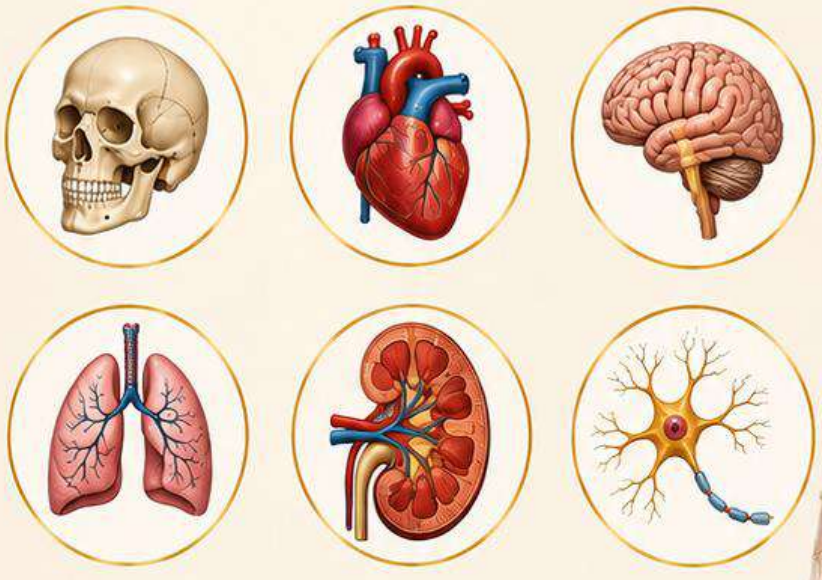
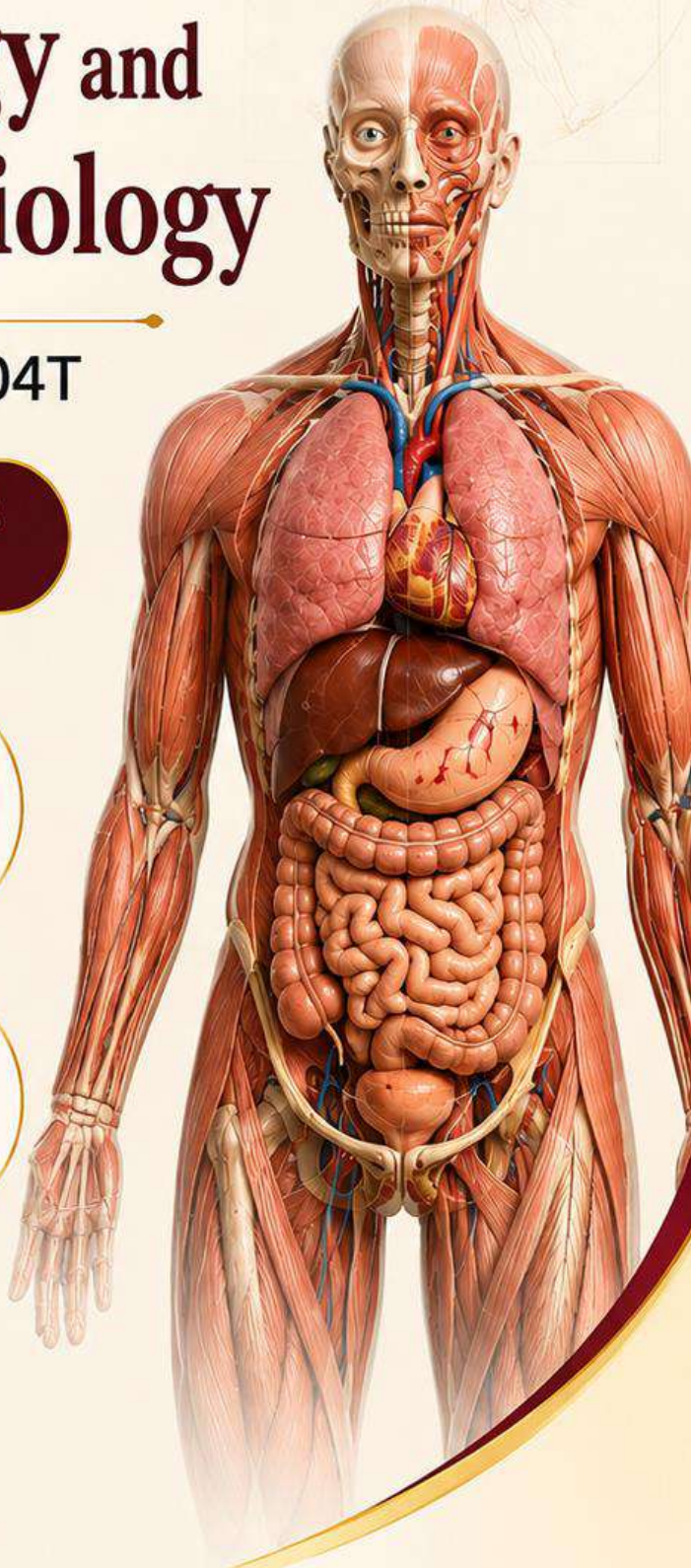
Human Anatomy, Physiology and Pathophysiology

(Theory) - BP 104T

As per B. Pharm 1st semester latest PCI Syllabus (2026) NEP 2020





Authors

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PREFACE

Human Anatomy, Physiology and Pathophysiology (Theory) is a fundamental subject in the Bachelor of Pharmacy (B.Pharm) programme, providing students with essential knowledge of the structure and functions of the human body, together with an understanding of the mechanisms underlying various diseases. This book has been designed in accordance with the Pharmacy Council of India (PCI) prescribed syllabus for B.Pharm First Semester, BP104T, aligned with the National Education Policy (NEP) 2020 framework.

The human body is a highly organized and integrated biological system in which different organs and organ systems work together to maintain normal physiological functions and homeostasis. A comprehensive understanding of anatomy and physiology forms the foundation for studying pharmacology, pharmaceutics, medicinal chemistry, pharmacotherapeutics, and other pharmaceutical sciences. Furthermore, knowledge of pathophysiology enables pharmacy students to understand the alterations occurring in normal body functions during disease conditions and provides a scientific basis for rational drug therapy and patient care.

This textbook has been systematically organized to facilitate conceptual learning and provide comprehensive coverage of the prescribed syllabus. It includes detailed discussions of the major human organ systems, including the skeletal, muscular, nervous, cardiovascular, respiratory, digestive, urinary, reproductive, endocrine, and other important systems. The pathophysiological aspects of selected disorders have also been incorporated to establish a clear relationship between normal physiological processes and disease conditions.

Special emphasis has been placed on simple, clear, and student-friendly language, supported by appropriate headings, illustrations, tables, flowcharts, and relevant examples wherever necessary. The presentation aims to simplify complex biological concepts and encourage students to develop a strong conceptual understanding rather than relying solely on memorization. The contents are structured to support classroom teaching, independent learning, examination preparation, and the development of professional competencies expected from future pharmacists.

In accordance with the educational objectives of NEP 2020, this book also emphasizes outcome-based learning, interdisciplinary understanding, critical thinking, and the practical application of theoretical knowledge in pharmaceutical and healthcare settings. It is intended to help students appreciate the importance of human anatomy, physiology, and pathophysiology in understanding drug actions, disease progression, therapeutic interventions, and patient-centered healthcare.

We sincerely hope that this textbook will serve as a valuable academic resource for B.Pharm students, pharmacy educators, and other healthcare learners. We acknowledge the contributions of all individuals who have supported the development of this work and welcome constructive suggestions from readers and academicians for its continuous improvement.

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We express our sincere gratitude to all those who have contributed directly or indirectly to the successful completion of this book, Human Anatomy, Physiology and Pathophysiology (Theory), prepared in accordance with the PCI B.Pharm First Semester syllabus (BP104T), 2026, based on the National Education Policy (NEP) 2020.

We would like to extend our heartfelt appreciation to the Pharmacy Council of India (PCI) for providing the academic framework and syllabus guidelines that serve as the foundation for pharmaceutical education. We are also thankful to our respective institutions, colleagues, mentors, and academic professionals for their valuable encouragement, guidance, and continuous support throughout the development of this book.

We sincerely acknowledge the contributions of researchers, academicians, and authors whose published literature, scientific findings, and educational resources have helped us present the concepts of human anatomy, physiology, and pathophysiology in a systematic, comprehensive, and student-friendly manner.

Special appreciation is extended to our students and fellow educators, whose academic needs and learning experiences inspired us to develop this book as a useful resource for understanding the structure and functions of the human body, physiological mechanisms, and the pathophysiological basis of various diseases.

Finally, we express our gratitude to Mantra Publication for providing the necessary publishing support and encouragement in bringing this academic work to the readers.

We hope that this book will serve as a valuable learning resource for B.Pharm students, teachers, and pharmacy professionals, and contribute meaningfully to the development of foundational knowledge in pharmaceutical sciences.

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UNIT- I

Chapter 1: Introduction to Anatomy, Physiology and Pathophysiology

1.1 Definition and Scope of Anatomy

Definition of Anatomy

Anatomy is the branch of medical and biological science that deals with the study of the structure, shape, size, location, and relationship of different parts of the human body. It provides fundamental knowledge about the organization of the human body, including cells, tissues, organs, and organ systems.

The term anatomy is derived from the Greek words **ana**, meaning apart, and **tome**, meaning cutting. Traditionally, anatomy involves the study of body structures through dissection. In modern science, anatomy is studied using various techniques, including microscopy, radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography.

Anatomy helps in understanding the structural organization of the human body and provides the foundation for studying physiology, pathology, pharmacology, and other medical sciences.

Scope of Anatomy

The scope of anatomy includes the study of different structural levels and body regions. It provides knowledge about the normal structure and organization of the human body.

The major branches of anatomy include:

1. **Gross Anatomy**: It deals with the study of body structures visible to the naked eye, such as the heart, lungs, brain, muscles, and bones.

2. **Microscopic Anatomy:** It involves the study of structures that cannot be observed with the naked eye and require a microscope. It includes cytology (study of cells) and histology (study of tissues).

3. **Developmental Anatomy:** It deals with the structural changes occurring in the human body from fertilization to adulthood. Embryology is a specialized branch that studies development before birth.

4. **Regional Anatomy:** It involves the study of all structures present within a particular region of the body, such as the head, neck, thorax, abdomen, and limbs.

5. Systemic Anatomy: It involves the study of the human body according to different organ systems, such as the skeletal, muscular, nervous, cardiovascular, and digestive systems.

6. Surface Anatomy: It deals with the study of external features of the body and their relationship with underlying internal structures.

7. Radiological Anatomy: It involves the study of internal body structures using imaging techniques such as X-rays, CT scans, MRI, and ultrasonography.

8. Applied Anatomy: It refers to the application of anatomical knowledge in clinical practice, diagnosis, surgical procedures, and medical treatment.

Importance of Anatomy

- Provides basic knowledge of human body structure.
- Helps in understanding the relationship between different organs and tissues.
- Forms the foundation for studying physiology and pathophysiology.
- Assists in understanding the location of organs and their anatomical relationships.
- Supports clinical examination, diagnosis, and surgical procedures.
- Helps in understanding the effects of diseases and injuries on body structures.

1.2 Definition and Scope of Physiology

Definition of Physiology

Physiology is the branch of biological science that deals with the study of normal functions and mechanisms of living organisms and their different parts. Human physiology specifically focuses on how cells, tissues, organs, and organ systems perform their activities to maintain life.

The term physiology is derived from the Greek words physis, meaning nature, and logos, meaning study. It explains how various structures of the body work individually and interact with one another to maintain normal body functions.

For example, physiology explains how the heart pumps blood, how the lungs exchange gases, how the kidneys regulate water and electrolyte balance, and how the nervous system controls body activities.

Scope of Physiology

Human physiology covers the functioning of the body at different levels, ranging from cellular activities to the coordinated functioning of complete organ systems.

The major areas of physiology include:

1. Cell Physiology: It deals with the functions of cells, including metabolism, membrane transport, cell communication, growth, and division.

2. Blood Physiology: It involves the study of blood composition, blood cells, blood clotting, and blood functions.

3. Cardiovascular Physiology: It deals with the functioning of the heart and blood vessels, including blood circulation, cardiac output, and blood pressure regulation.

4. Respiratory Physiology: It explains the mechanisms of breathing, exchange of oxygen and carbon dioxide, and transport of respiratory gases.

5. Digestive Physiology: It involves the study of digestion, absorption, and utilization of nutrients.

6. Renal Physiology: It deals with kidney functions, urine formation, and regulation of fluid, electrolyte, and acid–base balance.

7. Nervous System Physiology: It explains the functioning of the brain, spinal cord, and nerves in controlling and coordinating body activities.

8. Endocrine Physiology: It deals with the production and functions of hormones and their role in regulating body processes.

9. Reproductive Physiology: It involves the study of reproductive functions, including gamete formation, fertilization, and hormonal regulation.

10. Muscular Physiology: It deals with muscle contraction, relaxation, and the mechanisms responsible for body movements.

Importance of Physiology

- Explains the normal functioning of the human body.
- Helps in understanding the relationship between body structure and function.
- Provides a foundation for understanding disease conditions.
- Helps in understanding the mechanism of action of drugs.
- Supports the study of pharmacology and therapeutics.
- Explains how the body maintains internal stability through regulatory mechanisms.

1.3 Definition and Scope of Pathophysiology

Definition of Pathophysiology

Pathophysiology is the branch of medical science that deals with the study of abnormal physiological processes associated with diseases or injuries. It explains how normal body functions are altered due to pathological conditions and how these changes produce clinical signs and symptoms.

The term pathophysiology is derived from three components: pathos, meaning disease or suffering; physis, meaning nature; and logos, meaning study.

Pathophysiology combines the principles of physiology and pathology to explain the functional changes occurring in cells, tissues, organs, and organ systems during disease conditions.

For example, in diabetes mellitus, pathophysiology explains how insufficient insulin secretion or impaired insulin action results in increased blood glucose levels and disturbances in carbohydrate, lipid, and protein metabolism.

Scope of Pathophysiology

The scope of pathophysiology includes the study of disease mechanisms, cellular responses, functional abnormalities, and their effects on the human body.

The major areas include:

1. Cellular Pathophysiology: It deals with abnormal cellular functions, including cellular injury, adaptation, degeneration, and cell death.

2. Molecular Pathophysiology: It involves the study of molecular changes responsible for disease development, including alterations in genes, proteins, enzymes, and signalling pathways.

3. Tissue Pathophysiology: It explains structural and functional changes occurring in tissues due to injury, inflammation, infection, or other pathological conditions.

4. Organ Pathophysiology: It deals with abnormal functioning of individual organs, such as the heart, lungs, liver, kidneys, and brain.

5. Systemic Pathophysiology: It involves the study of diseases affecting entire organ systems and their interactions.

6. Disease Mechanisms: It explains the causes and development of diseases, including cellular injury, inflammation, immune responses, and metabolic disturbances.

7. Clinical Manifestations: It deals with the development of signs and symptoms resulting from abnormal physiological processes.

Importance of Pathophysiology

- Helps in understanding the mechanisms of disease development.
- Explains the relationship between cellular injury and clinical manifestations.
- Provides a foundation for understanding pathology and pharmacology.
- Helps in understanding the therapeutic effects of medicines.
- Supports the interpretation of laboratory investigations.
- Provides knowledge about disease progression and complications.

Relationship Between Anatomy, Physiology and Pathophysiology

Anatomy, physiology, and pathophysiology are closely related disciplines that collectively explain the structure, normal functioning, and abnormal functioning of the human body.

Table 1.1: Anatomy, Physiology, and Pathophysiology with Their Main Focus and Examples

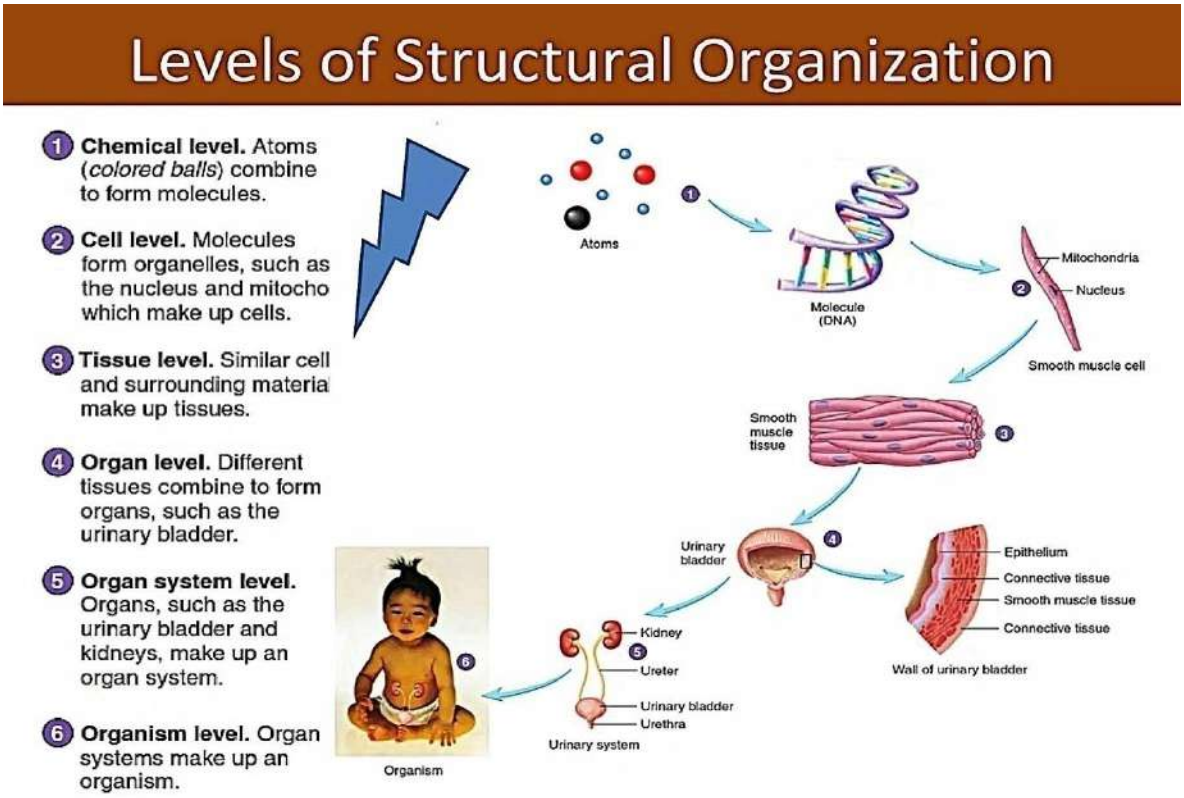
Discipline	Main Focus	Example
Anatomy	Structure of the body	Structure of the heart
Physiology	Normal functioning of the body	Pumping action of the heart
Pathophysiology	Abnormal functioning during disease	Changes in cardiac function during heart failure

1.4 Levels of Structural Organization

The human body is a highly organized biological system consisting of different structural levels. Each level is formed by the arrangement and interaction of simpler components, resulting in increasingly

complex structures. The structural organization of the human body begins with chemical substances and progresses through cells, tissues, organs, and organ systems to form the complete organism.

There are six major levels of structural organization in the human body.



1. Chemical Level

The chemical level represents the simplest level of structural organization. It consists of atoms and molecules that form the basic chemical substances required for life.

Atoms are the smallest units of elements that retain their chemical properties. Important atoms present in the human body include carbon, hydrogen, oxygen, nitrogen, calcium, and phosphorus.

Atoms combine through chemical bonds to form molecules. Examples include water, glucose, proteins, lipids, nucleic acids, and electrolytes.

These molecules perform essential functions such as energy production, structural support, cellular communication, and genetic information storage.

2. Cellular Level

The cellular level is the basic structural and functional level of living organisms. Cells are formed by the organization of different molecules and cellular components.

The human body contains numerous specialized cells that perform specific functions. Examples include:

- Nerve cells (neurons), which transmit nerve impulses.
- Muscle cells, which produce contraction and movement.
- Red blood cells, which transport oxygen.
- Epithelial cells, which provide protection and absorption.
- White blood cells, which participate in immune defence.

Each cell contains specialized structures called organelles that perform specific functions necessary for cellular survival.

3. Tissue Level

A tissue is a group of similar cells, together with their extracellular materials, organized to perform a particular function.

The human body contains four basic types of tissues:

1. Epithelial tissue: Covers body surfaces, lines internal cavities, and forms glands.
2. Connective tissue: Provides support, binding, protection, and transportation.
3. Muscular tissue: Produces movement through contraction.
4. Nervous tissue: Receives and transmits electrical signals.

Different tissues combine to form organs.

4. Organ Level

An organ is a structure composed of two or more different types of tissues working together to perform specific functions.

Each organ has a definite shape, location, and structural organization.

Examples include:

- Heart: Pumps blood throughout the body.
- Lungs: Facilitate gaseous exchange.
- Stomach: Performs mechanical and chemical digestion.
- Kidneys: Filter blood and regulate fluid balance.
- Brain: Controls and coordinates body activities.
- Liver: Performs metabolism, detoxification, and bile production.

5. Organ System Level

An organ system consists of two or more organs working together to perform major physiological functions.

The organs within an organ system are structurally and functionally interconnected.

For example, the digestive system consists of the mouth, oesophagus, stomach, small intestine, large intestine, liver, pancreas, and other associated structures. These organs work together to digest food, absorb nutrients, and eliminate undigested materials.

6. Organism Level

The organism level represents the highest level of structural organization. It consists of all organ systems working together to maintain the life of an individual.

The human organism performs various activities, including movement, nutrition, respiration, reproduction, metabolism, growth, and maintenance of internal balance.

All six levels are interdependent, and proper functioning at each level is necessary for maintaining normal body activities.

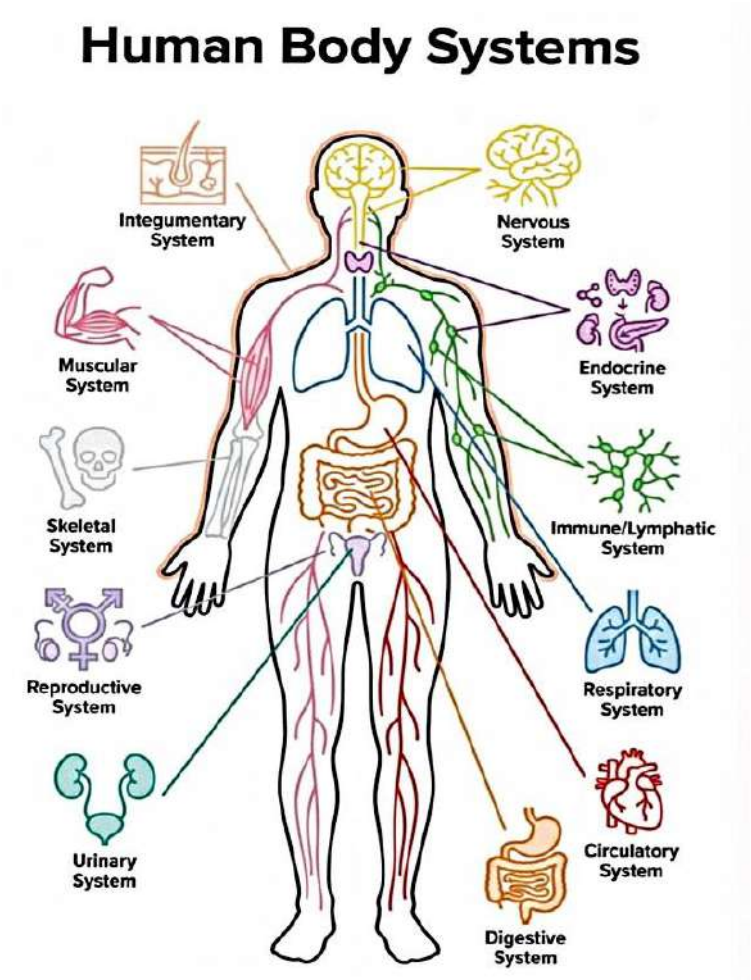
Summary of Structural Organization

Level	Description	Example
Chemical	Atoms and molecules	Water, glucose, proteins
Cellular	Basic structural and functional unit	Neuron, muscle cell
Tissue	Group of similar cells performing a function	Epithelial tissue
Organ	Different tissues working together	Heart, kidney
Organ system	Multiple organs performing related functions	Cardiovascular system
Organism	All organ systems functioning together	Human body

1.5 Body Systems

The human body consists of different organ systems that work together to maintain life and internal stability. Each system performs specific functions; however, their activities are coordinated and interdependent.

There are eleven major organ systems in the human body.



1. Integumentary System

The integumentary system forms the external covering of the body. It consists of the skin and its associated structures, including hair, nails, sweat glands, and sebaceous glands.

Functions:

- Protects the body from mechanical injury, microorganisms, and harmful environmental factors.
- Prevents excessive water loss.
- Regulates body temperature through sweating and changes in blood flow.
- Provides sensory information through receptors.
- Participates in vitamin D synthesis.

2. Skeletal System

The skeletal system consists of bones, cartilage, ligaments, and joints. It provides the structural framework of the body.

Functions:

- Provides support and shape to the body.

- Protects internal organs.
- Helps in movement by providing attachment sites for muscles.
- Produces blood cells through bone marrow.
- Stores minerals, particularly calcium and phosphorus.

3. Muscular System

The muscular system consists primarily of skeletal muscles responsible for body movement and posture.

It includes three types of muscle tissue: skeletal, smooth, and cardiac muscle.

Functions:

- Produces voluntary and involuntary movements.
- Maintains body posture.
- Generates heat during muscle contraction.
- Supports movement of substances within internal organs.
- Helps in locomotion and physical activities.

4. Nervous System

The nervous system consists of the brain, spinal cord, nerves, and sensory receptors. It is responsible for rapid communication and coordination throughout the body.

It is divided into the central nervous system (CNS) and peripheral nervous system (PNS).

Functions:

- Receives and processes sensory information.
- Controls voluntary and involuntary activities.
- Coordinates muscular movements.
- Regulates organ functions.
- Participates in memory, learning, emotions, and consciousness.

5. Endocrine System

The endocrine system consists of hormone-secreting glands, including the pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pancreas, pineal gland, ovaries, and testes.

Functions:

- Regulates growth and development.
- Controls metabolism.
- Maintains blood glucose levels.
- Regulates reproductive functions.
- Maintains water and electrolyte balance.
- Coordinates long-term physiological activities through hormones.

6. Cardiovascular System

The cardiovascular system consists of the heart, blood, and blood vessels.

The heart acts as a muscular pump that maintains blood circulation throughout the body.

Functions:

- Transports oxygen and nutrients to tissues.
- Carries carbon dioxide and metabolic waste products.
- Transports hormones and other chemical substances.
- Participates in immune defence.
- Helps regulate body temperature and blood pressure.

7. Lymphatic and Immune System

The lymphatic system consists of lymph, lymphatic vessels, lymph nodes, spleen, thymus, and other lymphoid tissues.

Functions:

- Returns excess tissue fluid to the bloodstream.
- Absorbs dietary fats from the intestine.
- Provides protection against infections.
- Supports immune responses.
- Filters lymph through lymph nodes.

8. Respiratory System

The respiratory system consists of the nose, nasal cavity, pharynx, larynx, trachea, bronchi, and lungs.

Functions:

- Supplies oxygen to the body.
- Removes carbon dioxide.
- Facilitates gaseous exchange between air and blood.
- Helps maintain acid–base balance.
- Participates in speech production.

9. Digestive System

The digestive system consists of the alimentary canal and associated organs, including the salivary glands, liver, gallbladder, and pancreas.

Functions:

- Ingests food and liquids.
- Performs mechanical and chemical digestion.

- Absorbs nutrients and water.
- Eliminates undigested waste materials.
- Provides nutrients required for energy production, growth, and tissue repair.

10. Urinary System

The urinary system consists of two kidneys, two ureters, the urinary bladder, and the urethra.

Functions:

- Removes metabolic waste products from the blood.
- Produces and eliminates urine.
- Regulates water and electrolyte balance.
- Maintains acid–base balance.
- Helps regulate blood pressure.
- Participates in erythropoietin production and vitamin D activation.

11. Reproductive System

The reproductive system consists of male and female reproductive organs responsible for reproduction and sexual functions.

Male reproductive organs: Testes, epididymis, vas deferens, seminal vesicles, prostate gland, penis, and associated structures.

Female reproductive organs: Ovaries, fallopian tubes, uterus, vagina, and associated structures.

Functions:

- Produces reproductive cells (gametes).
- Secretes sex hormones.
- Facilitates fertilization.
- Supports pregnancy and childbirth in females.
- Ensures continuation of the human species.

Interdependence of Body Systems

Although each organ system performs specific functions, no system operates independently. Different systems cooperate to maintain normal physiological activities.

For example, during physical exercise:

- The muscular system produces movement.
- The respiratory system increases oxygen intake.
- The cardiovascular system transports oxygen to active muscles.
- The nervous system coordinates muscle activity.
- The endocrine system regulates metabolic responses.

