basal ganglia also produces hyperkinetic movement disorders such as chorea, athetosis, and ballism. These are excessive abnormal involuntary movements.

Management

Parkinson's disease can be managed by administration of L-dopa (precursor of dopamine) as dopamine cannot cross the blood–brain barrier.

(*Contd.*)

Deep brain stimulation is one of the modalities of treatment for Parkinson's disease. In this procedure, the overactive areas of basal ganglia are destroyed. Electrodes are implanted into these areas and connected to pulse generators similar to cardiac pacemakers.

Resting Tremor (Static Tremor)

Tremor is a rhythmic, alternate contraction of the agonistic and antagonistic muscles of a joint.

Tremor in Parkinsonism is seen at rest but disappears during activity. Hence, it is called **resting tremor**. The possible cause for this tremor is damage to feedback circuits through basal ganglia. It might oscillate due to high feedback gain and loss of inhibition.

It can also be seen in thyrotoxicosis, anxiety states, mercury poisoning, and chronic alcoholics.

Intention Tremor

Intention tremors appear when the subject intends to do some work. They are seen in a cerebellar lesion. This is due to the failure of the system to dampen motor activity.

CEREBELLUM (Fig. 8.32)

The cerebellum is the part of the CNS located posterior and inferior to the cerebral hemispheres. It is situated in the posterior cranial fossa. It is located posterior to the pons, medulla, and fourth ventricle. It resembles the shape of a cauliflower and is also called the **small brain**.

The cerebellum has a thin outer cortex of gray matter and inner white matter. Paired masses of the gray matter situated deep in the white matter constitute the nuclei of the cerebellum.

It is divided into right and left cerebellar hemispheres. It is connected to the brainstem through superior, middle, and inferior cerebellar peduncles.

CEREBELLAR CORTEX

The cerebellar cortex is made of three layers and contains different types of cells. The three layers are as follows:

1. Outer molecular layer
2. Purkinje cell layer
3. Granular layer

The outer molecular layer contains a network of nerve processes and nerve fibers. This layer also contains basket cells. The Purkinje cell layer contains cell bodies of Purkinje cells. The inner granular layer contains granule cells and Golgi cells.

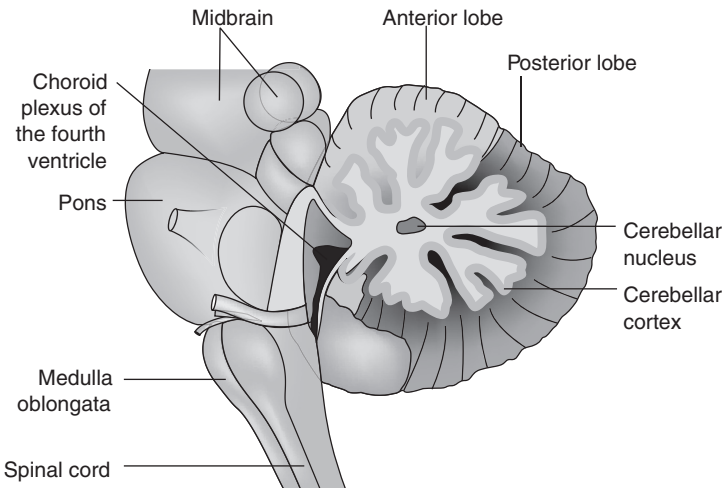


Figure 8.32 Sagittal section of cerebellum. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The cerebellum plays an important role in regulation of tone, posture, equilibrium, and coordinated movement of the body.

DIVISIONS OF CEREBELLUM

Anatomical Division

- Flocculonodular lobe
- Anterior lobe
- Posterior lobe

Phylogenetic Division

- Archicerebellum
- Paleocerebellum
- Neocerebellum

Functional Division

- Vestibulocerebellum
- Spinocerebellum
- Cerebrocerebellum (neocerebellum)

NUCLEI OF CEREBELLUM

Cerebellum has four deep nuclei (NC) present in the white matter:

1. Nucleus globosus
2. Nucleus emboliformis
3. Nucleus fastigius
4. Nucleus dentatus

INPUT TO CEREBELLUM (Fig. 8.33)

The cerebellum receives inputs through

- climbing fibers and
- mossy fibers.

Climbing fibers arise from the region of inferior olive in the medulla. They make synaptic connections with Purkinje cells (PC). The climbing fibers produce high-frequency bursts or **complex spikes**. They play a major role in motor learning.

Mossy fibers arise from different centers in the brainstem and spinal cord. They make synaptic connection with Golgi cells (GC). They produce **simple spikes**. They also synapse with granule cells (GR). The axons of granule cells bifurcate. They excite the Purkinje cells (through parallel fibers) which in turn inhibit the deeper nucleus.

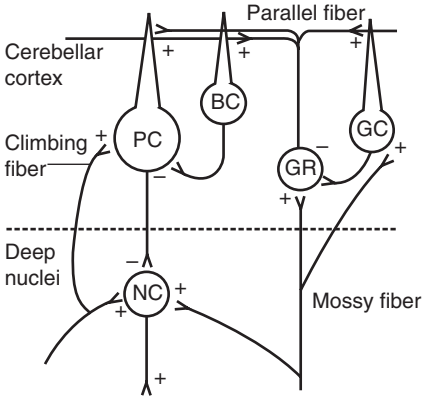


Figure 8.33 Connections in the cerebellum. *BC*, basket cell; *GC*, Golgi cell; *GR*, granule cell; *NC*, cell in deep nucleus; *PC*, Purkinje cell.

OUTPUT FROM THE CEREBELLUM (Fig. 8.33)

The output of the cerebellar cortex is from Purkinje cells. These outputs are always inhibitory.

GABA is the neurotransmitter. The output projects to deeper cerebellar nuclei and vestibular nucleus. The inhibitory inputs influence the output from the cerebellum to regulate range, direction, and rate of movement.

Deep cerebellar nuclei receive excitatory inputs from the climbing and mossy fibers. Hence, the output from deep cerebellar nuclei is always excitatory.

CONNECTIONS OF CEREBELLUM

Through Superior Cerebellar Peduncle

Afferent

- **Ventral spinocerebellar tract**: Carries proprioceptive impulses from the trunk and limbs

- **Tectocerebellar tract**: Carries visual and auditory impulses through superior and inferior colliculi

Efferent

- Dentatothalamocortical tract
- Dentatorubrothalamic tract

Through Middle Cerebellar Peduncle

Afferent

- **Pontocerebellar tract**: Impulses from the opposite motor cortex via pontine nucleus
- **Cerebellocerebellar tract**: Fibers from the dentate nucleus of one cerebellar hemisphere to that of the opposite side

Efferent

- Cerebellocerebellar tract

Through Inferior Cerebellar Peduncle

Afferent

- **Dorsal spinocerebellar tract**: Carries proprioceptive sensations from the trunk and limbs of the same side
- **Olivocerebellar tract**: Proprioceptive impulses from all over the body relayed through inferior olive
- **Vestibulocerebellar tract**: Carries impulses from the vestibular apparatus from the same side of the body
- **Cuneocerebellar tract**: Carries proprioceptive impulses from the arm and neck from the same side of the body
- **Reticulocerebellar tract**: Impulses from brainstem reticular formation
- **External arcuate fibers**: Originating from nucleus gracilis and cuneatus
- **Fibers arising from fifth**, **ninth**, and **tenth cranial nerves**

Efferent

- Fastigiobulbar and fastigiovestibular tracts
- Cerebello-olivary tract

FUNCTIONS OF CEREBELLUM

Vestibulocerebellum (Archicerebellum)

- Concerned with the maintenance of balance and equilibrium
- Responsible for regulating the stability of head and body in space
- Adjusts the tone of the trunk muscle and controls the ocular movements and other postural reflexes

Spinocerebellum (Paleocerebellum)

- Maintains the posture and helps in execution of gross movements
- Controls the interplay between the agonist and the antagonist groups of muscles
- Essential for the control of rapid muscular activities such as running and talking

Cerebrocerebellum (Neocerebellum)

- Controls fine, highly precise, and coordinated movements
- Involved in programming of voluntary and skilled movements
- Plays a major role in the timing of the motor activities and rapid progression from one movement to the next

SERVO CONTROL MECHANISM

The cerebellum acts as a comparator-and-error detector. It compares the information coming from the cortical regions involved in programming and execution of movements with those coming from the periphery (joints, muscles, and skin). If there is any difference between the two informations, the cerebellum adjusts the activity in the descending pathway to correct the ongoing movement. It sends an error signal to the motor cortex and subcortical structures for modification of program.

Cerebellar Processing

The role of cerebellum in processing information for motor activity has the following pattern:

1. The intention of initiating motor activity is conveyed to cerebellum by the frontal motor association area of the cerebral cortex through the collateral fibers of the pyramidal tract.
2. The cerebellum receives inputs from proprioceptors throughout the body regarding the state of muscle contraction and position of joints. It also gets the inputs from visual apparatus and structures responsible for maintenance of equilibrium. This helps the cerebellum to compare the position of various structures in space, change of position, and momentum.
3. The cerebellar cortex estimates the best way to coordinate the force, direction, and extent of muscle contraction needed to prevent overshoot and maintain the correct posture to facilitate smooth, coordinated, and purposeful movement.
4. The cerebellum sends its plan of action to the cerebral cortex through the superior cerebellar peduncle. It also sends information to the brainstem to influence the motor neurons of the spinal cord.
5. The cerebellum continuously compares the intention of higher brain centers with the actual performance of the body. It provides necessary corrective inputs periodically to produce the best output.

EFFECTS OF CEREBELLAR LESIONS

- Ataxia—incoordinated, intermittent jerky movements with drunken gait
- Hypotonia or atonia—reduced or absence of muscle tone
- Dysmetria—inability to judge the force and range of movement resulting in past pointing
- Dysdiadokokinesia—failure to perform rapid alternating movements
- Decomposition of movement—lack of smooth flow of movement
- Dysarthria: Speech defect—staccato speech or slurring speech
- Pendular knee jerk (a feature of hypotonia)
- Intention tremors
- Nystagmus (jerky movements of the eye)

CEREBRUM

The cerebrum is the largest part of the human brain. It is divided into right and left cerebral hemispheres separated by the median longitudinal fissure. The cerebral hemispheres are connected in the midline by a thick band of white matter called the **corpus callosum**. The corpus callosum is made up of axons passing between the right and left hemispheres.

Each hemisphere has an outer layer of gray matter that is 5 mm thick. This is termed the **cerebral cortex**. The cerebral cortex has a rich blood supply. It covers thick white matter.

The surface of the cerebral cortex exhibits depressions and elevations, termed **sulci** and **gyri**. Gyri and sulci increase the surface area of the brain. The deeper sulci are called **fissures**.

The white matter has axons connecting different parts of the brain with the cerebral cortex. It has lesser blood supply. The white matter of each hemisphere has a large collection of cell bodies forming the basal ganglia.

The motor cortex has extensive connection with different parts of the brain such as cerebellum, basal ganglia, thalamus, midbrain, reticular formation, brainstem, and spinal cord.

The cerebral cortex has primary areas and association areas. The primary area is concerned with the perception of respective sensation and the association area is needed for the interpretation of sensation perceived by the primary area.

The cerebral cortex is anatomically divided into the following lobes:

- Frontal lobe
- Parietal lobe
- Temporal lobe
- Occipital lobe

The cerebral cortex is made up of the following six layers:

1. Molecular or plexiform layer
2. External granular layer
3. Outer pyramidal cell layer
4. Inner granular layer
5. Inner pyramidal cell layer
6. Fusiform cell layer

Brodmann has divided the cerebral hemisphere into 52 cortical areas (**Fig. 8.34**).

The major cortical areas are as follows:

1. **Frontal lobe**

   It has three subdivisions:

   (a) Primary motor area

   (b) Premotor area

   (c) Supplementary motor area

   Primary motor area

   - *Area 4*: It is the primary motor area. It lies in front of the central sulcus. This area helps to initiate voluntary movements. Large neurons called pyramidal cells present in this area help to precisely control voluntary activity of skeletal muscles. The axons from the primary motor cortex pass through the brainstem and spinal cord. They synapse with motor neurons at different segments of the spinal cord. Damage to motor cortex paralyzes muscles of the opposite side of the body.

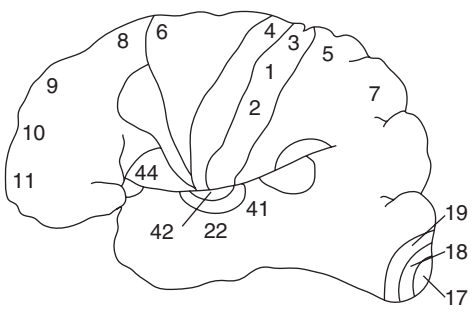


Figure 8.34 Brodmann areas of cerebral cortex.

Premotor area

- *Area 6*: It is the premotor area. The fibers to the pyramidal tract also arise from this region.

  The premotor area creates motor images of the intended motor activity. Then it sends signals to the primary motor cortex directly or through the basal ganglia and thalamus to activate a specific muscle group to complete the action. It is connected with skilled movement. It coordinates the actions initiated by area 4.

Supplementary motor area

- It lies in longitudinal fissure and extends to the superior frontal cortex.

  Stimulation of this area produces contraction of muscle groups bilaterally. Supplementary motor area coordinates the activities of other motor areas.
- *Area 8*: It is the frontal eye field area. It helps in voluntary and conjugate movements of the eye. It also controls the movement of eyelids, size of pupils, and lacrimation.
- *Area 44*: This is Broca's speech area. It is present in the dominant hemisphere. It is connected to premotor and primary motor areas.

  It helps in vocalization by controlling the movement of lips, tongue, larynx and respiratory muscles. The subject will not be able to utter complete words following damage to this area in spite of having clear thoughts (nonfluent aphasia).
- *Prefrontal cortex*: *Areas 9, 10, 11, 12, 13, 14, 29, and 32*: The prefrontal cortex present in the anterior part of the frontal lobe is the most complicated cortical region. It is connected with complex learning abilities, intelligence, personality, recall of information, production of abstract ideas, reasoning, judgment, long-term planning, and conscience.

The prefrontal cortex matures slowly and depends on positive and negative feedback during its development.

It is connected to the limbic system which caters to the emotional functions of the brain. It plays an important role in mood and intuitive judgment.

The lesion of the prefrontal cortex results in mental and personality disorders.

The other manifestations are mood swings, loss of judgment, and attentiveness. The affected individual is unmindful of social restraints.

2. **Parietal lobe**
   - *Areas 3, 1, 2*: The primary sensory cortex (somatosensory area) present in the postcentral gyrus.

     It receives information from receptors in the skin, joints, and muscles.

     Somatosensory cortex is also connected with integration of sensory information and conscious awareness of sensation.

     The map of the entire body is present in the somatosensory cortex. The area occupied by a particular part of the body depends on the number of receptors rather than on the size of the body part. Thus, the lips and the tip of a finger have larger representation than the trunk and thorax.
   - *Areas 5, 7*: These are sensory association areas. They are concerned with the synthesis and interpretation of the information received by the somatosensory cortex. They store the memory of past experience, thus helping to compare the present situation with the past experience. It helps to sense the relationship of one body part to another.
3. **Occipital lobe**
   - *Area 17*: It is the primary visual area. It is concerned with processing visual information.
   - *Areas 18, 19*: These are visual association areas. They are concerned with the interpretation of visual information received by the primary visual cortex. The visual association area uses the past experience to interpret the visual stimulus. This special feature helps to identify different objects and persons.

     They are also responsible for the movement of eyes.
4. **Temporal lobe**
   - *Areas 41, 42*: These are the primary auditory areas. They are responsible for the perception of auditory information.
   - *Area 22*: This is **Wernicke's area**. It is concerned with the interpretation of auditory information. It interprets the meaning of speech by recognizing spoken words. Damage to Wernicke's area results in fluent aphasia. The subject is able to speak but unable to arrange words in a coherent fashion.

Motor Homunculus

A topographical arrangement of different parts of the body in motor cortex is termed **motor homunculus** (**Fig. 8.35**). The body is represented upside down in the motor cortex except for the face which is not inverted. Stimulation of the medial part causes movement of toes and lower limbs.

The representation of body parts is contralateral but the face has ipsilateral representation.

The area of representation is proportional to the functional importance and activity of the area. Hands, fingers, lips, and tongue which have extensive use have a greater area of representation compared to the trunk.

Stimulation of the medial part causes movement of the toes and lower limbs. Stimulation of the lateral part causes movement of tongue.

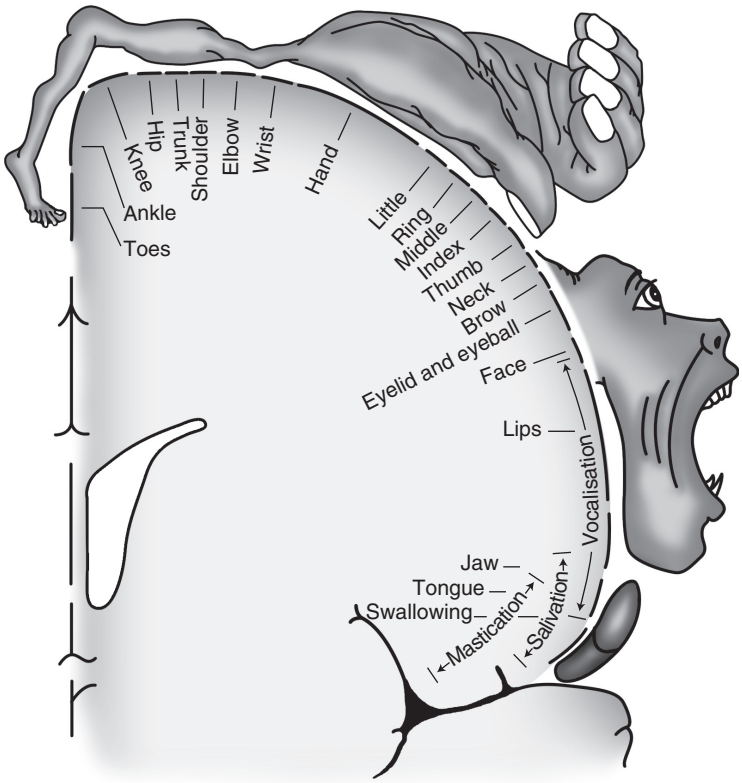


Figure 8.35 Motor homunculus. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

ELECTROENCEPHALOGRAM

Electroencephalogram (EEG) is the electrical activities of neurons in the brain. It is recorded from the surface of the scalp by using electrodes.

Spontaneous electrical activity is generated in the pyramidal cells of the cerebral cortex. This is due to summation of an innumerable number of excitatory and inhibitory synaptic potentials generated in the activated pyramidal cells. This cortical neuronal activity is greatly influenced by afferent inputs from thalamus and brainstem reticular formation.

An electroencephalogram recorded with electrodes in direct contact with the brain is called **electrocorticogram**.

EEG waves have two variables:

1. Amplitude
2. Frequency

The **amplitude** indicates the quantum of electrical activity beneath the recording electrode. It is measured in microvolts (μV).

The **frequency of wave** indicates the number of waves per unit time. It is measured as Hertz (Hz or cycles/s).

EEG waves have a very low voltage; hence, they are amplified during recording. EEG was first analyzed systematically by a German psychiatrist Hans Berger. Hence, it is also called *Berger's rhythm*.

EEG has four different waves (**Fig. 8.36**):

1. **Alpha-wave**: It has a frequency of 8–12 Hz with amplitude of 50–100 μV. It can be recorded mainly from the occipital region and also from the frontal and parietal regions. It is the most common wave seen in normal adults at rest with the eyes closed.

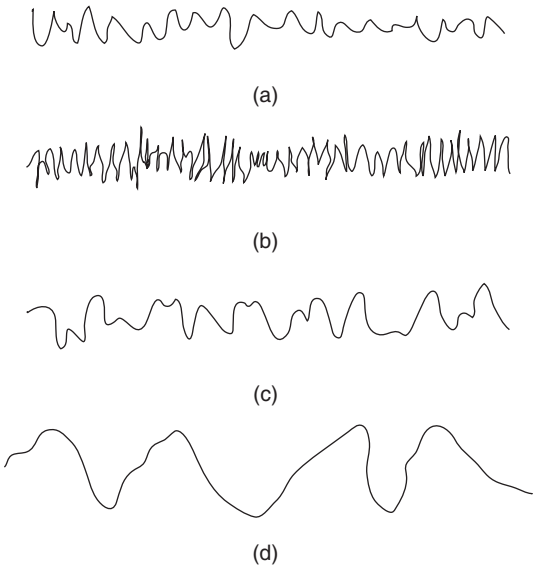


Figure 8.36 Waves of EEG: (a) alpha, (b) beta, (c) theta, and (d) delta.

2. **Beta-wave**: It has a frequency of 18–30 Hz with lower amplitude. It is recorded from the parietal and frontal regions. It is seen in adults when the eyes are open. In subjects shifting from a less attentive state to an attentive state, the EEG waves change from an alpha pattern to a beta pattern. This is called **EEG arousal**.
3. **Theta-wave**: This is a large-amplitude, regular wave with a frequency of 4–7 Hz. The theta-wave is seen in children. It is also seen when the individual falls asleep and in severely depressed patients. It is recorded from the parietal and temporal regions.
4. **Delta-wave**: This is a large, slow wave with a frequency of less than 4 Hz. It appears in deep sleep. It is also seen in infants. In adults, the presence of delta waves in an alert state indicates serious organic brain disease.

USES

- EEG is a widely accepted and reliable method of studying electrical changes occurring in brain during normal and abnormal conditions.
- It is helpful in localizing cerebral tumors and abscesses.
- It is of special importance in the diagnosis of epilepsy and other types of fits. In epilepsy, there is excessive discharge of signals from the cerebral cortex.
- It is helpful in the diagnosis of various diseases of cerebral cortex and impaired cerebral function.

SLEEP

Sleep is a reversible state of altered consciousness characterized by diminished excitability of the brain and reduction in physiological functions.

MECHANISM

- Activity of ascending reticular activating system (ARAS) leads to awakening. Conversely, inhibition of ARAS promotes sleep. Lesion of RAS produces coma.
- Serotonergic fibers arise from the raphe nucleus of pons. Stimulation of these fibers induces sleep.
- Sleep-promoting peptide and sleep peptides (muramyl peptides) accumulate during wakefulness. When its concentration in the brain increases, it promotes sleep.

PHYSIOLOGICAL CHANGES DURING SLEEP

The heart rate, blood pressure, and respiratory rate decrease. The blood vessels to the skin dilate. There is a decrease in the excitability of the nervous system.

The sympathetic activity decreases and the parasympathetic activity increases. There is muscle relaxation. The net effect aims at restoration of the natural balance among the neuronal centers.

Types of Sleep

- Nonrapid eye movement (NREM) sleep
- Rapid eye movement (REM) sleep

Nonrapid Eye Movement Sleep

- It is a slow-wave sleep.
- There is no rapid movement of the eyeball.
- It occupies a major part of the sleeping time.
- Each cycle lasts for about 70 minutes.
- There is pulsatile release of growth and gonadotropic hormones.
- Sleep begins with this form and is followed by REM sleep.
- It occurs due to inhibition of the reticular activating system.

Rapid Eye Movement Sleep (Paradoxical Sleep)

During REM sleep, eye movements are increased. Each cycle of REM sleep lasts for about 5–30 minutes. It alternates with NREM sleep.

- It is associated with dreaming.
- During this phase, it is difficult to arouse the person.
- Muscle tone is exceedingly depressed.
- Heart rate and respiration are irregular, but the brain is highly active.
- The overall metabolism is increased by 20%. Oxygen consumption of the brain increases.
- This is not a restful form of sleep.
- EEG shows a wave pattern similar to that seen during wakefulness. Hence, it is called **paradoxical sleep**.

Importance

- Sleep helps in consolidation of memory.
- It helps in restoration of neuronal balance.
- It facilitates structural and chemical changes in the neuronal network of the brain.
- It strengthens synapses in the pathway needed for learning and memory.
- It promotes growth as increased growth hormone secretion occurs during sleep.
- REM sleep produces muscle relaxation due to activity in pontine reticular formation.

EEG CHANGES FROM AN ALERT STATE TO DEEP SLEEP

An alert and awake person has **beta-wave**.

If a person is awake, relaxing with eyes closed, **alpha-waves** are seen.

When the individual becomes drowsy and falls asleep, alpha-waves are replaced by slower and larger **theta-waves**.

During deep sleep, very large irregular **delta-waves** are seen.

Alpha-Block

In a normal adult relaxing with eyes closed, alpha-waves are recorded. On opening the eyes, alpha-waves are replaced by low-voltage, fast, irregular waves. This is known as **alpha-block**.

CLINICAL NOTES

Disorders of Sleep

Insomnia

Insomnia is a condition of insufficient and nonrefreshing sleep in spite of an opportunity to sleep.

It is temporarily managed by using benzodiazepines (sleeping pills). Prolonged use of these drugs can result in addiction and can adversely affect the performance of the individual.

Somnambulism

Somnambulism is also called sleepwalking. It is common in children than in adults. They walk with eyes open but cannot recollect the incident when awakened. Somnambulism occurs during slow-wave sleep.

Narcolepsy

Narcolepsy is a disease characterized by an irresistible urge to sleep during daytime associated with sudden loss of muscle tone. The condition is characterized by a sudden onset of REM sleep. Human subjects with narcolepsy have a low level of **orexins** (hypocretin) in CSF. Orexins (hypocretin) is a polypeptide secreted from the neurons of lateral hypothalamus which regulates food intake and sleep.

(*Contd.*)

REM Behavior Disorder

In this condition, hypotonia is not seen during REM sleep. The subject reacts physically during dream. Jumping out of the bed or fighting with an imagined aggressor is a common feature. The condition is managed by benzodiazepines.

Sleep Apnea

Sleep apnea is a condition in which the stimulation of respiratory muscle stops temporarily. This decreases the oxygen level.

The subject is deprived of both slow wave and REM sleep due to repeated awakening. The condition is associated with excessive sleepiness during day time.

Coma

Coma is a term used to describe a severe decrease in the mental functions due to structural, functional, and metabolic defects in the brain.

The person in coma cannot be aroused by painful stimuli.

There is loss of the sleep–wakefulness cycle.

Coma can result from

- damage to the cerebral cortex,
- damage to the brainstem arousal mechanism,
- loss of connection between the brainstem and cortex,
- overdose of sedative drugs,
- metabolic dysfunction,
- infections of brain, and
- patients in irreversible coma enter a **persistent vegetative state**.

Brain Death

Brain death is a condition in which the brain no longer functions and does not have the possibility of functioning again despite functioning of other organs. Brain death is considered a criterion for death.

RETICULAR ACTIVATING SYSTEM

Reticular formation or reticular activating system (RAS) is a diffuse network of neurons and discrete collection of nuclei. It occupies the midventral portion of the medulla, pons, and midbrain.

The nerve fibers of RAS are multisynaptic. They begin at the medulla and receive numerous collaterals from specific sensory tracts such as the spinothalamic and trigeminal tracts. They relay at the thalamic nuclei. Further-order neurons terminate on parts of the cerebral cortex. Some fibers may bypass the thalamic region and terminate in the cerebral cortex.

These fibers carry nonspecific impulses concerned with alertness, wakefulness, and consciousness to the cerebrum and activate the whole of the cerebral cortex.

Reticular formation has

- ascending reticular activating system (ARAS) and
- descending reticular activating system.

ASCENDING RETICULAR ACTIVATING SYSTEM (Fig. 8.37)

The ascending reticular activating system (ARAS) is a polysynaptic pathway extending from the lower pons to the thalamus. It mainly has cholinergic fibers.

Connections of ARAS

The cholinergic fibers from the midbrain and pons project to the cerebral cortex passing through the thalamus.

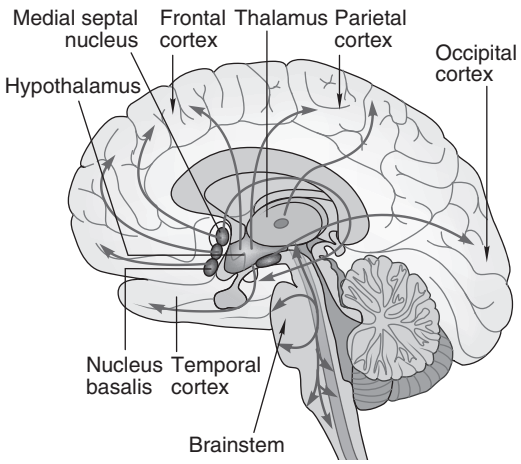


Figure 8.37 Ascending reticular activating system. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The adrenergic fibers from all over the reticular formation project to the cerebral cortex.

The serotonergic neurons from the raphe nucleus project to the thalamus, hypothalamus, cerebral cortex, and limbic system.

ARAS regulates sleep, wakefulness, and consciousness.

DESCENDING RETICULAR SYSTEM

The reticular fibers descending to the spinal cord form the descending reticular system. This system has both facilitatory and inhibitory projections.

Connections of Descending Reticular Activating System

The pontine and medullary reticulospinal tracts project to the spinal cord.

The noradrenergic fibers from different parts of the reticular formation project to the cerebellum.

The dopaminergic fibers from the midbrain reticular formation project to the basal ganglia.

The serotonergic neurons in the raphe nucleus of the medulla project to the spinal cord.

The descending reticular formation controls the tone of the extensor muscles.

The projections from reticular formation help to regulate respiratory, cardiovascular, and vasomotor functions.

The sensory inputs to the reticular formation come from the areas connected to the reticular formation by the projection. There is extensive sensory input from the fibers carrying slow pain.

The reticular formation has four distinct systems with a specific neurotransmitter. The neurotransmitters are as follows:

- Acetylcholine
- Norepinephrine
- Serotonin
- Dopamine

FUNCTIONS OF RETICULAR ACTIVATING SYSTEM

- ARAS is responsible for arousal and wakefulness.
- Reticular facilitatory and inhibitory areas influence the spinal motor neurons to excite or inhibit them.
- Several important autonomic centers such as cardiovascular and respiratory centers are located in reticular formation.
- Reticular activating system helps in the modulation of sensory impulses.
- Many behavioral functions are mediated through reticular formation.
- Descending reticular activating system controls muscle tone.

Sedatives and hypnotics prevent synaptic transmission in RAS to produce their effect.

LIMBIC SYSTEM

Limbus means rim. The limbic system or limbic lobe (**Fig. 8.38**) consists of cortical tissue around the hilum of cerebral hemisphere and subcortical structures associated with it. These structures include parts of frontal and temporal lobes on either side, namely, hippocampus, septal nucleus, cingulate gyrus, anterior thalamic nucleus, and amygdala.

The **cingulate gyrus** lies around the corpus callosum.

The **hippocampus** lies on the medial wall of the temporal lobe.

The **amygdala** lies in front of the hippocampus.

The **septum** lies in midline anterior to the hypothalamus.

The limbic cortex is the oldest part of the cerebral cortex. It is made up of primitive cortical tissue called the **allocortex**. The transitional cortex which forms the second ring is termed the **juxtallocortex**.

It is observed that the size of allocortex and juxtallocortex has not changed significantly with evolution.

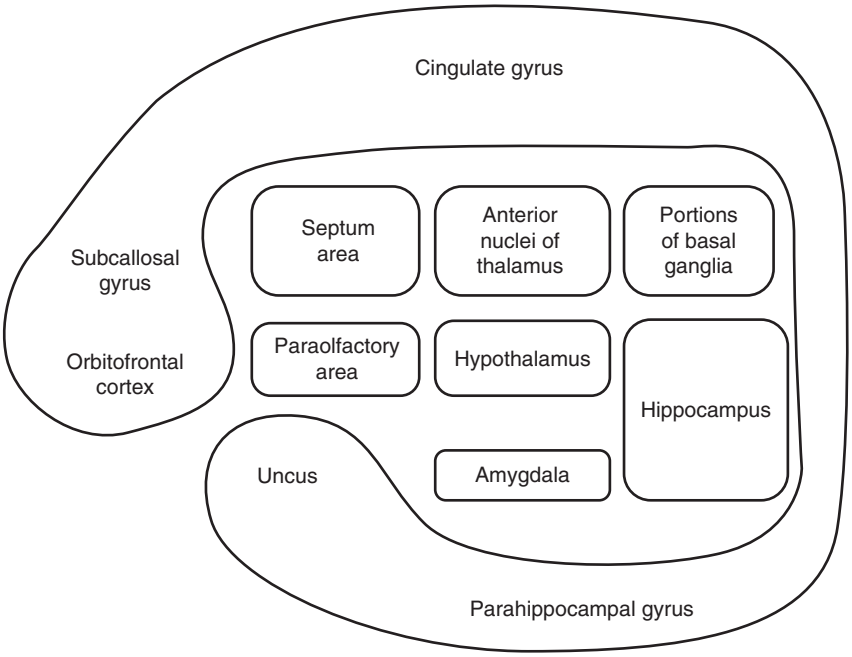


Figure 8.38 Limbic system.

CONNECTIONS OF THE LIMBIC SYSTEM (PAPEZ CIRCUIT)

The connections of the limbic system were first described by Papez and hence it is named as Papez circuit. The major tract of the limbic system connects four major structures. The hippocampus is connected to the mammillary body of the hypothalamus. The mammillary body is connected to the anterior nucleus of the thalamus. The anterior thalamic nucleus is connected to the cingulate gyrus. The cingulate gyrus projects back to the hippocampus completing the circuit.

Hippocampus
↓ Fornix
Mammillary body
↓ Mammillothalamic tract
Anterior nuclei of thalamus
↓
Cingulate cortex
↓
Connection back to hippocampus

The neocortical activity influences the emotional behavior. However, the connection between the limbic cortex and neocortex is limited.

The duration of emotions cannot be regulated by conscious effort. Emotional responses are prolonged due to prolonged after-discharges in the limbic cortex. The response exceeds the duration of the stimulus producing it.

FUNCTIONS OF LIMBIC SYSTEM

- Controls emotions of rage, fear, and motivation
- Regulates the sexual behavior in association with hypothalamus
- Plays a role in the process of olfaction
- Connected with autonomic responses
- Plays an important role in memory

Hippocampal formation is intimately connected with control of sensations and behavior.

Stimulation of hippocampus causes focal epileptic seizures. During seizures, the subject experiences visual, olfactory, auditory, and tactile hallucinations.

Bilateral removal of hippocampus results in the inability to establish long-term memory. This is termed **anterograde amnesia**.

Amygdala controls the choice of food and the time of consuming it. In lower animals, amygdala is connected with olfactory stimuli.

In human beings, it influences the behavior which is not associated with olfactory stimuli.

Stimulation of amygdala brings about alteration in heart rate, blood pressure, gastrointestinal motility, secretion, and evacuation of bowel and bladder.

It also causes secretion of hormones from the anterior pituitary, piloerection, and pupillary dilation.

The septal nucleus regulates taste preference and controls food intake and metabolism.

The limbic system generates emotional tone. Manifestation of emotional expression is by hypothalamus with the help of the autonomic and somatic nervous systems.

Prolonged emotional stress causes visceral illness commonly referred to as psychosomatic disorder or illness.

KLUVER–BUCY SYNDROME

Bilateral removal of amygdala and temporal lobes causes a significant change in the behavior of the experimental animal. The condition is termed Kluver–Bucy syndrome.

The features are as follows:

- Complete absence of fear for anything
- High degree of curiosity about everything
- Tendency to place all objects in the mouth
- Strong sex drive toward inappropriate animals (immature, wrong sex, and different species)
- Tendency to forget rapidly

EMOTIONS

Emotion is strong feeling as anger or joy. It is a feeling created by an interplay between the individual and the environment. Emotion evokes physical, hormonal, and autonomic responses.

It is also described as instinctive feeling as distinguished from reasoning.

Emotions have two components, namely,

1. Mental
2. Physical

The *mental component* involves

- **Cognition**: It is awareness of the sensation and cause for that sensation.
- **Affect**: It is the feeling produced by the sensation.
- **Conation**: It is the desire to take action.

The *physical component* involves an increase in blood pressure and heart rate associated with sweating.

TYPES OF EMOTIONS

Motivation, Reward, and Punishment

Motivation is a set of processes responsible for goal-directed behavior. It is the reason behind one's action or behavior. It is the enthusiasm to perform a task. Motivation leads to behavioral, autonomic, and hormonal responses.

Behavior is motivated by stimulation of the **reward system** and by inhibition of the **punishment system**.

Stimulation of the dopaminergic pathway of the ventral tegmentum to nucleus accumbens, medial forebrain bundle, and lateral and ventromedial hypothalamus produces pleasurable sensation. Hence, it is called a **reward** or **approach system**.

The animal which is given the option to self-stimulate the reward center or get tasty

food by pressing a lever chooses to stimulate the reward center than to go for the food. Weaker stimuli to these centers give a sense of reward. However, stronger stimuli give the sense of punishment.

Stimulation of the lateral part of posterior hypothalamus, dorsal midbrain, and entorhinal cortex produces sensation of fear or terror. This area is termed **punishment** or **avoidance system**.

The punishment center is located in the central gray area surrounding the aqueduct of Sylvius in mesencephalon extending into the periventricular zone of hypothalamus and thalamus. The other punishment areas are located in amygdala and hippocampus.

Punishment centers can inhibit the reward center, thus indicating the dominance of punishment over reward and pleasure. Electrodes are implanted in the punishment area, connected to pedal lever and presented to the animal. It learns to turn off the stimulus after a few bitter experiences.

Reward and Punishment in Learning

Electrical stimulation evoking a new experience excites a large area of brain. Repetition of the same stimulus which influences the reward or punishment center fails to excite the brain after sometime. The animal gets **habituated** to a specific sensory stimulus and ignores it.

If the stimulus causes a sense of reward or punishment, the cortical response becomes more intense with repeated stimulation over a period of time. The response is **reinforced**.

Thus, an animal develops a strong memory for the sensations that produce either reward or punishment. Hence, reward and punishment have a major role in the processes of learning and memory.

Fear

Fear is an unpleasant emotion caused by threat of danger, pain, or harm. It is the likelihood of something unwelcome happening. Stimulation of hypothalamus and amygdaloid nuclei produces the reaction of fear. Fear reactions to auditory and visual inputs disappear with destruction of amygdala.

Anxiety

Anxiety is a normal emotional response. However, excessive anxiety is considered abnormal. During anxiety reaction, there is increased blood flow to the anterior end of the temporal lobe. Anxiety is mediated by α_2-GABA receptors. It is relieved by benzodiazepines. They bind to the GABA receptor and increase conductance to chloride ions.

Mood

It is the inner emotion influencing the perception of the world. Moods can be normal, depressed, or elated. Loss of control over the mood resulting in serious mood swings can result in mood disorders such as **depressive disorder and bipolar disorder**.

Rage and Placidity

Rage is an emotional condition where a minor stimulus evokes a violent response.

Placidity is a condition in which anger-provoking and traumatic stimuli fail to disturb the animal.

Removal of neocortex and destruction of the ventromedial nucleus of hypothalamus produce rage in animals.

Lesion to amygdaloid nucleus produces placidity.

Addiction

Addiction is the repeated compulsive use of a substance in spite of its negative effect on the health. It is associated with the reward system in the brain, especially with nucleus accumbens.

Exogenous opiates are addictive drugs. They increase the amount of dopamine to act on D_3 receptors in nucleus accumbens. Prolonged use of addicting drugs produces tolerance, and sudden stoppage of the drug results in withdrawal symptoms.

CEREBROSPINAL FLUID

The cerebrospinal fluid (CSF) is a specialized extracellular fluid. It is present in the ventricles of the brain, central canal of the spinal cord, and subarachnoid space (**Fig. 8.39**).

FORMATION AND CIRCULATION OF CSF

The choroid plexus of the lateral and third ventricle of brain forms CSF by the processes of filtration and secretion.

It passes through the fourth ventricle and central canal in the spinal cord. The CSF in the ventricles flows through the foramens of Magendie and Luschka to the subarachnoid space.

It gets absorbed through the arachnoid villi present in sagittal sinus.

COMPOSITION AND PROPERTIES OF CSF

CSF is a colorless, transparent fluid with a specific gravity of 1005.

It is alkaline in reaction.

The volume of CSF is about 150 mL. (About 500 mL of CSF is produced per day.) The normal CSF pressure is 5–15 mm Hg.

CSF contains 99% water and 1% solids.

The organic constituents are amino acids, sugar, proteins, cholesterol, urea, uric acid, and creatinine.

The inorganic constituents are sodium, calcium, potassium, magnesium, chlorides, bicarbonates, and phosphates.

FUNCTIONS

- Acts as a cushion between the brain and the rigid cranium
- Supports the weight of the brain. The net weight of brain in CSF is about 50 grams as compared to its weight of 1400 grams in air
- Prevents brain damage under its own weight by reducing the weight
- Distributes the force of blows on the head
- Maintains intracranial pressure by balancing the volume of blood and CSF
- Drains metabolites from the brain
- Supplies nutrients and oxygen to the brain
- Carries hormones from one part to the other part of the brain

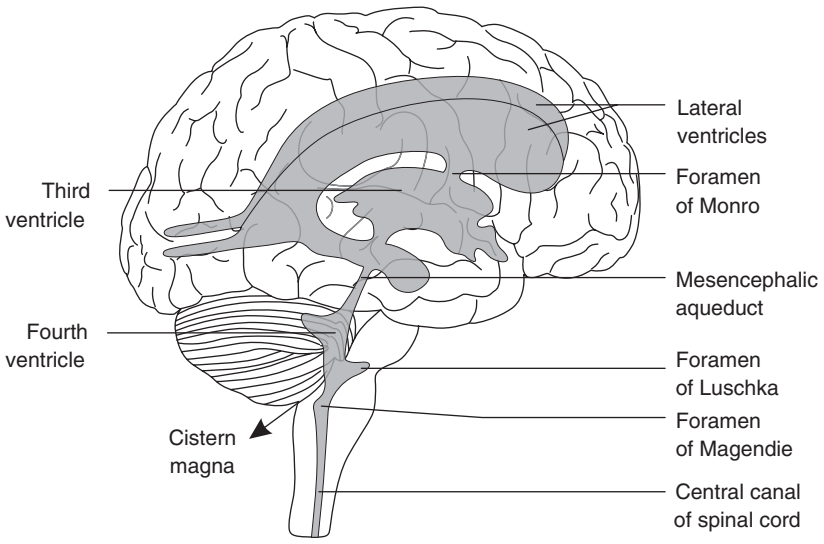


Figure 8.39 Formation and flow of cerebrospinal fluid.

CLINICAL NOTES

Hydrocephalus

Hydrocephalus is a condition of increased intracranial pressure due to defective absorption or circulation of CSF. The baby shows enlargement of the cranial cavity and associated damage to the brain because of pressure effect.

Hydrocephalus is of two types:

1. External or communicating hydrocephalus
2. Internal or noncommunicating hydrocephalus

In communicating hydrocephalus, a large quantity of CSF accumulates due to defective reabsorption by arachnoid villi.

Blockage of foramens of Magendie and Luschka results in accumulation of CSF proximal to the block, distending the ventricles. This results in noncommunicating hydrocephalus.

Hydrocephalus can produce brain damage. Accumulating fluid compresses the soft nervous tissue and blood vessels as the skull is rigid and hard.

Hydrocephalus is treated by draining the excess fluid through a shunt from ventricles to veins in the neck.

Lumbar Puncture

Lumbar puncture is a procedure by which CSF is taken out from the subarachnoid space. Normally, CSF is drawn by introducing a needle in between the third and fourth lumbar vertebrae. Histological and biochemical study of CSF gives an indication about various disease processes affecting the CNS.

CSF changes in common disorders are as follows:

- **Pressure**: It is increased in subarachnoid hemorrhage, acute bacterial meningitis, and tuberculous meningitis.
- **Color**: It is blood stained in subarachnoid hemorrhage and cloudy in acute bacterial meningitis and tuberculous meningitis.
- **RBC**: The RBC count is increased in subarachnoid hemorrhage.
- **Glucose**: It is decreased in acute bacterial meningitis and tuberculous meningitis.
- **Proteins**: They are increased in subarachnoid hemorrhage, acute bacterial meningitis, viral meningitis, multiple sclerosis, and tuberculous meningitis.
- **Microorganisms**: They are demonstrated in infective meningitis.

BLOOD–BRAIN BARRIER

The blood–brain barrier is a hypothetical barrier present between the brain and the blood.

It selectively permits the passage of substances from blood to brain and vice versa. Thus, it is a protective barrier maintaining stable environment for the brain.

The blood–brain barrier does not cover the vomiting center and hypothalamus.

It is incomplete in newborns and premature infants; hence, toxic substances can enter CNS and cause damage.

Oxygen, carbon dioxide, glucose, water, amino acids, electrolytes, and drugs such as sulfonamides and tetracycline cross this barrier.

Alcohol, anesthetics, and nicotine present in the blood can influence the brain by crossing this barrier.

STRUCTURE

- The capillaries of the brain consist of an endothelial lining which has tight junctions. These junctions close the pores in blood vessels.
- Astrocytes completely cover the capillaries and make them less porous.
- The blood vessels in the brain have a thick basement membrane. They prevent the passage of substances across them.

FUNCTIONS

- Maintains constancy of environment for the neurons in CNS
- Protects brain from the effect of endogenous toxins

- Prevents the escape of neurotransmitters from the CNS

Inflammation, irradiation, and tumors destroy the blood–brain barrier. This permits free entry to the substances, toxins, and drugs that do not cross the barrier under normal conditions.

Lipid-soluble drugs cross the blood–brain barrier more freely when compared to water-soluble drugs.

Circumventricular Organ

The areas of brain located outside the blood–brain barrier are called circumventricular organs, which are as follows:

- Posterior pituitary
- Median eminence of hypothalamus
- Subfornical organ
- Area postrema
- Organum vasculosum of lamina terminalis

TONE, POSTURE, AND EQUILIBRIUM

Tone is resistance offered by the muscle against passive stretch. Alternatively, tone is the partial contraction of the muscle at rest.

Posture is an intentionally or habitually assumed position of the body.

Equilibrium is maintenance of the stability of the body in space.

REGULATION OF TONE

Muscle tone is influenced by intact nerve supply (alpha motor neuron activity), viscosity, and elasticity. The resting length of muscle is regulated by muscle tone.

It is necessary for smooth and effective contraction.

It is tested by performing passive movement of the limb.

Muscle tone is maintained by a structure in the muscle called **muscle spindle** (**Fig. 8.40**).

Muscle spindles detect the stretch of the muscle and initiate a reflex that resists it.

STRUCTURE OF THE MUSCLE SPINDLE

The skeletal muscle contains two types of fibers:

1. **Extrafusal fibers**: These are regular contractile units of the muscle.
2. **Intrafusal fibers**: About 10 intrafusal fibers enclosed in the connective tissue capsule form the muscle spindle. Intrafusal fibers are parallel to the extrafusal fibers. The two ends of intrafusal fibers are striated and have limited ability to contract. The central portion of the intrafusal fibers lacks myofilaments. Hence, they are noncontractile.

   Intrafusal fibers are of two types:

- **Nuclear bag fibers**: They have a bulged central portion containing nuclei in them.

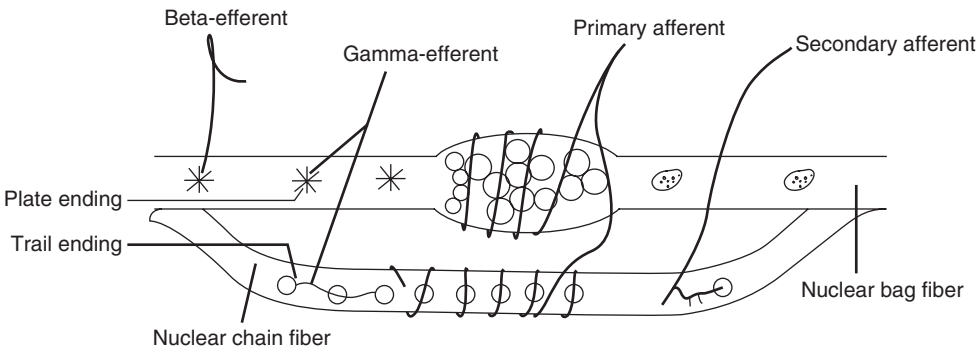


Figure 8.40 Muscle spindle.

- **Nuclear chain fibers**: They contain the nuclei arranged in a single row. They are connected to the spinal cord by sensory nerves.

  Group IA fibers arise from **primary** or **annulospiral ending** in the central portion of both types of fibers.

  Group II fibers arise from **secondary** or **flower spray endings** of nuclear chain fibers (located near the end of fibers).

MOTOR CONNECTION

The muscle spindle is innervated by a separate set of motor neurons called the γ (gamma) motor neurons. They arise from anterior horn cells and constitute 30% of the fibers in the ventral root. They end on the striated portion of the intrafusal fibers. They control the sensitivity of the spindle.

In addition, extrafusal fibers are supplied by α (alpha) motor neurons. Stimulation of these neurons will result in contraction of extrafusal fibers.

Regulation of muscle tone

Effect of stretch	Effect of stimulation
Stretch of the muscle	Stimulation of the skeletal muscle (alpha motor neutron stimulation)
↓	↓
Stretch of the muscle spindle	Contraction of muscle fibers
↓	↓
Distortion of sensory nerve endings	No reduction in the length of intrafusal fibers
↓	↓
Generation of receptor potential in muscle spindle	Reduced discharge of impulses from the muscle spindle
↓	↓
Increased alpha motor neuron discharge to the extrafusal fibers	Relaxation of the muscle
↓	
Reflex contraction of the muscle	

FUNCTIONS OF THE MUSCLE SPINDLE

The muscle spindle is stimulated by stretch giving rise to stretch reflex. This forms the basis for control of muscle tone.

Nuclear bag fibers respond to rapid stretch of the muscle (dynamic response).

Nuclear chain fibers respond to sustained stretch (static response).

The muscle spindle will discharge impulses at a low frequency at rest. This in turn will activate the extrafusal fibers through α-motor neurons and keep them in a partially contracted state (**Fig. 8.41a**).

Stretch of the entire muscle passively stretches the muscle spindle. The number of impulses generated by the muscle spindle increases (**Fig. 8.41b**). This increases the force of contraction of extrafusal muscle fibers restoring its length.

Activation of muscle by an external stimulus causes shortening of extrafusal fibers. As the muscle spindle has limited contractile ability, it bends due to the shortening of extrafusal fibers (**Fig. 8.41c**). The impulses from the muscle spindle stop. Extrafusal fibers relax in the absence of α-motor neuron activity regaining the original length.

The gamma efferent system is regulated by descending tracts. Stimulation of the gamma efferent nerve causes contraction of the contractile end of intrafusal fibers (**Fig. 8.41d**). This stretches the nuclear bag fibers. The annulospiral ending is distorted. There is an increased number of impulses generated in the muscle spindle. Consequently, there is contraction of extrafusal fibers.

Anxiety increases gamma efferent discharges. Hence, the tendon reflex becomes hyperactive in anxious patients.

Voluntary muscle contraction anywhere in the body increases the sensitivity of tendon reflex (stretch reflex). This is due to enhanced gamma efferent discharge to the muscle spindle.

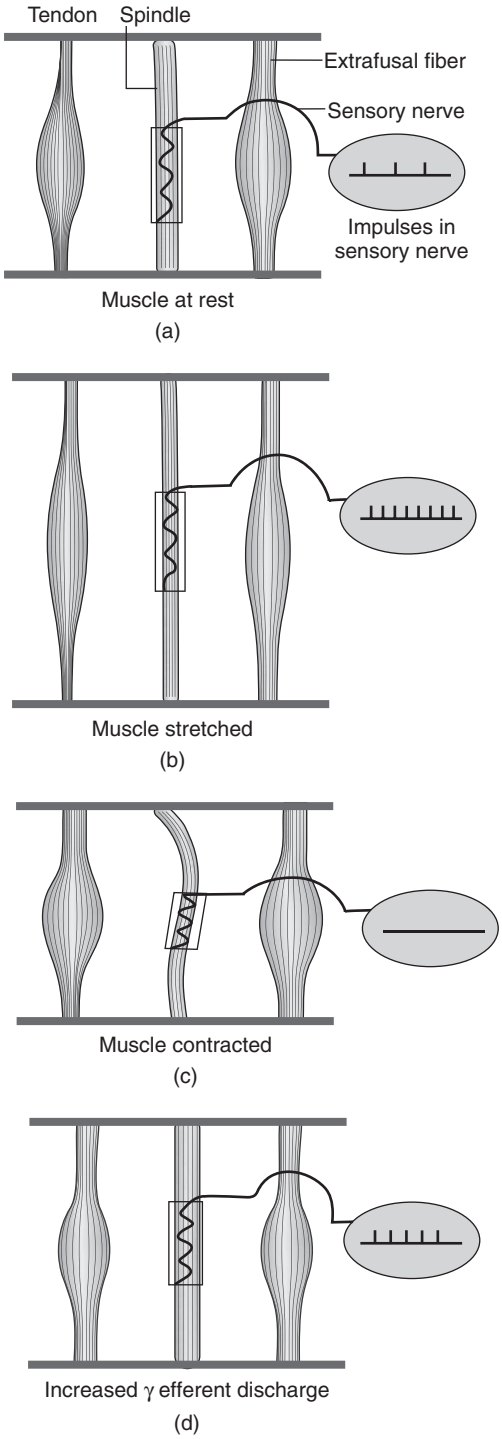


Figure 8.41 Pattern of muscle spindle discharge under different conditions. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

This procedure is termed **Jendrassik's maneuver or reinforcement**.

In this maneuver, the subject is asked to pull the hand when the flexed fingers are hooked. Alternatively, the subject is asked to clench the teeth.

Stretch Reflex

Sudden stretch of the muscle by tapping on the tendon results in contraction of the same group of muscles. The stretch stimulates muscle spindle contracting the muscle and relaxing the antagonistic group of muscle. Stretch reflex is a monosynaptic reflex.

CLINICAL NOTES

Abnormal Muscle Tone

Hypotonia

Hypotonia is a condition of abnormally low muscle tone associated with weakness and atrophy of the muscle. It may be associated with decreased or absent reflex response. It is common in disorders of alpha motor neurons and cerebellar disease.

Hypotonic muscles which are soft and weak are often described as **flaccid**.

Complete loss of muscle tone is termed **atonia**.

Hypertonia

There is increased resistance to passive stretch of the muscle. Hypertonia is due to increased alpha motor neuron activity. This keeps the muscle in a contracted state in spite of effort of the subject to relax.

Hypertonia is commonly seen in disorders of the descending tract. The inhibitory influence of the descending tract on the motor neuron is decreased.

Spasticity

Spasticity is a form of hypertonia in which the muscle develops an increased tone on stretching. There is an initial increase in the tone followed by reduced tone for a brief period. This is observed in the **clasp-knife phenomenon**.

(*Contd.*)

Rigidity

Rigidity is a type of hypertonia in which resistance to passive stretch is constant and the muscle contraction is prolonged.

A brief contraction of multiple muscle groups is called **spasm**.

Prolonged and painful contraction of muscle is termed **cramps**.

POSTURE

Posture is the maintenance of position of head, trunk, and limb in space for a period of time. It serves as a background for any movement.

The human body is built on the framework of skeleton. Skeleton is made up of long bones and vertebrae which have multiple joints. Human beings maintain the erect position with the support of muscles and their coordinated activity.

The major problems faced in the maintenance of posture are to

- maintain balance in upright position,
- balance the tall structure on a relatively small base,
- keep the body erect against forces of gravity, and
- counter the effect of center of gravity which is located very high.

The problems faced in the maintenance of posture are overcome by postural reflexes.

The afferent input to these postural reflexes comes from eyes, vestibular apparatus, and somatic receptors.

Alpha motor neurons to the skeletal muscles form the efferent pathway. These reflexes are generally integrated at brainstem and spinal cord.

Simple reflexes are integrated at the spinal level. Reflexes of little more complexity are integrated at the level of medulla and midbrain. However, more complex reflexes such as **anticipatory postural adjustments** involve the cerebral cortex.

Some parts of brain appreciate the position and orientation of body in space. This mechanism helps in planning and executing motor action.

Postural Reflexes

Postural reflexes are integrated at different levels.

Cortical Integration

Optical Righting Reflex This reflex is observed in animals with intact cerebral cortex. Visual signals to the animals activate the optical righting reflex to bring about the righting response. This reflex operates even in the absence of labyrinthine or body stimulation.

Hopping and Placing Reaction Pushing an animal which is blindfolded to a side exhibits hopping and placing reaction. An intact cerebral cortex is necessary for this response. Hopping reaction restores the standing position by supporting the body on its limbs. Placing reaction helps to place the foot firmly on the supporting surface.

Decorticate Rigidity

Removal of cerebral cortex produces minimal motor deficit in mammals. The reflex patterns of a midbrain animal are present but they are capable of movement. The decorticate animals can be managed easily compared to midbrain animals. A decorticate animal has the intact temperature control mechanism and visceral reflexes connected with the hypothalamus. The animal loses its capacity to react based on the past experience. The animal exhibits limited ability for learning and conditioning.

Integration at the Midbrain Level

Righting Reflexes These reflexes help to maintain the normal position of the animal and keep the head upright.

There are four types of righting reflexes:

1. **Labyrinthine righting reflex**: This type of reflex can be demonstrated in the midbrain animal. The midbrain animal is held by its body and moved from side to side. In spite of the movement, the position of the head is maintained by this righting reflex. Tilting of the head stimulates otolithic organs. It results in contraction of the neck muscles to maintain the level of head.

2. **Body on head righting reflex**: When the animal is placed on its side, the pressure on the side of the body initiates righting reflex. The animal tries to restore its normal position. Reflex righting of the head is functional even when the labyrinths have been destroyed.
3. **Neck righting reflex**: Righting of the head by the above two mechanisms leaves the body in a tilted position. This stretches the neck muscles. Contraction of neck muscle rights the thorax and initiates stretch reflex passing down the body to cause the righting of the abdomen and hind parts.
4. **Body on body righting reflex**: Pressure on the side of the body can initiate body righting reflex even when the head is prevented forcibly from righting.

Midbrain Animal

In this animal, a section is made in the neural axis at the superior border of midbrain. Extensor rigidity is seen when the animal lies on its back. The midbrain animals can stand, walk, and right themselves.

Integration at the Medullary Level

Tonic Neck Reflex This reflex is initiated by stretch of proprioceptors in the upper part of the neck.

Turning the head to one side results in extension of the limb on the same side with increased rigidity.

Flexion of head results in flexion of forelimbs and extension of hindlimbs.

Extension of head causes extension of forelimbs and flexion of hindlimbs.

Tonic Labyrinthine Reflex This reflex is produced due to action of gravity on vestibular apparatus. It is seen in a decerebrate animal. The pattern of rigidity varies with position.

Placing the animal on its back results in extension of all the four limbs.

Rigidity decreases when the animal is turned toward any side.

Rigidity is minimal in prone position.

Decerebrate Rigidity (Effects of Section of Brain at the Midcollicular Level) This is a type of rigidity produced in experimental animals by making a section between superior and inferior colliculi.

The animal shows the following:

- The tone in antigravity muscles increases.
- All the four limbs become rigid like pillars.
- The tail and neck are hyperextended.

Decerebrate rigidity is due to the removal of inhibitory influences from higher centers. Brainstem and vestibular nucleus normally send facilitatory impulse to the spinal center.

In decerebrate preparation, such facilitatory impulses are exaggerated or remain unopposed due to removal of cortical inhibition.

Integration at the Spinal Level

Stretch Reflex Stretch of the muscle results in its reflex contraction. This forms the basic mechanism in maintenance of posture. The receptor for this reflex is the muscle spindle.

Positive Supporting (Magnet) Reaction Stimulation of the sole or palm by contact causes the extension of the same limb to support the body. Since the extending limb appears to follow the object touching it, this response is also termed **magnet reaction**.

Negative Supporting Reaction Positive supporting reaction is lost by excessively stretching the limb resulting in loss of support.

These reflexes are demonstrated in a spinal animal.

VESTIBULAR APPARATUS AND EQUILIBRIUM (Fig. 8.42)

Vestibular apparatus are concerned with the maintenance of balance. They are made up of bony and membranous labyrinth. In between the bony and membranous labyrinth, a fluid called **perilymph** is present.

The membranous labyrinth has three semicircular canals and two large chambers termed **utricle** and **saccule**. Utricle and saccule are together called **otolith organs**. The membranous labyrinth contains

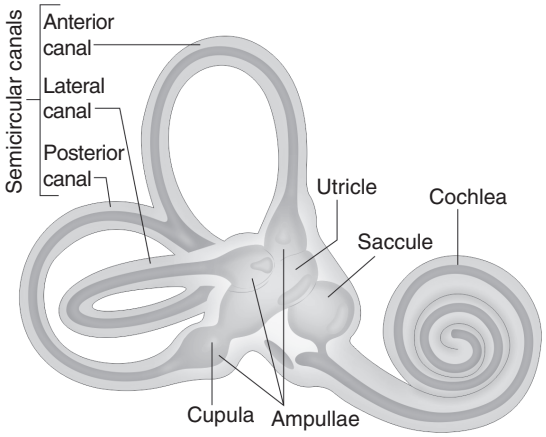


Figure 8.42 Vestibular apparatus. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

the fluid **endolymph**. The three semicircular canals are lying in three planes at right angles to each other. Crista ampullaris are the end organs in semicircular canals. Macula is the end organ of utricle and saccule.

NEURAL PATHWAY

The cell bodies of neurons supplying crista and macula are present in the vestibular ganglion.

The vestibular nerve ends in vestibular nucleus and flocculonodular lobe of the cerebellum. The vestibular nuclei also project to thalamus and somatosensory cortex.

CRISTA AMPULLARIS

Hair cells are the receptors. They are present on a ridge called **crista**. The hair cells of the vestibular apparatus have two types of hair or cilia. Kinocilium is long and located at one end on the hair cell.

Stereocilia show a gradually increasing length toward the kinocilium. Bending of stereocilia toward the kinocilium results in depolarization. The permeability of membrane increases to potassium ions. Rapid influx of potassium ions into the receptor cell produces depolarization. The depolarizing change in the hair (receptor) cell increases the release of neurotransmitter. There is a resultant increase in the discharge of impulses in the vestibular division of the VIII cranial nerve. The movement of stereocilia in the opposite direction causes hyperpolarization in the hair cells due to closure of ion channels. Hyperpolarization in the hair cells reduces the release of neurotransmitter. This in turn reduces the firing frequency of impulses in the nerve.

SEMICIRCULAR CANALS

There are three semicircular canals in each vestibular apparatus. They are as follows:

1. Anterior
2. Posterior
3. Lateral (horizontal)

Semicircular canals are arranged at right angles to each other. The semicircular canal has an enlargement at one of its end termed **ampulla**. Each ampulla has a small crest, called **cristae ampullaris**.

They give information about the degree, direction, and plane of the movement of head. In humans, they are stimulated by angular acceleration.

When the individual rotates, the bony labyrinth and the attached structures move. But the endolymph lags behind. Therefore, hairs in crista move toward the midline in one semicircular canal and away from the midline in the other. This bending of hair causes activation of hair cells and stimulation of the vestibular nerve (**Fig. 8.43**). If the individual continues to rotate, the endolymph also starts moving and the hair cells regain their initial position as seen at rest. Now the action potential in the vestibular nerve stops. But on stopping the rotatory movement, the hair bends in the opposite direction to stimulate the cell again. Thus, the direction of rotatory movement can be appreciated.

OTOLITH ORGAN

Utricle and **saccule** together form the otolith organ. They are sac-like structures forming a part of the membranous labyrinth. They communicate with each other through ductus endolymphaticus and contain the fluid endolymph.

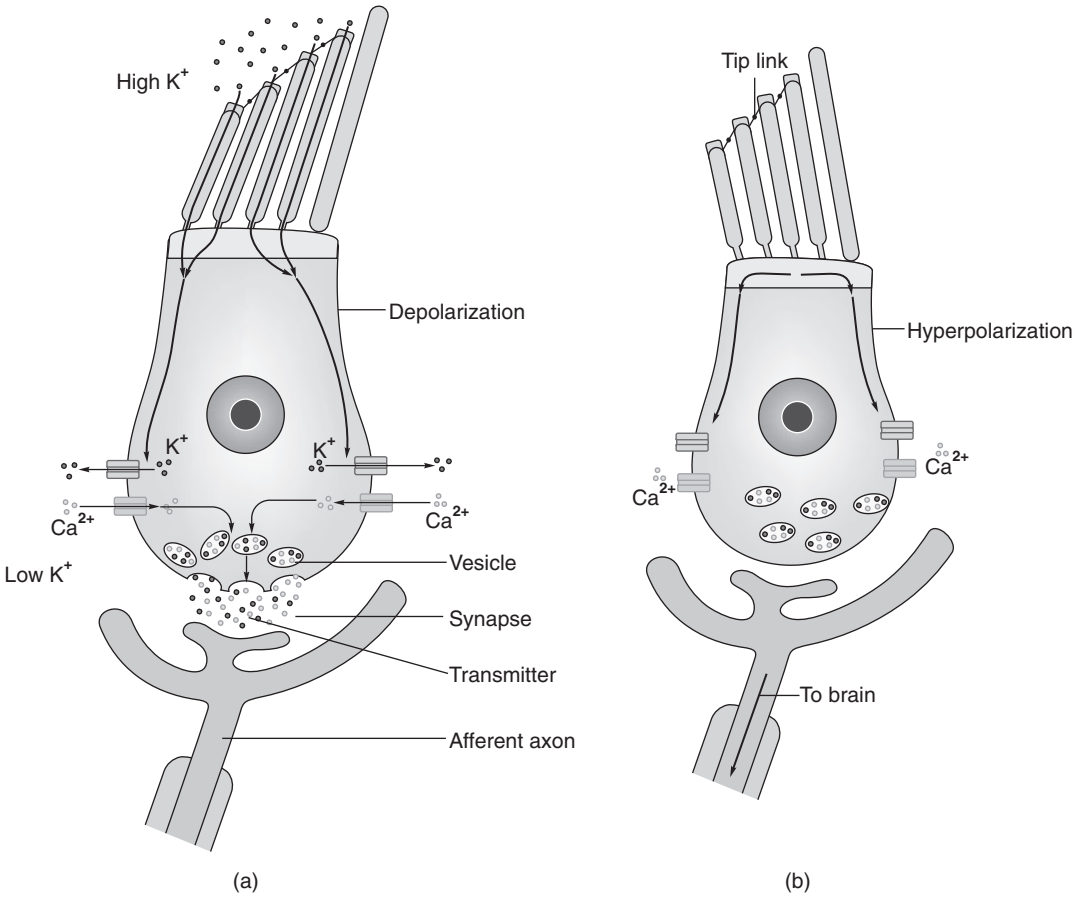


Figure 8.43 Mechanism of stimulation of hair cells. (a) Bending of stereocilia toward the kinocilium opens the K^+ channels in the stereocilia and Ca^{2+} enters the cell allowing vesicle fusion and the release of neurotransmitter. (b) Bending of stereocilia away from the kinocilium closes the K^+ channels in the stereocilia.

Hair cells are the receptors of the otolith organ, which are present over the ridge. Cilia are embedded in a jelly-like substance called **otolith membrane**. The membrane has deposition of calcium carbonate crystals termed **otolith**. This membrane is rigid.

Saccules respond to vertical acceleration. It is stimulated by side-to-side movement of the head. When the individual is in erect position, saccules are stimulated due to the effect of gravity. It gives information regarding the position of head in the lateral plane.

The utricle responds to horizontal acceleration. The anteroposterior movement of the neck stimulates the hair cells. The utricle gives information about the position of head in the anteroposterior plane.

CLINICAL NOTES

Motion Sickness

Motion sickness is produced by stimulation of vestibular apparatus due to jerky movement of the vehicle. The conflicting stimuli about movement within and outside the vehicle cause motion sickness in susceptible individuals. The subject has headache, giddiness, nausea, and vomiting. The manifestations are due to the stimulation of the vagus nerve, which lies close to the vestibular apparatus.

Meniere's Disease

Meniere's disease is a disease affecting the vestibular apparatus. The condition is characterized by sudden giddiness, ringing sound in the ear,

(*Contd.*)

vomiting, and temporary loss of hearing. The condition is produced due to differences in vestibular input from both the ears. There is abnormal increase of pressure in the inner ear.

Nystagmus

Nystagmus is the jerky back-and-forth or oscillatory movement of eyeballs in response to unusual vestibular inputs. It is a reflex which helps to fix the gaze on an object when the body moves. During movement, the eye moves slowly in the direction opposite to that of the body. After reaching the maximum limit, it quickly moves back to the point of new fixation. Slow movement of the eye is influenced by impulses from the labyrinths. The quick component is triggered by brainstem. Nystagmus is of different types, which are as follows:

- Horizontal
- Vertical
- Rotatory

The direction of eye movement in nystagmus is determined by the direction of quick component.

Nystagmus is seen at rest in patients with lesions of brainstem.

Vertigo

Vertigo is the sensation of rotation experienced by an individual in the absence of actual rotation. It is defined as illusion of movement, usually spinning, accompanied by feelings of nausea and light-headedness. Inflammation/irritation of the labyrinth due to infection, presence of loose particles of calcium carbonate in a semicircular canal, and excessive consumption of alcohol cause vertigo.

HIGHER FUNCTIONS

A change in the behavior of an animal based on previous experience is **learning**.

Registration, retention, and recollection of information is **memory**.

Expressing thoughts in the form of words, formulating and presenting a response to a spoken word, or a written question is **speech**.

LEARNING

Learning is alteration in the behavior of an individual based on the experience and information acquired. The capability to change with learning is due to the **plasticity** of the nervous system. Plasticity involves growth of new dendrites, strength of synaptic connections, and synthesis of different proteins in response to internal and external stimuli.

It can be of the following two types:

i. associative and
ii. nonassociative learning.

1. **Associative learning**: In this form of learning, a person appreciates the relationship between two given stimuli. Associative learning includes
   - classical conditioning and
   - operant conditioning.
2. **Nonassociative learning**: It is the process of learning about a single stimulus after repeated exposure to that stimulus. Habituation and sensitization are simple forms of nonassociative learning.

Associative Learning

Classical Conditioning

An unconditioned (inborn) response like salivation on giving the food is paired with a conditioned stimulus (acquired) of ringing the bell to produce a conditioned reflex. By this process of learning, the animal salivates on ringing the bell even without giving the food.

Operant Conditioning

The animal is taught to perform a task to get a reward or to avoid punishment.

Nonassociative Learning

Habituation

It is a form of learning in which the response diminishes with repeated stimulations. Non-noxious stimulus produces habituation. Habituation is associated with reduced release of the neurotransmitter from the presynaptic terminal.

Sensitization

It is a type of nonassociative learning in which the response amplifies with repeated stimulations. Painful stimulus evokes the response of sensitization. Sensitization is due to presynaptic facilitation. Sensitization is related to long-term potentiation, protein synthesis, and growth of presynaptic and postsynaptic neurons with their connection.

Conditioned Avoidance Reflex

It is the motor response of an animal to avoid an unpleasant sensation.

MEMORY

Memory is the ability to store learnt or acquired information and to recollect the same when it is needed.

Bits of information are stored in the brain by changing the sensitivity of synaptic transmission. Newly established pathways are termed **memory trace**.

Memory based on the type of information stored is of two types:

1. **Explicit or declarative or recognition memory**: It is a memory associated with awareness or consciousness. For retention of this memory, hippocampus and medial temporal lobe of the brain are necessary.
2. **Implicit or nondeclarative or reflexive memory**: It is associated with the acquired skills, habits which become unconscious and automatic.

Memory based on the duration of activity is of four types:

1. Short-term memory
2. Intermediate long-term memory
3. Long-term memory
4. Working memory

Short-Term Memory

This type of memory lasts for few seconds to few hours. Hippocampus processes the information and converts it into long-term memory. Short-term memory is produced by continual neural activity. The signals travel repeatedly over a temporary memory trace. The molecular mechanism for short-term memory is presynaptic facilitation or inhibition.

Short-term memory is likely to be lost during damage to the brain.

Release of serotonin at facilitator synapse on presynaptic terminal

↓

Serotonin binds to receptors, activates adenylyl cyclase, forms cAMP in presynaptic terminal

↓

cAMP activates protein kinase and phosphorylates the proteins which block potassium channels

↓

The action potential is prolonged due to lack of potassium conductance

↓

Prolonged action potential enhances calcium influx due to opening of calcium channel for a longer duration

↓

Neurotransmitter release is increased due to excessive entry of calcium ions

↓

Enhanced neurotransmitter release increases postsynaptic response

Intermediate Long-Term Memory

This lasts for a few minutes to few weeks. It is likely to be lost without activation to convert them into permanent memory.

This type of memory is established by temporary physical or chemical changes at the pre- or postsynaptic terminals.

Long-Term Memory

This type of memory stores the information for years. Long-term memory is likely to produce structural changes at the synapses, thus enhancing or reducing the conduction of signals.

Long-term memory is stable and is not susceptible for loss in brain damage.

Working Memory

Working memory is a form of short-term memory. Information is retained only for a short duration when a decision has to be made based on the information. It gets terminated after the objective is achieved.

Mechanism

Memory is dependent on alteration in the synaptic connection involving protein synthesis or activation of a related gene. Hippocampus, parahippocampal area of the medial temporal cortex, and prefrontal cortex are connected with different aspects of memory. Changes noted during the formation of memory are the following:

- The RNA content in the neuron is changed.
- The newly formed mRNA is moved to axons.
- There will be a change in the shape of dendritic spines.
- The number and size of presynaptic terminals will increase.
- More neurotransmitters will be released from the presynaptic terminal.
- There will be formation of new neurons in the hippocampus.

Short-term memory is converted to long-term memory by the process of consolidation. Activation of short-term memory repeatedly brings about structural, chemical, and physical changes required for long-term memory.

Consolidation of memory is better in a person who is awake and has an alert mind.

During the process of consolidation, bits of information are sorted and grouped into similar types. This process is **codification**. It helps in effective storage and easy retrieval of information.

CLINICAL NOTES

Amnesia

Amnesia is loss of memory.

Retrograde Amnesia

Retrograde amnesia is the inability to recall recent memories. It occurs in damage to the brain.

Anterograde Amnesia

Anterograde amnesia is a condition in which the subject is unable to establish new memory.

Alzheimer's Disease and Senile Dementia

It is a condition with progressive loss of short-term memory followed by loss of other functions of the brain.

The other features include

- Reduced attention span
- Disorientation
- Loss of language function
- Mood swings with increased irritability
- Confusion
- Hallucinations

This disease is common in the middle age. It is associated with damage to hippocampus and entorhinal cortex. Histopathologically, neurofibrillary tangles and senile plaques are seen. Damage is due to increased influx of calcium ions into neurons. AD is associated with deficiency of acetylcholine and structural change in brain areas involved in cognition and memory.

SPEECH

Speech is the ability to express oneself with the help of words. Speech is complex motor activity involving intricate sensory motor coordination. It is executed with the help of the following cortical centers.

- **Wernicke's area (area 22)**: It is located in the superior temporal gyrus in the dominant hemisphere. It helps to comprehend and understand visual and auditory information.
- **Broca's area (area 44)**: It is located in the inferior frontal gyrus in the dominant hemisphere. It prepares a detailed pattern for vocalization using the information received from Wernicke's area.
- **Exner's area (motor writing area)**: It is located in the middle frontal gyrus in the dominant hemisphere. In association with motor cortex, it initiates movement of hand and finger to produce written speech by using processed information from Broca's area.
- **Dejerine area (area 39)**: It is located in the angular gyrus behind Wernicke's area.

It processes a visual pattern of words (internal speech) to convert an auditory pattern of words by Wernicke's area.

The types of speech are as follows:

- Spoken speech
- Written speech

Mechanism

Spoken Speech

- The sound is heard with the help of auditory apparatus and primary auditory cortex (area 41).
- The sound is interpreted by the audiopsychic area (areas 20, 21).
- Wernicke's area (area 22) located at the posterior end of superior temporal gyrus comprehends and understands the auditory information.
- The information from Wernicke's area is fed to Broca's area (area 44) of speech through arcuate fasciculus.
- Broca's area analyzes the information received and prepares a pattern for vocalization.
- The pattern is conveyed to motor cortex (area 4) through the speech articulation area in the insula.
- The motor cortex brings about the necessary movements of larynx and lips to produce speech.

Written Speech

- The sound is heard with the help of auditory apparatus and primary auditory cortex (area 41).
- The sound is interpreted by the audiopsychic area (areas 20, 21).
- The printed information is seen by the primary visual area (area 17). The visual information is interpreted by the visual association area (area 18).
- Interpreted visual information is processed to internal speech by Dejerine area.
- Wernicke's area located at the posterior end of superior temporal gyrus comprehends the auditory and visual information.
- The information from Wernicke's area is fed to Broca's area of speech through arcuate fasciculus.
- Broca's area analyzes the information received and prepares a pattern for motor activity.
- The pattern is conveyed to motor cortex through the speech articulation area in the insula.
- Motor cortex, with the help of Exner's area (motor writing center), brings about the necessary movements of hand and fingers to produce written speech.

CLINICAL NOTES

Aphasia

Aphasia is a condition of defective speech without a defect in vision, audition, or motor system. It is the inability to comprehend and formulate speech following damage to related regions of brain.

Nonfluent Aphasia

It is a defect in Broca's area. Speech is slow and difficulty is experienced in producing the words.

Fluent Aphasia

It is a lesion in Wernicke's area. The patient has difficulty to understand the spoken and written words. Speech is fluent but with little sense.

Anomic Aphasia

It is the difficulty to understand the written language and pictures due to a lesion in the angular gyrus of the categorical hemisphere. The visual information is not analyzed and transmitted to Wernicke's area.

Global Aphasia

It is a condition in which Wernicke's area and Broca's area are damaged. An individual lacks the ability to speak, write, or understand the language.

Dyslexia

It is an inherited abnormality characterized by an impaired ability to read. The subject has difficulty in spelling words, reading quickly, writing words, and pronouncing words.

Slurring or Scanning Speech

It is seen in conditions of cerebellar dysfunction. There is a defect in skilled movements involved in production of speech.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) controls the visceral functions of the body.

The somatic nervous system is structurally and functionally different from the autonomic nervous system (**Table 8.1**).

It has two anatomic divisions:

1. Sympathetic nervous system
2. Parasympathetic nervous system

ORGANIZATION OF AUTONOMIC OUTFLOW

The ANS consists of the preganglionic and postganglionic neurons.

The cell bodies of preganglionic neurons are located in the intermediolateral gray column of the spinal cord and motor nuclei of the cranial nerves.

Axons are myelinated and they synapse with the cell bodies of postganglionic neurons located outside the CNS.

Sympathetic Division (Fig. 8.44)

The sympathetic fibers arise from thoracolumbar regions. The axons of the preganglionic sympathetic fibers leave the spinal cord through the ventral root. They pass through white rami communicantes to reach paravertebral ganglion chains.

In the ganglion, they make synaptic connections with the cell bodies of postganglionic neurons. The postganglionic neurons pass through sympathetic nerves to reach the viscera.

The sympathetic division mobilizes resources of the body during extreme conditions.

Parasympathetic Division (Fig. 8.45)

The parasympathetic fibers come from craniosacral regions. The preganglionic fibers end on short postganglionic neurons present on or near the viscera. The parasympathetic system maintains blood pressure, heart rate, and respiratory rate at low normal levels. It promotes active digestion by the gastrointestinal system.

The cranial division supplies the visceral structures in head, thorax, and upper abdomen through the facial, glossopharyngeal, and vagus nerves.

The sacral division supplies pelvic viscera through the pelvic branches of sacral nerves.

NEUROTRANSMITTERS IN ANS

Transmission of impulse across pre- and postganglionic neurons, between the postganglionic neuron and the effector organ, occurs with the help of a chemical mediator (**Fig. 8.46**).

Table 8.1 Differences Between Somatic and Autonomic Nervous Systems

Somatic Nervous System	Autonomic Nervous System
Stimulates skeletal muscles	Stimulates glands, smooth, and cardiac muscles
Cell bodies of motor neurons are present in the CNS	• Motor neurons of ANS have two neuron chains • Cell body of the first neuron is present in the brain or spinal cord (preganglionic neuron) • Preganglionic axon synapses with the autonomic ganglion present outside CNS • Axons of ganglionic neuron extend to the effector organ (postganglionic neuron)
Axons are well myelinated	Axons are poorly myelinated or unmyelinated
Transmission of impulse is faster	Transmission of impulse is slower

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

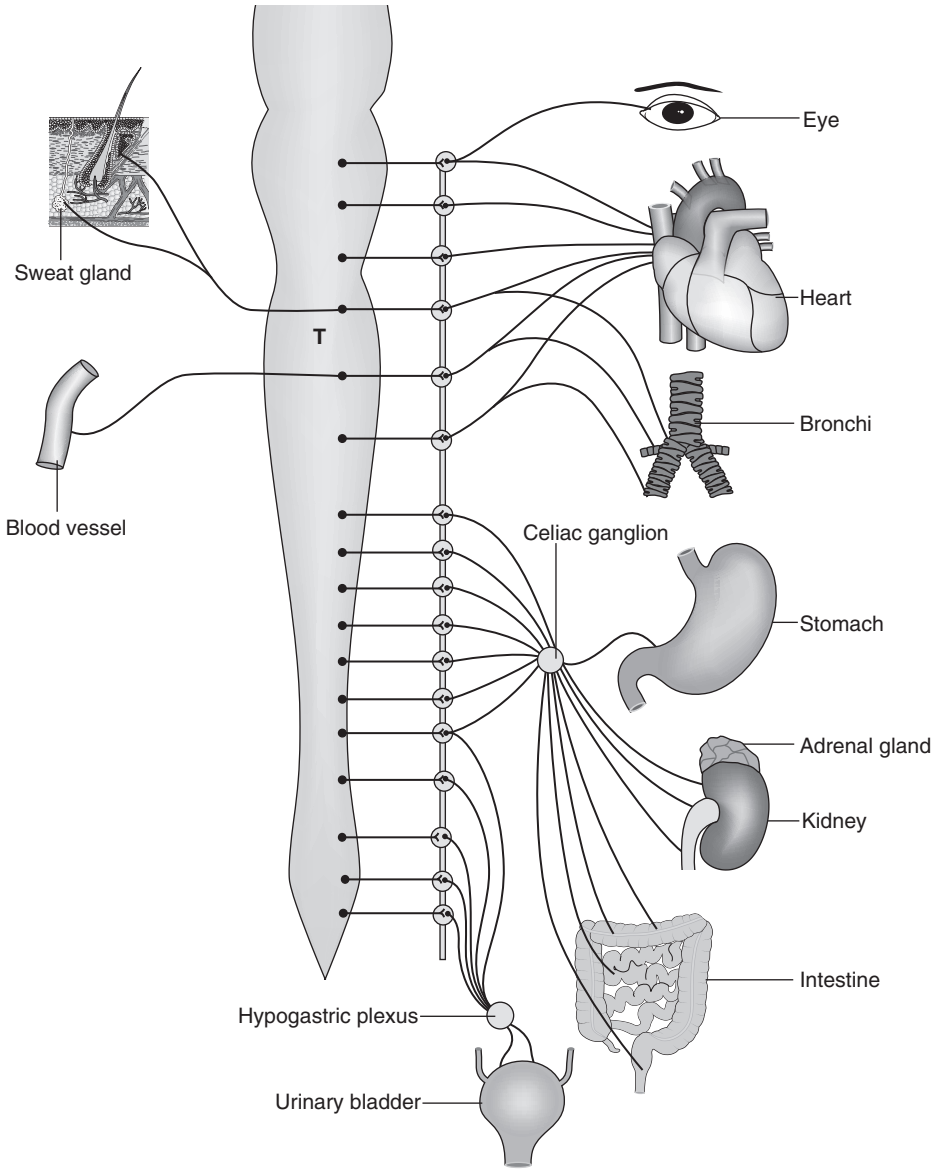


Figure 8.44 Sympathetic nervous system. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Based on the chemical mediator released, ANS is divided into

- cholinergic division and
- adrenergic division.

The principal neurotransmitters of the ANS are **acetylcholine, norepinephrine, and dopamine**.

Cholinergic Receptors

Acetylcholine has two types of receptors, which are as follows:

1. Nicotinic receptors
2. Muscarinic receptors

The neurotransmitters bring about the desired response by acting on the respective receptors.

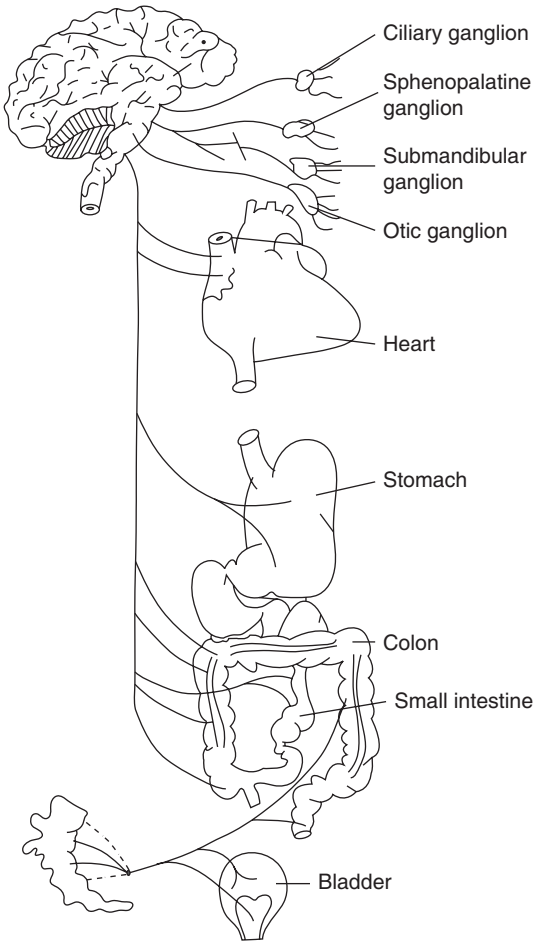


Figure 8.45 Parasympathetic nervous system.

Cholinergic Division

The cholinergic neurons are as follows:

- All preganglionic neurons
- Parasympathetic postganglionic neurons
- Sympathetic postganglionic neurons innervating the sweat gland
- Sympathetic neurons innervating the blood vessels to skeletal muscle. Stimulation of these fibers produces vasodilation.

Stimulation of cholinergic fibers increases the activity of GIT in terms of secretion and motility. This favors digestion and absorption. Hence, the cholinergic division is also called the **anabolic nervous system**.

The action of acetylcholine (the mediator of the cholinergic division) is localized and lasts for a short duration.

Adrenergic Receptors

The adrenergic receptors are as follows:

α_1 **Receptors:** They are located on the vascular smooth muscle of skin, GIT, bladder sphincter, and radial muscle of iris.

α_2 **Receptors:** They are located at the presynaptic nerve terminal, platelet, and walls of GIT.

β_1 **Receptors:** They are located in the SA node, AV node, and ventricular muscles of the heart.

β_2 **Receptors:** They are located at vascular smooth muscle supplying skeletal muscle, bronchial smooth muscle, wall of GIT, and bladder.

α and β_1 receptors are sensitive to epinephrine and norepinephrine.

β_2 receptor is more sensitive to epinephrine.

Stimulation of α_1 and β_1 receptors produces excitation. Stimulation of α_2 and β_2 receptors produces inhibition and relaxation.

Adrenergic Division

The adrenergic division is activated during fight or flight reactions. It prepares the individual to face the emergencies. The stimulation of adrenergic division brings about the following changes in the body:

- Dilation of pupil for better vision
- Increased heart beat and blood pressure for better tissue perfusion
- Sustained discharges to arterioles to maintain blood pressure
- Reduced threshold in reticular formation for enhancing arousal and alertness
- Increased plasma glucose and fatty acids for improved supply of energy.

Norepinephrine has a widespread action as compared to acetylcholine. Its actions are prolonged. The neurotransmitter and its metabolites are present in the plasma. A part of norepinephrine and dopamine comes from the adrenal medulla. The adrenal medulla acts as sympathetic ganglia without the postganglionic fibers.

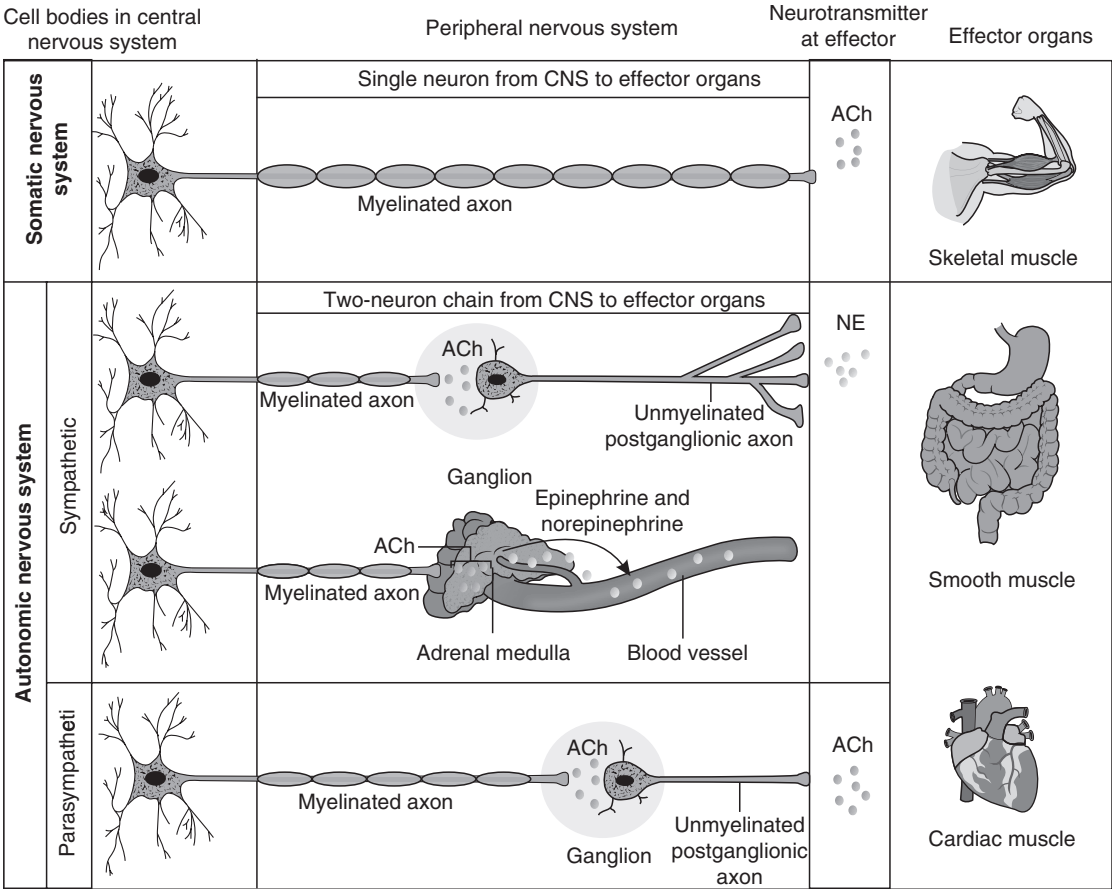


Figure 8.46 Comparison of somatic and autonomic motor systems. Ach, acetylcholine; NE, norepinephrine. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

EFFECT OF STIMULATION OF ANS

The smooth muscles of the viscera and internal organs are supplied by cholinergic and noradrenergic divisions. The stimulation of one of the divisions increases the activity in the same division and reduces the activity in the other division. Thus, there is a delicate balance between the activities in both the divisions of the ANS.

The ANS is not under voluntary control. The spinal cord, brainstem, reticular formation, and hypothalamus exercise control over it. The cerebral cortex controls the ANS by acting through the limbic system.

Autonomic functions are controlled to some extent by the technique of **biofeedback**. Biofeedback helps to alter or control involuntary functions by conscious efforts.

Autonomic Pharmacology

An alteration in the autonomic function is possible by manipulation of the junctions or pathways by suitable drugs. Drugs are used to influence the neurotransmitter synthesis, storage, release, and binding with the receptors.

The drugs which produce effects similar to sympathetic and parasympathetic stimulation are called **sympathomimetic** and **parasympathomimetic drugs**.

The sympathetic and parasympathetic blockers prevent the action of the respective neurotransmitter at the target site by blocking the receptors.

Some important actions of the autonomic nervous system are given in **Table 8.2**.

Table 8.2 Effect of Autonomic Stimulation on Different Systems

Organ	Parasympathetic Stimulation	Sympathetic Stimulation
Eye		
Iris	Pupillary constriction	Pupillary dilation
Heart		
Sinoatrial node	Decreased heart rate	Increased heart rate
Atria	Decreased contractility	Increased contractility
Atrioventricular node	Decreased conduction	Increased conduction velocity
Ventricles	Decreased contractility	Increased contractility
Arterioles		
Coronary	Dilation	Constriction/dilation
Skeletal muscle	Dilation	Constriction/dilation
Cerebral	Dilation	Constriction
Lungs		
Bronchial muscle	Contraction (bronchoconstriction)	Relaxation (bronchodilation)
Gastrointestinal tract		
Motility	Increased	Decreased
Sphincter	Relaxation	Contraction
Secretion	Increased	Decreased
Detrusor muscle	Contraction	Relaxation
Sphincter	Relaxation	Contraction

REVIEW QUESTIONS

Long Essay

1. Explain the mechanism of synaptic transmission. Explain briefly the properties of synapses.
2. Classify sensory receptors. Explain the properties of receptors.
3. Discuss the properties of sensations.
4. Describe with the help of a diagram the pathway for pain sensation. Explain the basis of phantom limb.
5. Describe the origin, course, and termination of the pyramidal tract with the help of a labeled diagram. Add a note on hemiplegia.
6. Describe the immediate and delayed effects of complete transection of spinal cord.
7. List the nuclei of hypothalamus. Explain the functions of hypothalamus.
8. List the nuclei and describe the connections and functions of thalamus.
9. Name the nuclei of basal ganglia. Describe the functions of basal ganglia with relevant connections. Add a note on Parkinsonism.
10. What are the functional divisions of the cerebellum? Describe their functions with relevant connections. Explain the signs of cerebellar dysfunction.

Short Essay

1. Explain the structure of a synapse. What are its types?
2. Mention the changes during synaptic transmission.
3. Explain EPSP and IPSP. Add a note on its ionic basis.
4. Explain presynaptic inhibition.
5. Explain postsynaptic inhibition.

6. Explain Renshaw's cell inhibition.
7. What is plantar reflex and its clinical importance?
8. Explain a reflex arc with the help of a diagram.
9. What is conditioned reflex? Explain it with an example.
10. Explain the structure and functions of muscle spindle.
11. Write the neural circuit for reciprocal innervation. Explain its functional importance.
12. What is referred pain? Explain the theories of referred pain.
13. Briefly outline the role of endogenous pain-inhibiting system?
14. List the differences between upper and lower motor neuron lesion.
15. Explain the sensory and motor changes in a hemisection of the spinal cord.
16. Draw a diagram showing Brodmann cortical areas. Mention functions corresponding to these areas.
17. Discuss the features of sensory and motor homunculus.
18. What is EEG? What are its normal waves? List the changes of EEG during sleep.
19. Discuss the mechanisms of sleep.
20. What are the different types of memory? Explain briefly the mechanism of formation of long-term memory.
21. Explain the role of hypothalamus in regulation of body temperature.
22. Explain the features of thalamic syndrome.
23. What is REM sleep? List the features associated with it.
24. What is reticular activating system? What are its functions?
25. Describe the formation, circulation, and functions of cerebrospinal fluid. Add a note on hydrocephalus.
26. Describe the structure and functions of vestibular apparatus.
27. Explain the formation and functions of blood brain barrier.
28. Explain the types and physiological basis for memory.
29. Explain the mechanism for speech. What is dyslexia?
30. Compare and contrast the actions of sympathetic and parasympathetic divisions on different systems.

Short Answer

1. Explain the division of nervous system.
2. Explain habituation and sensitization.
3. Name different types of synapses.
4. Name excitatory and inhibitory neurotransmitters.
5. What are neurotrophins and neuromodulators?
6. Classify reflexes.
7. What is withdrawal reflex?
8. What is inverse stretch reflex?
9. What is crossed extensor response?
10. What is axon reflex?
11. What is stereognosis?
12. List the ascending tracts. Indicate the sensations carried by them.
13. List the descending tracts.
14. List the features of Brown–Sequard syndrome.
15. List the clinical features of upper motor neuron lesion.
16. List the clinical features of lower motor neuron lesion.

17. What is Babinski's sign? Explain the physiological basis for it.
18. What is hemiplegia? List the clinical features of this condition.
19. List the features of facial palsy.
20. What is Weber-Fechner law?
21. What is decerebrate rigidity? What is its practical application?
22. What is decorticate rigidity?
23. List the clinical manifestations of the lesion of basal ganglia.
24. List the functions of limbic system.
25. Explain the features of NREM sleep.
26. Discuss the disorders of sleep.
27. Explain the structure and functions of blood–brain barrier.
28. What is lumbar puncture? What is its clinical importance?
29. What is aphasia? What are its types?
30. What is gate control theory with respect to pain perception?

CHAPTER

9 Special Senses

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the visual apparatus and functional anatomy of eye.
- Discuss the indication and procedure for corneal grafting.
- Explain the innervation and actions of extraocular muscles.
- Describe formation, circulation and functions of aqueous humor. Discuss the management of glaucoma.
- Explain the errors of refraction and their corrections.
- Explain the visual pathway and effect of lesion at different levels.
- Describe the central mechanism of vision. Discuss the light and accommodation reflex.
- Explain the photochemistry of vision. Discuss the tests for color vision. Classify color blindness.
- Discuss the changes during light and dark adaptation.
- Describe the functional anatomy of ear. Explain process involved in appreciation of sound. Discuss the mechanism of pitch discrimination.
- Discuss the test for hearing.
- Explain the mechanisms involved in perception of taste and smell sensations.
- Successfully answer the questions and MCQs at the end of this chapter.

The normal functioning of the body is influenced by changes in the external environment. These changes are perceived by the sensory system.

The sensations are of two types:

1. General sensations
2. Special sensations

The receptors for general sensations are present all over the body and respond to different types of stimuli.

The receptors for special sensations are located in regions close to the central nervous system. They respond to one type of stimulus.

Receptors are specialized cells converting different forms of energy to action potential.

The general sensations are necessary for the living being to appreciate the changes in the external environment and respond suitably.

The general sensations are as follows:

- Touch
- Temperature
- Pain
- Pressure
- Vibration
- Proprioception

The special sensations are functionally important as they can appreciate the stimulus from a distance.

The special senses are

- vision,
- hearing or auditory sense,
- taste,
- smell or olfaction, and
- skin

VISION

The eye is the receptor organ for vision. The visual stimuli provide information about the world around us.

Vision is a process by which the brain creates representation of the external world. A relatively large area of the brain is involved in perception and interpretation of the visual information. This clearly emphasizes the importance of vision.

PRINCIPLES OF OPTICS

It is necessary to be familiar with the physics of light to understand the functioning of the eye. The relevant physical principles are discussed.

LENS AND OPTICAL SYSTEM

The passage of light rays from one medium to the other medium with different optical densities at an angle results in its bending. Bending of the light ray occurs if the refractive indexes of both the medium are different. This is termed **refraction**.

When the gaze is fixed at a distant object, the light entering the eye gets bent and comes to focus on the retina. A major part of refraction occurs at the air–corneal interface.

The refracting media of the eye are

- cornea,
- aqueous humor,
- lens, and
- vitreous humor.

Lens systems are used for correcting the refractive errors of the eye. The commonly used lenses are as follows:

- Convex
- Concave
- Cylindrical

LIGHT

Human eyes are sensitive to electromagnetic radiation termed **visible light**.

It has the following attributes:

- Wavelength
- Frequency

WAVELENGTH

Wavelength is the distance between two consecutive wave peaks of electromagnetic radiation.

FREQUENCY

Frequency is the number of cycles per second. It is expressed in hertz.

REFRACTIVE INDEX

The refractive index is the ratio of velocity of light in air to the velocity in a medium. The velocity of light in air is about 3,00,000 km/sec. It reduces in solid and liquid media. The velocity of light in glass is 2,00,000 km/sec. The refractive

index is the ratio of velocity of light in air to that of the velocity in a medium. Thus, the refractive index of glass is 3,00,000 km/sec divided by 2,00,000 km/sec which is 1.50.

PRINCIPAL FOCUS (FOCAL POINT)

Principal focus is the point at which the parallel rays of light striking a convex lens are brought to focus.

The light rays coming from an object placed at a distance of more than 6 m (20 ft) are considered parallel. Hence, the chart to assess distant vision (Snellen's chart) is placed at a distance of 6 m from the patient.

The rays coming from an object closer than 6 m are divergent.

FOCAL LENGTH

Focal length is the distance between the principal focus and the center of the curvature of the lens.

PRINCIPAL AXIS

Principal axis is the line passing through the center of the curvature of the lens. The principal focus is located on the principal axis.

DIOPTER

The refractive power of the lens is expressed as diopter (D). It is the refracting capacity of the lens. The greater the curvature of the lens, the greater the refractive power is. It is reciprocal of the focal length in meters:

$$\text{Diopter} = \frac{1}{\text{Focal length (in meters)}}.$$

The power of convex lens is positive. It converges the light rays. Convex lens having a power of 1 D will converge the light rays passing through it at a point 1 m away on the other side of the lens.

The power of concave lens is negative. Biconcave lens diverges the light rays. If the concave lens diverges the light rays to the same extent as converged by the convex lens of 1 D, then the power of concave lens is expressed as –1 D.

The power of cylindrical lens is expressed similar to spherical lens, but the axis has to be mentioned. The axis is 0 when the focal line is horizontal and it is 90° when the focal line is vertical.

The normal human eye has a refractive power of about 60 D. The cornea contributes a refracting power of about 45 D whereas lens provides about 15 D.

REDUCED EYE

The refraction of light occurs at different refracting media of the eye before it comes to focus on the retina. This is a complex mechanism. Hence, a simplified model to explain the optics of the eye was developed by Listing. This is called the **reduced eye**.

The reduced eye has a single refracting surface. This is a resultant of all the refracting surfaces of the eye. The center of the optical system is termed the **nodal point**. It is located 1.5 mm behind the anterior surface of the cornea.

The focal length of reduced eye is 17 mm and the refractive power is about 59 D.

LACRIMAL APPARATUS

The lacrimal apparatus consists of lacrimal glands present in the upper and outer part of the orbit. It secretes a watery fluid called **tears.**

The tears spread over the eyes by blinking. They collect at the inner angle of the eye.

Functions of Tears

- Keep the exposed surface of the eye moist
- Protect the eye from microbes and irritant substances

Flow of Tears

Lacrimal punctum
↓
Lacrimal canaliculi
↓
Lacrimal sac
↓
Nasolacrimal duct
↓
Nasal cavity

VISUAL APPARATUS

The eye resembles a camera. It has a pupil which functions as a variable aperture regulating the entry of light into the eyes.

It has a system of lens and refracting surfaces, which focuses the light ray on the retina.

Retina is the screen containing the receptor to perceive the image.

Light falling on the eye passes through the following refracting surfaces:

- Anterior surface of cornea
- Posterior surface of cornea
- Aqueous humor
- Anterior surface of lens
- Posterior surface of lens
- Vitreous humor

ANATOMY OF THE EYE (Fig. 9.1)

The human eye is present in the orbit. The orbit is a bony structure which protects the eyeball.

Eyes have evolved from the light-sensitive spot present in invertebrates.

Each eye has

- a layer of light-sensitive receptors,
- a lens system to focus light on these receptors, and
- a system of nerves to carry impulses from receptors to the brain.

The wall of the eyeball is made up of three layers (**Fig. 9.1**):

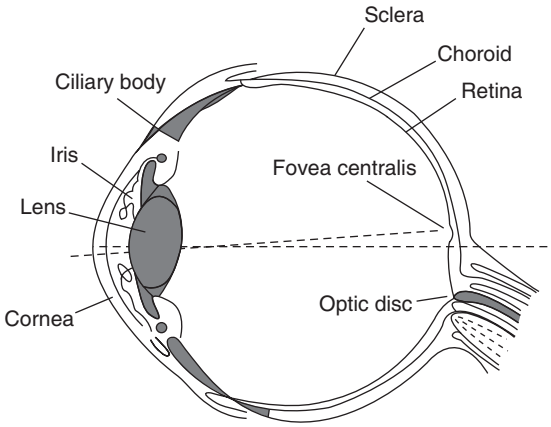


Figure 9.1 Structure of the eye.

1. Sclera (outer layer)
2. Choroid (middle layer)
3. Retina (inner layer)

Sclera

Sclera is a tough, white fibrous layer which continues as the transparent cornea anteriorly. The cornea is an avascular structure (i.e., it has no blood supply). Light passes through the cornea to enter the eye.

Cornea

Cornea is a transparent structure present in the anterior part of the eyeball. It is around 11 mm in diameter and 0.5–1 mm in thickness.

The cornea has a rich nerve supply. The free nerve endings in the cornea carry sensory information of pain, touch, and temperature.

Nutrition to the cornea is provided by the lymph and aqueous humor.

It has a refractive index of 1.38.

The cornea plays an important role in focusing light on the pigment layer, the **retina**. The major part of bending of the light ray occurs as it passes from air into the cornea.

The cornea is a curved structure. The light originating from a source reaches the cornea at different angles. It gets bent to varying extents to be focused on the most sensitive part of the retina, the **fovea centralis**. The image formed

on the retina is upside down with respect to the object.

The cornea contains the following layers:

- Corneal epithelium
- Bowman's membrane
- Substantia propria
- Descemet's membrane
- Corneal endothelium

The corneal endothelium maintains the transparency of cornea.

The cornea is transparent because of

- unique architecture of the collagen fibers,
- lack of blood vessels, and
- presence of an active mechanism that prevents the accumulation of water.

The epithelial layer can repair minor injuries to the surface of cornea. However, deeper corneal injuries result in the development of opacities.

Lens

The lens is the main refracting medium of the eye situated between the iris in front and the vitreous humor behind (**Fig. 9.2**).

It is a transparent, elastic, biconvex structure. It is encased by a capsule held in place by the lens ligament (zonule). The lens ligament is attached to the thickened anterior part of the choroid termed the **ciliary body**. The contraction of the ciliary body decreases tension in the ligament, and the anterior surface of the lens bulges.

The lens has a refractive index of 1.4 at the center and less at the periphery.

It is made up of ribbon-like transparent fibers arranged in concentric lamella. The peripheral part is nucleated while the central part is non-nucleated.

Functions of Lens

The lens helps in the refraction of light to focus it on the retina.

Choroid

The choroid is a vascular layer which forms the iris and the ciliary body anteriorly. The blood vessels in the choroid nourish structures in the eye.

The choroid is a thin, deeply pigmented layer consisting of blood vessels and connective tissue network.

Anteriorly, the choroid continues as uvea which thickens to form the **ciliary body**.

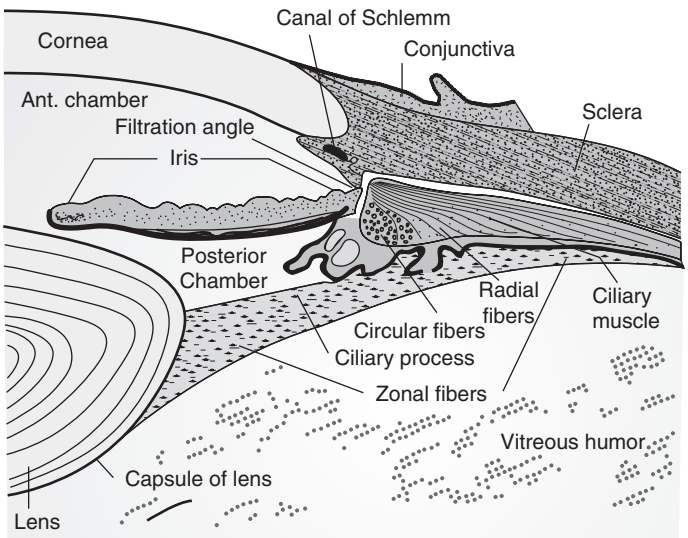


Figure 9.2 Detail of the anterior segment of the human eye. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edition. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

CLINICAL NOTES

Corneal Grafting

Blindness due to opacities in cornea is treated by replacing the defective cornea with a healthy cornea taken from a donor (eye donation). The procedure is termed corneal grafting. The cornea is an avascular structure; hence, the chances of graft rejection are very low. Rejection of a graft or transplanted organ is common in other locations due to vascularity and immune reactions.

Cataract

The opacity of the lens is termed **cataract**. The cataract that develops during the old age is called **senile cataract**. An injury to the lens can also cause opacity. This is called **traumatic cataract**.

A person exposed to the ultraviolet rays and heat is at a greater risk of developing cataract. An alteration in the ionic environment surrounding the lens is the cause for cataract.

There is an increase in the water content, sodium, and calcium ion, which is associated with a decrease in the potassium ion concentration.

An increase in the calcium ion concentration enhances the accumulation of high-molecular-weight lens proteins.

An aggregation of insoluble lens protein disturbs the arrangement of the protein molecules rendering the lens opaque.

Treatment

The treatment of cataract is removal of the opaque lens. Nowadays, **synthetic intraocular lens** is inserted to improve the vision.

The ciliary body is made up of ciliary muscle which helps in adjusting the curvature of the lens.

The anterior one-third of the ciliary body forms the ciliary process. It is involved in the production of aqueous humor.

From the ciliary body projects a thin contractile tissue called the **iris**. The iris is highly pigmented and is responsible for the color of the eye.

The central aperture of the iris is called the **pupil**. The iris contains the sphincter pupillae and dilator pupillae muscles which help to change the size of the pupil.

Stimulation of the sympathetic division causes the contraction of radially arranged muscle fibers resulting in dilation of the pupil. Parasympathetic stimulation causes contraction of circular muscles resulting in pupillary constriction.

Bright light decreases the diameter of the pupil. This reduces the light entering the eyes and restricts light to the central portion of the lens. Dim light causes pupillary dilation providing maximum illumination.

Functions of Iris

- Adjusts the amount of light falling on the retina
- Improves the clarity of image by cutting the peripheral rays of light
- Increases the depth of the focus

Retina

The retina is a layer containing the visual receptors, rods, and cones. It stops short anteriorly near the ciliary body.

Retina is the light-sensitive portion of the eye (**Fig. 9.3**). Retina converts the visual stimuli into nerve impulses and transmits them to the central nervous system.

Layers

The retina is organized into 10 layers. The layers from outside to inside are as follows:

1. Pigment epithelium
2. Rods and cones
3. Outer limiting membrane
4. Outer nuclear layer
5. Outer plexiform layer
6. Inner nuclear layer
7. Inner plexiform layer
8. Ganglion cell layer
9. Layer of optic nerve fibers
10. Inner limiting membrane

The rods are responsible for dim light vision and cones are responsible for bright light and color vision.

In addition to rods and cones, the retina contains bipolar cells, amacrine cells, horizontal cells, and ganglion cells.

The rods and cones synapse with bipolar cells and bipolar cells synapse with ganglion cells. The ganglion cells send axons which form the

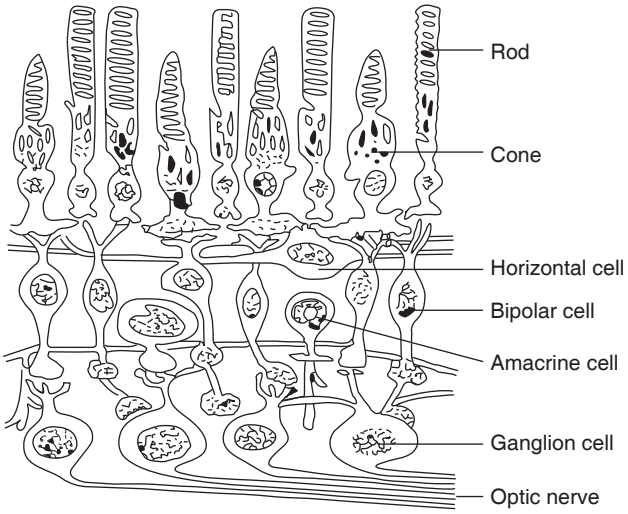


Figure 9.3 Retina.

optic nerve. The horizontal cells connect the receptor cells to one another in the outer plexiform layer. The amacrine cells connect the ganglion cells to one another in the inner plexiform layer.

The light entering the eye first passes through the inner limiting membrane and then through all other layers to finally reach the layer of rods and cones.

The receptor layer of the retina rests on the pigment epithelium. The pigment layer absorbs the light and prevents its reflection. The reflection of light results in blurring of the visual images.

The pigment layer stores large quantities of vitamin A, which is a raw material for the photosensitive pigment of visual receptors.

The optic nerve is formed by the axons of the ganglion cells. It leaves the eye, and the retinal blood vessels enter at a point 3 mm medial and slightly above the posterior pole of the eyeball. This region is the **optic disk**. There are no visual receptors in the optic disk and hence this forms the **blind spot**.

At the posterior pole of the eye, there is a yellowish pigmented spot called the **macula lutea**.

The central part of the macula is the **fovea centralis**. It is a minute area occupying about 1 mm^2. This area has only cones. Each cone synapses with a bipolar cell which in turn synapses with a ganglion cell. It provides a direct pathway to the brain.

The blood vessels, ganglion cells, and other layers are all displaced to one side, allowing the light to pass undisturbed to the cones in this region. The color vision and bright-light vision are best in this area. When attention is fixed on the object, the light rays coming from the object get focused at the fovea centralis.

CLINICAL NOTES

Age-Related Macular Degeneration

The sharp central vision is gradually destroyed in a disease termed **age-related macular degeneration** (AMD).Women are more prone to develop this disease. It is of two types:

1. Dry AMD
2. Wet AMD

Dry AMD is due to slow breakdown of cones in the macula causing loss of central vision.

In wet AMD, vascular endothelial growth factor (VEGF) promotes the formation of fragile blood vessels under the macula. Blood and fluid leaking from these blood vessels damage the macula.

Retinal Detachment

The neural part of retina detaches from the pigment layer when fluid or blood collects in between two layers following injury to the eyeball. Retinal detachment is also caused by contracture of collagen fibers in the vitreous body. It leads to blindness if it is not treated.

Blood Supply

The internal layers of the retina are supplied by the branches of the central retinal artery. The rods and cones layer of the retina is dependent on diffusion from the choroid for their nutrition. Therefore, the retinal detachment causes degeneration of the retina and blindness.

Extrinsic Muscles of the Eye (Table 9.1)

The movements of the eyeball are controlled by six extrinsic muscles. They originate from the bony orbit and get inserted into the outer surface of the eyeball.

The four rectus muscles originate from the tendinous ring called the annular ring at the back of the orbit, run straight, and get inserted into the eyeball.

The superior oblique muscle originates with the rectus muscle and gets inserted into the superolateral surface of the eyeball.

The inferior oblique muscle originates from the medial surface of the orbit and gets inserted into the inferolateral surface of the eyeball.

The extrinsic muscles of the eye are the most precisely and rapidly controlled skeletal muscles. Each motor unit has 8–12 muscle cells.

Table 9.1 Innervation and Actions of Extraocular Muscles

Name of the Muscle	Action	Nerve Supply
Lateral rectus	Lateral movement of eye (abduction)	VI (abducens)
Medial rectus	Medial movement of eye (adduction)	III (oculomotor)
Superior rectus	Elevates the eyeball	III (oculomotor)
Inferior rectus	Depresses the eyeball	III (oculomotor)
Inferior oblique	Elevates and turns the eye laterally	III (oculomotor)
Superior oblique	Depresses and turns the eye laterally	IV (trochlear)

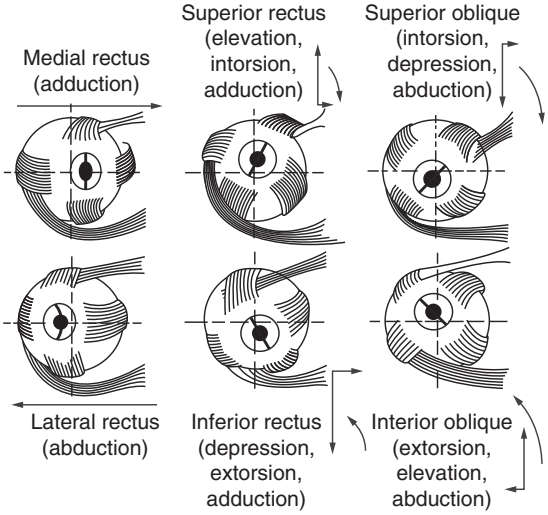


Figure 9.4 Action of extraocular muscles. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

These muscles

- help the eye to follow moving objects (**Fig. 9.4**),
- maintain the shape of the eyeball, and
- hold the eyeball in the orbit.

Critical Fusion Frequency

Critical fusion frequency (CFF) is the rate at which the visual stimuli presented to the eye are appreciated as separate stimuli. The stimuli presented at a higher rate than CFF are appreciated as continuous stimuli. In motion pictures, frames are projected at a rate greater than CFF.

Electroretinogram

Electroretinogram (ERG) is the recording of electrical activities from the eye. One electrode is placed over the cornea and the other over the skin of the head. A flash of light produces electrical activity in the eye. A typical recording shows rapid a- and b-waves due to the electrical activity in the retina and a slower c-wave produced by the pigment epithelium.

Uses

- To diagnose diseases in conditions where the retina cannot be visualized
- To detect congenital retinal dystrophy (in these conditions, the retina appears normal by ophthalmoscopic examination)

Ophthalmoscope

An ophthalmoscope is an instrument used to visualize the subject's eye and retina clearly.

Uses of Ophthalmoscopy

- To evaluate retinal blood vessels and detect vascular diseases
- To detect edema (papilledema) or cupping of the optic disk
- To identify retinopathy in conditions such as diabetes and hypertension

INTRAOCULAR FLUID

The eye contains two types of fluids:

1. **Aqueous humor**: Lies in front of the lens and behind the cornea
2. **Vitreous humor**: Lies between the lens and the retina

AQUEOUS HUMOR

Aqueous humor is a clear watery fluid occupying both the anterior and the posterior chambers of the eye.

It is produced by the ciliary body by diffusion and active transport.

It flows through the pupil to fill the anterior chamber of the eye.

It is absorbed through a network of trabeculae into the **canal of Schlemm**. It is a venous channel at the junction of the iris and the cornea.

Reticuloendothelial cells with high phagocytic capacity are present outside the canal of Schlemm. Aqueous humor is kept clear by the phagocytic action of epithelial cells on the iris by engulfing proteins and small particles.

This phagocytic system keeps trabecular spaces clean and prevent malabsorption of aqueous humor.

Properties

Reaction	Alkaline
Specific gravity	1.002–1.004
Refractive index	1.34

Aqueous humor closely resembles cerebrospinal fluid (CSF) in its chemical composition.

Functions

- Maintains intraocular pressure and shape of the eyeball
- Acts as a refractive medium
- Provides nutrition to the avascular tissues such as cornea, lens, and vitreous humor
- Drains metabolites from the surrounding structures
- Contains immunoglobulins, defending against pathogens

Regulation

- Parasympathetic stimulation: ↑ secretion
- Sympathetic stimulation: ↓ secretion

The normal intraocular pressure is 12–20 mm Hg with an average value of 15 mm Hg. Clinically, intraocular pressure is measured by using a tonometer. Presently, **applanation tonometry** is used to measure the intraocular pressure.

CLINICAL NOTES

Glaucoma

Glaucoma is a degenerative condition in which there is loss of retinal ganglia cells.

Increased intraocular pressure is a major risk factor for the development of glaucoma.

Glaucoma is caused by a defective absorption of the aqueous humor due to obstruction at the trabeculae or the canal of Schlemm.

The causes for obstruction are

- decreased permeability through the trabeculae (open-angle glaucoma) and
- forward movement of iris closing the angle (angle-closure glaucoma).

(*Contd.*)

Untreated glaucoma leads to compression of the optic disc and blindness.

Glaucoma is managed by drugs that decrease the secretion/production of aqueous humor or drugs that increase its outflow.

Carbonic anhydrase inhibitors decrease the secretion of aqueous humor.

Cholinergic agonists such as physostigmine and pilocarpine increase the outflow by causing ciliary muscle contraction.

VITREOUS HUMOR (VITREOUS BODY)

Vitreous humor is a jelly-like substance present in the vitreous chamber. It is present between the lens anteriorly and the retina posteriorly. It holds the retina over the choroid, providing an even surface for the reception of light. Vitreous humor is formed during embryonic life and does not get replaced later. It contains phagocytic cells which remove the debris. Vitreous humor does not have blood vessels. Electrical charges keep the fibers in the vitreous humor separated.

EMMETROPIC EYE

In a normal eye, parallel rays of light are focused on the retina. The image formed is inverted and reversed with respect to the object. However, we see it as upright because the brain is trained to appreciate an inverted image as normal. Accommodation of lens does not occur in an emmetropic eye. The lens is thin and the pupil is dilated.

Light rays passing through the refracting surfaces of the eye bend, and the image is focused on the retina. If the bending of light ray is not appropriate and the image is not properly focused on the retina, it results in refractive error.

ERRORS OF REFRACTION (Fig. 9.5)

AMETROPIC EYE

Parallel rays of light are not focused on the retina. The errors of refraction are

- myopia,
- hypermetropia,
- presbyopia, and
- astigmatism

Myopia (Short-Sightedness)

In myopia, the person is unable to see the distant objects clearly. The defect is due to elongation of the eyeball (increase in the anteroposterior diameter) or increased curvature of the cornea. The image of the distant object is focused in front of the retina. It is corrected by concave lens (diverging lens).

Myopia is seen in younger individuals. The defect increases as the age advances due to an increase in the size of the eyeball till adulthood.

Hypermetropia (Long-Sightedness)

In hypermetropia, the person is not able to see the nearby objects clearly. It is due to a decrease in the anteroposterior diameter or weak lens system of the eyeball. The light rays from the nearby objects are focused behind the retina. The correction is made by a convex lens (converging lens).

Presbyopia

Presbyopia is an adult type of hypermetropia. After the age of 40 years, the lens becomes rigid (less elastic) and hence there is a decrease in the power of accommodation. The lens loses its elasticity due to denaturation of proteins. Such persons are not able to see the nearby objects and letters clearly at the usual distance for reading.

This is corrected by using a convex lens. The condition is also corrected by using a bifocal lens/progressive lens with the upper segment suitable for distance and the lower segment for near vision (in subjects having different powers for distance and near vision).

A child has a power of accommodation of 14 D. It decreases to 2 D during the fifth decade of life.

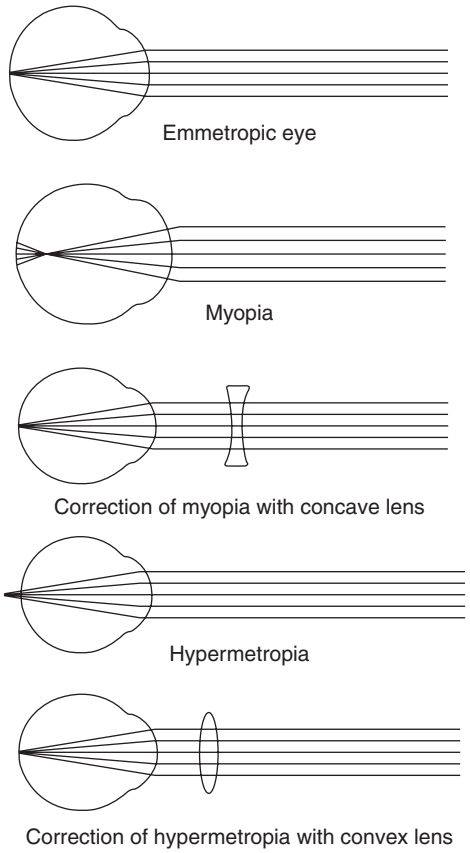


Figure 9.5 Errors of refraction.

It will be about 0 D at 70 years of age. Thus, the lens becomes nonaccommodating.

Astigmatism

In this condition, the curvature of the cornea and rarely the curvature of the lens vary from one plane to the other. As a result, the refractive power is different in different planes. An image from all parts of the object is not properly formed on the retina.

A clear image of the object from the vertical and horizontal axes does not form on the retina.

When the image from the horizontal axis is clear, the image from the vertical axis will not be clear.

The accommodation power of the natural lens cannot compensate for astigmatism because the curvature of the eye lens changes almost equally in both the planes.

The defect is corrected by a combination of spherical and cylindrical lens.

Contact Lens

Contact lens is a thin lens placed directly on the surface of the eye. The lens is held in position by a thin layer of tears present between the cornea and the lens. Contact lenses are worn to correct vision for cosmetic or therapeutic reasons. Contact lens provides better peripheral vision. It is useful in subjects with an irregularly shaped cornea.

VISUAL PATHWAY

The visual pathway (**Fig. 9.6**) conveys the visual signal from the eye to the CNS.

The receptors for vision are the rods and cones. They synapse with the bipolar cells. The bipolar cells synapse with the ganglion cells. The axons of the ganglion cells form the optic nerve.

The fibers of each optic nerve decussate (crossover) partially at the optic chiasma. The fibers from the nasal half of each retina cross to the opposite side, but those from the temporal halves do not cross.

After the decussation, an optic tract is formed. The fibers of the optic tract end in the lateral geniculate body. The optic tract contains temporal fibers of the same side and nasal fibers of the opposite side.

From the lateral geniculate body, the neurons proceed as the optic radiation (geniculocalcarine tract) to terminate in the primary visual cortex (Brodmann's area 17).

Visual fibers also end in other areas of the brain and are connected with specific functions.

Some of the axons of ganglion cells bypass the lateral geniculate body and reach the pretectal area.

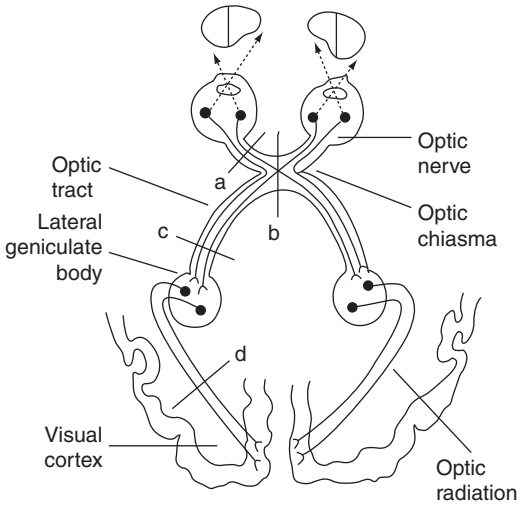


Figure 9.6 Visual pathway.

This pathway controls light reflex and movements of the eye. Frontal cortex and frontal eye fields are bilaterally concerned with eye movements and near response.

The fibers emerging from the visual pathway perform other functions in addition to visual perception. The biological process exhibiting oscillation of about 24 hours (circadian rhythm) depends on input from the optic tract.

- Circadian rhythm is controlled by the fibers of the optic tract reaching the hypothalamus.
- Rapid directional movement of both the eyes is controlled by fibers ending in superior colliculus.
- Behavioral functions of the body are controlled by fibers ending in the ventral lateral geniculate body.

EFFECTS OF LESIONS AT DIFFERENT LEVELS (Fig. 9.7)

- **Lesion of the optic nerve (Fig. 9.7a)**: *Blindness* of the corresponding eye (anopia)
- **Lesion in the midline at the optic chiasma (Fig. 9.7b)**: *Bitemporal hemianopia* (**hemi**: one-half, **anopia**: blindness; hemianopia is blindness in one-half of the eye.) In this condition, the temporal halves of both the eyes are blind.
- **Lesion of the lateral portions of the optic chiasma**: *Binasal hemianopia*
- **Lesion in the optic tract (Fig. 9.7c)**: *Homonymous hemianopia* (lesion of the left optic tract results in right-sided homonymous hemianopia). The blindness is present in the corresponding half of each eye. The nasal side of the left eye and the temporal side of the right eye are blind.
- **Lesion in the optic radiation (Fig. 9.7d)**: *Homonymous hemianopia with macular sparing*

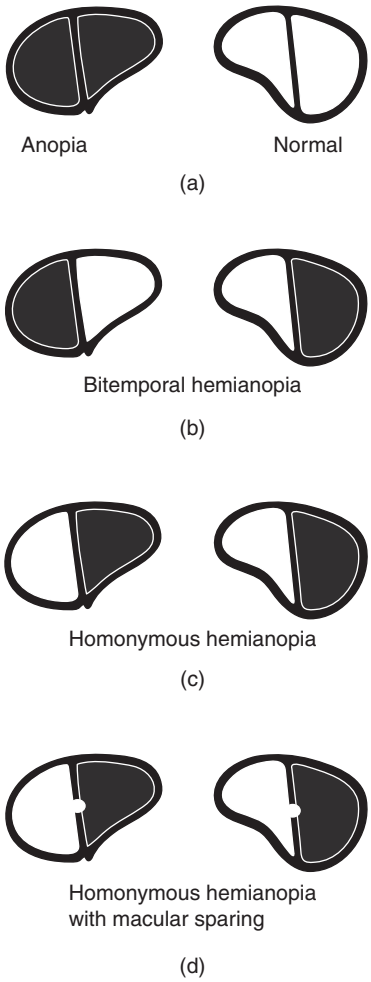


Figure 9.7 Lesions at different levels of the visual pathway.

(vision in the region of macula lutea is retained).
- **Lesion in the occipital cortex**: *Scotoma* in the opposite eye

MACULAR SPARING

Macular sparing is a condition characterized by loss of peripheral vision with an intact macular vision. Macular sparing is common in the occipital lesions. The macular representation in the visual cortex is very large and separate from that of the peripheral fields.

An extensive damage to the occipital cortex results in the loss of both peripheral and macular vision.

Bilateral destruction of the occipital cortex results in subjective blindness. There is still a residual response to visual stimuli. It is termed **blindsight**.

ANOPIA

The loss of vision in one eye is termed anopia.

HEMIANOPIA

The loss of vision in one-half of the eye is termed hemianopia.

HOMONYMOUS HEMIANOPIA

The loss of vision in the nasal half of one eye and in the temporal half of the other (loss of vision in the corresponding half of the eye) is termed homonymous hemianopia.

LATERAL GENICULATE BODY

The lateral geniculate body relays the visual information from the optic tract to the visual cortex by way of optic radiation.

It has six layers: layers 1, 4, and 6 receive inputs from the medial half of the eye of the opposite side (contralateral), and layers 2, 3, and 5 receive inputs from the lateral half of the eye of the same side (ipsilateral).

- Layers I and II contain large neurons and are called **magnocellular layers**. Large ganglion cells, magno or M cells (Y type of retinal ganglion cells) project to the magnocellular layer of the LGB.
- Layers III–VI have small- to medium-sized neurons and are called **parvocellular layers**. Smaller and medium-sized X types of retinal ganglion cells and parvo or P cells project to the parvocellular layer of the LGB.

The magnocellular pathway carries signals for the detection of movement, depth, and flicker.

The parvocellular pathway carries signals for color vision, texture, shape, and finer details of the object.

VISUAL CORTEX

The visual cortex is located in the occipital lobe. It is divided into primary visual cortex and secondary visual cortex (**Fig. 9.8**).

Primary Visual Cortex

The primary visual cortex lies on the sides of calcarine fissure. The signals from the macular area of the retina terminate near the occipital pole whereas the signals from the peripheral areas terminate in the concentric circles around it.

The macular part of the retina occupies a relatively large area in the visual cortex. This large representation is the basis for the highest degree of visual acuity in the fovea, which is the central area of the macula.

The primary visual cortex corresponds to area 17 of Brodmann's cortical area. The axons of the ganglion cell project a spatial representation of the retina on the lateral geniculate body. Further, from the lateral geniculate body, point-for-point representation projects to the primary visual cortex.

The visual cortex is arranged in vertical columns responsible for perception of orientation which are termed **orientation columns**.

The visual cortex has two types of cells. They are **simple** and **complex cells**. They are called

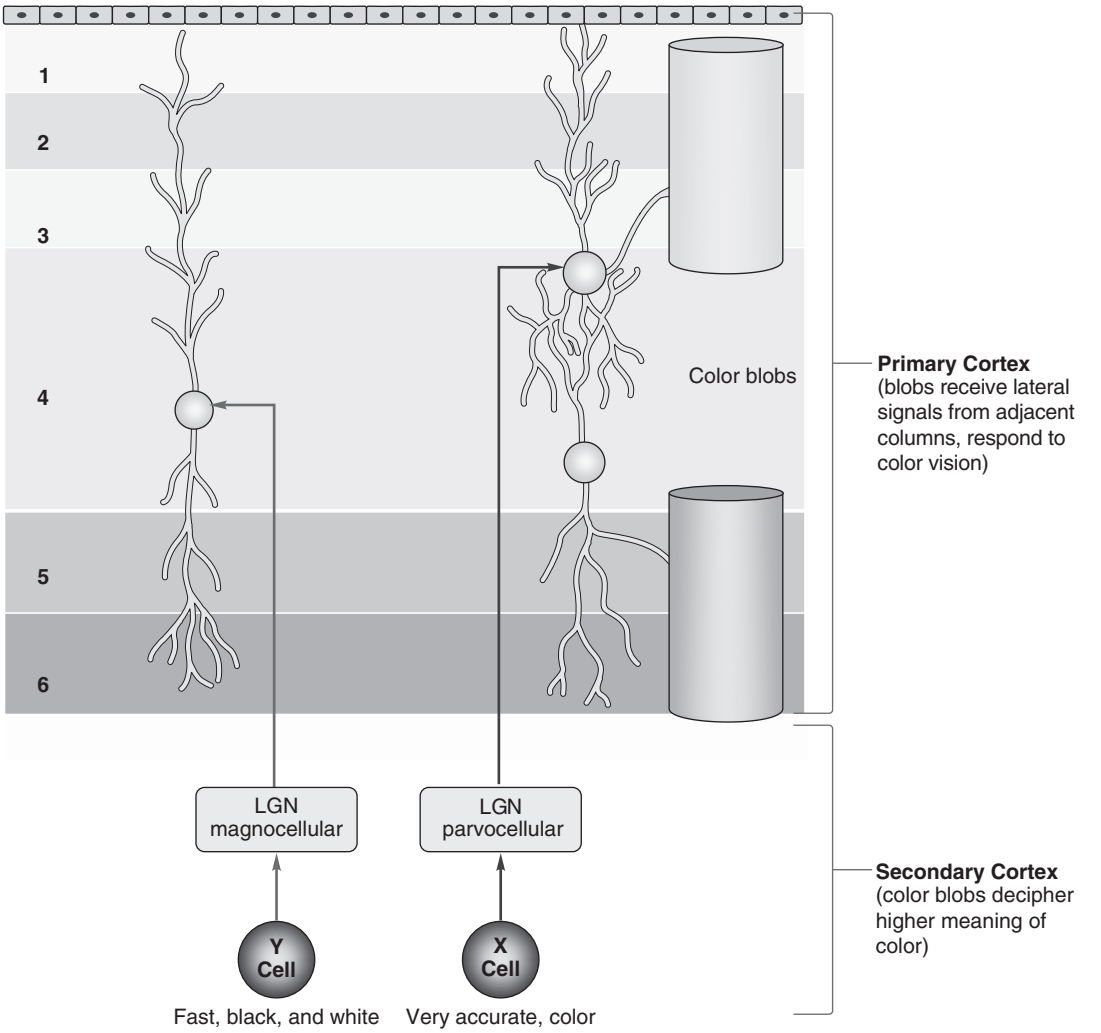


Figure 9.8 Layer and connections in the visual cortex (1–6 layers of cerebral cortex). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

feature detectors. These cells present in the cortex are capable of responding and analyzing features of the stimuli.

Simple cells respond to bars or lines of light with a particular orientation.

Complex cells respond to linear stimulus irrespective of its location in the visual field.

In the visual cortex, the inputs from the right and left eyes are separated but remain adjacent. The input from the right eye alternates with the input coming from the left eye. They appear like alternating columns; hence, they are named as **ocular dominance columns**.

Secondary Visual Cortex

The visual association areas surround the primary visual cortex. The signals transmitted to these areas are for interpretation of visual inputs. The secondary visual cortex corresponds to areas 18 and 19 of Brodmann's cortical area.

Analysis of Motion

Analysis of the motion of the object, its relative position, and color happens with the involvement of additional areas of the brain.

The position and motions of objects in the visual field are determined by the posterior midtemporal area and occipitoparietal cortex with the inputs from the posterior somatic association areas.

Analysis of Contrast

Appreciation of contrast is one of the important features of vision (**Fig. 9.9**).

It may be noted that maximum excitation occurs at the sharp borders of a visual pattern.

The receptor cells are stimulated in the area of full illumination in the retina and the adjacent cells are mutually inhibited.

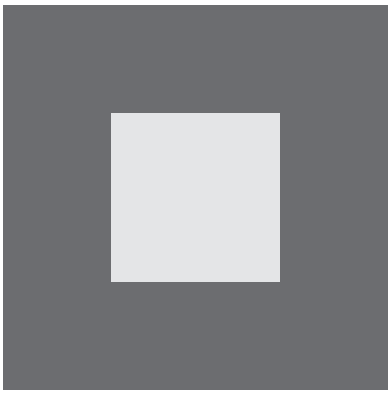


Figure 9.9 Color contrast. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

PUPILLARY REFLEXES

The diameter of the pupil changes in response to alteration in intensity of light and the distance of the object from the eye. Higher intensity light constricts the pupil and lower intensity light dilates the pupil.

Pupillary reflexes are

- light reflex and
- accommodation reflex

LIGHT REFLEX

The light reflex is a change in the size of the pupil as a reflex in response to a change in illumination.

When a beam of light is shone into the eye, it results in constriction of the pupil.

The change noted in the same eye is called the **direct light reflex**.

The corresponding change seen in the other eye is called the **indirect light reflex (consensual light reflex)**.

Functions

- Adjusts the amount of light entering the eye
- Prevents spherical aberration by cutting off the peripheral rays
- Increases the depth of focus

Pathway for Light Reflex

Visual impulse
↓
Rods and cones
↓
Optic nerve
↓
Optic chiasma
↓
Optic tract
↓
Midbrain
↓
Pretectal nucleus
↓
Edinger–Westphal nucleus
↓
Ciliary ganglion
↓
Sphincter pupillae

Conditions such as neurosyphilis, alcoholism, and encephalitis can block the light reflex. Block can be due to damage to fibers of the optic nerve and the pretectal region of the brainstem.

ACCOMMODATION

Accommodation is the adjustment of the visual apparatus to focus an image of the nearby object on the retina.

The afferent limb of accommodation reflex is the cranial nerve II and the efferent limb is cranial nerve III. Parasympathetic stimulation results in contraction of the ciliary muscle and relaxation of the suspensory ligament attached to the lens. The ciliary muscle is present at the lateral attachment of the lens ligament. This increases the convexity of the lens and hence its refractive power.

The changes during accommodation are

- convergence of the eyeball,
- constriction of the pupil, and
- change in the anterior curvature of the lens.

Changes During Accommodation

Convergence of the Two Optical/ Visual Axes

This is brought about by internal rotation of the eyeball due to contraction of the medial rectus.

This effect is also mediated by the III cranial nerve (oculomotor).

Constriction of Pupil

This effect is caused by the contraction of sphincter pupillae. The action is mediated by the III cranial nerve.

Change in the Curvature of Lens

At rest, the suspensory ligament of the lens is tense.

Traction on the capsule of lens causes flattening of the anterior surface of the lens.

During accommodation to near-vision, the ciliary muscle contracts causing relaxation of the suspensory ligament. Natural elasticity of the lens makes it more convex.

A more spherical shape of the lens provides additional bending of the light ray which is necessary to focus nearby objects on the retina.

Pathway for Accommodation Reflex

Rods and cones of retina
↓
Optic nerve
↓
Optic tract
↓
Lateral geniculate body
↓
Optic radiation
↓
Primary visual cortex
↓
Frontal eye field
↓
Oculomotor nucleus of the opposite side
↓
Ciliary ganglion
↓
Ciliary muscles and sphincter pupillae
↓
Constriction of pupil

Change in the Curvature of Lens

Activation of parasympathetic fibers
↓
Stimulation of ciliary muscles
↓
Contraction of ciliary muscles
↓
Relaxation of lens
(lens becomes more spherical)
↓
Image of the nearby object is focused on the retina

Near Point It is the nearest point to the eye at which an object placed can be brought into clear focus by accommodation. The near point changes with age. It is least in a young human eye and increases as the age advances.

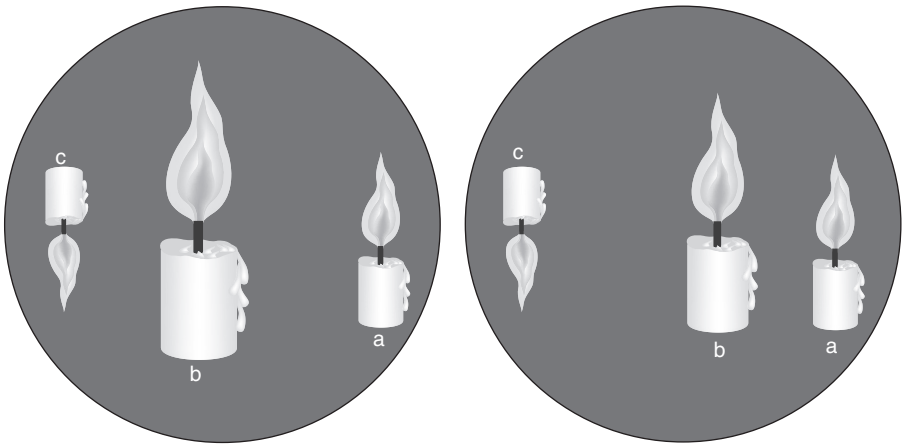


Figure 9.10 Purkinje–Sanson images. (a) Position of images looking at a distant object. (b) Changed position of images focusing on a nearby object. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The near point is about 9 cm at the age of 10 years. It recedes as the age advances, reaching about 83 cm at the age of 60 years.

Recession in near point of vision is due to an increase in the hardness of lens and loss of accommodation.

Purkinje–Sanson Images

During accommodation reflex, two of the three changes, namely constriction of pupil and convergence of eye ball, can be seen. However, the change in the curvature of lens cannot be seen. The Purkinje–Sanson images (**Fig. 9.10**) help to demonstrate the fact that the anterior curvature of the lens increases during accommodation.

Purkinje–Sanson images are named after a Czech anatomist Jan Evangelista Purkyně and French physician Louis Joseph Sanson.

When a lighted candle is held in front of the eyes with the subject looking at a distant object, three images of the candle are seen:

1. Bright, upright image formed by the anterior surface of the cornea (a)
2. Large, upright image produced by the anterior surface of the lens (b)
3. Bright, smaller inverted image formed by the posterior surface of the lens (c)

When the subject looks at a nearby object, there is no change in the position of images 1 and 3. However, image 2 becomes smaller and moves toward image 1, indicating that the anterior curvature of the lens has increased.

Argyll Robertson Pupil

In this condition, the light reflex is lost but the accommodation reflex is retained.

Site of Lesion

The fibers from the pretectal nucleus to the Edinger–Westphal nucleus are damaged.

This occurs in a syphilitic lesion of the CNS.

Argyll Robertson pupil may also be a sign of diabetic retinopathy.

VISUAL ACUITY

Visual acuity is the ability of the eye to identify two points separated in space as two distinct points.

It indicates the clarity of vision.

The two points of an object can be seen separately as two distinct points when they form

an angle of 1 minute or more (visual angle) at the nodal point of the eye. Alternatively if two points on the retina are separated by 2 μ, then the two points can be visualized as two separate points.

Snellen's chart or **Landolt C chart** (**Fig. 9.11**) is used to test the visual acuity for distant vision.

The chart contains letters/numbers/objects of different sizes.

The topmost row has the biggest size and a normal subject can see it from a distance of 60 m. The second line on the chart should be seen from a distance of 36 m. The subsequent lines should be seen from the distances of 24, 18, 12, 9, and 6 m.

The subject is seated at a distance of 6 m (20 ft) from the chart. At this distance, the eye receives the parallel rays of light.

The normal visual acuity is expressed as 6/6.

Figure 9.11 Snellen's chart. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

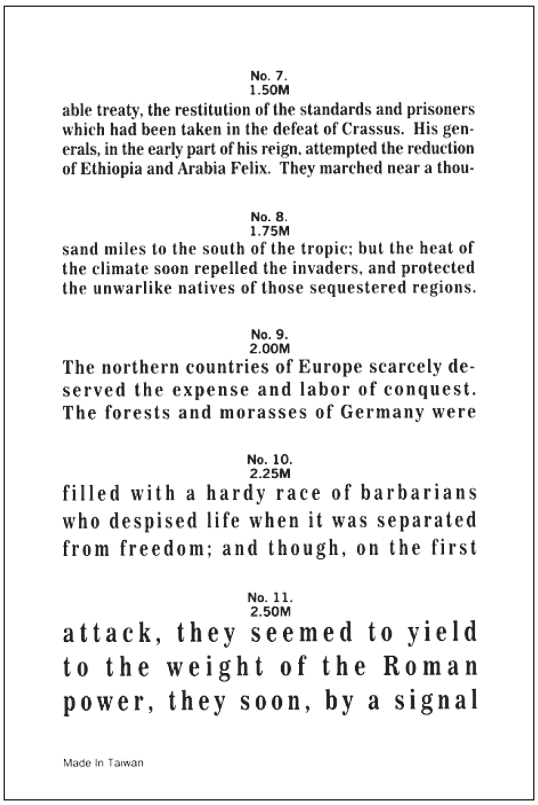


Figure 9.12 Jaeger's chart. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The numerator indicates the distance between the subject and the chart.

The denominator indicates the distance from which the letter should be read by a normal person.

The numerator is constant and the denominator varies.

The near vision is tested by using **Jaeger's test chart** (**Fig. 9.12**) held at a distance of 30 cm. The normal individual is able to read the smallest type with each eye separately.

Other Tests The perception of light, hand movements, and finger-counting tests are used to assess the retinal function.

PERCEPTION OF DEPTH

The ability to appreciate the distance of an object from the eye is termed **depth perception**.

The mechanisms for depth perception are as follows:

- Based on the size of the image formed on the retina. The brain has the ability to estimate the distance of the object when its size is known
- Relative movement of the object with movement of the eye (moving parallax)
- Relative size of the images
- Right and left eyes appreciate the object at different angles due to the separation of eyes
- Convergence of the eyeball. The degree of stretch on the extraocular muscle also helps in appreciating the distance

CLINICAL NOTES

Squint or Strabismus

Squint is a condition where the visual axes of the two eyes are not parallel. It is also called crossed eyes. Strabismus can occur due dysfunction of extraocular muscles, uncorrected refractive errors, and trauma.

Types of squint are as follows:

- Convergent squint (both the eyes turning inward—esotropia) (**Fig. 9.13a**)
- Divergent squint (both the eyes turning outward—exotropia) (**Fig. 9.13b**)
- Vertically misaligned—hypertropia

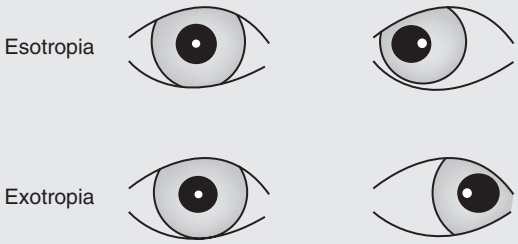


Figure 9.13 (a) Convergent squint (esotropia). (b) Divergent squint (exotropia). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Based on the development, squint is classified as follows:

- **Congenital squint**: It is present since birth. There is no paralysis of the extraocular muscles.

  It is commonly seen in subjects with uncorrected refractive errors.
- **Paralytic squint**: It is due to paralysis of the extraocular muscle. Damage to the III cranial nerve results in a lateral squint.

Double vision (diplopia) is a prominent feature of this condition.

Development of Squint

The formation of visual images in the noncorresponding points on the retina results in double vision or diplopia.

In children below the age of 6 years, diplopia is compensated by suppression of one of the defective images.

The visual axis of the defective eye is moved away from the line of focus. The deviation of the defective eye results in the development of squint. Thus, one of the eyes has strong vision and the other eye has poor vision. The eye with poor vision is also called **lazy eye**.

The suppression of one of the images results in **suppression scotoma**.

Uncorrected suppression of the image can result in permanent blindness.

The loss of vision in these cases is called **amblyopia** (anopia).

Symptoms of squint include double vision with eye strain. There can be associated loss of depth perception.

Children with strabismus exhibit inhibition and anxiety leading to emotional disorders.

Treatment

The treatment for squint must be started before the age of 6 years for best results.

Modalities for treatment are

- shortening of extraocular muscle surgically followed by training of muscles and
- use of glasses with prisms to bend the light rays to compensate the abnormal position of the eye.

PHOTOCHEMISTRY OF VISION

Rods and cones (**Fig. 9.14**) are the receptors for vision. The rods are narrower and longer than the cones. The outer segment of the cone is conical in shape. Rods help in dim light vision. Cones help in bright light and color vision.

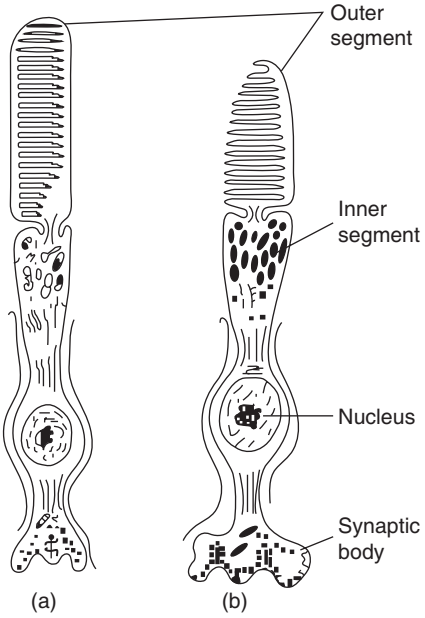


Figure 9.14 Structure of (a) rods and (b) cones.

STRUCTURE OF RODS AND CONES

The rods and cones contain the following:

- **Outer segment**: It is modified cilia and is made up of regular stacks of flattened saccules or disks. There are around 1000 disks in each rod or cone. They contain visual pigments.
- **Inner segment**: It consists of the usual cytoplasm of the cell with its organelles. Mitochondria play a major role in providing energy for the function of photoreceptors.
- **Nucleus**: It is similar to the nucleus of other cells in structure and function.
- **Synaptic body**: It connects visual receptors with other retinal cells.

There are approximately 3 million cones and 120 million rods in each eye and 1.2 million nerve fibers in each optic nerve.

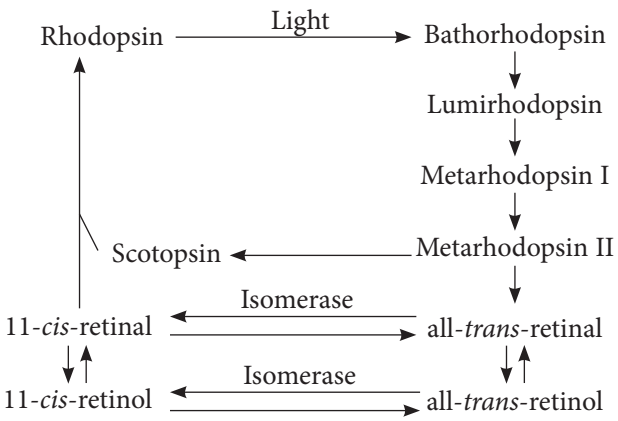
Both rods and cones contain chemicals that decompose on exposure to light. Rods contain rhodopsin (scotopsin and retinal). Cones contain cone pigments (photopsin and retinal).

Rhodopsin Cycle (Wald's Cycle)

Rhodopsin is the light-sensitive visual pigment present in the rods. It is a combination of the protein scotopsin and 11-*cis*-retinal. When light falls on the visual receptor (rods), rhodopsin present in the rods absorbs light and decomposes. The *cis* form gets converted to the *trans* form. The all-*trans*-retinal moves away from scotopsin resulting in the formation of bathorhodopsin. Lumirhodopsin is formed when bathorhodopsin undergoes decay. Further decay results in the formation of metarhodopsin I and II. Metarhodopsin II activates the rods and transmits visual impulses to the CNS.

Rhodopsin Synthesis

The all-*trans*-retinal has to be converted to 11-*cis*-retinal for resynthesis of rhodopsin. The reaction is catalyzed by the enzyme retinal isomerase. 11-*cis*-Retinal combines with scotopsin to form rhodopsin. The synthesis of visual pigment requires vitamin A. Vitamin A is present in the cytoplasm of the rods and in the pigment layer of



retina as all-trans-retinal. This is used to produce new retinal whenever needed. When there is excess retinal, it is converted back to vitamin A.

Photopsin

Cones contain a photosensitive pigment termed photopsin. Each cone has retinal and opsin. Opsin is similar to rhodopsin. The cone responds similar to rods on exposure to light. Light activates retinal which in turn activates transducin in the cones.

CLINICAL NOTES

Night-Blindness (Nyctalopia)

Night-blindness occurs in persons with severe vitamin A deficiency.

The nonavailability of vitamin A leads to decreased formation of rhodopsin.

The amount of light available in the night becomes too little to permit satisfactory vision.

Deficiency of vitamin A can also cause blindness by producing dryness of the eye and damage to the cornea and is termed **xerophthalmia**.

Prolonged deficiency of vitamin A causes degeneration of rods, cones, and neural layer of the retina.

Supplementation of vitamin A before the destruction of receptors can restore the retinal functions.

ELECTRICAL ACTIVITY IN RETINA

The membrane potential inside the rods is about –40 mV. The inner segment of the rod continuously pumps out sodium creating a negative potential in the inner segment.

The outer segment is leaky to sodium and, therefore, sodium ions continuously leak into the rods.

When rhodopsin in the outer segment is exposed to light, it begins to decompose. *11-cis*-retinal (retinal is also called *retinene*) gets converted to all-*trans*-retinal.

There is a change in the configuration of opsin. This activates a G-protein, transducin. These changes in turn activate cGMP phosphodiesterase. Phosphodiesterase reduces the concentration of cGMP, which acts directly on the sodium channel and keeps it closed.

Subsequently, the conductance of sodium ions in the outer segment is reduced even though sodium ions are pumped out of the inner segment.

This creates increased negativity inside the rods leading to hyperpolarization. Hyperpolarization reduces synaptic transmitter release. The response is produced in the bipolar cells and other neural elements.

A few retinal ganglion cells contain a pigment called **melanopsin**. The axons of these cells project to the suprachiasmatic nucleus of hypothalamus. They synchronize the circadian rhythm and endocrine functions with day and night cycles.

Exposure to light
↓
Changes in the structure of retinene
↓
Activation of transducin
↓
Activation of enzyme phosphodiesterase
↓
Decrease in intracellular cGMP
↓
Closure of sodium channels
↓
Hyperpolarization in the receptor cell
↓
Reduced release of synaptic transmitter
↓
Activation of bipolar cells and neural elements

NEUROTRANSMITTERS OF RETINAL NEURONS

The neurotransmitters released by retinal neurons are

- glycine,
- GABA,
- glutamate,
- dopamine, and
- acetylcholine

Majority of these are inhibitory neurotransmitters.

PROCESSING OF VISUAL INFORMATION

Processing of visual information occurs by formation of images at three different levels.

The first image is formed by the action of light on the photoreceptors in the retina.

It is converted to a second image at bipolar cells and third at the level of ganglion cells.

Horizontal cells modify the second image and amacrine cells alter the third image.

The third image with minor modifications in the lateral geniculate body reaches the visual cortex.

The bipolar and ganglion cells respond to circular stimulus in their receptive fields.

The center can be excitatory with inhibitory surround. This is "on-center" cell (**Fig. 9.15**).

The center may be inhibitory with excitatory surround, which is an "off-center" cell.