Thus, coordinated functioning of all body systems is essential for maintaining normal body activities and survival.

1.6 Basic Life Processes

Basic life processes are the essential activities performed by living organisms to maintain survival, growth, and normal functioning. These processes occur continuously at cellular, tissue, organ, and organism levels.

The major basic life processes include:

1. Metabolism

Metabolism refers to the sum of all chemical reactions occurring within the body. These reactions are necessary for energy production, growth, repair, and maintenance of cellular functions.

Metabolism is divided into two major processes:

A. Anabolism: It involves the synthesis of complex molecules from simpler substances. It requires energy.

Example: Formation of proteins from amino acids.

B. Catabolism: It involves the breakdown of complex molecules into simpler substances with the release of energy.

Example: Breakdown of glucose during cellular respiration.

Both processes work together to maintain normal cellular activities.

2. Responsiveness

Responsiveness refers to the ability of the body or its cells to detect and respond to changes in the internal or external environment.

Such changes are known as stimuli.

Examples:

- Withdrawal of the hand after touching a hot object.
- Increased heart rate during exercise.
- Constriction of the pupil in bright light.

Responsiveness helps organisms adapt to changing environmental conditions.

3. Movement

Movement refers to the change in position of the whole body, individual body parts, or internal substances.

Movement occurs at different levels:

- Whole-body movement through skeletal muscles.
- Movement of limbs and joints.
- Movement of food through the digestive tract.
- Movement of blood through blood vessels.
- Movement of cells, such as white blood cells toward infection sites.

Movement is essential for locomotion, circulation, digestion, and other physiological functions.

4. Growth

Growth refers to an increase in the size, mass, or number of cells in the body. It occurs through an increase in cell size, cell number, or both.

Examples include:

- Increase in body height during childhood.
- Enlargement of muscles through increased muscle fibre size.
- Growth and development of tissues.

Growth requires nutrients, energy, and appropriate hormonal regulation.

5. Differentiation

Differentiation is the process by which unspecialized cells develop into specialized cells with specific structures and functions.

For example, during development, stem cells differentiate into nerve cells, muscle cells, epithelial cells, and blood cells.

Differentiation is essential for tissue formation, organ development, and maintenance of normal body functions.

6. Reproduction

Reproduction refers to the formation of new cells or new individuals. At the cellular level, reproduction occurs through cell division, which is necessary for growth, development, and tissue repair. At the organism level, reproduction involves the production of offspring through the male and female reproductive systems.

7. Respiration

Respiration is the process through which the body obtains oxygen and uses it for cellular energy production, while eliminating carbon dioxide. It includes two major processes:

- External respiration: Exchange of oxygen and carbon dioxide between the atmosphere and blood through the lungs.
- Cellular respiration: Biochemical reactions through which cells generate usable energy in the form of ATP.

8. Excretion

Excretion refers to the removal of metabolic waste products from the body. Major excretory products include carbon dioxide, urea, uric acid, excess water, and electrolytes. The lungs, kidneys, skin, and liver participate in waste elimination and processing.

Importance of Basic Life Processes

All basic life processes are interconnected and essential for maintaining life. For example, metabolism provides energy for movement, growth, and cellular repair, while responsiveness allows the body to react to environmental changes. The failure of essential life processes may result in cellular dysfunction, tissue damage, organ failure, and eventually death.

1.7 Homeostasis

Definition of Homeostasis

Homeostasis is the ability of the human body to maintain a relatively stable internal environment despite continuous changes in external and internal conditions. It involves the regulation of various physiological parameters, including body temperature, blood glucose concentration, blood pressure, pH, water balance, and electrolyte levels.

The term homeostasis was introduced by Walter Cannon and refers to the maintenance of a relatively constant internal environment necessary for normal cellular and organ functions.

Homeostasis does not mean that body conditions remain completely unchanged. Instead, physiological parameters fluctuate within a narrow range around a normal value called the set point.

For example, normal human body temperature is maintained approximately around 37°C, although minor variations occur depending on physical activity, environmental conditions, and time of day.

Importance of Homeostasis

Homeostasis is essential for maintaining the normal functioning of cells, tissues, organs, and organ systems.

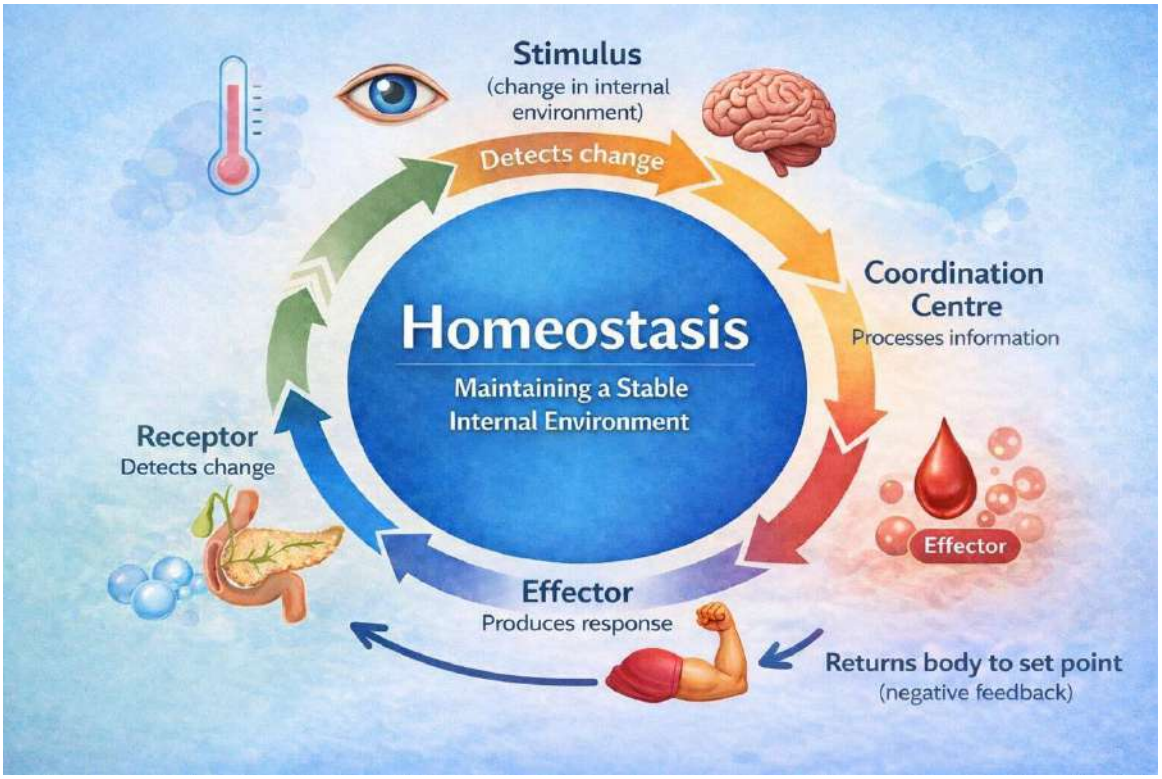
Its major functions include:

- Maintains a stable internal environment.
- Regulates body temperature.
- Maintains blood glucose concentration.
- Controls water and electrolyte balance.
- Regulates blood pressure and blood pH.

- Maintains oxygen and carbon dioxide levels.
- Supports normal enzyme activity and cellular metabolism.
- Helps the body respond to internal and external changes.

Components of Homeostatic Control System

A homeostatic control system consists of three major components:



1. Receptor (Sensor)

The receptor detects changes in a physiological condition or internal environment. It receives information about the deviation from the normal set point and sends signals to the control centre.

Example: Thermoreceptors detect changes in body temperature.

2. Control Centre (Integrator)

The control centre receives information from the receptor, compares it with the normal set point, and determines the appropriate response. The hypothalamus is an important control centre involved in regulating body temperature.

3. Effector

The effector receives signals from the control centre and produces a response to correct the deviation.

Examples: include sweat glands, skeletal muscles, blood vessels, and endocrine glands.

Types of Homeostatic Feedback Mechanisms

Feedback mechanisms are regulatory processes through which the body controls physiological activities.

There are two major types of feedback mechanisms.

A. Negative Feedback Mechanism

Negative feedback is a regulatory mechanism in which the response opposes the initial change and helps restore the physiological condition toward its normal range.

It is the most common mechanism involved in maintaining homeostasis.

Example 1: Regulation of Body Temperature

When body temperature increases:

1. Thermoreceptors detect the rise in temperature.
2. The hypothalamus receives the information.
3. Sweat glands become active.
4. Sweating increases heat loss through evaporation.
5. Body temperature moves toward the normal range.

Similarly, when body temperature decreases, shivering and reduced heat loss help increase body temperature.

Example 2: Regulation of Blood Glucose

When blood glucose levels increase after a meal, pancreatic beta cells release insulin. Insulin promotes glucose uptake by body cells and storage of glucose as glycogen, thereby decreasing blood glucose levels.

When blood glucose levels decrease, pancreatic alpha cells release glucagon, which promotes glucose release from the liver.

These opposing hormonal actions help maintain blood glucose homeostasis.

B. Positive Feedback Mechanism

Positive feedback is a regulatory mechanism in which the response amplifies or increases the initial stimulus rather than opposing it.

This mechanism continues until a specific event or endpoint is achieved.

Example 1: Childbirth

During childbirth, stretching of the cervix stimulates the release of oxytocin from the posterior pituitary gland. Oxytocin increases uterine contractions, resulting in further cervical stretching and additional oxytocin release.

This cycle continues until the baby is delivered.

Example 2: Blood Clotting

When a blood vessel is damaged, platelets adhere to the injured area and release chemical substances that attract additional platelets.

The accumulation of platelets increases the clotting response until a platelet plug and blood clot are formed.

Table 1.2: Difference Between Negative and Positive Feedback

Basis	Negative Feedback	Positive Feedback
Definition	Opposes the initial change	Amplifies the initial change
Main function	Maintains homeostasis	Promotes completion of a specific event
Effect on stimulus	Reduces the stimulus	Increases the stimulus
Occurrence	Most common	Less common
Examples	Temperature regulation, blood glucose regulation	Childbirth, blood clotting

Homeostatic Imbalance

Homeostatic imbalance occurs when the body's regulatory mechanisms fail to maintain normal internal conditions.

It may result from ageing, disease, injury, genetic abnormalities, or environmental factors.

Examples include:

- Diabetes mellitus due to impaired blood glucose regulation.
- Hypertension due to abnormal blood pressure regulation.
- Dehydration due to excessive fluid loss.
- Hypothermia due to an abnormal decrease in body temperature.
- Hyperthermia due to excessive elevation of body temperature.

Prolonged homeostatic imbalance may lead to cellular injury, tissue dysfunction, organ failure, and disease development.

1.8 Basic Anatomical Terminologies

Anatomical terminology provides a standardized language for describing the location, position, direction, and relationship of different body structures. These terms help healthcare professionals

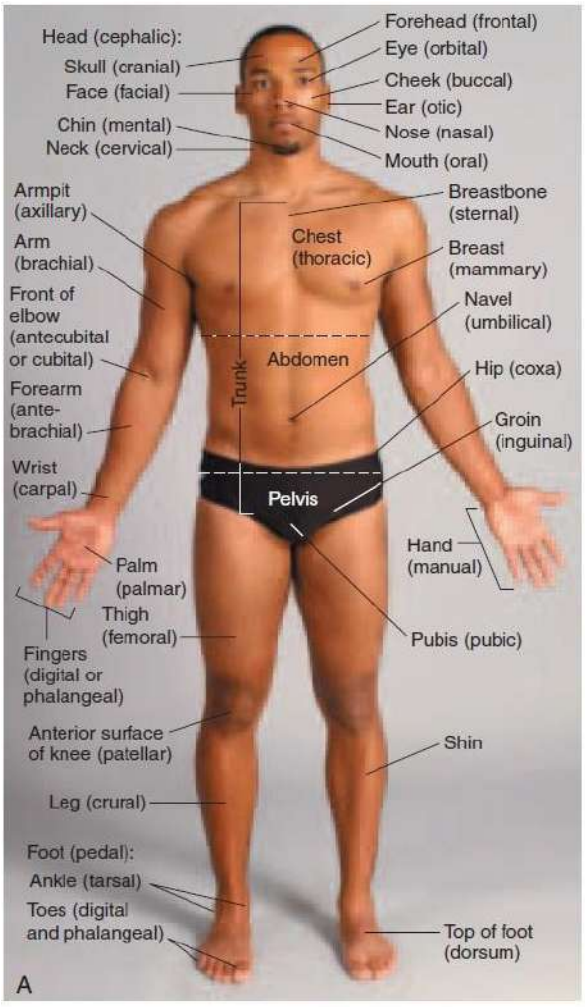
communicate accurately and avoid confusion during anatomical examination, clinical assessment, and medical procedures.

1. Anatomical Position

The anatomical position is the standard reference position used to describe the location and relationship of body structures.

In anatomical position:

- The body stands upright.
- The head and eyes face forward.
- The upper limbs are positioned at the sides.
- The palms face forward.
- The fingers are extended.
- The lower limbs are together or slightly apart.
- The feet point forward.



A. Anterior view B. Posterior view

All anatomical descriptions are based on this standard position, regardless of the actual posture of the individual.

2. Directional Terms

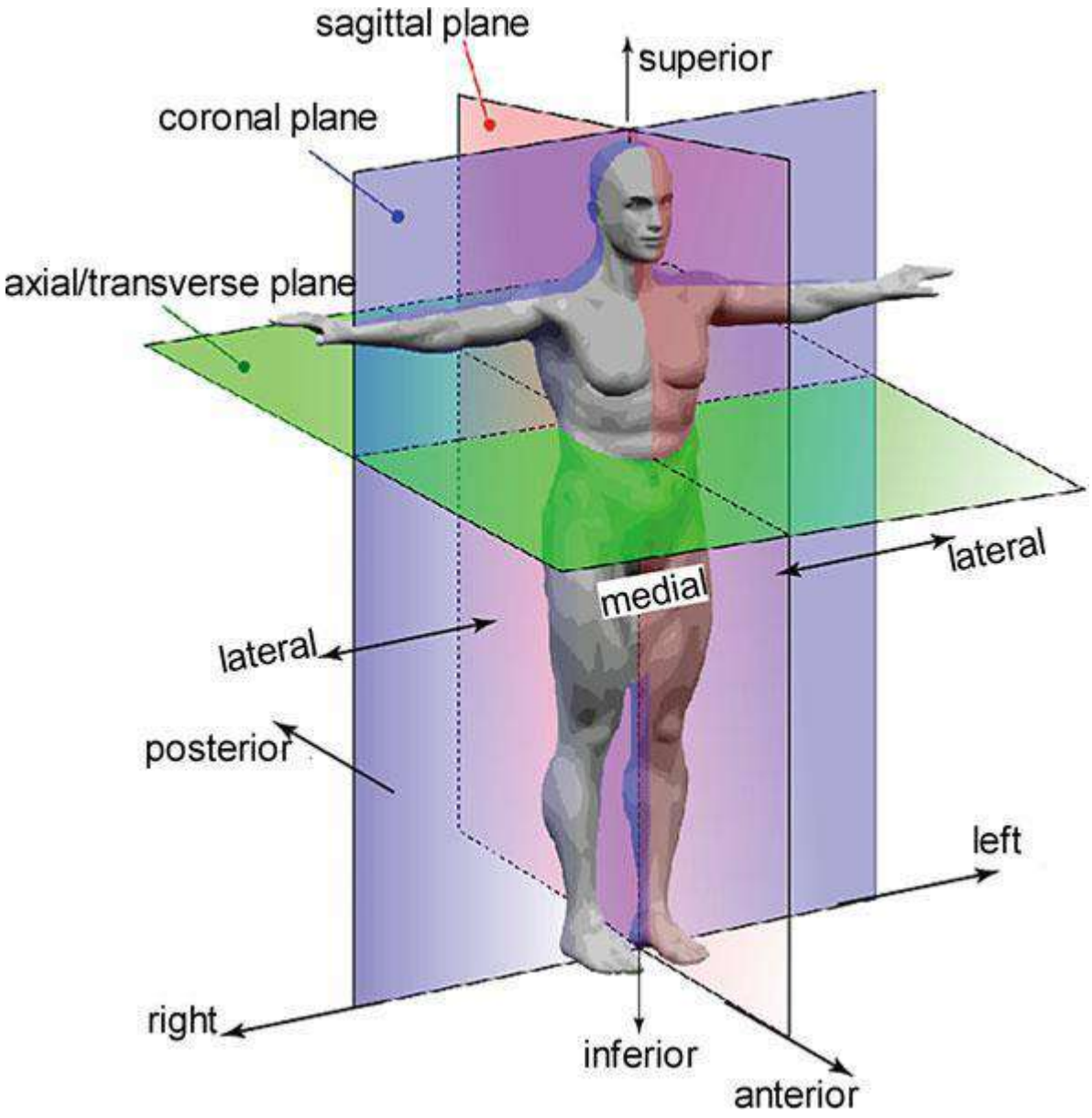
Table 1.3 describe the relative positions of different body structures.

Table 1.3: Anatomical Directional Terms, Definitions, and Examples

Anatomical Term	Definition	Example
Superior (Cranial)	Toward the head or upper part of the body	The head is superior to the chest.
Inferior (Caudal)	Away from the head or toward the lower part	The stomach is inferior to the heart.
Anterior (Ventral)	Toward the front of the body	The sternum is anterior to the heart.
Posterior (Dorsal)	Toward the back of the body	The vertebral column is posterior to the sternum.
Medial	Toward the midline of the body	The nose is medial to the eyes.
Lateral	Away from the midline	The ears are lateral to the eyes.
Proximal	Nearer to the point of attachment or origin	The shoulder is proximal to the wrist.
Distal	Farther from the point of attachment or origin	The fingers are distal to the elbow.
Superficial	Nearer to the surface of the body	The skin is superficial to muscles.
Deep	Away from the body surface	Bones are deep to muscles.
Ipsilateral	Located on the same side of the body	Right arm and right leg.
Contralateral	Located on opposite sides of the body	Right arm and left leg.
Intermediate	Between two structures	The collarbone is intermediate between the sternum and shoulder.

3. Anatomical Planes

Anatomical planes are imaginary flat surfaces used to divide the human body into different sections. They are important for describing body movements, anatomical relationships, and medical imaging findings.



A. Sagittal Plane

The sagittal plane divides the body into right and left portions.

- Median or midsagittal plane: Divides the body into equal right and left halves.
- Parasagittal plane: Divides the body into unequal right and left portions.

B. Frontal or Coronal Plane

The frontal plane divides the body into anterior (front) and posterior (back) portions.

C. Transverse or Horizontal Plane

The transverse plane divides the body into superior (upper) and inferior (lower) portions.

D. Oblique Plane

An oblique plane passes through the body at an angle that is not parallel to the sagittal, frontal, or transverse planes.

4. Anatomical Sections

A section refers to a cut or view through a body structure or organ.

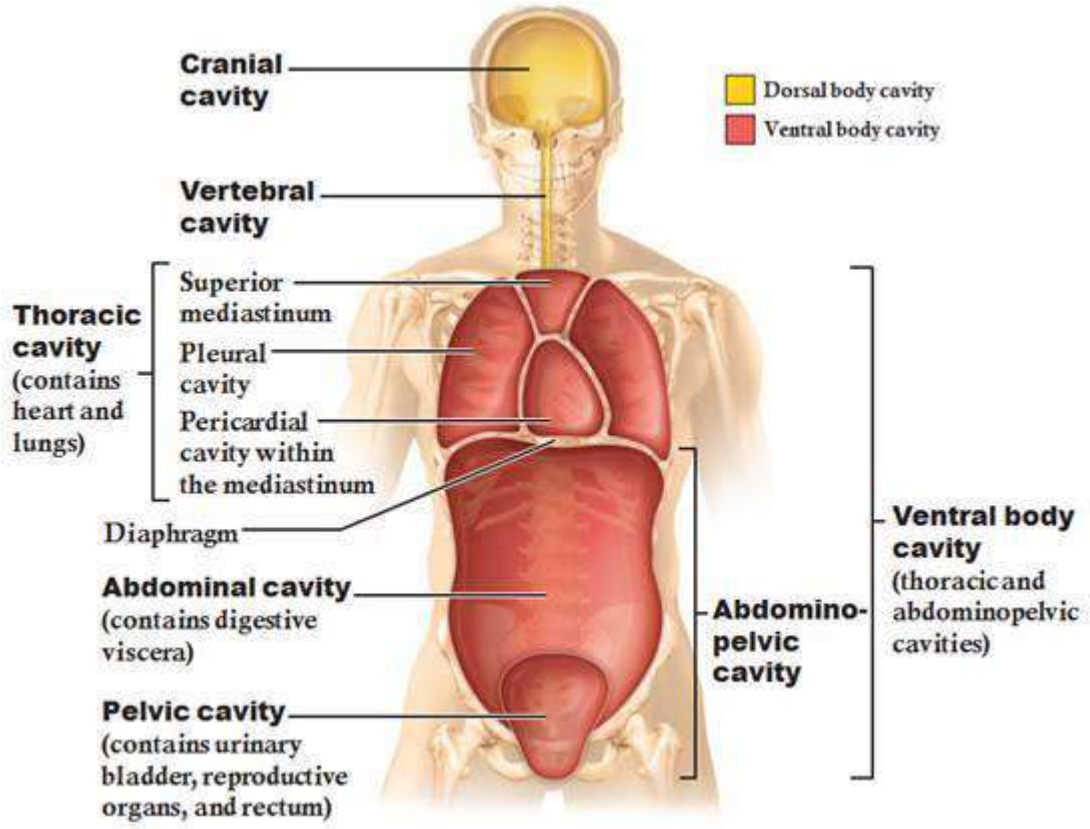
Common anatomical sections include:

1. Longitudinal section: A cut made along the long axis of a structure.
2. Cross-section: A cut made perpendicular to the long axis of a structure.
3. Oblique section: A cut made at an angle to the long axis.

5. Body Cavities

Body cavities are spaces within the body that contain and protect internal organs.

The human body has two major cavities:



A. Dorsal Body Cavity

The dorsal body cavity is located along the posterior side of the body and protects the central nervous system.

It is divided into:

i. Cranial Cavity: Contains and protects the brain.

ii. Vertebral or Spinal Cavity: Contains and protects the spinal cord.

B. Ventral Body Cavity

The ventral body cavity is located along the anterior side of the body and contains several internal organs.

It is divided into:

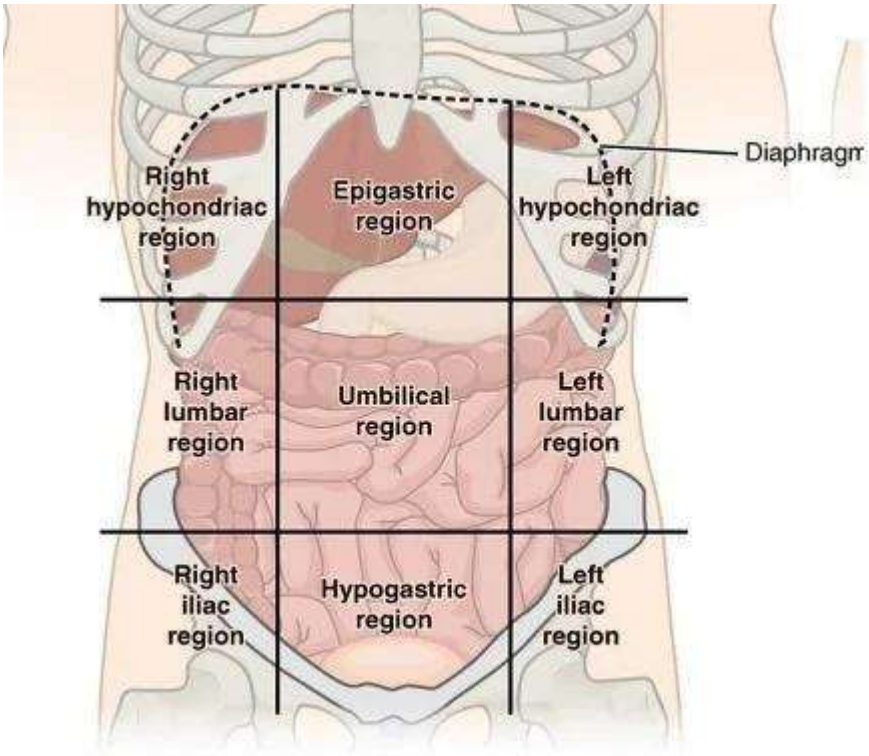
i. Thoracic Cavity: Located within the chest and contains the lungs, heart, trachea, oesophagus, and major blood vessels.

ii. Abdominal Cavity: Contains the stomach, liver, spleen, pancreas, kidneys, and most of the intestines.

iii. Pelvic Cavity: Contains the urinary bladder, reproductive organs, and rectum.

6. Anatomical Regions of the Abdomen

The abdomen is commonly divided into nine regions to describe the location of internal organs and clinical findings.



1. Right Hypochondriac Region: Contains part of the liver and gallbladder.

2. Epigastric Region: Contains part of the stomach, liver, and pancreas.

3. Left Hypochondriac Region: Contains part of the stomach and spleen.

4. Right Lumbar Region: Contains part of the ascending colon and right kidney.

5. Umbilical Region: Contains parts of the small intestine and transverse colon.

6. Left Lumbar Region: Contains part of the descending colon and left kidney.

7. Right Iliac Region: Contains the caecum and appendix.

8. Hypogastric Region: Contains parts of the urinary bladder and small intestine.

9. Left Iliac Region: Contains part of the sigmoid colon.

Table 1.4: Common Anatomical Terms Related to Body Position

Term	Definition
Supine Position	Lying horizontally with the face directed upward.
Prone Position	Lying horizontally with the face directed downward.
Lateral Position	Lying on either the right or left side.
Lithotomy Position	Lying on the back with hips and knees flexed and thighs separated.
Fowler's Position	A semi-sitting position in which the upper body is elevated.
Trendelenburg Position	A supine position in which the head is lower than the feet.

Table 1.5: Common Anatomical Terms Related to Movement

Term	Definition
Flexion	Bending movement that generally decreases the angle between two body parts.
Extension	Straightening movement that generally increases the angle between two body parts.
Abduction	Movement of a body part away from the midline.
Adduction	Movement of a body part toward the midline.
Rotation	Movement of a bone or body part around its longitudinal axis.
Circumduction	Circular movement combining flexion, extension, abduction, and adduction.
Pronation	Rotation of the forearm so that the palm faces downward or posteriorly in anatomical position.
Supination	Rotation of the forearm so that the palm faces upward or anteriorly in anatomical position.
Dorsiflexion	Movement of the foot upward toward the shin.
Plantar Flexion	Movement of the foot downward, away from the shin.
Inversion	Turning the sole of the foot inward.
Eversion	Turning the sole of the foot outward.

Anatomy, physiology, and pathophysiology are fundamental branches of medical science that describe the structure, normal functioning, and abnormal functioning of the human body, respectively. The human body is organized into six structural levels: chemical, cellular, tissue, organ, organ system, and organism. Eleven major organ systems perform specialized functions and work together to maintain life.

Basic life processes include metabolism, responsiveness, movement, growth, differentiation, reproduction, respiration, and excretion. Homeostasis maintains a relatively stable internal environment through coordinated regulatory mechanisms, particularly negative and positive feedback systems. Anatomical terminology provides standardized descriptions of body positions, directions, planes, cavities, regions, and movements, facilitating accurate communication in healthcare and pharmaceutical sciences.

Chapter 2: Structure and Functions of Cell

2.1 Structure and Functions of Cell

Introduction

The cell is the basic structural, functional, and biological unit of the human body. All living organisms are composed of cells, which perform essential activities required for growth, metabolism, reproduction, and maintenance of life. The human body consists of trillions of cells that vary in shape, size, structure, and function according to their specialization.

Cells are capable of carrying out various physiological activities, including nutrient absorption, energy production, waste removal, protein synthesis, communication, and cell division. Different cells combine to form tissues, which further organize into organs and organ systems.