Activation of a neural unit coupled with inhibition of the nearby unit is an example of **lateral inhibition**.

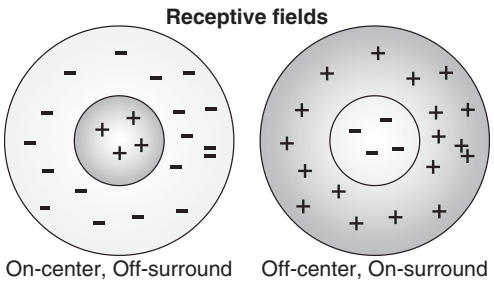


Figure 9.15 Retinal ganglion cell response to light focused on their receptive fields and when the light is turned off. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The CNS receives two kinds of inputs from the eye. The inputs are from rods and cones. Two kinds of inputs working maximally at different intensities of illumination are called the **duplicity theory**. It is also called **duplex retina theory**.

LIGHT ADAPTATION

When a person coming from a dark area is suddenly exposed to bright light, he/she requires some time to adjust to this bright light. The change in the visual apparatus to suit the altered condition is called the **light adaptation**. Exposure to bright light results in instantaneous breakdown to photopigments in both the rods and the cones. This increases signals generated at the retina producing glare.

A small part of light adaptation is contributed by a change in the size of pupil. There is constriction of pupil.

During light adaptation,

- the sensitivity of retina is decreased drastically and
- the retinal neurons adapt rapidly, switching from the rods-to-cones system. The cones are stimulated in about 60 seconds to take over the bright-light vision.

The visual acuity and color vision improve over the next 5–10 minutes. During light adaptation, retinal sensitivity (function of rod) is reduced but the visual acuity is increased.

Exposure to light will reduce the photochemicals in visual receptors decreasing the sensitivity of the eye. During light adaptation, the pupillary size decreases reducing the amount of light entering the eye.

DARK ADAPTATION

When a person moves from a brightly lit area to a dark area, the retina becomes more sensitive to light and visual threshold decreases. This is known as **dark adaptation**. These changes help in better visibility in the dark.

The perception of bright light and color vision is due to cones. When the subject enters a dark room, the rod vision takes over.

During the dark adaptation, there is regeneration of the rhodopsin pigment and the scotopic vision becomes possible.

The gain of optical system increases due to summation.

The efficiency of the visual apparatus increases.

It gives an increased response to low-intensity stimulation.

The dark adaptation commences as the subject enters the dark and is completed by about 40 minutes.

Sensitivity increases by 10-folds at the end of 1 minute. It increases 6000 folds by 20 minutes and 25,000 folds by 40 minutes.

The dark adaptation curve shows two distinct phases (**Fig. 9.16**). In the initial phase, changes are caused due to adaptation of the cones.

Cones adapt four times as fast as rods. However, the cones adapt for only a few minutes.

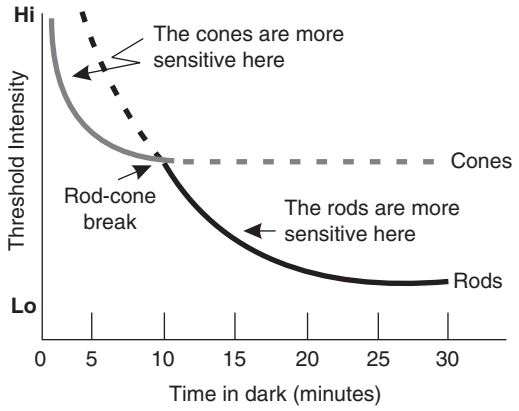


Figure 9.16 Dark adaptation curve.

Rods continue to adapt for a longer duration ranging from many minutes to hours. There is a significant increase in their sensitivity.

The dark adaptation time can be reduced by wearing red goggles when the subject is in bright light.

Subjects with vitamin A deficiency are susceptible to night-blindness and have a poor dark adaptation.

FIELD OF VISION

The part of space in which the objects are seen by each eye independently at a given instant with steady fixation of gaze in one direction is called the field of vision (**Fig. 9.17**).

The field of vision is not conical in cross-section.

It measures as follows:

- Medially—60°
- Superiorly—50°
- Laterally—100°
- Inferiorly—75°

The medial parts of the visual field of each eye overlap. Both the eyes see objects in this part of the visual field. This is called **binocular field of vision**.

The binocular field of vision is helpful for depth perception. The impulses from the retina of the right and left eyes are fused into a single image at the cortical level by the process of **fusion**.

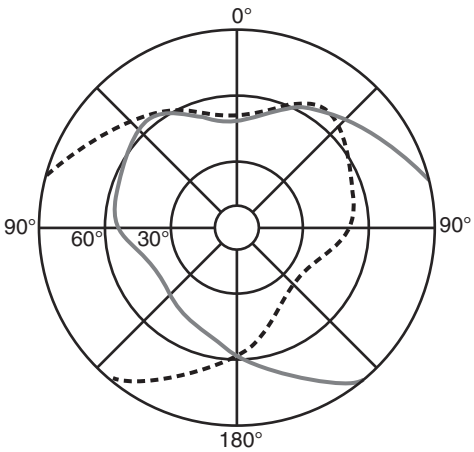


Figure 9.17 Lister's perimetry chart showing peripheral fields of vision for left (---) and right (—) eyes. The overlap area indicates binocular vision. (*Source*: Best & Taylor's Physiological Basis of Medical Practice, 13th edition. Tandon OP and Tripathi Y [eds]. Wolters Kluwer India, New Delhi; 2011.)

The points on the retina of both the eyes on which the image has to be formed to see a single object are **corresponding points**. If the image of an object is not formed on the corresponding point, it results in **double vision**, also known as **diplopia**.

The field of vision is restricted on the superior side by the orbital ridge, medially by the bridge of the nose, and inferiorly by the maxillary prominence. The lateral field of vision is the greatest because there is no obstruction.

Damage to the optic nerve fibers from the peripheral retina due to pressure near the optic disk results in reduced field of vision termed the **tubular vision**.

BINOCULAR VISION

The central part of visual fields of both the eyes overlaps. The objects located in this region are appreciated by both the eyes. This is termed the **binocular vision** (**Fig. 9.18**). The impression of a single object is formed by the fusion of retinal images from both the eyes at the cortical level. If the images are not formed at the corresponding points on the retina of both the eyes, the fusion becomes defective. This results in **diplopia** or **double vision**.

Binocular vision is helpful in perception of depth.

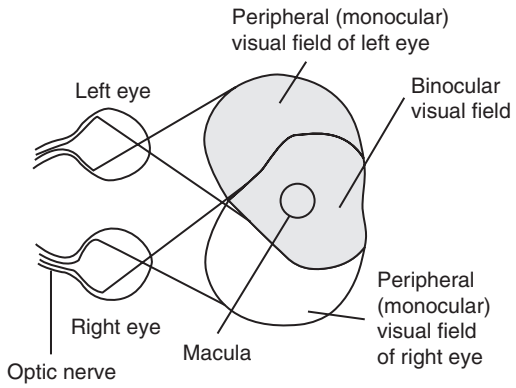


Figure 9.18 Binocular vision.

COLOR VISION

The ability of a person to identify different colors by a light-adapted eye is called **color vision**.

The colors that we appreciate are related to the wavelength of the light reflected, absorbed, or transmitted by the objects around us.

The color of the object is appreciated as red when the light of a longer wavelength (red) is reflected by the object.

The white light is a mixture of lights of all wavelengths.

The absence of all types of light gives the perception of black.

The primary colors of vision are

- **red,**
- **green, and**
- **blue**

A normal eye can see all wavelengths of light between violet and red.

PHOTOPIC AND SCOTOPIC VISION

The scotopic vision is dim light vision. The visual receptors for the night and dim light vision are the rods.

The scotopic visual apparatus are not capable of resolving the details and boundaries of the object or determining its color.

The visual receptors for photopic vision are cones. The cones have a higher threshold and a better acuity of vision.

Mechanism of Color Vision

Young and Helmholtz described the mechanism of color vision.

There are three different types of cones for three primary colors. The colors other than primary colors are appreciated by the differential stimulation of these cones.

Three types of cones (**Fig. 9.19**) are as follows:

1. **Red-sensitive**: Maximum sensitivity at 580 nm
2. **Green-sensitive**: Maximum sensitivity at 535 nm
3. **Blue-sensitive**: Maximum sensitivity at 440 nm

The pigments in the retinal cones that are sensitive to red, green, and blue range of colors in the spectrum are **erythrolabe**, **chlorolabe**, and **cyanolabe** respectively.

When a strong red light falls on the eye, only red cones are stimulated and the individual appreciates red color.

When any color other than the primary colors is seen, three types of cones get activated to a varying extent. The summated response results in perception of a nonprimary color.

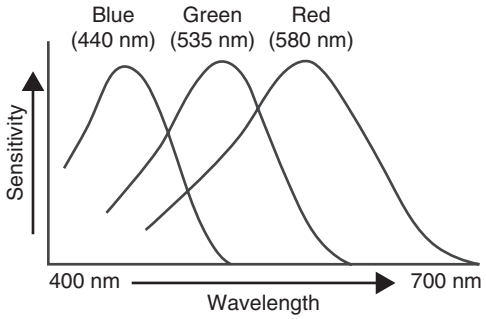


Figure 9.19 Spectral sensitivity of cones.

The visual impulses from different cones are carried to the occipital cortex. It is this area where differentiation of the visual impulses takes place and there is perception of various colors along with the complimentary colors. The color vision is grossly affected when this part of the cerebral cortex is damaged.

COLOR BLINDNESS

The subnormal or total absence of color vision is called color blindness.

Color blindness is inherited as an X-linked recessive character. It results from mutation of one or more genes coding the pigments in cones. Males have color blindness if their X chromosome has the abnormal gene. X-linked color blindness skips generations and appears more commonly in males of every second generation. The mother is the carrier for color blindness.

Very rarely, females exhibit the defect if both their X chromosomes have defective genes.

TYPES OF COLOR BLINDNESS

Monochromats

Monochromats have one type of cone. They are color blind. But the condition is rare.

Dichromats

Dichromats have two types of cones. One type of cone is absent.

- **Protanopia**: Red color blindness
- **Deuteranopia**: Green color blindness
- **Tritanopia**: Blue color blindness

Trichromats

Trichromats have all three types of cones but one of them is weak. They have subnormal color vision.

TESTS FOR COLOR VISION

- **Color-matching test (Holmgren's wool test)**: The subject is given a set of colored wool. He has to match the given sample color by selecting colored wool from the given set.
- **Ishihara's chart (pseudoisochromatic test)**: This test consists of specially designed cards containing a number or letter on a colored background. A normal person identifies the designated number or letter and the color-blind individual will identify it wrongly. The key given with the chart can be used to confirm the correctness of identification.
- **Edridge–Green lantern**: In this test, the different colors are focused through a small illuminated area and the subject identifies the same. This test is commonly used for testing the color vision of drivers.

- **Spectroscopic test**: In this test, the subject identifies the colors in the spectrum, their limit, and position.

Perception of an Image

When we look at an object, the light rays from it pass through the refracting medium of the eye, namely, cornea, aqueous humor, lens, and vitreous humor. During the passage of light through these refracting media, the light rays bend to varying degrees forming an inverted image on the retina.

An image of the object is formed in the corresponding parts of both the eyes. The images formed in both the eyes are superimposed in the visual cortex to produce a single final image.

If the images in both the eyes are not formed in the corresponding parts, then superimposition of images becomes defective, resulting in double vision (diplopia).

In order to avoid defective superimposition as in uncorrected refractive errors, the visual axis of one eye could be deviated from the line of focus, resulting in a squint.

(*Contd.*)

In the perception of an image, the visual information reaching the eye is processed and it forms images at three different stages. The first image is formed by the action of light on the rods and cones. The second image is formed in the bipolar cells modified by the horizontal cells. The third image is formed in the ganglion cells modified by the amacrine cells. The impulses generated in the ganglion cell reach the lateral geniculate body and then the visual cortex (occipital lobe) with little modifications.

The visual cortex is divided into primary and secondary visual areas. The primary visual area corresponds to area 17 and the secondary area corresponds to area 18. The visual cortex is organized into vertical columns which represent the functional unit. In between these vertical columns are specialized columns called **color blobs**.

The images in the cortex are perceived by contrast in the object. The intensity of neuronal stimulation depends on the difference in the intensity of contrast. Borders, lines, and their direction are detected by simple cells (layer 4). Further processing of these signals is performed by complex cells. The progressive processing of visual signals helps in appreciating the finer details of the object.

HEARING

The sense of hearing is based on sound. Sound is produced by vibration of objects. It causes alternate compression (molecules come close to each other, pressure increases) and rarefaction (molecules get widely separated, pressure decreases) of air present in front of the vibrating object.

Sound is transmitted through gas, liquid, and solid medium with different velocities of conduction. Sound is not transmitted through vacuum.

The character of sound is determined by the amplitude and frequency of the sound wave.

AMPLITUDE

Amplitude is the extent of displacement of molecules during vibration. It is determined by a difference between the pressures of the molecule in the zones of compression (increase in the density of medium) and rarefaction (decompression—reduction in the density of the medium). The amplitude influences the loudness of the sound. The greater the amplitude, the greater the loudness.

FREQUENCY

Frequency is the number of sound waves occurring in unit time. It is the number of compression and rarefaction in a given time. Frequency determines the pitch of the sound. The greater the frequency, the higher the pitch of sound.

Audible Frequency

A human ear can appreciate the sound with a frequency between 1,000 and 4,000 Hz (cycles per second).

The audible frequency ranges from 20 to 20,000 Hz. About 4,00,000 different sounds can be distinguished by the human ear.

EAR

The ear is divided into (**Fig. 9.20**)
- external ear,
- middle ear, and
- internal ear.

EXTERNAL EAR

The external ear has two parts:
1. Pinna
2. External auditory meatus

Functions of External Ear

The external ear collects the sound and conducts it to the tympanic membrane. The shape of the outer ear (pinna or auricle) and the external auditory canal amplifies and directs the sound toward the tympanic membrane.

Sound waves cause the movement of air molecules over the tympanic membrane making it to vibrate at the same frequency as the sound wave.

MIDDLE EAR

The middle ear or tympanic cavity is an air-filled cavity in the petrous part of the temporal bone lined by the mucosa. Laterally, it has the ear drum or tympanic membrane.

The medial side of the middle ear contains a bony wall with two openings. The superior opening is oval and the inferior opening is a round window.
- **Oval window**: The footplate of the stapes fits into it.
- **Round window**: It is closed by the secondary tympanic membrane.

The anterior wall has two canals:
1. Upper one contains the tensor tympani muscle.
2. Lower one is called the Eustachian tube.

The middle ear contains three small bones called *ossicles*. They are
1. malleus (hammer),
2. incus (anvil), and
3. stapes (stirrup).

The middle ear also contains two small muscles:
1. Tensor tympani (supplied by the mandibular division of the trigeminal nerve)
2. Stapedius (supplied by the facial nerve)

Functions of Middle Ear

- The ossicles of the middle ear conduct the sound from the external ear to the internal ear. They also amplify the sound.
- They provide **impedance matching** for the sound waves in air and movement of base of stapes in cochlear fluid.
- The small muscles, tensor tympani, and stapedius help in protecting the auditory

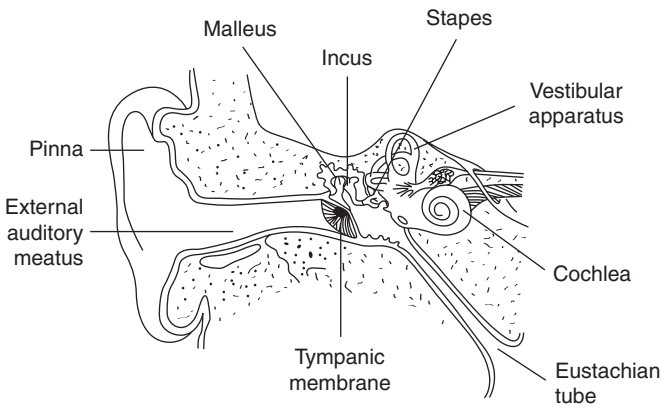


Figure 9.20 Structure of the ear.

receptors against loud sound **(tympanic reflex** or **attenuation reflex)**.

- The eustachian tube helps to equalize the pressure on either side of the tympanic membrane.

Tympanic Reflex (Attenuation Reflex)

The tympanic reflex is a protective reflex which prevents strong sound waves from causing excessive stimulation of auditory receptors resulting in their damage.

The loud sound initiates reflex contraction of the tensor tympani and the stapedius muscle present in the middle ear. This is known as **tympanic reflex**. The contraction of tensor tympani and stapedius pulls the handle of the malleus inward and the footplate of the stapes outward. This decreases the sound transmission. The reaction time for this reflex is 40–60 ms. This reflex reduces the intensity of sound transmission by 30–40 decibels.

The tympanic reflex protects the cochlea from being damaged by loud sounds.

The tympanic reflex fails to protect the auditory receptors against the gunshot sound which has a shorter reaction time.

It masks low-frequency sounds so that sounds in the normal audible range are heard better.

Impedance Matching

The ossicles amplify the sound during conduction of sound. The arrangement of ossicles increases the sound pressure by about 1.3 times. The tympanic membrane has an area of 55 sq. mm and the area of base of stapes is about 3.2 sq. mm. The difference in the size of the tympanic membrane and the base of stapes increases the sound pressure by about 17 times (**Fig. 9.21**).

The effective increase in sound pressure is 22 times. This amplification is required to overcome the resistance offered by the fluid in the internal ear for the movement of the base of stapes. This is called **impedance matching**.

Absence of amplification of sound would have reduced the hearing by about 15–20 decibels.

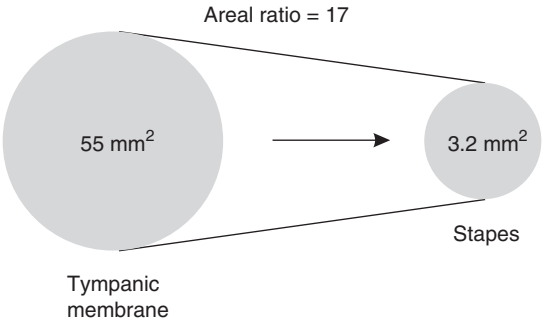


Figure 9.21 Areal ratio of tympanic membrane to stapes. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

INNER EAR

The inner ear is made of two parts:

1. Bony labyrinth
2. Membranous labyrinth

The **bony labyrinth** is a series of channels in the petrous part of the temporal bone. Inside these channels is the membranous labyrinth. The fluid surrounding it is called the **perilymph**.

The **membranous labyrinth** is filled with the **endolymph**.

The perilymph resembles the cerebrospinal fluid (CSF) and the endolymph resembles the intracellular fluid (ICF).

The inner ear has

- cochlea (for audition) and
- vestibular apparatus (for equilibrium)

Cochlea (Fig. 9.22)

Cochlea is a system of coiled tubes 35 mm long. It makes 2¾ of a turn.

The cochlea consists of three tubes lying side by side:

1. Scala vestibuli
2. Scala media
3. Scala tympani

Scala vestibuli and scala tympani contain perilymph. They communicate with each other at the apex of cochlea through a small opening called **helicotrema**.

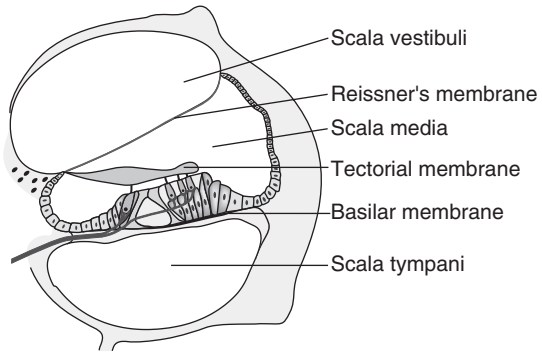


Figure 9.22 Structure of cochlea.

Scala media contains endolymph.

Scala vestibuli has an oval window, which is closed by the footplate of the base of stapes.

Scala tympani ends at the round window. It is covered by the secondary tympanic membrane.

Scala vestibuli and scala media are separated by **Reissner's membrane**.

Scala media and scala tympani are separated from each other by the **basilar membrane**. The basal portion of the membrane has stiff and elastic fibers attached to the bony structure.

The diameter of the fiber decreases progressively from base to apex and the length increases. The change in the length and diameter of the fiber decreases the stiffness.

Stiff and short fibers at the base vibrate to high-frequency sound and long and thinner fibers toward the apex vibrate to low-frequency sounds.

On the surface of the basilar membrane lies the organ of Corti containing hair cells.

Organ of Corti (Fig. 9.23)

The organ of Corti is the receptor organ that generates the nerve impulses in response to vibration of the basilar membrane.

The receptors of the organ of Corti are hair cells. They are of two types:

1. outer hair cells and
2. inner hair cells.

The outer hair cells are arranged in three rows. The inner hair cells form a single row.

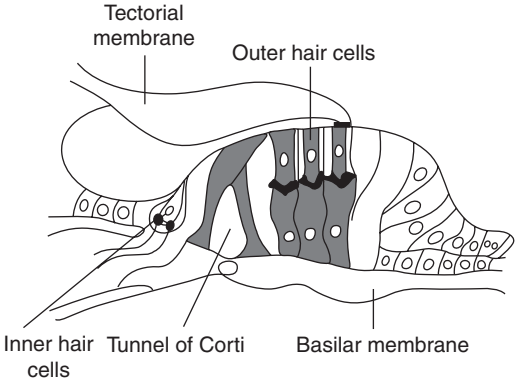


Figure 9.23 Organ of Corti.

The hair cells are covered by a thin, viscous elastic membrane called the **tectorial membrane**.

The base and sides of the hair cells synapse with a network of nerve endings of the cochlea. The nerve fibers from these endings lead to spiral ganglion of Corti which lies in the modiolus of the cochlea. The spiral ganglion in turn sends axon to the cochlear nerve.

Hair Cells and Their Excitation (Fig. 9.24) Hair cells are embedded in the epithelium made up of supporting cells. The basal part is in contact with the afferent neurons.

The apical part contains rod-shaped processes called *hairs*. They are called the **stereocilia**. Stereocilia progressively increase in length.

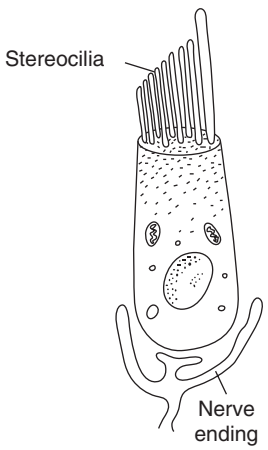


Figure 9.24 Hair cell.

These stereocilia are covered by a thin, viscous but elastic tectorial membrane.

Bending of the hairs (stereocilia) toward the longest one causes the opening of potassium channels. Rapid inward movement of the ion results in depolarization. Movement of stereocilia in the opposite direction results in hyperpolarization.

The resting membrane potential (RMP) of hair cells is −60 mV.

The inner hair cells are primary auditory receptors generating action potential.

The outer hair cells increase the amplitude and clarity of sound. They also regulate the sensitivity of the inner hair cells at different pitches.

APPRECIATION OF SOUND

The human ear can best appreciate the sound waves in the frequency of 1,000–4,000 Hz. However, the audible frequency range is 20–20,000 Hz.

- Sound waves cause the vibration of the tympanic membrane.
- These vibrations are amplified and transmitted by a chain of ossicles of the middle ear.
- The base of stapes moves forward and backward in the fluid of scala vestibuli setting up a wave. These waves cause the displacement of the basilar membrane (**Fig. 9.25**).
- Auditory receptors, the hair cells, are located on the basilar membrane. The hair cells on the basilar membrane move up and down along with the membrane. In the upward movement, the cilia of the hair cell touch the rigid tectorial membrane and get bent.
- Bending of cilia activates the cell by producing a receptor potential.
- This in turn activates cochlear nerve endings that synapse with the base of the hair cells.
- The action potential produced in the nerve travels along the auditory nerve.
- High-frequency sound produces maximum vibration of the basal part of the basilar membrane which is thin and narrow. Low-frequency sound produces maximum vibration of the apical part of the basilar membrane.
- Different regions of the basilar membrane vibrate maximally to different frequency sounds. This property helps in discrimination of pitch of the sound.

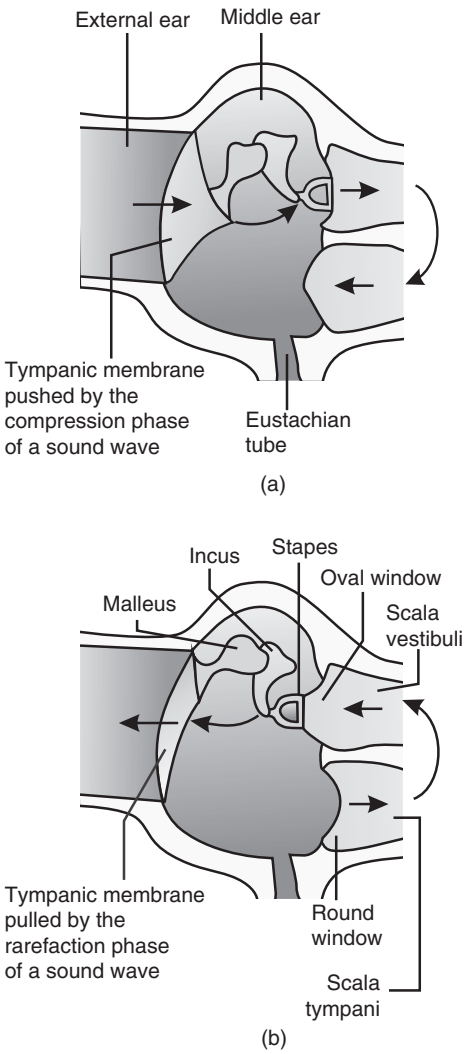


Figure 9.25 (a) Inward movement of the tympanic membrane and (b) outward movement of the tympanic membrane. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Sound wave causes
↓
Vibration of tympanic membrane
↓
Movement of ossicles (amplification of sound)
↓
To-and-fro movement of the base of stapes
↓
Vibration of basilar and Reissner's membrane
↓
Activation of hair cells of the organ of Corti
↓
Formation of cochlear microphonic and action potential
↓
Action potentials pass through VIII cranial nerve to spiral ganglion
↓
Pass to dorsal and ventral cochlear nuclei (cross to the opposite side)
↓
Reach superior olivary nucleus (through lateral lemniscus)
↓
Inferior colliculus
↓
Medial geniculate body
↓
Auditory cortex (superior gyrus of temporal lobe)

The mechanism of hearing and pitch discrimination is explained on the basis of **traveling wave theory**.

TRAVELING WAVE THEORY (Fig. 9.26)

The movement of the footplate of stapes causes displacement of the perilymph in the scala vestibuli. The movement of perilymph in the scala vestibuli displaces the fluid in scala media. This movement of fluid produces a wave in the basal portion of the basilar membrane. The wave setup at the base of the basilar membrane travels toward the apex. As the wave travels along the basilar membrane, it becomes strong at one part of the membrane causing significant vibrations at that region, called the **resonance point**.

The wave does not travel beyond the resonance point on the basilar membrane.

The traveling wave helps in appreciating the sound of a particular frequency by vibrating a specific part of the basilar membrane.

High-frequency sound travels a short distance on the basilar membrane before reaching the resonance point.

Medium-frequency sound travels halfway on the basilar membrane.

Low-frequency sound travels the entire length of the basilar membrane. Sound wave travels fastest at the base of the membrane and becomes progressively slow toward the apex. This difference is due to a high coefficient of elasticity of basilar fibers.

Rapid transmission of sound waves in the initial part helps to discriminate high-frequency sound.

Endolymphatic Potential

Endolymphatic potential is the potential difference between the perilymph and the endolymph. The potential difference is 80 mV, the endolymph being positive with respect to perilymph.

The endolymphatic potential is due to an increased level of potassium ions produced by the activity of the striae vascularis.

Cochlear Microphonic Potential

Cochlear microphonic potential is a potential developed in the cochlea due to auditory stimulation.

It is a nonpropagated (not transmitted) graded potential which depends on the intensity of stimulation.

It has no latent period. The cochlear microphonic potentials progress to form action potential.

(*Contd.*)

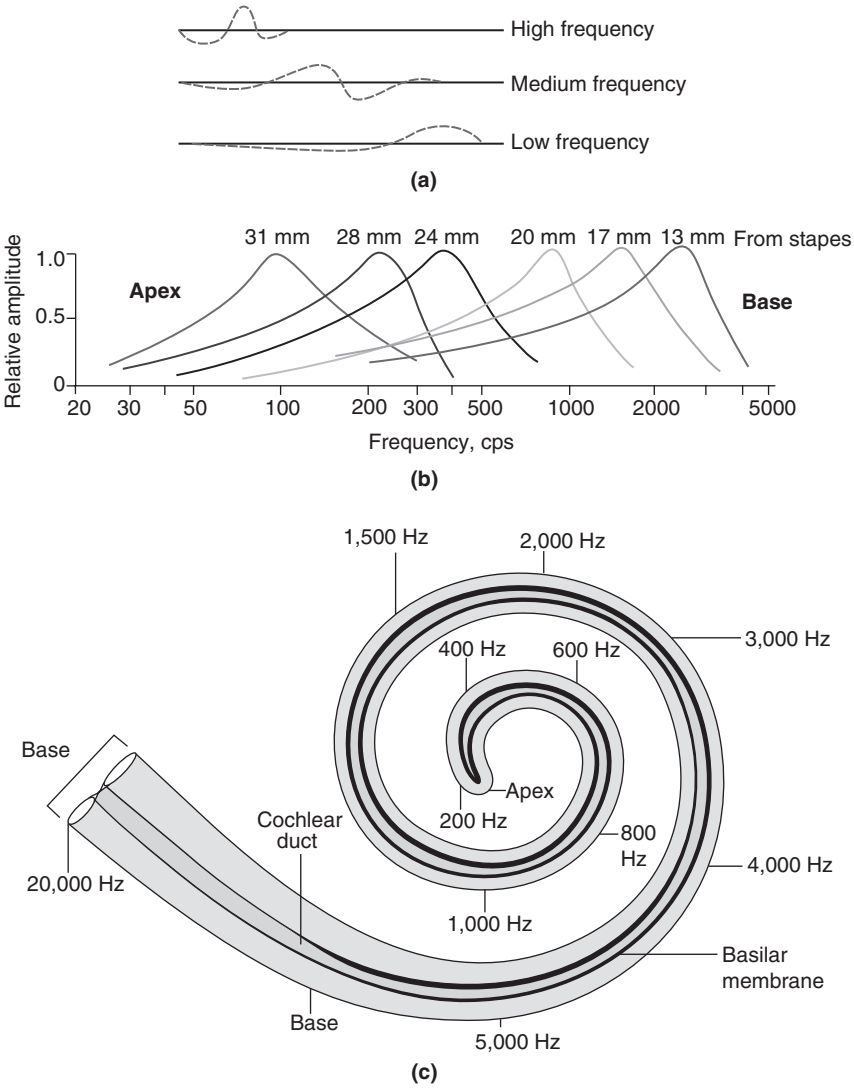


Figure 9.26 Traveling wave mechanism.

Action Potential in Cochlear Nerve

The stimulation of hair cells releases the chemical mediator glutamate. It activates the auditory nerve to set up the action potential after a brief latent period. The action potential depends on the character of the sound. The frequency of action potential determines the loudness of sound.

AUDITORY PATHWAY (Fig. 9.27)

The nerve fibers from the hair cells of the organ of Corti end in the spiral ganglion of Corti.

The fibers from the spiral ganglion of Corti pass to the dorsal and ventral cochlear nuclei located in the upper part of the medulla.

Second-order neurons pass to the opposite side of the brainstem to terminate in the superior olivary nucleus. Some fibers also pass to the superior olivary nucleus of the same side.

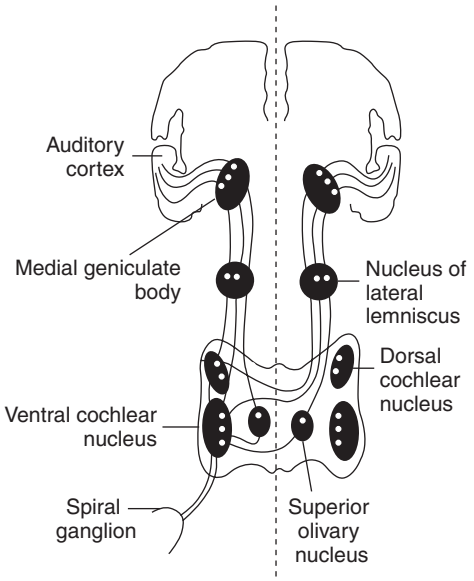


Figure 9.27 Auditory pathway.

From the superior olivary nucleus, the fibers pass through the lateral lemniscus and few fibers terminate in the nucleus of the lateral lemniscus. The remaining fibers bypass this nucleus and reach the inferior colliculus (through the cochlear nerve).

From the inferior colliculus, fibers pass to the medial geniculate body where all the fibers synapse.

The pathway then proceeds through the auditory radiation to the auditory cortex areas 41 and 42 (superior gyrus of the temporal lobe).

ROLE OF AUDITORY CORTEX IN AUDITION

The auditory cortex is located in the superior temporal gyrus. It has

1. primary auditory cortex and
2. secondary auditory cortex (auditory association cortex).

The primary auditory cortex is activated by inputs from the medial geniculate body. The secondary auditory cortex is stimulated by inputs from the primary auditory cortex.

The anterior portion of the primary auditory cortex is stimulated by low-frequency sounds and the posterior part is activated by high-frequency sounds.

The auditory inputs are processed at different levels during transmission. The sounds are perceived by the primary cortex. The auditory association cortex associates auditory information with other inputs from the sensory areas for the interpretation of sound.

TESTS FOR HEARING

WATCH TEST

The subject is asked to appreciate the tick sound by keeping the watch at a reasonable distance. This is compared with the sound perception of the examiner.

RINNE'S TEST (Fig. 9.28)

The base of a vibrating tuning fork (256 or 512 Hz) is kept on the mastoid process to study the bone conduction.

When the subject ceases to appreciate the sound, the vibrating prong of the tuning fork is held in front of the external auditory meatus (air conduction).

In a normal person, air conduction is better and longer than bone conduction. If the bone conduction is better, it indicates conductive deafness or middle ear deafness.

WEBER'S TEST (Fig. 9.29)

In this test, the base of a vibrating tuning fork is placed on the vertex of the skull or on the forehead. In a normal person, sound is heard equally in both ears.

In middle ear deafness and blockage in the external auditory meatus, sound is better heard on the defective side.

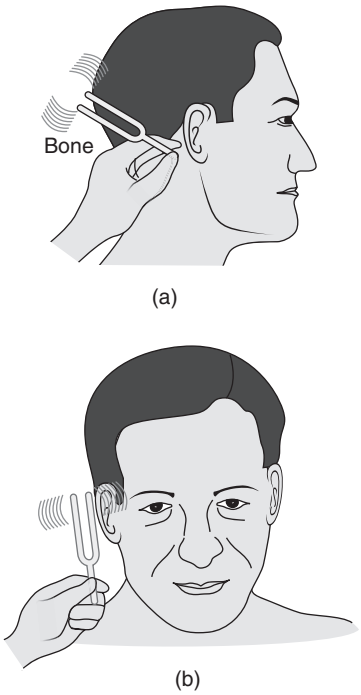


Figure 9.28 Rinne's test. (a) Bone conduction (512 Hz vibrating tuning fork kept over the mastoid process). (b) Air conduction (512 Hz vibrating tuning fork held in front of the ear). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Figure 9.29 Weber's test (512 Hz vibrating tuning fork placed over the vertex). (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

In unilateral nerve deafness, sound is better heard on the normal side. Weber's test is of no value in bilateral nerve deafness.

ABSOLUTE BONE CONDUCTION (ABC) TEST

The external auditory meatus of the subject and the examiner are occluded. A vibrating tuning fork is placed on the subject's mastoid bone. When the subject stops hearing the sound, a tuning fork is placed on the examiner's mastoid bone. If the examiner continues to hear the sound for a longer duration than the subject, the subject has reduced absolute bone conduction. This indicates nerve (sensorineural) deafness.

TYMPANOMETRY

Tympanometry is an objective test to assess the function of the middle ear. It measures the transmission of energy through the middle ear. It helps to distinguish between conductive and sensorineural deafness. It can be useful in confirming the presence of otitis media.

INTENSITY OF SOUND

The intensity of sound is measured in decibel scale. Bel is the logarithm of the ratio of intensity of given sound to that of the standard sound. A decibel (dB) is 1/10 bel. Intensity of 0 dB sound corresponds to the intensity of standard sound. It does not mean the absence of sound. Discomfort is experienced at an intensity level of 120 dB or above. The higher intensity sounds can damage the organ of Corti.

Masking

Masking is the decreased ability of a person to appreciate one sound fully in the presence of another sound (with different intensities). It is due to refractoriness (unresponsiveness to further immediate stimulation) of the receptors and the nerve by the earlier stimulation. The extent of masking of one tone over the other depends on the pitch of the sound.

Discrimination of Pitch and Loudness

Sounds of different frequencies cause maximum vibration at a specific portion on the

basilar membrane. This is termed **place principle** for determination of frequency of sound.

There is spatial organization of nerve fibers in the auditory pathway. It extends from cochlea to cerebral cortex. Specific sound frequency activates specific neurons in the brain. This specialized arrangement helps in accurate discrimination of different frequency sounds.

Loudness is appreciated by the extent of displacement of the basilar membrane. The greater the displacement, the higher the loudness. Increased amplitude of displacement of the basilar membrane increases the number of hair cells activated. This results in summation of impulses, which is perceived as loud sound.

Localization of Sound

The sound waves traveling in the horizontal plane reach the right and left ears at different times. This difference in the arrival of sound at each ear helps to determine the direction of sound.

The ear closer to the source of sound perceives it louder than the other ear. The cortical interpretation of loudness and the time difference in the perception of sound by both the ears help to determine the direction of sound (**Fig. 9.30**).

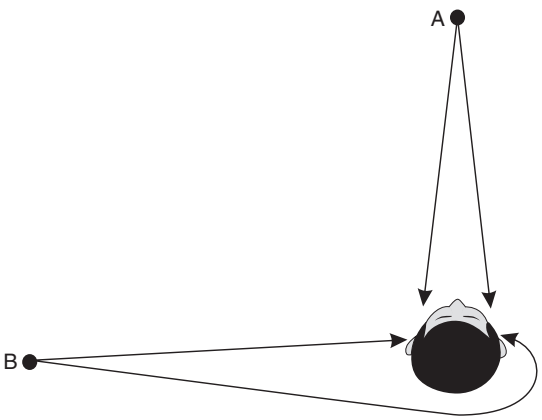


Figure 9.30 Difference in the time of perception of sound by two ears. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

CLINICAL NOTES

Deafness

The inability to appreciate sounds is called deafness.

If deafness is present since birth, then the individual is unable to speak (deaf mute). Hence, to have the ability to produce sound, the person has to hear the sound.

Types of deafness are as given in the following text.

Conductive Deafness

Conductive deafness is caused due to impaired sound transmission in the external or middle ear.

Causes

- Wax or foreign body in the external ear
- Otosclerosis in the middle ear (ossicles are resorbed and replaced by the sclerotic bone)
- Rupture of the tympanic membrane (perforation of the eardrum)
- Inflammation of the outer and middle ear with fluid accumulation

Nerve (Sensorineural) Deafness

Nerve deafness is caused by damage to auditory receptors in the inner ear, VIII cranial nerve, or auditory pathway. It impairs the ability to appreciate certain frequency sound while perception of other frequency sounds remains unaffected. Damage to hair cells can occur due to prolonged exposure to noise. Antibiotics such as streptomycin and gentamicin obstruct mechanosensitive channels in outer hair cells resulting in their degeneration. Tumor of the VIII cranial nerve also causes sensorineural deafness.

Presbycusis

Presbycusis is a gradual hearing loss associated with age. This occurs due to gradual loss of hair cells and neurons.

Tinnitus

Tinnitus is "ringing in the ears" due to persistent stimulation of cochlear neurons following damage to hair cell or its loss. It is noticed in temporary or permanent hearing loss.

Treatment

Hearing Aids

Hearing aids are electronic devices that compensate for the loss of hearing due to the damage in middle ear, cochlea, and neural structures.

(*Contd.*)

Hearing aids amplify the incoming sound and transmit the sound in the normal route of its perception.

The cochlear mechanism to appreciate the sound remains the same as in a normal person.

Cochlear Implants

Cochlear implants are used when the damage to the auditory apparatus is extensive and the loss of hearing is significant.

The implants directly stimulate the cochlear nerve with small currents in response to sound.

The sound signals are transmitted directly to the auditory nerve without the involvement of cochlea.

Research is in progress using embryonic and pluripotent stem cells to develop cells to replace damaged hair cells.

Audiometry

In this test, sounds of different frequencies and loudness produced by an instrument are presented to the subject through earphones. The threshold of hearing at each frequency for air conduction and bone conduction is plotted. The graph obtained is an audiogram.

The extent of hearing loss is evaluated by comparing the recorded values with the standard values obtained for normal subjects (**Fig. 9.31**).

Types of audiometry are

- pure tone audiometry,
- speech audiometry,
- impedance audiometry, and
- evoked response audiometry.

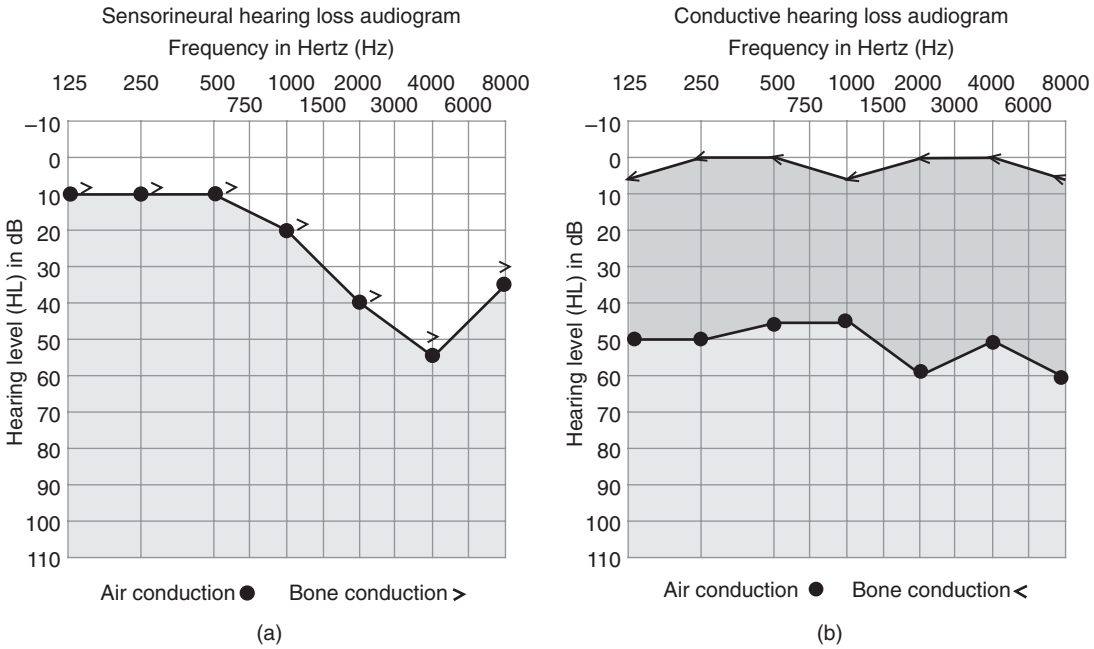


Figure 9.31 Pure tone audiometry in (a) sensorineural hearing loss and (b) conductive hearing loss. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

TASTE (GUSTATION)

The sensations of taste and smell are closely associated with the functioning of the gastrointestinal tract.

A combination of taste and smell sensations provides flavor for the food.

The sensation of taste is appreciated by receptors present in the taste buds. Taste buds are present in papillae, which are visible projections on the dorsal surface of the tongue. Each taste bud has 50–150 receptor cells. The number of taste buds ranges from 2000 to 5000. Taste buds help to select the food suitable to the needs of the body.

TASTE SENSATIONS

The primary taste sensations are
- sweet,
- salt,
- sour,
- bitter, and
- umami

Perception of different taste sensations other than the primary taste sensation is due to combination of primary taste sensations.

Sweet

- It is best appreciated at the tip of the tongue.
- It is produced by organic substances.
- Polysaccharides, glycerols, alcohols, ketones, chloroform, and amides of aspartic acid also produce sweet sensation.

Salt

- It is produced by ionizing substances releasing Na^+ ions.
- It is best appreciated on the lateral margin of the tongue.

Sour

- It is produced by acids which release H^+ ions.
- It is best appreciated on the lateral margin of the tongue.
- Sourness depends on the hydrogen ion concentration in the given acid.

  Organic acids are sourer when compared to mineral acid with similar hydrogen ion concentration because they penetrate the cells more rapidly than mineral acids.

Bitter

- It is best appreciated at the back of the tongue.
- It is produced by alkaloids such as quinine.
- Organic compounds such as morphine, caffeine, urea, inorganic salts of magnesium, ammonia, and calcium also taste bitter.
- Some of the substances which produce a sweet sensation can leave a bitter aftertaste.

  The bitter taste is due to cations.

Umami

- It is a Japanese word meaning "delicious."
- It is a pleasant and sweet taste sensation different from the standard sweet taste.
- It is produced by monosodium glutamate (MSG).

TASTE BUDS (Fig. 9.32)

The taste buds are the receptors for taste sensation. They are present on the walls of the papilla.

The papillae are of three types:
1. Circumvallate papillae form V line on the posterior portion of the tongue (they have the maximum number of taste buds)
2. Fungiform papillae present on the anterior portion of the tongue
3. Foliate papillae located in folds along the lateral portion of the tongue

The taste buds are oval-shaped structures containing
- receptor cells or taste cells,
- supporting cells or sustentacular cells, and
- basal cells.

At the tip of the taste bud, there is a taste pore. From the apical portion of the receptor cells, hair-like projections come out of the taste pore. These are called the **microvilli**.

Fine sensory nerve fibers which arise from the receptor cells carry the taste sensations.

The basal cells form the receptor cells which are replaced periodically.

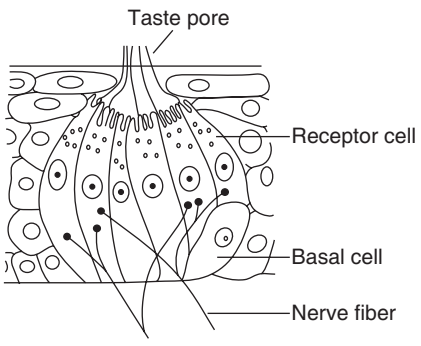


Figure 9.32 Taste bud.

NERVE SUPPLY TO THE TONGUE

The taste sensations from the anterior two-third of the tongue are carried by **chorda tympani**, a branch of the facial nerve. Taste sensation from the posterior one-third of the tongue is carried by the **glossopharyngeal** nerve.

TASTE PATHWAY (Fig. 9.33)

The nerve fibers from the anterior and posterior parts of the tongue end on the gustatory portion of the nucleus of tractus solitarius (NTS) present in the medulla oblongata (**Flowchart 9.1**).

The second-order neurons arising from NTS end in the ventral posteromedial (VPM) nucleus of the thalamus.

The third-order neurons arising from the thalamus end on the face area of the somatosensory cortex (lower lateral part of the post central gyrus deep in the lateral sulcus).

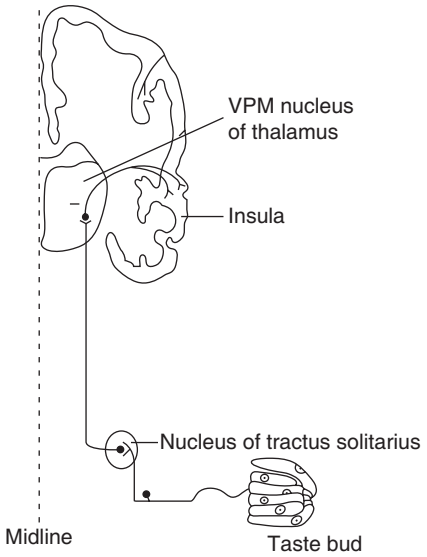
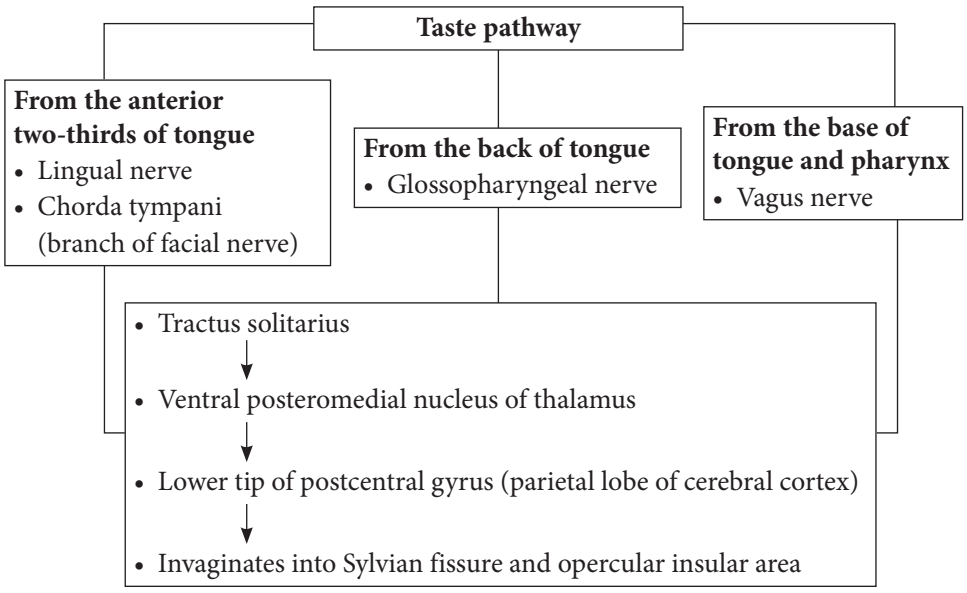


Figure 9.33 Taste pathway. *VPM*, ventral posteromedial nucleus.

MECHANISM OF APPRECIATION OF TASTE

The taste-producing substance dissolves in saliva and comes in contact with the villi through the taste pores present in the taste buds. The contact brings about changes in the receptor cells of the taste buds resulting in generation of the generator potential. This releases the neurotransmitter at the synapse between the receptor cell and the sensory nerve.



Flowchart 9.1 Pathway for taste sensation.

The action potential is generated at the sensory neuron. Impulses from the receptor cells are carried to the foot of the post central gyrus in the parietal lobe of the cerebral cortex where different taste sensations are appreciated.

An extreme degree of adaptation takes place for taste sensation. It occurs at the level of the central nervous system than at the receptors.

An unpleasant experience with food results in the development of taste aversion.

Each taste system is organized into a specific coded pathway to the CNS.

The single taste receptor cell responds to more than one type of taste sensation to a varying extent.

Appreciation of a specific taste sensation depends on the activation of a group of neurons from different receptor cells.

CLINICAL NOTES

Ageusia

Ageusia is absence of taste sensation. It is caused by damage to the lingual or the glossopharyngeal nerve.

Hypogeusia

Hypogeusia is decreased taste sensation. It is seen in conditions such as Bell's palsy, multiple sclerosis, and prolonged use of tobacco.

Dysgeusia or Parageusia

It is unpleasant perception of taste sensation. (It is distorted taste sensation.)

About 25% of population has increased sensitivity to taste due to an increased number of fungiform papillae.

Common causes for dysgeusia are diseases of gums, temporary use of medications, chemotherapy, and deficiency of zinc.

Perception of Salt Taste

Salt or sodium chloride receptor is the simplest form of receptor. Sodium ions and ions of alkali metals produce salty taste.

Entry of sodium ions into the taste cell opens voltage-gated calcium channels.

Entry of calcium ions leads to release of the neurotransmitter.

The potassium ions resemble sodium ions. Hence, the saltiness of potassium is similar to sodium ions.

Entry of sodium ions into the receptor cell through ion channels in plasma membrane
↓
Depolarization of receptor cell producing generator potential
↓
Release of neurotransmitter from the cell at the synapse
↓
Generation of action potential in the sensory nerve
↓
Transmission of impulses to the foot of postcentral gyrus for appreciation of taste

Perception of Sweet Taste

Sweet is a pleasurable sensation produced by sugars. Sweet is connected to aldehydes and ketones. Sweetness is detected by G protein–coupled receptors.

The second messenger system closes potassium ion channels leading to depolarization and release of neurotransmitter.

The binding of carbohydrate molecule to the receptor on the plasma membrane
↓
Activation of cascade of second messenger system
↓
Depolarization of receptor cell producing generator potential
↓
Release of neurotransmitter from the cell at the synapse
↓
Generation of action potential in the sensory nerve
↓
Transmission of impulses to the foot of postcentral gyrus for appreciation of taste

SMELL (OLFACTION)

The sensation of smell is perceived by the olfactory receptors.

The sensation of smell is useful for an individual in the following ways:

- It helps in the selection of food.
- A strong smell can stimulate human emotions.
- In animals, odors can influence sexual drive.

The olfactory receptors are located in the yellowish pigmented **olfactory mucus membrane** of the nasal cavity.

The olfactory receptors are called the **olfactory cells**. The basal cells are the source for the receptor cells.

There are about 10–20 million olfactory cells. They are interspersed between the sustentacular cells (supporting epithelial cells).

The olfactory cells are bipolar cells. The dendrite has an expansion called the **olfactory rod**. The cilia project into the mucus membrane from these rods. The axons arising from the olfactory receptors pierce the cribriform plate of the ethmoid bone and enter the olfactory bulb.

The olfactory neurons are the only neurons known to be replenished by cell division. Mucus is produced by Bowman's gland present below the basal lamina of the olfactory membrane (**Fig. 9.34**).

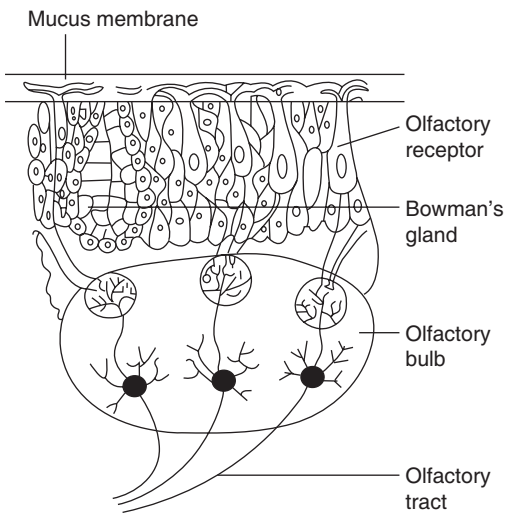


Figure 9.34 Olfactory membrane.

Many animals have an accessory olfactory system. The sensory receptors for this system are located in **vomeronasal organs**. The sensory neurons from the vomeronasal organ project to the accessory olfactory bulb.

STIMULATION OF THE OLFACTORY CELLS

The smell of volatile substances can be appreciated when they are sniffed into the nostrils. The stimulating substances must be water soluble.

The odor-producing substance diffuses into the mucus that covers the cilia (hair-like process). Then it binds with the receptor forming cAMP.

The membrane potential of the unstimulated olfactory cell is about –55 mV. The odorants cause depolarization of the olfactory cell by opening the sodium channels.

The olfactory receptors undergo adaptation to the extent of 50% in the first second.

Thereafter, they adapt very little and very slowly. Because of this mechanism, the intensity of smell is high in the beginning but decreases thereafter.

The human olfactory system can recognize more than 10,000 different odors. This is possible by the presence of about 1000 different genes.

Odorant substance attaches to receptor protein

↓

Stimulation of receptor activates G protein complex

↓

Activates adenylyl cyclase

↓

Formation of cAMP from ATP

↓

cAMP opens sodium channels depolarizing the membrane

OLFACTORY PATHWAY

The axons of the olfactory cells pierce the cribriform plate of the ethmoid bone and end in the olfactory bulb. (The olfactory bulb is an anterior outgrowth of brain tissue from the base of the brain.)

The short axons from the olfactory cells terminate in multiple globular structures within the olfactory bulb called **glomeruli**.

Each glomerulus has dendrites from mitral cells and tufted cells.

These cells in turn send axons through the olfactory tract to transmit olfactory sensations to the CNS.

The olfactory tract enters the brain at the anterior junction between the mesencephalon and the cerebrum.

The tract divides into two pathways: one passes medially to the medial olfactory area and the other laterally to the lateral olfactory area.

- **Medial olfactory area**: This consists of a group of nuclei located in the midbasal portions of the brain anterior to the hypothalamus.
- **Lateral olfactory area**: This is mainly composed of the prepyriform cortex, pyriform cortex, and cortical portion of the amygdaloid nuclei.

From these areas, signals pass into almost all the portions of the limbic system, especially to the hypothalamus.

The newer olfactory pathway passes through the thalamus, to the basomedial thalamic nucleus, and then to the lateral posterior quadrant of the orbitofrontal cortex.

CLINICAL NOTES

Dysosmia

Dysosmia is a condition of olfactory dysfunction. There is impairment in processing of olfactory stimulus resulting in altered smell sensation.

Anosmia

Anosmia is loss of sensation of smell or inability to smell.

Hyposmia (Hypesthesia)

Hyposmia is decreased olfactory sensation.

Causes

- Nasal congestion or nasal polyp
- Damage to the olfactory nerve
- Respiratory tract infections such as abscesses
- Tumors such as neuroblastoma and meningioma

Hyperosmia

Hyperosmia is enhanced olfactory sensitivity. It is commonly seen during pregnancy.

Parosmia

Parosmia is perverted smell sensation. The subject incorrectly identifies the smell. Pleasant and neutral odors are mistaken for unpleasant odor.

Pheromones

Pheromones are chemical substances produced by rodents and few mammals which can stimulate the sex drive in them.

Thus, pheromones play a major role in defense against the **predators**. They also influence **sexual and reproductive** behavior of animals. Vomeronasal organs have receptors capable of identifying odors arising from pheromones.

REVIEW QUESTIONS

Long Essay

1. Trace the visual pathway. Explain the effects of lesion at six levels in its course.
2. Explain the mechanism of hearing.

Short Essay

1. Explain the formation, drainage, and functions of aqueous humor. What is glaucoma?
2. Name the errors of refraction. Explain its corrections with the help of a diagram.

3. Explain direct and indirect light reflex with their pathways. What is Argyll Robertson pupil?
4. Trace the pathway for accommodation reflex. Explain the changes during accommodation.
5. How is visual acuity tested?
6. Explain rhodopsin cycle.
7. What are Purkinje–Sanson images?
8. Explain the activation of visual receptors.
9. Discuss the mechanism for the development of squint or strabismus
10. Explain Young–Helmholtz theory of color vision. Name the defects of color vision.
11. Explain the tests for color vision.
12. What is color-blindness? How is it classified?
13. Explain changes during dark adaptation.
14. What are the contents and functions of middle ear? Explain the tympanic reflex.
15. Explain the mechanism of appreciation of sound.
16. Discuss the mechanism of localization of sound.
17. Trace the auditory pathway with a neat, labeled diagram.
18. Explain the tests for hearing.
19. Trace the taste pathway.
20. Trace the olfactory pathway. What is anosmia?

Short Answer

1. What are the functions of iris?
2. List the functions of lacrimal secretion.
3. Name the functions of rods and cones.
4. Draw a labeled diagram of cone.
5. Explain the basis of visual acuity.
6. What is Argyll Robertson pupil?
7. Discuss the location and types of visual cortex.
8. What is macular sparing?
9. Mention extraocular muscles and movements produced by them.
10. What is squint? What are its types?
11. Explain the structure of rods and cones.
12. What is nyctalopia?
13. What are the changes during dark adaptation?
14. Mention the changes during light adaptation.
15. List the primary colors of vision.
16. Mention the disorders of color vision.
17. Explain the tests for color vision.
18. What is cataract? How is it managed?
19. Mention field of vision in different quadrants.
20. Draw a labeled diagram of the organ of Corti.
21. What is impedance matching
22. Explain traveling wave theory of hearing.
23. What is cochlear microphonic and endolymphatic potential?
24. What are the types of deafness?
25. Explain briefly audiometry.
26. Name auditory cortical areas.

27. Explain Rinne's test.
28. What is Weber's test? What is its clinical importance?
29. Name the primary taste sensations.
30. Draw a diagram of a taste bud.
31. Explain the mechanism for appreciation of taste.
32. Explain the terms (a) ageusia, (b) hypogeusia, and (c) dysgeusia.
33. Name four different types of taste sensations.
34. Draw a diagram of otolith organs.
35. What are pheromones?

CHAPTER

10 Endocrinology

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Define and classify hormones. Discuss the chemistry and regulation of hormone secretion. Explain the mechanism of secretion of hormones.
- Identify the role of hypothalamus as an endocrine organ. List the hormones secreted by the hypothalamus.
- List the hormones secreted by the pituitary. Describe the mechanism of action, actions, regulation, and clinical importance of growth hormone.
- Describe the actions, regulation, and clinical importance of posterior pituitary hormones.
- Describe the synthesis, actions, regulation, and clinical importance of thyroid hormones. List the thyroid function tests.
- Outline the importance of ionic calcium and phosphate in body functions. Discuss the role of parathormone, calcitriol, and calcitonin in the regulation of calcium level in the body.
- List the hormones of endocrine pancreas. Describe the synthesis, actions, regulation, and clinical importance of pancreatic hormones.
- Describe the anatomy and functional divisions of the adrenal gland. Describe the synthesis, actions, regulation, and clinical importance of adrenal cortical hormones.
- Discuss the synthesis and actions of adrenal medullary hormones.
- Discuss the role of pineal gland and thymus as endocrine organs.
- Successfully answer the questions and MCQs at the end of this chapter.

Endocrine and nervous systems are the two major regulatory systems of the body. The nervous system controls the other systems rapidly through neurotransmitters while the endocrine system is a much slower system which controls through chemical mediators. The endocrine system consists of glands present in different parts of the body.

They are called **endocrine glands** (**Fig. 10.1**) because they release their secretions directly into the bloodstream without the help of ducts (ductless glands).

The endocrine glands are present scattered throughout the body. They are connected to each other and other organs of the body through the vascular system. The chemicals secreted

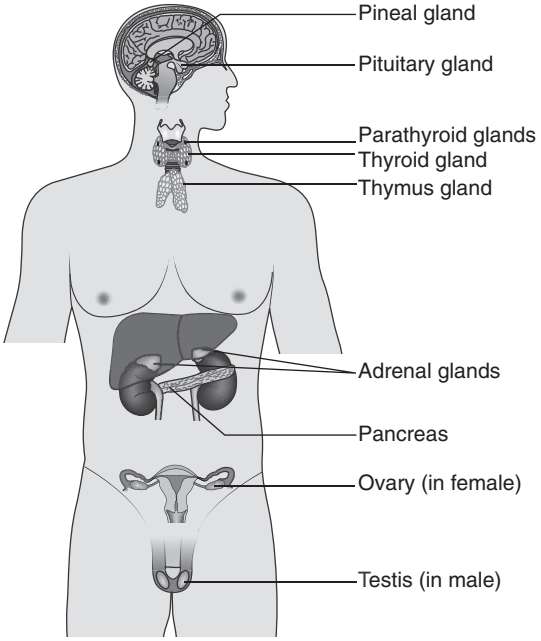


Figure 10.1 Endocrine glands. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

by the endocrine glands are called **hormones**. The hormones circulate in the blood and reach the tissue on which they act. These tissues are called the **target tissues**. The hormones combine with receptors present on the target tissues. This triggers various intracellular mechanisms that bring about changes in functions of the cell.

HORMONE

A hormone is a chemical substance secreted by the endocrine glands directly into the bloodstream. It regulates the function of a distant organ (target organ).

TYPES

Hormones are grouped into different types based on the site of secretion and place of action.

Classical Hormones

The hormones are liberated from the endocrine gland and carried by the blood or lymph. They reach the target cell and produce the desired effect. Examples include hormones of the thyroid and pancreas glands.

Neurohormones

Neurohormones are secreted from the axon terminals and released into the circulation. Examples are hypothalamic-releasing hormones which act on the anterior pituitary. Oxytocin and ADH, produced by the hypothalamus, and stored and released by the posterior pituitary, act on distant target organs.

Paracrine Hormones

Paracrine hormones are the hormones which have effect on the adjacent cells. For example, α and β cells of islets of Langerhans exert paracrine effect on each other. Similarly, histamine secreted from the cells of the stomach mucosa exerts its action on the parietal cells of the stomach to increase acid secretion.

Autocrine Hormones

Autocrine hormones are chemicals secreted by a cell into the fluid surrounding it that act upon the same cell to regulate its functions. For example, platelet-activating factor from the endothelium acts on itself. Norepinephrine released by adrenal medulla inhibits further release of norepinephrine by the same cells.

CHEMISTRY

Chemically, hormones are of three types:

1. Steroid hormones
2. Amines
3. Proteins or peptides

Steroid Hormones

Steroid hormones are synthesized from cholesterol. They have cyclopentanoperhydrophenanthrene ring. They are formed from smooth endoplasmic reticulum.

The different steroid hormones are cortisol, aldosterone, estrogens, progesterone, and testosterone.

Steroid hormones are usually not stored in the cells.

Amines

Amines are derivatives of amino acid tyrosine. They are synthesized in the cell cytoplasm.

They include hormones of adrenal medulla and thyroid glands. Thyroid hormones are stored in the form of thyroglobulin and released as and when required by simple diffusion. Adrenal hormones are stored as secretory vesicles.

- Thyroid hormones are thyroxine and triiodothyronine.
- Adrenal medullary hormones are epinephrine and norepinephrine.

Proteins or Peptides

Proteins are water-soluble hormones which are carried in an unbound form in the plasma. They are made up of chains of amino acids linked by peptide bonds. They are synthesized by rough endoplasmic reticulum. They are made up of chains of amino acids linked by peptide bonds.

Protein (or peptide) hormones are

- anterior pituitary hormones,
- posterior pituitary hormones, and
- insulin, glucagon, and parathormone.

REGULATION OF HORMONE SECRETION (Fig. 10.2)

Hormone secretion is regulated based on its requirement. The regulation of hormonal secretion is by feedback mechanisms. These mechanisms are of two types:

1. Negative feedback mechanism
2. Positive feedback mechanism

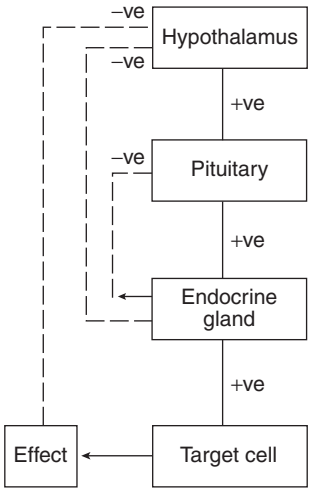


Figure 10.2 General pattern of regulation of hormone secretion.

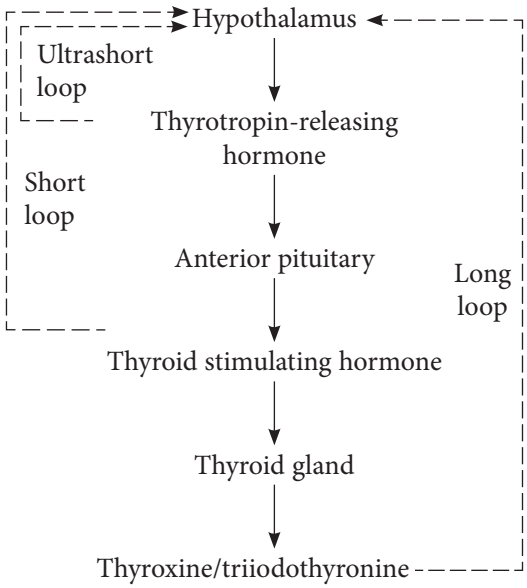
Negative Feedback Mechanism

Negative feedback mechanism is the commonest method of hormonal regulation. Increased levels of the hormone or its product inhibit the gland. This reduces the secretion of hormone from the gland.

The negative feedback mechanism operates by either of the two ways: (i) simple feedback

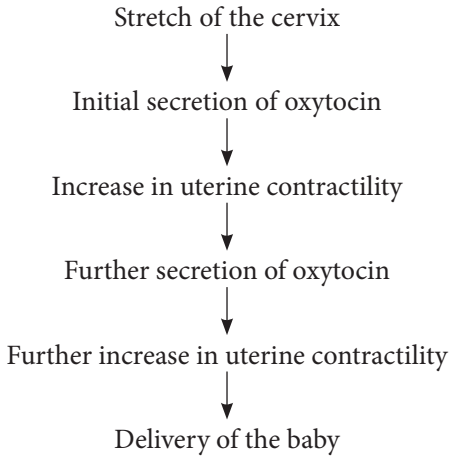
or (ii) complex feedback. In the simple feedback mechanism, an endocrine gland secretes a hormone. The hormone acts on the target organ and produces an effect. This in turn inhibits the endocrine gland. In the complex feedback mechanism, multiple endocrine glands and hormones are involved in regulating the production of a hormone.

Negative feedback becomes functional only when the target organ responds optimally to the hormone, e.g., hypothalamo-pituitary-thyroid axis



Positive Feedback Mechanism (Flowchart 10.1)

A hormone secreted from a gland acts on the same gland to enhance synthesis and release of the hormone. The positive feedback mechanism regulates optimal hormone secretion, e.g., mechanism of secretion of oxytocin during parturition.



Flowchart 10.1 Positive feedback mechanism. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

HORMONE RECEPTORS

Hormone receptors are modified proteins having specific binding sites for the respective hormone. The cells that have specific binding sites for that hormone are termed **target cell**. Receptors are present on the surface or inside the cells. In a cell, there are around 2,000 to 100,000 hormone receptors for a single hormone.

The locations of receptors are given in the following text.

Cell Membrane

Protein, peptide, and catecholamine hormones have specific membrane receptors.

Cytoplasm

Receptors for steroid hormones are usually found almost entirely in the cell cytoplasm.

Nucleus of the Cell

The receptors for the thyroid hormones are present in the nucleus.

Down-Regulation of Hormone Receptors
A decrease in the number of receptors due to an increase in the concentration of hormone is called **down-regulation** of receptors.

It is caused due to

- inactivation of receptors and
- decreased production of receptors.

Down-regulation of receptor causes a decrease in the response of target tissue to the hormone.

Up-Regulation of Hormone Receptors A decrease in the concentration of hormone triggers the formation of more receptors. This is called **up-regulation** of receptors. Up-regulation causes the target tissue to become more sensitive to the stimulating effects of the hormone. It is commonly seen in denervation hypersensitivity.

HORMONAL TRANSPORT

Hormones after secretion enter the bloodstream and circulate in the plasma. They are carried either in free form or bound to the proteins in the plasma. Steroid hormones are usually transported in the bound form. Proteins and amines are soluble in plasma and are transported in the free form.

MECHANISM OF ACTION

Hormone regulates functioning of its target tissues by activating the receptors.

Hormone binds to the receptor to form a hormone–receptor complex. This complex alters the structure and function of the receptor.

The altered receptor produces the desired response by

- change in the membrane permeability of the cell,
- G protein activation,
- activation of an intracellular enzyme, and
- activation of genes.

Change in Membrane Permeability of the Cell

Hormones such as epinephrine and norepinephrine secreted by the adrenal medulla act by this mechanism. They cause opening and closing of ion channels, thereby bringing about a change in the membrane permeability.

G Protein Activation

G proteins are a group of cell membrane proteins which are coupled with hormone receptors and regulate the activity of target cells. G proteins basically convert signals to biological activities.

G proteins are divided into two groups: (i) small G proteins and (ii) heterotrimeric G proteins.

Activation of an Intracellular Enzyme

Binding of hormone to its receptor activates an enzyme inside the cell membrane, e.g., activation of adenyl cyclase. This in turn catalyzes the formation of cyclic adenosine monophosphate (cAMP). It is called second messenger since it does not directly cause the effect.

Calcium ions, cAMP, cyclic guanosine monophosphate (cGMP), calmodulin, and products of membrane phospholipid breakdown are the various second messenger systems.

Cyclic AMP System

Cyclic AMP is the cyclic form of AMP. It is produced from ATP by the action of adenyl cyclase.

The binding of hormones with receptors causes coupling of the receptors to a G-protein-stimulating adenyl cyclase. The stimulation of adenyl cyclase converts ATP into cAMP inside the cell. Cyclic AMP activates cAMP-dependent protein kinase.

Once cAMP is formed, it activates a cascade of enzymes which ultimately leads to phosphorylation of specific proteins in the cell. These proteins bring about the action through hormones.

Some hormones acting through the cAMP second messenger system include ACTH, LH, and TSH.

Membrane Phospholipid Second Messenger System

Some hormones activate receptors that inactivate phospholipase C enzyme. This enzyme causes breakdown of some phospholipids in the cell membrane to inositol

triphosphate (IP_3) and diacylglycerol (DAG). IP_3 activates calcium and causes second messenger effects. DAG activates enzyme protein kinase C which phosphorylates proteins.

Calcium–Calmodulin Second Messenger System

This system operates in response to the entry of calcium ions into the cell. The entry of calcium is by the opening of calcium channels caused by a change in membrane potential or action of hormone. On entry into the cell, calcium binds to a protein called calmodulin. Calmodulin has four binding sites for calcium. Calmodulin changes its shape and initiates multiple effects inside the cell.

Activation of Genes

Some hormones bind to the protein receptors inside the cell. The hormone–receptor complex binds to the proteins of DNA in the nucleus. This initiates transcription of genes to form mRNA.

Hormones acting by this mechanism include steroid hormones and thyroid hormones.

HORMONAL ASSAY

Hormonal assay is the measurement of hormone concentration in the blood.

Since hormones are secreted in very minute quantities, it is difficult to measure them by conventional chemical methods. It is therefore measured by techniques called **radioimmunoassay** and **enzyme-linked immunosorbent assay (ELISA)**.

RADIOIMMUNOASSAY

Radioimmunoassay is based on competitive binding of hormone and radiolabeled hormone molecules to a specific antibody. By estimating the relative percentage of the radiolabeled hormone bound to the antibody, the natural hormone concentration in the given sample can be calculated.

ELISA

This technique is similar to radioimmunoassay since it is based on the antigen–antibody reaction. The antigen–antibody complex is stained with a suitable dye and the color intensity is measured by a spectrophotometer. ELISA is useful to estimate steroid and peptide hormones.

Hormonal Rhythm

Some of the endocrine glands exhibit a cyclic pattern of hormonal secretion (rhythm). These rhythms range from a few minutes to months. The rhythm having a 24-hour cycle is termed **circadian rhythm**. Cortisol and growth hormone have circadian rhythm. Pulsatile rhythms occur over half-an-hour to 2-hour period and appear as sudden bursts of secretion. Pulsatile rhythms with less than 24-hour periodicity are termed **ultradian rhythms**. These rhythms denote normal functioning of the glands and they are absent in disease conditions.

HYPOTHALAMUS

The hypothalamus secretes hypothalamic-releasing and -inhibiting factors which control the secretions of the pituitary gland. This control is by hormonal and neural mechanisms. The anterior pituitary is controlled by the hormonal mechanism and the posterior pituitary is controlled by the neural mechanism.

Hormones released by the hypothalamus are conducted through the hypothalamo-hypophyseal portal system (**Fig. 10.3**).

These are extensive capillary networks connecting the hypothalamus and the anterior pituitary.

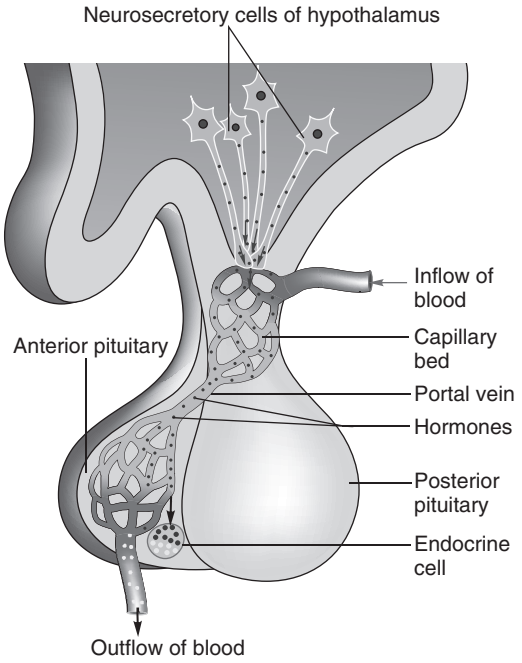


Figure 10.3 Hypothalamo-pituitary axis.

The hypothalamic hormones (releasing factors) are secreted by the specialized cells in it. The nerve cells terminate in the median eminence and tuber cinereum of the pituitary stalk. Hormones secreted from these nerve terminals are immediately absorbed into the hypothalamo-hypophyseal portal system and are carried to the sinuses of the anterior pituitary gland.

The anterior pituitary in turn secretes various hormones that act on other endocrine glands. These endocrine glands produce hormones which act on the target cells.

The hormones of the posterior pituitary are ADH and oxytocin. They are synthesized in the hypothalamus and stored and released from the posterior pituitary.

Important hypothalamic hormones are as follows:

- **GHRH (growth hormone–releasing hormone)**: It is a peptide hormone secreted from the arcuate nucleus of hypothalamus. It causes the release of growth hormone.
- **GHIH (growth hormone–inhibitory hormone, somatostatin)**: It is a peptide containing 14 amino acids. It is secreted from the anterior periventricular nucleus of hypothalamus. It inhibits the release of growth hormone, prolactin, and TSH.
- **TRH (thyrotropin-releasing hormone)**: It is a peptide hormone containing three amino acids. It is secreted from the paraventricular nucleus of hypothalamus. It causes release of the thyroid-stimulating hormone.
- **CRH (corticotropin-releasing hormone)**: It is a polypeptide hormone containing 41 amino acids. It is secreted from the paraventricular nucleus of hypothalamus. It influences the release of ACTH.
- **GnRH (gonadotropin-releasing hormone)**: It is a peptide containing 10 amino acids. It is secreted from the arcuate nucleus of hypothalamus. It regulates the release of two gonadotropic hormones, FSH and LH.
- **PIH (prolactin-inhibiting hormone)**: It is secreted from the arcuate nucleus of hypothalamus. It causes inhibition of prolactin secretion.

MECHANISM OF ACTION

Hypothalamic-releasing hormones act on the anterior pituitary by binding to specific membrane receptors on the cells. Most of the hormones act by stimulating cAMP.

PITUITARY GLAND

The pituitary gland is also called the **hypophysis cerebri**. It is a small gland measuring 1 cm in diameter and weighing about 0.5–1 grams. It is present at the base of the brain and lies in the sella turcica of the sphenoid bone. It is connected to the hypothalamus by its stalk (**Fig. 10.4**).

The pituitary gland is divided into two lobes:

1. Anterior lobe (adenohypophysis)
2. Posterior lobe (neurohypophysis)

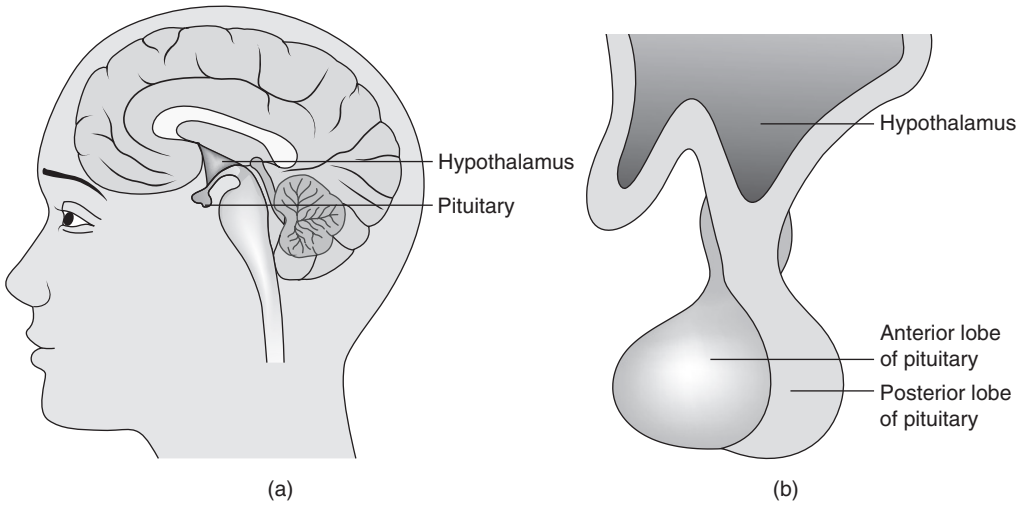


Figure 10.4 (a) Position of pituitary gland in brain. (b) Pituitary gland. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Pars intermedia is a small zone in between the anterior and the posterior lobes of the pituitary. It secretes melanocyte-stimulating hormone.

The anterior pituitary originates from **Rathke's pouch**, which is an invagination at the roof of the developing mouth (embryonic buccal cavity) in front of the pharyngeal epithelium. The cells of the anterior pituitary are therefore glandular in nature.

The posterior pituitary arises as an outgrowth of the hypothalamus. The posterior pituitary contains glial cells called **pituicytes**. The pituicytes are only supporting cells.

The hormones secreted by the anterior pituitary are as follows:

- **Growth hormone (GH)**: GH causes growth of the whole body by increasing protein synthesis and enhanced cell growth.
- **Thyroid-stimulating hormone (TSH)**: TSH controls the rate of secretion of T_3 and T_4 hormones by the thyroid gland.
- **Adrenocorticotropic hormone (ACTH)**: ACTH controls secretion of the adrenocortical hormones, which in turn control carbohydrate, protein, and fat metabolism.
- **Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)**: FSH and LH control the growth of ovaries and testes, thereby helping in the control of reproductive activity. The hormones of the posterior pituitary are secreted in the hypothalamus and stored in the posterior pituitary.
- **Prolactin**: Prolactin facilitates the development of the mammary glands and helps in milk production.

The hormones of the posterior pituitary are as follows:

- **Antidiuretic hormone (vasopressin)**: Antidiuretic hormone controls the amount of water in the body by regulating the urine output. It also constricts the blood vessels.
- **Oxytocin**: Oxytocin helps in expulsion of milk from breast. It also helps in delivery of the baby.

GROWTH HORMONE

The growth hormone is also called **somatotropin**. This is a small protein hormone containing 191 amino acids in a single chain. Its molecular weight is 22,000. It is secreted

by somatotrophs that constitute 40% of the anterior pituitary cells.

The half-life of growth hormone is 6–20 minutes.

Secretion of growth hormone shows diurnal rhythm. Peak secretion occurs in the early morning.

MECHANISM OF ACTION

The growth hormone binds to its receptor which is a polypeptide containing 620 amino acids. It is a tyrosine kinase–associated receptor, a member of the cytokine receptor superfamily. Binding of the hormone to its receptor activates a number of signaling pathways that initiate gene transcription and induce the formation of various intracellular enzymes.

Actions

The growth hormone is an anabolic hormone that promotes growth and also influences metabolic activity.

EFFECT ON GROWTH

The growth hormone causes growth of almost all tissues of the body.

- Promotes increase in the size of cells
- Increases the rate of mitosis, resulting in an increased number of cells
- Causes differentiation of cells in bone and muscle

EFFECT ON BONE AND CARTILAGE

The growth hormone stimulates bone growth.

- Increases the number of cells responsible for bone growth
- Increases deposition of protein by chondrocytic and osteogenic cells
- Causes growth of epiphyseal cartilage
- Delays fusion of epiphysis with the shaft

METABOLIC EFFECTS

Effect on Protein Metabolism

The growth hormone increases the rate of protein synthesis in all the cells by

- enhancing amino acid transport through the cell membrane,
- increasing nuclear transcription of DNA to form mRNA,
- enhancing RNA translation to promote protein synthesis by ribosomes, and
- decreasing the catabolism of protein and amino acids.

Effect on Carbohydrate Metabolism

- Decreases the use of glucose for energy; diminishes the uptake of glucose by the cells and increases blood glucose concentration
- Increases the secretion of insulin

Effect on Fat Metabolism

- Mobilizes fats from adipose tissue
- Increases free fatty acids in the blood
- Enhances use of fatty acids for energy
- Excess of growth hormone has a ketogenic effect

Effect on Electrolyte Metabolism

- Causes rise in plasma phosphorous and fall in blood urea, nitrogen, and amino acid levels
- Increases GI absorption of Ca^{++}
- Reduces Na^{+} and K^{+} excretion

Growth hormone is degraded in the liver and kidneys.

REGULATION OF GROWTH HORMONE

The normal plasma concentration of growth hormone in adults is between 1.6 and 3 ng/mL. It is about 6 ng/mL in children and adolescents.

Growth hormone secretion increases during starvation, excitement, exercise, trauma, hypoglycemia, and sleep.

Hormones such as testosterone and estrogens stimulate the secretion of growth hormone.

The secretion of growth hormone decreases with an increase in the blood glucose level, cortisol, and free fatty acid levels.

The secretion of growth hormone is controlled by two factors produced in the hypothalamus. They are as follows:

1. **Growth hormone–releasing hormone**: It is a member of the vasoactive intestinal peptide family. Its actions are mediated by cAMP. Dopamine stimulates the release of GRH.
2. **Growth hormone–inhibiting hormone**: It is also called somatostatin. It is secreted in many areas of the body. It inhibits GH and TSH release, mediating through the GI-associated receptors.

SOMATOMEDINS

Somatomedins are polypeptide growth factors secreted by the liver in response to stimulation by the growth hormone.

The effect of growth hormone on cartilage, protein metabolism, and general growth depends on its interaction with the somatomedins.

About four somatomedins have been isolated till now. The most important is somatomedin C. This is also called IGF-I (insulin-like growth factor I).

The pigmies of Africa and some congenital dwarfs are unable to synthesize IGF-I.

Insulin-like growth factors are multifunctional hormones that regulate cell growth, differentiation, and metabolism. They are proteins resembling insulin in structure and function. IGFs are produced in many tissues. They have autocrine and paracrine actions.

CLINICAL NOTES

Increased growth hormone secretion during childhood or adolescence results in gigantism.

Gigantism (Fig. 10.5)

Gigantism occurs due to an increased secretion of the growth hormone by the acidophilic tumor or excessive stimulation of the acidophilic cells before puberty (before fusion of epiphysis).

There is excessive growth of long bones and the individual can grow to a height of about 8 ft.

Overstimulation of β-cells of the islets of Langerhans by growth hormone results in its destruction. This leads to **pituitary diabetes**.

Treatment

Gigantism is treated by surgical removal of tumor or irradiation of the gland. If the condition is not treated early, the tumor grows and ultimately destroys the whole pituitary gland. This results in death of the individual in early age.

Acromegaly

Acromegaly is a condition in which the secretion of growth hormone is increased after puberty (after the fusion of epiphysis of long bones). Acromegaly means enlargement of the peripheral parts of the body. After puberty, the person cannot grow taller but the bones become thick and soft tissues continue to grow.

Clinical Features

- Excessive growth of mandible resulting in its protrusion (prognathism)
- Enlargement of the frontal bone and facial sinuses producing frontal bossing
- Enlargement of hands and feet
- Bowing of the spine due to excessive growth of vertebrae (kyphosis)
- Excessive soft-tissue growth associated with organomegaly
- Thickening of the skin
- Individual has gorilla appearance

Dwarfism

Dwarfism is due to reduced growth hormone production during childhood.

(*Contd*.)

Clinical Features

- There is stunted growth. However, all the physical parts of the body are proportional. A child aged 10 years may look like a child of 5 years.
- There is no mental retardation.
- They attain sexual maturity.

Treatment

Dwarfism can be treated by administration of human growth hormone.

Lorain Dwarf

This condition is characterized by the deficiency of somatomedin C. However, growth hormone secretion is normal. Lorain dwarfs are not responsive to growth hormone secreted by the body.

They have features of dwarfism but they do not respond to treatment with growth hormone.

Panhypopituitarism

The condition is due to a decreased secretion of all anterior pituitary hormones.

Panhypopituitary dwarfs do not attain puberty and do not develop sexual functions.

In adults, panhypopituitarism can occur due to destruction of the pituitary gland by tumors. The patient can develop thyroid, gonadal, and adrenocortical insufficiency.

Sheehan's Syndrome

Sheehan's syndrome occurs in women during childbirth.

Excessive blood loss during delivery results in circulatory shock. Reduced blood flow causes infarction of adenohypophysis and hence pituitary insufficiency.

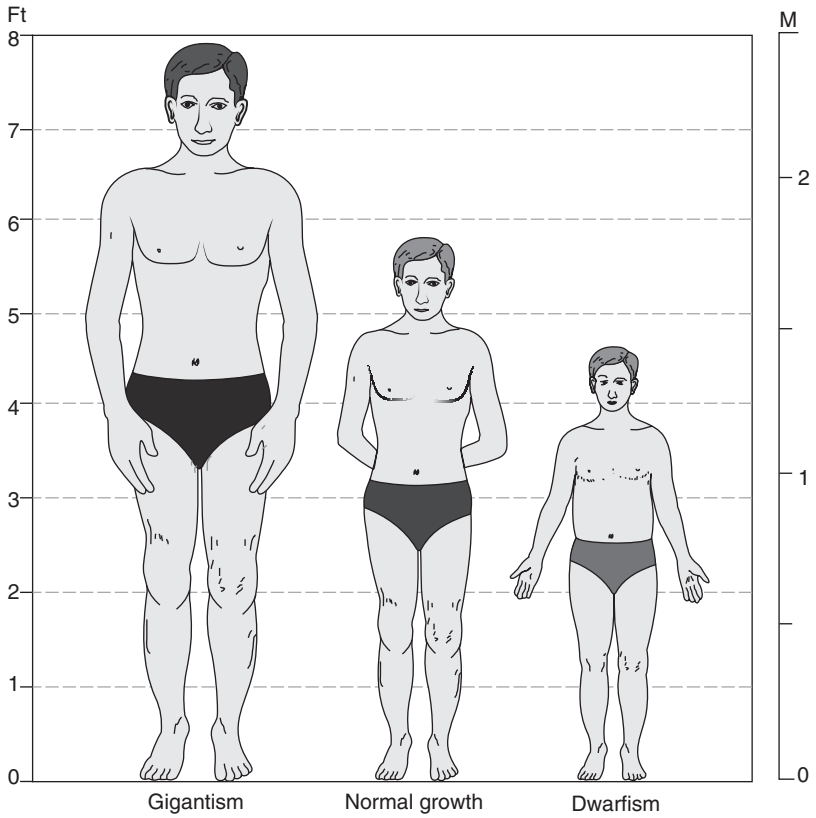


Figure 10.5 Gigantism and dwarfism compared with a normal-height individual. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

PROLACTIN

Prolactin is structurally similar to human growth hormone. It contains 199 amino acid residues and 3 disulfide bridges.

The half-life of prolactin is about 20 minutes.

Actions of Prolactin

Prolactin causes secretion of milk by the breast after it is adequately prepared by estrogen and progesterone.

It causes an increase in mRNA levels resulting in the formation of casein and lactalbumin.

It inhibits the effect of gonadotropins acting at the level of ovary.

High levels of prolactin prevent ovulation in nonlactating women.

In males, its action is not known but excess of prolactin secretion in males due to tumors results in impotence.

The normal plasma levels of prolactin are 8 ng/mL in women and 5 ng/mL in men.

Regulation of Prolactin Secretion

Prolactin secretion is increased by stress, exercise, and stimulation of the nipple. It is also increased during sleep.

The hypothalamus exerts an inhibitory control over prolactin secretion. Dopamine and its agonists inhibit prolactin secretion.

POSTERIOR PITUITARY

The posterior pituitary (**Fig. 10.6**) is an outgrowth of the floor of the III ventricle. It is mainly composed of glial cells called *pituicytes*. The pituicytes are only supporting cells.

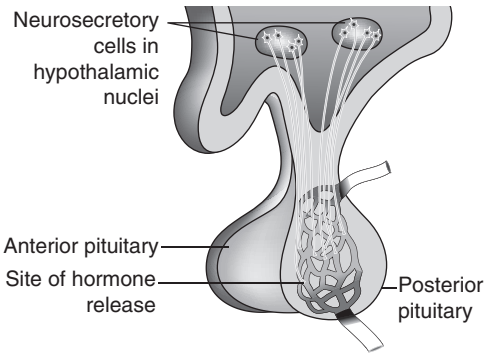


Figure 10.6 Posterior pituitary. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

The hormones of the posterior pituitary are synthesized in the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus. They are transported to the neurohypophysis by the axons of these cell bodies. The nerve endings of these cell bodies form bulbous knobs containing secretory granules. These secretory granules end on the surfaces of capillaries, thereby releasing secretions into circulation via the capillaries.

Two hormones of the posterior pituitary are

1. ADH (vasopressin) and
2. oxytocin.

ADH (VASOPRESSIN)

ADH is a hormone concerned with the regulation of body water. Since it also causes vasoconstriction, it is called **vasopressin**.

It is a polypeptide containing nine amino acids. ADH and oxytocin are chemically similar. However, phenylalanine and arginine of ADH are replaced by leucine and isoleucine in oxytocin.

ADH is formed mainly in the supraoptic nuclei of the hypothalamus. It is formed in the rough endoplasmic reticulum as prepropressophysin. Later, it is cleaved to form vasopressin and packed in the granules of the Golgi apparatus.

Actions

- Antidiuretic effect—ADH increases the permeability of the distal convoluted tubule (DCT) and the collecting ducts to water, promoting water reabsorption.

ADH causes insertion of protein water channels into the principal cells of the collecting ducts. These water channels are called **aquaporins**.

In the absence of ADH, DCT and collecting tubules become impermeable to water. This prevents reabsorption of water and therefore produces dilute urine (diabetes insipidus).

- In high doses, ADH causes vasoconstriction and increases blood pressure.
- It causes contraction of mesangial cells present in the juxtaglomerular apparatus (JGA) and reduces the glomerular filtration rate (GFR).
- It acts on the JGA cells and inhibits renin secretion.
- It causes secretion of CRH and ACTH during stress.
- In the brain, it acts as a neurotransmitter and is involved in memory and brain development.

Vasopressin Receptors

There are three kinds of vasopressin receptors: (i) V_{1A}, (ii) V_{1B}, and (iii) V_2. They are G protein–coupled receptors.

V_{1A} and V_{1B} increase the intracellular calcium concentration. V_2 receptors increase cAMP levels.

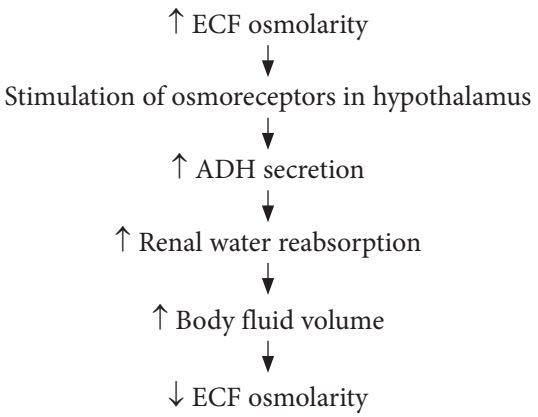
Metabolism

ADH is rapidly inactivated in the liver and kidneys. It has a biological half-life of 18 minutes.

Regulation

An increase in osmolarity of the blood causes increased ADH secretion.

In the hypothalamus, there are modified receptors called the osmoreceptors. When the extracellular fluid (ECF) becomes too much concentrated, fluid moves out of the osmoreceptors by osmosis. This causes a decrease in the size of the osmoreceptors. This initiates nerve signals in the hypothalamus for ADH secretion.



When ECF becomes too dilute, water moves into the cell by osmosis causing a decrease in the signals for ADH secretion.

Other factors influencing ADH secretion are as follows:

- Alcohol and epinephrine decrease ADH secretion and therefore cause diuresis.
- Stress, pain, and surgery increase ADH secretion.

CLINICAL NOTES

Diabetes Insipidus

Diabetes insipidus (insipid = tasteless) develops due to deficiency of ADH. It is caused by the disease of the supraoptic and paraventricular nuclei of the hypothalamus or the posterior pituitary gland.

The patient passes a large quantity of dilute urine with reduced specific gravity (polyuria). It is associated with increased fluid intake (polydipsia). Unlike diabetes mellitus, the blood sugar levels are normal in diabetes insipidus.

Treatment

Diabetes insipidus can be treated by administration of desmopressin, an analogue of ADH having a longer half-life through the mucous membrane of the nose.

Nephrogenic Diabetes Insipidus

In this type of diabetes insipidus, the kidneys are unable to respond to ADH. ADH production can be normal.

(*Contd.*)

Treatment

Nephrogenic diabetes insipidus is treated by administration of chlorpropamide as this drug increases the renal response to ADH.

SIADH (Syndrome of Inappropriate Hypersecretion of ADH)

SIADH is a condition in which patients tend to hypersecrete vasopressin.

It is seen in conditions of

- head injury;
- ectopic ADH producing tumors such as carcinoma of lungs, ovary, and urinary bladder;
- chronic pulmonary disease such as tuberculosis; and
- neurological conditions such as meningitis, encephalitis, and multiple sclerosis.

OXYTOCIN

Oxytocin is a polypeptide hormone containing nine amino acids. It is formed primarily in the paraventricular nucleus of the hypothalamus and stored in the posterior pituitary.

It is formed in the rough endoplasmic reticulum as preprooxyphysin. Later, it is cleaved to form oxytocin and packed in the granules of the Golgi apparatus.

Oxytocin circulates in the unbound form. It has a half-life of 3–5 minutes. Degradation occurs primarily in the liver and kidneys.

Oxytocin primarily acts on the breasts and uterus. These tissues have G protein–coupled receptors. Oxytocin triggers increase in intracellular calcium levels.

Actions

Oxytocin mainly acts on

- uterus and
- breasts

On Uterus

Oxytocin causes contraction of the smooth muscles of the estrogen-primed pregnant uterus and relaxation of the cervix.

In a nonpregnant uterus, oxytocin facilitates sperm transport. Oxytocin levels increase during sexual act. This causes uterine contractions, helping the sperm movement toward the fallopian tubes where the fertilization occurs. The passage of sperms through the female genital tract is mainly brought about by motility of the sperms and is assisted by uterine contractions.

Parturition (Delivery of the Baby)

The descent of the head of the baby at term causes stretch of the cervix. The impulses are carried to the hypothalamus. This results in the release of oxytocin from the posterior pituitary. Oxytocin acts on the gravid uterus to produce contraction of the uterus and relaxation of the cervix to deliver the baby. During labor, the number of oxytocin receptors gets increased.

This is an example of the positive feedback mechanism.

On Breast

Oxytocin plays an important role in lactation. It causes contraction of myoepithelial cells lining the ducts of the mammary gland, helping ejection of milk.

Milk Ejection Reflex (Milk Letdown Reflex; Fig. 10.7)

This is a neuroendocrine reflex. Touch receptors are present in the breast around the nipple. Suckling the nipple stimulates these touch receptors. Impulses from the nipple reach the supraoptic and paraventricular nuclei through the somatic touch pathway. This causes secretion of oxytocin from the posterior pituitary. Oxytocin is then carried by blood to the breasts where it causes contraction of myoepithelial cells resulting in the ejection of milk.

Other Actions

Oxytocin retains sodium and also has an antidiuretic effect.

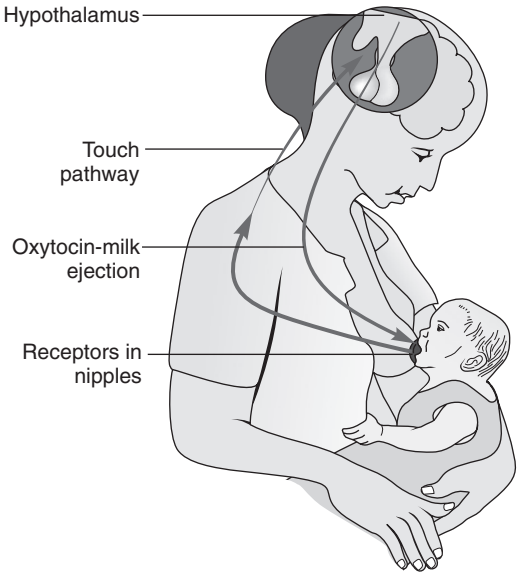


Figure 10.7 Milk ejection reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Males produce considerable amounts of oxytocin. It increases at the time of ejaculation and increases the contraction of smooth muscles of vas deferens. This causes forward movement of the sperm toward the urethra.

CLINICAL NOTES

Synthetic oxytocin is used during delayed labor to induce uterine contractions.

It is used to prevent postpartum (after delivery) hemorrhage by facilitating contraction of the uterus.

THYROID GLAND

The thyroid gland (**Fig. 10.8**) is a butterfly-shaped gland located in front of the larynx on either side and anterior to the trachea. It has two lobes connected by an isthmus.

It weighs 15–20 grams in a normal adult. This gland develops as an evagination of the floor of pharynx.

The thyroid gland has rich blood supply. The rate of blood flow is 4–6 mL/g/min.

HISTOLOGY (Fig. 10.9)

The thyroid gland is made up of multiple follicles (acini). Each follicle contains a single layer of cuboidal epithelium. It is filled with a clear, viscous material called **colloid**. The colloid contains thyroglobulin. When the gland

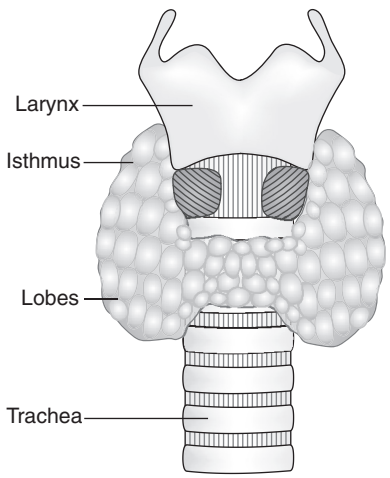


Figure 10.8 Thyroid gland. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

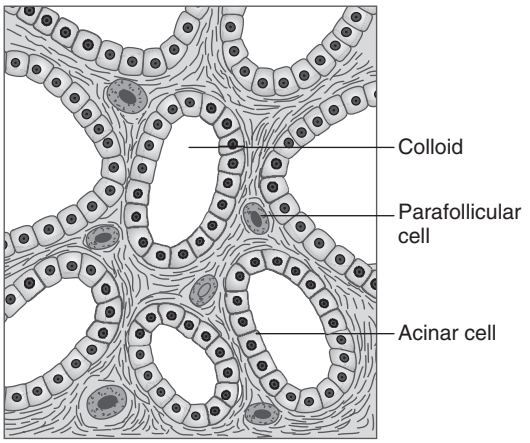


Figure 10.9 Histology of thyroid glands. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

is inactive, the cells are flat and the follicles are large in size and contain large amounts of colloid. The follicles become smaller in size, the colloid is less, and the cells become cuboidal when the gland is active. The parafollicular cells are present in between the thyroid acini. The parafollicular cells secrete **calcitonin**.

THYROID HORMONES

Thyroid hormones are iodothyronines, i.e., compounds formed by coupling two iodinated tyrosine molecules with an ether linkage.

Thyroid hormones include the following:

- **Thyroxine (T_4)**: It constitutes about 90% of the thyroid hormone.
- **Triiodothyronine (T_3)**: It constitutes about 9% of the thyroid hormone.
- **Reverse T_3 (RT_3)**: It constitutes only 1% of the thyroid hormone.
- **Calcitonin**: It is secreted from the parafollicular cells.

SYNTHESIS

Iodine is the most essential raw material for the synthesis of thyroid hormones (**Fig. 10.10**). In adults, the minimum daily intake of iodine required to synthesize normal amounts of thyroid hormones is 150 µg. Average diet contains around 500 µg of iodine. Food rich in iodine include fish, milk, and vegetables. Iodine is added to salt to prevent its deficiency. Ingested iodine is converted to iodide and absorbed by the gastrointestinal tract (GIT). Iodide enters the blood and it is taken up by the thyroid gland by a process known as **iodide trapping**.

Iodide Trapping

Iodine is a trace element. Therefore, it is selectively trapped by the thyroid gland.

The basal membrane of the acinar cell has the ability to pump iodide by secondary active transport along with Na^+. By this method, the concentration of iodide in the

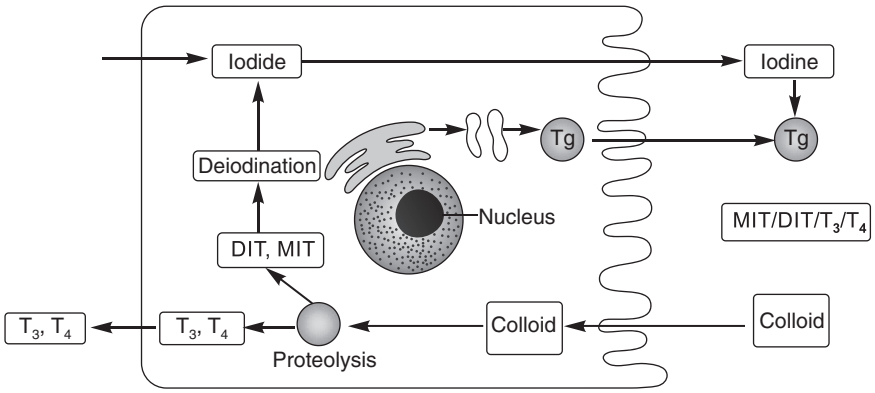


Figure 10.10 Thyroid hormone synthesis.

follicular cell is increased 30 times compared to its concentration in blood. Iodide trapping is stimulated by TSH. An antithyroid agent such as thiocyanate inhibits iodide trapping.

Oxidation of Iodide

Once the iodide is within the follicular cell, it is oxidized to iodine (I^o) an active intermediate. This reaction is catalyzed by thyroid peroxidase. It is a membrane-bound enzyme found in the apical portion of the follicular cell.

Organification of Iodine

The elemental iodine combines with the third position of tyrosine residues to form monoiodotyrosine (MIT).

Tyrosine is a part of the thyroglobulin molecule in the colloid. The addition of another iodine to this MIT at the fifth position of tyrosine results in the formation of diiodotyrosine (DIT).

Two DITs then condense to form T_4 (thyroxine). One MIT and one DIT condense to form T_3 (triiodothyronine). This is called **coupling reaction**. Thyroid peroxidase enzyme is involved in the coupling reaction:

I_2 + Tyrosine = MIT

MIT + MIT = DIT

MIT + DIT = T_3

DIT + DIT = T_4.

Storage

The thyroid hormones remain attached to the thyroglobulin molecule and are stored in the colloid. The thyroid hormone stored in the gland is sufficient to meet the requirement of the body for 2–3 months.

Release

When the hormone is required, the apical portion of the thyroid cells ingests a small portion of the colloid by endocytosis. The peptide bonds between iodinated tyrosine residue and thyroglobulin are broken down by proteases. Later, T_4, T_3, DIT, and MIT are released.

T_4 and T_3 are released into circulation. The remaining MIT and DIT are deiodinated. They are recycled for the synthesis of thyroid hormones.

Thyroglobulin

Thyroglobulin is a glycoprotein molecule secreted into the follicles of the thyroid gland. It is produced by the endoplasmic reticulum and the Golgi apparatus of thyroid acinar cells.

Thyroglobulin has two subunits with a molecular weight of 6,60,000. It contains 123 tyrosine residues, of which only 4–8 are incorporated into the thyroid hormones. The thyroid hormones are formed within the thyroglobulin molecule and are bound to it until secretion.

During secretion, the colloid is ingested by the thyroid cells. The peptide bonds are hydrolyzed; free T_4 and T_3 are released into the circulation.

The normal serum thyroglobulin level is 6 ng/dL. It is increased in hyperthyroidism.

SECRETION AND TRANSPORT

The human thyroid gland secretes about 80 μg of T_4, 4 μg of T_3, and 2 μg of RT_3 each day.

The normal plasma T_4 is 8 μg/dL and T_3 is 0.15 μg/dL.

On entering the blood, 99% of T_4 and T_3 combine with proteins. They combine with thyroid-binding globulin, thyroid-binding prealbumin, and albumin.

Only 1% of the total hormone is in the free form and it is physiologically active.

Thyroid hormones are released slowly because they are bound to proteins.

Inside the tissue, T_3 and T_4 bind with intracellular proteins. They are used slowly over a period of days or weeks.

The pituitary secretion of TSH depends on free thyroid hormone levels in the blood.

METABOLISM

T_3 and T_4 are deiodinated in the liver and kidney. One-third of circulating T_4 is converted to T_3. Forty-five percent is converted to reverse T_3.

MECHANISM OF ACTION

Thyroid hormones act at various sites including the nucleus, mitochondria, and plasma membrane.

Thyroid hormones enter the cells and bind to thyroid receptors in the nuclei. The hormone receptor complex then binds to DNA to form mRNA. Formation of mRNA and rRNA leads to the formation of a variety of proteins.

Proteins serve as structural and functional components of the cell and modify cell function.

FUNCTIONS

Physiological Actions

1. **Calorigenic action**: Thyroid hormones increase the metabolism of almost all the tissues of the body, except the brain, testes, uterus, lymph nodes, spleen, and anterior pituitary.

   Thyroid hormones produced in excess can increase the basal metabolic rate (BMR) by 60–100%.
2. **General growth and development**: Thyroid hormones are essential for general growth. They stimulate the secretion of the growth hormone. They also increase the synthesis of structural proteins.
3. **Metabolic actions**: Thyroid hormones have effects on various aspects of metabolism of carbohydrates, proteins, and lipids.
   (a) *Carbohydrate metabolism:* Thyroid hormones increase the blood glucose level by
      - increasing the absorption of glucose from the gut,
      - increasing gluconeogenesis (formation of glucose from lipid and protein),
      - increasing insulin degradation,
      - increasing glycogenolysis (breakdown of glycogen), and
      - causing rapid uptake of glucose by the cells.

   (b) *Lipid metabolism:* Lipid metabolism is enhanced by the thyroid hormones.
      - They increase the synthesis, mobilization, and degradation of lipids.
      - They decrease the serum cholesterol level.

   (c) *Protein metabolism:* The thyroid hormones are essential for protein synthesis and growth. But excess thyroid hormones lead to protein catabolism (breakdown).
4. **Body weight**: Excess of thyroid hormone decreases the body weight due to increased catabolism. Deficiency of thyroid hormone causes overweight.
5. **Effect on CVS**: Thyroid hormones alter cardiac output, heart rate, blood pressure, and diameter of blood vessels.
   - They increase the heart rate by directly increasing the excitability of the heart and indirectly by adrenergic stimulation.
   - Force of contraction is increased due to an increase in calcium uptake and adenyl cyclase activity of the myocardial cells.
   - Systolic BP increases due to increased strength and rate of cardiac contractions. Diastolic BP decreases due to peripheral vasodilation, but the mean arterial pressure remains unchanged.
   - Vasodilation occurs mainly due to accumulation of metabolites. It also causes dilation of the arterioles by direct action, decreasing systemic vascular resistance.
6. **Action on CNS**: Thyroid hormones are found in various areas of the brain. They are vital for the development of the nervous system in infants. In adults, they are required for the normal functioning of

the nervous system. The astrocytes convert T_4 to T_3.

- Thyroid hormones have a marked effect on brain development, especially cerebral cortex, basal ganglia, and cochlea.
- They help in synaptic development and myelination.
- They maintain the normal reaction time of stretch reflex.

Excess of thyroxine causes overstimulation of CNS resulting in restlessness and decreased reaction time of reflexes.

7. **Sleep**: Thyroid hormones maintain a normal sleep pattern. Sleep is disturbed in hyperthyroidism due to excessive stimulation of CNS. In hyperthyroidism, the subject is exhausted but unable to sleep. In hypothyroidism, the duration of sleep will be increased.
8. **Action on muscles**

   Thyroid hormones cause the growth and maintenance of skeletal muscles. They prevent muscle weakness.
9. **Effect on skin**: They maintain normal skin texture. Hypothyroidism causes rough and dry skin.
10. **Reproductive system**

    They maintain the normal ovarian cycle in females and spermatogenesis in males. They also maintain libido (sexual drive).

Other Functions

- Thyroid hormones stimulate erythropoiesis.
- They increase milk production.
- They exert permissive action on other hormones.
- They help in differentiation and maturation of cartilage.

REGULATION

The specific feedback mechanisms operate through the anterior pituitary and the hypothalamus.

The thyroid function is mainly regulated by the pituitary TSH.

Feedback Regulation

An increased level of thyroid hormones in the body decreases the secretion of TSH from the anterior pituitary. It also has an effect on the hypothalamus to decrease the secretion of TRH. This is an example of the negative feedback mechanism.

THYROID-STIMULATING HORMONE

The thyroid-stimulating hormone (TSH) is also known as thyrotropin. It is a glycoprotein containing 211 amino acid residues, secreted by the anterior pituitary.

Its molecular weight is 28,000. The biological half-life of TSH is about 60 minutes. The secretion of TSH is pulsatile reaching a peak at midnight. The normal TSH secretion is 110 μg/day. The average plasma level is about 2 μ units/mL.

Mechanism of Action

TSH binds to thyroid receptors and stimulates adenyl cyclase. This activates the second messenger cAMP system which initiates a cascade of reactions to produce biochemical effects.

Actions

- Increases the size and number of acinar cells
- Increases the activity of the iodide pump, which enhances the rate of iodide trapping
- Increases iodination of tyrosine and coupling to form thyroid hormones
- Increases proteolysis of thyroglobulin, releasing thyroid hormones into the blood

Regulation

Secretion of TSH by the anterior pituitary is controlled by thyrotropin-releasing hormone secreted by the hypothalamus. Increased levels of thyroid hormones inhibit the anterior pituitary causing decreased secretion of TSH.

Exposure to cold increases the rate of TSH secretion. Excitement and anxiety cause decreased secretion of TSH.

THYROID HORMONE-RELEASING HORMONE

This is secreted by the nerve endings in the median eminence of the hypothalamus and transported to the anterior pituitary by the hypothalamo-hypophyseal portal system.

TRH is a tripeptide amide. It acts on the anterior pituitary to increase the output of TSH.

TRH binds to the receptors present in the pituitary gland and activates the phospholipase second messenger system.

Cold increases TRH and TSH secretion. Stress and anxiety decrease it.

THYROID FUNCTION TESTS

T_3, T_4, and TSH Levels

Hormone levels are measured by radioimmunoassay. Serum T_3 and T_4 increase and serum TSH levels are reduced in hyperthyroidism.

The serum T_3 and T_4 decrease and serum TSH levels are increased in hypothyroidism.

Radioactive Iodine Uptake

Radiolabeled iodine is administered to the subject and the uptake of iodine by the thyroid gland is evaluated.

This test helps to differentiate between normal, toxic nodule, thyroid cyst, and malignant nodule. The normal radioiodine uptake is 20–40%. In hyperthyroidism, there is increased uptake, and in hypothyroidism, there is decreased uptake of iodine.

Serum Protein-Bound Iodine (PBI)

The normal serum protein-bound iodine (PBI) is 4–8 µg/dL. Less than 3.5 µg/dL indicates hypothyroidism.

Sleeping Pulse Rate

It is also called resting heart rate. It is the pulse/heart rate measured at rest. The normal sleeping pulse rate is between 50 and 60 beats/min. The sleeping pulse rate is high in thyrotoxicosis.

Basal Metabolic Rate

The basal metabolic rate (BMR) is the measure of the number of calories burnt by the body to perform life-sustaining functions. It is high in hyperthyroidism (+100%) and low in hypothyroidism (–40%).

Other Investigations

- Serum cholesterol (increased in hypothyroidism)
- Serum creatinine (increased in hyperthyroidism)
- Radiography of the neck
- Thyroid gland biopsy
- Indirect laryngoscopy

CLINICAL NOTES

Diseases of the Thyroid Gland

The abnormalities of thyroid secretion can be due to either excess of thyroid hormones or deficiency of thyroid hormones.

Hypothyroidism

Deficiency of thyroid hormone results in hypothyroidism.

There are two types of hypothyroidism:

- **Cretinism**: Hypothyroidism in children
- **Myxedema**: Hypothyroidism in adults

Cretinism

Cretinism is caused due to hypothyroidism during fetal life, infancy, and childhood.

Clinical Features

- The child will have stunted growth and mental retardation with idiotic appearance. The CNS manifestations are due to defective myelination

(*Contd.*)

- Potbelly with umbilical hernia
- Enlarged and protruded tongue
- Failure of sexual development
- Low BMR; reduced appetite
- Dry, rough, and thick skin

Causes are maternal iodine deficiency, fetal thyroid dysgenesis, and inborn errors of thyroid metabolism.

Treatment Supplementation with hormone thyroxine.

Myxedema (Fig. 10.11)

This condition develops due to hypothyroidism in adults. It is called myxedema due to the deposition of myxomatous tissue resulting in generalized edema.

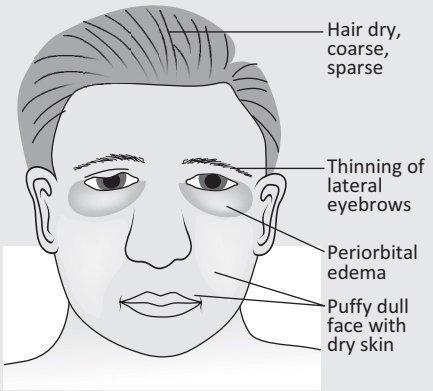


Figure 10.11 Myxedema. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Clinical Features

- Low BMR leading to increased body weight and puffiness of face
- Decreased heat production in the body causes intolerance to cold and decreased sweating
- Cardiovascular features include bradycardia, hypertension, and pericardial effusion
- Dermatological features include thin and sparse hair, and rough and dry skin
- Neuromuscular features include mental sluggishness, delayed reaction time, excessive sleep, and hoarse voice
- Nonpitting edema of feet due to deposition of mucopolysaccharides, protein hyaluronic acid, and chondroitin sulfate (myxomatous tissue)
- GIT features such as constipation and reduced appetite
- Menstrual irregularity and infertility
- Low serum T3–T4 levels; increased TSH level

Treatment Myxedema can be treated with lifelong supplementation with hormone thyroxine.

Goiter

Goiter is a condition of enlargement of the thyroid gland due to iodine deficiency.

- **Endemic goiter**: This disease occurs in people living in areas with deficiency of iodine in the food, e.g., Himalayan regions.

  Lack of iodine decreases the production of T_3 and T_4. This increases secretion of TSH. TSH increases the secretion of thyroglobulin. Accumulation of thyroglobulin causes enlargement of the gland.
- **Nonendemic goiter**: This disease occurs in persons with normal iodine uptake, but deficiency of enzymes involved in the synthesis of T_3 and T_4. Cabbage and turnip have goitrogenic effect.

Hyperthyroidism (Fig. 10.12)

Excess secretion of T_3 and T_4 leads to hyperthyroidism.

The common form of hyperthyroidism is **Grave's disease**. It is an autoimmune disease wherein the antibodies are produced by B-lymphocytes. These antibodies activate thyroid receptors resulting in hyperthyroidism.

Exophthalmos

Exophthalmos is the protrusion of eyeballs caused due to inflammation and edema of the retro-orbital structures.

Clinical Features

- Exophthalmos (protrusion of the eyeball)
- Nervousness and fine tremors
- Increased cardiac output, systolic blood pressure, and increased resting pulse rate
- Intolerance to heat associated with excessive sweating
- Increased BMR
- Hyperglycemia and decreased cholesterol
- Weight loss, polyphagia, and diarrhea

Treatment

- Surgical removal of the thyroid gland
- Use of antithyroid drugs

(*Contd.*)

- Radioactive iodine therapy for destruction of the gland

Thyroiditis

Thyroiditis is an inflammation of the thyroid gland which causes progressive destruction and fibrosis of the gland.

Hashimoto's Thyroiditis

Hashimoto's thyroiditis is an autoimmune disease caused due to the production of antibodies against thyroglobulin which ultimately destroys the gland.

Differences between hypothyroidism and hyperthyroidism are listed in Table 10.1.

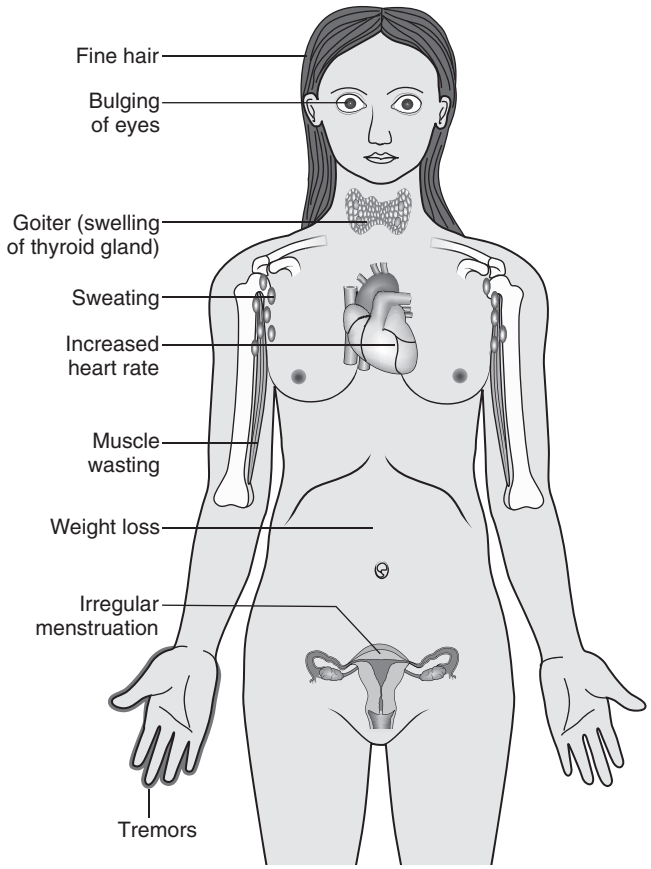


Figure 10.12 Features of hyperthyroidism. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Table 10.1 Differences Between Hyperthyroidism and Hypothyroidism

Features	Hyperthyroid	Hypothyroid
BMR	High	Low
T3 and T4 levels	Increased	Decreased
TSH levels	Decreased	Increased
Sleep	Decreased	Increased
Temperature	Intolerance to heat	Intolerance to cold
Heart rate	Increased	Decreased

(*Contd.*)

Table 10.1 (*Contd.*)

Features	Hyperthyroid	Hypothyroid
Serum cholesterol	Decreased	Increased
Weight	Loss	Gain
Appetite	Decreased	Increased
CNS	Restless, irritable	Lethargic, decreased alertness
Skin	Moist, increased sweating	Dry, decreased sweating

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

CALCIUM METABOLISM (Fig. 10.13)

Ionic calcium is important for the physiological functions of the body. It is necessary for nerve conduction, excitability of the cell, muscle contraction, blood coagulation, and synaptic transmission.

The normal serum calcium level is 9–11 mg/100 mL of blood.

SOURCE

Calcium is present in food and water. It is found in green leafy vegetables, milk, and dairy products.

DAILY INTAKE

One thousand milligrams of calcium is consumed per day. About 300 mg is absorbed in the upper part of the small intestine. About 125 mg is secreted in the digestive juices. The net absorption is 175 mg/day.

DISTRIBUTION OF CALCIUM

Calcium is the most abundant mineral present in the body. A healthy adult contains 1100 grams of calcium. Ninety-nine percent of this is present in the bones. One percent is in cells and extracellular fluid.

Of the remaining 1% calcium present outside the bones, 10–15 grams is present in the intracellular pool and only 1–1.5 grams is present in the extracellular pool. Inside the cell, majority of the calcium is stored in the mitochondria and endoplasmic reticulum and a small amount is present in the free form. The calcium of ECF is mainly present in the plasma. Ten percent of the plasma calcium is present in the form of nonionized compounds, such as calcium bicarbonate, and 40% of it is bound to albumin. The remaining 50% is present in the ionized form, and this is the biologically active form of calcium.

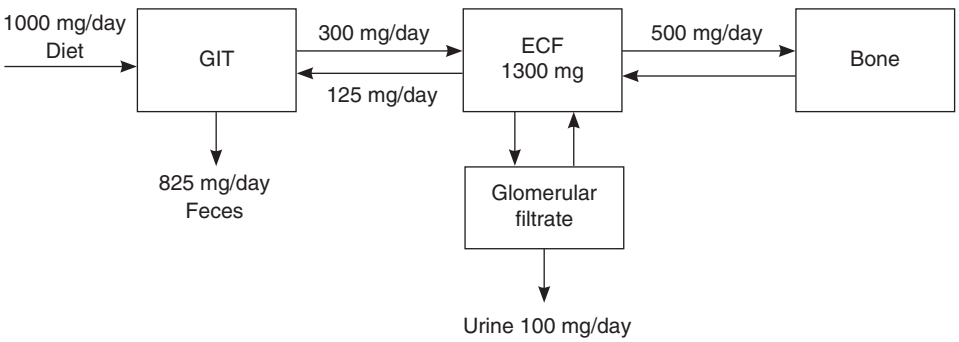


Figure 10.13 Distribution and exchange of calcium in the body.

ABSORPTION

Calcium is absorbed by both diffusion and carrier-mediated transport (with calbindin). Calcitriol increases the GI absorption of calcium.

High levels of phosphate and fat decrease calcium absorption; corticosteroids also inhibit calcium absorption.

Normal serum calcium levels are maintained by parathormone, calcitriol, and calcitonin. Regulation is by the action of hormones on the GI tract, kidneys, and bones.

REGULATION OF CALCIUM ION CONCENTRATION

Exchangeable calcium salts in the bone are calcium phosphate compounds. They are loosely bound in the bone and are in reversible equilibrium with calcium and phosphate ions in ECF.

An increased calcium and phosphate level in ECF causes immediate formation of calcium phosphate.

A decrease in the concentration of calcium and phosphate causes immediate absorption of calcium phosphate.

A sudden increase in the calcium ion concentration leads to a decreased rate of parathormone secretion. There is an increase in calcitonin secretion leading to deposition of calcium in bones.

FUNCTIONS OF CALCIUM

- **Formation of bone and teeth**: Calcium is required for mineralization of bones and teeth.
- **Action potentials**: Calcium is required for genesis and maintenance of action potential in cardiac and smooth muscles. It is also involved in the genesis of pacemaker potential.
- **Helps in coagulation of blood**: Calcium is a coagulation factor highly essential for clotting.
- **Regulates neuromuscular excitability**: Calcium increases the permeability of sodium and influences the generation of action potential. Low levels of calcium cause spontaneous generation of action potentials leading to tetany.
- **Needed for the contraction of muscle**: Release of calcium from the sarcoplasmic reticulum and subsequent binding of calcium with troponin C are crucial steps in the contraction of the muscle.
- **Facilitates the secretion of neurotransmitters and hormones**: Calcium acts as an important factor mediating secretions, thereby releasing neurotransmitters and hormones.
- **Second messenger action**: Calcium acts as a second messenger in various intracellular signaling pathways of hormonal action.

PHOSPHATE METABOLISM

Phosphate is a major intracellular ion. Intracellular levels are much greater than extracellular levels.

The total amount of phosphate in the body is 500–800 grams. It is mainly present in the skeleton (85–90%). Fourteen percent is present in the ICF and less than 1% of it is present in the ECF.

About 85% of plasma phosphate is in free form. Serum phosphate levels vary widely during the day. Phosphate enters the serum from the GIT, bone, and soft tissue. It leaves the serum by renal excretion and entry into bone and soft tissues.

The plasma phosphate level is 3–5 mg/dL.

FUNCTIONS

- Phosphate is found in ATP, NADP, ADP, and glucose-6-phosphate.

- cAMP and inositol triphosphate act as second messengers of the cell.
- Phosphate is necessary for the formation of phosphoproteins which mediate intracellular activities.
- It is a major component of bones and teeth.
- It takes part in intracellular buffer mechanisms.

REGULATION

Plasma phosphate is mainly controlled by parathormone.

Parathormone reduces tubular reabsorption of phosphate.

CLINICAL NOTES

Hypophosphatemia

Phosphate deficiency leads to muscle weakness and cardiac and respiratory dysfunction. A severe decrease in phosphate levels decreases nerve conduction and defective bone mineralization. In addition, it leads to hemolytic anemia due to reduced red cell ATP.

PARATHYROID GLANDS

There are four parathyroid glands (**Fig. 10.14**)—two in the superior pole of the thyroid and two in the inferior pole.

Each parathyroid gland measures 3 × 6 × 2 mm.

The total weight is 140 mg.

There are two types of cells in the parathyroid gland:

1. Chief cells
2. Oxyphil cells

Chief cells contain the Golgi apparatus, endoplasmic reticulum, and secretory granules. They secrete parathormone.

Oxyphil cells contain a large number of mitochondria. The function of the oxyphil cell is not known.

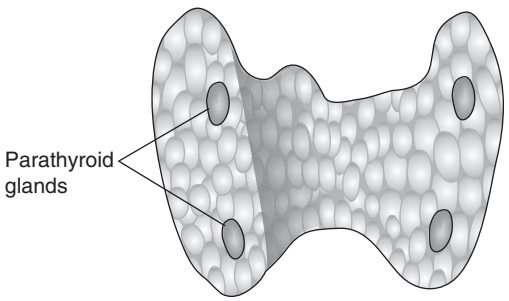


Figure 10.14 Back view of parathyroid glands. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

PARATHORMONE

Parathormone (PTH) is a polypeptide hormone with a molecular weight of 9,500, containing 84 amino acid residues.

The normal plasma value is 10–55 pg/mL. The plasma half-life is 10 minutes.

Actions

Parathormone mainly acts on the bones, kidneys, and intestine. It indirectly acts on the nervous system, muscles, and other endocrine glands.

Bones

Parathormone increases resorption of bone and mobilization of calcium from the bone.

It increases the activity of osteoclasts causing osteoclastic bone dissolution.

Kidneys

Parathormone increases the reabsorption of calcium in the DCT.

It increases phosphate excretion in the urine by decreasing phosphate reabsorption in the proximal tubules.

It increases reabsorption of Mg^{++} and H^{+} ions. It decreases reabsorption of Na^{+}, K^{+}, and amino acids.

Intestine

Parathormone increases the synthesis of vitamin D. Calcium is absorbed from the GIT under the influence of vitamin D (1-25-dihydroxy cholecalciferol).

It enhances phosphate absorption from the intestine.

Parathormone therefore increases the serum calcium level by

- increasing calcium mobilization from bones,
- increasing reabsorption in the kidney, and
- increasing reabsorption from the intestine.

Synthesis

Parathormone is synthesized as a preprohormone on the ribosomes. Later, it is cleaved to form prohormone and then to hormone containing 84 amino acids by the endoplasmic reticulum and Golgi apparatus. It is then packed in secretory granules in the cell cytoplasm.

Mechanism of Action

Three different receptor types have been identified. PTH activates the enzyme adenyl cyclase. This increases intracellular cAMP in the osteocytes, osteoclasts, and other target cells. Cyclic AMP is responsible for actions of the parathormone.

Regulation of Secretion

Parathormone secretion is regulated through negative feedback mechanism by the action of ionized calcium on the parathyroid glands.

When plasma calcium is high, parathormone secretion is inhibited. Calcium is deposited in the bones. When plasma calcium becomes low, calcium is mobilized from the bones.

Decreased serum Mg^{++} also stimulates parathormone secretion.

CLINICAL NOTES

Hypoparathyroidism

The deficiency of parathormone occurs due to accidental removal of the parathyroid glands during thyroid surgery. Decreased PTH reduces plasma Ca^{++} and increases plasma phosphate. Hypocalcemia leads to **tetany**.

A decreased serum calcium level in tetany increases neuromuscular excitability. This leads to spasm of laryngeal and intestinal muscles. Involvement of the laryngeal muscles causes laryngeal stridor, airway obstruction, convulsions, and death.

Low serum calcium level results in flexion at the wrist joint, adduction of thumbs, extension of fingers, and spasm of feet (pedal spasm). It is termed **carpopedal spasm**.

In pseudohypoparathyroidism, secretion of PTH is normal, but there is a defect in receptors. Hence, the response to PTH is decreased.

Tests for Latent Tetany

- **Chvostek's sign**: Tapping facial nerve causes contraction of facial muscles.
- **Trousseau's sign**: Occlusion of blood supply to the upper limb causes flexion at wrist and thumb, and extension of fingers.

Hyperparathyroidism

This condition is due to tumor or hyperplasia of the parathyroid gland.

This leads to hypercalcemia, hypophosphatemia, demineralization of bones, hypercalciuria, and formation of renal stones.

It diminishes neuronal excitability, and causes muscle weakness and constipation.

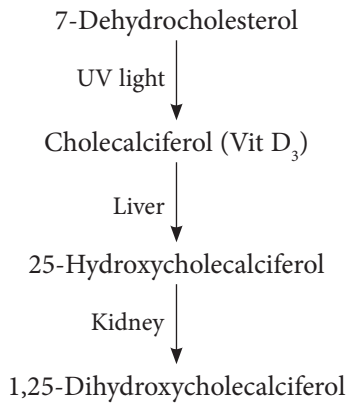
Secondary Hyperparathyroidism

Secondary hyperparathyroidism occurs in conditions of chronic renal disease and rickets. The serum calcium level is chronically low. Low calcium stimulates the parathyroid glands causing compensatory hypertrophy of the parathyroid and secondary hyperparathyroidism.

CALCITRIOL (1,25-DIHYDROXY-CHOLECALCIFEROL)

Calcitriol is an active form of vitamin D (D_3). It is formed by the action of UV radiation on 7-dehydrocholesterol present in the skin. Vitamin D_2 is available in the diet.

Synthesis



Functions

On GIT

Calcitriol stimulates the absorption of calcium from intestines by increasing the production of carrier protein for calcium.

It increases the intestinal absorption of phosphates as well as magnesium.

On Kidneys

Calcitriol increases the absorption of calcium from the DCT by increasing the number of calcium pumps. It also increases phosphate reabsorption from the kidney.

On Bones

Calcitriol influences mineralization of bone. It increases the synthetic activity of osteoblasts. It is necessary for normal calcification. In large quantities, it causes the absorption of bone.

Calcitriol has a role in muscle function. It stimulates transport of calcium into skeletal and cardiac muscles. The serum calcitriol level increases in pregnancy.

Transport

Calcitriol is sparingly soluble in blood. Ninety-nine percent of calcitriol is transported in a bound form with transcalciferin. The plasma half-life of calcitriol is 5–24 hours.

Mechanism of Action

Calcitriol acts through receptors in cytoplasm. The hormone–receptor complex causes synthesis of calcium-binding protein in the mucosa of the gastrointestinal tract.

Calbindin is a calcium-binding protein. It facilitates the transport of calcium, magnesium, and phosphate. Synthesis of calbindin is regulated by calcitriol.

Regulation

Reduced levels of calcium or phosphate lead to an increase in the formation of vitamin D_3 from vitamin D. Increased levels of calcium or phosphate lead to the formation of inactive forms of vitamin D_2 and vitamin D.

CLINICAL NOTES

Deficiency of vitamin D leads to **rickets** in children and **osteomalacia** in adults.

Rickets

Rickets manifests with defective bone formation leading to frontal bossing, knock-knee, and rickety rosary (thickening and prominence of the costochondral junction).

It can be corrected by exposure to sunlight and supplementation of vitamin D.

Osteomalacia

In this condition, the bones become soft due to defective mineralization.

Hypervitaminosis D

It occurs due to excessive intake of vitamin D. This is characterized by nausea and vomiting.

Osteoporosis

It occurs in old age and in postmenopausal females. The condition is due to loss of bone matrix. The bone loses calcium, becomes porous, and gets fractured easily.

CALCITONIN

Calcitonin is secreted by type C cells or parafollicular cells of the thyroid gland.

It is a polypeptide with 32 amino acids.

The molecular weight of calcitonin is about 3400.

Functions

- Promotes calcium deposition in the bones
- Inhibits resorption of bone by the osteoclasts
- Decreases serum calcium levels

Mechanism of Action

Calcitonin acts by stimulation of adenyl cyclase and increase in the levels of cAMP.

Regulation

High serum calcium levels stimulate calcitonin secretion.

CLINICAL NOTES

Calcitonin is used in the treatment of Paget's disease and senile osteoporosis.

Paget's Disease

Paget's disease is a disease characterized by increased osteoclastic activity. It causes localized areas of bone resorption followed by formation of patches of new bone. These bones are susceptible to develop deformities and fractures. Bone deformities lead to compression of nerves. Paget's disease is treated by daily injections of calcitonin.

ENDOCRINE PANCREAS

Pancreas has exocrine and endocrine functions. Endocrine function is performed by **pancreatic islets (islets of Langerhans)**. The islets of Langerhans are microscopic nests of cells mainly concentrated in the tail portion of the pancreas.

There are 1–2 million islets in humans.

These islets contain four types of cells:

1. **Alpha cells**: They constitute about 20–25% of the islet cells. They secrete glucagon.
2. **Beta cells**: They constitute about 60–70% of the islet cells. They secrete insulin.
3. **Delta cells**: They constitute about 10% of the islet cells. They secrete somatostatin.
4. **F cells**: They constitute 5% of the islet cells. They secrete pancreatic polypeptide.

Beta cells make up the large central mass of islets of Langerhans. They are surrounded by alpha, delta, and F cells.

INSULIN

Insulin was isolated in the year 1922 by Banting and Best.

It is a polypeptide hormone with 51 amino acids having two chains. Chain A has 21 amino acids and chain B has 30 amino acids.

The molecular weight is 5808.

Secretion

Insulin is secreted by the rough endoplasmic reticulum of β (beta) cells as preproinsulin with 110 amino acids. It is cleaved to form proinsulin with 86 amino acids. The proinsulin formed is transported to Golgi apparatus, and disulfide bridges are formed. The proinsulin molecule is folded and the two chains of insulin are connected by C peptide. This is cleaved to insulin, packed into membrane-bound granules, and later expelled by exocytosis.

Preproinsulin
↓
Proinsulin
↓
Insulin

Insulin circulates in blood in an unbound form. The plasma half-life is 5 minutes.

Plasma Level

The plasma level of insulin is 20 μ units/mL during fasting. It is 150 μ units/mL after the consumption of food.

Mechanism of Action

Insulin binds to the insulin receptors which are mainly present in the liver, skeletal muscle, and adipose tissue.

The insulin receptors are large membrane proteins with two α and two β subunits. They are bound to each other by disulfide bridges. The insulin receptors are located on chromosome 19.

- Binding of insulin to α subunits brings about conformational change in β subunits.
- Conformational change in β subunits activates tyrosine kinase activity producing autophosphorylation of β subunits.
- This leads to phosphorylation of intracellular enzymes including a group of enzymes called insulin receptor substrates (IRS).
- IRS causes a variety of changes such as activation or deactivation of target enzymes, translocation of GLUTs, and induction or suppression of genes.

In this way, insulin produces required effects on carbohydrate, fat, and protein metabolism.

Degradation

Insulin is cleared from circulation in 10–15 minutes. It is destroyed by insulin protease in the liver and kidney.

Actions

- **Rapid**: Increases transport of glucose, amino acids, and K^+ into insulin-sensitive cells
- **Intermediate**: Stimulates protein synthesis; inhibits protein degradation
- **Delayed**: Increases the formation of mRNA for lipogenic action

Functions

Insulin has a wide range of activities that are broadly divided into two groups:

1. metabolic functions and
2. effect on growth.

Metabolic Functions

Carbohydrate Metabolism The chief function of insulin is reduction of plasma glucose levels. It brings about this effect by the following mechanisms:

- Helps in cellular uptake of glucose
- Increases peripheral utilization of glucose
- Prevents glycogenolysis and neoglucogenesis
- Improves glycogen synthesis

Insulin increases the activity of glucokinase enzyme. This enhances the utilization of glucose by catalyzing its phosphorylation. Increased utilization of glucose decreases its intracellular concentration. This leads to the entry of glucose by facilitated diffusion.

Glucose enters the cells by facilitated diffusion with the help of glucose transporters. In the intestine and kidneys, it occurs by secondary transport with Na^+. In muscle and adipose tissue, insulin facilitates glucose entry into the cells by increasing the number of glucose transporters in the cell membrane.

Glucose Transporters

They are a family of closely related proteins having amino and carboxyl terminals inside the cell. They are different from sodium-dependent glucose transporters (SGLT-1 and SGLT-2). Seven glucose transporters (GLUT) have been identified (GLUT 1–7).

GLUTs are responsible for facilitated diffusion across the cell membranes.

GLUT 4 acts in the muscle and adipose tissue. GLUT 1 and 3 are involved in basal absorption of glucose in the brain, kidneys, placenta, and other organs. GLUT 2 acts as the β-cell glucose sensor in the pancreas. GLUT 5 causes fructose transport at the jejunum and sperm. GLUT 7 acts in the liver and acts as glucose 6 transporter. The function of GLUT 6 is not yet known.

Protein Metabolism Insulin facilitates the synthesis of proteins in the muscle and liver by the following mechanisms:

- Facilitates the transport of amino acids into cells

- Increases mRNA translation
- Increases protein synthesis in the ribosomes by inducing gene transcription for various proteins
- Prevents protein breakdown by decreasing lysosomal activity

  Hence, it is an anabolic hormone.

Lipid Metabolism Insulin increases storage of fat and decreases mobilization of fatty acids.

- Prevents lipolysis by inhibiting hormone-sensitive lipase
- Decreases free fatty acid in the blood, thereby decreasing the formation of ketoacids
- Promotes the synthesis and storage of fats

Ion Transport

Insulin increases K^+ and Mg^{2+} transport into the cells. It also increases reabsorption of Na^+, K^+, and HPO_4^- from the kidneys.

Growth and Development

Insulin potentiates the action of growth hormone to promote growth.

Insulin and growth hormone act synergistically to promote growth.

Food Intake Insulin decreases the food intake. However, chronic excess of insulin increases body weight and adipose tissue mass.

Regulation

Factors Enhancing Insulin secretion

Increased levels of glucose in the blood stimulate insulin secretion. Plasma insulin concentration rises linearly with plasma glucose (**Fig. 10.15**).

This response occurs in two phases: (i) rapid phase wherein plasma insulin rises within 1–2 minutes and decreases by 2–3 minutes and (ii) slow phase where it peaks by 1 hour and remains elevated for 3–4 hours.

Amino acids such as arginine, lysine, and alanine stimulate insulin secretion. These are formed during protein digestion.

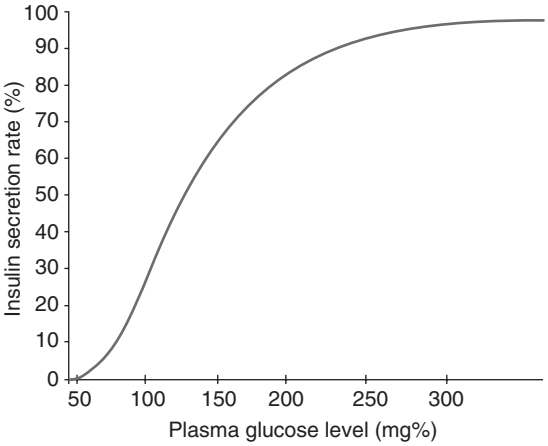


Figure 10.15 Relationship between plasma glucose level and insulin secretion. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

GI hormones such as gastrin, secretin, cholecystokinin (CCK), gastric inhibitory polypeptide (GIP), and glucagon enhance insulin secretion.

Parasympathetic stimulation substantially increases insulin secretion.

Factors Reducing Insulin Secretion

Increased secretion of somatostatin and sympathetic stimulation decreases insulin secretion.

Catecholamines acting through α receptors inhibit insulin secretion. This is seen during exercise, and the advantage is the prevention of hypoglycemia during exercise.

Control of Insulin Secretion

The serum insulin levels rise within 10 minutes after the ingestion of food. It reaches the peak in 30–45 minutes.

Insulin is released in two phases following stimulation:

1. Early phase due to the release of preformed insulin
2. Late phase due to the release of newly formed insulin

Insulin increases the uptake, storage, and utilization of glucose in almost all the tissues of the body. In a resting state, the muscle, adipose tissue, and liver utilize glucose under the influence of insulin. However during muscular activity, glucose enters the muscle without the influence of insulin.

Brain, RBC, kidney, and mucosa of the small intestine are not dependent on insulin for the uptake and utilization of glucose.

CLINICAL NOTES

Diabetes Mellitus

Diabetes mellitus is a condition caused due to the deficiency of insulin or decreased sensitivity of tissues to insulin. There is impaired carbohydrate, fat, and protein metabolism.

Types

- **Type 1**: This is also called insulin dependent diabetes mellitus (IDDM). It is caused by the lack of insulin secretion.
- **Type 2**: This is also called noninsulin dependent diabetes mellitus (NIDDM). It is caused by decreased sensitivity of tissues to insulin.

Symptoms

- Polyuria (increased urination)
- Polydipsia (increased fluid intake)
- Polyphagia (increased food intake)
- Weight loss

Polyuria

Increased blood glucose levels cause increased excretion of glucose in urine. This causes excessive excretion of water due to the osmotic effect of glucose (osmotic diuresis).

Polydipsia

Increased excretion of urine leads to decreased body water. This causes sensation of thirst, resulting in increased desire for water intake.

Polyphagia

There is reduced entry of glucose into glucostatic cells in the satiety center due to lack of insulin. This keeps the feeding center stimulated, thus enhancing the desire to eat. There is no sense of satisfaction in spite of excessive consumption of food.

Weight loss

In spite of increased intake of food, insulin deficiency leads to decreased entry and utilization of glucose by the cells. Glucose is lost in urine. Therefore, insulin deficiency causes weight loss and growth retardation.

Treatment

- **IDDM**: Administration of insulin
- **NIDDM**: Diet and exercise (lifestyle modification); oral antidiabetic drugs; supplementation of insulin

Gestational Diabetes

Gestational diabetes is a condition in which a woman who is not having diabetes before pregnancy develops high blood sugar during pregnancy. It affects 3–9% of all pregnancies. It is especially common during the last trimester of pregnancy.

Blood sugar levels come back to normal after delivery of the baby in 90% of the women. However, they are at an increased risk of developing type II diabetes later in life. The onset of diabetes may be earlier compared to that in the general population.

Glucose Tolerance Test

The glucose tolerance test (GTT) is a screening test for diabetes mellitus.

The individual is maintained on a balanced diet for 3 days. He is advised to fast overnight. The patient is given 75 grams of glucose orally and blood glucose levels are measured at periodic intervals.

If the fasting glucose level is less than 115 mg/dL, 2-hour level is <140 mg/dL, and none of the values exceed 200 mg/dL, then the oral GTT is considered normal.

Insulinoma

Insulinoma is tumor (adenoma) of the islet of Langerhans secreting insulin in excess of normal levels causing hypoglycemia. Chronic hypoglycemia leads to uncoordinated movement and slurring of speech.

GLUCAGON

Glucagon is a hormone secreted by the alpha cells of islets of Langerhans. It is a polypeptide composed of 29 amino acids. Its molecular weight is 3485.

Glucagon is a hyperglycemic hormone. The physiological functions of glucagon are opposite to those of insulin.

Actions

- Causes glycogenolysis and therefore increases the blood glucose level. Glycogenolysis occurs in the liver by activation of glycogen phosphorylase, and this increases the blood glucose within minutes.
- Gluconeogenesis: Glucagon increases the rate of amino acid uptake by the liver cells and converts them into glucose.
- Glucagon inhibits glycogen synthase, and therefore the conversion of glucose to glycogen is inhibited.
- It activates lipase which breaks down lipids into fatty acids.
- It stimulates the secretion of growth hormone, insulin, and pancreatic somatostatin.

In high concentrations, glucagon

- increases myocardial contractility,
- increases bile secretion,
- inhibits gastric acid secretion, and
- increases calorigenesis.

Glucagon has a half-life of 5–10 minutes in circulation. It is degraded mainly in the liver.

Mechanism of Action

Glucagon activates adenyl cyclase in the liver cells. This causes formation of cyclic AMP. cAMP activates protein kinase, which in turn activates phosphorylase. Phosphorylase promotes the conversion of glycogen to glucose.

Regulation

Glucagon secretion is mainly controlled by the blood glucose concentration.

- Decrease in the blood glucose causes an increase in glucagon secretion.
- Increase in the blood glucose causes a decrease in glucagon secretion.
- Increased amino acids, severe exercise, CCK, gastrin, and stress cause increased glucagon secretion.
- Increased glucose, free fatty acids, insulin, somatostatin, and GABA (gamma amino butyric acid) inhibit glucagon secretion.

SOMATOSTATIN

Somatostatin is a polypeptide which functions both as a neurotransmitter and as a hormone. It is of two types: (i) somatostatin 14 and (ii) somatostatin 28.

Secretion

Somatostatin is secreted by the delta cells of the islets of Langerhans. It is also secreted in the hypothalamus and GIT. It has a plasma half-life of 3 minutes.

Actions

Somatostatin acts as a major inhibitory hormone in the gastrointestinal system. It also acts as a neurotransmitter in various parts of the brain. It has an effect on the sensory input, locomotor activity, and cognitive function.

- In the hypothalamus, it acts as a growth hormone–inhibiting hormone.
- In the pancreas, it inhibits the secretion of insulin and glucagon.
- It reduces GI motility and is an important inhibitory GI hormone.
- It inhibits secretion of gastrin and secretin.
- It inhibits gastric emptying.
- It inhibits HCl secretion and intestinal secretion.
- It inhibits the exocrine secretion of pancreas.
- It inhibits absorption of glucose and triglycerides from the mucosal epithelium of the small intestine.

Increased blood glucose, amino acids, and fatty acids enhance somatostatin secretion.

PANCREATIC POLYPEPTIDE

Pancreatic polypeptide contains 36 amino acid residues. It is produced by F cells of the pancreas. It is closely related to polypeptide YY found in the intestine and neuropeptide Y found in the brain.

The secretion of pancreatic polypeptide is decreased by somatostatin and intravenous administration of glucose.

Pancreatic polypeptide slows the absorption of food but its exact function is still not known.

ADRENAL GLAND

ANATOMY

There are two adrenal glands, each weighing about 4 grams.

They lie at the superior pole of both the kidneys (**Fig. 10.16**).

The adrenal gland is highly vascular, receiving 6–7 mL of blood/g/min. It consists of two parts (**Fig. 10.17**):

1. **Adrenal cortex**: It occupies the outer 80% of the gland. It secretes glucocorticoids, mineralocorticoids, and sex steroids.
2. **Adrenal medulla**: It occupies the inner 20% of the gland. It secretes epinephrine, norepinephrine, and dopamine.

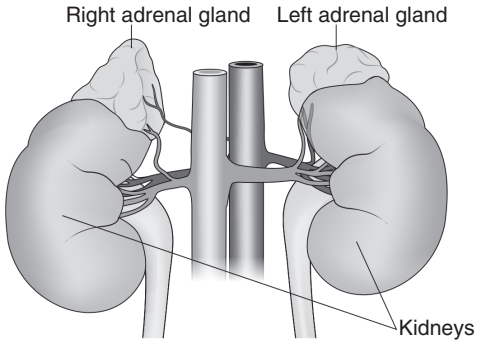


Figure 10.16 Adrenal glands. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

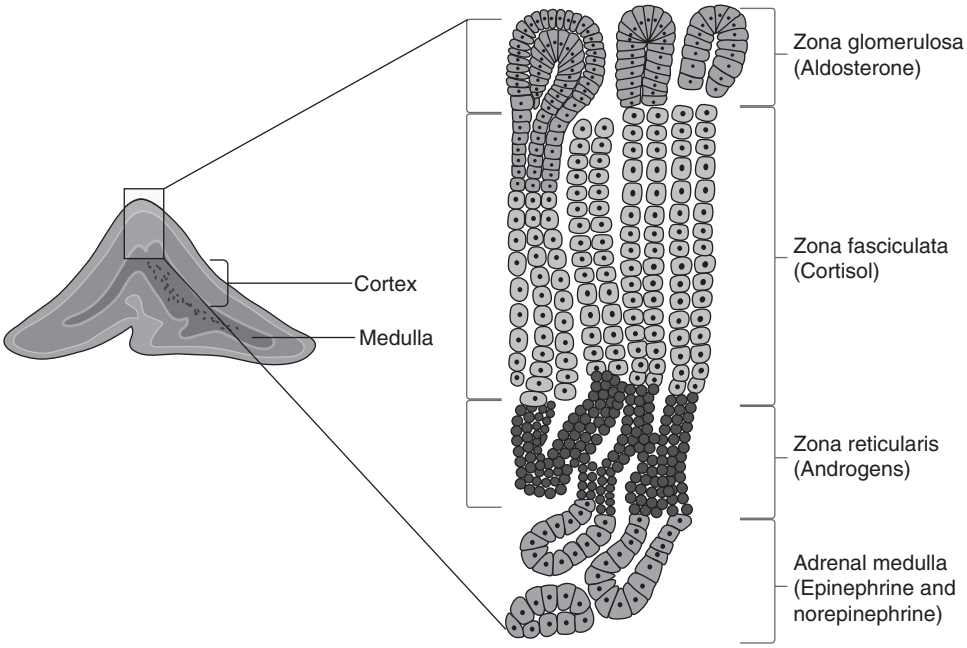


Figure 10.17 Structure and histology of the adrenal gland.

ADRENAL CORTEX

The adrenal cortex is a part of the adrenal gland, essential for the survival of an individual. It has a very rich blood supply resulting in direct entry of its hormones into systemic circulation. It develops from the mesodermal tissue.

Morphology

The adrenal cortex is composed of three relatively distinct layers:

1. **Zona glomerulosa** (outer 15–20%) secretes aldosterone.
2. **Zona fasciculata** (middle 50–55%) secretes cortisol, corticosterone, and small amounts of androgens.
3. **Zona reticularis** (inner 7–10%) secretes androgens and cortisol (glucocorticoids).

Chemistry

The adrenocortical hormones are steroid hormones derived from cholesterol.

The important adrenocortical hormones are as follows:

- **Mineralocorticoids**: Aldosterone and deoxycorticosterone
- **Glucocorticoids**: Cortisol and corticosterone
- **Sex steroids**: Dehydroepiandrosterone and androstenedione

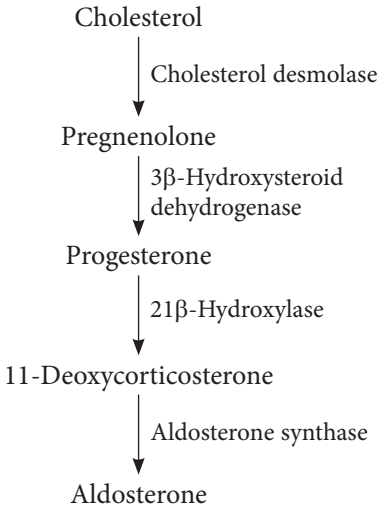
MINERALOCORTICOIDS

Aldosterone is the chief mineralocorticoid. It is secreted from the zona glomerulosa of the adrenal cortex.

Synthesis

Cholesterol is the chief substance required for the synthesis of steroid hormones. It is available from two sources: (i) from blood and (ii) synthesized de novo (afresh or from the beginning).

The steps in the synthesis of aldosterone are as follows:



Mechanism of Action

Aldosterone combines with receptors in the cytoplasm to form the hormone–receptor complex. This complex induces the portion of DNA to form mRNA. mRNA helps in the protein synthesis.

It takes around 30 minutes for mRNA to be formed and 45 minutes for an increase in sodium transport.

Transport and Secretion

Aldosterone combines loosely with the plasma proteins, and about 50% of it is in free form.

It stays in circulation for around 30 minutes.

It is mainly degraded in the liver.

Actions

- Increase Na^+ and Cl^- absorption and decrease the absorption of K^+ and PO_4^{3-} in the renal tubules
- Help in the regulation of body fluid volume by reabsorption of water
- Help in the regulation of acid–base balance
- Increase the reabsorption of Na^+ and Cl^- and secretion of K^+ ions in the sweat glands, salivary glands, and intestine

Regulation of Aldosterone Secretion

Increased K^+ ion concentration in ECF increases aldosterone secretion.