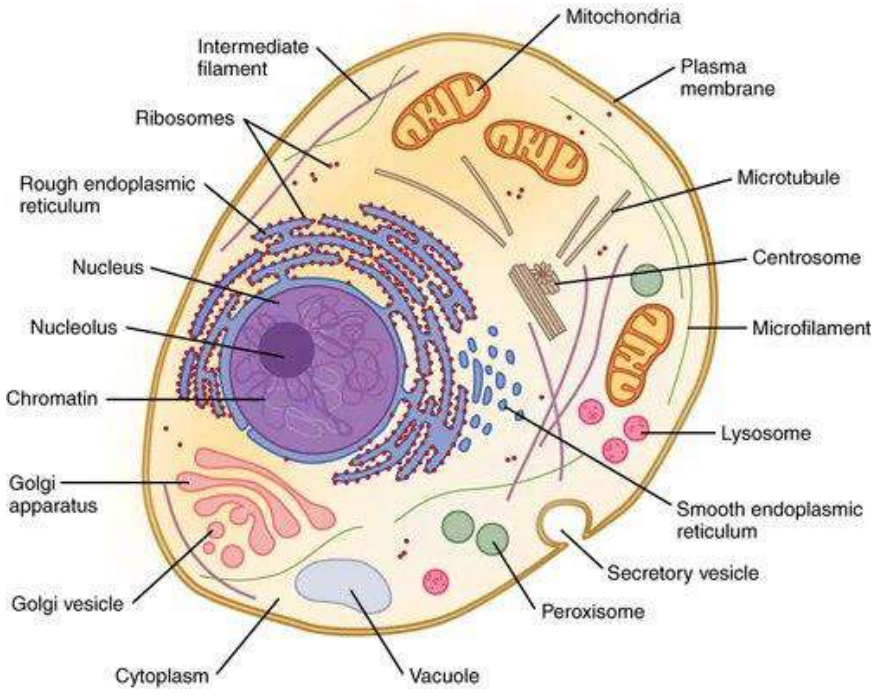
In the human body, cells are broadly classified into two major types:

1. Somatic cells: These are body cells responsible for the formation of tissues and organs. They generally contain 46 chromosomes arranged in 23 pairs.
2. Germ cells: These are reproductive cells involved in sexual reproduction. They include sperm and ova, which contain 23 chromosomes each.

General Structure of a Human Cell

A typical human cell consists of three major components:

1. Plasma membrane
2. Cytoplasm
3. Nucleus



A. Plasma Membrane

The plasma membrane is a thin, flexible, selectively permeable boundary that surrounds the cell and separates its internal environment from the extracellular fluid.

It regulates the movement of substances into and out of the cell and participates in cellular communication, recognition, and adhesion.

Structure of Plasma Membrane

The plasma membrane is primarily composed of a phospholipid bilayer containing proteins, cholesterol, and carbohydrates.

1. Phospholipid Bilayer

Phospholipids are arranged in two layers, with hydrophilic heads facing the aqueous environments and hydrophobic tails directed inward toward each other.

This arrangement forms a barrier that restricts the free movement of many water-soluble substances.

2. Membrane Proteins

Proteins are embedded within or attached to the phospholipid bilayer.

They are classified into:

- Integral proteins: Extend into or across the membrane and function as channels, carriers, receptors, and enzymes.
- Peripheral proteins: Remain attached to the inner or outer surface of the membrane and participate in structural support and cellular signalling.

3. Cholesterol

Cholesterol is present between phospholipid molecules and helps maintain membrane stability and fluidity.

4. Carbohydrates

Carbohydrates are attached to proteins and lipids, forming glycoproteins and glycolipids. These structures contribute to cell recognition, adhesion, and communication.

Functions of Plasma Membrane

- Provides protection and maintains the boundary of the cell.
- Regulates the entry and exit of substances.
- Maintains intracellular and extracellular environments.
- Participates in cell recognition and communication.
- Contains receptors for hormones and other signalling molecules.

- Helps in cellular adhesion and interaction.
- Maintains membrane potential through selective ion movement.

B. Cytoplasm

The cytoplasm is the cellular region located between the plasma membrane and the nucleus. It consists of cytosol, cell organelles, and various suspended substances.

The cytosol is a semi-fluid medium containing water, dissolved ions, proteins, nutrients, and metabolic substances.

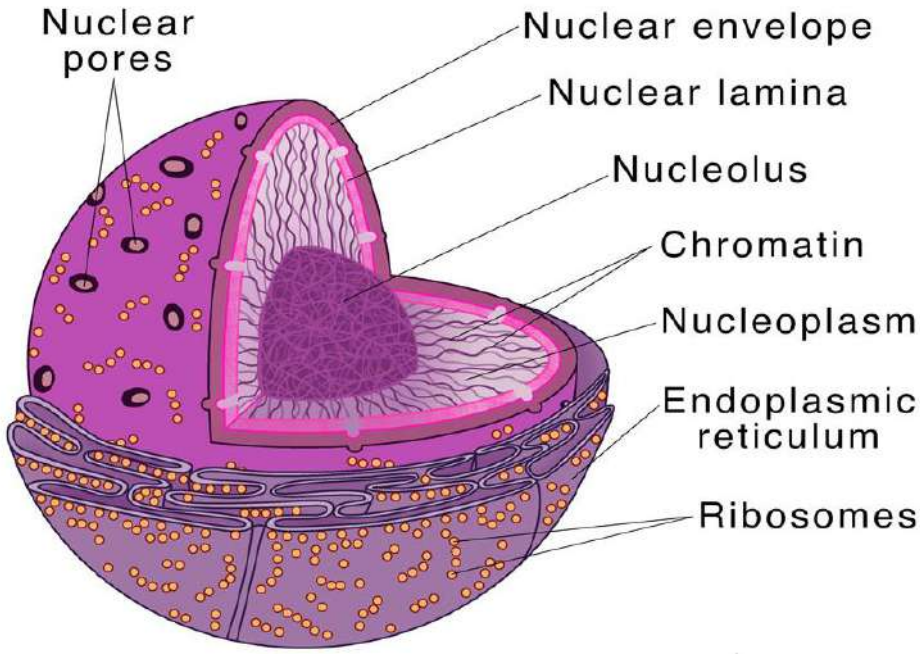
Most cellular metabolic activities occur within the cytoplasm or its organelles.

Functions of Cytoplasm

- Provides a medium for cellular biochemical reactions.
- Suspends and supports cellular organelles.
- Facilitates intracellular transport.
- Stores nutrients and other substances.
- Participates in cellular metabolism and energy utilization.

C. Nucleus

The nucleus is the largest membrane-bound organelle of most human cells and serves as the control centre of cellular activities. It contains genetic material in the form of DNA, which regulates protein synthesis, cellular growth, metabolism, and reproduction.



Structure of Nucleus

1. Nuclear Envelope

The nuclear envelope consists of two membranes that separate the nuclear contents from the cytoplasm. It contains nuclear pores that regulate the movement of molecules between the nucleus and cytoplasm.

2. Nucleoplasm

Nucleoplasm is the semi-fluid material present inside the nucleus. It contains enzymes, nucleotides, chromatin, and other nuclear components.

3. Chromatin

Chromatin consists of DNA associated with proteins, mainly histones. During cell division, chromatin condenses to form visible chromosomes.

4. Nucleolus

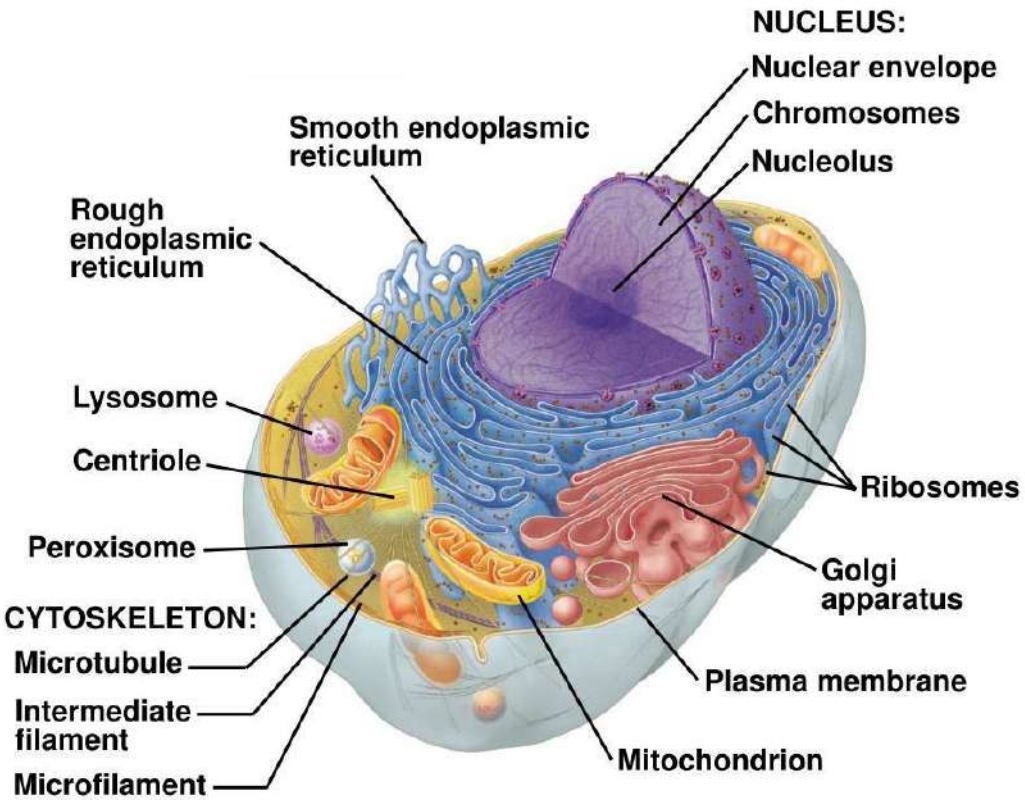
The nucleolus is a dense region within the nucleus responsible for ribosomal RNA synthesis and ribosomal subunit assembly.

Functions of Nucleus

- Stores and protects genetic information.
- Controls cellular activities through gene expression.
- Regulates protein synthesis.
- Participates in cell growth and division.
- Controls the transmission of hereditary information.

Cell Organelles and Their Functions

Cell organelles are specialized structures present within the cytoplasm that perform specific functions necessary for cellular survival and normal functioning.



1. Mitochondria

Mitochondria are double-membrane-bound organelles responsible for producing most of the ATP required for cellular activities through aerobic cellular respiration. They are commonly known as the powerhouses of the cell.

Structure:

- Outer membrane: Smooth outer covering.
- Inner membrane: Folded into structures called cristae.
- Intermembrane space: Space between the two membranes.
- Matrix: Inner compartment containing enzymes, mitochondrial DNA, and ribosomes.

Functions:

- Produces ATP through oxidative phosphorylation.
- Participates in cellular respiration.
- Regulates certain pathways of programmed cell death.
- Participates in calcium storage and regulation.
- Contains its own genetic material.

2. Endoplasmic Reticulum (ER)

The endoplasmic reticulum is a network of membrane-bound tubules and flattened sacs involved in protein and lipid synthesis.

It is classified into two types.

A. Rough Endoplasmic Reticulum (RER)

The rough endoplasmic reticulum contains ribosomes attached to its outer surface.

Functions:

- Synthesizes proteins for secretion and membranes.
- Participates in protein folding and modification.
- Helps transport newly synthesized proteins toward the Golgi apparatus.

B. Smooth Endoplasmic Reticulum (SER)

The smooth endoplasmic reticulum lacks attached ribosomes.

Functions:

- Synthesizes lipids and steroid molecules.
- Participates in detoxification of drugs and chemicals.
- Stores and releases calcium ions.
- Participates in carbohydrate metabolism.

3. Ribosomes

Ribosomes are small, non-membranous structures composed of ribosomal RNA and proteins. They are responsible for protein synthesis through translation of messenger RNA.

Ribosomes may be free in the cytoplasm or attached to the rough endoplasmic reticulum.

Functions:

- Synthesizes proteins.
- Free ribosomes mainly produce proteins used within the cell.
- Bound ribosomes mainly synthesize proteins for secretion, membranes, and certain organelles.

4. Golgi Apparatus

The Golgi apparatus consists of flattened membrane-bound sacs called cisternae. It receives proteins and lipids from the endoplasmic reticulum and modifies, sorts, and packages them.

Functions:

- Modifies newly synthesized proteins and lipids.
- Sorts and packages cellular products.
- Forms secretory vesicles.
- Participates in lysosome formation.

- Helps in intracellular transport and secretion.

5. Lysosomes

Lysosomes are membrane-bound organelles containing hydrolytic enzymes that digest cellular waste, damaged organelles, and foreign materials.

Functions:

- Digests cellular waste materials.
- Breaks down damaged organelles through autophagy.
- Helps destroy microorganisms.
- Recycles cellular components.
- Participates in intracellular digestion.

6. Peroxisomes

Peroxisomes are small membrane-bound organelles containing oxidative enzymes, including catalase.

Functions:

- Break down very-long-chain fatty acids.
- Participate in lipid metabolism.
- Convert hydrogen peroxide into water and oxygen through catalase.
- Participate in detoxification of certain harmful substances.

7. Centrosome and Centrioles

The centrosome is an important microtubule-organizing centre located near the nucleus in most animal cells. It generally contains a pair of centrioles arranged approximately perpendicular to each other.

Functions:

- Organizes microtubules.
- Helps in formation of the mitotic spindle during cell division.
- Participates in organization of cellular structures.
- Centrioles can contribute to the formation of basal bodies of cilia and flagella.

8. Cytoskeleton

The cytoskeleton is a network of protein filaments extending throughout the cytoplasm. It maintains cell shape and provides mechanical support.

It consists of three major components:

- Microfilaments: Mainly composed of actin.
- Intermediate filaments: Provide mechanical strength.

- Microtubules: Composed of tubulin and involved in intracellular transport and chromosome movement.

Functions:

- Maintains cell shape.
- Provides structural support.
- Facilitates intracellular movement.
- Participates in cell division.
- Supports cellular motility.

9. Vesicles

Vesicles are small membrane-bound sacs involved in storage and transportation of substances.

Functions:

- Transport proteins and lipids.
- Participate in secretion.
- Facilitate endocytosis and exocytosis.
- Store cellular substances.

Table 2.1: Summary of Cell Organelles and Functions

Cell Organelle	Major Function
Plasma membrane	Selective transport and cellular protection
Nucleus	Storage of genetic material and control of cellular activities
Nucleolus	Ribosomal subunit formation
Mitochondria	ATP production
Rough ER	Protein synthesis
Smooth ER	Lipid synthesis and detoxification
Ribosomes	Protein synthesis
Golgi apparatus	Modification, sorting, and packaging
Lysosomes	Intracellular digestion
Peroxisomes	Fatty acid oxidation and detoxification
Centrosome	Microtubule organization and spindle formation
Cytoskeleton	Structural support and intracellular movement
Vesicles	Intracellular transportation

Functions of the Cell

Cells perform various activities essential for maintaining the normal functioning of the human body.

1. Metabolism: Cells carry out biochemical reactions for energy production and synthesis of cellular components.
2. Growth: Cells increase in size and synthesize additional cellular materials.
3. Reproduction: Cells divide to produce new cells.
4. Transport: Cells regulate the movement of nutrients, gases, ions, and waste materials.

5. Communication: Cells receive and respond to chemical and physical signals.
6. Secretion: Specialized cells release hormones, enzymes, mucus, and other substances.
7. Excretion: Cells remove metabolic waste products.
8. Movement: Certain cells exhibit movement through specialized structures or cytoskeletal mechanisms.
9. Protection: Cells participate in immune defence and tissue protection.
10. Maintenance: Cells regulate their internal environment to maintain normal physiological activities.

2.2 Transport Across Cell Membrane

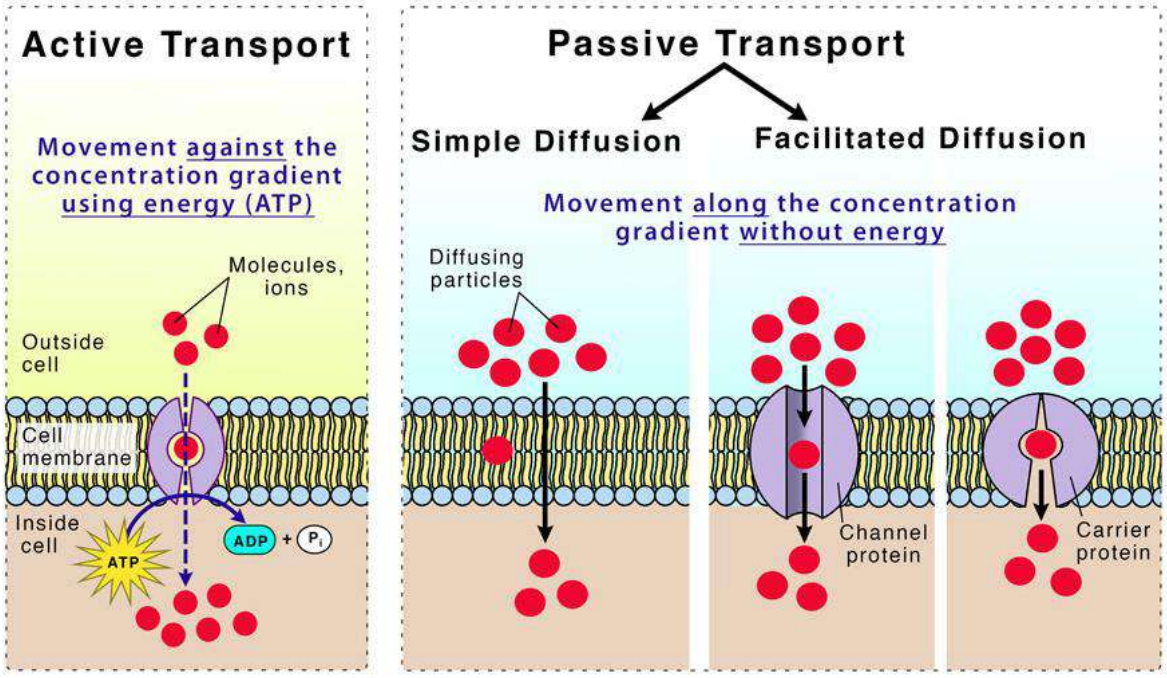
Introduction

The plasma membrane acts as a selectively permeable barrier that regulates the movement of substances between the intracellular and extracellular environments. The transport of substances across the cell membrane is essential for maintaining cellular nutrition, waste removal, ion balance, membrane potential, and normal cellular functions.

Different substances cross the membrane through different mechanisms depending on their size, electrical charge, lipid solubility, and concentration gradient.

Transport across the cell membrane is broadly classified into three major types:

A. Passive transport
B. Active transport
C. Vesicular or bulk transport



A. Passive Transport

Passive transport is the movement of substances across the cell membrane without direct expenditure of cellular energy (ATP). Substances generally move along their concentration or electrochemical gradient, from a region of higher concentration to a region of lower concentration.

The major types of passive transport include simple diffusion, facilitated diffusion, osmosis, and filtration.

1. Simple Diffusion

Simple diffusion is the movement of molecules from a region of higher concentration to a region of lower concentration directly through the phospholipid bilayer or through membrane channels, without requiring cellular energy.

The movement continues until equilibrium is reached.

Examples:

- Movement of oxygen from blood into cells.
- Movement of carbon dioxide from cells into blood.
- Movement of lipid-soluble substances across the membrane.

Factors Affecting Diffusion:

- Concentration gradient.
- Temperature.
- Molecular size.
- Surface area of the membrane.
- Membrane thickness.
- Lipid solubility of substances.

2. Facilitated Diffusion

Facilitated diffusion is the movement of substances across the cell membrane along their concentration or electrochemical gradient with the help of specific membrane proteins.

Unlike simple diffusion, it requires transport proteins but does not require ATP.

It occurs through two major types of proteins:

A. Channel Proteins

Channel proteins form selective pathways through the membrane, allowing specific ions or molecules to pass through.

Examples include sodium, potassium, calcium, and chloride channels.

B. Carrier Proteins

Carrier proteins bind to specific substances and undergo conformational changes to transport them across the membrane.

Example: Glucose transport through GLUT transporters.

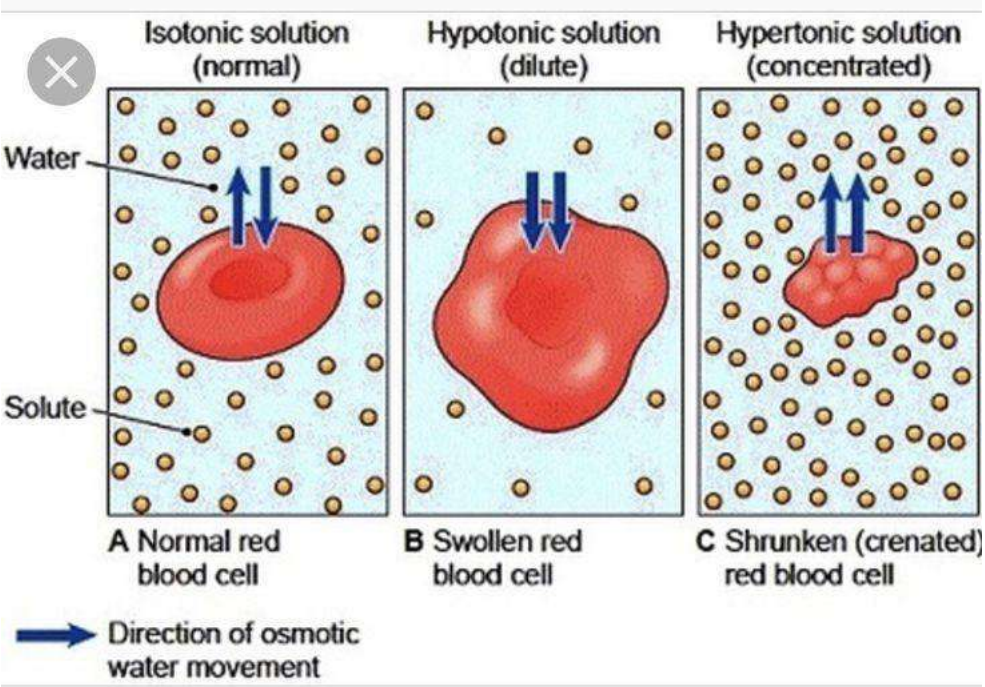
Characteristics of Facilitated Diffusion:

- Does not require ATP.
- Occurs along the concentration gradient.
- Requires specific transport proteins.
- Shows selectivity and saturation.
- Helps transport polar molecules and ions.

3. Osmosis

Osmosis is the movement of water molecules across a selectively permeable membrane from a region of lower solute concentration to a region of higher solute concentration.

Water movement occurs until osmotic equilibrium is achieved or opposed by other forces.



Types of Solutions Based on Osmotic Effect

A. Isotonic Solution

An isotonic solution has approximately the same effective osmotic pressure as the cell's internal environment. Therefore, there is no net movement of water, and the cell maintains its normal shape.

Example: 0.9% sodium chloride solution is approximately isotonic with blood plasma.

B. Hypotonic Solution

A hypotonic solution has a lower effective solute concentration than the intracellular fluid. Water enters the cell, causing it to swell.

In red blood cells, excessive water entry may result in haemolysis.

C. Hypertonic Solution

A hypertonic solution has a higher effective solute concentration than the intracellular fluid. Water moves out of the cell, causing it to shrink.

In red blood cells, this process is known as crenation.

4. Filtration

Filtration is the movement of water and dissolved substances across a membrane due to a pressure difference, particularly hydrostatic pressure.

Substances move from a region of higher pressure to a region of lower pressure.

Examples:

- Filtration of blood through the glomerular membrane in the kidneys.
- Movement of fluid across capillary walls.

B. Active Transport

Active transport is the movement of substances across the cell membrane against their concentration or electrochemical gradient with the expenditure of energy.

It requires specific membrane transport proteins and is important for maintaining ionic gradients and cellular homeostasis.

Active transport is classified into primary and secondary active transport.

1. Primary Active Transport

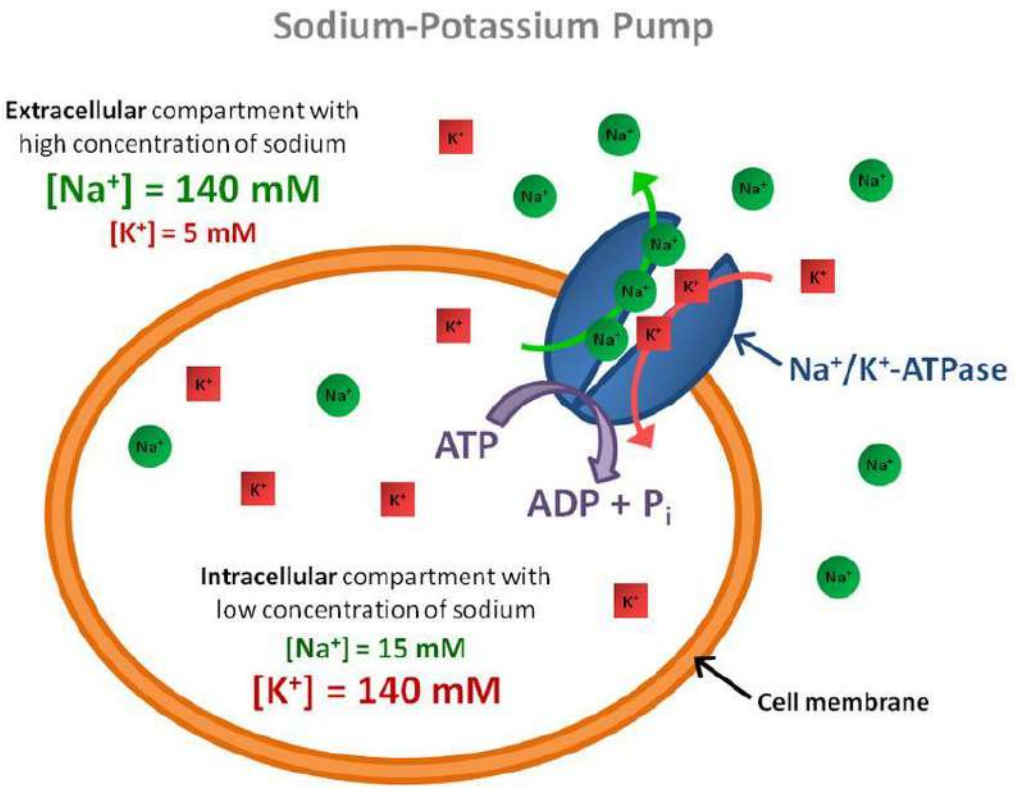
Primary active transport directly utilizes energy from ATP hydrolysis to move substances against their concentration or electrochemical gradient.

Example: Sodium-Potassium Pump (Na^+/K^+-ATPase)

The sodium-potassium pump is an important membrane protein that maintains sodium and potassium concentration gradients across the plasma membrane.

For each ATP molecule hydrolysed, it transports:

- Three sodium ions (Na^+) out of the cell.
- Two potassium ions (K^+) into the cell.



Functions of Sodium-Potassium Pump:

- Maintains intracellular sodium and potassium concentrations.
- Helps establish resting membrane potential.
- Regulates cellular volume.
- Supports nerve impulse transmission.
- Provides sodium gradients required for secondary active transport.

Other examples include calcium ATPase and proton pumps.

2. Secondary Active Transport

Secondary active transport uses energy stored in an electrochemical gradient, generally established by primary active transport, to move another substance against its concentration gradient. It does not directly hydrolyse ATP at the transport protein. Secondary active transport is classified into two types:

A. Symport (Co-transport)

In symport, two or more substances move across the membrane in the same direction.

Example: Sodium-glucose co-transport in intestinal epithelial cells.

B. Antiport (Counter-transport)

In antiport, two substances move across the membrane in opposite directions.

Example: Sodium-calcium exchanger, which facilitates sodium movement into the cell while transporting calcium out.

C. Vesicular or Bulk Transport

Vesicular transport involves the movement of large molecules, particles, or fluid across the plasma membrane through membrane-bound vesicles.

It is an energy-dependent process and includes endocytosis and exocytosis.

1. Endocytosis

Endocytosis is the process by which cells take up substances from the extracellular environment by forming membrane-bound vesicles.

The plasma membrane surrounds the material and forms an intracellular vesicle.

Major types of endocytosis include:

A. Phagocytosis

Phagocytosis is the process of engulfment of large solid particles, microorganisms, or cellular debris by specialized cells.

Examples:

- Engulfment of bacteria by macrophages.
- Removal of dead cells by phagocytic cells.