Increased activity of the renin–angiotensin system increases its secretion.

Increased Na^+ ion concentration in ECF marginally decreases its secretion.

ACTH stimulates aldosterone secretion.

Aldosterone Escape

Whenever aldosterone is increased, Na^+ ions are retained in the body. This causes osmotic absorption of water. Therefore, the ECF volume increases.

An increase in ECF leads to an increase in arterial pressure, causing excretion of salt and water by pressure diuresis. This secondary increase in water and salt excretion by kidneys is called **aldosterone escape**.

CLINICAL NOTES

Aldosterone Excess

Aldosterone excess is termed *hyperaldosteronism*. It is of two types:

1. **Primary hyperaldosteronism (Conn's syndrome)**: This occurs due to adenoma of zona glomerulosa. In this condition, there is K^+ depletion, Na^+ retention, weakness, hypertension, tetany, polyuria, and alkalosis.
2. **Secondary hyperaldosteronism**: This occurs due to the use of diuretics, nephrosis, cirrhosis of liver, and congestive cardiac failure. In this condition, circulating renin and angiotensin II levels are elevated.

Aldosterone Deficiency

Deficiency of aldosterone causes a rise in K^+ ion concentration leading to cardiac toxicity. This results in reduced force of cardiac contraction and development of arrhythmias leading to heart failure.

Absence of aldosterone secretion causes death within 2 weeks. Without aldosterone K^+ concentration in ECF increases. Na^+ and Cl^- concentration decreases. ECF volume and blood volume are greatly reduced. The person develops diminished cardiac output proceeding to a shock-like state followed by death.

GLUCOCORTICOIDS

Glucocorticoids are steroids secreted chiefly from the zona fasciculata of the adrenal cortex. They are called so since they increase blood glucose concentration.

They also have anti-inflammatory and immunosuppressive effects. The principal glucocorticoid is cortisol.

Cortisol

Cortisol is a C_{21} steroid produced mainly from the zona fasciculata.

It combines with cortisol-binding globulin.

Ninety-six percent of the cortisol is transported in a bound form. Only 4% is transported in the free form.

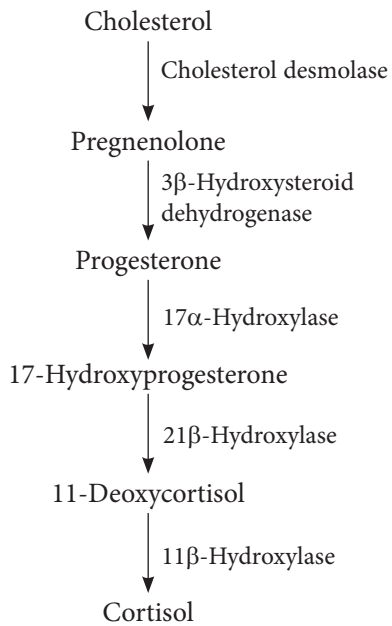
It stays in circulation for 1–2 hours.

It is degraded in the liver and conjugated to form glucuronides. It is excreted in the urine.

Synthesis

Cholesterol is the chief substance required for the synthesis of glucocorticoids.

The steps in the synthesis of cholesterol are as follows:



Mechanism of Action

These hormones enter the cell and combine with receptors in the cytoplasm. The hormone–receptor complex induces DNA to form mRNA.

The mRNA causes protein synthesis. These proteins are responsible for actions of glucocorticoids.

Actions

1. **On carbohydrate metabolism**: Cortisol increases blood glucose levels by various mechanisms. They include
   - stimulation of gluconeogenesis by the liver by activating glucose-6-phosphatase which converts glucose-6-phosphate to glucose,
   - increased secretion of glycogenolytic hormones such as glucagon and epinephrine,
   - decreased rate of glucose utilization by the cells.

   Adrenal diabetes: The blood glucose increases as a result of increased gluconeogenesis and reduced glucose utilization by the cells. This condition is termed **adrenal diabetes**. This is moderately insulin sensitive.
2. **On protein metabolism**: Cortisol reduces protein stores in all cells except the liver cells. This causes decreased protein synthesis. It facilitates conversion of protein to glycogen.

   Cortisol enhances amino acid uptake by the liver cells. Hence, the liver proteins and plasma proteins are increased.
3. **On fat metabolism**: Cortisol mobilizes fatty acid from adipose tissue, increasing free fatty acids in plasma.

   It stimulates the absorption of lipids from the intestine.

   It causes redistribution of fats in the body.
4. **Anti-inflammatory effect**: Cortisol inhibits all aspects of inflammation. It reduces leukocyte margination, chemotaxis, and phagocytosis of bacteria. Aggregation of monocytes is also inhibited.

   Cortisol inhibits the synthesis and release of chemical mediators of inflammation such as prostaglandins and arachidonic acid.

   It blocks the early stages of inflammation.

   If inflammation has already begun, it causes resolution of inflammation.
5. **Wound healing**: It prevents the development of fibroblasts and delays wound healing.
6. **In stress**: Stress increases ACTH secretion followed by an increase in secretion of cortisol.
7. **Effect on CVS**: Cortisol increases the performance of myocardial cells by increasing Na^+–K^+ ATPase activity. It also increases the responsiveness of arterioles to catecholamines and angiotensin II.
8. **Effect on CNS**: Cortisol increases NREM sleep and decreases REM sleep. It also influences the mood and behavior of an individual.
9. **Effect on muscle and bone**: Cortisol increases skeletal and cardiac muscle performance. This is due to increase in acetyl choline synthesis. It inhibits bone formation, thereby decreasing bone mass and mineralization.

Other Functions

- Cortisol has antiallergic effect.
- It decreases the number of eosinophils and lymphocytes in the blood.
- It stimulates gastric secretion.
- It suppresses immune response by reducing circulating T-lymphocytes.

Permissive Action

Glucocorticoids are required for normal physiological actions of other hormones. This is termed permissive action. The permissive actions of cortisol include

- Calorigenic effects of glucagon
- Lipolytic and bronchodilator effects of catecholamines
- Synthesis of the surfactant in fetal lungs
- Development of bacterial flora in the intestine

Regulation

Cortisol secretion is controlled by ACTH.

ACTH is secreted in irregular bursts throughout the day. Plasma cortisol rises and falls in response to these bursts. The plasma cortisol is high in the mornings (20 µg/dL) and very low (5 µg/dL) in the evenings.

Cortisol-Binding Globulin

This is also called *transcortin*. It is an α-globulin that binds to cortisol. It is synthesized in the liver. CBG levels rise during pregnancy. It decreases in cirrhosis, nephrosis, and multiple myeloma.

CLINICAL NOTES

Addison's Disease

This is caused due to failure of the adrenal cortex to produce adrenocortical hormones. It is mostly caused by primary atrophy of the adrenal cortex due to autoimmune disease, tuberculosis, and invasion by cancer.

Signs and Symptoms

- Loss of Na^+ and Cl^- ions through urine, leading to decreased ECF volume, hyponatremia, hyperkalemia, and mild acidosis
- Muscle weakness and depressed metabolic functions of the body
- Low blood glucose levels in spite of excess glucose in the body
- Highly susceptible to stress and infections
- Pigmentation of skin and mucus membrane

Addisonian Crisis

A person with Addison's disease succumbs to stress. This condition is called Addisonian crisis. The patient needs extra amounts of glucocorticoids.

If the patient is not treated properly, he/she dies of shock.

Cushing's Syndrome (Fig. 10.18)

Cushing's syndrome is a condition produced due to the excess secretion of glucocorticoids.

Causes

- Adrenocortical tumors
- Anterior pituitary tumors
- Ectopic ACTH-producing tumor such as bronchogenic carcinoma
- Prolonged glucocorticoid therapy

Cushing's syndrome caused due to tumors of the anterior pituitary is called **Cushing's disease**.

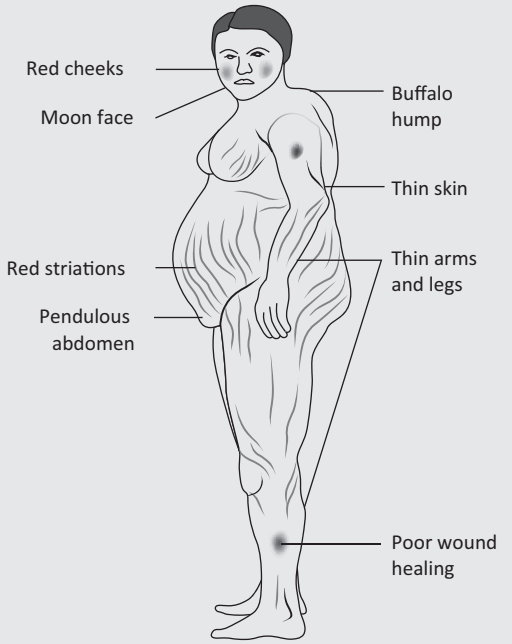


Figure 10.18 Cushing's syndrome. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Signs and Symptoms

- Fat collects in the abdominal wall, face, and upper back, producing buffalo hump and moon face.
- Skin and subcutaneous tissues are thin.
- Muscles are poorly developed.
- Wounds heal poorly; minor injuries cause bruises and ecchymoses.
- There is insulin-resistant diabetes mellitus due to gluconeogenesis.
- There is salt and water retention, K^+ depletion, and weakness due to mineralocorticoid activity of cortisol.

(*Contd*.)

- There occurs protein depletion due to its excessive catabolism.
- Hypertension develops due to increased deoxycorticosterone production.
- Reddish purple striae appear in the skin due to rupture of subdermal tissues.

Treatment

Treatment involves the removal of tumor in the adrenal or pituitary gland. If removal of pituitary tumor is not possible, then removal of both adrenals with supplementation of steroids is done.

ADRENOCORTICOTROPIC HORMONE (ACTH)

ACTH is a single-chain polypeptide containing 39 amino acids. It is secreted by the anterior lobe of the pituitary gland.

It is formed from a prohormone called pro-opiomelanocortin. Its plasma half-life is 10 minutes.

Actions

ACTH stimulates the growth and secretion of zona fasciculata and zona reticularis of the adrenal cortex. It controls the secretion of cortisol.

Mechanism of Action

ACTH acts through the cAMP system. Cyclic AMP causes activation of protein kinase A. This causes conversion of cholesterol to pregnenolone.

Control

ACTH secretion is mainly controlled by CRH secreted by the hypothalamus. It increases blood steroids and decreases ACTH secretion.

Stress causes an increase in ACTH secretion.

ACTH is secreted in irregular bursts throughout the day. These bursts occur more frequently in the mornings. Therefore, secretion of cortisol is more in the mornings and less in the evenings.

CORTICOTROPIN-RELEASING FACTOR

The corticotropin-releasing factor (CRF) hormone is secreted from the hypothalamus. It is a peptide with 41 amino acids. The cell bodies of neurons that secrete CRF are located in the paraventricular nucleus of the hypothalamus. CRF stimulates the secretion of ACTH.

SEX STEROIDS

The adrenal cortex secretes androgens. The major adrenal androgens secreted are dehydroepiandrosterone and androstenedione. In the peripheral blood and tissues, they are converted into estrogens.

Secretion of adrenal androgens increases during puberty, peaks by 20 years, and later decreases slowly with age. Their secretion is controlled by ACTH.

Functions

- They exert masculinizing effect in very high concentrations.
- They promote protein synthesis and growth.
- They are a source of estrogen in postmenopausal women.

CLINICAL NOTES

Adrenogenital Syndrome

An adrenocortical tumor secretes excess amounts of androgens causing intense masculinizing effects. There is insufficient biosynthesis of hormones such as cortisol and aldosterone. Females develop virile characteristics such as growth of beard, deep voice, baldness, masculine distribution of hair, and growth of clitoris.

A prepubertal male has rapid development of sexual organs (precocious puberty).

In an adult male, it is difficult to diagnose the condition because the signs are obscured by the normal virilizing characteristics of testosterone.

ADRENAL MEDULLA

The adrenal medulla is functionally related to the sympathetic system. It is present in the inner zone of the adrenal gland and constitutes 20–25% of its mass. It is a sympathetic ganglion in which the postganglionic neurons do not have axons and become secretory cells.

The adrenal medulla consists of strands of cells which have high affinity for chromium stains. Hence, they are called *chromaffin cells*. These cells contain vesicles having granules that store catecholamines.

CATECHOLAMINES

Catecholamines are organic compounds derived from amino acid tyrosine. These hormones are not essential for life but they help to prepare the individual to deal with emergencies.

The adrenal medulla secretes the following hormones:

- Epinephrine (adrenaline)
- Norepinephrine (noradrenaline)
- Dopamine

Eighty five to ninety percent of the cells are of the epinephrine-secreting type and 10% of the norepinephrine-secreting type. A small number of cells produce dopamine. Epinephrine is the major secretion of the adrenal medulla (85%). Norepinephrine constitutes 10–12% and dopamine 2–3%.

Synthesis

Catecholamines are synthesized from phenylalanine and tyrosine. Phenylalanine on hydroxylation gets converted to tyrosine. This is converted to dihydroxyphenylalanine (DOPA) by hydroxylation. DOPA is converted to dopamine by decarboxylation. Dopamine is converted to norepinephrine by hydroxylation. Norepinephrine is converted to epinephrine by phenylethanolamine-N-methyltransferase (PNMT). They are stored as granules in the chromaffin cells and secreted into venous blood as and when required.

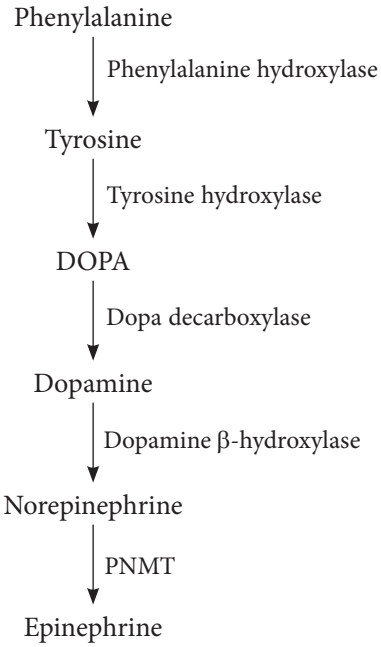
Eighty percent of norepinephrine in the adrenal cortex is transformed to epinephrine. The catecholamines have a half-life of 2 minutes in circulation. The actions of epinephrine and norepinephrine are mediated through receptors.

There are two types of adrenergic receptors, α and β.α receptors are of two types: (i) α_1 and (ii) α_2. β receptors are of three types: (i) β_1, (ii) β_2, and (iii) β_3. Norepinephrine excites mainly α receptors. Epinephrine excites both types of receptors equally. The differences between epinephrine and norepinephrine are listed in **Table 10.2.**

Table 10.2 Differences Between Epinephrine and Norepinephrine

Physiological Parameter	Epinephrine	Norepinephrine
Plasma level	30 pg/mL	300 pg/mL
Receptors	Both alpha and beta	Predominantly alpha
Heart rate	Increased	Decreased
Cardiac output	Increased	Decreased or no effect
Blood vessel	Vasodilation	Vasoconstriction
Peripheral resistance	Decreased	Increased
Systolic blood pressure	Increased	Slightly increased
Eosinophil count	Increased	No effect
Glycogenolysis	Decreased	Increased

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.



Actions

- Norepinephrine causes constriction of all the blood vessels of the body by acting through α_1 receptors.
- It inhibits the GIT, reducing motility and secretion.
- It causes dilation of pupils.
- Epinephrine dilates blood vessels in muscle and liver by acting on β_2 receptors.
- Both norepinephrine and epinephrine increase the rate and force of contraction of the heart.
- They increase alertness, cause glycogenolysis, and also increase the metabolic activity of the body.

Regulation of Catecholamine Secretion

The secretions from the adrenal medulla are mainly influenced through the nervous system. They increase in conditions of hypoglycemia, stress, anxiety, hemorrhage, exercise, and extremes of temperature.

Hemorrhage predominantly stimulates the epinephrine secretion.

Emotional stress and anger stimulate the norepinephrine secretion.

CLINICAL NOTES

Pheochromocytoma

Pheochromocytoma is tumor of the adrenal medulla. It occurs due to hyperplasia of chromaffin cells. In this condition, excess amounts of catecholamines are produced.

Signs and Symptoms

The commonest feature is hypertension. Other features include headache, palpitations, anxiety, and chest pain which occur during episodes of excess catecholamine release.

Treatment

Surgical removal of the tumor.

PINEAL GLAND

The pineal gland forms a major part of the epithalamus. It is formed by the evagination of the roof of the third ventricle. It is larger in infants and children. It regresses during adult life. It weighs about 150 mg. It contains cells termed *pinealocytes* (**Fig. 10.19**).

HORMONES

The pineal gland secretes the hormone **melatonin**. It also secretes many other peptides. Melatonin is synthesized from tryptophan. It exhibits diurnal variation with maximum secretion occurring at night. The normal plasma level of melatonin is around 70 pg/mL in adults and 250 pg/mL in children.

FUNCTIONS

- Controls reproductive function by inhibiting gonadal development
- Helps to maintain the sleep–wakefulness cycle

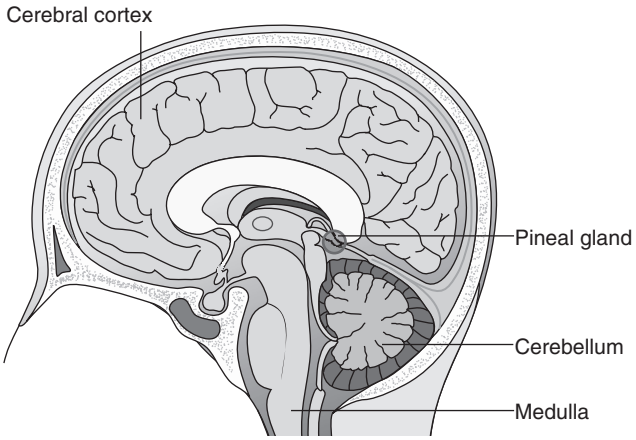


Figure 10.19 Pineal gland. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- Helps to maintain the biological rhythms of the body
- Peptides secreted by the pineal gland influence the function of other endocrine glands
- In lower animals, melatonin controls the color of skin

THYMUS

Thymus is present behind the upper part of the sternum (**Fig. 10.20**).

This gland processes the lymphocytes. These lymphocytes are called T-lymphocytes. They are responsible for cell-mediated immunity.

The endocrine role of the thymus gland is not clear. The thymus gland is known to interact with other endocrine glands.

The growth hormone promotes the growth of thymus. Excess of ACTH and glucocorticoids causes atrophy of thymus.

Thymus involutes at puberty possibly due to the effect of gonadal steroids.

An abnormal thymus function is implicated in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, hemolytic anemia, and myasthenia gravis.

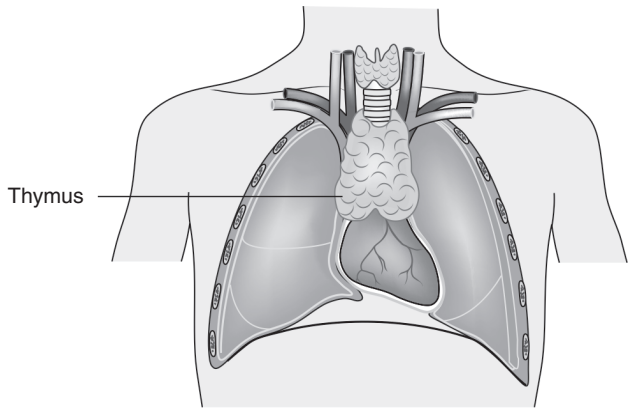


Figure 10.20 Thymus. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

REVIEW QUESTIONS

Long Essay

1. Name the anterior pituitary hormones. Describe the secretion, regulation, and functions of growth hormone.
2. Discuss the physiology of growth. Explain the role of different hormones in the growth of an individual.
3. Describe the steps involved in the synthesis of thyroid hormones. Explain its physiological functions. Add a note on cretinism.
4. What is the normal serum calcium level? Describe the hormonal regulation of serum calcium. What is tetany?
5. What is the normal blood sugar level? Describe its regulation. Add a note on diabetes mellitus.
6. Enumerate the adrenal cortical hormones. Describe briefly the functions of glucocorticoids.

Short Essay

1. Classify hormones. Explain the mechanism of action of hormones.
2. Explain negative and positive feedback mechanism of hormonal regulation.
3. Explain briefly radioimmunoassay (RIA).
4. Describe the hypothalamo-hypophyseal axis.
5. Explain the role of hypothalamus as an endocrine gland.
6. Name the posterior pituitary hormones. Explain their actions.
7. Describe the milk ejection reflex.
8. What are the functions of oxytocin?
9. What are the functions of antidiuretic hormone?
10. What are the differences between pituitary dwarf and thyroid dwarf?
11. What are second messengers? Explain the mechanism of action of any one of them.
12. Describe the iodide trapping mechanism in thyroid gland. How is it inhibited?
13. Enumerate the actions of thyroxine.
14. What are clinical features of cretinism? How are they produced?
15. Explain the clinical features of myxedema. Add a note on its management.
16. What is tetany? What are its clinical features?
17. Name the hyperglycemic hormones. Give the mechanism of action of any one of them.
18. Explain the symptoms of diabetes mellitus. Add a note on its management.
19. Discuss the actions, metabolism, and regulation of secretion of glucagon.
20. Discuss the actions, metabolism, and regulation of secretion of aldosterone.
21. Explain the actions of cortisol.
22. What is Cushing's syndrome? What are its clinical features?
23. Explain the cause and features of Addison's disease.
24. Compare and contrast the actions of epinephrine and norepinephrine.

Short Answer

1. Name the stimulating and inhibitory hormones of hypothalamus.
2. What is panhypopituitarism?
3. What is hormonal rhythm?
4. Name the clinical conditions associated with altered secretion of growth hormone.

5. Name the hormones secreted by anterior pituitary.
6. What is pituitary diabetes?
7. List the causes and clinical features of gigantism
8. List the signs and symptoms of acromegaly
9. Write a note on Diabetes Insipidus
10. Name the diabetogenic hormones.
11. Mention two examples of neuroendocrine reflex.
12. What is the difference between diabetes mellitus and diabetes insipidus?
13. What are somatomedins? Where are they secreted?
14. What are somatostatins? Where are they secreted?
15. List important tests for the assessment of thyroid functions.
16. Explain the term "goiter."
17. What is Graves' disease?
18. Explain the term "exophthalmos."
19. Explain the tests to detect latent tetany.
20. Explain the actions of calcitonin.
21. What is rickets? Mention its clinical features.
22. What is permissive action of hormones? Give an example.
23. Name the hormones secreted by pancreas.
24. Name the cell layer and hormones secreted by adrenal cortex.
25. List the functions of aldosterone.
26. What is aldosterone escape?
27. What is Addisonian crisis?
28. What is adrenogenital syndrome?
29. List the functions of pineal gland.

CHAPTER

11 Reproductive System

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Specific Learning Objectives

After studying this chapter, you should be able to:

- Explain the physiology of sex differentiation and development. List the abnormalities of sex differentiation.
- Define puberty. List the changes occurring in boys and girls at puberty.
- Describe the functional anatomy of female reproductive organs. Discuss the process of development of follicle and ovulation.
- Describe the hormonal regulation of ovulation. List the tests helpful in the detection of ovulation.
- Define menstrual cycle. Describe the phases and hormonal regulation of menstrual cycle.
- Describe the physiology of pregnancy. Discuss the maternal changes during pregnancy. Explain the basis of pregnancy tests. List the placental hormones.
- Discuss the stages of labor. Describe the factors influencing parturition. Explain milk ejection reflex.
- List the ovarian hormones. Describe the synthesis, transport, mechanism of action, and functions of estrogen and progesterone.
- Describe the functional anatomy of male reproductive system. Explain the process of spermatogenesis.
- Describe the synthesis, transport, mechanism of action, and functions of testosterone.
- List the contraceptive methods in males and females. Discuss the advantages and disadvantages of each of the methods.
- Successfully answer the questions and MCQs at the end of this chapter.

The members of the same species are formed by the process of reproduction. The main aim of reproduction is preservation and continuation of the species. All living organisms reproduce and express their identity in their offspring through genes.

Reproduction occurs in two ways: (i) asexual and (ii) sexual. Asexual reproduction is production of offspring by a single organism without the fusion of gametes. Participation of two organisms of the opposite sex in the reproductive process involving fusion of male and female gametes is called *sexual reproduction*.

Reproduction occurs in a unicellular organism by division of the parent cell. It is an asexual type of reproduction. The offspring produced is an exact replica of the parent organism.

Asexual reproduction is also seen in animals with a relatively simple organization.

In complex multicellular organisms, there is the sexual type of reproduction. Each of the male and female gametes has a haploid number of chromosomes which fuse to form the fertilized egg or zygote. Sexual reproduction results in offsprings that are not identical to their parents in all respects.

Sexual reproduction is a complex process and needs a specialized reproductive system. The male reproductive system produces the male gamete, the **sperm**, and transfers it to the female reproductive system where it fuses with the female gamete **ovum** leading to **fertilization**. This results in the formation of a **zygote**. Implantation of zygote occurs in the uterine cavity and develops into a fetus. This process is termed **pregnancy**.

Later, the mature fetus is delivered by a process called **parturition**. The nutrition to the newborn is provided by milk produced and delivered through **lactation**. The newborn grows and later becomes sexually mature to acquire the ability to reproduce, and this process is termed **puberty**. This sexually mature adult then reproduces in a similar way and continues the species.

SEX DIFFERENTIATION AND DEVELOPMENT

Human beings have 23 pairs of chromosomes, out of which 22 pairs are autosomes and 1 pair is the sex chromosome.

Sex is genetically determined by two chromosomes called **sex chromosomes**. In humans, these are X and Y chromosomes. Females have two X chromosomes and males have one X and one Y chromosome.

Genetic Male: The sperm containing Y chromosome fertilizes an ovum; the resultant zygote develops into a genetic male. The karyotype is 44 XY.

Genetic Female: The sperm containing X chromosome fertilizes an ovum; the resultant zygote develops into a genetic female. The karyotype is 44 XX.

SEX DIFFERENTIATION

Sex differentiation is the process of development of an undifferentiated gonad to a completely matured gonad of either gender, male or female.

During pregnancy, the differentiation between the male and the female fetus begins in the sixth week and continues even after birth till maturation of the gonad.

After fertilization, two cell lines develop in the undifferentiated gonad. One cell line forms the granulosa cells of the ovarian follicle and the Sertoli cells of the testicular seminiferous tubules. The other cell line forms theca cells in the ovary and Leydig cells in the testis.

DIFFERENTIATION OF GENETIC SEX

Male Genetic Sex

The sex chromosomes in a normal male are X and Y. The Y chromosome determines the male characters. The Y chromosome contains the *SRY* gene (sex determining region of Y) located in the distal part of its short arm. This gene encodes the TDF (testis determining factor). Another gene codes for H-Y antigen which helps in the development of male gonads and masculinization.

Female Genetic Sex

The pattern of sex chromosomes in females is XX. The *SRY* gene is absent. TDF and H-Y antigen do not develop and this causes the development of ovaries.

GONADAL SEX

Male

In a genetic male, the formation of the seminiferous tubule commences between 6 and 7 weeks of gestation. The Leydig cells appear

around 8–9 weeks. The testis starts producing testosterone and the *SRY* gene prevents synthesis of estrogen.

Female

In a normal genetic female, the female gonad differentiation starts at 9 weeks of gestation. The X chromosomes in the germ cells undergo division to form oogonia which develop to form the primary oocyte.

GENITAL SEX

In males at about 9–10 weeks the Wolffian ducts develop which give rise to epididymis, vas deferens, seminal vesicles, and ejaculatory ducts. The Leydig cells of fetal testes secrete testosterone and Sertoli cells produce Mullerian inhibiting substance (MIS).

MULLERIAN INHIBITING SUBSTANCE

MIS is a 536 amino acid peptide. It is secreted by Sertoli cells until 2 years of age in boys. It is also secreted in girls in minute quantities. It causes regression of Mullerian ducts by apoptosis.

Functions

- During the early embryonic life, it inhibits the development of female gonads.
- In males, it helps in testicular descent.
- In both sexes, it helps in maturation of germ cells.

ABNORMALITIES OF SEX DIFFERENTIATION

Turner's Syndrome (Fig. 11.1)

The chromosomal pattern is XO. Turner's syndrome is also called ovarian or gonadal dysgenesis.

It is characterized by diminished sexual development, dwarfism, and webbing of neck. The gonads are rudimentary or absent. No sexual maturation occurs at puberty. External genitalia are of the female type.

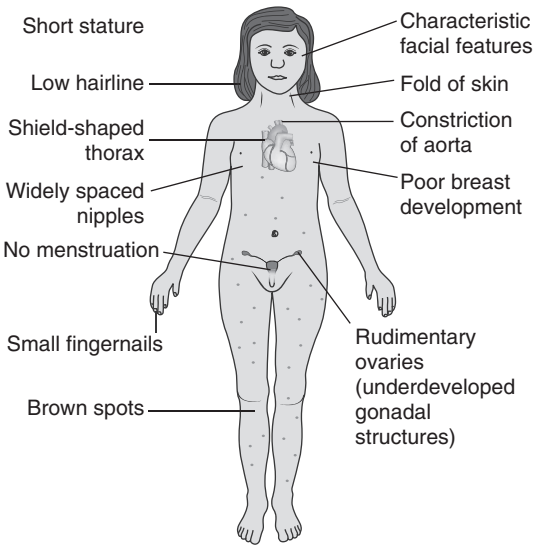


Figure 11.1 Turner syndrome.

Klinefelter Syndrome (Fig. 11.2)

The chromosomal pattern is XXY. Klinefelter syndrome is also called seminiferous tubule dysgenesis.

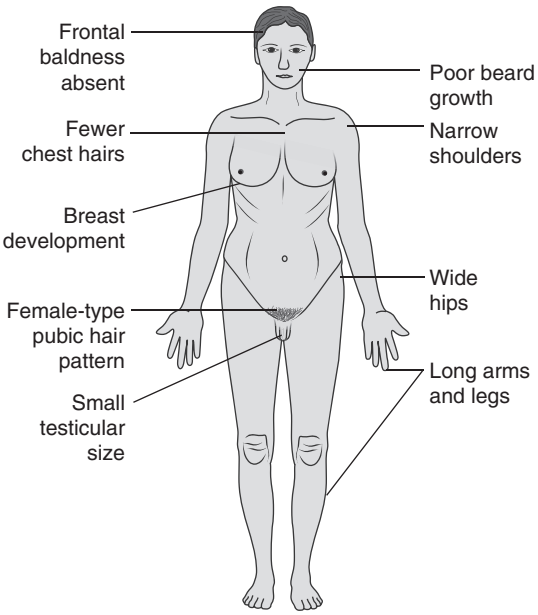


Figure 11.2 Klinefelter syndrome.

The person is genetically female but the presence of an extra Y chromosome causes the development of testis and male genitalia. The seminiferous tubule is not developed and results in infertility and mental retardation.

Super Females

Super females have XXX chromosomes. It is not associated with any abnormality.

True Hermaphroditism

True hermaphroditism is a condition in which the individual has both the testes and the ovaries. The external and internal genitalia are of the combined type. The karyotype pattern is 46 XX-XY.

Pseudohermaphroditism

Pseudohermaphroditism is a condition where the genetic pattern and gonads are of one sex but the external genitalia is of the other sex.

Female Pseudohermaphroditism

The male external genitalia develop in genetic females exposed to androgen. It is caused due to congenital virilizing adrenal hyperplasia.

Male Pseudohermaphroditism

The female external genitalia develop in genetic males. It is caused due to defective testicular development. Another cause is androgen resistance, e.g., 5α-reductase deficiency.

PUBERTY

Puberty is the period in life when the boys and girls become sexually mature. There are increased endocrine and gametogenic functions. The individual acquires the capacity to reproduce.

Puberty occurs between the ages of 8 and 13 years in girls and 9 and 14 years in boys.

ADRENARCHE

Adrenarche occurs 1–2 years before the onset of puberty. There is an increase in the secretion of adrenal androgens. It is believed to stimulate the production of gonadal hormones.

MECHANISM OF ONSET OF PUBERTY

The secretion of GnRH, LH, and FSH is nonpulsatile in nature before the onset of puberty. At the time of puberty, secretion of GnRH becomes pulsatile in nature. Increased pulsatile secretion of GnRH causes increased secretion of FSH (follicle-stimulating hormone) and LH (luteinizing hormone).

In males, FSH and LH stimulate Leydig cells to secrete testosterone.

In females, FSH and LH stimulate the production of estrogen and progesterone.

CHANGES OCCURRING AT PUBERTY IN BOYS

- Growth of the external genitalia
- Hypertrophy of the laryngeal mucosa and enlargement of the larynx causing a typical male voice
- Increased thickness of the skin, increased sebaceous secretion, and development of acne
- The pelvis becomes long, funnel shaped, and stronger
- Development of aggressive behavior and interest in opposite sex
- Increased muscular development
- Development of hair on face, axilla, and pubic region

Stages of Puberty in Boys

- **Stage 1:** Adrenarche (increase in adrenal androgen)
- **Stage 2:** Enlargement of testis to 2.5 cm; beginning of appearance of pubic hairs

- **Stage 3:** Enlargement of the penis, scrotum, and testis; pubic hairs becoming darker and coarser
- **Stage 4:** Further enlargement of the penis, scrotum, and testis; commencement of ejaculation
- **Stage 5:** Development of the full adult pattern of genitalia

CHANGES OCCURRING AT PUBERTY IN GIRLS

- Development of breasts
- Enlargement of the uterus, fallopian tube, ovaries, and vagina
- Onset of the menstrual cycle
- Deposition of fat in the buttocks, thighs, and breast giving a feminine appearance
- Growth of axillary and pubic hair
- Enlargement and widening of pelvis

Stages of Puberty in Girls

- **Stage 1:** Adrenarche (increase in adrenal androgen)
- **Stage 2:** Thelarche (development of breasts, increase in secretion of estrogen from ovary, appearance of hair along labia majora)
- **Stage 3:** Pubarche (breasts and areola enlarge; pubic hairs develop and become dark; axillary hair appears)
- **Stage 4:** Menarche (the onset of the first menstruation is called menarche; it occurs at around 11–14 years of age; breasts enlarge further)
- **Stage 5:** Full adult pattern of breast development and pubic hair; regularity of the menstrual cycle

CLINICAL NOTES

Precocious Puberty

Attainment of puberty at an early age is termed precocious puberty.

It is of two types:

(i) true and

(ii) pseudoprecocious puberty.

True Precocious Puberty

In this type, secondary sexual characteristics develop early with premature development of gonads.

This may be due to

- tumor or infection of hypothalamus,
- increased sensitivity of LH receptors to gonadotropins,
- tumor of pineal gland, and
- constitutional precocity.

Pseudo-Precocious Puberty

This occurs due to abnormal exposure to hormones.

1. **Adrenal causes**
   - Congenital virilizing adrenal hyperplasia
   - Androgen-secreting tumors
2. **Gonadal causes**
   - Leydig cell tumor of testis
   - Granulosa cell tumor of ovary

Delayed Puberty

If puberty is not attained before 18 years of age in females and 20 years in males, the condition is termed delayed puberty.

It can be caused due to conditions such as panhypopituitarism and gonadal dysgenesis.

Delayed puberty in spite of normal gonads results in eunuchoidism.

FEMALE REPRODUCTIVE SYSTEM

The female reproductive system is more complex compared to the male reproductive system. It is composed of primary sex organ and accessory sex organs (**Fig. 11.3**).

PRIMARY SEX ORGAN—OVARIES

Ovaries are the primary sex organs that correspond to testes in males. They are two in number producing ova and female sex hormones.

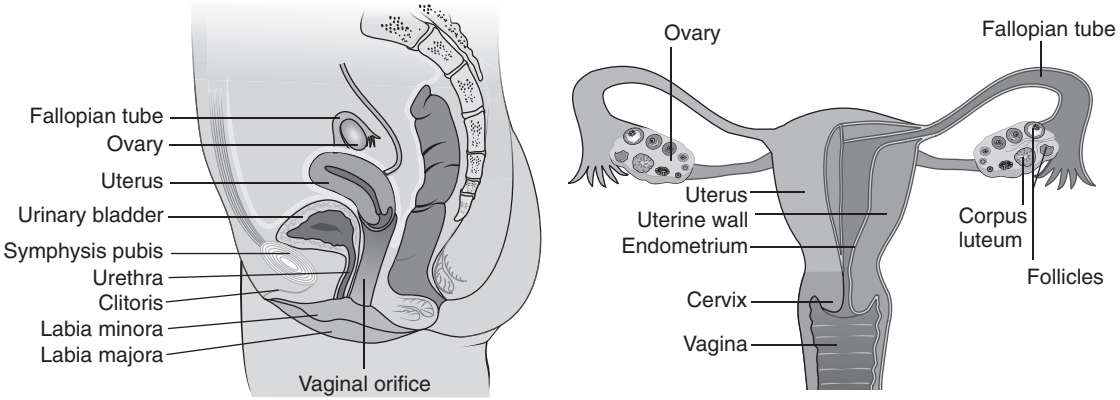


Figure 11.3 Female reproductive organs. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

ACCESSORY SEX ORGANS

Accessory sex organs include the internal and external genital organs.

The external genital organs include mons pubis, labia majora, labia minora, clitoris, vestibule of vagina, and vestibular glands.

The internal genital organs are vagina, uterus, and fallopian tubes.

Vagina

The vagina is a tubular structure measuring around 8–10 cm in length. The pH of vagina is around 4.5 and this acidic pH prevents infection. During parturition, the vagina relaxes and stretches to facilitate the birth of the baby.

Uterus

The uterus is a hollow muscular organ present in between the urinary bladder anteriorly and the rectum posteriorly. It is composed of two parts: (i) the body and (ii) the cervix. During childbirth, the cervix dilates and allows the fetus to pass through it.

Fallopian Tubes

The fallopian tubes are a pair of long, hollow tubes that extend from the lateral side of the uterus and open into the peritoneal cavity near the ovaries. They are around 10 cm in length and 8 mm in diameter.

Ovaries

The ovaries are ovoid organs measuring 3–5 cm in length and weighing about 7–8 grams each. They are present behind and below the fallopian tubes. They are attached to the uterus by ovarian ligaments.

The ovary consists of two zones: (i) outer cortex and (ii) inner medulla.

The ovaries perform two important functions:

1. Gametogenesis
2. Secretion of hormones

GAMETOGENESIS

The formation of female gamete (ova) from the primitive germ cell is termed oogenesis. This process begins in the fetal life and continues until menopause.

Oogenesis occurs in two stages:

1. Fetal oogenesis
2. Postnatal oogenesis

FETAL OOGENESIS

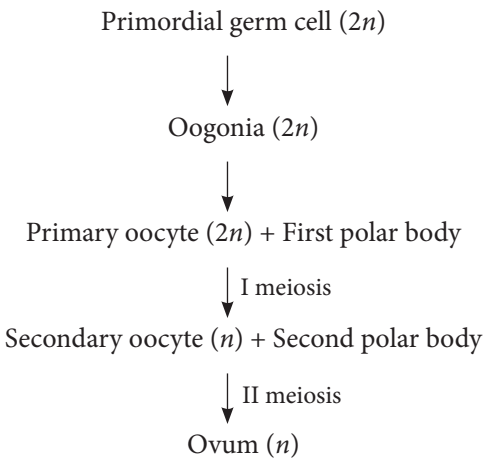
The primordial germ cells are formed from the endoderm of the yolk sac at the end of the third week of the intrauterine life. The mitotic proliferation of the primordial germ cell forms the **oogonia** (sixth week). It later differentiates to form the **primary oocyte**. This process reaches a peak between the 20th and 28th weeks of gestation.

The primary oocyte undergoes two meiotic divisions to produce a haploid ovum. It enters a prolonged prophase of the first meiotic division and remains in that stage for years. This is termed **meiotic arrest**. The first meiotic division is completed only before ovulation.

POSTNATAL OOGENESIS

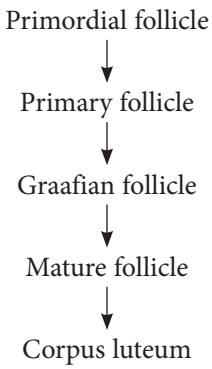
Just before ovulation, the first meiotic division is completed in the primary oocyte that is destined for ovulation. This division results in the formation of two cells. One of the daughter cells receives most of the cytoplasm. This is termed the **secondary oocyte** while the other cell is called the **first polar body**, which disappears.

After ovulation, the second meiotic division starts in the secondary oocyte but it stops in metaphase and is completed only when the sperm enters the oocyte. In this meiotic division, the ovum containing 23 chromosomes and the second polar body is formed. The second polar body disappears and only the ovum remains. Thus, each primary oocyte produces only one ovum.



DEVELOPMENT OF THE FOLLICLE

The oocyte grows throughout life inside the ovarian follicle till it is released during ovulation. Along with the oocyte, the follicles also grow in different phases. This is termed **folliculogenesis**. It starts during the intrauterine life and ends at the time of ovulation. Folliculogenesis occurs in various stages (**Fig. 11.4**).



Primordial Follicle

The primary oocyte (ovum) is surrounded by a single layer of spindle cells and is called a **primordial follicle**. At this stage, the ovum is still immature. The primordial follicle is formed in the intrauterine life.

Primary Follicle

At the onset of the ovarian cycle (at puberty), the follicles mature. The primordial follicle becomes a **primary follicle** due to the conversion of spindle cells into cuboidal epithelium. There is moderate enlargement of the ovum. A homogenous layer appears between the oocyte and the granulosa cells. Later, the oocyte enlarges to around 100 μ in size.

Approximately 6–12 follicles develop each month under the influence of FSH and LH. The rapid proliferation of granulosa cells forms

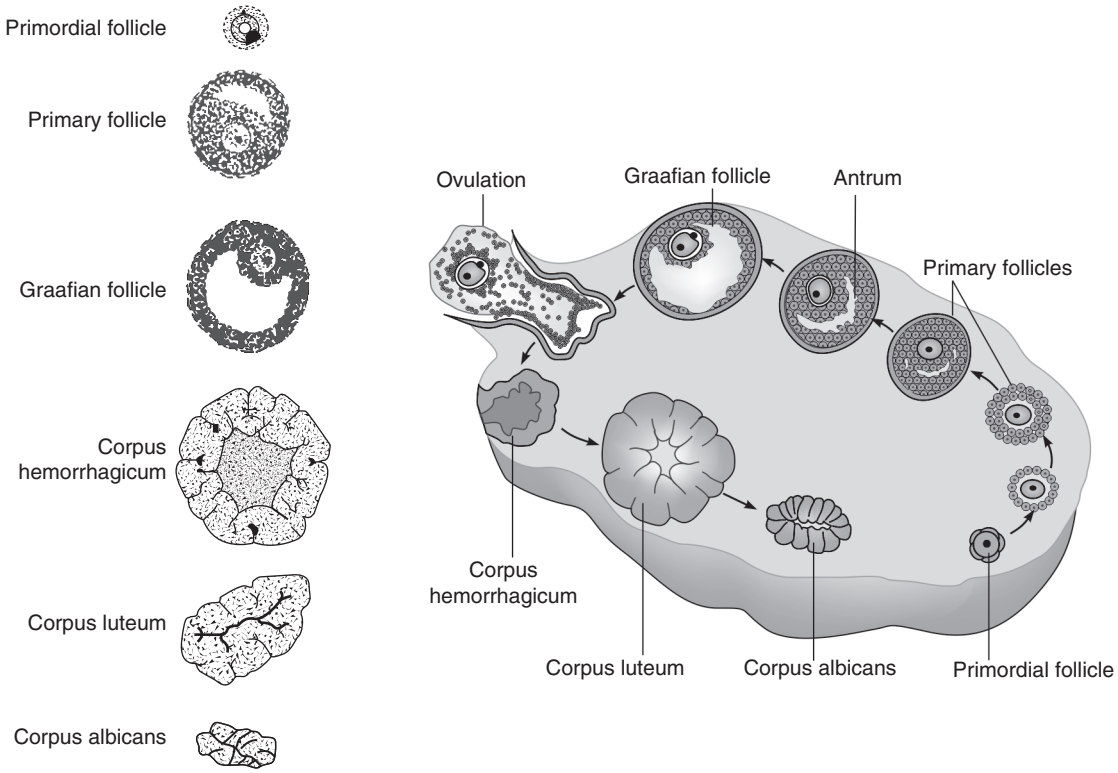


Figure 11.4 Ovarian cycle.

multiple layers. It also secretes fluid creating a cavity called **antrum**. The proliferation and differentiation of spindle cells forms the theca interna and theca externa.

The theca interna secretes steroid hormones.

The theca externa transforms into a vascular connective tissue capsule.

Graafian Follicle

Out of the 6–12 follicles produced every month, only one develops and increases in size to form a mature follicle called the **Graafian follicle** (**Fig. 11.5**). The remaining follicles undergo atresia.

A fully mature Graafian follicle has the following characteristic features:

- The follicular size increases to about 3–5 mm due to growth of granulosa and theca cell layers.
- The antrum enlarges and distends with fluid. The follicular fluid collects in large amounts

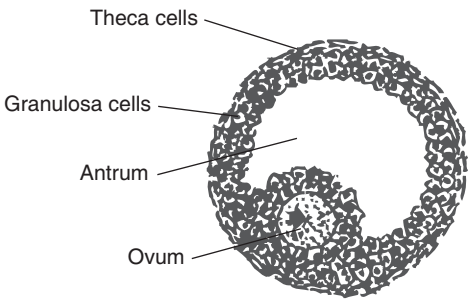


Figure 11.5 Mature (Graafian) follicle.

and surrounds the ovum all around except at one area where it is in contact with the granulosa cells. This area is called **cumulus oophorus**. The ovum is covered by a layer of cells called **corona radiata**.

- As the amount of antral fluid increases, the ovum and its surrounding cells are pushed to the periphery of the follicle.
- The theca cells of the mature follicle secrete estrogen. The estrogen that is secreted exerts

a positive feedback to secrete more estrogen. Estrogen enhances FSH and LH receptors on theca cells.
- The primary oocyte of a fully mature follicle completes the first meiotic division and forms the secondary oocyte (n) and the first polar body.
- At the time of ovulation, the mature follicle attains the size of 1–1.5 cm.

OVULATION

Ovulation is release of the secondary oocyte from the mature follicle of the ovary into the peritoneal cavity. In women having a menstrual cycle of 28 days, ovulation occurs around the 14th day.

The following changes occur in the mature follicle during ovulation:
- Just before ovulation, the outer wall of a mature Graafian follicle protrudes to form the stigma due to rapid swelling of the follicle.
- The cells of theca externa are activated by progesterone and cause release of proteolytic enzymes. These proteolytic enzymes further weaken the capsular wall.
- Rupture of the stigma releases viscous fluid containing the ovum into the abdominal cavity near the fimbrial end of the fallopian tube.
- The released ovum is surrounded by a number of granulosa cells forming the corona radiata.
- The released ovum is ready for fertilization and is viable for 24 hours. It is picked up by the fallopian tube through its fimbria.
- Only one ovum is usually released from one of the two ovaries during each cycle.

HORMONAL REGULATION OF OVULATION

Ovulation is a cyclical phenomenon.

The cycle begins with bursts of GnRH secretion from the hypothalamus.

GnRH secretion increases the release of FSH and LH. FSH acts on granulosa cells to produce estrogen.

Increased estrogen production and FSH increase the production of LH.

LH surge initiates a series of changes in the follicle resulting in ovulation.

The hormones regulating ovulation are
- GnRH,
- pituitary gonadotropins, and
- estrogens.

GnRH

GnRH is a 10 amino peptide secreted by neurons in the arcuate nucleus of the hypothalamus. The secretion from the arcuate nucleus is in turn controlled by the limbic system.

GnRH influences the secretion of FSH and LH from the anterior pituitary.

It is secreted intermittently, in pulses of 5–25 minutes every 1 hour. This pulsatile release of GnRH causes intermittent output of LH secretion every 90 minutes.

Pituitary Gonadotropins

Pituitary gonadotropins such as FSH and LH are secreted by the anterior pituitary gland. Secretion of these hormones begins at the age of 9–10 years and initiates menstruation by 11–14 years.

FSH

FSH is a small-molecular-weight glycoprotein with a molecular weight of 30,000.

The normal serum level of FSH is 5–30 million IU/mL.

Actions
- FSH causes the growth of primary follicles every month. It stimulates the mitotic division of granulosa cells increasing their numbers and layers.

- It helps the theca interna to form estrogen.
- It helps in the formation of new FSH and LH receptors on the granulosa cells.

Regulation FSH secretion is controlled by GnRH secreted from the hypothalamus. The secretion is regulated by feedback inhibition through gonadal hormones such as estrogen and testosterone.

LH

The normal serum level of LH is 5–25 million IU/mL.

Actions

- LH is necessary for follicular growth and ovulation.
- LH secretion increases 10-fold before ovulation, causing secretion of follicular steroid hormones.
- It helps in the formation and maintenance of corpus luteum.
- It acts on granulosa cells and theca cells and converts them into progesterone-secreting cells. It also changes granulosa and theca cells into lutein cells after ovulation.
- It plays a role in the development of atretic follicles.

Regulation LH secretion is mainly controlled by GnRH secreted from the hypothalamus. The secretion is regulated by feedback inhibition through gonadal hormones such as estrogen and testosterone.

Estrogens

- Estrogens act synergistically with FSH to cause follicular development.
- They cause LH surge.
- They cause involution of the corpus luteum.

CORPUS LUTEUM

After the extrusion of ovum, the remains of the Graafian follicle are together called the corpus luteum. Immediately after ovulation, it is filled with blood and is therefore called corpus hemorrhagicum. Later, the granulosa cells and theca cells enlarge and get filled with lipid inclusions giving it a yellow appearance (luteinization).

The granulosa cells in the corpus luteum start forming large quantities of progesterone and small quantities of estrogens.

Theca cells form androgens, androstenedione, and testosterone. These are converted mainly to female hormones by granulosa cells.

In a normal female, the corpus luteum grows to about 1.5 cm in diameter in about 7–8 days after ovulation. If there is no pregnancy, it loses the secretory functions by about the 12th day. The yellowish color is lost and it becomes corpus albicans. During the next few weeks, it is replaced by fibrous tissue.

During pregnancy, the corpus luteum increases in size. It is maintained by hCG (human chorionic gonadotropin) up to 90 days after fertilization. It is an important source of estrogen and progesterone during the first 12 weeks of pregnancy and is therefore essential for the maintenance of pregnancy. After 12 weeks, the placenta takes over its function.

CLINICAL NOTES

Detection of Ovulation

This is helpful in the diagnosis and treatment of infertility.

The tests to detect ovulation are as follows:

- **Ultrasonography**: This method is widely used in recent times. The size of the Graafian follicle is measured periodically; rupture of the follicle and occurrence of ovulation can be detected.
- **Basal body temperature (BBT) test**: In this test, the core body temperature (oral or rectal) should be recorded daily in the morning before the subject gets out of her bed (basal state). **In the postovulatory phas**e, BBT increases by about 0.5°C due to increased secretion of the thermogenic hormone, progesterone.
- **Plasma progesterone levels**: Plasma progesterone is measured periodically

(*Contd.*)

throughout the menstrual cycle by using the enzyme-linked immunosorbent assay (ELISA) method. A sharp increase in plasma progesterone indicates ovulation.

- **Progesterone metabolites**: The estimation of urinary metabolites of progesterone gives an indication about ovulation.
- **Endometrial biopsy**: The histological examination of the uterine endometrium in the second half of the menstrual cycle demonstrating secretory changes indicates ovulation.
- **Fern test**: The cervical mucus is spread on a glass slide and observed. The absence of fern pattern in the endocervical mucus indicates ovulation. Under the effect of estrogen, the cervical mucus forms a fern pattern when spread on the slide. After ovulation, the fern pattern is lost due to thickening of mucus due to the effect of progesterone.

MENSTRUAL CYCLE

The periodic discharge of blood and cellular debris from the female genital tract is termed menstruation. The cyclical changes occurring from one menstruation to the next comprise a **menstrual cycle**.

The duration of the menstrual cycle is about 28 ± 4 days. However, the duration of the cycle varies from individual to individual. It also varies from one cycle to another in the same individual. The menstrual cycle is usually calculated from the first day of menstrual bleeding.

PHASES

The menstrual cycle has three phases **(Fig. 11.6)**:

1. Proliferative phase
2. Secretory phase
3. Menstrual phase

Proliferative Phase (Follicular Phase)

The proliferative phase begins from the end of the menstrual phase. Its duration is about 10 days. At the beginning of this phase, most of the endometrium has been desquamated. Later, the endometrium starts healing and then proliferates rapidly from the fifth to the fourteenth day of the menstrual cycle. This proliferation occurs under the influence of estrogen. There is growth of simple tubular glands and blood vessels. The endometrium increases in thickness to about 3–5 mm. The endometrial glands produce thick mucus. At the end of the proliferative phase, ovulation occurs.

Secretory Phase (Luteal Phase)

The secretory phase lasts for about 14 days. It starts after ovulation and extends up to the next menstrual phase. The endometrium thickens up to 6 mm. The glands become bigger, tortuous, and filled with secretions. The stromal cells proliferate; spiral arteries become more coiled and dilated. This is caused due to the action of progesterone and estrogen on the uterine endometrium.

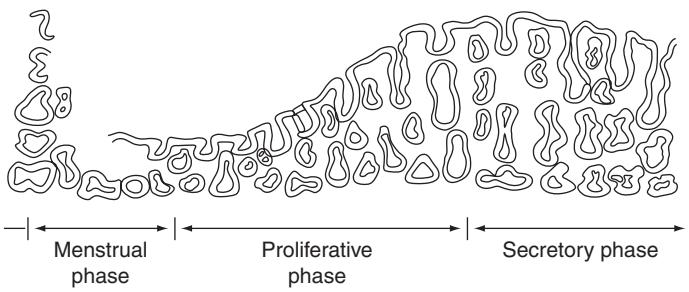


Figure 11.6 Phases of menstrual cycle.

Menstrual Phase

The menstrual phase lasts for about 3–5 days.

If the ovum is not fertilized, the corpus luteum regresses from the 24th day of the cycle. This decreases the estrogen and progesterone levels. It results in shrinkage of the endometrium, coiling and spasm of the arteries leading to focal necrosis of the endometrium. The necrosed endometrium is shed along with blood and other secretions.

The normal quantity of blood loss during menstruation is about 50–60 mL.

The normal menstrual blood does not clot due to the release of fibrinolysin along with the necrotic endometrial material.

OVARIAN CHANGES DURING MENSTRUATION

During the proliferative phase, FSH from the anterior pituitary acts on the Graafian follicle of the ovary to produce estrogen. By the end of the proliferative phase, LH is produced in large amounts. LH surge results in ovulation. It is produced by high levels of estrogen.

During the secretory phase, the ovary produces estrogen and progesterone.

During the menstrual phase, involution of the corpus luteum causes a sudden decrease in the levels of estrogen and progesterone.

HORMONAL CONTROL OF MENSTRUATION

- GnRH from the hypothalamus increases gonadotropic secretion from the pituitary.
- Secretion of FSH causes development and maturation of the Graafian follicle.
- The granulosa cells of the developing follicles produce estrogen.
- An increased level of estrogen stimulates the pituitary glands to produce the LH surge.
- A rapid rise in LH secretion causes ovulation.
- The Graafian follicle after ovulation becomes the corpus luteum.
- The corpus luteum secretes progesterone and estrogen, which are responsible for the secretory phase of the menstrual cycle.
- If there is fertilization, the corpus luteum continues to produce progesterone and becomes corpus luteum of pregnancy. Hormonal secretions continue till the placenta takes over the function.
- If there is no fertilization, the corpus luteum degenerates. It results in decreased secretion of estrogen and progesterone. This reduced hormonal level causes menstrual bleeding.

MENOPAUSE

The permanent stoppage of menstruation is called menopause. It marks the end of menstrual cycles. It occurs between 45 and 50 years of age.

Menopause is due to the depletion of functional follicles. Since follicles do not develop in response to LH and FSH secretion, the levels of estrogen and progesterone drop.

The symptoms associated with menopause are due to deficiency of estrogen. The vaginal epithelium atrophies and becomes dry. Bone loss is increased. There is increased incidence of cardiovascular diseases.

Hot flashes due to peripheral vasodilation and sweating are seen.

CLINICAL NOTES

Amenorrhea

The absence of menstruation is called amenorrhea. Physiologically, it occurs during pregnancy.

Polymenorrhea

Polymenorrhea is increased frequency of menstruation. Usually, the duration and amount of bleeding remains normal.

Menorrhagia

Menorrhagia is excessive bleeding during menstruation. The amount and duration of bleeding is increased. This occurs in uterine pathology and bleeding disorders.

(*Contd.*)

Dysmenorrhea

Dysmenorrhea is painful menstruation. It is of two types: (i) primary and (ii) secondary. In primary dysmenorrhea there is no known pelvic cause, whereas secondary dysmenorrhea is associated with uterine or pelvic pathology.

Oligomenorrhea

Oligomenorrhea is irregular and inconsistent menstrual flow. The duration of cycle is increased. It usually occurs due to ovarian disorders and use of hormonal contraceptives.

Premenstrual Syndrome

Premenstrual syndrome is seen in the secretory phase of the menstrual cycle. The symptoms include irritability, depression, mood swings, fatigue, weight gain, breast tenderness, and headache. The symptoms subside following the commencement of menstruation.

PHYSIOLOGY OF PREGNANCY

Pregnancy is the process of development of a fertilized ovum into a full-term fetus. The normal duration of pregnancy in human beings is around 280 days. Pregnancy is the process of development of a fertilized ovum into a full-term fetus.

Pregnancy occurs when the ovum is fertilized. The fertilized ovum eventually develops into a full-term fetus.

FERTILIZATION

Fertilization is the process of union of male and female gametes to form a zygote. It generally occurs at the outer end of the fallopian tube.

After the sexual act, the sperms travel toward the uterus and enter the fallopian tube. An ovum released from the mature Graafian follicle is taken up by the fimbrial end of the fallopian tube. The ovum meets the sperms in the fallopian tube. A single sperm enters the ovum to fertilize it (**Fig. 11.7**).

The ovum survives in the genital tract for about 24 hours and the sperm for 72 hours.

ZYGOTE

The fertilized ovum is called a zygote. The zygote has 46 chromosomes. It undergoes repeated division and forms a **morula**. The morula moves through the fallopian tube and gets implanted into the cavity of the uterus.

The morula touches the endometrium of the uterus to form a **blastocyst** by about fifth day after fertilization.

The blastocyst loses its zona pellucida (membranous structure surrounding the ovum). A cavity is slowly formed inside the blastocyst.

The outer layers of the blastocyst form the trophoblasts. They are further divided into an outer **syncytiotrophoblast** and an inner **cytotrophoblast** (**Fig. 11.8**).

The process of implantation is over by about 11 days.

PLACENTA

The placenta is a temporary organ formed during pregnancy. The trophoblastic cells begin to grow in the form of cords inside the endometrium of the uterus. These cords or processes are called the chorionic villi. The chorionic villi are surrounded by intervillous spaces which contain maternal blood. The fetal blood circulates through the chorionic villi. The maternal blood circulates through the intervillous space. Thus, the placenta connects the growing embryo with the mother (**Fig. 11.9**).

Functions

- Provides nutrition to the growing embryo
- Prevents entry of harmful substances into the fetus

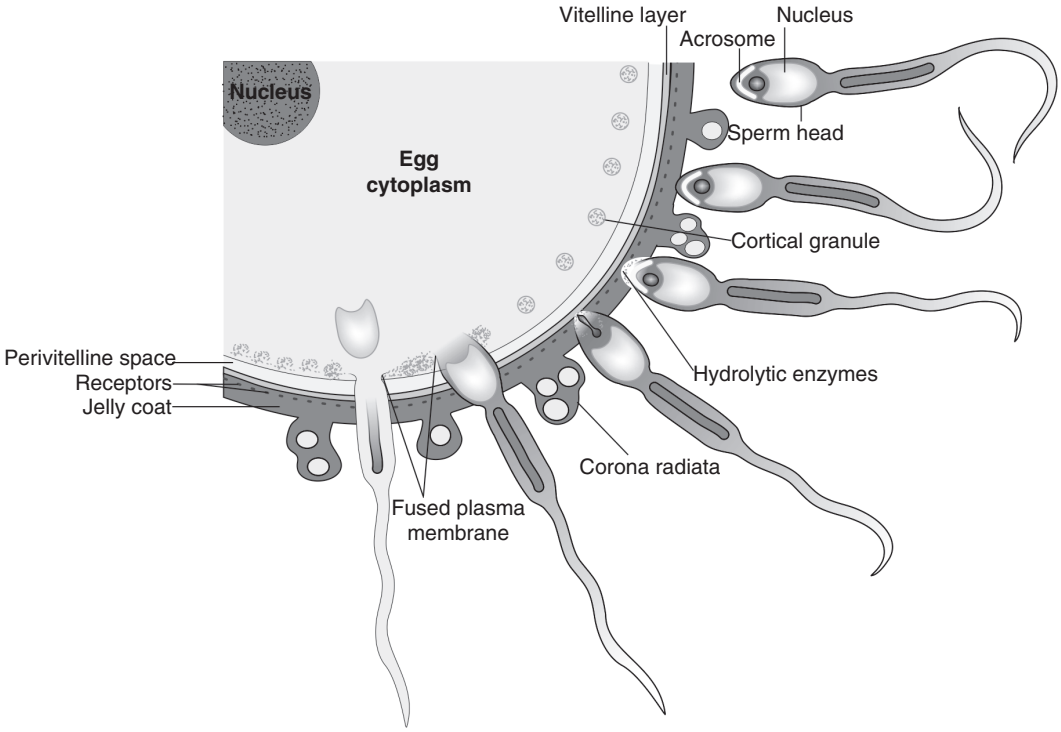


Figure 11.7 Process of fertilization. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

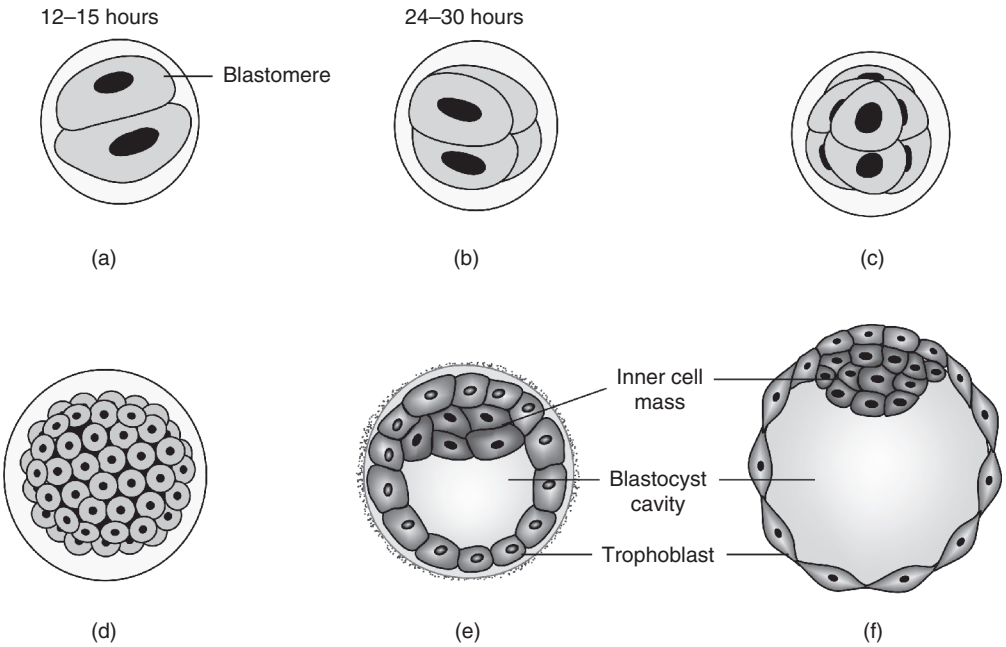


Figure 11.8 Stages of conversion of zygote to blastocyst. (a) Two-cell stage, (b) four-cell stage, (c) eight-cell stage, (d) morula, (e) early blastocyst, and (f) late blastocyst. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

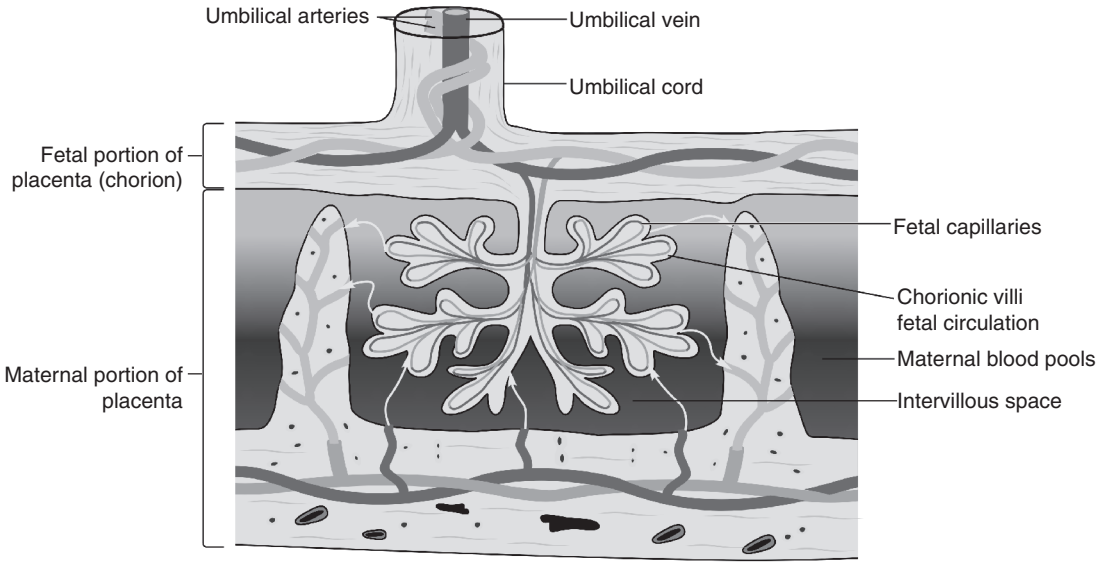


Figure 11.9 Structure of placenta. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

- Transfers waste products from the fetus to the maternal circulation
- Secretes hormones such as hCG, hCS, estrogen, progesterone, prostaglandins, and β-endorphins

Placental Hormones

The syncytiotrophoblast of the placenta functions as an endocrine gland. It secretes various hormones and chemical substances that help in the maintenance of pregnancy. The major placental hormones are as follows:

- Human chorionic gonadotropin
- Human chorionic somatomammotropin
- Estrogen
- Progesterone

Human Chorionic Gonadotropin (hCG)

This is produced by the syncytiotrophoblast.

It is a glycoprotein hormone similar to LH. It is essential for the maintenance of corpus luteum in the early part of the pregnancy.

hCG production starts by 7 days after fertilization, reaches peak by 60 days, and decreases thereafter.

hCG is also necessary for the production of testosterone.

Human Chorionic Somatomammotropin (hCS)

hCS is also called human placental lactogen secreted from the syncytiotrophoblast.

This hormone is responsible for the development of mammary glands and growth of the fetus.

MATERNAL CHANGES DURING PREGNANCY

Body Weight

A woman puts on about 10–12 kg of weight during pregnancy. This is due to fetal weight, placental weight, fat deposition, and accumulation of fluid.

Blood

Erythropoiesis is increased during pregnancy.

The bone marrow becomes hypercellular.

The concentration of plasma proteins is reduced.

The blood volume increases by 30% during the latter half of pregnancy. The ESR (erythrocyte sedimentation rate) increases.

Cardiovascular System

The cardiac output increases by about 30%.

The systolic blood pressure is not altered significantly, but the diastolic blood pressure is reduced.

Respiratory System

The O_2 consumption increases by 20%. The tidal volume and respiratory rate increase to meet the demand for the excess supply of oxygen.

Central Nervous System

Excitement, irritability, and depression are commonly seen.

Gastrointestinal System

Morning sickness, nausea, and vomiting occur especially during the first 3 months of pregnancy.

Endocrine System

The anterior pituitary is depressed as hCG takes over the function.

The placenta secretes estrogen and progesterone.

Thyroid hormone secretion is increased.

Oxytocin, prolactin, and cortisol secretion increases.

Reproductive System

The uterus increases in weight and size. There is hypertrophy and hyperplasia of the myometrium. The uterus weighs about 30 grams in a nulliparous woman. It increases to about 1 kg at term (**Fig. 11.10**).

The mammary glands develop under the influence of estrogen and progesterone.

PREGNANCY TESTS

Immunological Test

The immunological test is the latest test based on the reaction between hCG and its antibody. The various immunological tests used are bioassay, immunoassay (antigen–antibody reaction), and radioimmunoassay.

Principle

The urine of a woman with suspected pregnancy is mixed with hCG antiserum (contains hCG antibodies). Later, hCG-coated latex

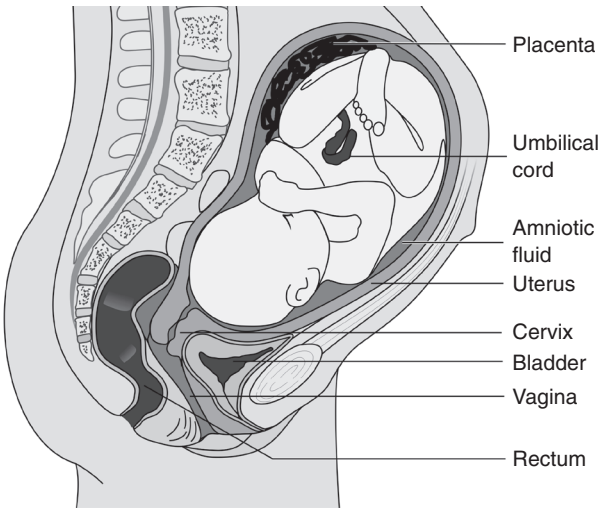


Figure 11.10 Normal position of fetus in the mother's womb. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

particles are added to this mixture. Absence of agglutination is a positive pregnancy test.

Agglutination does not occur if the woman is pregnant because hCG present in the urine will be neutralized by the antibodies.

Advantages

The immunological test is the most accurate test available, easier to perform, and less expensive.

It gives result in 5–30 minutes.

Disadvantages

Proteinuria may give false-positive results. Similarly, the test becomes positive in the presence of hCG-producing tumors. The test becomes negative in the later stages of the pregnancy.

Biological Tests

- Aschheim–Zondek test
- Friedman test
- Galli–Mainini test

These tests are done using laboratory animals and are not regularly performed.

Ultrasonography

Pregnancy can be detected as early as the fifth week after conception by ultrasound examination.

INFERTILITY

Infertility is the inability of an individual to reproduce by natural means. If a couple are unable to conceive after 1 year of intercourse without contraception, it is considered as infertility.

Males are responsible for infertility in 20–30% of the cases and females in 25–30% of the cases. In the remaining 35–40% of the cases, problems are present in both the partners.

Causes

In men, infertility is mainly due to low sperm count or poor semen quality. Low sperm count can be due to endocrine disorders, drugs, infection, or repeated exposure to radiation.

In women, infertility is due to structural defect in the uterus and fallopian tube, pelvic inflammatory disease, polycystic ovaries, endometriosis, and advanced maternal age.

PARTURITION

Parturition is the process of delivery of the baby (childbirth). This usually occurs after pregnancy reaches term (40 weeks). If the delivery occurs between 28 and 37 weeks of pregnancy, it is termed **premature labor**. If the pregnancy terminates before the 28th week of pregnancy, it is termed **abortion**.

FACTORS INITIATING PARTURITION

The factors are broadly divided into two categories:

1. Hormonal factors
2. Mechanical factors

Hormonal Factors

- Fetal hormones
- Maternal hormones

Role of Fetal Hormones

Increase of fetal CRH (corticotropin-releasing hormone) causes increased ACTH secretion. This increases the fetal androgens. The fetal androgens are converted to estrogens. Estrogen increases the secretion of prostaglandins. Prostaglandins enhance uterine contractions, which help in the delivery of the baby.

Role of Maternal Hormones

Estrogen–Progesterone Ratio Progesterone has an inhibitory effect on uterine contractility. Estrogen has a stimulatory effect. Throughout pregnancy, both estrogen and progesterone are secreted. But from seventh month onward, the estrogen content increases and the progesterone level decreases. This alteration in the estrogen–progesterone ratio favors increased contractility of the uterus.

Effect of Oxytocin Oxytocin increases uterine contractions by causing direct stimulation of the uterine smooth muscle and also by the formation of prostaglandins. Estrogen increases the number of oxytocin receptor at full term.

As pregnancy approaches full term, there is

- increase in sensitivity of the uterus to circulating oxytocin and
- increase in the rate of oxytocin secretion.

Relaxin This hormone is produced by the corpus luteum of pregnancy. It relaxes the pelvic joints and softens the uterine cervix, helping in easy delivery of the baby.

Mechanical Factors

Stretch of the Uterine Muscle

This increases uterine contractility. Intermittent stretch of smooth muscle caused by the movement of fetus also causes uterine contraction.

Stretch of the Cervix

This increases uterine contractions. Stretching of nerves in the cervix causes reflex contraction of the uterine muscles by release of oxytocin.

Braxton Hick's Contractions

These are weak and slow contractions of the uterus occurring throughout the pregnancy. Toward the end of pregnancy, these contractions become very strong resulting in dilation of the cervix and delivery (expulsion) of the baby.

LABOR

The process of birth of the baby is termed labor. Labor is due to a mechanism of positive feedback. The uterine contractions stimulate stronger uterine contractions subsequently resulting in birth of the baby. The contraction of the abdominal muscles facilitates labor.

The process of parturition occurs in three stages (**Fig. 11.11**).

First Stage

- It involves dilation of cervix and opening of the vaginal canal. The cervix dilates to about 10 cm.
- This stage lasts for 8–24 hours in primigravida (first pregnancy).
- In subsequent pregnancies, this stage lasts for 6–8 hours.

Second Stage

- Membranes rupture and the fetal head descends down the birth canal and the baby is delivered.
- This lasts for about 20–30 minutes in primigravida.

Third Stage

- It involves expulsion of placenta.
- It occurs 10–15 minutes after the delivery of the baby.
- During this stage, about 350 mL of blood is lost from the mother.

INVOLUTION OF UTERUS

The uterus starts decreasing in size. By 4–5 weeks after the delivery of the child, it reaches the pre-pregnant state. This process of involution is facilitated by lactation.

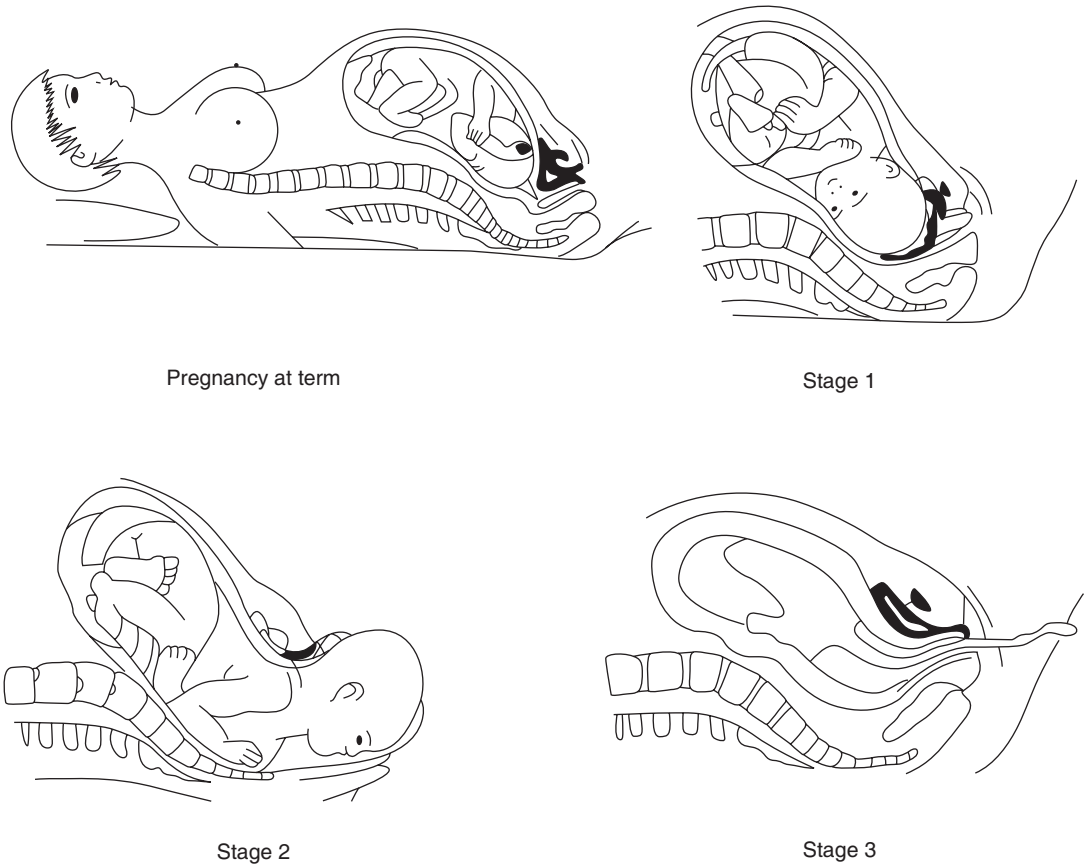


Figure 11.11 Stages of labor.

CLINICAL NOTES

If the uterine contractions are not strong enough, it can be enhanced by giving *synthetic oxytocin.*

If the progress is not satisfactory, the baby is delivered by the application of forceps. This is a form of assisted delivery, helping the mother to deliver the baby through the normal passage.

If the pelvic canal is small, the size of the baby is big, and there is obstruction to childbirth (labor) or if the uterine contractions are not strong, *cesarean section* operation is performed.