B. Pinocytosis

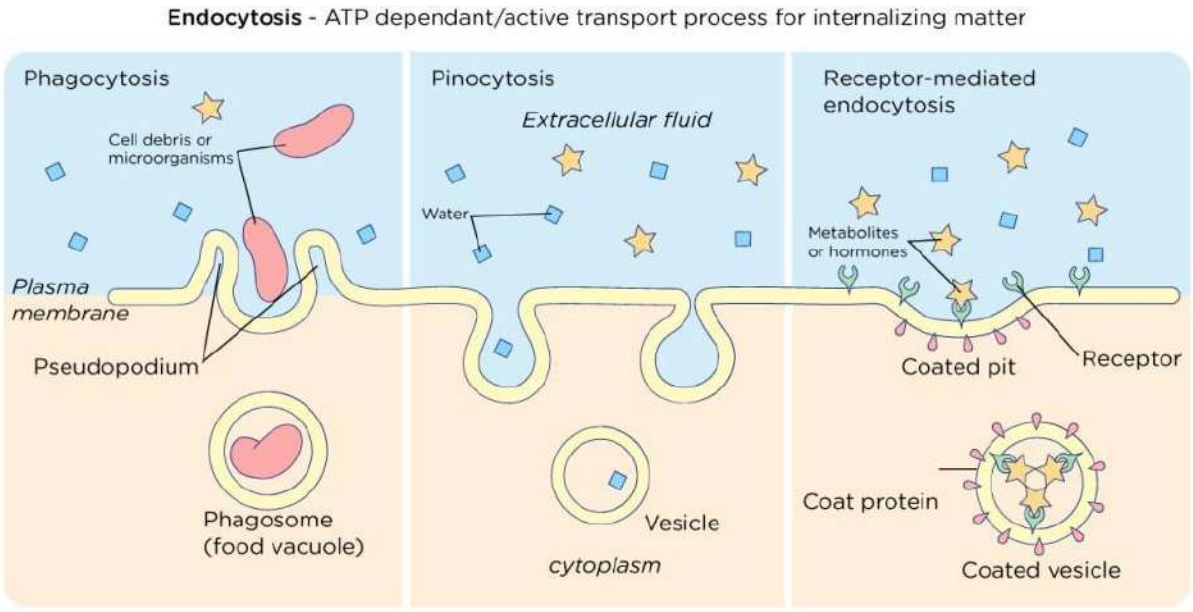
Pinocytosis is the uptake of extracellular fluid and dissolved substances through small vesicles.

It is also known as cellular drinking.

C. Receptor-Mediated Endocytosis

This is a selective process in which specific extracellular molecules bind to membrane receptors and are internalized through vesicle formation.

Example: Uptake of low-density lipoprotein (LDL) by cells.



2. Exocytosis

Exocytosis is the process by which intracellular vesicles fuse with the plasma membrane and release their contents into the extracellular environment.

It is important for secretion and removal of substances from cells.

Examples:

- Release of neurotransmitters from nerve cells.
- Secretion of insulin from pancreatic beta cells.
- Release of digestive enzymes from glandular cells.

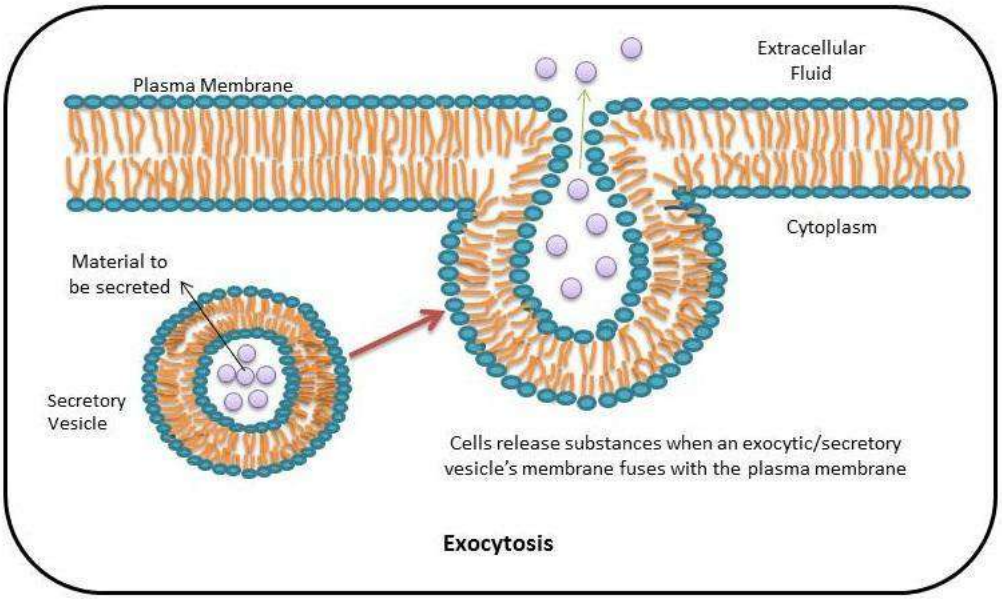


Table 2.2: Comparison of Transport Mechanisms

Feature	Passive Transport	Active Transport	Vesicular Transport
Energy requirement	No direct ATP requirement	Requires energy directly or indirectly	Requires energy
Direction	Along gradient	Can occur against gradient	Through vesicle formation
Transport proteins	May be required	Required	Not required for vesicle movement itself
Substances	Ions and small molecules	Ions and molecules	Large molecules and particles
Examples	Diffusion, osmosis	Na^+/K^+ pump	Endocytosis, exocytosis

2.3 Cell Division

Introduction

Cell division is the biological process through which a parent cell divides to produce daughter cells. It is essential for growth, development, tissue repair, replacement of damaged cells, and reproduction.

In the human body, cell division occurs mainly through two processes: mitosis and meiosis.

- Mitosis produces two genetically similar daughter cells and is primarily involved in growth and tissue maintenance.
- Meiosis produces reproductive cells containing half the chromosome number of the parent cell.

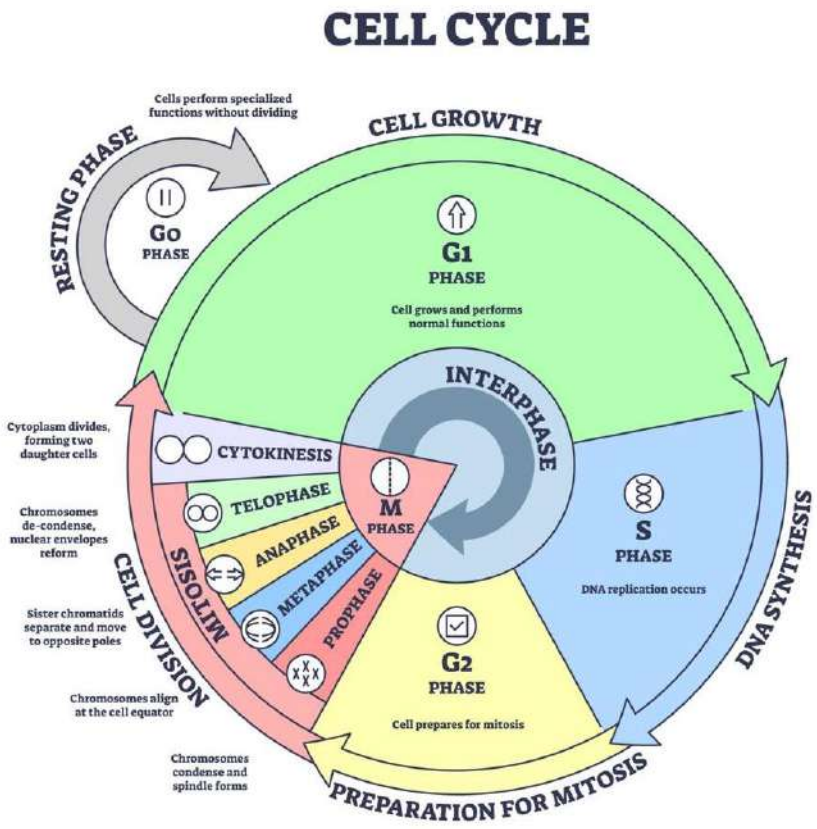
Before division, cells undergo a series of organized events collectively known as the cell cycle.

Cell Cycle

The cell cycle refers to the sequence of events through which a cell grows, duplicates its DNA, and divides into daughter cells.

It is divided into two major phases:

1. Interphase
2. M phase (Mitotic phase)



A. Interphase

Interphase is the period between successive cell divisions during which the cell grows, performs normal functions, and prepares for division.

It is divided into three phases.

1. G1 Phase (First Gap Phase)

During the G1 phase:

- The cell increases in size.
- RNA and proteins are synthesized.
- Cellular organelles increase in number.
- Normal metabolic activities continue.
- The cell prepares for DNA replication.

2. S Phase (Synthesis Phase)

The S phase is characterized by DNA replication.

During this phase:

- DNA content is doubled.

- Each chromosome forms two identical sister chromatids.
- Histone proteins are synthesized.
- Genetic material is prepared for distribution into daughter cells.

3. G2 Phase (Second Gap Phase)

During the G2 phase:

- The cell continues to grow.
- Proteins required for cell division are synthesized.
- Organelles and cellular components are prepared.
- DNA replication is checked.
- The cell prepares for mitosis.

Some cells may enter a resting or non-dividing state called the G0 phase.

B. Mitotic Phase (M Phase)

The mitotic phase involves nuclear division followed by cytoplasmic division. It produces two daughter cells from one parent cell.

It consists of mitosis and cytokinesis.

Mitosis

Mitosis is a type of cell division in which one parent cell produces two genetically similar daughter cells, each generally containing the same chromosome number as the parent cell.

In humans, a typical diploid somatic cell containing 46 chromosomes produces two daughter cells, each containing 46 chromosomes.

Mitosis is divided into four major stages: prophase, metaphase, anaphase, and telophase.

1. Prophase

Prophase is the first stage of mitosis.

Major events include:

- Chromatin condenses into visible chromosomes.
- Each chromosome consists of two sister chromatids joined at the centromere.
- The nucleolus gradually disappears.
- Centrosomes move toward opposite poles.
- Mitotic spindle formation begins.
- The nuclear envelope breaks down by late prophase/prometaphase.

2. Metaphase

During metaphase:

- Chromosomes align at the equatorial plane of the cell.
- Spindle fibres attach to chromosome kinetochores.
- Each sister chromatid is connected to spindle microtubules from opposite poles.
- Chromosomes are positioned for equal separation.

3. Anaphase

During anaphase:

- Sister chromatids separate at the centromere.
- Separated chromatids move toward opposite poles.
- Each chromatid becomes an independent chromosome.
- The cell begins to elongate.

4. Telophase

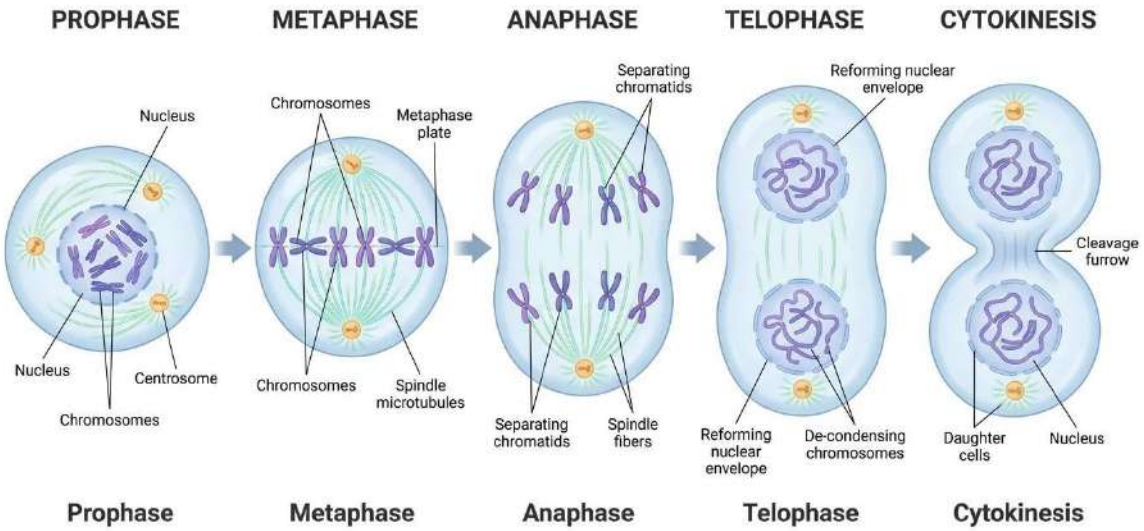
During telophase:

- Chromosomes reach opposite poles.
- Chromosomes begin to decondense.
- Nuclear envelopes reform around each chromosome set.
- Nucleoli reappear.
- Two daughter nuclei are formed.

Cytokinesis

Cytokinesis is the division of cytoplasm following nuclear division, resulting in the formation of two separate daughter cells.

In animal cells, cytokinesis occurs through the formation of a contractile ring composed mainly of actin and myosin filaments. This ring creates a cleavage furrow that gradually separates the two daughter cells.



Importance of Mitosis

- Helps in growth and development.
- Replaces damaged and dead cells.
- Supports tissue repair and wound healing.
- Maintains chromosome number in somatic cells.
- Helps maintain genetic stability.
- Supports continuous renewal of certain tissues.

Regulation of Cell Cycle

Cell division is controlled by regulatory proteins that ensure proper progression through different stages of the cell cycle.

Important regulatory molecules include cyclins and cyclin-dependent kinases (CDKs).

The cell cycle contains important checkpoints:

1. G1/S Checkpoint: Determines whether the cell is ready to initiate DNA replication.

2. G2/M Checkpoint: Ensures that DNA replication is completed and DNA damage is appropriately addressed before mitosis.

3. Spindle Assembly Checkpoint: Ensures that chromosomes are properly attached to spindle fibres before sister chromatid separation.

Abnormal regulation of the cell cycle may lead to uncontrolled cell proliferation and contribute to cancer development.

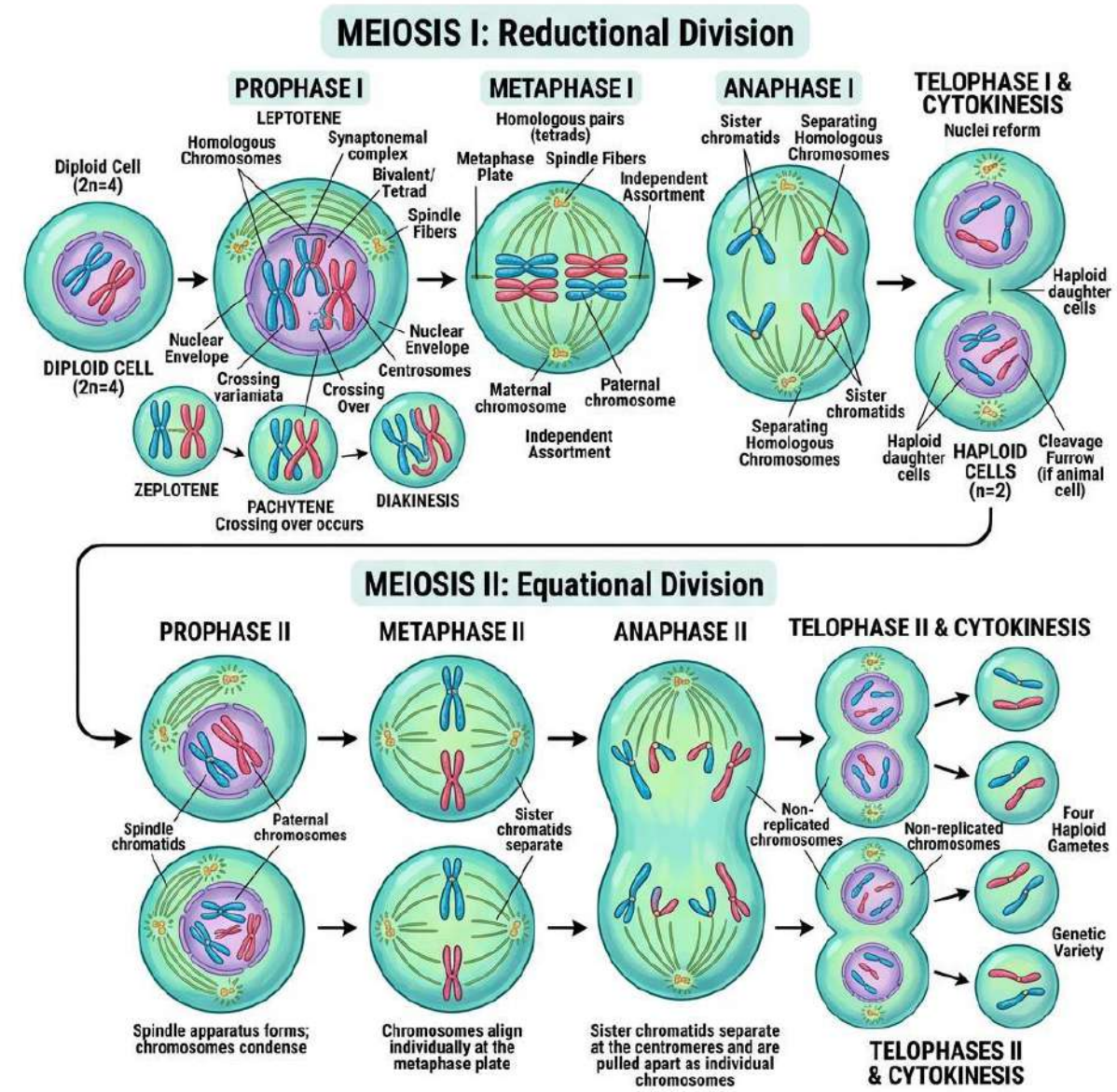
Meiosis

Meiosis is a specialized type of cell division that occurs during the formation of reproductive cells. It reduces the chromosome number from diploid (2n) to haploid (n).

In humans, meiosis produces gametes containing 23 chromosomes from precursor cells containing 46 chromosomes.

It involves two successive divisions:

1. Meiosis I
2. Meiosis II



Meiosis I (Reductional Division)

Meiosis I reduces the chromosome number by half.

1. Prophase I

This is the longest phase of meiosis and includes the following events:

- Chromosomes condense.
- Homologous chromosomes pair through synapsis.
- Paired homologous chromosomes form bivalents.
- Crossing over occurs between non-sister chromatids.
- Genetic material is exchanged, producing genetic variation.

2. Metaphase I

- Homologous chromosome pairs align at the equatorial plane.
- Their orientation is random, contributing to genetic variation.

3. Anaphase I

- Homologous chromosomes separate and move toward opposite poles.
- Sister chromatids remain joined at their centromeres.

4. Telophase I

- Chromosomes reach opposite poles.
- Nuclear envelopes may reform.
- Cytokinesis produces two haploid cells, each containing duplicated chromosomes.

Meiosis II (Equational Division)

Meiosis II resembles mitosis and separates sister chromatids.

1. Prophase II: Chromosomes condense and spindle fibres form.

2. Metaphase II: Chromosomes align at the equatorial plane.

3. Anaphase II: Sister chromatids separate and move toward opposite poles.

4. Telophase II: Nuclear envelopes reform and cytokinesis occurs, resulting in four haploid cells.

Table 2.3: Difference Between Mitosis and Meiosis

Basis	**Mitosis**	**Meiosis**
Occurrence	Somatic cells	Germ-cell lineage
Number of divisions	One	Two
Daughter cells	Two	Four haploid products
Chromosome number	Maintained	Reduced by half
Genetic composition	Generally genetically similar	Genetically variable
Crossing over	Normally absent	Occurs during prophase I
Main function	Growth and tissue repair	Gamete formation

DNA replication	Once before division	Once before meiosis I
Chromosome separation	Sister chromatids separate	Homologous chromosomes separate in meiosis I; sister chromatids in meiosis II

Clinical Importance of Cell Division

Normal cell division is essential for maintaining tissue integrity and replacing damaged cells. Abnormal cell-cycle regulation may result in excessive or insufficient cell proliferation.

Uncontrolled cell division may contribute to tumour formation, whereas impaired cell division can affect tissue repair and regeneration.

Meiotic errors may result in abnormal chromosome numbers, which can cause genetic disorders.

2.4 Cell Junctions

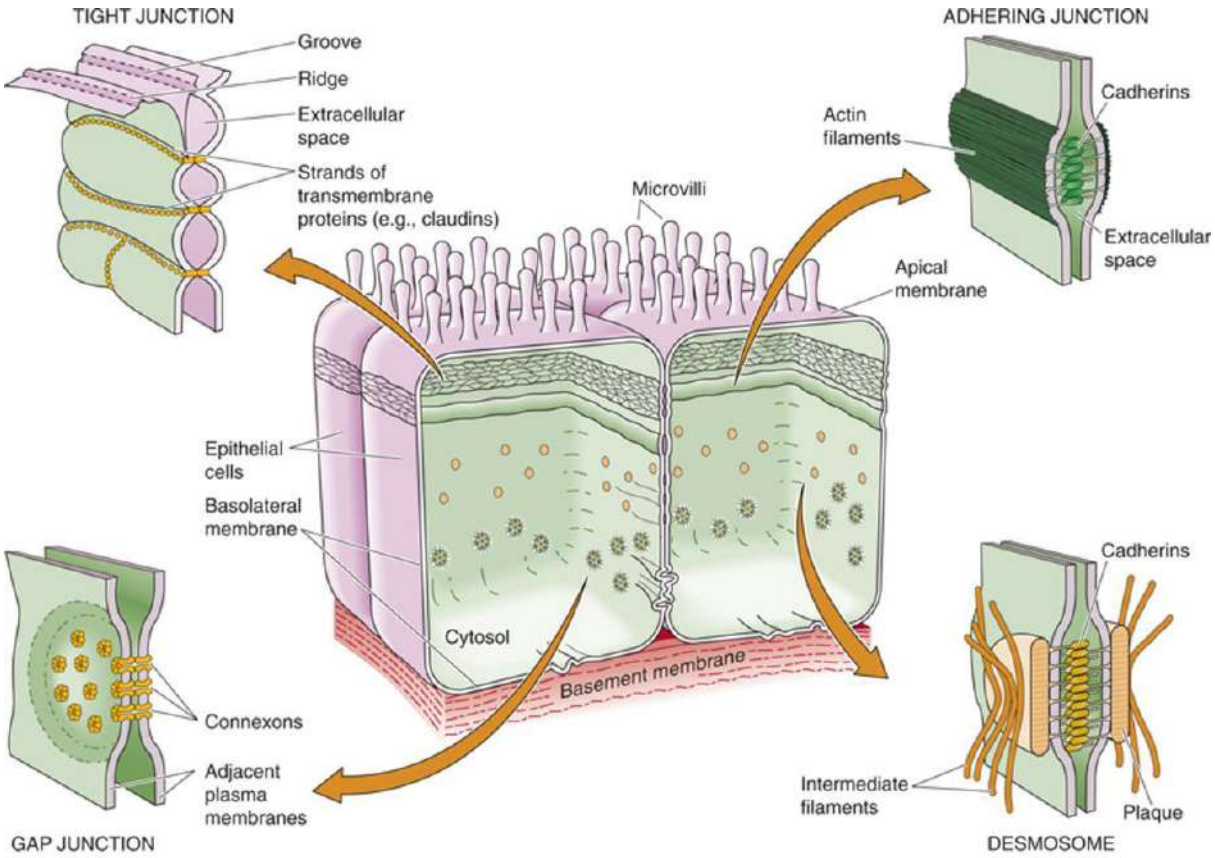
Introduction

Cell junctions are specialized structures that connect adjacent cells or attach cells to the extracellular matrix. They are essential for maintaining tissue integrity, providing mechanical support, regulating the movement of substances between cells, and facilitating intercellular communication.

Cell junctions are particularly important in epithelial tissues, where cells are closely arranged to form protective barriers and regulate the movement of substances.

Cell junctions are broadly classified into three major categories:

1. Occluding junctions
2. Anchoring junctions
3. Communicating junctions



1. Tight Junctions (Occluding Junctions)

Tight junctions are specialized connections between adjacent epithelial cells that seal the intercellular space and restrict the movement of substances through the space between cells.

They are generally located near the apical surface of epithelial cells.

Structure:

Tight junctions are formed by transmembrane proteins, mainly claudins and occludins, which interact with corresponding proteins of adjacent cells. These proteins are connected to intracellular scaffolding proteins and the cytoskeleton.

Functions:

- Prevents uncontrolled passage of substances between adjacent cells.
- Maintains epithelial barrier function.
- Regulates paracellular transport.
- Helps maintain cell polarity by separating apical and basolateral membrane regions.
- Protects underlying tissues from harmful substances.

Location:

- Intestinal epithelial lining.

- Renal tubular epithelium.
- Blood-brain barrier endothelial cells.

2. Adherens Junctions

Adherens junctions are anchoring junctions that connect adjacent cells through interactions between cadherin proteins and the actin cytoskeleton.

They provide mechanical attachment and help maintain the structural organization of tissues.

Structure:

Adherens junctions contain cadherin proteins that connect adjacent cells. On the intracellular side, cadherins interact with catenins, which connect them to actin filaments.

Functions:

- Provide mechanical attachment between adjacent cells.
- Maintain tissue architecture.
- Support changes in cell shape.
- Participate in tissue development and organization.
- Help coordinate cellular movements.

Location:

- Epithelial tissues.
- Cardiac tissues.
- Developing embryonic tissues.

3. Desmosomes

Desmosomes are strong anchoring junctions that provide mechanical stability by connecting intermediate filaments of neighbouring cells.

They are particularly important in tissues exposed to mechanical stress.

Structure:

Desmosomes contain specialized cadherin proteins, including desmogleins and desmocollins. These proteins connect adjacent cells and attach intracellularly to plaque proteins associated with intermediate filaments.

Functions:

- Provide strong mechanical attachment between cells.
- Maintain tissue integrity.
- Resist stretching and mechanical stress.
- Prevent separation of cells during physical activity.

Location:

- Epidermis of the skin.
- Cardiac muscle tissue.

4. Gap Junctions (Communicating Junctions)

Gap junctions are specialized intercellular channels that allow direct communication between adjacent cells through the movement of ions and small molecules.

They are important for coordinating the activities of neighbouring cells.

Structure:

Gap junctions are formed by protein channels called connexons. Each connexon consists of six connexin proteins. Connexons from adjacent cells align to form continuous channels connecting their cytoplasm.

Functions:

- Allow passage of ions between neighbouring cells.
- Facilitate electrical communication.
- Permit movement of small signalling molecules.
- Coordinate cellular activities.
- Support synchronized contraction in cardiac and smooth muscle.

Location:

- Cardiac muscle.
- Smooth muscle.
- Certain epithelial tissues.

5. Hemidesmosomes

Hemidesmosomes are anchoring junctions that attach epithelial cells to the underlying basement membrane.

Unlike desmosomes, which connect adjacent cells, hemidesmosomes connect individual cells to the extracellular matrix.

Structure:

They contain integrin proteins that connect intracellular intermediate filaments to components of the basement membrane.

Functions:

- Attach epithelial cells to the basement membrane.

- Provide mechanical stability.
- Prevent separation of epithelial layers.
- Maintain tissue integrity during mechanical stress.

Location:

- Basal surface of epidermal cells.
- Epithelial basement membranes.

Table 2.4: Classification of Cell Junctions

Type of Junction	Main Function	Major Proteins	Location
Tight junction	Seals intercellular spaces	Claudins, occludins	Intestinal epithelium, blood-brain barrier
Adherens junction	Connects actin cytoskeletons	Cadherins, catenins	Epithelial tissues
Desmosome	Provides mechanical strength	Desmogleins, desmocollins	Skin, cardiac tissue
Gap junction	Intercellular communication	Connexins	Cardiac and smooth muscle
Hemidesmosome	Anchors cells to basement membrane	Integrins	Epidermis

Importance of Cell Junctions

Cell junctions are essential for the proper organization and functioning of tissues.

- Maintain structural integrity of tissues.
- Regulate movement of substances between adjacent cells.
- Facilitate intercellular communication.
- Provide mechanical strength and stability.
- Maintain epithelial polarity.
- Support tissue development and repair.
- Coordinate electrical activities in certain tissues.

Clinical Significance of Cell Junctions

Abnormalities in cell junction proteins may contribute to several pathological conditions.

For example:

- Defective tight junctions may increase epithelial or endothelial permeability.
- Desmosomal abnormalities may contribute to skin blistering disorders.
- Alterations in cardiac gap junctions may affect electrical conduction.
- Defects in hemidesmosomal proteins may cause separation of the epidermis from the basement membrane.

The cell is the basic structural and functional unit of the human body. It consists of three major components: plasma membrane, cytoplasm, and nucleus. Various cellular organelles, including mitochondria, endoplasmic reticulum, ribosomes, Golgi apparatus, lysosomes, peroxisomes, centrosomes, and cytoskeleton, perform specialized functions essential for cellular survival.

Transport across the cell membrane occurs through passive transport, active transport, and vesicular transport. Passive transport includes simple diffusion, facilitated diffusion, osmosis, and filtration, whereas active transport involves primary and secondary mechanisms. Vesicular transport includes endocytosis and exocytosis.

Cell division is essential for growth, tissue repair, and reproduction. Mitosis produces two genetically similar daughter cells, whereas meiosis involves two successive divisions and produces haploid reproductive cells. The cell cycle is regulated through specific checkpoints to ensure accurate DNA replication and chromosome distribution.

Cell junctions are specialized structures responsible for connecting cells with one another or with the extracellular matrix. Tight junctions provide barrier functions, adherens junctions and desmosomes provide mechanical attachment, gap junctions facilitate communication, and hemidesmosomes anchor cells to the basement membrane.

Chapter 3: Cell Communication and Intracellular Signalling

3.1 General Principles of Cell Communication

Introduction

Cell communication is the process through which cells exchange information and coordinate their activities to maintain normal physiological functions. In the human body, millions of cells continuously communicate with one another to regulate growth, development, metabolism, immune responses, tissue repair, and other essential biological processes.

Cells communicate through chemical messengers, electrical signals, direct physical contact, and specialized intercellular connections. These communication mechanisms allow individual cells to respond appropriately to changes in their internal and external environments.

Cell communication is particularly important in multicellular organisms because different cells perform specialized functions but must work together to maintain tissue and organ functions.

For example, pancreatic beta cells release insulin in response to increased blood glucose levels. Insulin travels through the bloodstream and binds to specific receptors on target cells, promoting glucose uptake and helping regulate blood glucose concentration.

Definition of Cell Communication

Cell communication refers to the process by which cells transmit, receive, and respond to signals through specific molecular or physical mechanisms to regulate cellular activities and maintain coordination within the body.

Importance of Cell Communication

Cell communication plays an essential role in maintaining normal physiological activities.

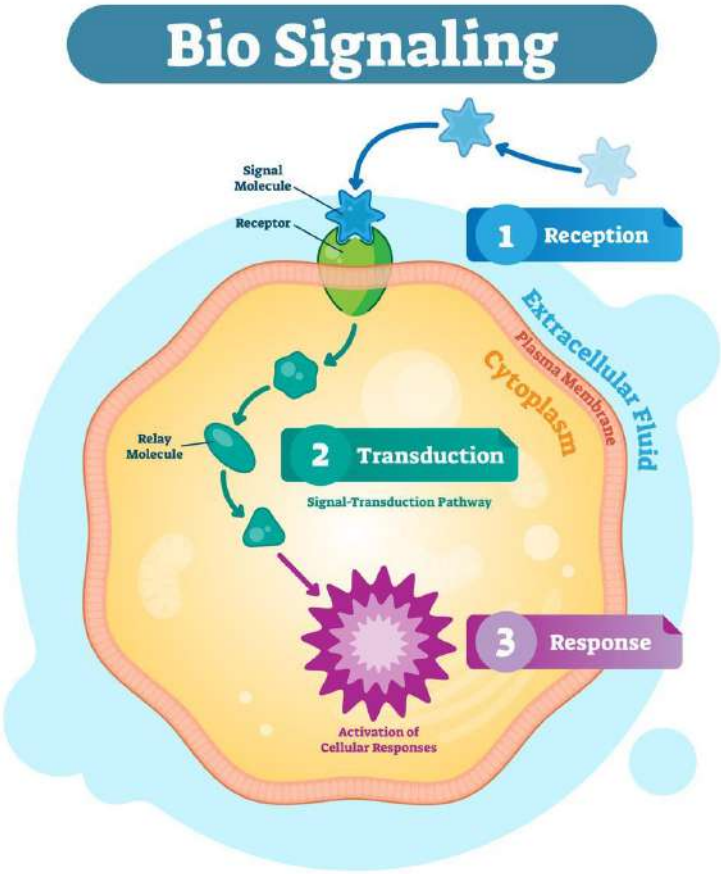
Its major functions include:

1. Coordination of Cellular Activities: Helps different cells perform their functions in a coordinated manner.
2. Regulation of Growth and Development: Controls cell proliferation, differentiation, and tissue formation.
3. Maintenance of Homeostasis: Regulates blood glucose, body temperature, fluid balance, and other physiological parameters.
4. Immune Responses: Enables immune cells to recognize foreign substances and coordinate defence mechanisms.
5. Metabolic Regulation: Controls cellular metabolism through hormones and other signalling molecules.
6. Tissue Repair: Coordinates cellular responses during wound healing and tissue regeneration.
7. Nervous System Function: Facilitates transmission of information between neurons and target cells.

8. Reproductive Functions: Regulates reproductive processes through hormonal and cellular signalling.

Basic Components of Cell Communication

Cell communication generally involves three major components:



1. Signalling Cell

A signalling cell is a cell that produces and releases a signalling molecule or ligand.

The ligand carries information from the signalling cell to the target cell.

Examples include:

- Pancreatic beta cells releasing insulin.
- Neurons releasing neurotransmitters.
- Immune cells releasing cytokines.

2. Signalling Molecule (Ligand)

A ligand is a chemical messenger that binds specifically to a receptor present on or within a target cell.

Signalling molecules may include:

- Hormones
- Neurotransmitters
- Cytokines
- Growth factors
- Chemical mediators

Examples include insulin, adrenaline, acetylcholine, and epidermal growth factor.

3. Target Cell and Receptor

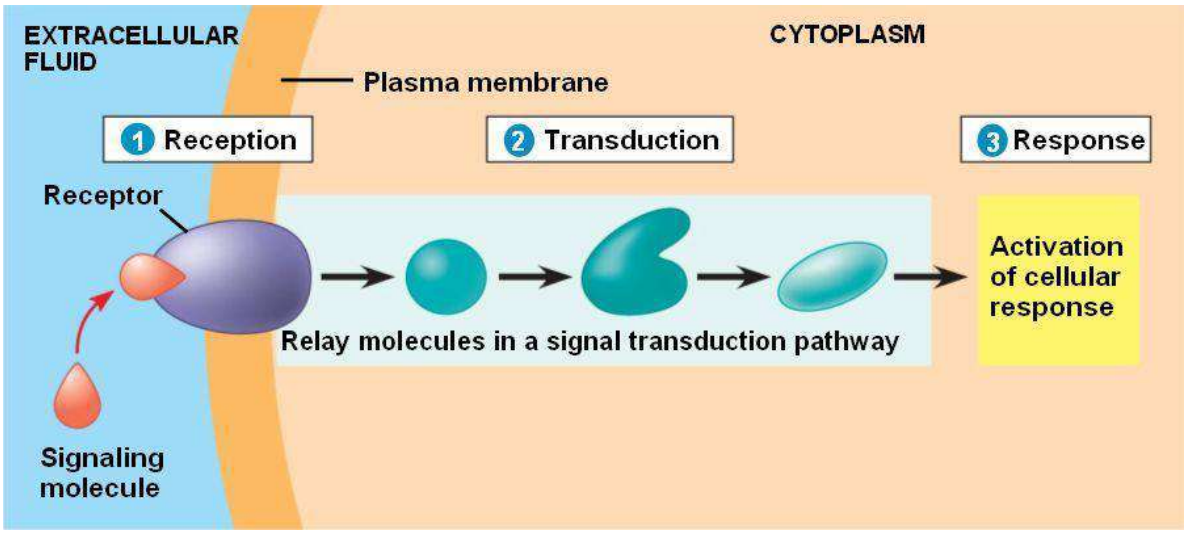
A target cell is a cell that possesses specific receptors capable of recognizing and binding to a signalling molecule.

Receptors are proteins that detect signals and initiate cellular responses.

Only cells expressing the appropriate receptors can respond to a particular signalling molecule.

General Mechanism of Cell Signalling

Cell signalling generally occurs through a sequence of events involving signal production, reception, transduction, and response.



Step 1: Signal Production and Release

The signalling cell produces a specific signalling molecule in response to an internal or external stimulus.

The signalling molecule may be released into the extracellular fluid, bloodstream, or synaptic cleft, depending on the type of communication.

Step 2: Signal Reception

The signalling molecule reaches the target cell and binds to a specific receptor.

Receptors may be located on the plasma membrane or inside the cell.

The interaction between a ligand and its receptor initiates the signalling process.

Step 3: Signal Transduction

Signal transduction refers to the conversion of an extracellular signal into intracellular biochemical events.

Receptor activation may initiate a series of molecular reactions involving enzymes, ion channels, second messengers, and signalling proteins.

These reactions transmit and sometimes amplify the original signal within the cell.

Step 4: Cellular Response

The final stage involves a specific response by the target cell.

Cellular responses may include:

- Changes in enzyme activity.
- Alterations in gene expression.
- Opening or closing of ion channels.
- Secretion of cellular products.
- Changes in cell growth and division.
- Modification of cellular metabolism.
- Changes in cell movement.

Types of Cellular Receptors

Receptors are specialized proteins that recognize specific signalling molecules and initiate cellular responses. They are broadly classified into two major types.

1. Cell-Surface Receptors

Cell-surface receptors are located on the plasma membrane and bind signalling molecules that generally cannot pass directly through the lipid bilayer. They are important for the recognition of water-soluble signalling molecules. Major types include:

A. G-Protein-Coupled Receptors (GPCRs)

GPCRs are membrane receptors that activate intracellular G proteins following ligand binding. They participate in various physiological processes, including sensory perception, neurotransmission, and hormonal regulation.

Examples: Adrenergic receptors and muscarinic acetylcholine receptors.

B. Enzyme-Linked Receptors

These receptors possess intrinsic enzymatic activity or are associated with intracellular enzymes. They regulate cellular growth, metabolism, differentiation, and survival.

Example: Insulin receptor, which is a receptor tyrosine kinase.

C. Ligand-Gated Ion Channels

These receptors function as ion channels that open or close in response to ligand binding. They allow selective movement of ions across the plasma membrane.

Example: Nicotinic acetylcholine receptor.

2. Intracellular Receptors

Intracellular receptors are located within the cytoplasm or nucleus of target cells. They generally bind lipid-soluble signalling molecules that can cross the plasma membrane.

Following ligand binding, these receptors may regulate gene expression.

Examples include receptors for:

- Steroid hormones.
- Thyroid hormones.
- Vitamin D.
- Retinoic acid.

Second Messengers in Cell Signalling

Second messengers are small intracellular molecules or ions that transmit signals from activated receptors to intracellular target proteins. They help amplify and distribute signalling information within the cell. Major second messengers include:

1. Cyclic Adenosine Monophosphate (cAMP)

cAMP is produced from ATP by the enzyme adenylyl cyclase. It activates protein kinase A (PKA) and regulates several cellular activities.

2. Calcium Ions (Ca^{2+})

Calcium ions act as important intracellular messengers involved in muscle contraction, secretion, enzyme regulation, and other cellular processes.

3. Inositol 1,4,5-Trisphosphate (IP_3)

IP_3 promotes the release of calcium ions from intracellular stores, particularly the endoplasmic reticulum.

4. Diacylglycerol (DAG)

DAG remains associated with the plasma membrane and activates protein kinase C (PKC).

5. Cyclic Guanosine Monophosphate (cGMP)

cGMP functions as a second messenger in pathways involved in smooth muscle relaxation, vision, and other physiological activities.

Signal Amplification

Signal amplification refers to the process in which a single signalling event produces multiple downstream molecular responses.

For example, one activated receptor may activate several intracellular signalling proteins, which subsequently activate numerous target molecules.

This mechanism enables cells to respond effectively even to small concentrations of signalling molecules.

Termination of Cell Signalling

Cell signalling must be properly regulated to prevent continuous or excessive cellular activation.

Signal termination occurs through several mechanisms:

- Removal or degradation of signalling molecules.
- Dissociation of ligands from receptors.
- Receptor internalization or inactivation.
- Breakdown of second messengers.
- Inactivation of signalling proteins.
- Dephosphorylation of target proteins.

For example, cAMP is degraded by phosphodiesterase enzymes, thereby terminating cAMP-mediated signalling.

Clinical Significance of Cell Communication

Abnormalities in cell communication may contribute to several diseases.

Examples include:

- Diabetes mellitus due to impaired insulin signalling or insulin secretion.
- Cancer due to abnormal growth factor signalling.
- Myasthenia gravis due to autoantibodies affecting acetylcholine receptors.

- Certain endocrine disorders due to abnormal hormone receptor function.
- Inflammatory diseases involving dysregulated cytokine signalling.

Therefore, understanding cell communication is important for studying the mechanisms of disease and the pharmacological actions of medicines.

3.2 Forms of Intracellular Signalling

Introduction

Cell signalling occurs through different mechanisms depending on the distance between the signalling cell and the target cell, the nature of the signalling molecule, and the method of signal transmission.

The major forms of cell signalling included in this chapter are:

1. Contact-dependent signalling
2. Paracrine signalling
3. Synaptic signalling
4. Endocrine signalling

These mechanisms enable cells to communicate locally or over long distances and regulate various physiological activities.

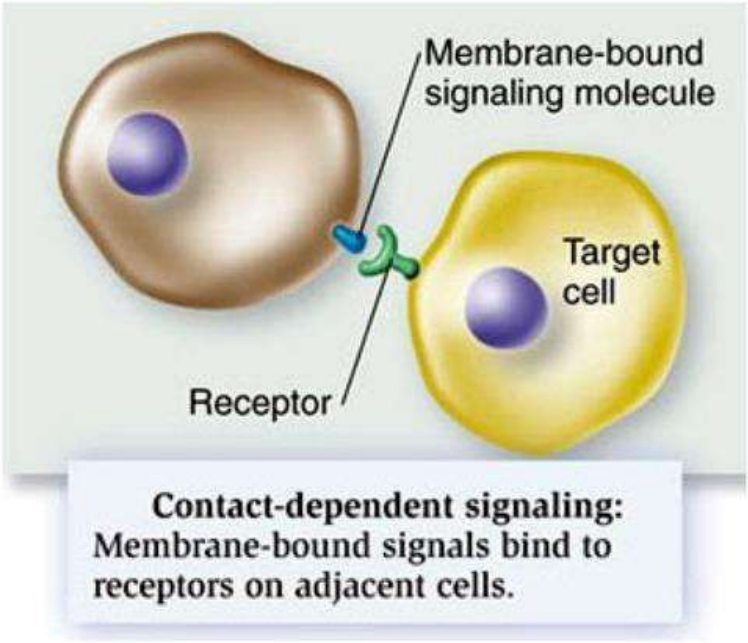
3.2.1 Contact-Dependent Signalling

Definition

Contact-dependent signalling, also known as juxtacrine signalling, is a type of cell communication in which a signalling molecule attached to the surface of one cell interacts directly with a receptor present on the adjacent target cell.

In this mechanism, physical contact between the signalling cell and target cell is necessary for signal transmission. The signalling molecule is not released into the extracellular fluid for long-distance transport.

Mechanism of Contact-Dependent Signalling



The mechanism involves the following steps:

Step 1: Presence of Membrane-Bound Ligand

The signalling cell expresses a specific signalling molecule on its plasma membrane.

Step 2: Contact Between Adjacent Cells

The signalling cell comes into direct physical contact with the target cell.

Step 3: Ligand-Receptor Interaction

The membrane-bound ligand binds to a specific receptor present on the surface of the adjacent target cell.

Step 4: Signal Transmission

Receptor activation initiates intracellular signalling pathways within the target cell.

Step 5: Cellular Response

The target cell produces an appropriate response, such as differentiation, proliferation, or changes in gene expression.

Example: Notch Signalling

Notch signalling is a well-known example of contact-dependent communication.

In this pathway, a membrane-bound ligand, such as Delta or Jagged, present on one cell binds to the Notch receptor on an adjacent cell.

This interaction causes cleavage of the Notch receptor and release of its intracellular domain. The released domain enters the nucleus and regulates gene expression.

Notch signalling plays an important role in:

- Cell differentiation.
- Tissue development.
- Stem cell regulation.
- Formation of different cell types during embryonic development.

Other Examples

- Interaction between immune cells through membrane-bound molecules.
- Communication between developing embryonic cells.
- Cell adhesion-mediated signalling.

Functions of Contact-Dependent Signalling

- Regulates cell differentiation.
- Controls tissue development.
- Maintains cellular organization.
- Participates in immune responses.
- Coordinates the behaviour of neighbouring cells.

Characteristics of Contact-Dependent Signalling

- Requires direct physical contact between cells.
- Uses membrane-bound signalling molecules.
- Does not require release of signalling molecules into circulation.
- Acts over a very short distance.
- Helps regulate tissue formation and cellular specialization.

3.2.2 Paracrine Signalling

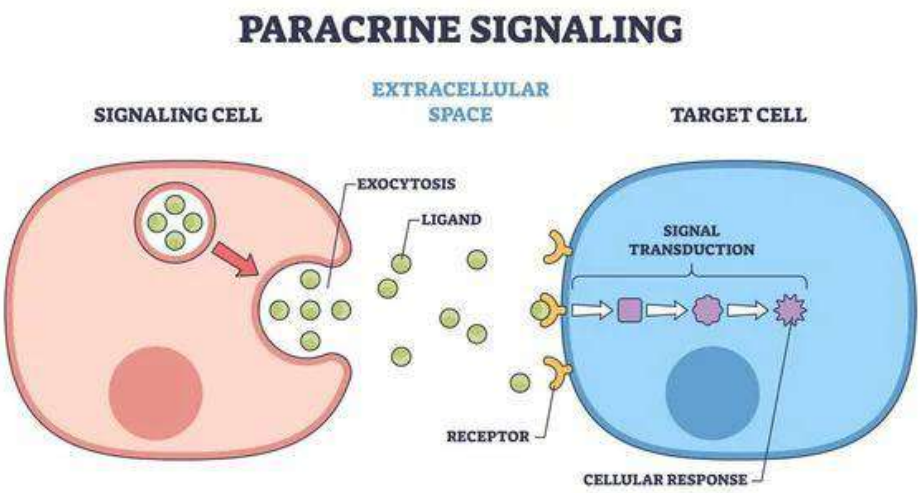
Definition

Paracrine signalling is a form of cell communication in which signalling molecules are released by a cell and act on nearby target cells within the same tissue or surrounding region.

The signalling molecules diffuse through the extracellular fluid and produce local responses without travelling through the bloodstream over long distances.

The cells involved in paracrine signalling are generally located close to each other.

Mechanism of Paracrine Signalling



The mechanism involves the following steps:

Step 1: Signal Production

A signalling cell produces a chemical messenger in response to a specific stimulus.

Step 2: Signal Release

The signalling molecule is released into the extracellular fluid.

Step 3: Local Diffusion

The signalling molecule diffuses through the surrounding tissue toward nearby target cells.

Step 4: Receptor Binding

The signalling molecule binds to specific receptors present on the target cells.

Step 5: Cellular Response

Receptor activation produces a local physiological response in the target cells.

Examples of Paracrine Signalling

1. Nitric Oxide (NO)

Nitric oxide is a gaseous signalling molecule produced by endothelial cells. It diffuses into nearby vascular smooth muscle cells and activates guanylyl cyclase, increasing intracellular cGMP levels.

This results in relaxation of smooth muscle and vasodilation.

2. Histamine

Histamine is released by mast cells during inflammatory and allergic responses. It acts on nearby blood vessels and increases vascular permeability.

3. Prostaglandins

Prostaglandins are locally acting lipid mediators involved in inflammation, pain, vascular regulation, and other physiological processes.

4. Growth Factors

Growth factors released by cells may act on nearby cells to regulate proliferation, differentiation, and tissue repair.

Functions of Paracrine Signalling

- Regulates local tissue responses.
- Participates in inflammation.
- Controls cell growth and differentiation.
- Helps in wound healing and tissue repair.
- Regulates vascular tone.
- Coordinates activities of neighbouring cells.

Characteristics of Paracrine Signalling

- Acts over a short distance.
- Involves locally released chemical messengers.
- Generally does not depend on bloodstream transport.
- Target cells are located near the signalling cells.
- Signalling molecules are often rapidly degraded or removed.

Note: Autocrine signalling is a related form of local communication in which a cell releases a signalling molecule that acts on the same cell or similar neighbouring cells. However, it is distinct from paracrine signalling.

3.2.3 Synaptic Signalling

Definition

Synaptic signalling is a specialized form of cell communication in which neurons transmit information to another neuron, muscle cell, or glandular cell through a specialized junction called a synapse.

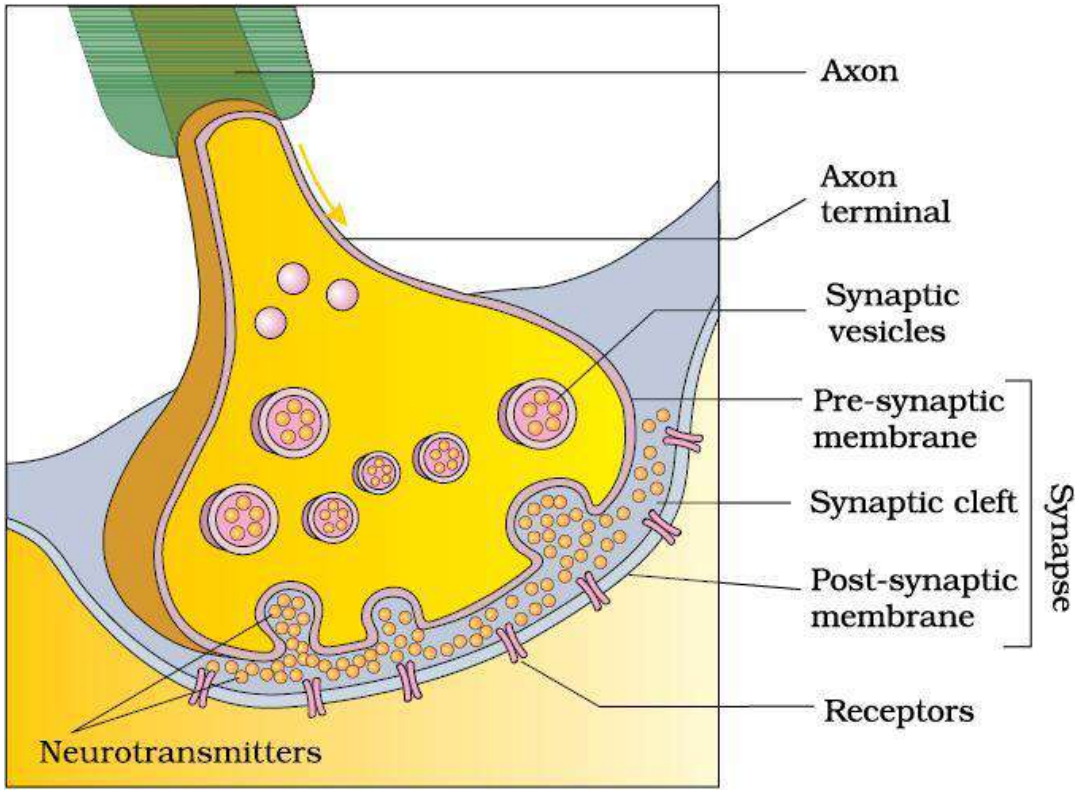
It involves the release of chemical messengers called neurotransmitters from the presynaptic neuron, which bind to receptors on the postsynaptic cell.

Synaptic signalling is essential for nervous system function and enables rapid and specific transmission of information.

Structure of a Chemical Synapse

A chemical synapse consists of three major components:

1. Presynaptic terminal
2. Synaptic cleft
3. Postsynaptic membrane



1. Presynaptic Terminal

The presynaptic terminal is the end portion of the neuron that releases neurotransmitters. It contains synaptic vesicles filled with neurotransmitter molecules.

2. Synaptic Cleft

The synaptic cleft is the narrow extracellular space between the presynaptic and postsynaptic membranes.

3. Postsynaptic Membrane

The postsynaptic membrane contains specific receptors that bind neurotransmitters and initiate responses in the target cell.

Mechanism of Synaptic Signalling

The process of chemical synaptic transmission occurs through the following steps:

Step 1: Arrival of Nerve Impulse

An action potential reaches the presynaptic terminal of the neuron.

Step 2: Opening of Calcium Channels

The arrival of the action potential causes voltage-gated calcium channels to open, allowing calcium ions to enter the presynaptic terminal.

Step 3: Neurotransmitter Release

The increased intracellular calcium concentration triggers synaptic vesicles to fuse with the presynaptic membrane, releasing neurotransmitters into the synaptic cleft through exocytosis.

Step 4: Receptor Binding

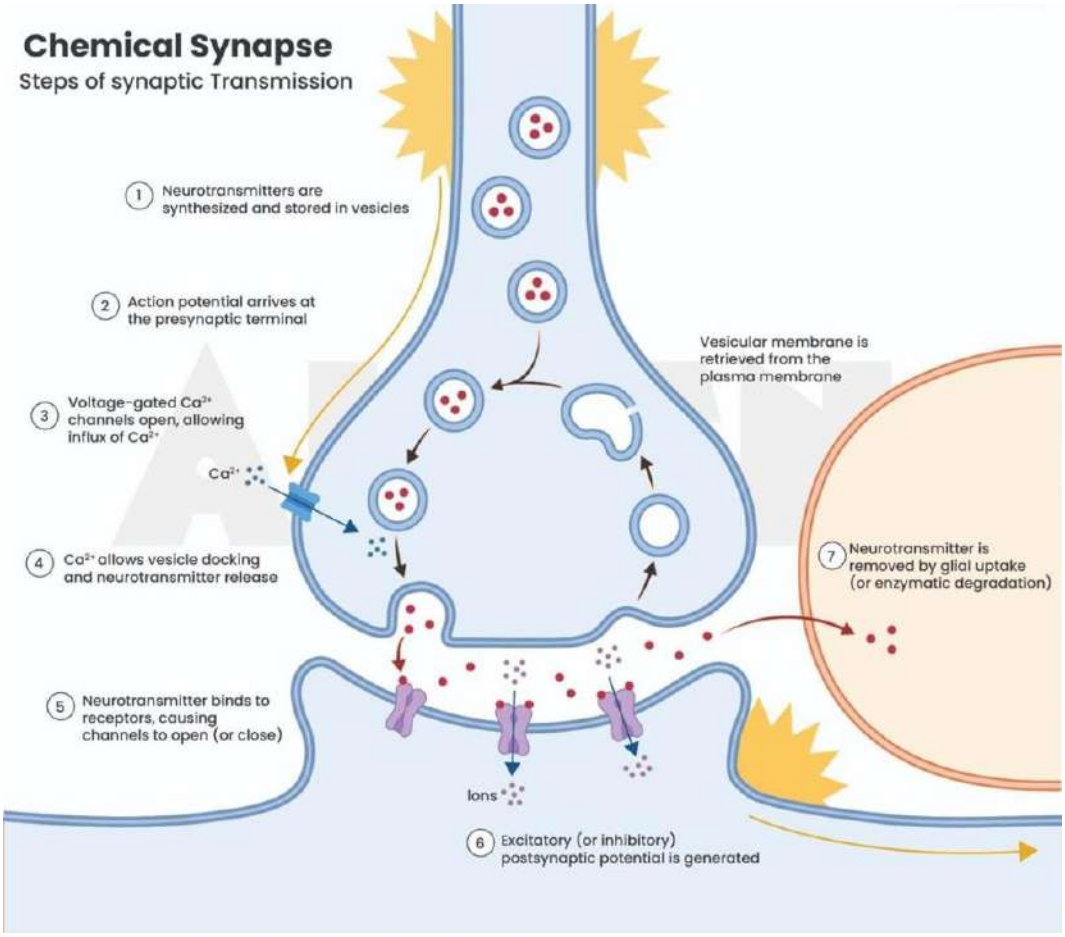
Neurotransmitters diffuse across the synaptic cleft and bind to specific receptors on the postsynaptic membrane.

Step 5: Postsynaptic Response

Receptor activation produces a response in the postsynaptic cell, such as excitation, inhibition, or modulation of cellular activity.

Step 6: Signal Termination

Neurotransmitter action is terminated through enzymatic degradation, reuptake into cells, or diffusion away from the synaptic cleft.



Types of Neurotransmitters

Neurotransmitters are chemical messengers that transmit signals across synapses. Important neurotransmitters include:

Table 3.1: Major Neurotransmitters and Their Principal Functions

Neurotransmitter	Major Functions
Acetylcholine	Muscle contraction, autonomic transmission, and memory-related functions
Dopamine	Regulation of movement, motivation, and reward-related processes
Serotonin	Regulation of mood, sleep, appetite, and other functions
Noradrenaline	Attention, alertness, and sympathetic responses
Gamma-Aminobutyric Acid (GABA)	Major inhibitory neurotransmitter in the central nervous system
Glutamate	Major excitatory neurotransmitter in the central nervous system
Glycine	Inhibitory neurotransmission, particularly in the spinal cord

Types of Synaptic Responses

1. Excitatory Response

An excitatory response increases the likelihood of generating an action potential in the postsynaptic cell.

2. Inhibitory Response

An inhibitory response decreases the likelihood of generating an action potential in the postsynaptic cell.

Functions of Synaptic Signalling

- Transmits information between neurons.
- Regulates muscle contraction.
- Controls glandular secretion.
- Participates in sensory processing.
- Supports learning and memory.
- Regulates autonomic nervous system activities.

Characteristics of Synaptic Signalling

- Involves specialized synaptic connections.
- Uses neurotransmitters for chemical transmission.
- Produces rapid and localized responses.
- Provides precise communication between specific cells.
- Signal transmission is generally unidirectional at chemical synapses.

3.2.4 Endocrine Signalling

Definition

Endocrine signalling is a form of long-distance cell communication in which endocrine cells release hormones into the bloodstream, allowing them to reach and regulate target cells located in distant parts of the body.

Hormones act only on target cells that possess appropriate receptors.