Loss of more than 500 mL of blood during placental delivery is termed *postpartum hemorrhage.*

LACTATION

Lactation is the process of synthesis, secretion, and ejection of milk by the mammary glands.

A mother's milk has the ideal composition suitable for an infant. It contains proteins, carbohydrates, fat, minerals, vitamins, and immunoglobulins.

HORMONAL CONTROL

- Estrogen causes development of the duct system of breast and collection of fat tissue.
- Progesterone helps in the development of alveoli of the breast.

- Prolactin helps in the formation of milk.
- Oxytocin causes ejection of milk.

DEVELOPMENT OF BREASTS

The breasts begin to develop at puberty under the influence of estrogen. During pregnancy, estrogen and progesterone help in further development of the breasts. By the sixth month of pregnancy, the breasts become fully capable of producing milk.

Growth of the Ductal System

Throughout pregnancy, there is significant growth of the ductal system and stroma of the breasts. A large amount of fat is stored in the stroma. These changes occur under the influence of estrogen.

Development of the Alveolar System

The lobules and alveoli develop under the influence of progesterone. The secretory characteristics develop in these alveoli due to the action of progesterone.

FORMATION OF MILK

Prolactin, an anterior pituitary hormone is responsible for the production of milk. During pregnancy, there is no milk production because of the inhibitory effect of estrogen and progesterone on prolactin.

Once the baby is delivered and placenta is expelled, the levels of these two hormones diminish and, therefore, the lactogenic effect of prolactin is seen.

The influence of prolactin in the formation of milk is aided by growth hormone, cortisol, parathyroid hormone, and insulin.

Each time the mother nurses the child, the prolactin level rises and causes the secretion of milk.

EXPULSION OF MILK

The milk secreted by the mammary gland is ejected out from the alveoli into the ducts. This is called *letdown of milk*.

Milk Ejection Reflex

When the baby suckles the nipple, the sensory impulses travel through the somatic nerves from the nipples to the hypothalamus, which causes secretion of oxytocin. Oxytocin is carried in the blood to the breast causing contraction of the myoepithelial cells resulting in expulsion of milk. This is also called milk letdown reflex (**Fig. 11.12**).

The average milk production in humans is about 500–800 mL/day.

Breastfeeding is very important for both the mother and the child.

The advantages of breastfeeding are as follows:

- The baby gets sterile, easily digestible, nutritive, and inexpensive food which is delivered at the right temperature.
- It promotes an emotional bonding between the mother and the child.
- Women who breastfeed their babies are less likely to suffer from breast cancer.
- It is a form of contraception.
- It provides immunity to the child.

In nursing mothers, the ovarian cycle and ovulation do not occur till the mother stops nursing the child. This is because of the inhibition of secretion of FSH and LH by prolactin.

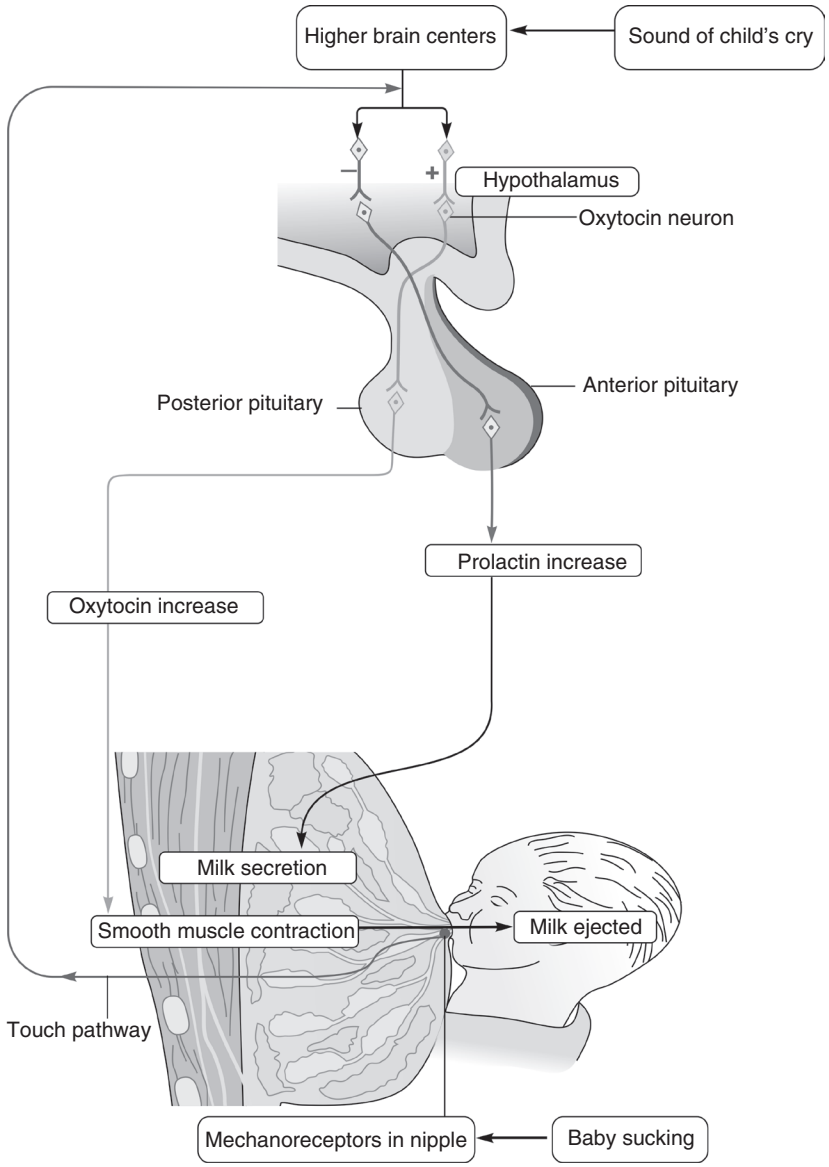


Figure 11.12 Pathway for milk ejection reflex. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

OVARIAN HORMONES

The ovarian hormones are estrogens and progesterone.

ESTROGENS

Estrogens are secreted from

- granulosa and theca cells of the ovary,
- corpus luteum,
- placenta during pregnancy, and
- adrenal cortex.

Three main estrogens present in humans are

- 17-β-estradiol
- estrone, and
- estriol.

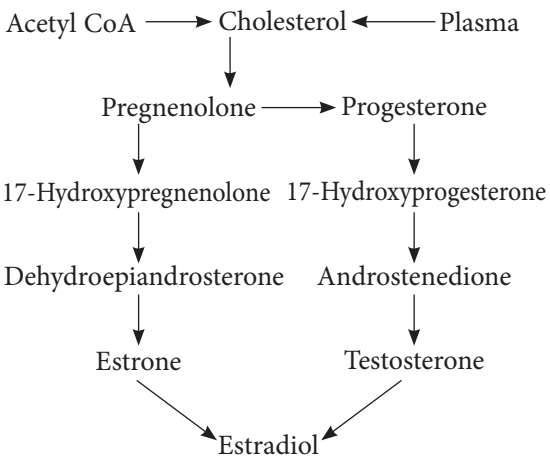
The 17-β-estradiol is the most potent form of estrogen. It is produced primarily in granulosa and luteal cells.

Estriol is less potent when compared to 17-β-estradiol. It is produced by ovaries during pregnancy. In nonpregnant women, it is produced in the liver.

Estrone is the least potent of all the estrogens. Most of the estrone is produced from peripheral conversion of estradiol.

Biosynthesis

All the three forms of estrogens are C18 steroids. They are formed from cholesterol which is derived from acetate or drawn from the plasma pool.



Transport and Secretion

Estrogen is transported in the blood mainly bound to the plasma albumin (60%) and specific estrogen-binding globulin called the **gonadal-binding globulin** (38%). This binding is loose and is released into the tissues in about 30 minutes. Only 2% of the circulating estradiol is in free form.

Daily Secretion

In the early follicular phase, the daily estradiol secretion is 30 μg/day. It peaks to 380 μg/day before ovulation. It is around 250 μg/day in the midluteal phase.

Mechanism of Action

The estrogens penetrate the cell membrane of the target cells and combine with the cytosol receptor in the cytoplasm.

The hormone–receptor complex enters the nucleus and gets attached to the DNA molecules. This stimulates DNA to produce mRNA facilitating protein synthesis.

The action of DNA also stimulates mitosis, resulting in hypertrophy and hyperplasia of the target organs.

Metabolism

The estrogens are degraded in the liver to inactive metabolites. They are later excreted through urine.

Functions

Action on Uterus and External Genital Organs

- Increases the size of the female reproductive organs
- Helps to convert vaginal epithelium into stratified squamous epithelium
- Causes acidification of vagina, thus preventing infections
- Promotes the development of endometrial glands

Action on Breasts

- Causes enlargement of breasts and pigmentation of areola during puberty
- Helps in the development of stromal tissue and ductal system of breasts during pregnancy
- Facilitates fat deposition in the breasts

Action on Skeleton

- Causes rapid growth of bones at puberty and early union of epiphysis with shaft of long bones

Other Actions

- It is responsible for the feminine shape: narrow shoulders, broad hips, converging thighs, and diverging arms
- Its action leads to the skin becoming smooth and soft with increased fat deposition in subcutaneous tissues
- Lowers plasma cholesterol, thereby preventing atherosclerosis, coronary artery disease, and hypertension
- Increases body protein
- Increases basal metabolic rate
- Causes sodium and water retention by kidneys
- Inhibits the formation of acne and blackheads
- Causes typical female behavior and is responsible for increased libido

CLINICAL NOTES

Synthetic Estrogens

They are synthetic analogs of estrogen. They include ethinylestradiol and diethylstilbestrol.

Uses

- Synthetic estrogens are used as oral contraceptives.
- They are used in the treatment of postmenopausal syndrome, e.g., ethinylestradiol and diethylstilbestrol.

PROGESTERONE

Progesterone is a C21 steroid, secreted by

- corpus luteum,
- placenta during pregnancy, and
- zona reticularis of the adrenal cortex.

Biosynthesis

The chief precursor of progesterone is cholesterol which is derived from acetate or drawn from the plasma pool.

Acetate
↓
Cholesterol
↓
Pregnenolone
↓
Progesterone

Transport and Secretion

Progesterone is mainly transported bound to albumin (80%). Eighteen percent is bound to steroid-binding globulin. Only 2% is in free form.

Plasma Progesterone

- **In women:** 0.9 ng/mL in the follicular phase and 18 ng/mL in the luteal phase
- **In men:** 0.3 ng/mL

It is mainly degraded in the liver into pregnanediol and excreted in urine.

Mechanism of Action

Like other steroids, its action is brought about by the action on DNA to initiate the synthesis of new mRNA.

Metabolism

Progesterone is degraded in the liver to inactive metabolites. They are later excreted in the urine.

Functions

1. **Effect on uterus**
   - Promotes secretory changes in the uterine endometrium and, therefore, prepares the uterus for implantation of the fertilized ovum
   - Decreases the frequency and intensity of uterine contractions
   - Has antiestrogenic effect on myometrial cells
   - Decreases the excitability of myometrium, sensitivity to oxytocin, and increases the membrane potential

2. **Effect on fallopian tubes**
   - Promotes secretory changes in the mucosa of fallopian tubes
   - Provides nutrition to the ovum
3. **Effect on cervix**
   - Makes the cervical mucus thick and thereby prevents the entry of sperms into the cervical canal
4. **Action on breasts**
   - Causes development of the alveoli of the breasts and makes them secretory in nature
5. **Effect on electrolyte balance**
   - Reduces the total body water and sodium since it blocks the effect of aldosterone
6. **Effect on body temperature**
   - Raises the body temperature. Therefore, the basal body temperature is raised after ovulation.
7. **Effect on respiration**
   - Stimulates respiration causing a decrease in alveolar PCO_2
8. **Effect on blood pressure**
   - Causes vasodilation resulting in decreased blood pressure

RELAXIN

Relaxin is a polypeptide hormone secreted by the corpus luteum, uterus, placenta, and mammary glands.

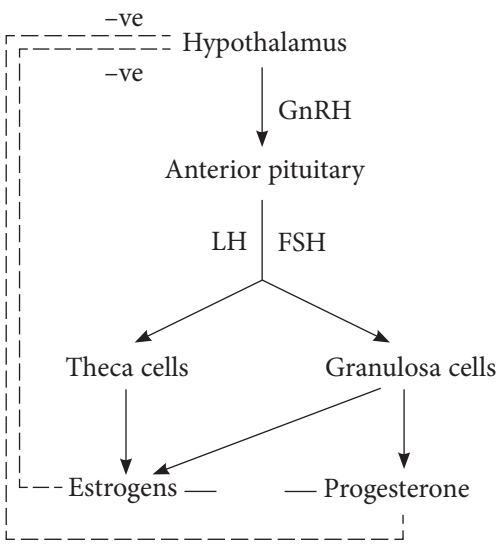
In men, relaxin is secreted by the prostate gland.

It has α and β chains connected by two disulfide bridges.

Functions

- Relaxes the pubic symphysis during pregnancy
- Softens and dilates the cervix, thus facilitating the delivery
- Inhibits uterine contractions
- Plays a role in the development of mammary glands
- In males, it is found in semen and helps in sperm motility and penetration

REGULATION OF OVARIAN HORMONES



MALE REPRODUCTIVE SYSTEM

The male reproductive system consists of the primary sex organ (**testes**) and accessory sex organs (**epididymis**, **vas deferens**, **seminal vesicles**, **prostate**, and **penis**) **(Fig. 11.13).**

TESTES

The testes are a pair of oval organs, each weighing about 10–15 grams, 5 cm long, and 2.5 cm wide. They are present in the scrotum.

The testis is made up of loops of convoluted seminiferous tubules in which sperms are formed. There are up to 900 seminiferous tubules in each testis. The average length of each tubule is around 0.5 m.

The seminiferous tubules open into the epididymis, which is a coiled tube about 6 m in length.

The tail portion of epididymis continues as vas deferens. The vas deferens enlarges to form

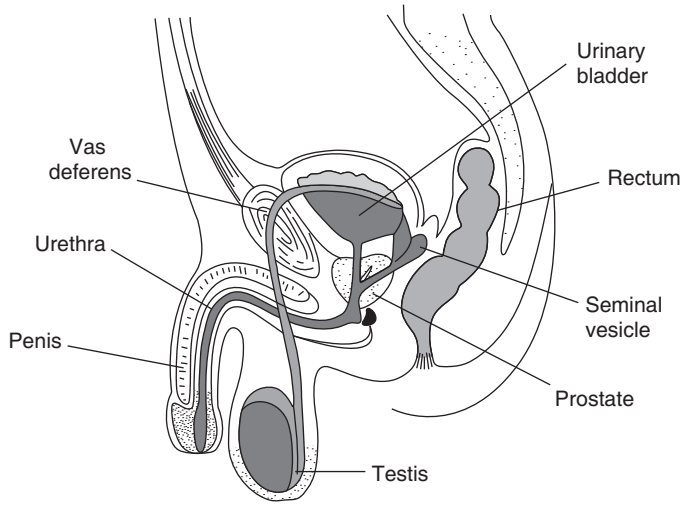


Figure 11.13 Male reproductive system.

the ampulla before it enters the body of the prostate gland. The seminal vesicles located on either side of the prostate gland empty their secretions into the prostatic end of the ampulla.

The contents of both the ampulla and the seminal vesicle pass into the ejaculatory duct, emptying into the internal urethra. The prostatic ducts also empty into the internal urethra.

The testis also has interstitial cells of Leydig and Sertoli cells.

The interstitial cells of Leydig are present in the space between the seminiferous tubules. They secrete androgens, mainly testosterone.

Sertoli Cells

Sertoli cells are special cells present in the seminiferous tubules. They are large cells with abundant cytoplasm.

Functions

- Form blood–testis barrier
- Provide nutrition to sperms
- Destroy defective sperms
- Produce inhibin, Mullerian regression factor, estradiol, and androgen-binding protein

SPERMATOGENESIS

Spermatogenesis is the process of formation of sperms in the seminiferous tubules (**Figs 11.14** and **11.15**). It begins at around 13 years of age and continues throughout life.

The germ cells undergo development to form spermatozoa. The germ cells remain inactive during childhood. They become active at puberty under the influence of gonadotropins and testosterone.

STAGES OF SPERMATOGENESIS

Spermatogonia ($2n$)
↓ Mitosis
Primary spermatocyte ($2n$)
↓ Meiosis
Secondary spermatocyte (n)
↓
Spermatids (n)
↓
Spermatozoa (n)

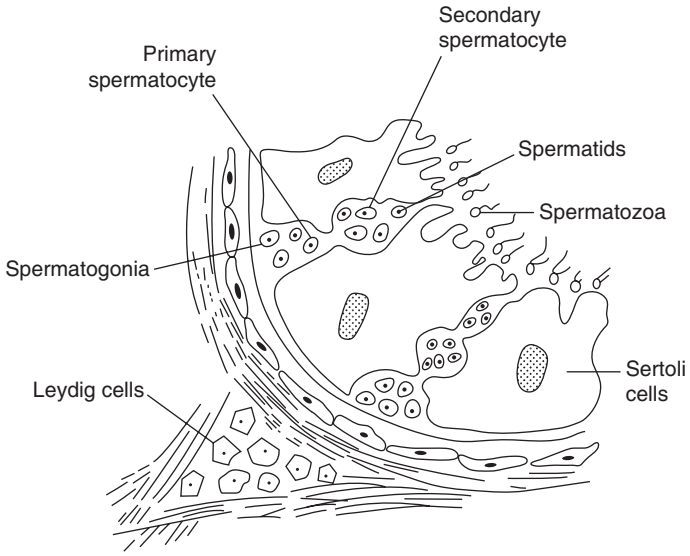


Figure 11.14 Section of a seminiferous tubule.

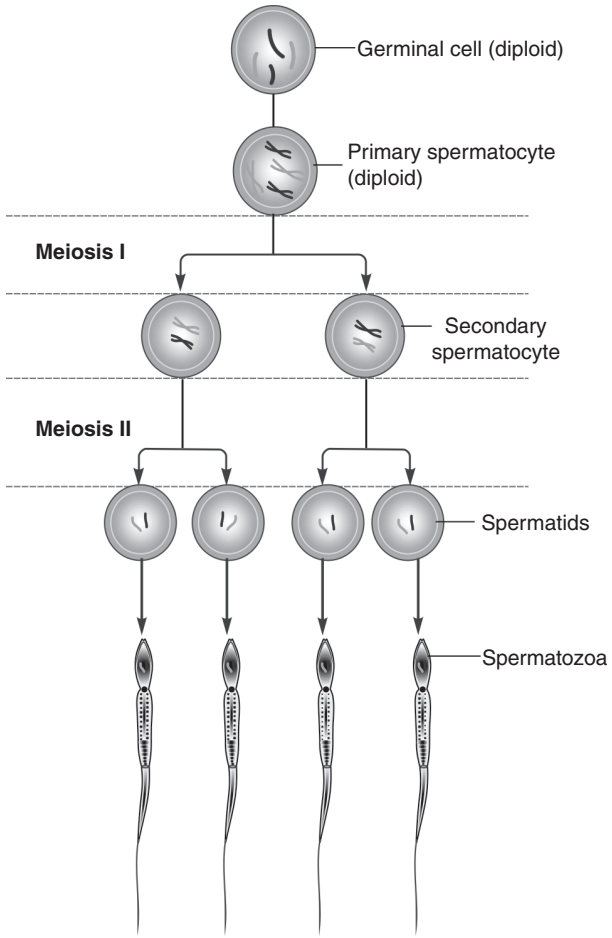


Figure 11.15 Spermatogenesis.

Spermatogonia

The seminiferous tubules contain a large number of germinal epithelial cells, spermatogonia. They continually proliferate, and a portion of them differentiates to form the sperm.

The primordial spermatogonia which is present near the basement membrane of the germinal epithelium is called **type A spermatogonia**. Type A spermatogonia divide 4 times to form 16 cells called **type B spermatogonia**.

The spermatogonia penetrate the blood–testis barrier and become enveloped within the folds of Sertoli cells.

Primary Spermatocyte

Type B spermatogonia become progressively modified and enlarged to form the primary spermatocyte by 24 days.

Secondary Spermatocyte

At the end of 24 days, each primary spermatocyte divides to form two secondary spermatocytes. This division occurs by meiosis.

I Meiotic Division

The primary spermatocyte divides into two secondary spermatocytes, each containing 23 chromosomes with two chromatids.

II Meiotic Division

Within 2–3 days, a second meiotic division occurs forming two daughter spermatids with 23 chromosomes each.

Each spermatogonium produces 512 spermatids after undergoing several mitotic and two meiotic divisions. 50% of them have X chromosomes and the other 50% have Y chromosomes.

The spermatids are small, round cells with a spherical nucleus. They undergo a change in shape, and the position of different organelles also gets altered.

Spermiogenesis

Spermiogenesis is the conversion of spermatids into spermatozoa. The spermatid is in the form of an epithelial cell. It is then gradually differentiated to form the spermatozoa. The spermatozoa are then released into the seminiferous tubule through a process called **spermiation**.

CAPACITATION OF SPERM

It is the functional maturation of the spermatozoa. The movement of sperm is sluggish inside the male genital tract. The sperms move vigorously when they enter the female genital tract and develop the ability to fertilize the ovum.

Capacitation brings about changes in the acrosomal head helping to penetrate the outer layer of egg and biochemical changes in the tail improving its motility. The movement of sperm inside the female genital tract is assisted by cervical and uterine movements and the sucking effect of the uterus.

The process of formation of sperm from a spermatogonium takes about of 72–74 days.

FACTORS INFLUENCING SPERMATOGENESIS

- **Luteinizing hormone (LH)**: Secreted from the anterior pituitary, LH stimulates Leydig cells to secrete testosterone. High concentrations of testosterone in the testis are required for the formation of sperms.
- **FSH**: Secreted from the anterior pituitary, FSH facilitates maturation of sperm. It is also required for initiation of spermatogenesis at puberty.
- **Testosterone**: Secreted by Leydig cells, testosterone is essential for growth, multiplication, and maturation of sperm.
- **Estrogens**: Formed from testosterone in the Sertoli cells, estrogens are essential for spermiogenesis.

- **Growth hormone**: It is necessary for controlling metabolic functions of testis and promoting division of spermatogonia.
- **Temperature**: A uniform temperature of 32°C is ideal for spermatogenesis. The scrotal sac that contains the testes maintains the temperature of the testes at around 32°C.
- **Exposure to X-rays**: Repeated exposure to X-rays reduces spermatogenesis.

SPERM

The sperms are elongated cells measuring about 55–65 μ. They are motile, moving at the rate of 1–4 mm/min. After production, they are stored in the epididymis and are viable for a month.

The sperm has a head, middle piece, and tail (**Fig. 11.16**).

Head

The head is 4–5 μ long and contains the nucleus. The anterior portion of the head is covered by the acrosomal cap. The acrosomal cap contains hyaluronidase, mucopolysaccharide, and acid phosphatase enzymes.

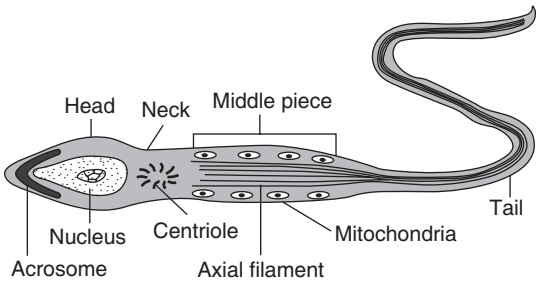


Figure 11.16 Structure of sperm.

Middle Piece

The middle piece is made up of the axial filament surrounded by the mitochondria. The mitochondria provide energy for the movement of sperm.

Tail

The tail helps the movement of sperm.

Nutrition for the sperm is provided by Sertoli cells and the fluid in the seminiferous tubule.

SEMEN

Semen is the fluid ejaculated from the male genital tract during orgasm.

The normal sperm count is 60–120 million/mL of semen.

pH of semen is 7.4–7.5.

CONTENTS

The normal volume is 2–6 mL per ejaculation. It contains the following:

- Sperms and fluid from vas deferens—10%
- Seminal fluid—60%
- Prostatic fluid—30%

Semen contains fructose which is necessary for providing nutrition to the sperms.

It also contains prostaglandins, phospholipids, citric acid, spermin, and clotting factor.

FUNCTIONS

- Fructose provides nutrition to the sperms.
- Fibrinogen causes the semen to coagulate soon after the ejaculation.

Lower Reference Limits for Semen Characteristics (WHO)	
Semen volume	1.5 mL
Total sperm number	39 million
Sperm concentration	15 million/mL
Total motility	40%
Progressive motility	32%
Vitality	58%
Morphologically normal forms	4%
pH	7.2 or more

- Prostaglandins help in fertilization of the ovum.
- Semen provides medium for the sperm.

CLINICAL NOTES

Oligospermia

Sperm count less than 20 million/mL in semen is termed oligospermia. Sperm counts below this value lead to infertility.

Azoospermia

Absence of sperms is termed azoospermia. It affects about 1% of the population.

Abnormal Morphology and Motility of Sperms

About 70% of the sperms should be of normal morphology. Abnormal sperms include bifid head, bifurcated tail, abnormal shape, and absence of head.

More than 60% of the sperms should have normal forward motility. If the sperms have abnormal morphology and motility, it leads to infertility. Normally, sperms travel at a speed of 1–4 mm/min in the female genital tract.

MALE SEX HORMONES

Androgens are male sex hormones secreted by the testis.

They include testosterone, dihydrotestosterone, and androstenedione.

Zona reticularis of the suprarenal cortex produces androstenedione and dehydroepiandrosterone.

TESTOSTERONE

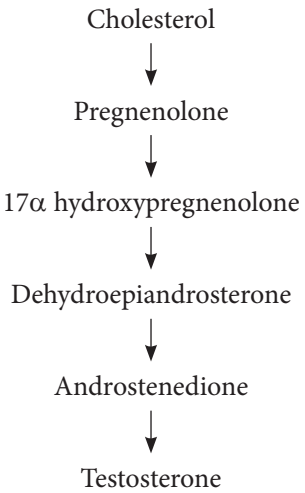
Testosterone is the most powerful male sex hormone.

It is formed by interstitial cells of Leydig present in between the seminiferous tubules. Interstitial cells constitute 20% of the adult testicular mass.

The activity of Leydig cells begins at the seventh week of fetal life. The Leydig cells are normally stimulated by hCG secreted by the placenta. These Leydig cells go into quiescence after the birth of the child because hCG is no longer available. But at the time of puberty, they again get activated due to LH secretion and continue to function till death.

Chemistry

Testosterone is a C19 steroid hormone. It is synthesized from either cholesterol or acetyl coenzyme A.



Secretion

The rate of testosterone secretion is 4–9 mg/day in a normal adult male. A small amount of testosterone is also secreted in females by ovaries and adrenal glands.

Transport

Almost 98% of testosterone is transported either loosely bound to the **plasma albumin** (33%) or tightly bound to the **testosterone-binding globulin** (65%). It circulates in blood for 1 hour. About 2% of testosterone circulates in free form.

The plasma testosterone level in an adult male is 525 ng/dL.

In the target tissues, testosterone is converted to dihydrotestosterone.

Degradation and Excretion

Testosterone is converted to androsterone and dehydroepiandrosterone. It is conjugated in the liver. These are excreted into the gut either through bile or through urine.

Functions

- Helps in the development of male sex organs, secondary sex characteristics, and sexual behavior
- Acts as an anabolic hormone

Action on Sex Organs in the Fetus

- Testosterone is produced at around the seventh week of intrauterine life. Before 7 weeks of intrauterine life, the fetus has both **Wolffian** and **Mullerian** ducts. Male sex chromosomes cause the genital ridge to secrete testosterone. This causes disappearance of the Mullerian duct system and development of male accessory sex organs. Absence of testosterone causes development of the Mullerian duct into accessory female sex organs.
- Testosterone helps in the descent of testis into the scrotum during the last trimester of pregnancy.
- The exposure of hypothalamus and other parts of the brain to testosterone in the male fetus influences the sexual behavior in adult life.

Action on Sex Organs After Birth

1. Testosterone causes the growth of external genitalia and accessory sex organs.
2. It causes appearance of secondary sexual characteristics such as
   - growth of beard, moustache, pubic, and axillary hair;
   - enlargement of larynx causing a typical adult male voice;
   - increased thickness of the skin; and
   - increased sebaceous secretion which causes acne.
3. It is necessary for spermatogenesis and sperm motility.
4. It is responsible for aggressive behavior.

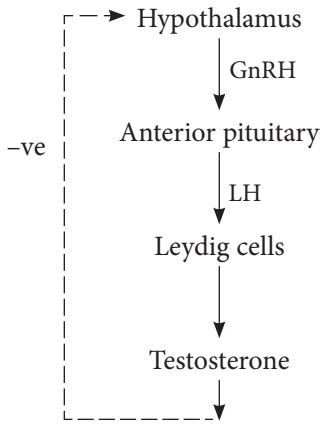
Anabolic Effect

- Testosterone increases the synthesis and decreases the breakdown of proteins.
- It causes linear growth of skeleton and muscle tissue.

Other Effects

- Testosterone increases the basal metabolic rate (BMR).
- It increases RBC production.

Regulation



INHIBIN

Inhibin is produced by Sertoli cells in males and the granulosa cells in females.

It is a glycoprotein. Its molecular weight is 10,000–30,000.

Functions

Inhibin helps in the regulation of spermatogenesis by inhibiting FSH secretion by acting directly on the anterior pituitary and on the hypothalamus inhibiting secretion of GnRH.

CLINICAL NOTES

Cryptorchidism

The failure of the testes to descend into the scrotum is called cryptorchidism. The testis develops in the abdominal cavity and migrates into the scrotum during fetal life under the influence of testosterone. Approximately 10% of the newborn babies can have undescended testis but they later descend by the age of 1 year.

Treatment

- Administration of gonadotropic hormones
- Surgery to mobilize the testis and bring it down to the scrotum

Treatment should be done as early as possible; otherwise, higher temperature in the abdominal cavity can damage spermatogenic epithelium causing sterility. The testis located in the abdominal cavity may develop malignancy.

Hypogonadism

Hypogonadism is due to the absence or deficiency of testicular functions.

Hypergonadism

Hypergonadism results from excessive secretion of male sex hormones.

Anabolic Steroids

- Anabolic steroids are synthetic substances having anabolic effects.
- They are used to enhance performance in sports by increasing the strength and bulk of the muscle. Use of these drugs is known as doping. Consumption of the drug is banned in view of the serious side effects. Examples include nandrolone and stanozolol.

CONTRACEPTIVE METHODS

India has surpassed China and has become the most populated country in the world in March 2023. With only 2.4% of the world's land area, we support 18% of the world's population. In order to check the growing population, it is necessary to follow family welfare methods. They mainly involve various methods of contraception. Contraceptive methods are aimed at preventing conception and restricting the size of the family.

CONTRACEPTION IN MALES

1. **Temporary methods**
   - Barrier methods
   - Hormonal methods
2. **Permanent method**: Vasectomy

CONTRACEPTION IN FEMALES

1. **Temporary methods**
   - Barrier methods
   - Intrauterine devices
   - Hormonal methods
   - Postconceptional methods
2. **Permanent method**
   - Tubectomy

Temporary Methods

Barrier Methods

1. **Physical methods (males)**
   - *Condom*
     - This is the most widely used male contraceptive method.
     - The advantages are that it is easily available, safe, inexpensive, and easy to use, prevents sexually transmitted diseases, and has very little side effects.
     - The disadvantage is that incorrect use leads to tear of condom.

Physical methods (females)

- *Diaphragm*: This is a rubber cup to be inserted into the vagina of the female

before intercourse. It is not used because of the difficulty in using it.

2. **Chemical methods:** Foams, creams, jellies, and suppositories are available in the market. All these contain spermicides, e.g., polyurethane foam sponge, which is saturated with spermicide nonoxynol-9.

Intrauterine Contraceptive Devices

Intrauterine contraceptive devices (IUCDs) are small inert substances inserted into the cavity of the uterus **(Fig. 11.17)**. The use of IUCD was known to ancient Arabs. They used to insert small stones into the uterus of camels.

- **First-generation IUCD**: Lippe's loop. It is made of polyethylene.
- **Second-generation IUCD**: Copper T. Copper is used since it has antifertility effect.
- **Third-generation IUCD**: Progestasert. This is a device filled with progesterone. This device releases the progesterone slowly.

Mechanism of Action IUCDs act as foreign bodies in the uterine cavities, thereby preventing fertilization and implantation. They reduce the motility and effectiveness of the sperm.

Advantages Simple, insertion takes few minutes, inexpensive, and no systemic side effects.

Disadvantages Excessive menstrual bleeding, pain, pelvic infection, uterine perforation, and increased chances of ectopic pregnancy.

Hormonal Contraceptives

Hormonal contraceptives are the most effective contraceptives. They are classified as

- oral pills and
- depot preparations.

Oral Pills

1. **Combined pill**: This pill contains synthetic estrogen and progesterone. The pill is given orally for 21 days beginning from the fifth day of the menstrual cycle.
2. **Progesterone-only pill**: This is called mini pill. It contains only progesterone and is not as effective as the combined pill.
3. **Postcoital pill**: It contains high doses of estrogens. It is used daily for 5 days after the sexual act.
4. **Once-a-month pill**: It is not commonly used due to high bleeding and high failure rate.

Mechanism of Action

- Prevent ovulation
- Prevent implantation of ovum
- Restrict the entry of sperm by altering the character of cervical mucus

Disadvantages

- Increased risk of myocardial infarction, thrombosis, cancer cervix, weight gain, migraine, and liver disorders

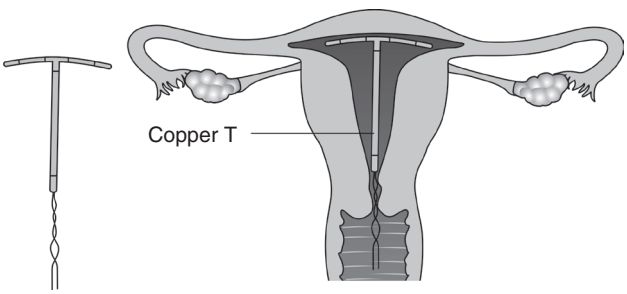


Figure 11.17 Position of Copper T inside the uterine cavity. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

5. **Male pill**: It is still in the trial stage. Gossypol tried as a male contraceptive is toxic and may result in permanent azoospermia.

Depot Preparations

1. **Injectable contraceptives**
   - DMPA (depot medroxyprogesterone acetate).
   - NET-EN (norethisterone enanthate): These injections are not widely used because they are painful. Women may have irregular cycles and sometimes it may even lead to permanent amenorrhea.
2. **Subdermal implant**: It is a surgical procedure of implanting contraceptive capsules beneath the skin. It can provide long-term reversible contraception.

Postconceptional Methods

- **Menstrual regulation**: This is aspiration of uterine contents 6–14 days after missed periods.
- **Medical termination of pregnancy (abortion)**: According to the MTP (Amendment) Act 2021, MTP can be done up to 24 weeks of gestation with the clause that *if the period of gestation (POG) is ≤20 weeks*, the opinion of one registered medical practitioner is required to take the decision regarding abortion and *if POG is between 20 and 24 weeks*, the opinion of two registered medical practitioners is required to take the decision regarding abortion.

Permanent Methods

Male Sterilization—Vasectomy

In this procedure, the vas deferens is clamped and cut; the cut ends are ligated. It is a very safe procedure but not widely practiced probably due to male ego or fear of decreased sexual vigor (**Fig. 11.18**).

Precaution The person undergoing vasectomy is not immediately sterile. A minimum of 30 ejaculations are required for all the remaining sperms to be washed off.

Female Sterilization—Tubectomy

Tubectomy is done by identifying the fallopian tubes and ligating them. Later, the ligated ends are cut and sutured (**Fig. 11.19**).

BIOLOGICAL METHODS

Abstinence

Abstinence means avoiding sexual intercourse. Temporary abstinence can be practiced during the unsafe period of the menstrual cycle.

Coitus Interruptus

This method was practiced during olden days. In this method, the male withdraws from the

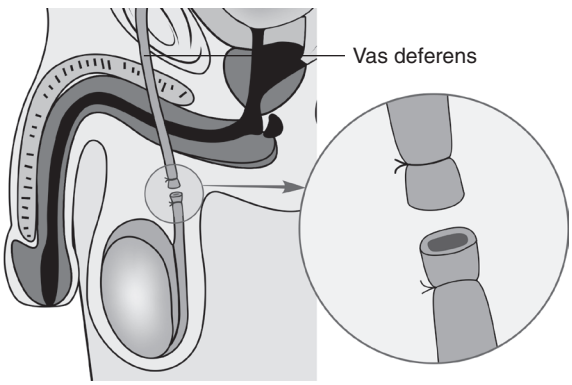


Figure 11.18 Vasectomy. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

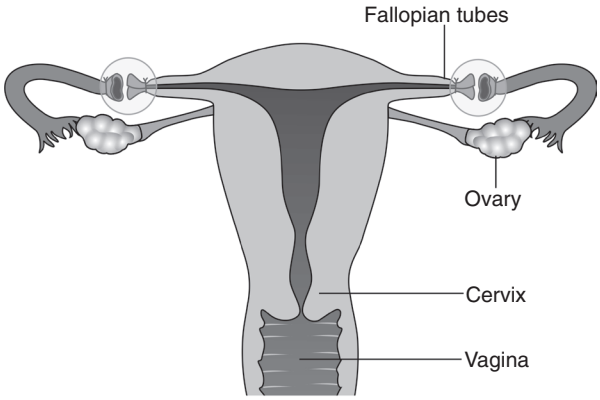


Figure 11.19 Tubectomy. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

act just before ejaculation. The failure rate is very high since a small change in the timing of withdrawal can result in pregnancy.

Safe Period (Rhythm Method)

This is based on the fact that ovulation occurs between the 12th and 16th day in the menstrual cycle of the duration of 28 days. The couple is advised to avoid intercourse from the 8th to the 22nd day of the menstrual cycle. Its disadvantages are a high failure rate and cannot be practiced in women having an irregular menstrual cycle.

REVIEW QUESTIONS

Long Essay

1. Describe the hormonal, uterine, ovarian, and vaginal changes during different phases of menstrual cycle.
2. Describe the ovarian cycle and hormones regulating it. Add a note on indicators of ovulation.

Short Essay

1. Explain gametogenesis in a female.
2. What are the changes occurring during puberty?
3. What is ovulation? Explain its hormonal control.
4. Write briefly about corpus luteum.
5. Explain the tests to detect ovulation.
6. Describe the immunological test for pregnancy.
7. Describe briefly fetoplacental unit.
8. Discuss physiological changes during pregnancy.
9. Explain the contraceptive methods in females.
10. Explain the mechanism of action of oral contraceptive pill.
11. Briefly describe the functions of placenta.
12. Discuss the hormonal control of lactation.
13. Describe the formation and actions of estrogens.
14. Describe the formation and actions of progesterone.

15. Explain the stages of spermatogenesis. Add a note on the factors influencing it.
16. Describe the actions of testosterone.
17. Explain the methods of contraception in males.

Short Answer

1. Mention the primary organ of sex in males and females.
2. Define menarche and menopause.
3. List the functions of estrogen.
4. List the functions of progesterone.
5. List the hormones of placenta.
6. Explain the role of oxytocin during parturition.
7. List the functions of FSH.
8. Mention the functions of LH.
9. Define the terms (a) amenorrhea, (b) menorrhagia, and (c) polymenorrhea.
10. List the methods of contraception in females.
11. Describe oral contraceptives.
12. Give an account of the source and action of inhibin.
13. Give an account of actions of relaxin.
14. List contraceptive methods in males.
15. List the functions of Sertoli cells.
16. What is cryptorchidism?
17. Describe an intrauterine contraceptive device.

CHAPTER

12 Integrated Physiology

Outline

Physiology of Infancy, Growth, and Development 483
Physiology of Aging 488
Obesity and Sedentary Lifestyle 491
Sports and Exercise Physiology 495
Skin and Body Temperature Regulation 497
Brain Death 501

Specific Learning Objectives

After studying this chapter, you should be able to:

- Describe the functions of organ systems of an infant in comparison with those of an adult.
- Explain the pattern and factors influencing growth. Describe the domains of development in a child.
- Explain the theories of aging. Describe the systemic changes occurring with aging.
- Describe the etiology, consequences, and management of obesity.
- Explain metabolic syndrome. Discuss the consequences of a sedentary lifestyle.
- Classify and grade exercise. Explain the cardiovascular and respiratory changes during different grades of exercise.
- List the layers of the skin and their functions. Describe the regulation of body temperature. Explain various mechanisms that increase/reduce body temperature.
- Define brain death. List its causes and clinical signs.
- Successfully answer the questions and MCQs at the end of this chapter.

PHYSIOLOGY OF INFANCY, GROWTH, AND DEVELOPMENT

PHYSIOLOGY OF INFANCY

Infancy is the period from the birth of a child to the completion of 1 year of life. The first 28 days after birth is called the neonatal period and after 28–365 days is considered as the post-neonatal period.

The salient features of various organs and organ systems of an infant are discussed next.

Cardiovascular System

The heart rate at birth is around 140 beats/min. During infancy, the heart rate gradually decreases and reaches 110 beats/min. Thereafter, it gradually decreases to reach adult values by puberty.

The mean arterial blood pressure is around 70/50 mm Hg at birth and declines during the next few hours. Later it slowly increases to reach 90/60 mm Hg by 1 year. Later it gradually increases to reach the adult values by around puberty.

The cardiac output is about twice the adult values in relation to body weight (550 mL/min). It gradually reduces and reaches adult values by puberty.

Respiratory System

The lungs are filled with fluid before birth. This fluid will be replaced by air at birth. Respiration is initiated by hypoxia, hypercapnia, and increased sensitivity of the chemoreceptors. The baby

begins to breathe within seconds after birth as a high intrapleural negative pressure of about 60 mm Hg is created. The normal breathing pattern is established within a few hours.

The respiratory rate at birth is 30–60/min and it gradually reduces during infancy and reaches the adult value by 10 years of age. The tidal volume at birth is around 16 mL and the total lung capacity in a newborn is 150 mL.

Blood

The total blood volume is around 300 mL, and if the placenta is left attached for few minutes after birth, an additional 75 mL of blood enters the infant.

The hemoglobin concentration is 16–18 g/dL at birth and slowly reaches adult values by 1 year. The RBC count is around 6 million/cu mm at birth and reduces to 3.5–4 million by 8–10 weeks. It returns to normal by 2–3 months.

The total leukocyte count is around 20,000 cells/cu mm at birth. It markedly decreases by around 1 month. Later it increases and reaches adult values by 5 years of age.

Nervous System

The neural growth is complete by 5 years of age. The brain grows rapidly in the first year of life, reaching about 70% of the adult values. However, the overall growth of the nervous system is around 50% by the end of 1 year.

Myelination of neurons starts in the fetal life itself and continues for several years during the postnatal life. The blood–brain barrier is incomplete at birth. This results in increased levels of sugar, proteins, and leukocytes in the CSF. Kernicterus occurs in newborns due to an ill-developed blood–brain barrier.

Special Senses

The visual apparatus is not fully developed at birth. The eyeball is small at birth resulting in hypermetropia. The adult size is reached by 5 years and therefore the visual acuity becomes 6/6 at this age.

The infant is able to appreciate color fully by 4–6 months as the macula and fovea are well differentiated by this time.

Hearing is well developed at birth. Newborns respond to sound by startle, cry, or change in activity. The ability to exactly localize the sound is acquired by around 10 months.

Taste sensation is also well developed by birth. However, the ability to perceive different tastes is fully developed by 2–3 months.

Olfactory sensation is very well developed at birth. The newborn can identify flavors and can like or reject a particular flavor clearly by around 4 months of age.

Gastrointestinal System

The gastrointestinal system is fairly developed at birth. Gastrointestinal growth spurt occurs in the first 24 hours after birth, largely due to the effect of enteral nutrition.

The metabolism in the gastrointestinal tract is not fully developed at birth. It undergoes substantial postnatal development during the neonatal period and mainly depends on the diet of the infant.

In the liver, most of the enzymatic pathways become fully active by 3 months of age.

Renal System

The nephrons are immature at birth. They have a low GFR and limited concentrating ability. Therefore, the infant is susceptible to both dehydration and volume overload. The active transport pumps in the PCT are also immature.

Temperature Regulation

Temperature regulation is a major problem in infants and they are very much susceptible to changes in temperatures. This is because of the following reasons:

- They have a greater surface area in relation to body weight.
- Their BMR is high.
- They have a limited insulating capacity from subcutaneous fat.

- They are unable to generate heat by shivering.
- The sweating mechanism is not fully developed.

In neonates, thermogenesis is by limb movements and by stimulation of brown fat. Infants develop the shivering ability by 3 months of age. As they grow, the BMR reduces and body surface area in relation to body weight also decreases.

PHYSIOLOGY OF GROWTH

Growth is a complex phenomenon which increases the size of different tissues and organs of the body. It also includes mental and psychological growth.

General Growth (Fig. 12.1)

General growth is the growth of the whole body. This includes increase in height, weight, and size of all the organ systems of the body. The rate of growth is rapid during two phases of life: (i) during infancy and (ii) during puberty.

Growth During Infancy

After birth, the infant loses weight for a few days and later starts gaining weight. He/she doubles his/her weight in 6 months and triples by 1 year. Height gain is maximum during the first 2 years of life. It is around 25 cm/yr. The rate of height gain decreases in the next 8–10 years and it is around 5–10 cm/yr.

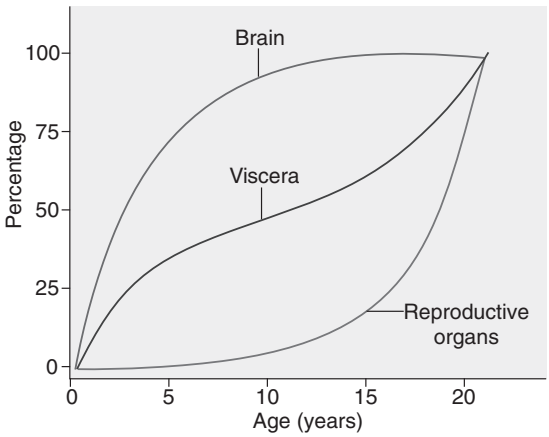


Figure 12.1 Growth curve. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Growth During Puberty

Pubertal growth occurs between 12 and 18 years of age and growth spurt occurs 2–3 years earlier in girls compared to in boys. There is an increase in height and weight during this period. The gain in height will be around 10 cm/yr and it stops after puberty due to the closure of epiphysis. The weight gain is 3–4 kg/yr during puberty.

Neural Growth

Neural growth includes growth of the brain, spinal cord, and nerves. The brain grows rapidly in the first year of life, reaching about 70% of the adult values. The remaining 30% of brain growth occurs by 5 years of age. The head circumference also increases proportionately.

Gonadal Growth

The gonads remain rudimentary during infancy and childhood. They start growing at puberty and attain the maximum rate between 14 and 18 years of age.

Lymphoid Growth

Lymphoid organs grow rapidly during childhood and start involution at puberty. These organs include lymph nodes, spleen, thymus, tonsils, and adenoids.

Factors Affecting Growth

The important factors affecting growth are as follows:

- Genetic
- Hormonal
- Nutritional
- Environmental
- Psychosocial

Genetic Factors

Genetic factors are the major determinants of the growth of an individual. The height and body constituents are determined chiefly by genetic factors. Both maternal and paternal factors influence the growth of an individual.

Hormonal Factors

Hormones such as growth hormone, thyroid hormones, insulin, and gonadal hormones play a major role in growth. Deficiency of these hormones diminishes the physical and mental growth.

Growth hormone plays an important role in influencing the height of an individual.

Thyroid hormone is required for the development of the nervous system, body, and skeletal system.

Insulin promotes the growth of the tissues.

Gonadal hormones control the growth during puberty and adolescence.

Nutritional Factors

Adequate balanced nutrition is required for the normal growth of the tissues. Inadequate nutrition leads to growth retardation.

Proteins, carbohydrates, fats, minerals, and vitamins contribute to the growth of tissues through various mechanisms.

Environmental Factors

Environmental factors including temperature, humidity, altitude, and sunlight play a major role in the growth. Individuals living at a high altitude have short stature compared to those living at sea levels. Lack of personal hygiene and lack of sunshine also affect the growth.

Psychosocial Factors

The psychosocial environment has a major role in both physical and mental development of a child. Proper care, attention, and good family support are very much essential for the psychological development.

CLINICAL NOTES

Catch-Up Growth

Catch-up growth is seen in children following a period of starvation or illness. In this phase, the rate of growth becomes faster than normal. This rapid growth is to make up for the reduced level of growth during the illness. The exact mechanism of catch-up growth is not known.

Developmental Deficiencies

Developmental deficiencies lead to dwarfism. Dwarfism is a condition characterized with a short stature in comparison to the age of the child. The different types of dwarfism are as follows:

- Pituitary dwarfism
- Thyroid dwarfism (**Table 12.1**)
- Laron dwarfism
- Gonadal dwarfism: Metabolic dwarfism
- Psychosocial dwarfism
- Constitutional dwarfism

Table 12.1 Differences Between Pituitary Dwarfism and Thyroid Dwarfism

	Pituitary Dwarfism	Thyroid Dwarfism
Cause	Decreased growth hormone	Decreased thyroid hormone
IQ	Normal	Decreased (mental retardation)
Stature	Short, but body parts are proportionate	Short and disproportionate body parts
Sexual maturity	Attained	Not attained
Treatment	Human growth hormone injections	Oral thyroxine
Facial appearance	Normal	Idiotic
Tongue	Normal	Protruded and enlarged
Abdomen	Normal	Pot belly with umbilical hernia
Skin	Normal	Dry, rough, and thick

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

DEVELOPMENT

Development is the process of acquiring various skills and maturation of various functions for optimum functioning of an individual.

Development in a child is assessed under various domains:

- Gross motor development
- Fine motor development
- Social and personal development
- Language
- Vision and hearing

Gross Motor Development

The head control develops starting by 6 weeks and it is almost achieved by 12 weeks. The child develops complete neck control by 20 weeks. By the age of 5 months, he/she can sit steadily with support. By around 8 months, the child can sit without support.

The child begins to stand holding onto furniture by around 9 months and stand independently by around 12 months. He/she starts walking independently by 13–15 months and can run by around 18 months.

Fine Motor Development

Hand–eye coordination starts between 12 and 20 weeks. At around 3–4 months, the child fixes his/her attention on an object and tries to reach for it. Hand–mouth coordination starts at around 6 months.

The child tries to feed self from a cup by around 1 year and can feed himself/herself by around 18 months. By 2 years, he/she can draw circular strokes and turn pages of a book one at a time.

Personal And Social Development

The child watches the mother when she talks to him/her by 1 month of age. He/she starts smiling back by 6–8 weeks of age when anyone smiles or talks to him/her.

The child becomes anxious of strangers by 6–7 months of age. By 1 year, he/she can understand simple questions. By around 2 years of age, he/she can identify five to six familiar objects when asked to point out the object.

Language

The child produces musical vowel sounds by 3 months of age. He/she learns to say monosyllable words by 6 months. By around 9–10 months, he/she learns to imitate sounds of his/her native language. He/she can utter 1–2 words by 1 year and 8–10 words by 18 months. Thereafter, the vocabulary increases rapidly to around 100 words by 2 years.

Vision and Hearing

At birth, the newborn can fix and follow a moving person to a range of 45°. This increases to 180° by 12 weeks. Binocular vision begins around 6 weeks and becomes well established by 4 months. The child can follow rapidly moving objects by 1 year.

A newborn responds to sounds by blinking, crying, startling, or change in an ongoing activity. The child turns his/her head toward the source of sound by 3–4 months. By the age of 10 months, the infant can directly look at the source of sound.

CLINICAL NOTES

Developmental delay can occur in about 10% of the children. Serious developmental disorders are seen in around 3–5% of the children.

Some of the common causes of developmental delay include the following:

- Antenatal
  - Chromosomal disorders
  - Congenital malformations
  - Intrauterine infections
- Neonatal
  - Hypoxic ischemic encephalopathy
  - Kernicterus
  - Hypoglycemic brain injury
- Postnatal
  - Vitamin B_{12} deficiency
  - Iodine deficiency
  - Lead toxicity

PHYSIOLOGY OF AGING

Aging is the process of getting older. It represents accumulation of various changes over time related to physical, psychological, and social aspects resulting in decline of the biological functions of the individual.

Aging is multifactorial and complex. It occurs at molecular, cellular, tissue, organ, and organism (whole body) levels. It is characterized by reduced ability to respond to stress and increased homeostatic imbalance. Death is the ultimate consequence of aging. However, the definite cause of aging remains unknown. The common diseases related to aging are dementia, Parkinson's disease, cataract, arteriosclerosis, diabetes mellitus, congestive cardiac failure, osteoporosis, osteoarthritis, immunosenescence, prostatic hypertrophy, and malignancies.

THEORIES OF AGING

Various theories have been put forth which explain different aspects of aging. However, there is no single theory that explains all the phenomena of aging. Some of the selected theories are discussed here.

Evolutionary Theories

One of the evolutionary theories is **mutation theory**. Random mutations occur in the cells which render them inefficient. As age advances, there is a progressive increase in the number of inefficient cells causing impaired function of the organ. There are numerous mutations with aging which are termed "mutation accumulation." However, there is limited experimental evidence for this theory.

Molecular Theories

Gene Regulation Theory

According to the genetic theory, the life span of an organism or its cell is genetically determined. Aging results from changes in the expression of genes. Life span is influenced by selection of genes promoting longevity.

Cellular Theories

The cellular senescence and telomere theory indicates that senescence limits the number of cell divisions. Repeated division of the cell finally results in the formation of a terminally arrested cell with an altered physiology.

Free Radical Theory Reactions occurring inside the cells result in oxidation of proteins and other cellular elements. This results in the formation of free radicals (reactive oxygen species) which damages cellular components, DNA, proteins, and lipid molecules, resulting in aging.

Somatic Mutation Theory Accumulation of products of genetic mutation in somatic cells is supposed to be the cause for aging. The damage due to free radical is an important source for somatic mutation.

Neuroendocrine and Immune Theory Aging is due to changes in endocrine and neural functions regulating cellular communication, physiological response to environmental stimuli, and functional aspects of reproduction. The hypothalamic–pituitary–adrenal axis is necessary for the maintenance of internal homeostasis. Repeated exposure to severe stress during one's life span can exhaust this regulatory system leading to **disease of adaptation** and death.

Error Catastrophe Theory The error catastrophe theory suggests that as the cells get older, there is an increase in errors during protein synthesis. This results in the formation of defective and inefficient proteins.

SYSTEMIC CHANGES DURING AGING

Age-related system changes are described individually. However, these changes occur in

a parallel fashion and affect each other through feedback loops.

Blood and Body Fluids

- Cellularity of the bone marrow decreases resulting in anemia. Fat infiltrates into the bone marrow and thymus reducing hematopoietic cells.
- Age-related decline in the secretion of growth hormone promotes deposition of fat in the bone marrow.
- Inactivation of the X chromosome, telomere shortening, accumulation of mitochondrial DNA mutations, and micronuclei formation lead to cellular dysfunction.
- The incidence of anemia increases with age.
- Adaptive immunity decreases. Bone marrow–derived T lymphocyte precursors reduce with age. Memory T cells undergo senescence resulting in impaired response to old and new antigens.
- Neutrophils develop structural deformities, defective phagocytosis, and impaired migration to the site of injury.
- The risk of myeloproliferative diseases increases.

Cardiovascular System

- Cardiac output declines linearly after the third decade of life. This decrease can be attributed to reduced inotropic response to circulating catecholamines.
- There is increased myocardial stiffness due to increased interstitial fibrosis.
- Progressive thickening of the blood vessels, especially abdominal aorta, increases afterload on the heart.

Content of lipid, particularly cholesterol, increases in the blood vessel leading to the development of arteriosclerosis.

Respiratory System

- Vital capacity decreases linearly with age after 20 years. Total lung capacity remains the same with an increase in residual volume.
- There is a progressive decline in the partial pressure of oxygen in the arterial blood due to mismatch in the ventilation and perfusion.
- Elastic recoil of the lung decreases with age resulting in greater tendency of collapse of the airways.

Infections are more common due to decline in the function of the immune system, reduced clearance from the tracheobronchial tree by mucociliary apparatus, and aspiration of oropharyngeal secretions.

Genitourinary System

- There is a gradual decline in the size of the kidney and the number of nephrons (glomeruli) per kidney.
- Creatinine clearance reduces with age.
- There is a gradual increase in blood urea nitrogen as the age advances.
- Tubular functions like maximal tubular reabsorption and concentrating or diluting capacity decrease.
- The capacity of the urinary bladder decreases coupled with stress incontinence.

There is age-related prostatic hypertrophy.

Gastrointestinal System

- There is a decrease in peristalsis and delay in transit time resulting in dysphagia and reduced calorie intake.
- Atrophy of gastric mucosa occurs with age leading to achlorhydria, deficiency of intrinsic factor, and decline in the production of pepsinogen.
- There is chronic constipation due to reduced intestinal motility, hypotonia of the colon, longer stool transit time, and greater stool dehydration.
- Fecal incontinence is a common manifestation due to reduced control of the internal and external anal sphincter.

Endocrine System

- There is a progressive decrease in the number and function of insulin-producing β cells in the pancreas.
- Progressive peripheral insulin resistance is seen with aging.
- Bone mass decreases resulting in osteoporosis. This occurs due to relative increase in bone resorption compared to its formation.
- Menopause occurs in females due to the disappearance of oocyte through ovulation and atresia. It is associated with vasomotor instability resulting in hot flushes.

The epidermis of the skin becomes thin and undergoes atrophy. The tone and elasticity of the skin is reduced.

Musculoskeletal System

- Lean body mass decreases due to atrophy of muscle cells. Changes in the skeletal system and muscles lead to poor locomotion in elderly subjects.

Joint disease is produced by degeneration of the cartilage, thickening of the subchondral bone, and its remodeling with the formation of marginal spur.

Nervous System

- Neurons stop reproduction soon after birth and their number decreases progressively with age.
- Age-related brain damage is the cause for decline in cognitive, autonomic, and motor functions.
- There is diminished coordination between different parts of the brain leading to poor cognitive performance.

Degeneration of the cortical and subcortical structure manifests as slow and unstable gait, poor balance, and prolonged reaction time.

Body Weight and Composition

- Body weight tends to decrease during the sixth and the seventh decade of life.
- Weights of muscle and visceral organs, and fat mass decrease with the advancement of age.
- Muscle mass and strength are reduced causing reduced functional ability and mobility.
- Waist circumference increases indicating the accumulation of visceral fat, which is responsible for pathological manifestation of obesity.
- Structural changes in the bone and its progressive demineralization reduce the bone strength and increase the risk of fractures.

Homeostasis

- There is a steady decline in sex hormones in both males and females with aging.
- There is an increase in proinflammatory activity and oxidative stress resulting in tissue damage.
- Aging increases susceptibility to disease, weakened response to stress, and reduced ability to recover after acute illness.

It is also associated with impaired response to treatment and high risk for disability.

DELAYING AGING

Aging is a natural process which cannot be prevented. However, the onset and progression of aging can be delayed.

The factors which are known to delay aging are restricted calorie intake and regular exercise.

It has been demonstrated in experimental animals that calorie restriction prolongs life span.

Exercise improves cardiac performance, reduces obesity, and prevents/postpones atherosclerosis. It helps an individual to have a better musculoskeletal activity.

OBESITY AND SEDENTARY LIFESTYLE

OBESITY

Obesity is a state (complex disease) with excess amount of body fat or adipose tissue mass.

It should not be mistaken for overweight or increased body weight as muscular subjects may have weight more than the standards without increased adiposity.

A widely used method to measure obesity is *body mass index (BMI)*, which is equal to weight/(height)^2.

The other methods to quantify obesity include the following:

- Measurement of skinfold thickness (anthropometry)
- Underwater weighing (densitometry)
- Estimation of electrical impedance
- Fat evaluation using CT or MRI

The normal BMI for males and females with a moderate body frame range from 19 to 26 kg/m^2. BMI of more than 30 kg/m^2 is considered as obesity (**Fig 12.2**).

However, the morbidity due to cardiovascular diseases, metabolic diseases, and cancer increases with BMI more than 25 kg/m^2. The subjects with BMI between 25 and 30 kg/m^2 are considered overweight.

A BMI between 25 and 30 kg/m^2 should be considered for therapeutic intervention to reduce the risk of morbidity (having a disease or symptoms of a disease/mortality).

Waist–hip ratio of more than 0.9 for females and 1.0 for males is considered abnormal.

The body weight is under endocrine and neural control. They influence the energy intake and expenditure. A small imbalance in energy intake and expenditure will have a large effect on body weight.

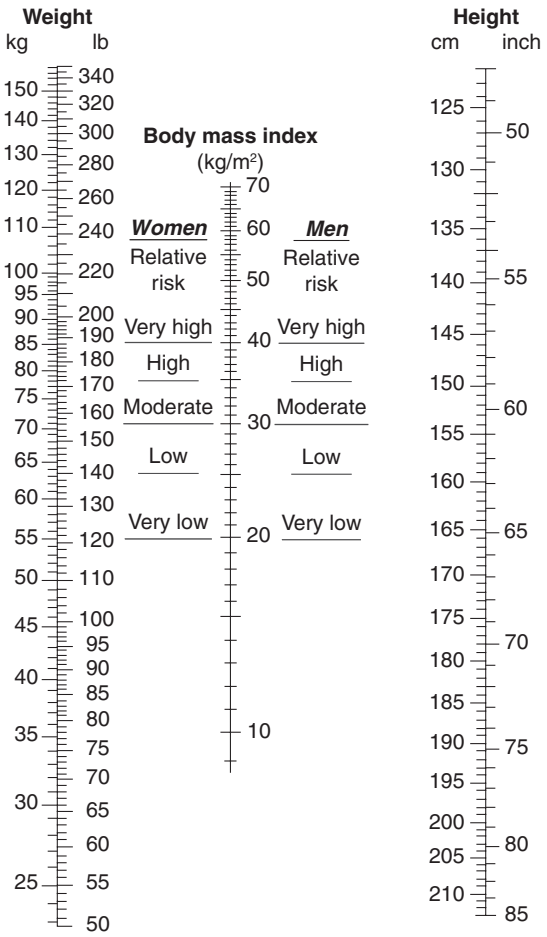


Figure 12.2 Nomogram for determining body mass index. *Procedure*: Place a ruler between the body weight (kg/lb) on the left and height (cm/inch) on the right line. Body Mass index (BMI) can be read from the middle line for males and females. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Etiology of Obesity

Obesity is caused due to excess of nutrient intake over a period of time in relation to energy expenditure.

Obesity develops due to

- unhealthy eating habits,
- lack of exercise, and
- inherited genetic and environmental factors.

Obesity is seen in families and it is inherited. This provides a strong evidence for genetic influence on obesity. Environment and cultural factors also play an important role

in its causation. High fat, rapidly absorbed carbohydrates in diet, reduced physical activity, and sleep deprivation result in obesity.

Early onset and morbid obesity is caused by mutations resulting in inactivation of leptin or leptin receptors. Mutations in genes encoding proopiomelanocortin (POMC) cause severe obesity.

Consequences of Obesity

Obesity is associated with an increase in mortality mostly due to cardiovascular causes. The mortality rate is enhanced with rise in obesity particularly with an increase in intra-abdominal fat.

Obesity increases the risk of developing various diseases. These include those given next.

Cardiovascular Disease

Obesity is an independent risk factor of cardiovascular disease resulting in coronary artery disease, stroke, and congestive cardiac failure.

Respiratory Disease

Obesity, due to increased metabolic rate, is associated with reduced compliance of the chest wall, increased work of breathing, and decreased functional residual capacity.

Metabolic Disease

Hyperinsulinemia and insulin resistance are related to obesity. They increase with weight gain and reduce with weight loss. Insulin resistance is strongly related to intra-abdominal fat.

Obese subjects develop diabetes mellitus when the impaired insulin secretion is associated with insulin resistance. It is reported that 80% of patients with diabetes are obese.

Weight loss and exercise improve insulin sensitivity resulting in better control of blood glucose.

Hepatobiliary Disease

Obesity leads to nonalcoholic fatty liver disease progressing on to cirrhosis and hepatocellular carcinoma in unmanaged cases.

Musculoskeletal Disease

Obesity is associated with osteoarthritis due to excess weight causing trauma to the joints and inflammatory changes promoting synovial pathology.

Reproductive Disorders

In obese males, testosterone levels are decreased and estrogen levels are increased.

Obesity in females is associated with menstrual abnormalities. Obese females have polycystic ovarian syndrome (PCOS), oligomenorrhea, anovulation, and hyperandrogenism.

STRESS AND OBESITY

Stress is a challenge to natural homeostasis of an organism. Stress-induced increase in the level of cortisol plays a major role in the development of obesity. Patients with Cushing's syndrome develop abdominal obesity, metabolic syndrome, and cardiovascular disease.

Stress arising out of sleep deprivation is linked with an increased risk for obesity. The cortisol level increases with sleep deprivation.

Management of Obesity

Prevalence of obesity is on the rise at an alarming rate in the industrialized world. It is necessary to identify and treat the patients with obesity.

Weight reduction by lifestyle modification (dietary changes, increased physical activity, and behavioral changes) reduces the risks associated with obesity.

Secondary causes like PCOS, hypothyroidism, Cushing's syndrome, and drug-induced weight gain (steroids, antidepressants, mood stabilizers, antiepileptic, and antidiabetic) should also be taken into consideration while managing obesity.

Evaluation of Obesity

BMI and waist circumference are key anthropometric measurements to evaluate obesity and predict the risk associated with it (**Table 12.2**). Lower BMI values are recommended for the Asia-Pacific region as people in this region exhibit greater risk for glucose and lipid abnormalities at lower body weight.

Waist–hip ratio is an independent risk factor for diabetes mellitus and cardiovascular disease.

Table 12.2 Relationship Between Weight and Risk of Disease

BMI (kg/m²)	Category	Obesity Class	Risk of Disease
<18.5	Underweight		
18.5–24.9	Healthy weight		
25.0–29.9	Overweight		Increased
30.0–34.9	Obesity	I	High
35.0–39.9	Obesity	II	Very high
≥40.0	Extreme obesity	III	Extremely high

BMI, body mass index.

Measurement of waist circumference is an indicator of visceral adipose tissue. It is measured in the horizontal plane above the level of iliac crest.

The desirable waist circumference varies with different ethnic groups. Waist circumference up to 90 cm (35 in) for males and 80 cm (31.5 in) for females is recommended for South Asian and Chinese population.

Treatment of Obesity

The goal of treatment is to improve obesity-related comorbid conditions and reduce the risk of their development in future.

Diet therapy should aim at reducing overall calorie intake. It can be achieved by consuming smaller portion of food coupled with enhanced intake of fruits and vegetables. It is desirable to consume low–energy density food. Addition of water and fibers decreases energy density by increasing the bulk without altering the calorie content.

Calorie deficit of 500–1000 kcal/day compared to the patient's regular intake is recommended to initiate the treatment.

Physical Activity Therapy

The World Health Organization (WHO) recommends 150 minutes of moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity aerobic activity or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for adults aged 18–64 years.

Behavioral therapy is used to manage the dietary changes and physical activity. The various strategies are self-monitoring, stress management, and control of stimulus to avoid overeating. Behavioral therapy helps the patient to develop positive and realistic thoughts.

Medical and surgical management of obesity can be considered when the lifestyle changes fail to give the desired results.

Use of medications can be considered for patients with BMI >30 kg/m^2.

Bariatric surgery is considered for patients with moderate and severe obesity. Surgical weight loss procedure reduces calorie intake and macronutrient absorption.

METABOLIC SYNDROME

Metabolic syndrome (known earlier as syndrome X) is a condition with the following features. It is diagnosed when three of the following five risk factors are present:

1. High blood pressure (more than 130/85 mmHg)
2. High blood glucose level (fasting glucose of 100 mg/dL or more)
3. Excess of fat around the waist (apple-shaped body/central obesity)—waist circumference of 40 in for men and 35 in for women
4. High levels of triglycerides (more than 150 mg/dL) and cholesterol in the blood
5. Low levels of HDL (men, less than 40 mg/dL; and women, less than 50 mg/dL)

Metabolic syndrome increases the risk of heart disease and stroke.

It is associated with the following:

- Overweight/obesity
- Inactivity

Signs and Symptoms

An important sign of metabolic syndrome is

- large waist circumference.

The other symptoms (when the blood sugar is high) are

- increased thirst,
- higher frequency of urination,

- fatigue, and
- blurred vision.

Risk Factors

The risk factors for developing metabolic syndrome are the following:

- Age: There is an increased risk of developing metabolic syndrome with advancement of age.
- Diabetes: Diabetes during pregnancy (gestational diabetes) predisposes the subject to develop metabolic syndrome.
- Obesity: Abdominal obesity increases the risk of developing the diseases.
- Ethnicity: Certain ethnic groups have a greater risk of developing metabolic syndrome.
- Metabolic syndrome is common in subjects having nonalcoholic liver disease, PCOS, and sleep apnea.

Complications

Subjects with metabolic syndrome develop complications like the following:

- Type 2 diabetes mellitus and insulin resistance (if they do not regulate their weight and do not implement changes in lifestyle)
- Heart attack and stroke due to narrowing and hardening of the blood vessels (the changes in blood vessel are due to plaque formation associated with high cholesterol)

Prevention

Lifestyle modification is a key factor for preventing metabolic syndrome, which includes the following:

- Limited consumption of saturated fats and salt
- Use of plenty of vegetables, fruits, lean proteins, and whole grains in the diet
- Regular physical activity for a duration of 30 minutes every day
- Maintaining optimum body weight
- Avoiding smoking

SEDENTARY LIFESTYLE

Sedentary lifestyle is a condition in which the individual does not perform regular physical activity. It is a type of lifestyle with little or no physical activity. Sedentary life can lead to ill health and it is a preventable cause of death.

Sedentary lifestyle is due to advancement of technology bringing inactive mode of transport and desk jobs. It is a common problem seen in developed and developing countries.

Physical inactivity leading to sedentary lifestyles produces the following health conditions:

- Increased risk of coronary artery diseases, cardiovascular diseases, and hypertension due to altered lipid profile with elevated cholesterol levels
- Overweight and obesity associated with metabolic disorders like diabetes mellitus (physical inactivity reduces the calories burnt leading to weight gain; metabolism is affected, and breakdown of fats and carbohydrates may be defective)
- Decreased skeletal muscle mass and endurance because of disuse of the muscles
- Osteoporosis and loss of mineral content of the bone due to reduced or no physical activity (these changes can lead to fall associated with pathological fractures)
- Stress, anxiety, and depression
- Increased susceptibility to infection due to blunted immune response and poorer blood flow (it is often associated with enhanced inflammatory response)
- Increased risk of cancers (breast and colon cancers)
- Development of hormonal imbalance

Mortality

Sedentary behavior is associated with cardiovascular mortality. Each 2 hours of sitting time increases cardiovascular mortality by 5%.

Metabolic Effects

Sedentary lifestyle has a strong positive relationship with overweight, obesity, adiposity, and type 2 diabetes mellitus.

Mental Health

Studies have indicated an association between sedentary life and depression in children, adolescents, and adults.

Solutions

- Encourage active travel by promoting walking/cycling.
- Organize exercise classes during leisure.
- Set up gym/health clubs with free/discounted membership.
- Promote use of stairs.
- Provide sit–stand desks to increase standing time at the workplace.
- People involved in desk work should be encouraged to take a break every 20–30 minutes, and walk or stand for a few minutes as prolonged sitting can also have a bad effect on health.
- Prevent weight gain and encourage weight reduction.
- Supply healthy food.
- Start smoking cessation programs and tobacco-free public building and workplace.

SPORTS AND EXERCISE PHYSIOLOGY

Exercise is a stressful condition that calls for adjustment in functioning of the various systems. Depending on the degree of exercise, there are adjustments in the body.

Physical exercise of low to high intensity depends on aerobic energy. Use of free oxygen to meet the energy requirement during activity is termed *aerobic exercise*.

GRADING OF EXERCISE

Exercise is classified into different grades based on the heart rate, oxygen consumption, and metabolic equivalent of task (MET) values.

Based on heart rate, exercise is graded as

- light (mild),
- moderate, and
- vigorous (strenuous).

The intensity of exercise is assessed by measuring the heart rate. The target heart rate is calculated. It is 220 minus the age of the individual performing the exercise. It is clear from the formula that the target heart rate will decrease with age.

Exercise is considered to be of moderate intensity when the heart rate reaches 50–70% of the target heart rate (maximum heart rate).

In strenuous exercise, the heart rate should reach 70–85% of the maximum heart rate.

It is suggested to perform exercise of moderate to vigorous grade for maximum benefit.

Moderate-intensity exercise is good for improving fitness.

Vigorous exercise is recommended for weight loss.

It is desirable for a beginner to commence exercise at mild-to-moderate intensity and increase to the desired level.

Examples of light, moderate, and vigorous physical activities are given in **Table 12.3**.

Table 12.3 Examples of Light, Moderate, and Vigorous Physical Activity

Light	Moderate	Vigorous
Slow walking	Brisk walking	Walking upstairs
Mild stretching	Weight lifting	Running, jogging
Playing billiards	Gardening	Swimming, cycling
Cooking and dish washing	Playing golf	Playing basketball, tennis (singles)

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

Exercise is classified into four grades based on oxygen consumption. It is expressed in terms of liter per minute.

Type of exercise	Oxygen consumption (L/min)
Light	0.4 – 0.8
Moderate	0.8 – 1.6
Heavy	1.6 – 2.4
Severe	>2.4

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

Oxygen consumption is also expressed in terms of MET. One MET is equal to resting oxygen uptake of 250 mL/min for an average adult male and 200 mL/min for an average adult female. Based on MET, grading of exercise is done as follows:

Type of exercise	MET
Light	<3
Moderate	3.1 – 4.5
Heavy	4.6 – 7
Severe	>7

Source: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.

ROLE OF MUSCLE IN EXERCISE

The critical factors that determine the performance of the muscle are as follows:

- **Strength:** It is the maximal contractile force that depends on the cross-sectional area of the muscle.
- **Endurance:** It is the ability of the muscle to perform a sustained action. This depends on the nutrition of the muscle. It depends on the glycogen stores in the muscle. Endurance is significantly enhanced by a high-carbohydrate diet.
- **Power:** It is the quantum of work done by the muscle in unit time. Training influences the power of the muscle. It is expressed as kilogram meter per minute.
- **Mechanical work** performed by the muscle is the force applied by it multiplied by the distance over which the force is applied.

RESPIRATORY CHANGES DURING EXERCISE

A demanding condition such as exercise increases oxygen consumption and pulmonary ventilation.

Two major functions of the respiratory system are to

- provide oxygen to the tissues of body and
- eliminate carbon dioxide from the tissues.

During exercise, there is a greater need for oxygen and increased accumulation of carbon dioxide due to enhanced metabolic activity in the muscle.

Pulmonary ventilation increases in direct proportion to the metabolic needs and intensity of exercise. A respiratory minute volume of 6 L/min at rest can increase up to 100–120 L/min during exercise.

An oxygen consumption of 250 mL/min at rest can increase up to 5000 mL/min during vigorous exercise.

There is an abrupt increase in the ventilation at the beginning of the exercise followed by a gradual increase as it progresses.

The abrupt increase in respiration at the commencement of the exercise is due to the stimuli arising from the joints and muscles. The thought of exercise and rise in body temperature may also play a role.

Neurogenic impulses arising from the motor cortex to activate the muscles may stimulate the brainstem and respiratory centers leading to hyperpnea.

The increase is seen in the depth of respiration during moderate exercise. However, during strenuous exercise, there is an increase in both the rate and the depth of respiration.

Hypercapnia (increased carbon dioxide) and hypoxia (reduced oxygen supply) stimulate the peripheral and central chemoreceptors. There is an increase in the rate and depth of respiration.

The blood gases do not show significant variation in their concentration even in severe exercise.

Breathing returns to a resting level within 10–20 minutes after cessation of aerobic exercise.

Oxygen Debt

Muscular exercise increases demand for the supply of oxygen. Initially, the increased demand is met by enhanced flow of blood due to local vasodilation. With the progress of exercise, the oxygen demand increases

and the body is unable to maintain adequate supply of oxygen.

The energy requirement is satisfied by phosphorylcreatine and the energy derived by conversion of glucose to lactate by the anaerobic mechanism.

The anaerobic pathway acts as a self-limiting step for the reactions.

The lactates produced during the reaction accumulate in the muscle reducing the pH. A substantial decrease in pH inhibits the enzymes needed for chemical reactions.

After the cessation of exercise or a high degree of physical activity, extra oxygen is consumed to

- eliminate lactate,
- replenish ATP,
- make up for phosphorylcreatine stores, and
- replace oxygen released by myoglobin.

The extra amount of oxygen consumed by a tissue during its increased activity is termed oxygen debt. It is estimated that oxygen debt can be about six times the basal oxygen consumption.

CARDIOVASCULAR CHANGES DURING EXERCISE

The exercising muscle needs more oxygen and nutrients.

This increased demand is met by an increase in blood flow to the muscle, cardiac output, and blood pressure.

Cardiac Output

An increase in cardiac output is due to an increase in stroke volume and heart rate. During exercise, cardiac output can increase by four to eight times depending on the intensity.

Cardiac output increases due to enhanced filling during diastole. The greater the preload, the greater is the force of contraction.

The normal blood flow of the resting skeletal muscle is 2–4 mL/100 g/min. The blood flow increases up to 25-fold during strenuous exercise. This is accomplished by increasing the cardiac output.

Exercising muscles, especially of the lower limbs, squeeze the blood vessels and move the blood toward the heart (muscle pump).

An increase in the depth of respiration reduces the intrathoracic pressure and increases the intra-abdominal pressure. These changes draw more blood toward the heart from the lower parts of the body (respiratory pump).

Venous return is increased due to respiratory and muscle pumps.