Endocrine signalling is essential for regulating metabolism, growth, development, reproduction, blood glucose concentration, and maintenance of homeostasis.

Mechanism of Endocrine Signalling

The mechanism involves the following steps:

Step 1: Hormone Synthesis

Endocrine cells synthesize hormones in response to physiological or chemical stimuli.

Step 2: Hormone Release

Hormones are secreted into the extracellular fluid and subsequently enter the bloodstream.

Step 3: Transportation Through Blood

The bloodstream transports hormones throughout the body.

Some hormones circulate freely, while others bind to plasma proteins.

Step 4: Target Cell Recognition

Hormones reach target cells containing specific receptors capable of recognizing and binding the hormone.

Step 5: Receptor Activation

Hormone binding activates specific signalling pathways within the target cell.

Step 6: Physiological Response

The target cell produces an appropriate response, such as altered metabolism, gene expression, growth, or secretion.

Chapter 4: Classification and Organization of Tissues

4.1 Classification of Tissues

4.1.1 Introduction

The human body is composed of millions of cells that are organized into tissues, organs, and organ systems. Although cells are the basic structural and functional units of the body, most cells do not function independently. Similar cells, together with their supporting materials, are organized to perform specific functions. Such an organized group of cells is known as a tissue.

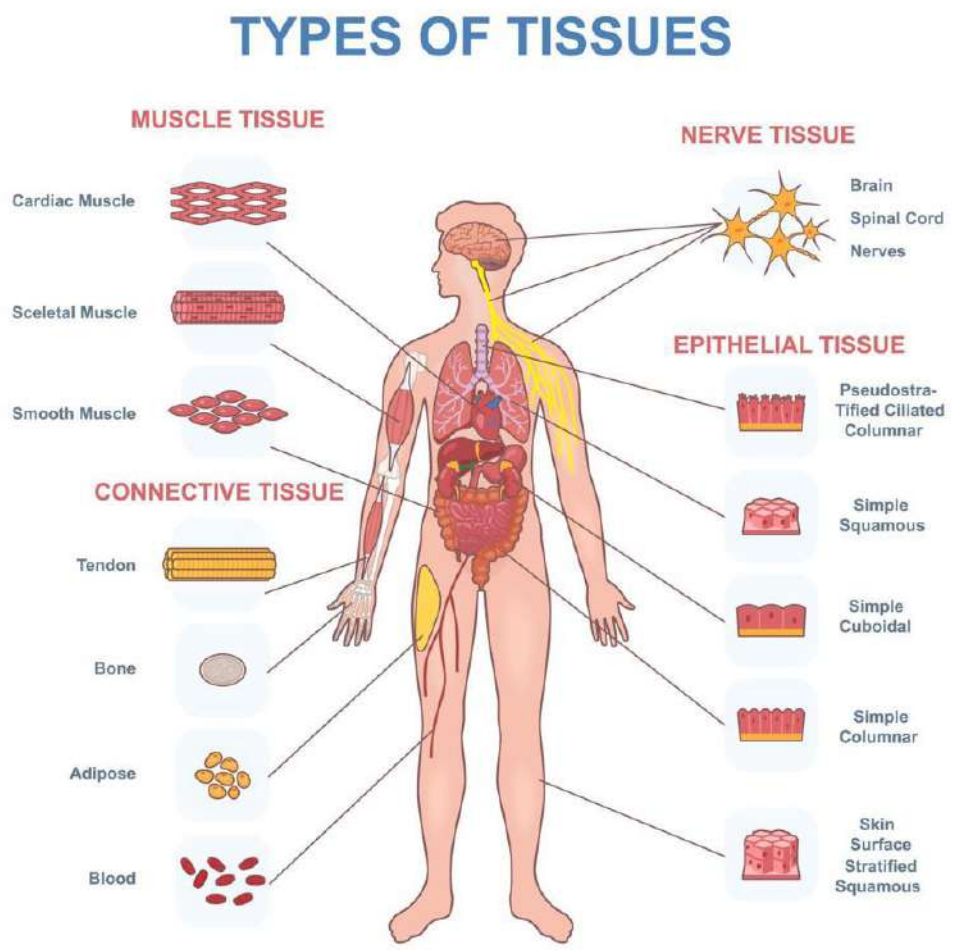
A tissue may contain cells of the same type or different types, along with an extracellular matrix. The extracellular matrix consists of substances present between cells and provides structural support, strength, elasticity, and a suitable environment for cellular activities.

The study of tissues is called histology. Histology helps in understanding the normal microscopic structure of the body and provides a foundation for studying tissue damage, disease processes, and tissue repair.

4.1.2 Classification of Tissues

The human body contains four basic types of tissues:

1. Epithelial tissue
2. Connective tissue
3. Muscular tissue
4. Nervous tissue



Each tissue type has a characteristic structure and performs specific functions. These tissues are present in different proportions in various organs and work together to maintain normal body functions.

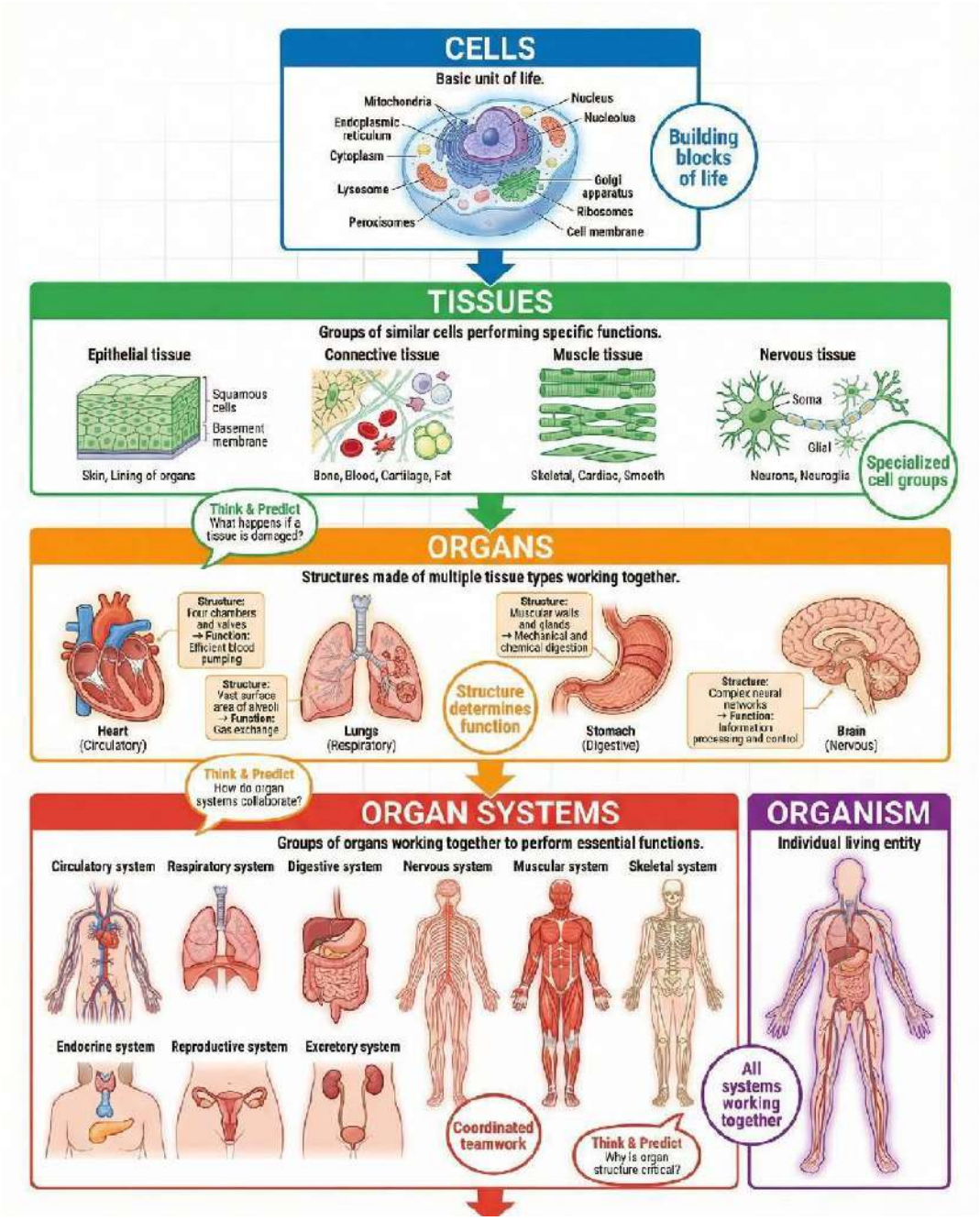
Table 4.1: Classification of the Four Basic Tissues

Tissue type	General characteristics	Major functions
Epithelial tissue	Closely packed cells with very little intercellular material	Protection, absorption, secretion, filtration and sensation
Connective tissue	Cells separated by an abundant extracellular matrix	Support, binding, protection, storage and transport
Muscular tissue	Elongated contractile cells or fibres	Movement, posture and production of heat
Nervous tissue	Neurons and supporting neuroglial cells	Reception, processing and transmission of nerve impulses

4.1.3 Organization of Tissues

Tissues combine to form organs, and organs work together as organ systems. For example, the stomach contains epithelial tissue that lines its inner surface, connective tissue that supports its structure, smooth muscle that produces contractions, and nervous tissue that regulates its activity.

Thus, the four basic tissues are not isolated structures. Their coordinated activities enable organs to perform complex physiological functions.



4.2 Epithelial Tissue: Structure, Location and Functions

4.2.1 Definition

Epithelial tissue is a tissue composed of closely arranged cells that cover the external surfaces of the body, line internal cavities and organs, and form glands. The cells are arranged in continuous sheets and are separated by very little intercellular material.

Epithelial tissue forms protective coverings and selectively regulates the movement of substances into and out of the body and its organs.

4.2.2 General Characteristics of Epithelial Tissue

Epithelial tissue has the following characteristic features:

1. Closely packed cells: The cells are arranged close to one another, leaving very little space between adjacent cells.
2. Polarity: Epithelial cells generally have an apical surface, a lateral surface, and a basal surface. The apical surface faces an external environment, body cavity, or lumen, whereas the basal surface rests on the basement membrane.
3. Basement membrane: Epithelial tissue is supported by a thin extracellular layer called the basement membrane, which separates it from the underlying connective tissue.
4. Avascular nature: Epithelial tissue does not contain blood vessels. Nutrients and oxygen reach epithelial cells by diffusion from blood vessels in the underlying connective tissue.
5. Innervation: Many epithelial tissues are supplied by sensory nerve endings.
6. Cell junctions: Adjacent epithelial cells are connected by specialized junctions that provide attachment, sealing, and communication.
7. Regeneration: Most epithelial tissues have a considerable capacity for renewal and repair because their cells divide regularly.

4.2.3 Classification of Epithelial Tissue

Epithelial tissue is classified mainly according to the number of cell layers and the shape of the cells.

A. Classification Based on Number of Layers

1. Simple epithelium

Simple epithelium consists of a single layer of cells. All cells rest on the basement membrane. It is generally associated with absorption, secretion, diffusion, and filtration.

2. Stratified epithelium

Stratified epithelium consists of two or more layers of cells. Only the deepest layer rests on the basement membrane. Its major function is protection against mechanical stress and injury.

3. Pseudostratified epithelium

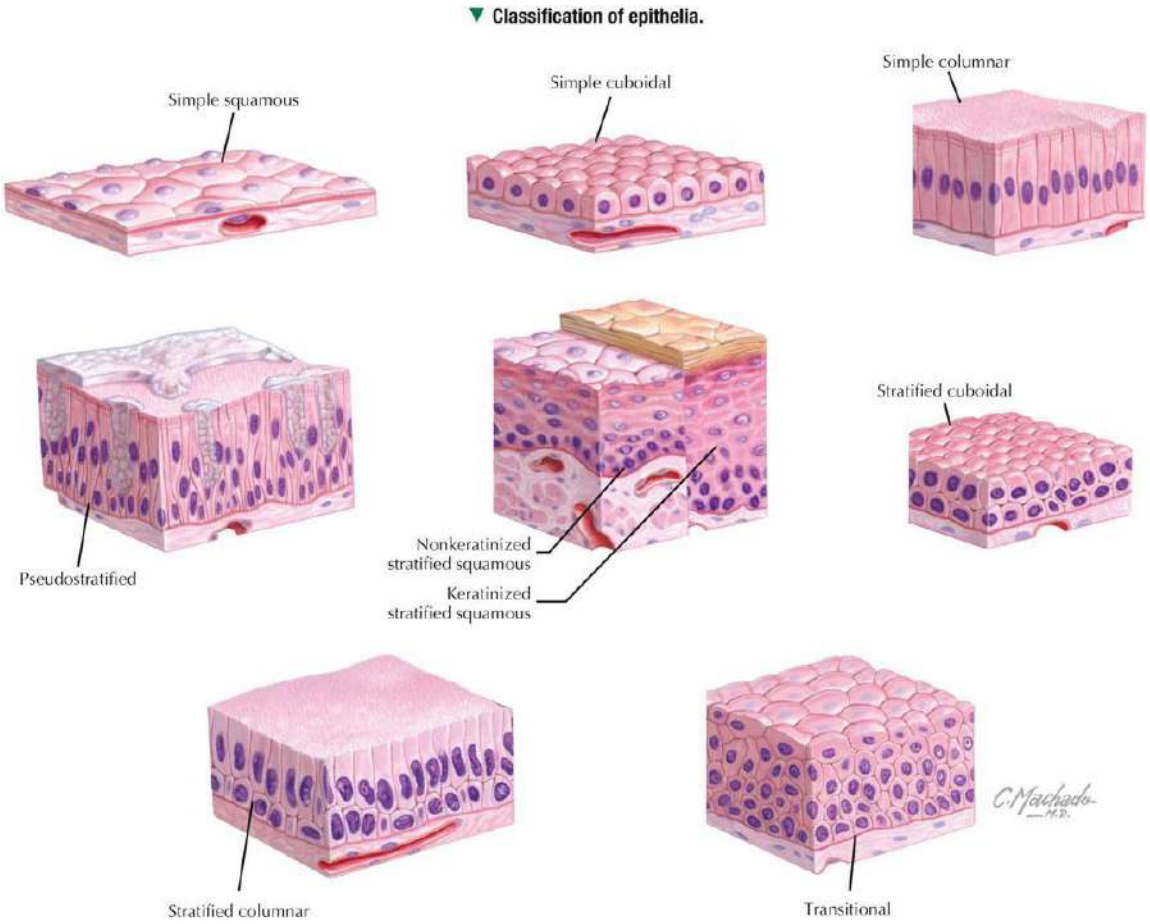
Pseudostratified epithelium appears to have multiple layers because the nuclei are located at different levels. However, all cells are in contact with the basement membrane. It is commonly found in parts of the respiratory tract.

4. Transitional epithelium

Transitional epithelium is a specialized stratified epithelium that can stretch and change its shape. It is present in parts of the urinary system, particularly the urinary bladder.

B. Classification Based on Cell Shape

- Squamous cells: Thin, flat cells with flattened nuclei.
- Cuboidal cells: Cube-shaped cells with centrally located, rounded nuclei.
- Columnar cells: Tall, column-shaped cells with oval nuclei, usually near the basal region.



4.2.4 Types of Epithelial Tissue: Structure, Location and Functions

1. Simple Squamous Epithelium

Structure: It consists of a single layer of thin, flat cells. The cells have flattened nuclei and are arranged closely together, forming a delicate lining.

Location:

- Alveoli of the lungs
- Inner lining of blood vessels and lymphatic vessels, called endothelium
- Serous membranes, called mesothelium
- Bowman's capsule of the kidney

Functions:

- Allows rapid diffusion of gases.

- Facilitates filtration in the kidneys.
- Provides a smooth surface that reduces friction.
- Permits exchange of substances between blood and surrounding tissues.

2. Simple Cuboidal Epithelium

Structure: It consists of a single layer of cube-shaped cells with centrally located, rounded nuclei.

Location:

- Kidney tubules
- Small ducts of glands
- Surface of the ovary
- Thyroid follicles

Functions:

- Absorption and secretion.
- Formation of glandular secretions.
- Transport and modification of substances in kidney tubules.

3. Simple Columnar Epithelium

Structure: It consists of a single layer of tall, column-shaped cells. The nuclei are generally oval and located near the basal surface. Some cells contain microvilli or cilia, and goblet cells may be present.

Location:

- Inner lining of the stomach and intestines
- Gallbladder
- Parts of the female reproductive tract, where ciliated cells are present

Functions:

- Absorption of nutrients.
- Secretion of mucus and digestive substances.
- Movement of materials by ciliary action in ciliated regions.

4. Pseudostratified Columnar Epithelium

Structure: It consists of a single layer of cells of different heights. The nuclei occur at different levels, creating the appearance of several layers. In the respiratory tract, it is commonly ciliated and contains mucus-secreting goblet cells.

Location:

- Nasal cavity
- Trachea

- Larger bronchi
- Parts of the male reproductive tract, where non-ciliated forms occur

Functions:

- Secretion of mucus.
- Trapping of dust and microorganisms.
- Movement of mucus towards the pharynx by ciliary action.
- Protection of respiratory passages.

5. Stratified Squamous Epithelium

Structure: It consists of several layers of cells. The basal cells are usually cuboidal or columnar, while the surface cells are flattened. It occurs in two forms:

- Keratinized stratified squamous epithelium: The surface cells contain keratin and are generally dead.
- Non-keratinized stratified squamous epithelium: The surface cells remain alive and moist.

Location:

- Keratinized: Epidermis of the skin
- Non-keratinized: Mouth, oesophagus, vagina and anal canal

Functions:

- Protects underlying tissues from abrasion.
- Provides resistance to mechanical injury.
- Keratinized epithelium reduces water loss and provides a protective barrier.
- Non-keratinized epithelium protects moist internal surfaces.

6. Stratified Cuboidal and Stratified Columnar Epithelium

Structure: Stratified cuboidal epithelium usually consists of two or more layers of cuboidal cells. Stratified columnar epithelium has columnar cells at the surface with underlying supporting layers.

Location:

- Stratified cuboidal: Ducts of sweat glands and some larger glandular ducts
- Stratified columnar: Parts of the male urethra and large ducts of certain glands

Functions:

- Provides protection to ducts.
- Contributes to secretion in selected glandular regions.

7. Transitional Epithelium

Structure: It is a specialized stratified epithelium. Its surface cells are large and dome-shaped when the organ is relaxed. When the organ stretches, the cells become flatter and the epithelial lining becomes thinner.

Location:

- Urinary bladder
- Ureters
- Renal pelvis
- Part of the urethra

Functions:

- Allows stretching and expansion of urinary organs.
- Forms a protective barrier against urine.
- Prevents urine from passing into underlying tissues.

Table 4.2: Summary of Epithelial Tissue

Type	Main structural feature	Common location	Major function
Simple squamous	One layer of flat cells	Alveoli, blood vessels	Diffusion and filtration
Simple cuboidal	One layer of cube-shaped cells	Kidney tubules, glands	Absorption and secretion
Simple columnar	One layer of tall cells	Stomach, intestine	Absorption and secretion
Pseudostratified columnar	One layer appearing multilayered	Trachea, bronchi	Mucus secretion and movement
Stratified squamous	Multiple layers; surface cells flat	Skin, mouth, oesophagus	Protection
Stratified cuboidal	Multiple layers of cuboidal cells	Sweat gland ducts	Protection
Stratified columnar	Multiple layers with columnar surface cells	Large glandular ducts, urethra	Protection and secretion
Transitional	Stretchable stratified cells	Urinary bladder, ureters	Stretching and barrier function

4.2.5 Glandular Epithelium

Glandular epithelium is specialized epithelial tissue adapted for secretion. It forms glands that produce substances such as mucus, enzymes, sweat, sebum, and hormones.

Glands are classified into two major types:

1. Exocrine glands

Exocrine glands release their secretions through ducts onto an epithelial surface or into the lumen of an organ.

Examples:

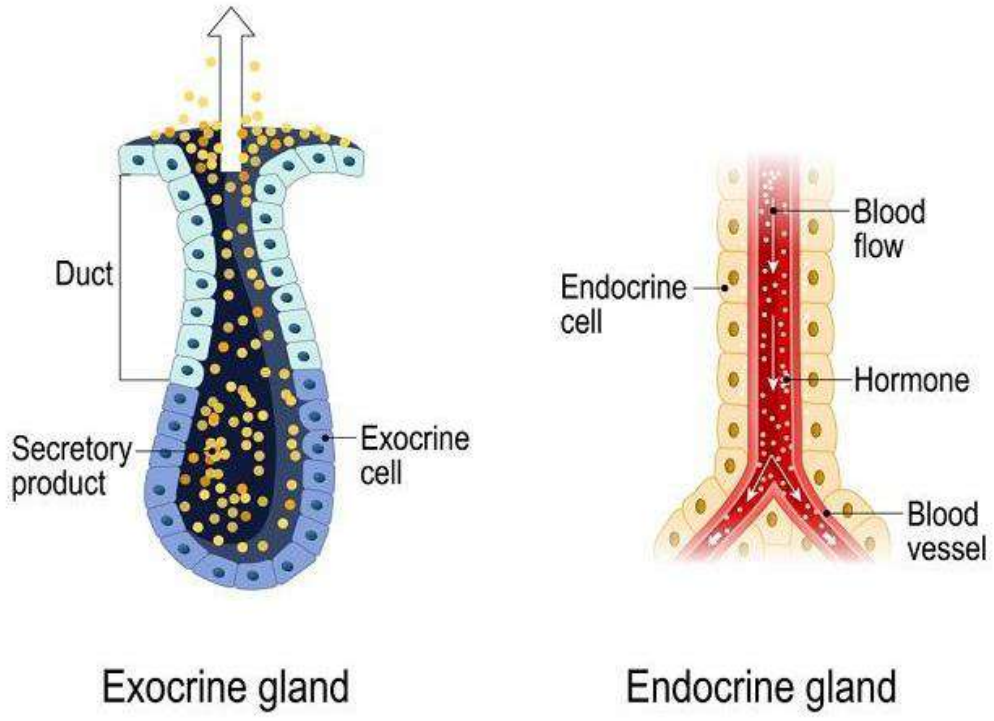
- Sweat glands
- Salivary glands
- Sebaceous glands
- Exocrine pancreas

2. Endocrine glands

Endocrine glands are ductless glands. They release hormones into the surrounding tissue fluid, from where the hormones enter the bloodstream.

Examples:

- Thyroid gland
- Pituitary gland
- Adrenal glands
- Endocrine portion of the pancreas



4.2.6 General Functions of Epithelial Tissue

The major functions of epithelial tissue include:

1. Protection: It protects underlying tissues from physical injury, microorganisms, chemicals, and water loss.
2. Absorption: It absorbs nutrients, water, and other substances, particularly in the digestive tract.
3. Secretion: It produces and releases mucus, enzymes, hormones, and other substances.
4. Excretion: It contributes to the removal of certain waste products, particularly through kidney tubules.
5. Filtration: It participates in filtration processes, such as those occurring in the kidney.
6. Diffusion: It permits the exchange of gases and dissolved substances across thin epithelial surfaces.
7. Sensation: Specialized epithelial cells and associated sensory nerve endings contribute to the detection of environmental stimuli.

4.2.7 Clinical Significance of Epithelial Tissue

Epithelial tissues form important protective barriers. Damage to the skin epithelium may increase the risk of infection and fluid loss. Injury to respiratory epithelium may impair mucociliary clearance, allowing particles and microorganisms to remain in the airways. Abnormal proliferation of epithelial cells may contribute to the development of epithelial cancers, including carcinomas.

4.3 Connective Tissue: Structure, Location and Functions

4.3.1 Definition

Connective tissue is a tissue that connects, supports, binds, protects, and separates different structures of the body. It is characterized by cells distributed within an extracellular matrix, which may contain fibres and ground substance.

Unlike epithelial tissue, connective tissue generally contains more extracellular material than cells. The nature and quantity of the matrix vary according to the type and function of the tissue.

4.3.2 General Characteristics of Connective Tissue

The major characteristics of connective tissue are:

1. Cellular diversity: It contains different types of cells, including fibroblasts, adipocytes, macrophages, mast cells, and other specialized cells.
2. Abundant extracellular matrix: The matrix provides support and determines the mechanical properties of the tissue.
3. Fibres: The matrix may contain collagen, elastic, and reticular fibres.
4. Variable vascularity: Most connective tissues have blood vessels, but some, such as cartilage, are avascular.
5. Protective and supportive role: It provides structural support and helps protect organs.
6. Repair capacity: Many connective tissues participate in wound healing and tissue repair.

4.3.3 Components of Connective Tissue

Connective tissue consists of cells and an extracellular matrix.

A. Cells

1. Fibroblasts: Fibroblasts are the principal cells of many connective tissues. They produce collagen, elastic fibres, reticular fibres, and ground substance.

2. Adipocytes: Adipocytes are fat-storing cells. They store energy in the form of triglycerides and provide insulation and cushioning.

3. Macrophages: Macrophages are phagocytic cells that engulf microorganisms, cellular debris, and foreign particles. They contribute to immune defence.

4. Mast cells: Mast cells contain granules with substances such as histamine. They participate in inflammatory and allergic responses.

5. Plasma cells: Plasma cells are derived from B lymphocytes and produce antibodies.

6. Leukocytes: White blood cells may migrate into connective tissue, particularly during inflammation and immune responses.

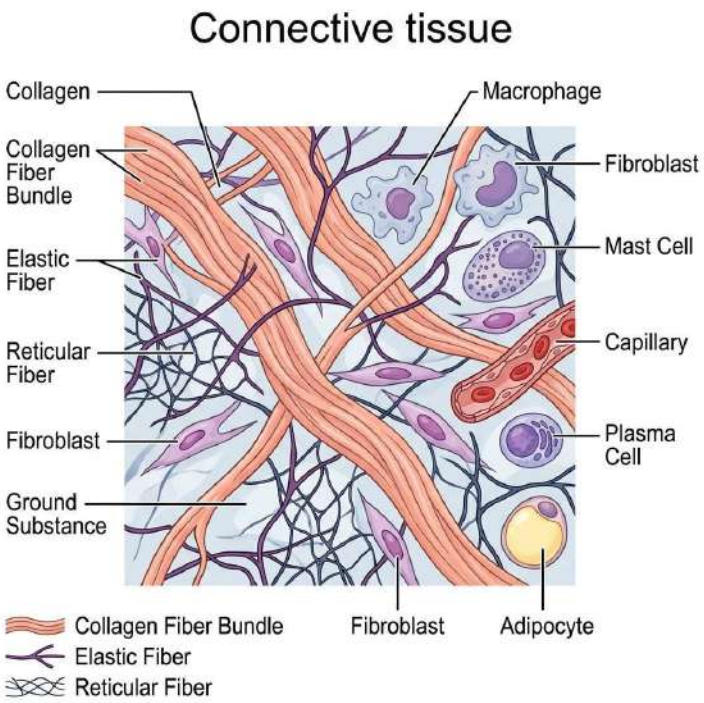
B. Extracellular Matrix

The extracellular matrix consists of ground substance and fibres.

1. Ground substance: Ground substance is a hydrated material that fills the spaces between cells and fibres. It contains water, glycosaminoglycans, proteoglycans, and adhesive glycoproteins. It supports diffusion of nutrients and waste products.

2. Fibres: The major types of connective tissue fibres are:

- Collagen fibres: Provide tensile strength and resist stretching.
- Elastic fibres: Allow tissues to stretch and return to their original shape.
- Reticular fibres: Form delicate supporting networks around cells and small blood vessels.



4.3.4 Classification of Connective Tissue

Connective tissue is broadly classified into:

1. Embryonic connective tissue
2. Connective tissue proper
3. Supporting connective tissue
4. Fluid connective tissue

4.3.5 Types of Connective Tissue: Structure, Location and Functions

A. Embryonic Connective Tissue

Embryonic connective tissue is present mainly during development.

1. Mesenchyme

Structure: It consists of loosely arranged, undifferentiated cells within a soft ground substance.

Location: It is found in the developing embryo.

Functions:

- Gives rise to various connective tissues.
- Contributes to the development of blood vessels, cartilage, bone, and other tissues.

2. Mucous Connective Tissue

Structure: It contains widely spaced cells embedded in a jelly-like ground substance.

Location: It is found mainly in Wharton's jelly of the umbilical cord.

Functions:

- Provides cushioning and support to umbilical blood vessels.
- Helps prevent compression of the vessels.

B. Connective Tissue Proper

Connective tissue proper is divided into loose and dense connective tissue.

1. Loose Connective Tissue

Loose connective tissue contains relatively fewer fibres, abundant ground substance, and several types of cells. It provides flexible support and allows the exchange of substances.

a. Areolar connective tissue

Structure: It contains loosely arranged collagen and elastic fibres, fibroblasts, macrophages, mast cells, and other cells.