Blood Pressure

Blood pressure changes with the severity of exercise. During mild to moderate exercise, there is an increase in the systolic blood pressure. However, the diastolic pressure remains the same or shows a small decline. During strenuous exercise, there is a significant increase in the systolic blood pressure with a decrease in the diastolic blood pressure. Hence, there is an increase in the pulse pressure.

As the intensity of exercise increases, the blood flow to the muscle increases. The vasodilatation in the muscle decreases the peripheral resistance reducing the diastolic blood pressure.

SKIN AND BODY TEMPERATURE REGULATION

SKIN

The skin forms the outer protective covering of the body. It is the largest organ with the thickness ranging from 1 to 5 mm.

Layers

The skin has two layers:

1. Outer epidermis
2. Inner dermis (**Fig. 12.3**)

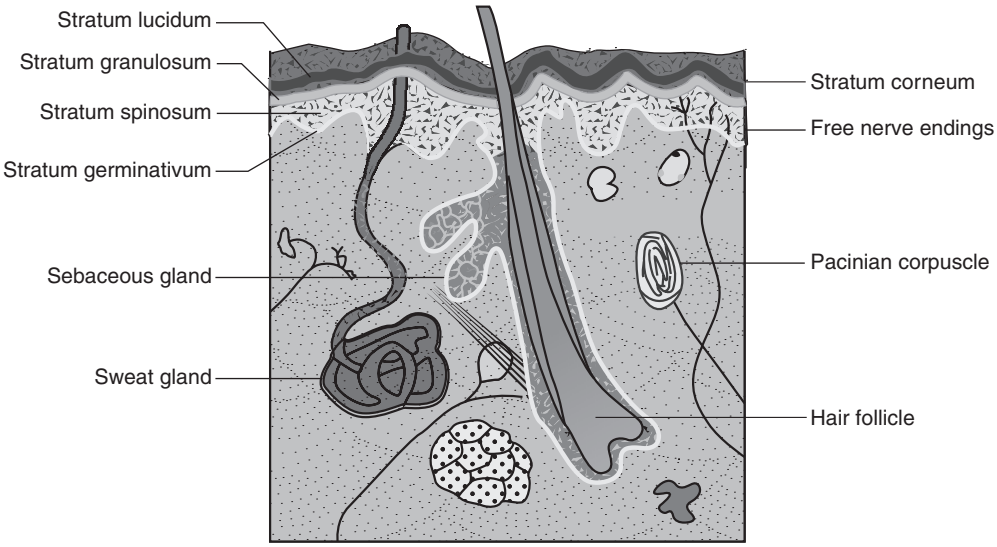


Figure 12.3 Structure of skin. (*Source*: Venkatesh D, Sudhakar HH. Textbook of Medical Physiology, 3rd edn. New Delhi: Wolters Kluwer (I) Pvt Ltd; 2020.)

Epidermis

The epidermis is made of stratified squamous epithelium. It does not contain blood vessels.

It has the following layers:

- **Stratum corneum:** It is the outermost layer. It is made up of dead cells containing keratin.
- **Stratum granulosum:** This is three to five layers thick. The cytoplasm has keratohyalin granules.
- **Stratum spinosum:** It contains cells having spine-like processes on their surface.
- **Stratum germinativum:** This layer contains cells which divide by mitosis. The newly formed cells move toward the stratum corneum. These cells contain melanin, a pigment responsible for the color of the skin.

Dermis

The dermis is a layer of skin between the epidermis and the subcutaneous tissue. It is made up of elastic, collagen fibers, and extrafibrillar matrix. The dermis has two layers:

1. Superficial papillary layer
2. Deep reticular layer

Papillary Layer The papillary layer forms papillae that project into the epidermis. This contains blood vessels, lymphatics, and nerves.

Reticular Layer The reticular layer is made up of reticular and elastic fibers along with fat and loose areolar tissue. This layer merges with the subcutaneous layer.

Glands

Skin contains two types of glands:

1. Sweat glands
2. Sebaceous glands

Sweat Glands

Sweat glands are present all over the skin except the eardrum and lips.

They are of two types:

1. Apocrine
2. Eccrine

Apocrine glands are present in the axilla, pubic region, and areola of the breast. They become active only after puberty.

Eccrine glands are more numerous and are present all over the body. They secrete a clear watery fluid, sweat.

Sebaceous Glands

Sebaceous glands are present in the epidermis of the skin. They develop from the hair follicle. Sebum is produced from these glands.

At puberty, sex hormones stimulate sebaceous glands leading to the development of **acne**.

Functions

- Form a protective layer around the body
- Protect the body against infections and UV radiation
- Regulate body temperature by secreting sweat
- Are a sensory organ which has specialized receptors
- Enable the synthesis of vitamin D_3
- Regulate water and electrolyte balance
- Excrete waste materials such as salts and urea

Appendages

Hairs

Hairs are keratinized, thread-like structures that develop from the epidermis.

Hair is divided into an outer shaft, root, and hair bulb. The hair bulb is embedded in the hair follicle. The hair follicle is an invagination of the epidermis.

The arrector pili are small, smooth muscles attached to hair follicles. Contraction of these muscles brings hairs into vertical position with the elevation of the epidermis. This is termed **goose flesh** appearance.

Functions

- Help in perception of sensations
- Help in thermoregulation
- Protect against injury to the scalp

Nails

Nails are homologous to the stratum corneum layer of the epidermis. They consist of compact non-nucleated, keratin-filled squamous filaments.

REGULATION OF BODY TEMPERATURE

The normal body temperature (core temperature) is maintained at a constant level irrespective of changes in the external temperature.

The normal body temperature is 37°C (98.6°F). It has a diurnal variation of about 0.6°C. It is highest in the evening and lowest in the early morning.

The body temperature is regulated by a balance between heat production and heat loss.

Heat Production

Heat production occurs due to

- metabolic activities of the body,
- food intake (specific dynamic action), and
- muscular activity.

Heat Loss

Heat loss occurs due to

- radiation and conduction (70%),
- vaporization of sweat (27%),
- respiration (2%), and
- urination and defecation (1%).

Heat is lost mainly by radiation, conduction, and evaporation.

Radiation

This loss is in the form of infrared heat rays. The wavelength of these rays is around 5–20 microns. The human body radiates heat in all directions.

Conduction

Heat is transferred from the body to air by conduction. Once the temperature of the air adjacent to the skin rises to the skin temperature, further loss of heat stops. Conduction is assisted by convection caused by air currents.

Convection

When the body is exposed to wind, the air present adjacent to the skin is replaced by new air which is cooler. Continuous replacement of air by **convection** reduces the skin temperature rapidly.

Evaporation

Evaporation of water from the body surface causes heat loss. Even when a person is not sweating, the skin and lungs lose water at a rate

of 500–600 mL/day. When the temperature of the surroundings becomes greater than the skin temperature, evaporation is the major means of heat loss. Reduction of the skin temperature occurs by the mechanism of sweating.

Neural Regulation

The body temperature is regulated by nervous feedback mechanisms. The temperature-regulating centers are present in the hypothalamus.

Heat Loss Center

The heat loss center is present in the anterior hypothalamus. Stimulation of this center produces cutaneous vasodilation and sweating.

Heat Gain Center

The heat gain center is present in the posterior hypothalamus. Stimulation of this center causes shivering and raises the body temperature.

Sweating Sweating is a mechanism that controls the body temperature. Sweat is produced by sweat glands.

The water present in the sweat comes out of the skin through the sweat pore and water vaporizes from the surface of the skin. This vaporization of water causes heat loss from the body.

Sweat secretion can increase to very high values of around 1600 mL/h on a hot day and during exercise.

Temperature-Reducing Mechanisms

Heat is lost by
- cutaneous vasodilation,
- sweating, and
- increased respiration.

Heat production decreases in
- anorexia,
- apathy, and
- reduced activity.

Temperature-Increasing Mechanisms

Heat production increases by
- shivering,
- hunger,
- increased voluntary activity, and
- increased secretion of epinephrine and norepinephrine.

Heat loss is prevented by
- cutaneous vasoconstriction,
- curling up, and
- horripilation (piloerection).

CLINICAL NOTES

Set Point for Temperature Control

The core temperature is maintained exactly at the level of 37.1°C. At temperatures above this level, the rate of heat loss becomes greater than the rate of heat production.

At temperatures below this level, the rate of heat production becomes greater than the rate of heat loss.

Fever

Fever is an increase in the body temperature above the normal range. It is commonly caused by bacterial and viral infections.

Cause

The protein breakdown products and toxins released by bacteria raise the set point of temperature, resulting in fever. Substances causing this effect are termed pyrogens. These pyrogens produce interleukin-1 which on reaching the hypothalamus increases the set point of the temperature-regulating center.

Hypothermia

Exposure of a person to extreme cold causes a drop in the body temperature. The temperature-regulating ability of a person becomes impaired if the body temperature falls below 34°C and the hypothalamus totally falls below 29°C.

Frostbite

Frostbite is found in the extremities of persons exposed to extreme cold temperature. The earlobes and digits of hands and feet are affected. Frostbite results in tissue damage and gangrene.

Artificial Hypothermia

The temperature of the person is artificially maintained below 32°C during procedures such as heart surgery. Artificial cooling is done to stop the heart beating for 30 minutes to 1 hour without causing damage to the cells.

BRAIN DEATH

Brain death is defined as irreversible loss of all functions of the brain including the brain stem. A person who is brain dead has no chance of revival.

Brain death includes three essential features:

- Coma
- Absent brain stem reflexes
- Apnea

Until late 20th century, death was defined as cessation of functions of heart and lungs. However, modern technology has enabled maintenance of heart and lung functions even when the brain is dead.

Brain death is different from coma and vegetative state. Coma is a state of profound unresponsiveness as a result of brain injury or severe illness. The person cannot be awakened and does not initiate voluntary actions. The patient fails to respond to painful stimulus, and visual and auditory stimuli. Patients in coma can either die or regain consciousness. They may even progress to a vegetative state.

The patient is said to be in a vegetative state when the cerebral cortex may be dead, but brain stem is still functioning. Functions of brain stem of the patients and their consciousness may be depressed but can breathe without support. These patients may respond to loud sound or deep pain and exhibit involuntary movements. In persistent vegetative state, the person is alive with some autonomic functions.

A patient who is in vegetative state for more than a year has extremely low chance of recovery.

CAUSES FOR BRAIN DEATH

Brain death can be caused by

- Cardiac arrest
- Myocardial infarction
- Stroke
- Blood clot

The blood flow to the brain is stopped suddenly in the above-mentioned conditions. The other conditions are

- Severe head injury
- Encephalitis
- Brain tumor

DIAGNOSIS OF BRAIN DEATH

The clinical diagnosis of brain death is performed in three steps:

1. Establishing the cause
2. Excluding potentially reversible conditions that are similar to brain death
3. Demonstrating clinical signs of brain death that includes coma, brain stem areflexia and apnea.

Signs of Brain Death

- Fixed and dilated pupils
- Lack of eye movement
- Absence of respiratory reflexes
- Unresponsive to pain

In diagnosing brain death, the physician should rule out a variety of conditions like hypothermia, hypoglycemia, overdose of drugs like sedatives, barbiturates, shock, alcohol intoxication, metabolic and endocrine disorders which can mimic brain death.

Final determination of brain death involves demonstration of total lack of electric activity in the brain recorded by EEG (flat line) taken 12–24 hours apart. Other confirmatory tests that can be used to confirm brain death include angiography, radionucleotide angiography, cerebral arteriography, transcranial Doppler ultrasonography, somatosensory evoked potential and nuclear brain scanning to demonstrate the absence of intracranial blood flow.

CERTIFICATION OF BRAIN DEATH

The criteria for certification of brain death vary among different countries. In few countries,

brain death can be certified by a single physician authorized by law to make brain death certification. However, organ donation of such patient requires certification by two physicians and neither of them should participate in the process of organ transplantation.

In India, brain death is to be certified by a board of medical experts designated according to Transplantation of Human Organs (THO) Act, 1994.

ORGAN DONATION

Multiple organs from brain dead patient can be utilized for transplantation to the needy patients. These organs include kidney, liver, heart, lung, pancreas, cornea and bone. Organ donation is a noble act which helps save other patient's life. It also provides consolation for the grieving family members of the brain dead individual that their loved one is saving many lives.

REVIEW QUESTIONS

Long Essay

1. Describe the cardiorespiratory changes seen during exercise.
2. Describe the physiological changes occurring in various organs of an infant.

Short Essay

1. Describe the characteristic features of cardiovascular and respiratory systems in an infant.
2. Describe the factors affecting growth of an individual.
3. Explain the various domains under which development of an infant is assessed.
4. Describe the general, neural, and gonadal patterns of growth.
5. Explain the various theories of aging.
6. Describe the gastrointestinal, respiratory, and nervous system changes seen in old age.
7. Discuss the consequences of obesity.
8. Describe the risk factors, complications, and prevention of metabolic syndrome.
9. Discuss the health abnormalities caused due to sedentary lifestyle.
10. Describe the cardiovascular changes seen during exercise.
11. Describe the respiratory changes seen during exercise.
12. Describe the mechanisms of heat loss and heat gain.

Short Answers

1. Briefly describe catch-up growth.
2. List the respiratory changes occurring in old age.
3. What is BMI? State its normal value.
4. List the risk factors of metabolic syndrome.
5. List the steps that can be taken to avoid sedentary lifestyle.
6. Explain oxygen debt.
7. Describe the terms activation heat and recovery heat.
8. List the functions of the skin.
9. List the temperature-increasing mechanisms of the body.
10. List the temperature-decreasing mechanisms of the body.
11. Briefly describe heat stroke.
12. Briefly describe hypothermia.

Multiple Choice Questions

1. GENERAL PHYSIOLOGY

1. **The movement of particles from the region of higher concentration to the region of lower concentration is termed**
   (a) Diffusion
   (b) Osmosis
   (c) Endocytosis
   (d) Pinocytosis
2. **The movement of solvent from the region of higher concentration to the region of lower concentration through semipermeable membrane is**
   (a) Diffusion
   (b) Osmosis
   (c) Endocytosis
   (d) Pinocytosis
3. **The powerhouse of the cell is**
   (a) Centriole
   (b) Centrosome
   (c) Mitochondria
   (d) Lysosomes
4. **The structure in the cell that helps in digestion of bacteria is**
   (a) Centriole
   (b) Centrosome
   (c) Mitochondria
   (d) Lysosomes
5. **The system of fibers maintaining the structure of the cell is**
   (a) Actin
   (b) Myosin
   (c) Cytoskeleton
   (d) Troponin
6. **The part of the cell that monitors the steps of cell division is**
   (a) Ribosome
   (b) Centrosome
   (c) Mitochondria
   (d) Lysosomes
7. **The type of intercellular connection through which the molecules move easily is**
   (a) Desmosomes
   (b) Gap junction
   (c) Tight junction
   (d) Ion channels
8. **Each chromosome is made up of a giant molecule of**
   (a) Gene
   (b) Chromatin
   (c) DNA
   (d) RNA
9. **The ultimate units carrying hereditary characters are**
   (a) Gene
   (b) Chromatin
   (c) DNA
   (d) RNA
10. **Germ cell is a**
    (a) Haploid cell
    (b) Diploid cell
    (c) Zygote
    (d) Mature cell
11. **The number of lipid layers present in the cell membrane is**
    (a) One
    (b) Two
    (c) Three
    (d) Four
12. **Ribosomes are present on**
    (a) Centriole
    (b) Endoplasmic reticulum

(c) Nucleus
(d) Lysosomes

13. Granular endoplasmic reticulum forms
(a) Proteins
(b) Lipids
(c) Carbohydrates
(d) Steroids

14. Smooth endoplasmic reticulum forms
(a) Proteins
(b) Lipids
(c) Carbohydrates
(d) Vitamins

15. The processing of protein and formation of secretory granules is done by
(a) Ribosomes
(b) Centrosome
(c) Golgi apparatus
(d) Cytoskeleton

16. The type of cell division in which the chromosomal number gets reduced to half is
(a) Mitosis
(b) Meiosis
(c) Prophase
(d) Telophase

17. The cell division in which the chromosomal number remains the same is
(a) Mitosis
(b) Meiosis
(c) Prophase
(d) Telophase

18. Release of contents of vesicles outside the cell with the membrane kept intact is termed
(a) Phagocytosis
(b) Pinocytosis
(c) Exocytosis
(d) Endocytosis

19. The other name for "cell eating" is
(a) Phagocytosis
(b) Pinocytosis
(c) Exocytosis
(d) Endocytosis

20. Cell drinking is also known as
(a) Phagocytosis
(b) Pinocytosis
(c) Exocytosis
(d) Endocytosis

21. The form of transport that requires the expenditure of energy is
(a) Diffusion
(b) Osmosis
(c) Active transport
(d) Facilitated diffusion

22. The movement of a substance along its concentration gradient with the help of carrier protein is
(a) Diffusion
(b) Osmosis
(c) Countertransport
(d) Facilitated diffusion

23. Transport of sodium and glucose is an example of
(a) Antiport
(b) Symport
(c) Uniport
(d) Diffusion

24. Transport of sodium and hydrogen ions is an example of
(a) Antiport
(b) Symport
(c) Uniport
(d) Diffusion

25. The second messenger systems are the following *except*
(a) cAMP
(b) cGMP
(c) Calmodulin
(d) GABA

26. Maintenance of constancy of the internal environment is
(a) Hemostasis
(b) Homeostasis
(c) Hypoxia
(d) Hypercapnia

27. **The type of cellular connection for the tissue to function as syncytium is**
    (a) Desmosomes
    (b) Gap junctions
    (c) Tight junction
    (d) Hemidesmosomes

28. **The phases of meiotic cell division are the following *except***
    (a) Prophase
    (b) Anaphase
    (c) Telophase
    (d) Interphase

29. **The chromosomal number in a normal human being is**
    (a) 23
    (b) 44
    (c) 46
    (d) 48

30. **The process of formation of mRNA is**
    (a) Translation
    (b) Transcription
    (c) Duplication
    (d) Cell division

2. BLOOD

1. **The fluid component of plasma present in the blood constitutes about**
    (a) 40%
    (b) 55%
    (c) 75%
    (d) 90%

2. **The total volume of blood present in an adult human is around**
    (a) 3 L
    (b) 5 L
    (c) 8 L
    (d) 10 L

3. **Normal plasma protein value is**
    (a) 2 g/dL
    (b) 2–4 g/dL
    (c) 6–8 g/dL
    (d) 8–10 g/dL

4. **Most of the plasma proteins are synthesized by**
    (a) Liver
    (b) Kidney
    (c) Spleen
    (d) Pancreas

5. **The most abundant plasma protein present in the blood is**
    (a) Albumin
    (b) Globulin
    (c) Fibrinogen
    (d) Prothrombin

6. **Normal RBC diameter is**
    (a) 3.8 μ
    (b) 5.4 μ
    (c) 7.2 μ
    (d) 8.6 μ

7. **Erythropoiesis normally occurs in the adult in**
    (a) Liver
    (b) Yolk sac
    (c) Spleen
    (d) Bone marrow

8. **The process of erythropoiesis takes**
    (a) 7 min
    (b) 7 h
    (c) 7 days
    (d) 7 weeks

9. **Normal RBC count in males is**
    (a) 5–5.5 lac cells/mm^3
    (b) 1.4–4 million cells/mm^3
    (c) 4–11 million cells/mm^3
    (d) 5–5.5 million cells/mm^3

10. **The most common type of anemia found in our country is**
    (a) Thalassemia
    (b) Aplastic anemia
    (c) Vitamin B_{12} deficiency anemia
    (d) Iron-deficiency anemia

11. Erythropoietin is mainly produced in
(a) Kidneys
(b) Bone marrow
(c) Spleen
(d) Lungs

12. Increase in RBC count is called
(a) Anemia
(b) Leukocytosis
(c) Polycythemia
(d) Leukemia

13. The granulocytes include all *except*
(a) Neutrophils
(b) Lymphocytes
(c) Basophils
(d) Eosinophils

14. Normal WBC count in adults is
(a) 400–1100 cells/mm^3
(b) 4000–11000 cells/mm^3
(c) 4–11 lac cells/mm^3
(d) 4–11 million cells/mm^3

15. The percentage of neutrophil is
(a) 10–15
(b) 40–45
(c) 60–65
(d) 90–95

16. The diameter of an eosinophil is
(a) 2–4 μ
(b) 4–6 μ
(c) 7.2 μ
(d) 10–14 μ

17. The least numerous of WBCs are
(a) Neutrophils
(b) Monocytes
(c) Eosinophils
(d) Basophils

18. The largest WBC is
(a) Neutrophil
(b) Monocyte
(c) Eosinophil
(d) Basophil

19. The antiallergic cell is
(a) Neutrophil
(b) Monocyte
(c) Eosinophil
(d) Basophil

20. Phagocytic cell is
(a) Neutrophil
(b) RBC
(c) Platelet
(d) Astrocyte

21. Cell-mediated immunity is produced by
(a) T-lymphocytes
(b) B-lymphocytes
(c) Eosinophils
(d) Basophils

22. Increase in WBC count is termed
(a) Leukocytosis
(b) Leukopenia
(c) Leukopoiesis
(d) Leukocytes

23. The type of WBC increased in tuberculosis is
(a) Neutrophils
(b) Lymphocytes
(c) Basophils
(d) Eosinophils

24. Normal size of platelet is
(a) 1–1.5 μ
(b) 2–4 μ
(c) 4–6 μ
(d) 7–8 μ

25. Platelets are formed from
(a) Early normoblasts
(b) Myelocytes
(c) Megakaryocytes
(d) Proerythroblasts

26. Purpura is caused due to the deficiency of
(a) RBCs
(b) WBCs
(c) Clotting factors
(d) Platelets

27. The most important ion required for clotting is
(a) Mg^{++}
(b) Ca^{++}

(c) Na^+
(d) K^+

28. Fibrinogen is converted into fibrin by
(a) Thrombin
(b) Prothrombin
(c) Prothrombin activator
(d) Calcium

29. Clotting time is prolonged in all *except*
(a) Hemophilia
(b) Thrombocytopenia
(c) Vitamin K deficiency
(d) Afibrinogenemia

30. Normal bleeding time is
(a) 2–4 s
(b) 4–8 s
(c) 2–4 min
(d) 4–8 min

31. Normal clotting time by capillary tube method is
(a) 1–4 s
(b) 3–8 s
(c) 1–4 min
(d) 3–8 min

32. Blood group antigens are present on
(a) RBCs
(b) WBCs
(c) Platelets
(d) Hemoglobin

33. Individual with O blood group has
(a) A antigen
(b) B antigen
(c) Both AB antigens
(d) No antigen

34. Blood groups were discovered by
(a) William Harvey
(b) Louis Pasteur
(c) Duffy
(d) Karl Landsteiner

35. Erythroblastosis fetalis can occur when Rh+ child is born to
(a) Rh– mother
(b) Rh+ mother
(c) Rh+ mother and Rh– father
(d) Rh– mother and Rh– father

36. Indications of blood transfusion include all *except*
(a) Major surgeries
(b) Severe burns
(c) Severe anemia
(d) Cardiac failure due to MI

37. Kernicterus is caused due to accumulation of bilirubin in
(a) Liver
(b) Spleen
(c) Kidneys
(d) Brain

38. Heparin is released by
(a) Neutrophils
(b) Basophils
(c) Lymphocytes
(d) Eosinophils

39. Histamine is released by
(a) Neutrophils
(b) Monocytes
(c) Eosinophils
(d) Basophils

40. The percentage of eosinophil is around
(a) 0–1
(b) 1–4
(c) 10–14
(d) 25–30

41. The percentage of monocyte is around
(a) 0–1
(b) 1–4
(c) 2–8
(d) 20–30

42. ESR decreases in
(a) Infections
(b) Tuberculosis
(c) Rheumatoid arthritis
(d) Polycythemia

43. Hemoglobin mainly contains
(a) Copper
(b) Magnesium

(c) Iron
(d) Nickel

44. Hemophilia is caused due to the deficiency of clotting factor
(a) VII
(b) VIII
(c) XI
(d) X

45. The anticoagulants include the following *except*
(a) Heparin
(b) EDTA
(c) Vitamin K
(d) Trisodium citrate

46. Life span of an RBC is
(a) 100 days
(b) 102 days
(c) 120 days
(d) 135 days

47. The percentage of neutrophils present is
(a) 0–1
(b) 1–4
(c) 25–30
(d) 60–65

48. The normal plasma volume is
(a) 1–1.5 L
(b) 3–3.5 L
(c) 5–6 L
(d) 7–8 L

49. The percentage of basophils present is
(a) 0–1
(b) 1–4
(c) 10–14
(d) 25–30

50. The percentage of lymphocytes present is
(a) 0–1
(b) 1–4
(c) 10–14
(d) 25–30

51. Specific gravity of whole blood is
(a) 1010–1015
(b) 1030–1035
(c) 1055–1060
(d) 1075–1080

52. Normal albumin–globulin ratio is
(a) 1:2.3
(b) 1:1.7
(c) 1.7:1
(d) 2.3:1

53. The molecular weight of albumin is
(a) 22,000
(b) 44,000
(c) 66,000
(d) 88,000

54. The main function of albumin is maintenance of
(a) Heart rate
(b) Colloid osmotic pressure
(c) Body temperature
(d) Blood flow

55. The most abundant cells present in blood are
(a) RBCs
(b) WBCs
(c) Platelets
(d) Natural killer cells

56. Surface area of an RBC is
(a) 85 μ^2
(b) 102 μ^2
(c) 135 μ^2
(d) 185 μ^2

57. Normal RBC count in infants is
(a) 2–3 million/mm^3
(b) 3–4 million/mm^3
(c) 6–7 million/mm^3
(d) 10–12 million/mm^3

58. Volume of normal RBC is
(a) 87 μ^3
(b) 104 μ^3
(c) 127 μ^3
(d) 135 μ^3

59. RBC mainly contains
(a) Carbohydrates
(b) Lipids
(c) Hb
(d) Electrolytes

60. Metabolic needs of an RBC are met by
(a) Fatty acids
(b) Amino acids

(c) Glucose
(d) Cholesterol

61. Red bone marrow is found in
(a) Cranial bones
(b) Vertebrae
(c) Pelvic bones
(d) All the above

62. All of the following facilitate erythropoiesis *except*
(a) Erythropoietin
(b) Estrogens
(c) Vitamin B_{12}
(d) Folic acid

63. Increase in RBC count above 8 million cells/mm^3 is termed
(a) Anemia
(b) Leukopenia
(c) Leukocytosis
(d) Polycythemia

64. The polypeptide chains present in HbA are
(a) $\alpha_2 \beta_2$
(b) $\alpha_2 \delta_2$
(c) $\alpha_2 \gamma_2$
(d) $\beta_2 \delta_2$

65. The polypeptide chains present in HbA_2 are
(a) $\alpha_2 \beta_2$
(b) $\alpha_2 \delta_2$
(c) $\alpha_2 \gamma_2$
(d) $\beta_2 \delta_2$

66. The polypeptide chains present in HbF are
(a) $\alpha_2 \beta_2$
(b) $\alpha_2 \delta_2$
(c) $\alpha_2 \gamma_2$
(d) $\beta_2 \delta_2$

67. Under normal conditions, one molecule of Hb carries
(a) 1.34 mL of O_2
(b) 1.72 mL of O_2
(c) 2.34 mL of O_2
(d) 2.72 mL of O_2

68. Oxidation of ferrous iron to ferric iron forms
(a) Carboxyhemoglobin
(b) Oxyhemoglobin
(c) Methemoglobin
(d) Sulfhemoglobin

69. In a Hb molecule, 1 molecule of globin combines with
(a) 2 heme molecules
(b) 4 heme molecules
(c) 6 heme molecules
(d) 8 heme molecules

70. HbS is an abnormal hemoglobin in which glutamic acid is replaced by
(a) Leucine
(b) Isoleucine
(c) Methionine
(d) Valine

71. During breakdown of Hb, heme is broken down into iron and
(a) Stercobilinogen
(b) Urobilinogen
(c) Biliverdin
(d) Bilirubin

72. Abnormal condition caused due to decreased production of alpha and beta chains of Hb is called
(a) Sickle cell anemia
(b) Thalassemia
(c) Hereditary spherocytosis
(d) Iron-deficiency anemia

73. Normal amount of iron present in the body is
(a) 10–20 mg
(b) 1–2 g
(c) 3–5 g
(d) 10–20 g

74. The rate at which red cells settle down is termed
(a) ESR
(b) Fragility
(c) Specific gravity
(d) PCV

75. Normal color index is
(a) 0.1–0.3
(b) 0.45–0.6
(c) 0.85–1.15
(d) 1.15–1.65

76. Normal MCH is
(a) 28–32 pg
(b) 42–46 pg
(c) 87–93 pg
(d) 125–132 pg

77. The relative percentage of Hb in a single RBC is called
(a) CI
(b) MCH
(c) MCHC
(d) MCV

78. Life span of neutrophils in blood is
(a) 6–7 h
(b) 6–7 days
(c) 6–7 months
(d) 6–7 weeks

79. The multilobed leukocyte is
(a) Monocyte
(b) Small lymphocyte
(c) Neutrophil
(d) Large lymphocyte

80. Kidney-shaped nucleus is present in
(a) Monocyte
(b) Basophil
(c) Neutrophil
(d) Eosinophil

81. The size of monocyte is around
(a) 6–8 μ
(b) 8–10 μ
(c) 10–12 μ
(d) 12–18 μ

82. The size of a small lymphocyte is around
(a) 7 μ
(b) 11 μ
(c) 13 μ
(d) 18 μ

83. The process of squeezing of neutrophils through pores of blood vessels is termed
(a) Margination
(b) Chemotaxis
(c) Diapedesis
(d) Phagocytosis

84. Parasitic infestations produce increase in
(a) Neutrophils
(b) Eosinophils
(c) Basophils
(d) Lymphocytes

85. Most abundant immunoglobulin present in the body is
(a) IgG
(b) IgA
(c) IgM
(d) IgE

86. Immunoglobulin secreted in saliva, tears, and milk is
(a) IgG
(b) IgA
(c) IgM
(d) IgE

87. ABO antibodies are formed by
(a) IgG
(b) IgA
(c) IgM
(d) IgE

88. HIV virus causes destruction of
(a) Helper T cells
(b) Cytotoxic T cells
(c) Suppressor T cells
(d) Memory T cells

89. All the following are autoimmune diseases *except*
(a) Myasthenia gravis
(b) Rheumatoid arthritis
(c) Grave's disease
(d) Typhoid

90. Immunoglobulins are produced by
(a) Neutrophils
(b) Basophils
(c) Eosinophils
(d) Lymphocytes

91. The normal platelet count is
(a) 150–400 cells/mm^3
(b) 1.5–4 thousand cells/mm^3
(c) 1.5–4 lac cells/mm^3
(d) 1.5–4 million cells/mm^3

92. Deficiency of platelets is termed as
(a) Anemia
(b) Leukopenia
(c) Thrombocytopenia
(d) Polycythemia

93. Vitamin K deficiency reduces the formation of all clotting factors *except*
(a) Factor V
(b) Factor VII
(c) Factor IX
(d) Factor X

94. Normal prothrombin time is
(a) 1–4 s
(b) 2–4 s
(c) 2–8 s
(d) 11–16 s

95. Bleeding time is prolonged in
(a) Afibrinogenemia
(b) Hemophilia
(c) Christmas disease
(d) Purpura

96. A person is said to be Rh+ if he has
(a) D antigen
(b) d antigen
(c) E antigen
(d) e antigen

97. Blood is stored at
(a) –80°C
(b) 2–4°C
(c) Room temperature
(d) 42°C

98. All are hazards of mismatched blood transfusion *except*
(a) Shock
(b) Renal failure
(c) Jaundice
(d) Iron overload

99. A group individual has
(a) α-agglutinin
(b) β-agglutinin
(c) α- and β-agglutinin
(d) No agglutinin

100. Anticoagulation within the body is brought about by all of the following *except*
(a) Prostacyclin
(b) Antithrombin III
(c) EDTA
(d) Thrombomodulin

101. Abnormal, uncontrolled increase in the number of WBCs is termed
(a) Leukocytosis
(b) Leukopoiesis
(c) Leukopenia
(d) Leukemia

102. Dead neutrophils, necrotic tissue, dead bacteria all combine to form
(a) Pus
(b) Lymph
(c) Serum
(d) Plasma

103. Mean corpuscular volume is reduced in
(a) Vitamin B_{12} deficiency anemia
(b) Folic acid deficiency anemia
(c) Iron deficiency anemia
(d) Aplastic anemia

104. Packed cell volume is increased in
(a) Pregnancy
(b) Anemia
(c) Polycythemia
(d) Overhydration

3. NERVE–MUSCLE PHYSIOLOGY

1. The structural and functional unit of nervous system is
(a) Neuroglia
(b) Nephron
(c) Neuron
(d) Renshaw's cell

2. The following factors influence the velocity of the nerve impulse *except*
(a) Myelination
(b) Diameter
(c) Temperature
(d) Size of the cell body

3. Resting membrane potential in a motor nerve is
(a) –90 mV
(b) –70 mV
(c) 70 mV
(d) 90 mV

4. Resting membrane potential is produced by the following *except*
(a) Greater permeability of the membrane to potassium ions
(b) Presence of large, nondiffusible, negatively charged proteins within the cell
(c) Efflux of chloride ions
(d) Action of sodium–potassium ATPase pump

5. The following features are true for a local response *except*
(a) It is graded
(b) It is nonpropagated
(c) It has a long latent period
(d) It decays exponentially

6. Depolarization in a motor nerve action potential is due to
(a) Entry of potassium ion
(b) Entry of sodium ion
(c) Exit of potassium ion
(d) Entry of calcium ion

7. Repolarization in a motor nerve is due to
(a) Influx of chloride ion
(b) Efflux of potassium ion
(c) Efflux of calcium ion
(d) Influx of sodium ion

8. Hyperpolarization in a motor nerve is due to
(a) Influx of chloride ion
(b) Continued efflux of potassium ion
(c) Efflux of calcium ion
(d) Influx of sodium ion

9. Depolarization in an excitable tissue
(a) Increases its excitability
(b) Decreases its excitability
(c) Keeps the excitability unchanged
(d) Makes it functionless

10. Hyperpolarization in an excitable tissue
(a) Increases its excitability
(b) Decreases its excitability
(c) Keeps the excitability unchanged
(d) Makes it functionless

11. Saltatory conduction
(a) Increases the velocity of nerve impulse
(b) Decreases the velocity of nerve impulse
(c) Has no influence on the velocity of nerve impulse
(d) Alters the direction of nerve impulse

12. Myelin sheath for the peripheral nerve is formed by
(a) Schwann cells
(b) Microglia
(c) Oligodendroglia
(d) Astrocytes

13. The following are the glial cells *except*
(a) Pyramidal cells
(b) Microglia
(c) Oligodendroglia
(d) Astrocytes

14. The myelin sheath for the neuron of the CNS is formed by
(a) Schwann cells
(b) Microglia
(c) Oligodendroglia
(d) Astrocytes

15. Neurotransmitter is released at the neuromuscular junction due to
(a) Entry of calcium
(b) Entry of sodium
(c) Entry of potassium
(d) Exit of calcium

16. The neurotransmitter at neuromuscular junction is
(a) Acetylcholine
(b) Epinephrine
(c) Dopamine
(d) GABA

17. Neurotransmitter at the neuromuscular junction is broken down by
(a) Cholinesterase
(b) Acetylcholine synthetase

(c) Phosphodiesterase
(d) Decarboxylase

18. Myasthenia gravis is produced due to
(a) Defective production of acetylcholine
(b) Excessive destruction of acetylcholine
(c) Delayed breakdown of acetylcholine
(d) Destruction of acetylcholine receptors

19. Myasthenia gravis is treated effectively by using
(a) Acetylcholine receptor blockers
(b) Acetylcholinesterase
(c) Acetylcholinesterase inhibitors
(d) L-dopa precursor of dopamine

20. Compound action potential is produced by
(a) A single motor nerve
(b) A group of nerve fibers
(c) A myelinated nerve fiber
(d) An unmyelinated nerve fiber

21. Structural and functional unit of the muscle is
(a) Sarcomere
(b) Sarcotubular system
(c) Sarcoplasmic reticulum
(d) Sarcolemma

22. The voluntary muscle in the following is
(a) Biceps
(b) Multiunit smooth muscle
(c) Visceral smooth muscle
(d) Cardiac muscle

23. Resting membrane potential in a cardiac muscle is
(a) –80 to –90 mV
(b) –70 mV
(c) 70 mV
(d) 80 to 90 mV

24. The following are the properties of skeletal muscle *except*
(a) Excitability
(b) Autorhythmicity
(c) Conductivity
(d) Contractility

25. Starlings' law states that
(a) Force of contraction of muscle is directly proportional to initial length of the muscle
(b) Force of contraction is not related to initial length
(c) Force of contraction is indirectly proportional to the initial length
(d) Force of contraction is proportional to initial length within physiological limits

26. In isotonic contraction
(a) Length of the muscle increases
(b) Tone of the muscle changes
(c) Tone remains the same
(d) Length remains the same

27. In isometric contraction
(a) Length of the muscle changes
(b) Tone of the muscle decreases
(c) Tone remains the same
(d) Length remains the same

28. Lifting a weight of 2 kg from the ground is an example of
(a) Isotonic contraction
(b) Isometric contraction
(c) Clonus
(d) Fatigue

29. The muscle fails to respond to second stimuli of any magnitude if it is in
(a) Isotonic contraction
(b) Isometric contraction
(c) Relative refractory period
(d) Absolute refractory period

30. The muscle responds to second stimuli of a greater magnitude if it is in
(a) Isotonic contraction
(b) Isometric contraction
(c) Relative refractory period
(d) Absolute refractory period

31. Pushing the wall is an example of
(a) Isotonic contraction
(b) Isometric contraction
(c) Relative refractory period
(d) Absolute refractory period

32. All-or-none law is applicable to the following *except*
(a) A motor nerve fiber
(b) A single skeletal muscle fiber
(c) Entire cardiac muscle
(d) A bundle of skeletal muscle fibers

33. Chronaxie is
(a) Minimum strength of current given indefinitely to excite a tissue
(b) Minimum time required to excite with twice the rheobasic strength of current
(c) Minimum time needed to excite with rheobasic strength of current
(d) Maximum strength of current to excite the tissue

34. Rheobase is
(a) Minimum strength of current given indefinitely to excite a tissue
(b) Minimum time required to excite a tissue
(c) Maximum time needed to excite a tissue with maximum strength of current
(d) Maximum strength of current given indefinitely to excite a tissue

35. Utilization time is
(a) Minimum strength of current given indefinitely to excite a tissue
(b) Minimum time required to excite a tissue with twice the rheobasic strength of current
(c) Minimum time needed to excite a tissue with rheobasic strength of current
(d) Maximum strength of current to excite a tissue

36. The electrical changes occurring at the anode of the recording electrode is
(a) Catelectrotonic potential
(b) Anelectrotonic potential
(c) Action potential
(d) Receptor potential

37. The electrical changes occurring at the cathode of the recording electrode is
(a) Catelectrotonic potential
(b) Anelectrotonic potential
(c) Action potential
(d) Receptor potential

38. End-plate potential has the following characteristics *except*
(a) It is graded
(b) It is nonpropagated
(c) It has no latency
(d) It is propagated

39. Transmission of impulse away from the cell body is termed
(a) Orthodromic conduction
(b) Antidromic conduction
(c) Saltatory conduction
(d) Axoplasmic flow

40. Transport of substances from the cell body to the nerve terminal occurs by
(a) Orthodromic conduction
(b) Antidromic conduction
(c) Saltatory conduction
(d) Axoplasmic flow

41. Transmission of impulse toward the cell body is termed
(a) Orthodromic conduction
(b) Antidromic conduction
(c) Saltatory conduction
(d) Axoplasmic flow

42. Denervation hypersensitivity is true in the following conditions *except*
(a) Occurs in denervated muscle
(b) Due to increased Ach receptors
(c) Results in rigidity of the muscle
(d) Responds to circulating acetylcholine

43. The following are the contractile proteins *except*
(a) Actin
(b) Myosin
(c) Troponin
(d) Myoglobin

44. A threshold stimulus produces
(a) Action potential
(b) Local response
(c) Impulse
(d) Tetanus

45. A subthreshold stimulus produces
(a) Action potential
(b) Local response
(c) Receptor potential
(d) No response

46. Action potential in a motor nerve has the following phases *except*
(a) Depolarization
(b) Repolarization
(c) Hyperpolarization
(d) Plateau

47. Responding property of the excitable tissue are the following *except*
(a) Excitability
(b) Conductivity
(c) Contractility
(d) Rigor mortis

48. The property of the motor nerve is
(a) Conductivity
(b) Contractility
(c) Autorhythmicity
(d) Clonus

49. Following are the properties of motor nerve *except*
(a) Excitability
(b) Conductivity
(c) All-or-none law
(d) Tetanus

50. The components of the neuromuscular junction are the following *except*
(a) Prejunctional terminal
(b) Synaptic cleft
(c) Motor end plate
(d) Gap junction

51. The period in which a second stimulus of greater intensity produces a response is termed
(a) Latent period
(b) Relative refractory period
(c) Absolute refractory period
(d) Contraction period

52. The period during which a second stimulus of greater intensity does not produce a response is termed
(a) Latent period
(b) Relative refractory period
(c) Absolute refractory period
(d) Contraction period

53. Thin filaments of muscles are made up of the following proteins *except*
(a) Actin
(b) Myosin
(c) Troponin
(d) Tropomyosin

54. The following statement is not true for skeletal muscle
(a) It can be tetanized
(b) It obeys all-or-none law
(c) It can be fatigued
(d) It shows autorhythmicity

55. The following statement is not true for smooth muscle
(a) It is voluntary
(b) It can contract with external stimuli
(c) It is nonstriated
(d) It is supplied by autonomic nervous system

56. The following statement is not true for cardiac muscle
(a) It is involuntary
(b) It can be tetanized
(c) It exhibits autorhythmicity
(d) It obeys all-or-none law

57. The action potential in a cardiac muscle is different from that of skeletal muscle by the presence of phase
(a) Depolarization
(b) Repolarization
(c) Hyperpolarization
(d) Plateau

58. Smooth muscle does not restore original length immediately after relaxation due to
(a) Actin and myosin filaments
(b) Presence of latch bridges
(c) Absence of sarcotubular system
(d) Absence of striation

59. The potential developed at the postjunctional membrane in a neuromuscular junction is
(a) Receptor potential
(b) Pacemaker potential

(c) End-plate potential
(d) Action potential

60. End-plate potential has the following characters *except*
(a) It is an all-or-none response
(b) It is a graded response
(c) It is a nonpropagated response
(d) It has no latency

61. Miniature end-plate potential is produced due to
(a) Stimulation of presynaptic terminal
(b) Release of small quantity of acetylcholine at rest
(c) Activation of postjunctional membrane
(d) Alteration in permeability of motor end-plate to calcium

62. Troponin has the binding sites for the following *except*
(a) Actin
(b) Tropomyosin
(c) Calcium ions
(d) Myosin

63. The sarcotubular system consists of the following structures *except*
(a) Sarcoplasmic reticulum
(b) T-tubules
(c) Terminal cistern
(d) Ribosomes

64. The theory that explains the basis of skeletal muscle contraction is
(a) Sliding filament theory
(b) Traveling wave theory
(c) Myogenic theory
(d) Metabolite theory

65. Causes for fatigue are the following *except*
(a) Accumulation of metabolic end products
(b) Exhaustion of neurotransmitter
(c) Depletion of ATP
(d) Decreased temperature

66. The site of fatigue in an intact animal is
(a) Neuromuscular junction
(b) Synapse
(c) Spinal cord
(d) Medulla

67. A state of sustained contraction is
(a) Tetanus
(b) Clonus
(c) Treppe
(d) Fatigue

68. Incomplete tetanus is called
(a) Clonus
(b) Tetanus
(c) Tetany
(d) Treppe

69. Following are the features of red muscle *except*
(a) Has a short latency
(b) Responds slowly
(c) They are postural muscles
(d) They are the muscles of the back

70. The character of white muscle is
(a) It has a short latency
(b) It has a long latency
(c) They respond slowly
(d) They are postural muscles

71. The calcium-binding protein which acts as second messenger is
(a) Calmodulin
(b) cAMP
(c) cGMP
(d) Adenosine

72. Recording of electrical activities of the muscle is
(a) EEG
(b) EMG
(c) EOG
(d) ECG

4. CARDIOVASCULAR SYSTEM

1. Human heart has
(a) Four chambers
(b) Three chambers
(c) Two chambers
(d) One chamber

2. The layers in the heart wall are the following *except*
(a) Epicardium
(b) Myocardium
(c) Pericardium
(d) Endocardium

3. In pulmonary circulation, the blood is pumped from
(a) Right atrium
(b) Right ventricle
(c) Left atrium
(d) Left ventricle

4. In systemic circulation, the blood is pumped from
(a) Right atrium
(b) Right ventricle
(c) Left atrium
(d) Left ventricle

5. In pulmonary circulation blood reaches
(a) Right atrium
(b) Right ventricle
(c) Left atrium
(d) Left ventricle

6. In systemic circulation, the blood reaches
(a) Right atrium
(b) Right ventricle
(c) Left atrium
(d) Left ventricle

7. The atrioventricular opening on the right side is guarded by
(a) Tricuspid valve
(b) Mitral valve
(c) Semilunar valve
(d) None of the above

8. The atrioventricular opening on the left side is guarded by
(a) Tricuspid valve
(b) Mitral valve
(c) Semilunar valve
(d) None of the above

9. The opening of aorta is guarded by
(a) Tricuspid valve
(b) Mitral valve
(c) Semilunar valve
(d) None of the above

10. The opening of pulmonary artery is guarded by
(a) Tricuspid valve
(b) Mitral valve
(c) Semilunar valve
(d) None of the above

11. _____ are called resistance vessels.
(a) Arteriole
(b) Veins and venules
(c) Capillaries
(d) Large-sized arteries

12. _____ are called capacitance vessels.
(a) Arteriole
(b) Veins and venules
(c) Capillaries
(d) Large-sized arteries

13. _____ are called exchange vessels.
(a) Arteriole
(b) Veins and venules
(c) Capillaries
(d) Large-sized arteries

14. Following are the properties of cardiac muscle *except*
(a) Excitability
(b) Conductivity
(c) Autorhythmicity
(d) Irradiation

15. The cause for depolarization in ventricular muscle action potential is
(a) Entry of sodium ions
(b) Exit of potassium ions
(c) Entry of calcium ions
(d) Entry of chloride ions

16. The cause for repolarization in ventricular muscle action potential is
(a) Entry of sodium ions
(b) Exit of potassium ions
(c) Entry of calcium ions
(d) Entry of chloride ions

17. Cause for sustained depolarization (plateau) in ventricular muscle action potential is
(a) Entry of sodium ions
(b) Exit of potassium ions

(c) Entry of calcium ions
(d) Entry of chloride ions

18. The pacemaker of the human heart is
(a) SA node
(b) AV node
(c) Sinus venosus
(d) Bundle of His

19. Conducting system of the heart has the following parts *except*
(a) SA node
(b) AV node
(c) Mossy fibers
(d) Purkinje fibers

20. Velocity of conduction of cardiac impulse is fastest in
(a) Internodal fibers
(b) SA node
(c) Purkinje fibers
(d) Ventricular muscle

21. Long absolute refractory period in a cardiac muscle is useful as
(a) It cannot be tetanized
(b) It improves efficiency
(c) It decreases excitability
(d) It prolongs contraction

22. All-or-none law in a cardiac muscle is applicable to
(a) Single muscle fiber
(b) Both the atria
(c) One ventricle
(d) One atrium

23. Following is not an event in the ventricular systole
(a) Isometric contraction phase
(b) Diastasis
(c) Maximum ejection phase
(d) Reduced ejection phase

24. Following is an event in the ventricular diastole
(a) Isometric contraction phase
(b) Rapid-filling phase
(c) Maximum ejection phase
(d) Reduced ejection phase

25. Following are the events in ventricular diastole *except*
(a) Isovolumetric relaxation phase
(b) First rapid-filling phase
(c) Diastasis
(d) Rapid ejection phase

26. First heart sound is produced due to closure of
(a) Semilunar valves
(b) Mitral valve
(c) Tricuspid valve
(d) Both mitral and tricuspid valves

27. Second heart sound is produced due to the closure of
(a) Semilunar valves
(b) Mitral valve
(c) Tricuspid valve
(d) Atrioventricular valves

28. The heart sound that corresponds with carotid artery pulsation is
(a) First sound
(b) Second sound
(c) Third sound
(d) Fourth sound

29. Stimulation of sympathetic nerve to the heart results in
(a) Increased heart rate
(b) Decrease in the heart rate
(c) Vasodilation
(d) No change in the heart rate

30. Stimulation of parasympathetic nerve to the heart results in
(a) Increased heart rate
(b) Decrease in the heart rate
(c) Vasoconstriction
(d) No change in the heart rate

31. First heart sound is heard best in
(a) Mitral area
(b) Aortic area
(c) Pulmonary area
(d) All the above areas

32. Second heart sound is heard best in
(a) Mitral area
(b) Tricuspid area

(c) Pulmonary area
(d) All the above areas

33. In human heart, right vagus supplies
(a) SA node
(b) AV node
(c) Ventricular musculature
(d) Purkinje fibers

34. In human heart, left vagus supplies
(a) Ventricular musculature
(b) AV node
(c) SA node
(d) Purkinje fibers

35. First-degree heart block is detected by
(a) Increased PR interval
(b) Inverted T wave
(c) Elevated ST segment
(d) Inverted P wave

36. Myocardial infarction is diagnosed by
(a) Increased PR interval
(b) Inverted T wave
(c) Depressed ST segment
(d) Inverted P wave

37. P wave in ECG is produced due to
(a) Atrial depolarization
(b) Ventricular depolarization
(c) Atrial repolarization
(d) Ventricular repolarization

38. QRS complex in ECG is produced due to
(a) Atrial depolarization
(b) Ventricular depolarization
(c) Atrial repolarization
(d) Ventricular repolarization

39. T wave in ECG is produced due to
(a) Atrial depolarization
(b) Ventricular depolarization
(c) Atrial repolarization
(d) Ventricular repolarization

40. Normal heart rate in humans is
(a) 40–60 beats/min
(b) Less than 60 beats/min
(c) 72–80 beats/min
(d) More than 90 beats/min

41. Normal systolic blood pressure is
(a) Less than 90 mm Hg
(b) 60–90 mm Hg
(c) 60–160 mm Hg
(d) 100–140 mm Hg

42. Normal diastolic blood pressure is
(a) Less than 90 mm Hg
(b) 60–90 mm Hg
(c) 60–160 mm Hg
(d) 100–140 mm Hg

43. Blood pressure depends on the following *except*
(a) Stroke volume
(b) Heart rate
(c) Peripheral resistance
(d) End systolic volume

44. Marey's law states that
(a) Heart rate varies directly as blood pressure
(b) Heart rate varies inversely as blood pressure
(c) Heart rate and blood pressure do not have any relationship
(d) Heart rate varies directly as the cardiac output

45. Korotkoff sound is produced due to
(a) Turbulence to the flow of blood
(b) Laminar flow of blood
(c) Closure of AV valves
(d) Closure of semilunar valve

46. Stimulation of baroreceptor results in
(a) Increased respiratory rate
(b) Inhibition of vasomotor center
(c) Increased heart rate
(d) Increased peripheral resistance

47. Stimulation of chemoreceptor results in
(a) Stimulation of vagal nuclei
(b) Stimulation of vasomotor center
(c) Decreased heart rate
(d) Decreased peripheral resistance

48. Normal cardiac output is
(a) 5–6 mL/min
(b) 70–80 mL/min

(c) 5–6 L/min
(d) 20–30 L/min

49. Normal stroke volume is
(a) 5–6 mL/beat
(b) 70–80 mL/beat
(c) 5–6 L/beat
(d) 20–30 L/beat

50. Cardiac output is measured by the following methods *except*
(a) Dye dilution method
(b) Thermodilution method
(c) Fick's principle
(d) Inulin clearance

51. Ischemia of vasomotor center results in
(a) Increased heart rate
(b) Decreased blood pressure
(c) Decreased peripheral resistance
(d) Reduced cardiac output

52. Following are not the mechanisms of intermediate-term regulation of blood pressure
(a) Stress relaxation
(b) Fluid shift mechanism
(c) Sinoaortic mechanism
(d) Renin–angiotensin mechanism

53. The mechanism for long-term regulation of blood pressure is
(a) Renin–angiotensin–aldosterone mechanism
(b) Stress relaxation
(c) Fluid shift mechanism
(d) Sinoaortic mechanism

54. Stretch of great vein results in increased heart rate. This relationship is explained by
(a) Bainbrige reflex
(b) Marey's law
(c) Starling's law
(d) Laplace law

55. Stretch of great vein results in
(a) Increased heart rate
(b) Decreased heart rate
(c) Decreased cardiac output
(d) Decreased blood pressure

56. Stimulation of right atrial stretch receptors causes
(a) Increased heart rate
(b) Decreased heart rate
(c) Decreased cardiac output
(d) Decreased blood pressure

57. Stimulation of left atrial stretch receptors causes
(a) Decreased heart rate
(b) Increased heart rate
(c) Increased blood pressure
(d) Increased cardiac output

58. Alteration of heart rate in different phases of respiration is
(a) Tachycardia
(b) Bradycardia
(c) Sinus arrhythmia
(d) Fibrillation

59. Collapsing pulse is pathologically seen in
(a) Exercise
(b) Emotions
(c) Aortic regurgitation
(d) Shock

60. Rolling back of blood in aorta at the beginning of ventricular diastole causes _____ in arterial pulse.
(a) Dicrotic notch
(b) Dicrotic wave
(c) *a*-wave
(d) *c*-wave

61. Following are the positive waves in jugular venous pulse *except*
(a) *c*-wave
(b) *a*-wave
(c) *x*-wave
(d) *v*-wave

62. Dicrotic wave in the arterial pulse tracing is due to
(a) Sudden closure of AV valves
(b) Sudden closure of semilunar valves
(c) Sudden rush of blood
(d) Opening of AV valves

63. Increased intracranial pressure reflexly increases blood pressure acting through vasomotor center. This reflex is
(a) Cushing's reflex
(b) Marey's reflex
(c) Bainbridge reflex
(d) Stretch reflex

64. Increase of blood pressure without a demonstrable cause is
(a) Primary hypertension
(b) Secondary hypertension
(c) Hypotension
(d) Orthostatic hypotension

65. Increase of blood pressure with a demonstrable cause is
(a) Primary hypertension
(b) Secondary hypertension
(c) Hypotension
(d) Orthostatic hypotension

66. Venous return depends on the following factors *except*
(a) Respiratory pump
(b) Muscle pump
(c) Gravity
(d) Blood pressure

67. The law which states greater the preload greater the force of contraction is
(a) Starling's law
(b) Laplace law
(c) Bell–Magendie law
(d) Marey's law

68. The condition of circulatory failure is termed
(a) Shock
(b) Bradycardia
(c) Tachycardia
(d) Coma

69. Excessive bleeding and sudden loss of fluid results in
(a) Hypovolemic shock
(b) Cardiogenic shock
(c) Septicemic shock
(d) Anaphylactic shock

70. The type of shock seen immediately after myocardial infarction is
(a) Hypovolemic shock
(b) Cardiogenic shock
(c) Septicemic shock
(d) Anaphylactic shock

71. The shock produced due to hypersensitivity reaction is
(a) Hypovolemic shock
(b) Cardiogenic shock
(c) Septicemic shock
(d) Anaphylactic shock

72. The shock produced due to uncontrolled and fulminant infection is
(a) Hypovolemic shock
(b) Cardiogenic shock
(c) Septicemic shock
(d) Anaphylactic shock

73. Following are the properties of cardiac muscle *except*
(a) Fatigue
(b) Excitability
(c) Conductivity
(d) Contractility

74. Staircase phenomenon in a cardiac muscle is due to the following *except*
(a) Accumulation of calcium ions
(b) Increased temperature
(c) Decreased viscosity
(d) Increased permeability to sodium

75. All-or-none law is applicable to
(a) Single cardiac muscle fiber
(b) Entire cardiac muscle
(c) A group of skeletal muscle fibers
(d) A bundle of nerve fibers

76. Entire phase of cardiac contraction is in absolute refractory period. Hence, cardiac muscle
(a) Can be tetanized
(b) Cannot be tetanized
(c) Can be excited
(d) Cannot be excited

77. **During moderate exercise, the following changes are seen *except***
    (a) Increased heart rate
    (b) Decreased peripheral resistance
    (c) Increased systolic blood pressure
    (d) Decreased cardiac output
78. **Following are the internodal pathway (conducting system of the heart) *except***
    (a) Wenckebach
    (b) Thorel
    (c) Bachman
    (d) Burdach
79. **Irreversible shock results in the following changes *except***
    (a) Acidosis
    (b) Vasodilation
    (c) Toxemia
    (d) Increased BP
80. **General principle in the management of shock is**
    (a) Maintenance of fluid and electrolyte balance
    (b) Correction of alkalosis
    (c) Increasing the cardiac output
    (d) Maintenance of oxygen supply
81. **Increase in heart rate is termed**
    (a) Shock
    (b) Bradycardia
    (c) Tachycardia
    (d) Coma
82. **Decrease in heart rate is called**
    (a) Shock
    (b) Bradycardia
    (c) Tachycardia
    (d) Coma

5. RESPIRATORY SYSTEM

1. **The normal respiratory rate is**
    (a) 6–8 cycles/min
    (b) 12–16 cycles/min
    (c) 30–40 cycles/min
    (d) 72 cycles/min
2. **The thickness of respiratory membrane is**
    (a) 0.6 μ
    (b) 2.5 μ
    (c) 0.6 mm
    (d) 2.5 mm
3. **Nonrespiratory function of lungs include all *except***
    (a) Synthesis of surfactant
    (b) Voice production
    (c) Acid–base balance
    (d) Gas exchange
4. **Normal tidal volume is**
    (a) 300 mL
    (b) 500 mL
    (c) 700 mL
    (d) 1000 mL
5. **Normal inspiratory reserve volume is**
    (a) 1000 mL
    (b) 2000 mL
    (c) 3000 mL
    (d) 4000 mL
6. **Normal residual volume in an adult male is**
    (a) 500 mL
    (b) 1100 mL
    (c) 3000 mL
    (d) 5600 mL
7. **Inspiratory capacity is**
    (a) TV + IRV
    (b) TV + ERV
    (c) VC + RV
    (d) ERV + RV
8. **The amount of air remaining in the lungs after a normal expiration is**
    (a) Tidal Volume
    (b) Functional residual capacity
    (c) Vital capacity
    (d) Total lung capacity
9. **The maximum amount of air that a person can expel from the lungs after a maximum inspiration is called**
    (a) Functional residual capacity
    (b) Tidal volume

(c) Vital capacity
(d) Inspiratory capacity

10. The normal ventilation–perfusion ratio is
(a) 0.2
(b) 0.8
(c) 1.4
(d) 1.6

11. Lung volumes and capacities are measured by
(a) Spirometer
(b) Sphygmomanometer
(c) Stethoscope
(d) None

12. The amount of air expelled forcefully in a given unit of time is termed
(a) Maximum ventilation volume
(b) Respiratory minute volume
(c) Peak respiratory flow rate
(d) Timed vital capacity

13. Normal value of anatomical dead space is
(a) 50 mL
(b) 150 mL
(c) 200 mL
(d) 250 mL

14. That part of respiratory passage in which air does not take part in gaseous exchange process is called
(a) Dead space
(b) Intrapleural space
(c) Alveolar space
(d) Pulmonary space

15. Muscles of inspiration include all *except*
(a) Diaphragm
(b) External intercostals
(c) Sternocleidomastoid
(d) Internal intercostals

16. The muscles of expiration includes
(a) Diaphragm
(b) Abdominal wall muscles
(c) Serratus anterior
(d) Sternocleidomastoid

17. Normal intrapleural pressure is
(a) –11 to –14 cm of water
(b) –5 to –8 cm of water
(c) +3 to +5 cm of water
(d) +7 to +11 cm of water

18. Surfactant is produced by
(a) Enterocytes
(b) Type 2 alveolar cells
(c) Gastric cells
(d) Type 1 alveolar cell

19. Normal FEV_1 is around
(a) 63%
(b) 73%
(c) 83%
(d) 93%

20. Normal peak expiratory flow rate is around
(a) 50 L/min
(b) 200 L/min
(c) 400 L/min
(d) 800 L/min

21. The extent to which the lungs expand for each unit increase in transpulmonary pressure is called
(a) Impedance
(b) Compliance
(c) Resistance
(d) Dyspnea

22. Compliance of the respiratory system is
(a) 50 mL/cm of H_2O
(b) 100 mL/cm of H_2O
(c) 150 mL/cm of H_2O
(d) 300 mL/cm of H_2O

23. Production of surfactant starts at
(a) Immediately after conception
(b) Seventh month of fetal life
(c) 6 months after birth
(d) One year after birth

24. Hyaline membrane disease is caused due to the deficiency of
(a) Rennin
(b) Gastrin
(c) Surfactant
(d) CSF

25. The PO_2 of arterial blood is
(a) 40 mm Hg
(b) 45 mm Hg

(c) 95 mm Hg
(d) 104 mm Hg

26. O_2 transported by physical solution is
(a) 3%
(b) 10%
(c) 15%
(d) 23%

27. O_2 dissociation curve shifts to right when there is
(a) Decreased CO_2
(b) Decreased H^+ ions
(c) Increased 2,3-DPG
(d) Decreased temperature

28. The O_2 dissociation curve is
(a) Straight line
(b) Sigmoid curve
(c) Circular curve
(d) Rhombus shaped

29. Increased CO_2 content of blood helps to release more O_2 from Hb is called
(a) Bohr's effect
(b) Chloride shift
(c) Haldane's effect
(d) Reverse chloride shift

30. Carbon dioxide transport occurs in blood in the form of
(a) Physical solution
(b) Combination with Hb
(c) As bicarbonate
(d) All of the above

31. Most of the CO_2 transport occurs in the blood in the form of
(a) Physical solution
(b) Combination with Hb
(c) As bicarbonate ion
(d) Combination with O_2

32. Dorsal respiratory group of neurons is present in
(a) Medulla
(b) Pons
(c) Hypothalamus
(d) Thalamus

33. Ventral respiratory group of neurons is present in
(a) Medulla
(b) Pons
(c) Hypothalamus
(d) Thalamus

34. Pneumotaxic center is present in
(a) Medulla
(b) Pons
(c) Hypothalamus
(d) Thalamus

35. Apneustic center is present in
(a) Medulla
(b) Pons
(c) Hypothalamus
(d) Thalamus

36. Basic rhythm of respiration is maintained by
(a) VRG
(b) Pneumotaxic center
(c) Apneustic center
(d) DRG

37. Ramp signal is produced by
(a) VRG
(b) Pneumotaxic center
(c) Apneustic center
(d) DRG

38. The chemosensitive area responsible for regulation of respiration is present in
(a) Pons
(b) Medulla
(c) Spinal cord
(d) Thalamus

39. The chemosensitive area for control of respiration is excited by
(a) H^+ ions
(b) K^+ ions
(c) Cl^- ions
(d) HCO_3^- ions

40. Manual methods of artificial respiration include all *except*
(a) Mouth-to-mouth respiration
(b) Schaffer's method
(c) Holger Neilson's method
(d) Drinker's method

41. Temporary arrest of breathing is called
(a) Eupnea
(b) Apnea
(c) Dyspnea
(d) Orthopnea

42. Normal respiration is called
(a) Apnea
(b) Eupnea
(c) Dyspnea
(d) Orthopnea

43. Difficulty in breathing is called
(a) Apnea
(b) Eupnea
(c) Dyspnea
(d) Hiccups

44. Dyspnea occurring in lying-down position and not in erect posture is termed
(a) Eupnea
(b) Apnea
(c) Dyspnea
(d) Orthopnea

45. Periodic breathing characterized by alternate apnea and hyperventilation is termed as
(a) Biot's breathing
(b) Kussmaul breathing
(c) Cheyne–Stokes breathing
(d) Dyspneic breathing

46. Bluish discoloration of skin and mucus membrane is termed
(a) Cyanosis
(b) Anemia
(c) Asphyxia
(d) Dyspnea

47. Condition characterized by decreased O_2 and increased CO_2 in the body is termed
(a) Hypoxia
(b) Asphyxia
(c) Dyspnea
(d) Cyanosis

48. Condition characterized by deficiency of O_2 at the tissue level is termed
(a) Hypoxia
(b) Asphyxia
(c) Dyspnea
(d) Hypercapnia

49. Exposure to high altitude causes
(a) Hypoxic hypoxia
(b) Stagnant hypoxia
(c) Histotoxic hypoxia
(d) Anemic hypoxia

50. Cyanide poisoning is an example of
(a) Hypoxic hypoxia
(b) Stagnant hypoxia
(c) Histotoxic hypoxia
(d) Anemic hypoxia

51. Circulatory shock is an example of
(a) Hypoxic hypoxia
(b) Stagnant hypoxia
(c) Histotoxic hypoxia
(d) Anemic hypoxia

52. The compensatory changes during acclimatization are the following *except*
(a) Hyperventilation
(b) Polycythemia
(c) Decreased cardiac output
(d) Excretion of alkaline urine

53. The gas responsible of the causation of decompression sickness is
(a) Oxygen
(b) Carbon dioxide
(c) Nitrogen
(d) Helium

54. Caisson's disease is seen in
(a) Pilots
(b) Doctors
(c) Divers
(d) Engineers

55. Residual volume can be measured by
(a) Nitrogen washout method
(b) Spirometer
(c) Stethography
(d) Ballistocardiography

56. Functions of the nasal cavity are the following *except*
(a) Humidification
(b) Olfaction
(c) Filtration
(d) Regulation of respiration

57. Increased respiratory rate is termed
(a) Hypoxia
(b) Hyperventilation
(c) Tachypnea
(d) Tachycardia

58. **Increased rate and depth of respiration is**
    (a) Hyperventilation
    (b) Tachypnea
    (c) Dyspnea
    (d) Asphyxia

59. **Influence of carbon dioxide on the release and uptake of oxygen is**
    (a) Bohr's effect
    (b) Haldane's effect
    (c) Venturi effect
    (d) Windkessel effect

60. **Influence of oxygen on the release of uptake of carbon dioxide is**
    (a) Haldane's effect
    (b) Venturi effect
    (c) Bohr's effect
    (d) Windkessel effect

61. **Carbon dioxide is carried in the following form *except***
    (a) Bicarbonates
    (b) Carbamino compounds
    (c) Simple solution
    (d) Carboxyhemoglobin

6. GASTROINTESTINAL SYSTEM

1. **Myenteric plexus of Auerbach is present between**
    (a) Serosal and mucosal layers
    (b) Circular muscle and submucosal layers
    (c) Longitudinal and circular muscle layers
    (d) In the mucosa

2. **Submucosal plexus of Meissner is present in between**
    (a) Serosal and mucosal layers
    (b) Circular muscle and submucosal layers
    (c) Longitudinal and circular muscle layers
    (d) In the mucosa

3. **Slow waves**
    (a) Are action potentials
    (b) Are caused due to calcium pump
    (c) Cause muscle contraction
    (d) Control the appearance of spike potentials

4. **All of the following regarding spike potentials are true *except***
    (a) They are true action potentials
    (b) They occur due to slow undulation of Na^+–K^+ pump
    (c) They last for 10–20 ms
    (d) Higher the spike potential, greater its frequency

5. **Stages of deglutition include all *except***
    (a) Buccal phase
    (b) Pharyngeal phase
    (c) Esophageal phase
    (d) Intestinal phase

6. **Interruption of respiration during swallowing is called**
    (a) Deglutition apnea
    (b) Sleep apnea
    (c) Hyperpnea
    (d) Dyspnea

7. **Deglutition center is present in**
    (a) Lower pons and upper medulla
    (b) Upper pons
    (c) Midbrain
    (d) Hypothalamus

8. **Condition in which lower esophageal sphincter fails to relax is during**
    (a) Gastritis
    (b) Achalasia cardia
    (c) Esophagitis
    (d) Peptic ulcer

9. **Factor that increases gastric emptying is**
    (a) Gastrin
    (b) CCK
    (c) Secretin
    (d) Products of digestion

10. **Haustrations are found in**
    (a) Esophagus
    (b) Stomach

(c) Small intestine
(d) Large intestine

11. Salivary glands include all *except*
(a) Submandibular
(b) Sublingual
(c) Parotid
(d) Oxyntic

12. Secretions from parotid glands are predominantly
(a) Serous
(b) Mucus
(c) Mixed
(d) None of the above

13. Parotid glands open through
(a) Wharton's duct
(b) Stenson's duct
(c) Pancreatic duct
(d) Duct of Rivinus

14. Submandibular salivary glands open through
(a) Wharton's duct
(b) Stenson's duct
(c) Pancreatic duct
(d) Duct of Rivinus

15. Sublingual glands open through
(a) Wharton's duct
(b) Stenson's duct
(c) Pancreatic duct
(d) Duct of Rivinus

16. Daily salivary secretion is about
(a) 500 mL
(b) 750 mL
(c) 1200 mL
(d) 2500 mL

17. The functions of saliva include
(a) Lubrication of food
(b) Keeps the mouth moist
(c) Digestion of starch
(d) All of the above

18. Involuntary phase of deglutition is
(a) Buccal phase
(b) Pharyngeal phase
(c) Esophageal phase
(d) None of the above

19. Factors inhibiting gastric emptying include
(a) Gastrin
(b) Increased food volume
(c) Parasympathetic activity
(d) CCK

20. Ptyalin is an enzyme present mainly in
(a) Saliva
(b) Gastric juice
(c) Pancreatic juice
(d) Bile

21. Decreased salivation occurs due to
(a) Parasympathetic stimulation
(b) Eating favorite foods
(c) Atropine administration
(d) Presence of irritating food in stomach

22. Mumps affects
(a) Submaxillary glands
(b) Parotid glands
(c) Gastric glands
(d) Intestinal glands

23. Reduced salivary secretion leads to
(a) Xerophthalmia
(b) Xerostomia
(c) Parosmia
(d) Ageusia

24. Chief cells secrete
(a) HCl
(b) Mucus
(c) Pepsinogen
(d) Intrinsic factor

25. Parietal cells secrete
(a) HCl
(b) Intrinsic factor
(c) HCl and intrinsic factor
(d) Secretin

26. Intrinsic factor is required for the absorption of
(a) Vitamin C
(b) Vitamin A
(c) Vitamin B_1
(d) Vitamin B_{12}

27. Gastrin is produced from
(a) Mucus cells
(b) Parietal cells
(c) Peptic cells
(d) G-cells

28. Gastrin
(a) Is an enzyme
(b) Is produced from parietal cells
(c) Inhibits gastric secretion
(d) Is a polypeptide

29. Cephalic phase of gastric secretion
(a) Occurs before the food enters the stomach
(b) Accounts for 20% of gastric secretion
(c) Occurs due to sight, smell, and thought of food
(d) All of the above

30. Hormone responsible for gastric phase of gastric secretion is
(a) Gastrin
(b) CCK–PZ
(c) Secretin
(d) VIP

31. Phases of gastric secretion include all *except*
(a) Cephalic phase
(b) Gastric phase
(c) Pharyngeal phase
(d) Intestinal phase

32. Gastric secretion is inhibited by
(a) Gastrin
(b) Secretin
(c) Histamine
(d) Products of protein digestion

33. Sham feeding experiment proves the
(a) Cephalic phase of gastric secretion
(b) Gastric phase
(c) Intestinal phase
(d) Interdigestive phase

34. Volume of gastric secretion produced per day is
(a) 500 mL
(b) 1200 mL
(c) 2500 mL
(d) 4000 mL

35. Gastric juice is
(a) Highly acidic
(b) Mildly acidic
(c) Highly alkaline
(d) Mildly alkaline

36. Functions of gastric juice include
(a) Digestion of proteins
(b) Bacteriolytic action
(c) Excretion of toxins and heavy metals
(d) All of the above

37. Normal basal acid output is
(a) 0.5–2 mEq/h
(b) 3.5–6 mEq/h
(c) 5–8 mEq/h
(d) 17–35 mEq/h

38. Peak acid can be measured by all *except*
(a) Histamine test
(b) Pentagastrin test
(c) Insulin test
(d) Glucose tolerance test

39. Basal acid output decreases in
(a) Zollinger–Ellison syndrome
(b) Duodenal ulcer
(c) Atrophic gastritis
(d) Acute gastritis due to drugs

40. Peptic ulcer is caused due to infection of
(a) *Helicobacter pylori*
(b) *Pneumocystis carini*
(c) *Staphylococcus*
(d) *H. influenza*

41. Normal bile secretion in a day is
(a) 500 mL
(b) 1500 mL
(c) 2000 mL
(d) 2500 mL

42. Liver weighs around
(a) 500 g
(b) 750 g
(c) 1500 g
(d) 2500 g

43. Secretions of liver and bile enter the duodenum through
(a) Hepatic duct
(b) Cystic duct

(c) Common bile duct
(d) Intralobular duct

44. Kupffer cells are
(a) Present in the liver
(b) Protective in function
(c) Modified macrophages
(d) All of the above

45. pH of bile is
(a) 1.2–1.5
(b) 3.5–4
(c) 7–7.5
(d) 9.5–10

46. Bilirubin is a
(a) Bile salt
(b) Bile pigment
(c) Bile acid
(d) None of the above

47. Bile is produced in the
(a) Liver
(b) Gallbladder
(c) Spleen
(d) Pancreas

48. The capacity of gallbladder is around
(a) 50 mL
(b) 150 mL
(c) 250 mL
(d) 500 mL

49. The main stimulus for contraction of gallbladder is
(a) Gastrin
(b) Secretin
(c) Cholecystokinin
(d) Thyroxine

50. Sodium taurocholate is a
(a) Bile salt
(b) Bile pigment
(c) Bile acid
(d) None of the above

51. The percentage of bile salts reabsorbed by small intestine is about
(a) 30
(b) 50
(c) 70
(d) 90

52. The substances that increase bile secretion are called
(a) Cholagogues
(b) Choleretics
(c) Secretogogues
(d) Cholic acid

53. Cholecystectomy is removal of
(a) Liver
(b) Gallbladder
(c) Spleen
(d) Pancreas

54. Cholelithiasis is presence of stones in
(a) Salivary gland
(b) Gallbladder
(c) Kidney
(d) Pancreas

55. Excessive breakdown of RBC leads to
(a) Prehepatic jaundice
(b) Hepatic jaundice
(c) Posthepatic jaundice
(d) None of the above

56. Stones in the gallbladder lead to
(a) Prehepatic jaundice
(b) Hemolytic jaundice
(c) Obstructive jaundice
(d) Hepatic jaundice

57. Physiological jaundice is
(a) Seen in newborn babies
(b) Self-limiting condition requiring no treatment
(c) Both a and b are true
(d) Neither a or b is true

58. Normal serum bilirubin is
(a) 0.1–0.3 mg%
(b) 0.2–0.8 mg%
(c) 1–3 mg%
(d) 2–8 mg%

59. The enzyme markedly increased in obstructive jaundice is
(a) SGOT
(b) SGPT
(c) CCK–MB
(d) Alkaline phosphatase

60. pH of pancreatic juice is
(a) 1.2–2
(b) 3–4.5
(c) 6–7.4
(d) 8–8.3

61. Steatorrhea occurs due to the deficiency of
(a) Gastric enzymes
(b) Saliva
(c) Pancreatic enzymes
(d) Succus entericus

62. Intestinal phase of pancreatic secretion is due to hormone
(a) Gastrin
(b) Motilin
(c) GIP
(d) CCK

63. Amylase is a
(a) Proteolytic enzyme
(b) Fat-splitting enzyme
(c) Carbohydrate-splitting enzyme
(d) None of the above

64. Trypsin helps in the digestion of
(a) Proteins
(b) Carbohydrates
(c) Fats
(d) Minerals

65. Lipase helps in the digestion of
(a) Proteins
(b) Carbohydrates
(c) Fats
(d) Minerals

66. Mucus produced in large intestine causes all *except*
(a) Protects the wall against excoriation
(b) Digestion and absorption of proteins
(c) Adherent medium for holding fecal matter together
(d) Protects intestinal wall from bacterial activity

67. Vomiting center is present in the
(a) Medulla
(b) Pons
(c) Midbrain
(d) Cortex

68. Mass peristalsis usually occurs in
(a) Esophagus
(b) Stomach
(c) Small intestine
(d) Large intestine

69. All the following are functions of gastrin *except*
(a) Stimulation of gastric acid secretion
(b) Stimulation of mucosal growth of stomach
(c) Causes contraction of gastroesophageal sphincter
(d) Inhibits gastric motility

70. CCK–PZ is produced from
(a) G-cells of gastric gland
(b) I-cells of small intestine
(c) D-cells of pancreas
(d) Hepatocytes of liver

71. CCK–PZ causes
(a) Relaxation of gallbladder
(b) Inhibition of pancreatic secretion
(c) Enhance motility of small intestine
(d) Decreases intestinal secretion

72. The first hormone to be discovered was
(a) Gastrin
(b) CCK–PZ
(c) Motilin
(d) Secretin

73. Somatostatin
(a) Increases gastric secretion
(b) Increases gallbladder contraction
(c) Inhibits secretion of secretin
(d) Increases secretion of exocrine pancreas

74. Gastrointestinal hormones include all *except*
(a) Gastrin
(b) Trypsin
(c) CCK–PZ
(d) Secretin

75. Somatostatin is produced from
(a) Pancreas
(b) Gastrointestinal mucosa
(c) Hypothalamus
(d) All of the above

76. Secretin is produced from
(a) Liver
(b) Spleen
(c) Small intestine
(d) Stomach

77. Pancreatic juice mainly contains
(a) Bicarbonate ions
(b) Calcium ions
(c) Chloride ions
(d) Sodium ions

78. Cholecystography involves visualization of
(a) Ureter
(b) Gallbladder
(c) Intestine
(d) Esophagus

79. Micelles are produced due to the formation of complexes of bile salts with
(a) Proteins
(b) Carbohydrates
(c) Lipids
(d) Vitamins