Location:

- Beneath epithelial tissues
- Around blood vessels and nerves
- Between organs
- In the subcutaneous region

Functions:

- Binds skin to underlying structures.
- Supports blood vessels and nerves.
- Holds tissue fluid.
- Participates in inflammation and tissue repair.

b. Adipose connective tissue

Structure: It is composed mainly of adipocytes containing large lipid droplets. The nucleus is usually pushed towards the periphery in white adipose tissue.

Location:

- Beneath the skin
- Around kidneys and other organs
- In the abdominal cavity
- In the breasts

Functions:

- Stores energy in the form of fat.
- Provides thermal insulation.
- Cushions and protects organs.
- Produces signalling substances involved in energy regulation.

c. Reticular connective tissue

Structure: It contains a network of reticular fibres and supporting cells.

Location:

- Lymph nodes
- Spleen
- Bone marrow

Functions:

- Forms a supporting framework for blood-forming and immune cells.
- Provides structural support to lymphoid organs.

2. Dense Connective Tissue

Dense connective tissue contains abundant fibres, particularly collagen, and relatively fewer cells and less ground substance.

a. Dense regular connective tissue

Structure: It contains parallel bundles of collagen fibres with fibroblasts arranged between them.

Location:

- Tendons
- Most ligaments
- Aponeuroses

Functions:

- Attaches muscles to bones through tendons.
- Connects bones to bones through ligaments.
- Resists pulling forces mainly in one direction.

b. Dense irregular connective tissue

Structure: It contains thick collagen fibres arranged in different directions.

Location:

- Dermis of the skin
- Fibrous capsules surrounding organs
- Submucosa of certain organs

Functions:

- Provides strength in multiple directions.
- Resists mechanical stress.
- Protects and supports organs.

c. Elastic connective tissue

Structure: It contains abundant elastic fibres arranged in bundles or networks.

Location:

- Walls of large arteries
- Certain ligaments
- Elastic ligaments of the vertebral column

Functions:

- Allows stretching and recoil.
- Maintains elasticity in structures exposed to repeated expansion.

C. Supporting Connective Tissue

Supporting connective tissue includes cartilage and bone.

1. Cartilage

Cartilage is a firm but flexible connective tissue. Its cells, called chondrocytes, are present in spaces known as lacunae and are surrounded by an extracellular matrix. Cartilage does not contain blood vessels; nutrients reach its cells by diffusion.

Types of cartilage

a. Hyaline cartilage

Structure: It has a smooth, glassy-looking matrix containing fine collagen fibres that are not easily visible under a light microscope.

Location:

- Articular surfaces of bones
- Costal cartilages
- Nose
- Trachea and bronchi

- Growing regions of long bones

Functions:

- Provides smooth surfaces for joint movement.
- Supports respiratory passages.
- Provides flexible support.
- Contributes to bone growth during development.

b. Elastic cartilage

Structure: It contains abundant elastic fibres in its matrix, making it flexible.

Location:

- External ear
- Epiglottis
- Auditory tube

Functions:

- Maintains shape while allowing flexibility.
- Supports structures that require repeated bending.

c. Fibrocartilage

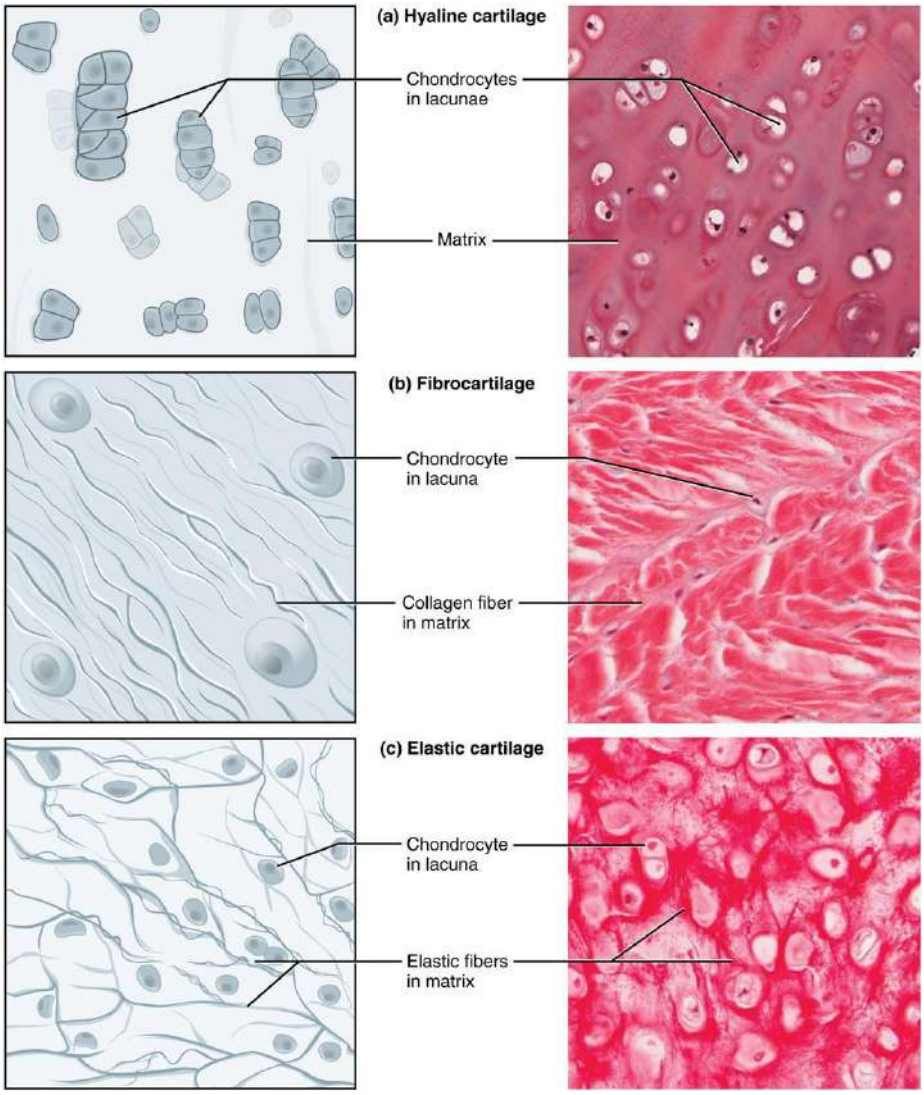
Structure: It contains thick bundles of collagen fibres and relatively fewer chondrocytes.

Location:

- Intervertebral discs
- Pubic symphysis
- Menisci of the knee

Functions:

- Resists compression and tensile forces.
- Acts as a shock absorber.
- Provides strong support at sites exposed to mechanical stress.



2. Bone

Bone is a hard, mineralized connective tissue that forms the skeleton. Its matrix contains collagen fibres and mineral salts, mainly calcium phosphate. Bone cells include osteoblasts, osteocytes, and osteoclasts.

Types of bone tissue

a. Compact bone

Structure: It is dense and organized into structural units called osteons or Haversian systems. Each osteon contains concentric lamellae around a central canal.

Location: It forms the outer layer of most bones and the shaft of long bones.

Functions:

- Provides strength and support.
- Protects internal structures.

- Resists mechanical stress.

b. Spongy bone

Structure: It consists of a network of bony trabeculae with spaces that commonly contain bone marrow.

Location:

- Ends of long bones
- Interior of flat bones
- Vertebrae and other irregular bones

Functions:

- Reduces the weight of the skeleton.
- Provides structural support.
- Contains spaces for bone marrow.

Functions of bone tissue:

- Supports the body.
- Protects organs.
- Provides attachment sites for muscles.
- Stores minerals, particularly calcium and phosphate.
- Houses bone marrow, where blood cell formation occurs.

D. Fluid Connective Tissue

Fluid connective tissue has a liquid extracellular matrix and is involved in transport and defence.

1. Blood

Structure: Blood consists of a fluid matrix called plasma and formed elements, including red blood cells, white blood cells, and platelets.

Location: It circulates through the heart and blood vessels.

Functions:

- Transports oxygen, carbon dioxide, nutrients, hormones, and waste products.
- Helps regulate body temperature and pH.
- Provides defence against infection.
- Participates in blood clotting.

2. Lymph

Structure: Lymph is a clear fluid derived from interstitial fluid. It contains water, dissolved substances, and white blood cells, particularly lymphocytes.

Location: It circulates through lymphatic vessels and lymphoid structures.

Functions:

- Returns excess tissue fluid to the bloodstream.
- Transports absorbed fats from the intestine.
- Supports immune surveillance and defence.

Table 4.3: Summary of Connective Tissue

Type	Structure	Common location	Major function
Areolar	Loose fibres and various cells	Beneath epithelia, around vessels	Binding and support
Adipose	Closely packed adipocytes	Beneath skin, around organs	Energy storage and insulation
Reticular	Network of reticular fibres	Lymph nodes, spleen, bone marrow	Supporting framework
Dense regular	Parallel collagen bundles	Tendons and ligaments	Strong attachment
Dense irregular	Irregular collagen bundles	Dermis, organ capsules	Strength in multiple directions
Elastic	Abundant elastic fibres	Large arteries, elastic ligaments	Stretch and recoil
Hyaline cartilage	Smooth, firm matrix	Trachea, joints, nose	Support and smooth movement
Elastic cartilage	Matrix rich in elastic fibres	External ear, epiglottis	Flexible support
Fibrocartilage	Thick collagen bundles	Intervertebral discs, menisci	Shock absorption
Compact bone	Dense mineralized matrix	Outer bone layer	Strength and protection
Spongy bone	Trabecular network	Bone interiors	Support and marrow housing
Blood	Plasma and formed elements	Blood vessels	Transport and defence
Lymph	Fluid matrix with lymphocytes	Lymphatic vessels	Fluid return and immunity

4.3.6 General Functions of Connective Tissue

Connective tissue performs several important functions:

1. Binding: Connects tissues and organs, such as tendons connecting muscles to bones.
2. Support: Provides structural support to organs and the body.
3. Protection: Cushions organs and protects them from mechanical injury.
4. Storage: Stores energy in adipose tissue and minerals in bone.
5. Transport: Blood transports gases, nutrients, hormones, and waste products.
6. Defence: Macrophages, mast cells, and other immune cells contribute to protection against infection.
7. Repair: Fibroblasts and other cells participate in wound healing and tissue repair.
8. Insulation: Adipose tissue reduces heat loss from the body.

4.3.7 Clinical Significance of Connective Tissue

Connective tissue abnormalities may affect the strength, elasticity, support, or transport functions of the body. For example, disorders affecting collagen may weaken connective tissues, while cartilage degeneration may contribute to joint pain and reduced movement. Abnormal bone remodelling can reduce bone strength and increase fracture risk. Inflammation of connective tissue may also occur in several systemic disorders.

4.4 Muscular Tissue: Structure, Location and Functions

4.4.1 Definition

Muscular tissue is a specialized tissue composed of elongated cells capable of contraction. Its main function is to generate force and produce movement. Muscular tissue also helps maintain posture, move substances through internal organs, and generate body heat.

The ability of muscular tissue to contract depends on specialized proteins, mainly actin and myosin, which interact to produce shortening or tension.

4.4.2 General Characteristics of Muscular Tissue

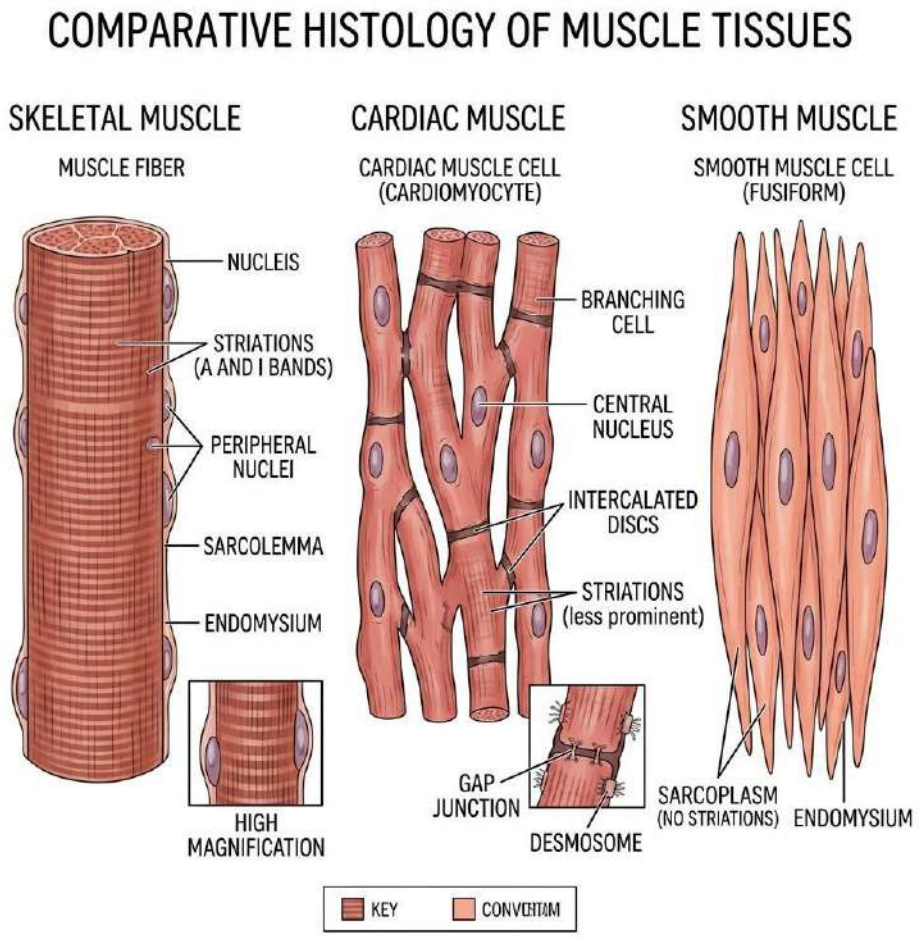
Muscular tissue has the following characteristic properties:

1. Excitability: Ability to respond to stimuli.
2. Contractility: Ability to develop tension or shorten.
3. Extensibility: Ability to be stretched without damage under normal conditions.
4. Elasticity: Ability to return towards its original shape after stretching or contraction.
5. Specialized contractile proteins: Actin and myosin are responsible for force generation.
6. High energy requirement: Muscle cells require ATP to support contraction and relaxation.

4.4.3 Classification of Muscular Tissue

Muscular tissue is classified into three types:

1. Skeletal muscle
2. Cardiac muscle
3. Smooth muscle



4.4.4 Types of Muscular Tissue: Structure, Location and Functions

1. Skeletal Muscle

Structure: Skeletal muscle consists of long, cylindrical, unbranched fibres. Each fibre is multinucleated, with nuclei usually located near the periphery. The fibres show alternating light and dark bands, giving them a striated appearance.

Skeletal muscles are generally attached to bones by tendons. Their contraction is usually under voluntary control through the somatic nervous system.

Location:

- Muscles attached to the skeleton
- Muscles of the face
- Diaphragm
- Certain muscles associated with the tongue and upper oesophagus

Functions:

- Produces voluntary body movements.

- Maintains posture and body position.
- Stabilizes joints.
- Generates heat during contraction.
- Supports breathing through contraction of respiratory muscles.

2. Cardiac Muscle

Structure: Cardiac muscle consists of short, branched cells with one, or occasionally two, centrally located nuclei. The cells are striated and connected by specialized structures called intercalated discs. These discs contain junctions that provide mechanical attachment and electrical communication between adjacent cells.

Cardiac muscle is involuntary and contracts rhythmically under the influence of intrinsic pacemaker activity and autonomic regulation.

Location: It is found in the myocardium, the muscular wall of the heart.

Functions:

- Produces rhythmic contractions of the heart.
- Pumps blood into pulmonary and systemic circulation.
- Maintains continuous blood circulation.
- Responds to electrical signals coordinated through the cardiac conduction system.

3. Smooth Muscle

Structure: Smooth muscle consists of spindle-shaped cells with a single, centrally located nucleus. The cells do not show visible striations because their contractile proteins are not arranged into sarcomeres in the same way as skeletal and cardiac muscle.

Smooth muscle is involuntary and is commonly regulated by the autonomic nervous system, hormones, local chemical factors, and stretch.

Location:

- Walls of the stomach and intestines
- Walls of blood vessels
- Urinary bladder
- Ureters
- Uterus
- Respiratory passages
- Iris and ciliary body of the eye

Functions:

- Moves food through the digestive tract by peristalsis.
- Regulates the diameter of blood vessels.
- Controls the movement of urine.

- Produces uterine contractions.
- Regulates the diameter of airways.
- Controls certain movements within the eye.

Table 4.4: Comparison of the Three Types of Muscular Tissue

Feature	Skeletal muscle	Cardiac muscle	Smooth muscle
Cell shape	Long and cylindrical	Short and branched	Spindle-shaped
Striations	Present	Present	Absent
Number of nuclei	Multiple	Usually one; sometimes two	One
Nuclear position	Peripheral	Central	Central
Control	Usually voluntary	Involuntary	Involuntary
Location	Attached to bones and selected structures	Heart wall	Walls of hollow organs and vessels
Intercalated discs	Absent	Present	Absent
Contraction	Generally rapid and forceful	Rhythmic and continuous	Usually slow and sustained
Major function	Body movement and posture	Pumping blood	Movement of substances and regulation of organ diameter

4.5 Nervous Tissue: Structure, Location and Functions

4.5.1 Definition

Nervous tissue is a specialized tissue responsible for receiving stimuli, processing information, and transmitting electrical and chemical signals throughout the body. It forms the structural basis of the nervous system and enables rapid communication between different body regions.

Nervous tissue consists mainly of two types of cells:

1. Neurons
2. Neuroglial cells, or glia

4.5.2 General Characteristics of Nervous Tissue

The main characteristics of nervous tissue are:

- It is specialized for communication and coordination.
- It responds to internal and external stimuli.
- It generates and conducts electrical signals.
- It communicates with other neurons, muscles, and glands.
- It contains neurons supported by neuroglial cells.
- It has a high metabolic requirement and depends on a continuous supply of oxygen and nutrients.

4.5.3 Structure of a Neuron

A neuron is the structural and functional unit of nervous tissue. It is specialized to receive, integrate, and transmit information.

A typical neuron consists of three main parts:

1. Cell Body (Soma)

The cell body contains the nucleus and most of the cytoplasm. It also contains organelles such as mitochondria, Golgi apparatus, and rough endoplasmic reticulum. The rough endoplasmic reticulum and ribosomes form structures called Nissl bodies, which are involved in protein synthesis.

Functions:

- Maintains the metabolic activities of the neuron.
- Synthesizes proteins and other cellular components.
- Integrates incoming signals.

2. Dendrites

Dendrites are short, branched extensions arising from the cell body. They receive signals from other neurons or sensory receptors and conduct them towards the cell body.

Functions:

- Receive incoming information.
- Increase the surface area available for communication.
- Conduct signals towards the cell body.

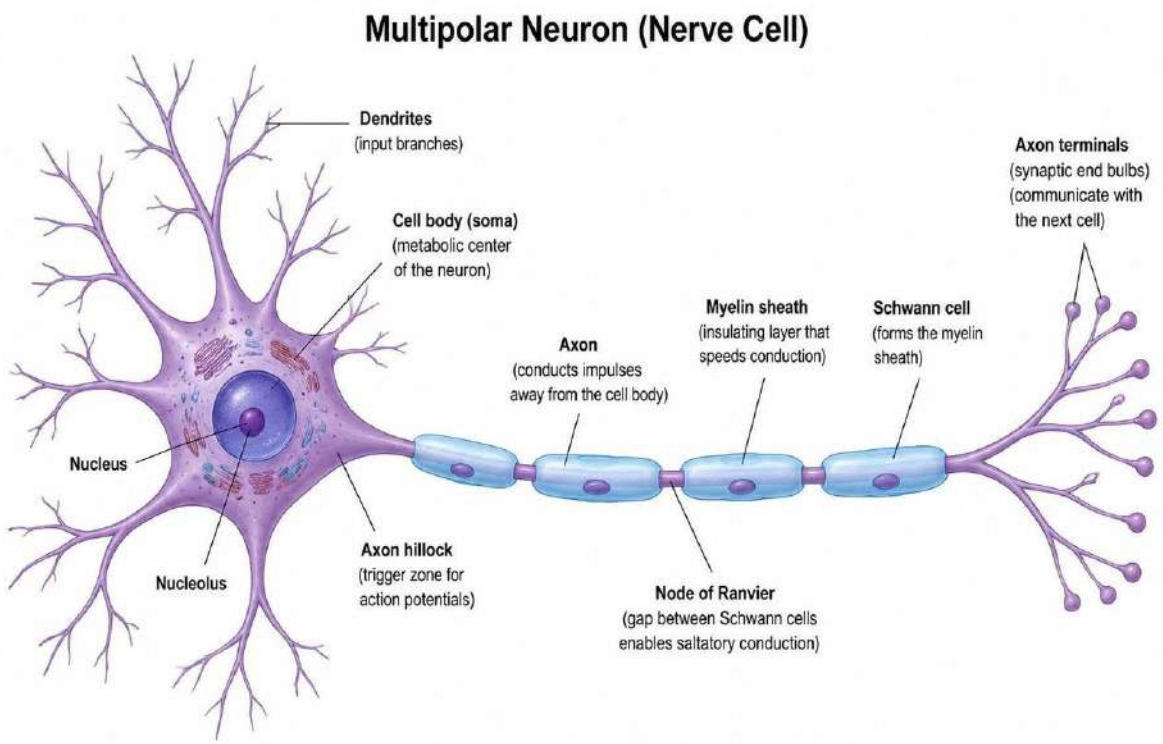
3. Axon

The axon is a single, usually long process that carries nerve impulses away from the cell body. Some axons are covered by a myelin sheath, which is a lipid-rich insulating layer formed by supporting cells.

The gaps between adjacent myelin segments are called nodes of Ranvier. In myelinated axons, nerve impulses can travel by saltatory conduction, in which the impulse appears to jump from one node to another.

Functions:

- Conducts impulses away from the cell body.
- Transmits information to other neurons, muscles, or glands.
- May be covered by myelin to increase the speed of impulse conduction.



4.5.4 Types of Neurons

Neurons may be classified according to their structure or function.

A. Structural Classification

1. Multipolar neurons

These neurons have one axon and multiple dendrites. They are the most common type of neuron and are found in the brain and spinal cord.

2. Bipolar neurons

These neurons have one axon and one dendrite. They occur in specialized sensory structures, such as the retina and olfactory epithelium.

3. Unipolar or pseudounipolar neurons

These neurons have a single process that divides into two branches. They are commonly associated with sensory pathways and are found in sensory ganglia.

B. Functional Classification

1. Sensory neurons (afferent neurons)

Sensory neurons carry information from receptors towards the central nervous system.

2. Motor neurons (efferent neurons)

Motor neurons transmit signals from the central nervous system to effectors such as muscles and glands.

3. Interneurons

Interneurons connect neurons within the central nervous system and participate in the processing and integration of information.

Table 4.5: Classification of Neurons

Classification	Type	Main characteristic or function
Structural	Multipolar	One axon and multiple dendrites
Structural	Bipolar	One axon and one dendrite
Structural	Pseudounipolar	One process that divides into two branches
Functional	Sensory	Carries information towards the CNS
Functional	Motor	Carries commands from the CNS to effectors
Functional	Interneuron	Connects and integrates neurons within the CNS

4.5.5 Neuroglial Cells

Neuroglial cells, also called glial cells, are supporting cells of nervous tissue. They do not generally transmit nerve impulses in the same way as neurons, but they are essential for neuronal survival, protection, nutrition, and normal functioning.

A. Neuroglial Cells of the Central Nervous System

1. Astrocytes

Astrocytes are star-shaped glial cells found in the brain and spinal cord.

Functions:

- Provide structural and metabolic support to neurons.
- Regulate the extracellular chemical environment.
- Participate in the maintenance of the blood–brain barrier.
- Contribute to repair responses after injury.

2. Oligodendrocytes

Oligodendrocytes form the myelin sheath around axons in the central nervous system.

Functions:

- Insulate axons.
- Increase the speed of nerve impulse conduction.
- Support axonal function.

3. Microglia

Microglia are small immune-related cells of the central nervous system.

Functions:

- Engulf cellular debris and microorganisms.
- Participate in immune surveillance.
- Respond to injury and inflammation.

4. Ependymal Cells

Ependymal cells line the ventricles of the brain and the central canal of the spinal cord.

Functions:

- Form a lining for fluid-filled spaces.
- Participate in the movement and regulation of cerebrospinal fluid.
- Contribute to the function of the choroid plexus.

B. Neuroglial Cells of the Peripheral Nervous System

1. Schwann Cells

Schwann cells form the myelin sheath around axons in the peripheral nervous system. A single Schwann cell forms one segment of myelin around an axon.

Functions:

- Provide insulation to peripheral axons.
- Support rapid nerve impulse conduction.
- Assist in the repair and regeneration of peripheral nerve fibres.

2. Satellite Cells

Satellite cells surround the cell bodies of neurons in peripheral ganglia.

Functions:

- Provide structural and metabolic support.
- Regulate the chemical environment around neuronal cell bodies.
- Help maintain the microenvironment of ganglia.

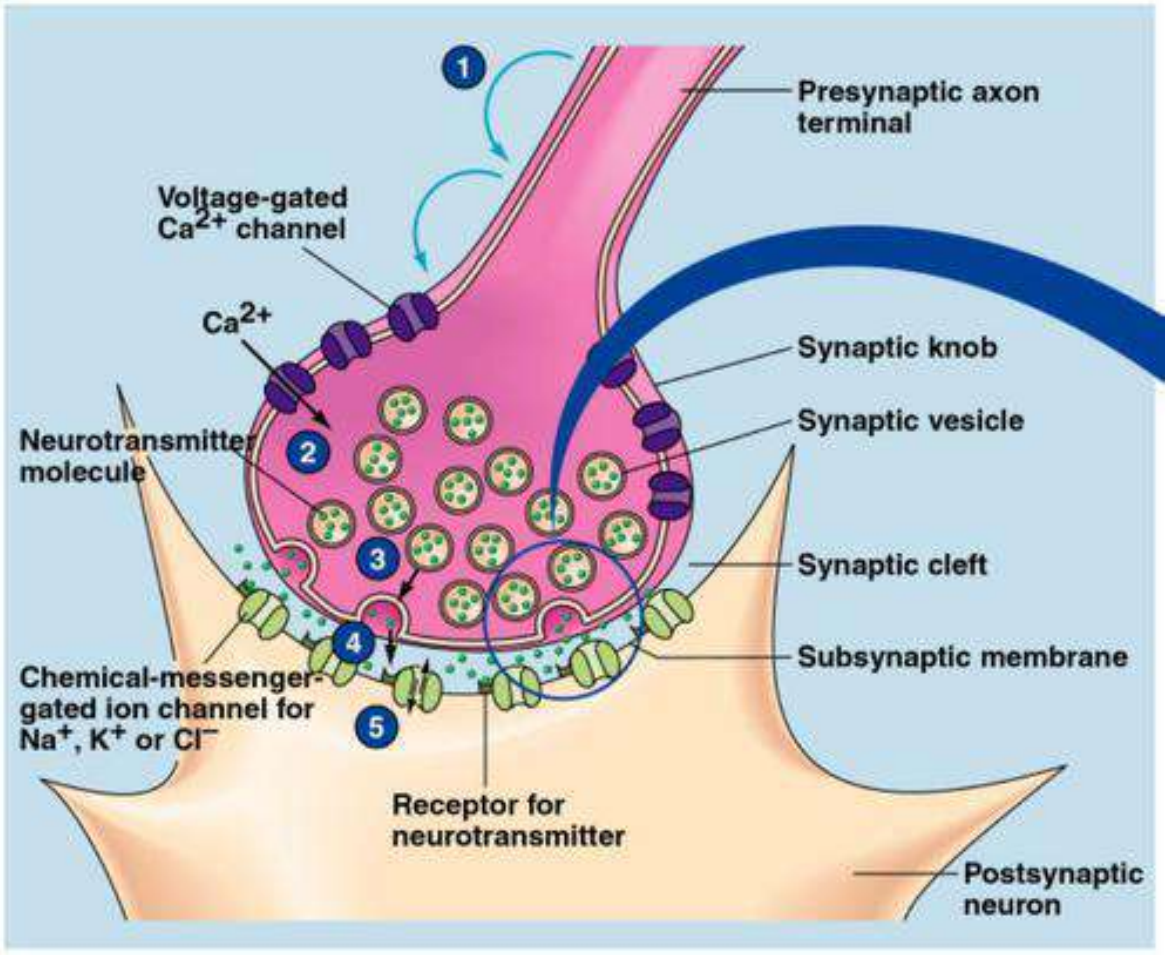
4.5.6 Synapse and Communication Between Neurons

A synapse is a specialized junction through which a neuron communicates with another neuron or with an effector cell, such as a muscle or gland cell.