80. Peptic ulcer is caused due to
(a) Anti-inflammatory drugs
(b) Alcohol
(c) Smoking
(d) All of the above

81. Hormonal control of gastric secretion can be studied by
(a) Pavlov's pouch
(b) Heidenhain's pouch
(c) Sham feeding
(d) All of the above

82. Parasympathetic supply to GIT is mainly through
(a) Glossopharyngeal nerve
(b) Vagus nerve
(c) Facial nerve
(d) Trigeminal nerve

83. Muscles of mastication are innervated by
(a) Hypoglossal nerve
(b) Trigeminal nerve
(c) Glossopharyngeal nerve
(d) Facial nerve

84. Gastric phase accounts for
(a) 20% of gastric secretion
(b) 30% of gastric secretion
(c) 70% of gastric secretion
(d) 90% of gastric secretion

85. Normal peak acid output secretion is
(a) 0.5–2 mEq/h
(b) 10–15 mEq/h
(c) 15–20 mEq/h
(d) 40–60 mEq/h

86. Pavlov's experiment was done to study
(a) Salivary secretion
(b) Gastric secretion
(c) Intestinal secretion
(d) Pancreatic secretion

87. The pH of gastric juice is
(a) 1–2
(b) 5–6
(c) 6.5–7
(d) 7–8

7. EXCRETORY SYSTEM

1. The functioning unit of the kidney is
(a) Neuron
(b) Nephron
(c) Sarcomere
(d) Juxtaglomerular apparatus

2. The following are the parts of nephron *except*
(a) Bowman's capsule
(b) Loop of Henle
(c) Distal convoluted tubule
(d) Vasa recta

3. The process of concentrating urine is the main function of
(a) Cortical nephron
(b) Descending loop of Henle
(c) Juxtamedullary nephron
(d) Collecting duct

4. Urine is formed by the following processes *except*
(a) Ultrafiltration
(b) Tubular reabsorption
(c) Tubular secretion
(d) Micturition

5. The effective filtration pressure depends on the following pressures *except*
(a) Hydrostatic pressure
(b) Bowman's capsular pressure
(c) Interstitial pressure
(d) Colloidal osmotic pressure

6. The normal renal blood flow is
(a) 125 mL/min
(b) 650 mL/min
(c) 700 mL/h
(d) 1200 mL/min

7. The normal GFR is
(a) 125 mL/h
(b) 125 mL/d
(c) 125 L/min
(d) 125 L/d

8. The substance used for the estimation of GFR is
(a) Insulin
(b) Inulin
(c) Renin
(d) Rennin

9. The normal filtration fraction is
(a) 20%
(b) 30%
(c) 60%
(d) 75%

10. The substance used to estimate GFR should have the following properties *except*
(a) Nontoxic
(b) Easily filtered
(c) Should not alter renal function
(d) Should be secreted

11. Renal threshold for glucose is
(a) 180 mg/dL
(b) 325 mg/dL
(c) 180 mg/min
(d) 375 mg/min

12. Tubular maximum for glucose is
(a) 180 mg/min
(b) 375 mg/min
(c) 180 g/min
(d) 325 g/min

13. Following are the abnormal constituents of urine *except*
(a) Blood
(b) Urea
(c) Bile
(d) Ketone bodies

14. Following is an abnormal constituent of urine
(a) Urea
(b) Uric acid
(c) Creatinine
(d) Proteins

15. The facultative reabsorption of water takes place in
(a) PCT
(b) DCT
(c) Loop of Henle
(d) Bowman's capsule

16. The facultative reabsorption of water takes place under the influence of hormone
(a) Vasopressin
(b) Oxytocin
(c) Aldosterone
(d) Renin

17. The hormone produced from the kidney is
(a) Gastrin
(b) Erythropoietin
(c) Aldosterone
(d) ADH

18. The hormone acting on the kidney is
(a) Aldosterone
(b) Thyroxin
(c) Secretin
(d) Erythropoietin

19. The sodium ion is absorbed in the renal tubules by the following mechanism *except*
(a) Cotransport
(b) Countertransport

(c) Active–passive transport
(d) Osmosis

20. Stimulation of sympathetic nerve to the bladder results in
(a) Atonic bladder
(b) Emptying of the bladder
(c) Automatic bladder
(d) Alteration of blood flow

21. Stimulation of parasympathetic nerve to the urinary bladder results in
(a) Atonic bladder
(b) Emptying of the bladder
(c) Automatic bladder
(d) Filling of the bladder

22. Cystometrogram is
(a) Pressure–volume relationship of urinary bladder
(b) Measure of intravesical pressure
(c) Measure of intravesical volume
(d) None of the above

23. The normal maximal urea clearance is
(a) 75 mg/d
(b) 75 mL/h
(c) 75 mg/min
(d) 75 mL/min

24. The patient with diabetes mellitus will have
(a) Osmotic diuresis
(b) Water diuresis
(c) No diuresis
(d) Voluntary diuresis

25. Water diuresis is a feature of
(a) Diabetes mellitus
(b) Diabetes insipidus
(c) Acromegaly
(d) Cushing's syndrome

26. Normal renal plasma flow is
(a) 70–80 mL/min
(b) 125 mL/min
(c) 650 mL/min
(d) 1200 mL/min

27. The normal standard urea clearance is
(a) 54 mL/h
(b) 75 mL/h
(c) 54 mL/min
(d) 75 mL/min

28. Following are the excretory organs of the body *except*
(a) Skin
(b) Kidney
(c) GIT
(d) Spleen

29. The maintenance of constancy of interval environment is
(a) Homeostasis
(b) Hemostasis
(c) Adaptation
(d) Acclimatization

30. The chemical agents increasing urination are called
(a) Anesthetics
(b) Antidiuretics
(c) Cathartics
(d) Diuretics

31. Following are the functions of the kidney *except*
(a) Secretion of renin
(b) Acid–base balance
(c) Fluid balance
(d) Glycogen storage

32. Ureter is the continuation of
(a) Pelvis
(b) Pyramid
(c) Cortex
(d) Bowman's capsule

33. Urethra is the continuation of
(a) Pelvis
(b) Pyramid
(c) Urinary bladder
(d) Bowman's capsule

34. Urine is temporarily stored in
(a) Gallbladder
(b) Urinary bladder
(c) Kidney
(d) Nephrons

35. The efferent arteriole of cortical nephron divides into capillary network to form
(a) Vasa recta
(b) Peritubular capillary

(c) Glomerulus
(d) Renal vein

36. The efferent arteriole of juxtamedullary nephron divides into capillary network to form
(a) Vasa recta
(b) Peritubular capillary
(c) Glomerulus
(d) Renal vein

37. _____ constitutes the countercurrent exchange system.
(a) Nephron
(b) Vasa recta
(c) Peritubular capillary
(d) Glomerulus

38. _____ constitutes the countercurrent multiplier system.
(a) Loop of Henle
(b) Vasa recta
(c) Peritubular capillary
(d) Glomerulus

39. Theories of autoregulation are the following *except*
(a) Myogenic theory
(b) Interstitial tissue pressure theory
(c) Metabolite theory
(d) Traveling wave theory

40. The process of autoregulation is explained on the basis of
(a) Myogenic theory
(b) Traveling wave theory
(c) Kinetic theory
(d) None of the above

41. Ability of an organ to maintain a constant flow of blood in spite of a variation in the arterial blood pressure is called
(a) Autoregulation
(b) Acclimatization
(c) Feedback mechanism
(d) Autorhythmicity

42. Each kidney has about _____ nephrons.
(a) One lac
(b) One million
(c) Two million
(d) One billion

43. The percentage distribution of cortical nephron is
(a) 15
(b) 35
(c) 55
(d) 85

44. The percentage distribution of juxtamedullary nephron is
(a) 15
(b) 35
(c) 55
(d) 85

45. Juxtaglomerular apparatus secretes
(a) Renin
(b) Erythropoietin
(c) Rennin
(d) Aldosterone

46. Juxtaglomerular apparatus consists of the following *except*
(a) Macula densa
(b) Juxtaglomerular cells
(c) Lacis cells
(d) Glial cells

47. Normal urine output is
(a) 1.5–2 L/d
(b) 5–6 L/d
(c) 10–20 mL/min
(d) 125 mL/min

48. The proteins responsible for absorption of water in the kidney is
(a) Sialoprotein
(b) Aquaporin
(c) Calmodulin
(d) Receptor proteins

49. PAH clearance is used to estimate
(a) Renal blood flow
(b) Renal plasma flow
(c) GFR
(d) Filtration fraction

50. The filtration membrane consists of the following *except*
(a) Endothelium of glomerular capillary
(b) Epithelial lining of Bowman's capsule
(c) Interstitium
(d) Juxtaglomerular cells

51. **Glucose is reabsorbed from the PCT by the following transport mechanism**
    (a) Antiport
    (b) Symport
    (c) Uniport
    (d) Osmosis
52. **Inability of the kidney to respond to ADH results in**
    (a) Nephrogenic diabetes
    (b) Renal glycosuria
    (c) Diabetes insipidus
    (d) Diabetes mellitus
53. **The substances secreted from DCT are the following *except***
    (a) Hydrogen ions
    (b) Ammonia
    (c) Potassium ions
    (d) Calcium ions
54. **External sphincter to the urinary bladder is supplied by**
    (a) Pudendal nerve
    (b) Hypogastric nerve
    (c) Sympathetic nerve
    (d) Parasympathetic nerve

8. CENTRAL NERVOUS SYSTEM

1. **Structural and functional unit of nervous system is**
    (a) Neuron
    (b) Nephron
    (c) Neuroglia
    (d) Giant cell
2. **The short branching process of a neuron is**
    (a) Axon
    (b) Dendrite
    (c) Climbing fiber
    (d) Mossy fiber
3. **The process that carries sensation away from the cell body is**
    (a) Axon
    (b) Dendrite
    (c) Climbing fiber
    (d) Mossy fiber
4. **The process which carries sensation toward the cell body**
    (a) Axon
    (b) Dendrite
    (c) Climbing fiber
    (d) Mossy fiber
5. **The neurons classified based on the number of processes are the following *except***
    (a) Unipolar
    (b) Bipolar
    (c) Apolar
    (d) Polar
6. **Nissl granules are found in neuron *except* in**
    (a) Cell body
    (b) Axon hillock
    (c) Cytoplasm
    (d) Endoplasmic reticulum
7. **Nissl granules are also called**
    (a) Tigroid bodies
    (b) Carotid body
    (c) Neuroglia
    (d) Betz cells
8. **Disappearance of Nissl granules during nerve injury is termed**
    (a) Chromatolysis
    (b) Autolysis
    (c) Hemolysis
    (d) Proteolysis
9. **Basement membrane of cell of Schwann is**
    (a) Myelin sheath
    (b) Neurilemma
    (c) Descemet's membrane
    (d) Outer limiting membrane
10. **The process of formation of myelin sheath is**
    (a) Myelinogenesis
    (b) Neurogenesis
    (c) Dysgenesis
    (d) Agenesis

11. The process of degeneration of peripheral nerve distal to the site of injury is termed
(a) Starling's degeneration
(b) Marey's degeneration
(c) Wallerian degeneration
(d) Brodmann's degeneration

12. The junction between two neurons is
(a) Soma
(b) Synapse
(c) Telodendria
(d) Reflex

13. Following are the parts of chemical synapse *except*
(a) Presynaptic terminal
(b) Synaptic cleft
(c) Postsynaptic terminal
(d) Motor end plate

14. Gap junctions are present in _____ synapse.
(a) Chemical
(b) Electrical
(c) Axoaxonic
(d) Axosomatic

15. Ionic basis for EPSP is
(a) Entry of Na^+ ions
(b) Exit of Na^+ ions
(c) Entry of Cl^- ions
(d) Exit of Cl^- ions

16. Ionic basis for IPSP is
(a) Entry of Na^+ ions
(b) Exit of Na^+ ions
(c) Entry of Cl^- ions
(d) Exit of Cl^- ions

17. The types of synaptic inhibitions are the following *except*
(a) Post synaptic
(b) Presynaptic
(c) Negative feedback
(d) Positive feedback

18. Following are the properties of synapse *except*
(a) Delay
(b) Summation
(c) Regeneration
(d) Occlusion

19. The excitatory neurotransmitter is
(a) GABA
(b) Glycine
(c) Dopamine
(d) Epinephrine

20. Following are excitatory neurotransmitter *except*
(a) Acetylcholine
(b) Epinephrine
(c) Histamine
(d) GABA

21. An example of inhibitory neurotransmitter is
(a) Acetylcholine
(b) Epinephrine
(c) Histamine
(d) GABA

22. Following are the inhibitory neurotransmitters *except*
(a) GABA
(b) Glycine
(c) Dopamine
(d) Epinephrine

23. The normal synaptic delay is
(a) 0.5 ms
(b) 5 ms
(c) 0.5 s
(d) 5 s

24. Addition of two stimuli given in relation to time is
(a) Temporal summation
(b) Spatial summation
(c) Quantal summation
(d) Wave summation

25. Addition of two stimuli given in relation to space is
(a) Temporal summation
(b) Spatial summation
(c) Quantal summation
(d) Wave summation

26. Following are the components of reflex arc *except*
(a) Receptor
(b) Center

(c) Effector organ
(d) Astrocyte

27. Stretch reflex is an example of _____ type of reflex.
(a) Monosynaptic
(b) Polysynaptic
(c) Bisynaptic
(d) Asynaptic

28. Withdrawal reflex is an example of _____ type of reflex.
(a) Monosynaptic
(b) Polysynaptic
(c) Bisynaptic
(d) Asynaptic

29. Axon reflex is an example of _____ type of reflex.
(a) Monosynaptic
(b) Polysynaptic
(c) Bisynaptic
(d) Asynaptic

30. The receptor for stretch reflex is
(a) Muscle spindle
(b) Golgi tendon organ
(c) Pacinian corpuscles
(d) Ruffini's end organ

31. The receptor for inverse stretch reflex is
(a) Muscle spindle
(b) Golgi tendon organ
(c) Pacinian corpuscles
(d) Ruffini's end organ

32. Inverse stretch reflex is also termed
(a) Autogenic inhibition
(b) Renshaw's cell inhibition
(c) Postsynaptic inhibition
(d) Presynaptic inhibition

33. Crossed extensor response is due to the property of
(a) Summation
(b) Occlusion
(c) Irradiation
(d) Sensitization

34. In decerebrate rigidity, the lesion is made at
(a) Midcollicular level
(b) Cerebral cortex
(c) Medulla
(d) Cerebellum

35. The structure in the ear responsible for maintenance of balance is
(a) Cochlea
(b) Cerebellum
(c) Vestibular apparatus
(d) Incus

36. Semicircular canals help in the detection of _____ movement.
(a) Rotatory
(b) Side-to-side
(c) Anteroposterior
(d) Oblique

37. Utricles help in the detection of _____ movement.
(a) Rotatory
(b) Side-to-side
(c) Anteroposterior
(d) Oblique

38. Saccules help in the detection of _____ movement.
(a) Rotatory
(b) Side-to-side
(c) Anteroposterior
(d) Oblique

39. The receptors in the semicircular canals are
(a) Crista ampullaris
(b) Macula
(c) Organ of Corti
(d) Otolith

40. The receptors in the utricle and saccule are
(a) Crista ampullaris
(b) Macula
(c) Organ of Corti
(d) Otolith

41. The otolith organs consist of
(a) Utricle
(b) Cochlea
(c) Scala media
(d) Helicotrema

42. Inborn reflex is called _____ reflex.
(a) Conditioned
(b) Unconditioned

(c) Superficial
(d) Polysynaptic

43. Following are the properties of the reflex *except*
(a) Summation
(b) Habituation
(c) Specificity
(d) Irradiation

44. The reflex acquired by experience is
(a) Conditioned
(b) Unconditioned
(c) Superficial
(d) Polysynaptic

45. Phantom limb is an example of the following property of sensation
(a) Doctrine of specific nerve energy
(b) Law of projection
(c) Intensity discrimination
(d) Adaptation

46. Weber–Fechner law explains the following property of the receptor
(a) Doctrine of specific nerve energy
(b) Law of projection
(c) Intensity discrimination
(d) Adaptation

47. A low-intensity stimuli given for a prolonged period results in
(a) Habituation
(b) Specificity
(c) Sensitization
(d) Summation

48. Painful stimuli given to animal result in
(a) Habituation
(b) Specificity
(c) Sensitization
(d) Summation

49. Following is a rapidly adapting receptor
(a) Touch
(b) Pain
(c) Temperature
(d) Pressure

50. Following is a slowly adapting receptor
(a) Touch
(b) Pain
(c) Temperature
(d) Pressure

51. The perception of pain in the region of skin away from the site of its production internally is
(a) Referred pain
(b) Visceral pain
(c) Somatic pain
(d) Slow pain

52. The pain due to the inflammation of appendix felt around the umbilicus is an example for
(a) Referred pain
(b) Visceral pain
(c) Somatic pain
(d) Slow pain

53. Following are the endogenous opioids *except*
(a) Pethedine
(b) Enkephalin
(c) Endorphin
(d) Dynorphin

54. Temporary cessation of function of the nerve due to its compression is
(a) Neuropraxia
(b) Axonotmesis
(c) Neurotmesis
(d) Chromatolysis

55. Crush injury to a nerve with intact endoneural tube results in
(a) Neuropraxia
(b) Axonotmesis
(c) Neurotmesis
(d) Chromatolysis

56. Complete disruption of nerve trunk due to injury results in
(a) Neuropraxia
(b) Axonotmesis
(c) Neurotmesis
(d) Chromatolysis

57. Maximum conduction velocity of Aα nerve fiber is
(a) 120 ft/min
(b) 120 m/min

(c) 120 ft/s
(d) 120 m/s

58. Following properties are true for receptor potential *except*
(a) It is graded
(b) Nonpropagated
(c) Has no latency
(d) Shows all-or-none response

59. Following are the parts of muscle spindle *except*
(a) Nuclear bag fibers
(b) Nuclear chain fibers
(c) Annulospiral ending
(d) Mossy fibers

60. Contraction of one group of muscle leads to relaxation of antagonistic group of muscle is an example for
(a) Postsynaptic inhibition
(b) Presynaptic inhibition
(c) Crossed extensor response
(d) Negative feedback inhibition

61. Painful stimuli given to animal results in _____ reflex.
(a) Axon reflex
(b) Stretch reflex
(c) Withdrawal reflex
(d) Postural reflex

62. Somatosensory cortex corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 8
(d) 17

63. Primary motor cortex corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 8
(d) 17

64. Premotor cortex corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 8
(d) 5, 7

65. Primary visual area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 8
(d) 17

66. Visual association area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 17

67. Primary auditory area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 41, 42

68. Audiopsychic area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 22

69. Frontal eye field corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 8
(d) 18, 19

70. Wernicke's area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 22

71. Broca's speech area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 44

72. In spinal cord, the dorsal root is sensory and ventral root is motor. The law which states arrangement is
(a) Laplace law
(b) Bell–Magendie law
(c) Marey's law
(d) Weber–Fechner law

73. Dorsal column tracts carry the following sensations *except*
(a) Pain
(b) Touch
(c) Pressure
(d) Vibration

74. Anterolateral tracts carry the following sensations *except*
(a) Pain
(b) Temperature
(c) Crude touch
(d) Proprioception

75. Following are the ascending tracts *except*
(a) Pyramidal tract
(b) Spinotectal
(c) Spino-olivary
(d) Spinothalamic

76. Following are the descending tracts *except*
(a) Spinocerebellar
(b) Rubrospinal
(c) Tectospinal
(d) Corticospinal

77. Following are the extrapyramidal tracts *except*
(a) Vestibulospinal
(b) Rubrospinal
(c) Tectospinal
(d) Corticospinal

78. Features of the upper motor neuron lesion are the following *except*
(a) Rigidity in the muscle
(b) Loss of superficial reflexes
(c) Exaggerated deep reflexes
(d) Negative Babinski's sign

79. Features of the lower motor neuron lesion are the following *except*
(a) Flaccidity of the muscles
(b) Loss of superficial reflexes
(c) Exaggerated deep reflexes
(d) Muscle wasting

80. Dorsiflexion of the great toe and fanning of the other toes when the sole of foot is scratched indicates
(a) Positive Babinski's sign
(b) Normal plantar reflex
(c) Negative Babinski's sign
(d) Exaggerated deep reflex

81. Positive Babinski's sign is seen in the following conditions *except*
(a) Upper motor neuron lesion
(b) During deep sleep
(c) Infant below the age of 18 months
(d) Lower motor neuron lesion

82. In the hemisection of spinal cord, the following statement is not true
(a) Loss of all sensation on the same side below the level of lesion
(b) Loss of pain on the opposite side below the level of lesion
(c) Loss of fine touch on the same side below the level of lesion
(d) Loss of all sensation on the same side at the level of lesion

83. Theories of referred pain are the following *except*
(a) Dermatomal rule
(b) Convergence theory
(c) Facilitation theory
(d) Myogenic theory

84. Fast pain is carried by
(a) Aα fiber
(b) Aδ fiber
(c) B fiber
(d) C fiber

85. Slow pain is carried by
(a) Aα fiber
(b) B fiber
(c) C fiber
(d) Aδ fiber

86. Endogenous opioid analgesic pathway passes through the following parts *except*
(a) Magnus raphe nucleus
(b) Periaqueductal gray matter

(c) Hypothalamus
(d) Substantia gelatinosa of Rolando

87. Ability to identify the object by touching utilizing the past experience is termed
(a) Stereognosis
(b) Barognosis
(c) Astereognosis
(d) Graphesthesia

88. The tract which carries proprioceptive sensation is
(a) Spinotectal
(b) Corticospinal
(c) Dorsal spinothalamic tract
(d) Tectospinal

89. The example of synthetic sensation is
(a) Touch
(b) Pain
(c) Vibration
(d) Temperature

90. Hemiplegia is produced when the corticospinal tract is damaged at the level of
(a) Pons
(b) Midbrain
(c) Medulla
(d) Internal capsule

91. Majority of the fibers of the pyramidal tract cross to the opposite side at the lower border of
(a) Pons
(b) Midbrain
(c) Medulla
(d) Internal capsule

92. The condition of the patient with complete transection of spinal cord is explained under the following stages *except*
(a) Spinal shock
(b) Recovery
(c) Reflex failure
(d) Paralysis

93. Functional divisions of the cerebellum are the following *except*
(a) Archicerebellum
(b) Vestibulocerebellum
(c) Spinocerebellum
(d) Cerebrocerebellum

94. The nuclei of the cerebellum are the following *except*
(a) Dentatus
(b) Globosus
(c) Emboliformis
(d) Striatum

95. The function of cerebellum is
(a) To maintain tone, posture, and equilibrium
(b) Control voluntary activity
(c) Relay different sensations
(d) Regulate body temperature

96. The features of cerebellar dysfunction are the following *except*
(a) Nystagmus
(b) Static tremor
(c) Dysmetria
(d) Ataxia

97. Nuclei of basal ganglia are the following *except*
(a) Caudate nucleus
(b) Putamen
(c) Globus pallidus
(d) Dentatus

98. Striatum is formed by caudate nucleus along with
(a) Caudate nucleus
(b) Putamen
(c) Globus pallidus
(d) Dentatus

99. Lentiform nucleus is formed by putamen along with
(a) Caudate nucleus
(b) Putamen
(c) Globus pallidus
(d) Dentatus

100. Neurotransmitter for nigrostriatal pathway is
(a) GABA
(b) Dopamine
(c) Histamine
(d) Glycine

101. Neurotransmitter for strionigral pathway is
(a) GABA
(b) Dopamine
(c) Histamine
(d) Glycine

102. Damage to nigrostriatal pathway causes
(a) Parkinsonism
(b) Sham rage
(c) Tabes dorsalis
(d) Syringomyelia

103. Parkinsonism is treated by administration of
(a) L-dopa
(b) Dopamine
(c) Prostaglandins
(d) Histamine

104. Akinesia, pill-rolling tremors, and mask-like face are the features of
(a) Parkinsonism
(b) Sham rage
(c) Tabes dorsalis
(d) Syringomyelia

105. The sensation which has no relay in thalamus is
(a) Olfaction
(b) Pain
(c) Temperature
(d) Fine touch

106. Ascending reticular activating system is concerned with
(a) Sleep
(b) Tone
(c) Feeding
(d) Equilibrium

107. Descending reticular activating system is concerned with
(a) Sleep
(b) Tone
(c) Feeding
(d) Equilibrium

108. Meniere's disease is due to the defective functioning of
(a) Cochlea
(b) Cerebellum
(c) Vestibular apparatus
(d) Basal ganglia

109. Jerky movement of the eye ball is termed
(a) Akinesia
(b) Nystagmus
(c) Dysmetria
(d) Tremor

110. The autonomic nervous system with craniosacral outflow is
(a) Sympathetic
(b) Visceral
(c) Parasympathetic
(d) Somatic

111. The autonomic nervous system with thoracolumbar outflow is
(a) Sympathetic
(b) Visceral
(c) Parasympathetic
(d) Somatic

112. Stimulation of sympathetic nervous system results in the following changes *except*
(a) Dilation of pupil
(b) Increased heart rate
(c) Increased cardiac output
(d) Increased GI motility

113. Stimulation of parasympathetic nervous system results in the following changes *except*
(a) Vasodilation
(b) Decreased heart rate
(c) Bronchodilation
(d) Increased GI motility

114. Following are the functions of cerebrospinal fluid *except*
(a) Nourishes the brain
(b) Removes metabolic waste
(c) Forms blood–brain barrier
(d) Protects the brain against injury

115. CSF is formed in
(a) Lateral ventricle
(b) Sagittal sinus
(c) Fourth ventricle
(d) Central canal

116. CSF is absorbed by
(a) Choroid plexus
(b) Central canal
(c) Arachnoid villi
(d) Third ventricle

117. EEG wave recorded in an awake person with mind wandering and eyes closed is
(a) Alpha wave
(b) Beta wave
(c) Theta wave
(d) Delta wave

118. EEG wave recorded in an alert person doing a mathematical calculation is
(a) Alpha wave
(b) Beta wave
(c) Theta wave
(d) Delta wave

119. EEG wave recorded during deep sleep is
(a) Alpha wave
(b) Gamma wave
(c) Theta wave
(d) Delta wave

120. Dreaming is common during _____ type of sleep.
(a) REM sleep
(b) NREM sleep
(c) Both REM and NREM
(d) None of the above

121. Following are the features of REM sleep *except*
(a) Rapid movement of the eye ball
(b) It is associated with dreaming
(c) Muscle tone is grossly reduced
(d) Theta-wave pattern in EEG recording

122. Following are the functions of hypothalamus *except*
(a) Fluid and water balance
(b) Temperature regulation
(c) Relay center for different sensations
(d) Control of feeding and satiety

123. Normal core temperature in human beings is
(a) 37 °F
(b) 98.6 °F
(c) 32 °C
(d) 98.6 °C

124. Feeding center is located in _____ nucleus of hypothalamus.
(a) Ventromedial
(b) Lateral
(c) Paraventricular
(d) Preoptic

125. Satiety center is located in _____ nucleus of hypothalamus.
(a) Ventromedial
(b) Lateral
(c) Paraventricular
(d) Preoptic

126. Changes that occur when a person is exposed to extreme cold are the following *except*
(a) Peripheral vasoconstriction
(b) Piloerection or horripilation
(c) Shivering
(d) Vasodilation

127. Changes that occur when a person is exposed to warm environment are the following *except*
(a) Vasodilation
(b) Sweating
(c) Piloerection
(d) None of the above

128. The functions of limbic system are the following *except*
(a) It controls rage and fear
(b) It regulates sexual behavior
(c) It has a role in the process of olfaction
(d) It regulates circadian rhythm

129. The disorder of speech is
(a) Aphasia
(b) Anosmia
(c) Amnesia
(d) Ageusia

130. Conditioned learning is an example of
(a) Associative learning
(b) Nonassociative learning
(c) Short-term memory
(d) Long-term memory

131. Sleep is produced due to
(a) Stimulation of ARAS
(b) Inhibition of ARAS

(c) Stimulation of cerebral cortex
(d) Stimulation of limbic system

132. Loss of memory is termed
(a) Amnesia
(b) Anosmia
(c) Ageusia
(d) Aphakia

133. The part of thalamus which forms a component of visual pathway is
(a) Lateral geniculate body
(b) Medial geniculate body
(c) Ventral posterolateral nucleus
(d) Anterior nucleus

134. The part of thalamus which forms a component of auditory pathway is
(a) Lateral geniculate body
(b) Medial geniculate body
(c) Ventral posterolateral nucleus
(d) Anterior nucleus

135. The part of thalamus which relays dorsal spinothalamic tract is
(a) Lateral geniculate body
(b) Medial geniculate body
(c) Ventral posterolateral nucleus
(d) Anterior nucleus

136. Paralysis of one-half of the body is termed
(a) Hemiplegia
(b) Monoplegia
(c) Quadriplegia
(d) Paraplegia

137. Paralysis of all the four limbs is
(a) Hemiplegia
(b) Monoplegia
(c) Quadriplegia
(d) Paraplegia

138. Paralysis of one limb is
(a) Hemiplegia
(b) Monoplegia
(c) Quadriplegia
(d) Paraplegia

139. Paralysis of both the lower limbs is
(a) Hemiplegia
(b) Monoplegia
(c) Quadriplegia
(d) Paraplegia

9. SPECIAL SENSES

1. Following are the special sensations *except*
(a) Vision
(b) Olfaction
(c) Audition
(d) Vibration

2. The receptors for visions are
(a) Rods
(b) Hair cells
(c) Macula
(d) Crista

3. The receptor for audition is
(a) Rods
(b) Hair cells
(c) Macula
(d) Crista

4. The receptor for smell is
(a) Rods
(b) Hair cells
(c) Macula
(d) Olfactory bulb

5. The outermost layer of eye ball is
(a) Sclera
(b) Choroid
(c) Retina
(d) Conjunctiva

6. The vascular layer of the eyes is
(a) Sclera
(b) Choroid
(c) Retina
(d) Conjunctiva

7. The photoreceptor containing layer of the eye is
(a) Sclera
(b) Choroid
(c) Retina
(d) Conjunctiva

8. The color of the eye is due to
(a) Cornea
(b) Iris
(c) Choroid
(d) Retina

9. Dilator pupillae is supplied by
(a) Sympathetic nerve
(b) Visceral nerve
(c) Parasympathetic nerve
(d) Somatic nerve

10. Constrictor pupillae is supplied by
(a) Sympathetic nerve
(b) Visceral nerve
(c) Parasympathetic nerve
(d) Somatic nerve

11. Stimulation of sympathetic nerve results in _____ of pupil.
(a) Constriction
(b) Dilation
(c) No change
(d) Fixation

12. Stimulation of parasympathetic nerve results in _____ of pupil.
(a) Constriction
(b) Dilation
(c) No change
(d) Fixation

13. Site of production of aqueous humor is
(a) Ciliary body
(b) Iris
(c) Choroid
(d) Cornea

14. The normal intraocular pressure is
(a) 0–15 mm Hg
(b) 5–6 mm Hg
(c) 10–20 mm Hg
(d) 10–20 cm Hg

15. Increased intraocular pressure results in
(a) Glaucoma
(b) Cataract
(c) Presbyopia
(d) Nyctalopia

16. Refractive media of the eye are the following *except*
(a) Cornea
(b) Lens
(c) Aqueous humor
(d) Sclera

17. Refractive power of the eye is expressed as
(a) Diopters
(b) Focal length
(c) Positive
(d) Negative

18. Opacity of the lens is
(a) Cataract
(b) Myopia
(c) Hypermetropia
(d) Astigmatism

19. The receptor for taste is
(a) Taste buds
(b) Hair cells
(c) Cones
(d) Rods

20. The refractive error in which the image is formed in front of the retina is
(a) Myopia
(b) Hypermetropia
(c) Presbyopia
(d) Astigmatism

21. The refractive error in which the image is formed behind the retina is
(a) Myopia
(b) Hypermetropia
(c) Presbyopia
(d) Astigmatism

22. The refractive error in which the accommodation of the lens is reduced is
(a) Myopia
(b) Hypermetropia
(c) Presbyopia
(d) Astigmatism

23. The refractive error due to altered curvature of cornea and lens is
(a) Myopia
(b) Hypermetropia
(c) Presbyopia
(d) Astigmatism

24. Myopia is corrected by
(a) Concave lens
(b) Convex lens

(c) Cylindrical lens
(d) Bifocal lens

25. Hypermetropia is corrected by
(a) Concave lens
(b) Convex lens
(c) Cylindrical lens
(d) Bifocal lens

26. Presbyopia is corrected by
(a) Concave lens
(b) Planoconvex lens
(c) Cylindrical lens
(d) Bifocal lens

27. Astigmatism is corrected by
(a) Concave lens
(b) Convex lens
(c) Cylindrical lens
(d) Bifocal lens

28. Distant vision is tested by
(a) Snellen's chart
(b) Jaeger's chart
(c) Ishihara's chart
(d) Color ribbon

29. Near vision is tested by
(a) Snellen's chart
(b) Jaeger's chart
(c) Ishihara's chart
(d) Color ribbon

30. Color vision is tested by
(a) Snellen's chart
(b) Jaeger's chart
(c) Ishihara's chart
(d) Landold's chart

31. Primary colors of vision are the following *except*
(a) Red
(b) Green
(c) Yellow
(d) Blue

32. Protanopia is the blindness for
(a) Red color
(b) Green color
(c) Blue color
(d) Yellow color

33. Deuteranopia is the blindness for
(a) Red color
(b) Green color
(c) Blue color
(d) Yellow color

34. Tritanopia is the blindness for
(a) Red color
(b) Green color
(c) Blue color
(d) Yellow color

35. Primary visual cortex corresponds to Brodmann area number
(a) 3, 1, 2
(b) 8
(c) 17
(d) 22

36. Lesion of the optic nerve causes
(a) Blindness in the same eye
(b) Blindness in the opposite eye
(c) Bitemporal hemianopia
(d) Homonymous hemianopia

37. Lesion of the optic tract causes
(a) Blindness in the same eye
(b) Blindness in the opposite eye
(c) Bitemporal hemianopia
(d) Homonymous hemianopia

38. Lesion of the optic radiation causes
(a) Blindness in the same eye
(b) Blindness in the opposite eye
(c) Bitemporal hemianopia
(d) Homonymous hemianopia with macular sparing

39. Lesion of the optic chiasma in the midline causes
(a) Blindness in the same eye
(b) Blindness in the opposite eye
(c) Bitemporal hemianopia
(d) Homonymous hemianopia with macular sparing

40. Lesion to the optic chiasma in the lateral portion causes
(a) Blindness in the same eye
(b) Binasal hemianopia

(c) Bitemporal hemianopia
(d) Homonymous hemianopia with macular sparing

41. Visual association area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 18, 19
(d) 41, 42

42. In Argyll Robertson pupil _____ reflex is lost.
(a) Light
(b) None
(c) Accommodation
(d) Both light and accommodation

43. Deficiency of vitamin A causes
(a) Myopia
(b) Astigmatism
(c) Cataract
(d) Nyctalopia

44. The receptor for dim light vision is
(a) Rods
(b) Cones
(c) Rhodopsin
(d) Retinol

45. The receptor for bright light and color vision is
(a) Rods
(b) Cones
(c) Rhodopsin
(d) Retinol

46. The following changes occur during accommodation *except*
(a) Constriction of pupil
(b) Convergence of eye ball
(c) Change in curvature of lens
(d) Dilation of pupil

47. The area where the optic nerve leaves the retina corresponds to
(a) Macula lutea
(b) Fovea centralis
(c) Blind spot
(d) Field of vision

48. The part of retina having best visual acuity is
(a) Retina
(b) Fovea centralis
(c) Blind spot
(d) Iris

49. Aqueous humor is absorbed through
(a) Ciliary body
(b) Cornea
(c) Iris
(d) Canal of Schlemm

50. The function of the external ear is
(a) Transmission of sound
(b) Amplification of sound
(c) Equalization of pressure
(d) Dampening of sound

51. The functions of the middle ear are the following *except*
(a) Transmission of sound
(b) Amplification of sound
(c) Equalization of pressure
(d) Altering of sound

52. Ossicles of the middle ear are the following *except*
(a) Malleus
(b) Incus
(c) Stapes
(d) Stapedius

53. The muscle of middle ear is
(a) Malleus
(b) Incus
(c) Stapes
(d) Stapedius

54. The muscle of middle ear is
(a) Malleus
(b) Incus
(c) Sternocleidomastoid
(d) Tensor tympani

55. The function of the Eustachian tube is
(a) Transmission of sound
(b) Amplification of sound
(c) Equalization of pressure
(d) Dampening of sound

56. Fluid present in the internal ear is
(a) Endolymph
(b) Lymph
(c) CSF
(d) Serum

57. Fluid present in the internal ear is
(a) Perilymph
(b) Lymph
(c) CSF
(d) Serum

58. Compartments present in the internal ear are the following *except*
(a) Scala vestibuli
(b) Scala media
(c) Helicotrema
(d) Scala tympani

59. Scala vestibuli and scala media are separated by
(a) Basilar membrane
(b) Reissner's membrane
(c) Tectorial membrane
(d) Secondary tympanic membrane

60. Scala tympani and scala media are separated by
(a) Basilar membrane
(b) Reissner's membrane
(c) Tectorial membrane
(d) Secondary tympanic membrane

61. The auditory receptors are present on
(a) Basilar membrane
(b) Reissner's membrane
(c) Tectorial membrane
(d) Secondary tympanic membrane

62. Base of stapes is located in
(a) Round window
(b) Oval window
(c) Scala vestibuli
(d) Middle ear

63. Secondary tympanic membrane covers
(a) Round window
(b) Oval window
(c) Scala vestibuli
(d) Middle ear

64. The longest hair-like process of the hair cell of the organ of Corti is
(a) Kinocilium
(b) Stereocilium
(c) Otolith
(d) Crista

65. The hair-like process with gradually increasing length present in hair cell is
(a) Kinocilium
(b) Stereocilium
(c) Otolith
(d) Crista

66. Bending of the hairs toward kinocilium results in
(a) Depolarization
(b) Hyperpolarization
(c) Repolarization
(d) IPSP

67. Bending of the hairs away from kinocilium results in
(a) Depolarization
(b) Hyperpolarization
(c) Repolarization
(d) No change

68. The potential difference between endolymph and perilymph is
(a) End-plate potential
(b) Endolymphatic potential
(c) Action potential
(d) Cochlear microphonic potential

69. The primary auditory cortex corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 21, 22
(d) 41, 42

70. Audiopsychic area corresponds to Brodmann area number
(a) 3, 1, 2
(b) 4, 6
(c) 21, 22
(d) 41, 42

71. Basal part of the basilar membrane responds to
(a) High-pitched sound
(b) Low-pitched sound
(c) No sound
(d) All sounds

72. Apical part of the basilar membrane responds to
(a) High-pitched sound
(b) Low-pitched sound
(c) No sound
(d) All sounds

73. In a normal person, air conduction is
(a) Better than bone conduction
(b) Same as bone conduction
(c) Less than bone conduction
(d) None of the above

74. While performing Weber's test in conduction deafness, the sound is lateralized to (heard better in)
(a) Normal ear
(b) Defective ear
(c) Both the ears
(d) None of the ear

75. In nerve deafness while performing Weber's test, the sound is lateralized to (heard better in)
(a) Normal ear
(b) Defective ear
(c) Both the ears
(d) None of the ear

76. The frequency of tuning fork used for Weber's test is _____ Hz.
(a) 50
(b) 100
(c) 128
(d) 256

77. Tympanic reflex helps in
(a) Protecting auditory receptors
(b) Amplifying sound
(c) Equalizing the pressure
(d) Transmission of sound

78. Endolymph is present in
(a) Scala vestibuli
(b) Scala media
(c) Helicotrema
(d) Scala tympani

79. The auditory pathway passes through the following structures *except*
(a) Medical geniculate body
(b) Lateral geniculate body
(c) Ventral cochlear nucleus
(d) Inferior colliculus

80. Minimal intensity of sound that can be appreciated by human ear is _____ Hz.
(a) 20
(b) 1,000
(c) 3,000
(d) 20,000

81. Maximum frequency of sound that can be appreciated by human ear is _____ Hz.
(a) 20
(b) 1,000
(c) 3,000
(d) 20,000

82. The primary taste sensations are the following *except*
(a) Sweet
(b) Salt
(c) Sour
(d) Spicy

83. Bitter sensation is appreciated at _____ of the tongue.
(a) Tip
(b) Sides
(c) Back
(d) All parts

84. Sweet sensation is appreciated at _____ of the tongue.
(a) Tip
(b) Sides
(c) Back
(d) All parts

85. Salt sensation is appreciated at _____ of the tongue.
(a) Tip
(b) Sides
(c) Back
(d) All parts

86. Sour sensation is appreciated at _____ of the tongue.
(a) Tip
(b) Sides
(c) Back
(d) All parts

87. Perilymph is present in
(a) Scala vestibuli
(b) Scala media
(c) Helicotrema
(d) Middle ear

88. Taste sensation from anterior two-third of the tongue is carried by
(a) Facial nerve
(b) Vagus nerve
(c) Glossopharyngeal
(d) Hypoglossal

89. Taste sensation from posterior one-third of the tongue is carried by
(a) Facial nerve
(b) Vagus nerve
(c) Glossopharyngeal
(d) Hypoglossal

90. Sweet sensation is produced by
(a) Alkaloids
(b) Organic substances
(c) Ionizing substances
(d) Acidic substances

91. Disturbed taste sensation is
(a) Ageusia
(b) Dysgeusia
(c) Parosmia
(d) Anosmia

92. Salt sensation is produced by
(a) Alkaloids
(b) Organic substances
(c) Ionizing substances
(d) Acidic substances

93. Sour sensation is produced by
(a) Alkaloids
(b) Organic substances
(c) Ionizing substances
(d) Acidic substances

94. Bitter sensation is produced by
(a) Alkaloids
(b) Organic substances
(c) Ionizing substances
(d) Acidic substances

95. Absence of smell sensation is
(a) Ageusia
(b) Dysgeusia
(c) Hypogeusia
(d) Anosmia

96. Perverted sense of smell is
(a) Ageusia
(b) Dysgeusia
(c) Parosmia
(d) Anosmia

97. Absence of taste sensation is
(a) Ageusia
(b) Dysgeusia
(c) Hypogeusia
(d) Anosmia

98. Decreased taste sensation is
(a) Ageusia
(b) Dysgeusia
(c) Hypogeusia
(d) Anosmia

10. ENDOCRINOLOGY

1. Hormones which have effect on the adjacent cells are called
(a) Classical hormones
(b) Neurohumors
(c) Paracrine hormones
(d) Autocrine hormone

2. Hormones acting on the cells from which they are produced are called
(a) Classical hormones
(b) Neurohormones
(c) Paracrine hormones
(d) Autocrine hormones

3. Chemical substances produced by endocrine glands having their effect on distant target organs are called
(a) Hormones
(b) Vitamins
(c) Enzymes
(d) Lipids

4. The pituitary gland weighs around
(a) 1 mg
(b) 10 mg
(c) 1 g
(d) 10 g

5. The hormones secreted by anterior pituitary are all *except*
(a) Growth hormone
(b) FSH
(c) Oxytocin
(d) TSH

6. The hormone secreted by posterior pituitary is
(a) LH
(b) FSH
(c) Vasopressin
(d) Growth hormone

7. The hormones produced by hypothalamus is
(a) Thyrotropin-releasing hormone
(b) Thyroid-stimulating hormone
(c) Follicle-stimulating hormone
(d) Growth hormone

8. Decreased secretion of growth hormone leads to
(a) Cretinism
(b) Dwarfism
(c) Acromegaly
(d) Gigantism

9. Increased secretion of growth hormone after puberty leads to
(a) Cretinism
(b) Dwarfism
(c) Acromegaly
(d) Gigantism

10. Increased secretion of growth hormone before puberty leads to
(a) Cretinism
(b) Dwarfism
(c) Acromegaly
(d) Gigantism

11. Antidiuretic hormone is a
(a) Glycolipid
(b) Polypeptide
(c) Steroid
(d) Lipoprotein

12. ADH acts on
(a) Glomerulus
(b) Loop of Henle
(c) PCT
(d) DCT

13. Diabetes insipidus occurs due to the deficiency of
(a) Growth hormone
(b) Insulin
(c) ADH
(d) Thyroxine

14. Total number of parathyroid glands present in humans is
(a) 1
(b) 2
(c) 3
(d) 4

15. Parathormone
(a) Increases serum calcium level
(b) Increases phosphate excretion in urine
(c) Acts on bones, kidneys, and intestine
(d) All of the above

16. Tetany is caused due to decrease in
(a) Thyroid hormone
(b) Parathyroid hormone
(c) Pituitary hormone
(d) Pancreatic hormone

17. Calcitonin is produced by
(a) Thyroid gland
(b) Parathyroid gland
(c) Adrenal gland
(d) Pancreas

18. Normal serum calcium level is
(a) 1–3 mg/100 mL
(b) 9–11 mg/100 mL
(c) 1–3 g/100 mL
(d) 9–11 g/100 mL

19. Adrenal glands are present over the
(a) Spleen
(b) Pituitary
(c) Kidneys
(d) Liver

20. Adrenal cortical hormones are
(a) Steroids
(b) Polypeptides
(c) Glycolipids
(d) Carbohydrates

21. The layers of adrenal cortex include all *except*
(a) Zona fasciculata
(b) Zona reticularis
(c) Zona glomerulosa
(d) Zona pellucida

22. Aldosterone is chiefly secreted by
(a) Zona fasciculata
(b) Zona reticularis
(c) Zona glomerulosa
(d) Zona pellucida

23. Cortisol-binding globulin is synthesized in
(a) Liver
(b) Spleen
(c) Adrenals
(d) Pituitary

24. Conn's syndrome occurs due to excess of
(a) Glucocorticoids
(b) Mineralocorticoids
(c) Sex steroids
(d) Insulin

25. Cortisol secretion is high during
(a) Evening
(b) Night
(c) Afternoon
(d) Mornings

26. Addison's disease is due to the deficiency of
(a) Thyroid hormones
(b) Pituitary hormones
(c) Adrenal cortical hormones
(d) Adrenal medullary hormones

27. Cushing's syndrome is due to an increase in
(a) Glucocorticoids
(b) Mineralocorticoids
(c) Sex steroids
(d) All of the above

28. The adrenal medulla secretes
(a) Epinephrine
(b) Norepinephrine
(c) Dopamine
(d) All of the above

29. Hypothalamic-releasing hormones are
(a) Classical hormones
(b) Neurohumors
(c) Paracrine hormones
(d) Autocrine hormones

30. Islets of Langerhans are mainly present in
(a) Head of pancreas
(b) Body of pancreas
(c) Tail of pancreas
(d) Neck of pancreas

31. Alpha cells of pancreas secrete
(a) Insulin
(b) Glucagon
(c) Somatostatin
(d) Pancreatic polypeptide

32. Beta cells of pancreas secrete
(a) Insulin
(b) Glucagon
(c) Somatostatin
(d) Pancreatic polypeptide

33. Delta cells of pancreas secrete
(a) Insulin
(b) Glucagon
(c) Somatostatin
(d) Pancreatic polypeptide

34. F cells of pancreas secrete
(a) Insulin
(b) Glucagon
(c) Somatostatin
(d) Pancreatic polypeptide

35. Insulin is a
(a) Glycolipid
(b) Polypeptide

(c) Carbohydrate
(d) Glycoprotein

36. Insulin causes
(a) Increased blood glucose levels
(b) Increased protein breakdown
(c) Decreased blood glucose
(d) Lipolysis

37. The symptoms of diabetes mellitus include all the following *except*
(a) Polyuria
(b) Polyphagia
(c) Polydipsia
(d) Polychromasia

38. Diabetes mellitus is caused due to the deficiency of
(a) Glucagon
(b) Insulin
(c) Somatostatin
(d) Pancreatic polypeptide

39. Somatostatin is a hormone found in
(a) Brain
(b) Pancreas
(c) GIT
(d) All of the above

40. The follicles of thyroid gland contain
(a) Thyroglobulin
(b) Globulin
(c) Thyrotropin
(d) Gamma globulin

41. The hormones secreted by thyroid gland are all of the following *except*
(a) Thyroxine
(b) Triiodothyronine
(c) Calcitonin
(d) Parathormone

42. The thyroid gland is present
(a) Inside the brain
(b) In the neck region
(c) Below the liver
(d) Above the kidneys

43. Thyroxine is made up of
(a) Two DIT molecules
(b) Two MIT molecules
(c) One DIT and one MIT molecule
(d) None of the above

44. Most essential element required for the formation of thyroid hormones is
(a) Calcium
(b) Iron
(c) Magnesium
(d) Iodine

45. The thyroid gland weighs around
(a) 150 mg
(b) 222 mg
(c) 20 g
(d) 40 g

46. Iodine is taken up by thyroid cells through
(a) Primary active transport
(b) Diffusion
(c) Osmosis
(d) Secondary active transport

47. Triiodothyronine is formed due to coupling of
(a) One MIT and one DIT molecule
(b) Two DIT molecules
(c) Two MIT molecules
(d) None of the above

48. Thyroxine causes
(a) Decreased BMR
(b) Decreased blood sugar
(c) Increased skeletal growth
(d) Increased serum cholesterol

49. Excess of thyroxine causes
(a) Decreased heart rate
(b) Decreased BMR
(c) Defective myelination
(d) Increased systolic BP

50. Thyroglobulin is a
(a) Glycoprotein
(b) Steroid
(c) Carbohydrate
(d) Glycolipid

51. Thyroid-stimulating hormone is secreted from
(a) Adrenals
(b) Hypothalamus
(c) Thyroid
(d) Pituitary

52. Thyroid-releasing hormone is secreted from
(a) Anterior pituitary
(b) Posterior pituitary
(c) Hypothalamus
(d) Thyroid

53. Myxedema occurs due to
(a) Hypothyroidism in children
(b) Hypothyroidism in adults
(c) Hyperthyroidism in children
(d) Hyperthyroidism in adults

54. Cretinism occurs due to
(a) Hypothyroidism in children
(b) Hypothyroidism in adults
(c) Hyperthyroidism in children
(d) Hyperthyroidism in adults

55. Grave's disease usually occurs due to
(a) Hypothyroidism in children
(b) Hypothyroidism in adults
(c) Hyperthyroidism in children
(d) Hyperthyroidism in adults

56. Features of hyperthyroidism include the following *except*
(a) Intolerance to cold
(b) Diarrhea
(c) Exophthalmos
(d) Weight loss

57. Features of hypothyroidism include the following *except*
(a) Low BMR
(b) Slow and husky voice
(c) Increased mental alertness
(d) Intolerance to cold

58. Chemically hormones can be of the following types *except*
(a) Steroids
(b) Peptides
(c) Amines
(d) Lipids

59. Receptors for the thyroid hormones are located
(a) On the cell membrane
(b) In the cytoplasm
(c) In the nucleus
(d) In the ribosomes

60. The pulsatile rhythm of the hormonal secretion with less than 24-h periodicity is termed
(a) Circadian rhythm
(b) Ultradian rhythm
(c) Biological rhythm
(d) None of the above

61. The regulation of thyroid hormone secretion is an example for
(a) Positive feedback
(b) Negative feedback
(c) Bio feedback
(d) Downregulation

62. Following are the hypothalamic hormones *except*
(a) Prolactin-inhibiting hormone
(b) Thyroid-stimulating hormone
(c) Growth hormone–releasing hormone
(d) Growth hormone–inhibiting hormone

63. The endocrine abnormality associated with acromegaly is
(a) Diabetes insipidus
(b) Diabetes mellitus
(c) Conn's disease
(d) Cushing's syndrome

64. Growth hormone acts through
(a) Somatomedin C
(b) Somatostatin
(c) Calmodulin
(d) Sialoprotein

65. The clinical condition in which the growth hormone secretion is normal but the individual does not respond to it is termed
(a) Panhypopituitarism
(b) Sheehan's syndrome
(c) Lorain dwarf
(d) Dwarfism

66. Regulation of oxytocin secretion is an example for
(a) Positive feedback
(b) Negative feedback
(c) Bio feedback
(d) Downregulation

67. Nephrogenic diabetes insipidus is due to
(a) Reduced secretion of vasopressin
(b) Nonresponsive kidney for ADH secretion
(c) Increased secretion of ADH
(d) Increased water intake

68. The hormone responsible for milk ejection reflex is
(a) Oxytocin
(b) Estrogen
(c) Progesterone
(d) Prolactin

69. Following are the features of cretinism *except*
(a) Mental retardation
(b) Stunted growth
(c) Increased thyroxine level
(d) Sexual immaturity

70. Following are the features of myxedema *except*
(a) Intolerance to cold
(b) Nonpitting edema
(c) Mental retardation
(d) Menstrual irregularities

71. Following are the features of Graves' disease *except*
(a) Exophthalmos
(b) Fine tremors
(c) Increased BMR
(d) Decreased thyroid function

72. Trousseau's sign is test for detecting
(a) Tetanus
(b) Tetany
(c) Cretinism
(d) Cushing's syndrome

11. REPRODUCTIVE SYSTEM

1. Number of ovaries present in humans is
(a) 1
(b) 2
(c) 4
(d) 8

2. Primordial follicle is converted into primary follicle
(a) At birth
(b) Inside the fetus
(c) At puberty
(d) After menopause

3. At ovulation, mature follicle attains the size of
(a) 1–2 mm
(b) 3–4 mm
(c) 1–1.5 cm
(d) 3–4 cm

4. Mitosis occurs in the developing ovum till
(a) Birth
(b) After puberty till menopause
(c) Fifth month of fetal life
(d) Puberty

5. The second meiotic division is completed in the ovum
(a) At birth
(b) Fifth month of fetal life
(c) Puberty
(d) Fertilization

6. In a women menstrual cycle of 28 days, ovulation occurs on
(a) 5th day
(b) 11th day
(c) 14th day
(d) 28th day

7. Ovum released from the ovary is viable for
(a) 12 h
(b) 24 h
(c) 72 h
(d) 7 days

8. The remains of Graafian follicle after extrusion of ovum is called
(a) Primordial follicle
(b) Corona radiata
(c) Cumulus oophorus
(d) Corpus luteum

9. FSH is secreted from
(a) Anterior pituitary
(b) Posterior pituitary
(c) Ovary
(d) Placenta

10. FSH secretion starts at
(a) Birth
(b) 5–7 years
(c) 9–11 years
(d) 25–28 years

11. FSH is a
(a) Carbohydrate
(b) Glycoprotein
(c) Glycolipid
(d) Derivative of cholesterol

12. Actions of FSH include the following *except*
(a) Causes growth of primary follicle
(b) Helps in forming estrogen
(c) Helps in forming new FSH and LH receptors
(d) Production of hCG

13. LH is secreted from
(a) Anterior pituitary
(b) Posterior pituitary
(c) Ovary
(d) Placenta

14. The main hormone responsible for ovulation is
(a) FSH
(b) LH
(c) GnRH
(d) Estrogen

15. GnRH is secreted from
(a) Anterior pituitary
(b) Posterior pituitary
(c) Hypothalamus
(d) Ovary

16. Recording basal body temperature is a test for
(a) Pregnancy
(b) Menstruation
(c) Ovulation
(d) Menarche

17. Progesterone at ovulation increases the body temperature by
(a) No rise in temperature
(b) 0.5°C
(c) 1°C
(d) 2.5°C

18. Changes in boys seen during puberty include all *except*
(a) Growth of external genitalia
(b) Increased skin thickness
(c) Hypertrophy of laryngeal mucosa
(d) Pelvis becomes broad and wide

19. Changes in girls seen during puberty include all *except*
(a) Growth of external genitalia
(b) Occurrence of menstrual cycle
(c) Enlargement and widening of pelvis
(d) Hoarseness of voice

20. Occurrence of first menstruation is called
(a) Puberty
(b) Menarche
(c) Thelarche
(d) Menopause

21. The normal duration of menstrual cycle is
(a) 22 days
(b) 28 days
(c) 32 days
(d) 36 days

22. The phases of menstrual cycle include all *except*
(a) Proliferative phase
(b) Secretory phase
(c) Hypertrophic phase
(d) Menstrual phase

23. The phase occurring immediately after cessation of menstrual bleeding is called
(a) Proliferative phase
(b) Secretory phase
(c) Midluteal phase
(d) Bleeding phase

24. Ovulation occurs at the end of
(a) Proliferative phase
(b) Secretory phase

(c) Midluteal phase
(d) Bleeding phase

25. The phase of menstrual cycle occurring after ovulation is
(a) Proliferative phase
(b) Secretory phase
(c) Midluteal phase
(d) Bleeding phase

26. Proliferation of endometrium, secretion in glands coiling, and tortuous spiral arteries are seen in
(a) Proliferative phase
(b) Secretory phase
(c) Midluteal phase
(d) Bleeding phase

27. Normal menstrual flow is around
(a) 50 mL
(b) 250 mL
(c) 350 mL
(d) 1.5 L

28. Permanent stoppage of menstrual cycle is called
(a) Puberty
(b) Menarche
(c) Menopause
(d) Menorrhagia

29. Normal duration of pregnancy in humans is around
(a) 150 days
(b) 186 days
(c) 280 days
(d) 320 days

30. Process of union of male and female gametes is called
(a) Luteinization
(b) Implantation
(c) Neutralization
(d) Fertilization

31. Fertilization occurs in the
(a) Fallopian tube
(b) Uterine cavity
(c) Cervix
(d) Vagina

32. The fertilized ovum is called
(a) Trophoblast
(b) Graafian follicle
(c) Zygote
(d) Granulosa cell

33. Growing embryo is connected with the mother through
(a) Placenta
(b) Corpus luteum
(c) Ovary
(d) Fallopian tube

34. Placental hormones include the following *except*
(a) hCG
(b) hCS
(c) Progesterone
(d) FSH

35. hCG is produced in
(a) First two months of pregnancy
(b) Second trimester of pregnancy
(c) Third trimester of pregnancy
(d) After delivery of the child

36. Maternal changes in pregnancy include all *except*
(a) Blood volume increases
(b) Erythropoiesis increases
(c) Plasma protein concentration increases
(d) Body weight increases

37. The main basis of immunological test for pregnancy is the detection of hormone
(a) Estrogen
(b) Progesterone
(c) hCG
(d) LH

38. The process of delivery of baby is called
(a) Fertilization
(b) Parturition
(c) Menstruation
(d) Ovulation

39. Dilation of cervix and opening of vaginal canal constitutes
(a) First stage of labor
(b) Second stage of labor
(c) Third stage of labor
(d) Fourth stage of labor

40. Delivery of baby through the birth canal constitutes
(a) First stage of labor
(b) Second stage of labor
(c) Third stage of labor
(d) Fourth stage of labor

41. Expulsion of placenta constitutes
(a) First stage of labor
(b) Second stage of labor
(c) Third stage of labor
(d) Fourth stage of labor

42. Normal blood loss during delivery of child is
(a) 50 mL
(b) 350 mL
(c) 1000 mL
(d) 5 L

43. Enhancement of uterine contractions can be done by giving synthetic
(a) Estrogens
(b) hCG
(c) Oxytocin
(d) LH

44. Postpartum hemorrhage is
(a) Loss of excess blood during placental delivery
(b) Loss of excess blood during menstruation
(c) Hemorrhage occurring in fetus during delivery
(d) Intermittent hemorrhage occurring throughout pregnancy

45. The best food available for baby is
(a) Mother's milk
(b) Cow's milk
(c) Skimmed milk
(d) Flavored milk

46. Prolactin is secreted from
(a) Hypothalamus
(b) Pituitary
(c) Thyroid
(d) Ovary

47. Milk ejection reflex is brought about by
(a) Vasopressin
(b) Oxytocin
(c) Thyroxine
(d) Ovary

48. All are forms of estrogens *except*
(a) Estrone
(b) Estradiol
(c) Estrone
(d) Ethisterone

49. Estrogens are
(a) Proteins
(b) Steroids
(c) Carbohydrates
(d) Glycolipids

50. Transport of estrogens occurs mainly by
(a) Binding with albumin
(b) Binding with globulin
(c) Binding with prealbumin
(d) Free form

51. Estrogens cause
(a) Inhibition of bone growth
(b) Prevention of fat deposition in the body
(c) Acne and black heads
(d) Lowering of plasma cholesterol

52. Progesterone is a
(a) Protein
(b) Steroid
(c) Carbohydrate
(d) Glycolipid

53. The precursor of progesterone is
(a) Estrogen
(b) Cholesterol
(c) Oxytocin
(d) Glycogen

54. Transport of progesterone occurs mainly by
(a) Binding with albumin
(b) Binding with globulin
(c) Binding with prealbumin
(d) Free form

55. Progesterone is secreted by
(a) Corpus luteum
(b) Placenta during pregnancy
(c) Adrenal cortex
(d) All of the above

56. All of the following actions regarding progesterone are true *except*
(a) Promotes secretory changes in uterine endometrium
(b) Cause development of lobules of breast
(c) Reduces body temperature
(d) Provides nutrition to the ovum

57. Sperms are produced in
(a) Epididymis
(b) Seminal vesicles
(c) Prostate
(d) Seminiferous tubules

58. Sertoli cells are present in
(a) Epididymis
(b) Seminal vesicles
(c) Prostate
(d) Seminiferous tubules

59. Hormones influencing spermatogenesis include
(a) LH
(b) FSH
(c) Testosterone
(d) All of the above

60. Sperms are stored in
(a) Prostate
(b) Seminal vesicle
(c) Bulbourethral glands
(d) Epididymis

61. Capacitation of sperm occurs in
(a) Seminiferous tubule
(b) Sertoli cells
(c) Female genital tract
(d) Epididymis

62. Normal sperm count is
(a) 6,000–12,000/mL
(b) 60,000–1.2 million/mL
(c) 6–12 million/mL
(d) 60–120 million/mL

63. Transport of testosterone mainly occurs in
(a) Combination with albumin
(b) Combination with globulin
(c) Free form
(d) Combination with fibrinogen

64. Testosterone is produced in a male
(a) Only after puberty
(b) During childhood
(c) During intrauterine life and after puberty
(d) After 25 years

65. Testosterone
(a) Causes increase in RBC count
(b) Causes muscular growth
(c) Causes bone growth
(d) All of the above

66. Failure of descent of testis is called
(a) Cholecystitis
(b) Cryptorchidism
(c) Hypogonadism
(d) Sterility

67. Permanent method of sterilization is
(a) Use of condoms
(b) Copper T
(c) Oral contraception
(d) Tubectomy

68. Permanent method of sterilization in males is
(a) Vasectomy
(b) Appendicectomy
(c) Tubectomy
(d) Splenectomy

69. Intrauterine contraceptive devices include all *except*
(a) Lippe's loop
(b) Copper T
(c) Progestasert
(d) Combined pills

12. INTEGRATED PHYSIOLOGY

1. Neonatal period refers to
(a) First 1 week after birth
(b) First 4 weeks after birth
(c) First 1 month after birth
(d) First 1 year after birth

2. The heart rate at birth is around
(a) 80 beats/min
(b) 100 beats/min
(c) 120 beats/min
(d) 140 beats/min

3. The total lung capacity in newborn is
(a) 100 mL
(b) 150 mL
(c) 200 mL
(d) 250 mL

4. During neonatal period, the immunoglobulin levels which is high is
(a) IgG
(b) IgM
(c) IgD
(d) IgA

5. The infant appreciates color fully by the age of
(a) 3 months
(b) 6 months
(c) 9 months
(d) 12 months

6. The infant doubles its weight by
(a) 3 months
(b) 6 months
(c) 9 months
(d) 12 months

7. The infant triples its weight by
(a) 3 months
(b) 6 months
(c) 9 months
(d) 12 months

8. Condition wherein the growth hormone receptors are unresponsive to growth hormone is termed
(a) Pituitary dwarfism
(b) Thyroid dwarfism
(c) Gonadal dwarfism
(d) Laron dwarfism

9. The clinical feature not found in thyroid dwarf is
(a) Small and atrophied tongue
(b) Dry skin
(c) Deceased IQ
(d) Pot belly abdomen

10. The child can draw circular strokes using a pencil by
(a) 6 months
(b) 1 year
(c) 2 years
(d) 3 years

11. The genetic locus associated with longer life is present on
(a) Chromosome 4
(b) Chromosome 9
(c) Chromosome 13
(d) Chromosome 21

12. Aging results in increase in
(a) Vital capacity
(b) Functional residual capacity
(c) Tidal volume
(d) Residual volume

13. The enzyme supposed to help in preventing senescence is
(a) Ligase
(b) Hydrolase
(c) Helicase
(d) Telomerase

14. Linear decline in cardiac output is seen after which decade of life?
(a) First decade
(b) Third decade
(c) Fifth decade
(d) Sixth decade

15. Aging reduces all of the above except
(a) Muscle weight
(b) Bone strength
(c) Visceral fat
(d) Muscle mass

16. The body mass index to be considered as obesity is
(a) More than 30 kg/m^2
(b) More than 25 kg/m^2
(c) Between 20–24 kg/m^2
(d) Less than 20 kg/m^2

17. The cardiovascular morbidity increases with body mass index of
(a) More than 30 kg/m^2
(b) More than 25 kg/m^2

(c) Between 20–24 kg/m^2
(d) Less than 20 kg/m^2

18. Following are the features of metabolic syndrome EXCEPT
(a) Blood pressure of more than 130/85 mmHg
(b) Fasting glucose of 100 mg/dL or more
(c) Triglycerides of more than 150 mg/dL in the blood.
(d) HDL more than 40 mg/dL in men

19. Morbid obesity is caused by
(a) Functional leptin resistance
(b) Insulin resistance
(c) Increased secretion of proopiomelanocortin (POMC)
(d) Increased secretion of insulin

20. Obesity-induced hypertension is associated with
(a) Altered sympathetic tone
(b) Insulin-mediated salt retention
(c) Salt sensitivity
(d) All of the above

21. Insulin resistance is caused due to following EXCEPT
(a) Downregulation of receptors
(b) Increased level of free fatty acids
(c) Intracellular fat depletion
(d) High level circulating cytokines and adiponectin

22. Exercise is considered to be of moderate intensity when the heart rate reaches _____ of the target heart rate.
(a) Less than 50%
(b) Between 50–70%
(c) Between 71–85%
(d) More than 85%

23. The ability of muscle to perform sustained action is
(a) Strength
(b) Power
(c) Endurance
(d) Efficiency

24. Quantum of work done by the muscle in unit time is
(a) Strength
(b) Power
(c) Endurance
(d) Efficiency

25. Maximal contractile force generated by the muscle is
(a) Strength
(b) Power
(c) Endurance
(d) Efficiency

26. The number of ATP molecules produced by fully oxidized fat molecule is
(a) 3
(b) 10
(c) 39
(d) 129

27. The oxygen consumption can go up to _____ during vigorous exercise.
(a) 250 mL/min
(b) 1,000 mL/min
(c) 5,000 mL/min
(d) 100 L/min

28. Oxygen debt helps in the following EXCEPT
(a) Eliminate lactate
(b) Replenish ATP
(c) Restore phosphocreatine stores
(d) Reduce consumption of oxygen

29. Normal blood flow to the resting skeletal muscle is
(a) Less than 2 mL/100 g/min
(b) 2–4 mL/100 g/min
(c) 40–50 mL/100 g/min
(d) More than 50 mL/100 g/min

30. During exercise, vasodilatation to the active muscle is caused by the following EXCEPT
(a) Accumulation of metabolites like adenosine
(b) Increase in hydrogen and potassium concentration
(c) Local increase in carbon dioxide concentration
(d) Parasympathetic stimulation

31. Endurance training produced the following changes EXCEPT
(a) Increases density of mitochondria
(b) Enhances capillary density

(c) Decreases intramuscular stores of triglycerides
(d) Lowers serum triglycerides

32. The layer of epidermis made up of dead cells containing keratin is
(a) Stratum corneum
(b) Stratum granulosum
(c) Stratum spinosum
(d) Stratum germinativum

33. The vitamin synthesized by skin is
(a) Vitamin B12
(b) Vitamin C
(c) Vitamin A
(d) Vitamin D3

34. Normal body temperature is
(a) 36°C
(b) 37°C
(c) 38°C
(d) 39°C

35. Heat loss center is present in
(a) Lateral pons
(b) Medial pons
(c) Anterior hypothalamus
(d) Posterior hypothalamus

36. The organ commonly affected by frostbite is all the following EXCEPT
(a) Ear lobe
(b) Digits of hand
(c) Digits of foot
(d) Stomach

37. Heat production is increased by all of the mechanisms EXCEPT
(a) Shivering
(b) Hunger
(c) Curling up
(d) Increased voluntary activity

ANSWERS TO MCQs

1. GENERAL PHYSIOLOGY

1. a	7. b	13. a	19. a	25. d
2. b	8. c	14. b	20. b	26. b
3. c	9. a	15. c	21. c	27. b
4. d	10. a	16. b	22. d	28. d
5. c	11. b	17. a	23. b	29. c
6. b	12. b	18. c	24. a	30. b

2. BLOOD

1. b	22. a	43. c	64. a	85. a
2. b	23. b	44. b	65. b	86. b
3. c	24. b	45. c	66. c	87. c
4. a	25. c	46. c	67. a	88. a
5. a	26. d	47. d	68. c	89. d
6. c	27. b	48. b	69. b	90. d
7. d	28. a	49. a	70. d	91. c
8. c	29. b	50. d	71. c	92. c
9. d	30. c	51. c	72. b	93. a
10. d	31. d	52. c	73. c	94. d
11. a	32. a	53. c	74. a	95. d
12. c	33. d	54. b	75. c	96. a
13. b	34. d	55. a	76. a	97. b
14. b	35. a	56. c	77. c	98. d
15. c	36. d	57. c	78. a	99. b
16. d	37. d	58. a	79. c	100. c
17. d	38. b	59. c	80. a	101. d
18. b	39. d	60. c	81. d	102. a
19. c	40. b	61. d	82. a	103. c
20. a	41. c	62. b	83. c	104. c
21. a	42. d	63. d	84. b	

3. NERVE–MUSCLE PHYSIOLOGY

1. c	10. b	19. c	28. a	37. a
2. d	11. a	20. b	29. d	38. d
3. b	12. a	21. a	30. c	39. a
4. c	13. a	22. a	31. b	40. d
5. c	14. c	23. a	32. d	41. b
6. b	15. a	24. b	33. b	42. c
7. b	16. a	25. d	34. a	43. d
8. b	17. a	26. c	35. c	44. a
9. a	18. d	27. d	36. b	45. b

46. d
47. d
48. a
49. d
50. d
51. b
52. c
53. b
54. d
55. a
56. b
57. d
58. b
59. c
60. a
61. b
62. d
63. d
64. a
65. d
66. b
67. a
68. a
69. a
70. a
71. a
72. b

4. CARDIOVASCULAR SYSTEM

1. a
2. c
3. b
4. d
5. c
6. a
7. a
8. b
9. c
10. c
11. a
12. b
13. c
14. d
15. a
16. b
17. c
18. a
19. c
20. c
21. a
22. b
23. b
24. b
25. d
26. d
27. a
28. a
29. a
30. b
31. a
32. c
33. a
34. b
35. a
36. b
37. a
38. b
39. d
40. c
41. d
42. b
43. d
44. b
45. a
46. b
47. b
48. c
49. b
50. d
51. a
52. c
53. a
54. a
55. a
56. a
57. a
58. c
59. c
60. a
61. c
62. b
63. a
64. a
65. b
66. d
67. a
68. a
69. a
70. b
71. d
72. c
73. a
74. d
75. b
76. b
77. d
78. d
79. d
80. a
81. c
82. b

5. RESPIRATORY SYSTEM

1. b
2. a
3. d
4. b
5. c
6. b
7. a
8. b
9. c
10. b
11. a
12. d
13. b
14. a
15. d
16. b
17. b
18. b
19. c
20. c
21. b
22. b
23. b
24. c
25. c
26. a
27. c
28. b
29. a
30. d
31. c
32. a
33. a
34. b
35. b
36. d
37. d
38. b
39. a
40. d
41. b
42. b
43. c
44. d
45. c
46. a
47. b
48. a
49. a
50. c
51. b
52. c
53. c
54. c
55. a
56. d
57. c
58. a
59. a
60. a
61. d

6. GASTROINTESTINAL SYSTEM

1. c
2. b
3. d
4. b
5. d
6. a
7. a
8. b
9. a
10. d
11. d
12. a
13. b
14. a
15. d
16. c
17. d
18. c
19. d
20. a
21. c
22. b
23. b
24. c
25. c
26. d
27. d
28. d
29. d
30. a
31. c
32. b
33. a
34. b
35. a
36. d
37. a
38. d
39. c
40. a
41. a
42. c
43. c
44. d
45. c
46. b
47. a
48. a
49. c
50. a
51. d
52. b
53. b
54. b
55. a
56. c
57. c
58. b
59. d
60. d
61. c
62. d
63. c
64. a
65. c
66. b
67. a
68. d
69. d
70. b
71. c
72. d
73. c
74. b
75. d
76. c
77. a
78. b
79. c
80. d
81. b
82. b
83. b
84. c
85. d
86. b
87. a

7. EXCRETORY SYSTEM

1. b
2. d
3. c
4. d
5. c
6. d
7. c
8. b
9. a
10. d
11. a
12. b
13. b
14. d
15. b
16. a
17. b
18. a
19. d
20. d
21. b
22. a
23. d
24. a
25. b
26. c
27. c
28. d
29. a
30. d
31. d
32. a
33. c
34. b
35. b
36. a
37. b
38. a
39. d
40. a
41. a
42. b
43. d
44. a
45. a
46. d
47. a
48. b
49. b
50. d
51. b
52. a
53. d
54. a

8. CENTRAL NERVOUS SYSTEM

1. a
2. b
3. a
4. b
5. d
6. b
7. a
8. a
9. b
10. a
11. c
12. b
13. d
14. b
15. a
16. c
17. d
18. c
19. d
20. d
21. d
22. d
23. a
24. a
25. b
26. d
27. a
28. b
29. d
30. a
31. b
32. a
33. c
34. a
35. c

36. a
37. c
38. b
39. a
40. b
41. a
42. b
43. c
44. a
45. b
46. c
47. a
48. c
49. a
50. b
51. a
52. a
53. a
54. a
55. b
56. c
57. d
58. d
59. d
60. a
61. c
62. a
63. b
64. d
65. d
66. c
67. d
68. d
69. c
70. d
71. d
72. b
73. a
74. d
75. a
76. a
77. d
78. d
79. c
80. a
81. d
82. a
83. d
84. b
85. c
86. c
87. a
88. c
89. c
90. d
91. c
92. d
93. a
94. d
95. a
96. b
97. d
98. b
99. c
100. b
101. a
102. a
103. a
104. a
105. a
106. a
107. b
108. c
109. b
110. c
111. a
112. d
113. c
114. c
115. a
116. c
117. a
118. b
119. d
120. a
121. d
122. c
123. b
124. b
125. a
126. d
127. c
128. d
129. a
130. a
131. b
132. a
133. a
134. b
135. c
136. a
137. c
138. b
139. d

9. SPECIAL SENSES

1. d
2. a
3. b
4. d
5. a
6. b
7. c
8. b
9. a
10. c
11. b
12. a
13. a
14. c
15. a
16. d
17. a
18. a
19. a
20. a
21. b
22. c
23. d
24. a
25. b
26. d
27. c
28. a
29. b
30. c
31. c
32. a
33. b
34. c
35. c
36. a
37. d
38. d
39. c
40. b
41. c
42. a
43. d
44. a
45. b
46. d
47. c
48. b
49. d
50. a
51. d
52. d
53. d
54. d
55. c
56. a
57. a
58. c
59. b
60. a
61. a
62. b
63. a
64. a
65. b
66. a
67. b
68. b
69. d
70. c
71. a
72. b
73. a
74. b
75. a
76. d
77. a
78. b
79. b
80. a
81. d
82. d
83. c
84. a
85. b
86. b
87. a
88. a
89. c
90. b
91. b
92. c
93. d
94. a
95. d
96. c
97. a
98. c

10. ENDOCRINOLOGY

1. c
2. d
3. a
4. c
5. c
6. c
7. a
8. b
9. c
10. d
11. b
12. d
13. c
14. d
15. d
16. b
17. a
18. b
19. c
20. a
21. d
22. c
23. a
24. b
25. d
26. c
27. a
28. d
29. b
30. c
31. b
32. a
33. c
34. d
35. b
36. c
37. d
38. b
39. d
40. a
41. d
42. b
43. a
44. d
45. c
46. a
47. a
48. c
49. d
50. a
51. d
52. c
53. b
54. a
55. d
56. a
57. c
58. d
59. c
60. b
61. b
62. b
63. b
64. a
65. c
66. a
67. b
68. a
69. c
70. c
71. d
72. b

11. REPRODUCTIVE SYSTEM

1. b
2. c
3. c
4. c
5. d
6. c
7. b
8. d
9. a
10. c
11. b
12. d
13. a
14. b
15. c
16. c
17. b
18. d
19. d
20. b
21. b
22. c
23. a
24. a
25. b
26. b
27. a
28. c
29. c
30. d
31. a
32. c
33. a
34. d
35. a
36. c
37. c
38. b
39. a
40. b
41. c
42. b
43. c
44. a
45. a
46. b
47. b
48. d
49. b
50. a
51. d
52. b
53. b
54. a
55. d
56. c
57. d
58. d
59. d
60. d
61. c
62. d
63. b
64. c
65. d
66. b
67. d
68. a
69. d

12. INTEGRATED PHYSIOLOGY

1. b
2. d
3. b
4. a
5. b
6. b
7. c
8. d
9. a
10. c
11. a
12. d
13. d
14. b
15. c
16. a
17. b
18. d
19. a
20. d
21. c
22. b
23. c
24. b
25. a
26. d
27. c
28. d
29. b
30. d
31. c
32. a
33. d
34. b
35. c
36. d
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