A typical chemical synapse consists of:

1. Presynaptic terminal: The end of the transmitting neuron containing synaptic vesicles.
2. Synaptic cleft: The narrow space between the two communicating cells.
3. Postsynaptic membrane: The membrane of the receiving cell containing receptors for neurotransmitters.

When an action potential reaches the presynaptic terminal, calcium channels open and calcium enters the terminal. This promotes the release of neurotransmitters into the synaptic cleft. The neurotransmitters bind to receptors on the postsynaptic membrane and produce a response.



4.5.7 Location of Nervous Tissue

Nervous tissue is present in:

- Brain
- Spinal cord
- Cranial nerves
- Spinal nerves
- Peripheral ganglia
- Sensory organs and sensory pathways

The brain and spinal cord form the central nervous system, while nerves and ganglia outside the brain and spinal cord form the peripheral nervous system.

4.5.8 Functions of Nervous Tissue

The major functions of nervous tissue include:

1. Reception of stimuli: Detects changes in the internal and external environment through sensory receptors.
2. Transmission of impulses: Conducts electrical signals from one region of the body to another.
3. Integration: Processes and interprets incoming information.
4. Coordination: Coordinates activities of different organs and organ systems.
5. Control of muscles: Regulates voluntary and involuntary muscle activities.
6. Regulation of glands: Controls secretion from various glands.
7. Maintenance of homeostasis: Participates in the regulation of body temperature, blood pressure, respiration, and other physiological functions.
8. Higher functions: Supports memory, learning, language, emotion, and cognition.

4.5.9 Clinical Significance of Nervous Tissue

Nervous tissue is essential for sensory perception, movement, coordination, and regulation of organ functions. Damage to neurons may result in loss of sensation, weakness, paralysis, or impaired coordination, depending on the affected region. Disorders involving myelin can interfere with nerve impulse conduction. Injury to peripheral nerves may affect the function of the muscles or sensory regions supplied by those nerves.

The human body is composed of four basic types of tissues: epithelial, connective, muscular, and nervous tissue. These tissues differ in their cellular arrangement, extracellular matrix, structural organization, and functions.

Epithelial tissue covers body surfaces, lines cavities, and forms glands. It performs protection, absorption, secretion, filtration, and diffusion. Connective tissue supports, binds, protects, stores, transports, and repairs body structures. It includes connective tissue proper, cartilage, bone, blood, and lymph. Muscular tissue is specialized for contraction and is classified into skeletal, cardiac, and smooth muscle. It produces body movement, maintains posture, pumps blood, and moves substances through internal organs. Nervous tissue consists of neurons and neuroglial cells and is responsible for receiving, processing, and transmitting information.

The coordinated activities of these four tissue types form the structural and functional basis of organs and organ systems.

Chapter 5: Basic Principles of Cell Injury and Adaptation

5.1 Basic Principles of Cell Injury and Adaptation

5.1.1 Introduction

Cells are the basic structural and functional units of the human body. Under normal conditions, cells maintain a stable internal environment and perform specialized activities required for the survival of tissues and organs. However, cells are continuously exposed to changes in their external and internal environments, including variations in oxygen supply, nutrient availability, temperature, chemical exposure, and physical stress.

When cells encounter mild or short-term stress, they may adapt by changing their structure, metabolism, or function. These adaptive responses help cells maintain viability and continue functioning. When the stress is excessive, prolonged, or beyond the adaptive capacity of the cell, cellular injury occurs.

Cell injury refers to a series of biochemical and structural changes that develop when cells are exposed to harmful stimuli or conditions. Cellular injury may be reversible or irreversible, depending on the severity and duration of the insult and the type of cell involved.

5.1.2 Cellular Adaptation

Cellular adaptation is a reversible change in the size, number, phenotype, metabolic activity, or function of cells in response to physiological or pathological stimuli. Adaptation enables cells to survive under altered conditions.

For example, skeletal muscle cells may increase in size in response to increased workload, while cells of the uterus increase in size and number during pregnancy under hormonal stimulation.

The major forms of cellular adaptation include:

- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia
- Dysplasia

These adaptive changes are discussed in detail in Chapter 6.

5.1.3 Cell Injury

Cell injury develops when a cell is unable to maintain normal homeostasis in response to a harmful stimulus. The injury may affect cellular membranes, mitochondria, ribosomes, the nucleus, and other organelles.

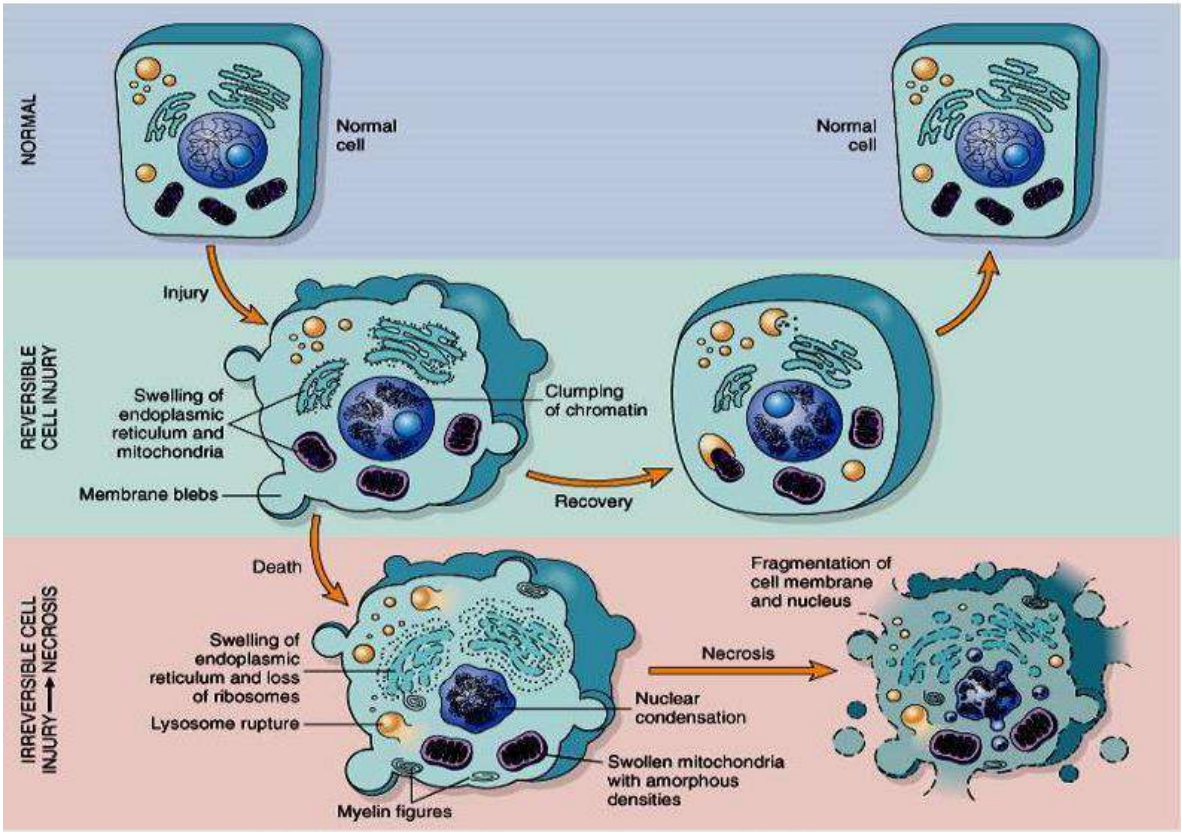
Cell injury is broadly classified into two types:

1. Reversible cell injury

Reversible injury refers to cellular damage from which the cell can recover when the harmful stimulus is removed. It is generally associated with cellular swelling, fatty change in certain organs, and temporary disturbances in cellular function.

2. Irreversible cell injury

Irreversible injury occurs when cellular damage becomes sufficiently severe that recovery is no longer possible. It commonly involves severe membrane damage, mitochondrial dysfunction, and irreversible nuclear changes, ultimately leading to cell death.



5.1.4 Factors Determining the Outcome of Cell Injury

The response of a cell to injury depends on several factors:

1. Nature of the harmful stimulus: Different agents produce different patterns of cellular damage.
2. Duration of exposure: Prolonged exposure generally increases the severity of injury.
3. Intensity of the stimulus: Severe insults may rapidly cause irreversible injury.
4. Type of cell: Different cells vary in their metabolic requirements, antioxidant capacity, and ability to regenerate.
5. Physiological condition of the cell: Nutritional status, age, and pre-existing disease may influence cellular resistance.

6. Availability of oxygen and nutrients: Cells with high energy requirements are particularly vulnerable to reduced oxygen supply.
7. Genetic factors: Genetic differences may influence cellular responses to stress and toxic substances.

5.1.5 Relationship Between Adaptation, Injury and Cell Death

Cellular adaptation, cell injury, and cell death are related processes. When a cell encounters stress, it may first adapt to maintain its function. If the stress continues or exceeds the capacity for adaptation, injury develops. Mild injury may be reversible, whereas severe or persistent injury may become irreversible and result in cell death.

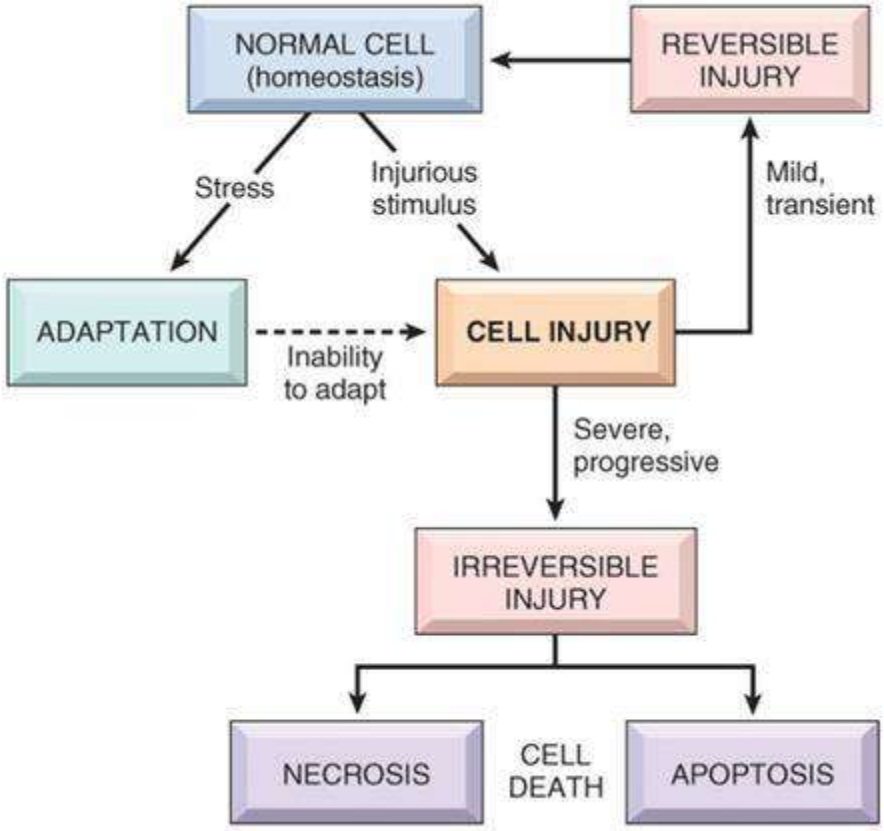


Table 5.1: Comparison of Cellular Adaptation and Cell Injury

Feature	Cellular adaptation	Cell injury
Meaning	Reversible response to altered conditions	Damage caused by harmful stimuli
Cellular viability	Generally maintained	May be maintained or lost
Structural changes	Usually controlled and stimulus-related	May include swelling, membrane damage, and organelle changes
Functional effect	Helps cells maintain survival	May impair normal cellular functions
Outcome	May return to normal after removal of	May recover or progress to cell

	stimulus	death

5.2 Components and Types of Feedback Systems

5.2.1 Introduction

The human body maintains a relatively stable internal environment through regulatory mechanisms. These mechanisms detect changes, process information, and produce responses that help regulate physiological variables such as body temperature, blood glucose, blood pressure, and blood calcium levels.

A feedback system is a regulatory mechanism in which the output or response of a system influences its own activity. Feedback systems are important for maintaining homeostasis and coordinating physiological processes.

5.2.2 Components of a Feedback System

A typical feedback system consists of the following components:

1. Stimulus

A stimulus is a change in a regulated condition that moves a physiological variable away from its normal range. For example, an increase in body temperature acts as a stimulus for thermoregulatory responses.

2. Receptor or Sensor

The receptor detects the change in the regulated variable and sends information to the control centre.

3. Afferent Pathway

The afferent pathway carries information from the receptor to the control centre. It may involve sensory nerves or chemical signals.

4. Control Centre or Integrator

The control centre receives and processes information, compares the detected value with the desired range, and determines an appropriate response.

5. Efferent Pathway

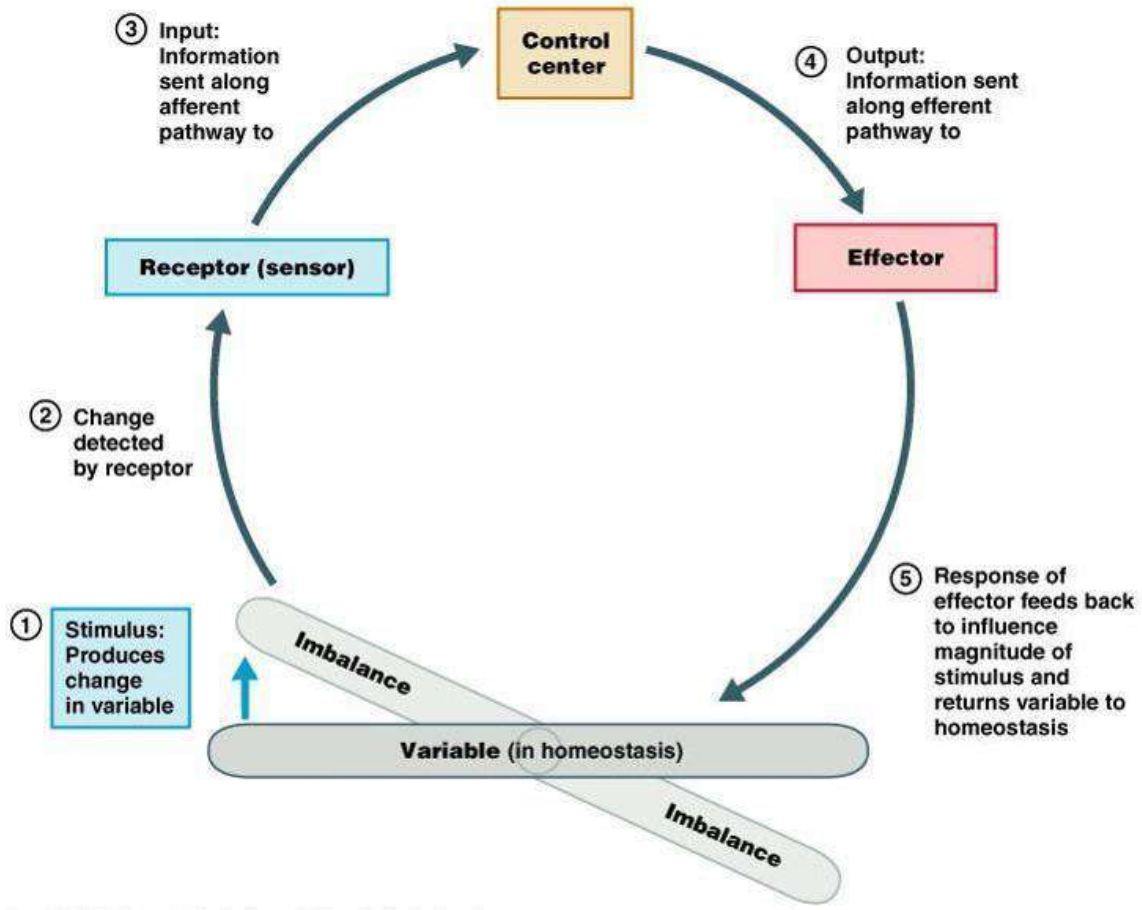
The efferent pathway carries instructions from the control centre to the effector.

6. Effector

The effector is a cell, tissue, or organ that produces the response. Examples include muscles and glands.

7. Response

The response changes the regulated variable and may reduce or increase the original stimulus, depending on the type of feedback mechanism.



5.2.3 Types of Feedback Systems

Feedback systems are commonly classified into negative feedback and positive feedback.

A. Negative Feedback

Negative feedback is a regulatory mechanism in which the response opposes or reduces the initial change in a physiological variable. It is the most common type of feedback system involved in maintaining homeostasis.

Mechanism:

1. A physiological variable changes from its normal range.
2. Receptors detect the change.
3. Information is transmitted to the control centre.
4. The control centre activates appropriate effectors.
5. The effectors produce a response that opposes the original change.
6. The variable moves towards its normal range.

Examples:

- Regulation of body temperature
- Regulation of blood glucose
- Regulation of blood pressure
- Regulation of blood calcium

B. Positive Feedback

Positive feedback is a regulatory mechanism in which the response amplifies or increases the initial change. Unlike negative feedback, it does not directly oppose the original stimulus. Positive feedback generally continues until a specific event or endpoint stops the process.

Mechanism:

1. An initial stimulus produces a response.
2. The response increases the original stimulus.
3. The increased stimulus produces a stronger response.
4. The cycle continues until a terminating event occurs.

Examples:

- Uterine contractions during childbirth
- Blood clot formation
- Milk ejection during breastfeeding

Example: Childbirth

During childbirth, stretching of the cervix stimulates sensory receptors. Signals reach the hypothalamus, leading to the release of oxytocin from the posterior pituitary gland. Oxytocin increases uterine contractions, which further stretch the cervix and promote additional oxytocin release. This cycle continues until delivery of the baby removes the initiating stimulus.

Table 5.2: Comparison of Negative and Positive Feedback

Feature	Negative feedback	Positive feedback
Effect on initial stimulus	Opposes or reduces the change	Amplifies or increases the change
Main role	Maintains homeostasis	Drives a process towards a defined endpoint
Frequency	Very common in the body	Less common
Regulation	Stabilizes physiological variables	Produces a self-amplifying response
Examples	Body temperature and blood glucose regulation	Childbirth and blood clotting

5.2.4 Importance of Feedback Systems

Feedback systems are essential for maintaining normal physiological function. They help regulate body temperature, blood glucose, blood pressure, electrolyte concentrations, and hormone levels. Failure of these regulatory mechanisms may contribute to homeostatic imbalance and disease.

5.3 Causes of Cellular Injury

Cellular injury may result from several harmful stimuli. These causes are commonly grouped into physical, chemical, biological, nutritional, immunological, genetic, and oxygen-related factors.

5.3.1 Oxygen Deprivation and Hypoxia

Hypoxia refers to inadequate oxygen availability at the tissue level. It may occur due to reduced blood supply, respiratory disorders, anaemia, or impaired oxygen utilization.

Oxygen is required for mitochondrial oxidative phosphorylation and ATP production. When oxygen availability decreases, ATP production falls, affecting energy-dependent cellular processes such as ion transport and protein synthesis.

Examples:

- Myocardial injury due to reduced coronary blood flow
- Brain injury following interruption of cerebral circulation
- Tissue damage associated with severe respiratory failure

5.3.2 Physical Agents

Physical agents can damage cells directly or interfere with normal tissue function.

Major physical causes include:

- Mechanical trauma, such as cuts, crushing, and fractures
- Excessive heat or cold
- Radiation, including ultraviolet and ionizing radiation
- Electric shock
- Changes in atmospheric pressure

Effects: Physical agents may cause membrane disruption, protein denaturation, DNA damage, burns, and tissue necrosis.

5.3.3 Chemical Agents and Drugs

Many chemicals and drugs can produce cellular injury depending on their dose, duration of exposure, and metabolic effects.

Examples include:

- Strong acids and alkalis
- Heavy metals

- Industrial chemicals
- Pesticides
- Certain solvents
- Drug overdose or toxic drug metabolites

Chemical agents may damage cellular membranes, inhibit enzymes, generate reactive oxygen species, interfere with DNA, or disrupt mitochondrial function.

5.3.4 Infectious Agents

Microorganisms may cause cell injury directly or indirectly through the host immune response.

Examples include:

- Viruses
- Bacteria
- Fungi
- Protozoa
- Parasitic organisms

Infectious agents may enter cells, alter cellular metabolism, produce toxins, or trigger inflammatory responses that damage surrounding tissues.

5.3.5 Immunological Reactions

The immune system protects the body against harmful agents. However, excessive or inappropriate immune responses may injure normal tissues.

Examples include:

- Autoimmune reactions
- Hypersensitivity reactions
- Chronic inflammation
- Immune-mediated tissue damage

In these conditions, antibodies, immune cells, cytokines, and inflammatory mediators may contribute to cellular injury.

5.3.6 Nutritional Imbalances

Both deficiency and excess of nutrients may cause cellular injury.

Nutritional deficiencies:

- Protein deficiency
- Vitamin deficiency
- Mineral deficiency
- Severe calorie deficiency

Nutritional excess:

- Excessive lipid accumulation
- Excessive caloric intake
- Certain vitamin or mineral toxicities

Nutritional imbalance may interfere with energy production, enzyme activity, membrane synthesis, and cellular repair.

5.3.7 Genetic Factors

Genetic abnormalities may cause cellular injury by altering the structure or function of proteins, enzymes, receptors, or other cellular components.

Examples include:

- Inherited enzyme deficiencies
- Abnormal haemoglobin production
- Defects in membrane proteins
- Genetic abnormalities affecting DNA repair

Some genetic disorders produce cellular injury directly, while others increase susceptibility to environmental stress.

5.3.8 Ageing

Ageing is associated with gradual changes in cellular function, including reduced capacity for repair, altered mitochondrial activity, accumulation of damaged molecules, and changes in cellular responses to stress. These changes may increase vulnerability to injury, although ageing itself is not equivalent to a specific cellular injury.

Table 5.3: Major Causes of Cellular Injury

Cause	Examples	Possible cellular effects
Oxygen deprivation	Ischaemia, respiratory failure, anaemia	Reduced ATP production and cellular dysfunction
Physical agents	Trauma, heat, cold, radiation	Membrane, protein, and DNA damage
Chemical agents	Toxins, heavy metals, drug overdose	Enzyme inhibition, oxidative stress, organelle damage
Infectious agents	Viruses, bacteria, fungi	Direct cellular damage and inflammation
Immunological reactions	Autoimmunity, hypersensitivity	Immune-mediated cellular damage
Nutritional imbalance	Deficiency or excess of nutrients	Metabolic disturbance and impaired repair
Genetic factors	Enzyme or protein defects	Abnormal cellular function and increased susceptibility

Ageing	Reduced repair and altered cellular function	Increased vulnerability to cellular stress

5.3.9 Importance of Understanding the Causes of Cell Injury

Knowledge of the causes of cellular injury is important in understanding disease development, identifying risk factors, selecting appropriate preventive measures, and explaining the actions and adverse effects of medicines. It also provides a foundation for studying the cellular mechanisms that lead to tissue damage and cell death.

5.4 Pathogenesis of Cellular Injury

5.4.1 Introduction

The pathogenesis of cellular injury refers to the sequence of biochemical and molecular events through which a harmful stimulus produces cellular dysfunction and structural damage. Although different harmful agents may act through different mechanisms, several common pathways are involved.

Major mechanisms include:

- Depletion of ATP
- Mitochondrial dysfunction
- Increased intracellular calcium
- Formation of reactive oxygen species
- Damage to cellular membranes
- Impaired protein synthesis
- DNA and nuclear damage

These mechanisms often occur together and may reinforce one another.

5.4.2 Major Mechanisms of Cellular Injury

1. ATP Depletion

ATP is the principal energy source for many cellular activities. It is required for ion transport, protein synthesis, membrane maintenance, and other metabolic processes.

A reduction in ATP may occur due to hypoxia, mitochondrial damage, or certain toxic substances.

Consequences of ATP depletion:

- Failure of the sodium-potassium pump
- Accumulation of sodium and water inside cells
- Cellular swelling
- Increased anaerobic glycolysis
- Accumulation of lactic acid
- Decreased intracellular pH

- Reduced protein synthesis

Severe ATP depletion may contribute to irreversible injury.

2. Mitochondrial Dysfunction

Mitochondria produce ATP through oxidative phosphorylation. Damage to mitochondria reduces energy production and may increase the generation of reactive oxygen species. Severe mitochondrial dysfunction may also promote the release of proteins that activate programmed cell death pathways.

3. Increased Intracellular Calcium

Calcium ions act as important intracellular signalling molecules. Under normal conditions, cytoplasmic calcium concentration is maintained at a low level. Cellular injury may cause calcium to enter the cytoplasm from outside the cell or be released from intracellular stores.

Excess intracellular calcium activates enzymes such as phospholipases, proteases, endonucleases, and ATPases. These enzymes may damage membranes, cytoskeletal proteins, DNA, and energy stores.

4. Oxidative Stress

Oxidative stress occurs when the production of reactive oxygen species exceeds the capacity of antioxidant defence systems.

Reactive oxygen species may damage:

- Lipids in cellular membranes
- Proteins and enzymes
- DNA and other nucleic acids

This damage may impair cellular function and contribute to cell death.

5. Membrane Damage

Damage to the plasma membrane and organelle membranes can disturb ionic balance, increase membrane permeability, and impair essential cellular processes. Severe membrane damage may cause leakage of cellular contents and loss of cell viability.

5.4.3 Cell Membrane Damage

The plasma membrane maintains the internal environment of the cell by regulating the movement of ions, nutrients, and waste products. It also contains receptors and proteins involved in cellular communication and transport.

Cell membrane damage is an important mechanism of cellular injury.

Causes of membrane damage:

- Reactive oxygen species and lipid peroxidation
- Increased intracellular calcium and activation of phospholipases
- Mechanical trauma
- Toxic chemicals
- Severe ATP depletion
- Inflammatory mediators

Mechanisms of membrane damage:

1. Lipid peroxidation: Reactive oxygen species attack membrane lipids, reducing membrane integrity and increasing permeability.
2. Phospholipid degradation: Activation of phospholipases promotes the breakdown of membrane phospholipids.
3. Cytoskeletal damage: Injury to proteins supporting the membrane may weaken its structure.
4. Loss of membrane proteins: Damage to membrane transporters and receptors interferes with normal cellular activity.
5. Increased permeability: Loss of membrane integrity allows abnormal movement of ions and water.

Consequences of membrane damage:

- Entry of excessive sodium and water
- Loss of potassium from the cell
- Increased intracellular calcium
- Leakage of enzymes and other cellular components
- Impaired transport and communication
- Loss of cellular integrity in severe injury

Damage to the plasma membrane may be accompanied by damage to lysosomal membranes. Release of lysosomal enzymes into the cytoplasm can contribute to the breakdown of cellular components.

5.4.4 Mitochondrial Damage

Mitochondria are essential organelles responsible for ATP production and regulation of several cellular processes. They are particularly vulnerable to hypoxia, oxidative stress, calcium overload, and certain toxic substances.

Causes of mitochondrial damage:

- Oxygen deprivation
- Reactive oxygen species
- Increased intracellular calcium
- Toxic chemicals
- Severe metabolic disturbances

Mechanisms of mitochondrial damage:

1. Damage to the mitochondrial membrane may interfere with normal ion balance.

2. Disruption of oxidative phosphorylation reduces ATP production.
3. Increased formation of reactive oxygen species may cause further damage.
4. Changes in mitochondrial membrane permeability may lead to the release of pro-apoptotic proteins.
5. Severe mitochondrial dysfunction may activate cell death pathways.

Consequences of mitochondrial damage:

- Reduced ATP production
- Failure of energy-dependent transport systems
- Increased oxidative stress
- Disturbance of cellular metabolism
- Activation of apoptosis under appropriate conditions
- Progression towards irreversible cell injury when damage is severe

5.4.5 Ribosome Damage

Ribosomes are responsible for protein synthesis. They may be present freely in the cytoplasm or attached to the rough endoplasmic reticulum. Cellular injury may interfere with ribosomal structure, function, or attachment to the endoplasmic reticulum.

Causes of ribosomal dysfunction:

- ATP depletion
- Severe hypoxia
- Toxic substances
- Disturbance of cellular metabolism
- Damage to the rough endoplasmic reticulum

Mechanisms and consequences:

1. Damage to ribosomes reduces the synthesis of proteins.
2. Detachment of ribosomes from the rough endoplasmic reticulum may impair protein production.
3. Reduced synthesis of enzymes and structural proteins interferes with cellular maintenance.
4. Impaired production of membrane proteins affects transport and membrane repair.
5. Severe and persistent inhibition of protein synthesis may contribute to cellular dysfunction and death.

Protein synthesis is essential for cell survival, growth, repair, and replacement of damaged components. Therefore, ribosomal dysfunction can significantly affect the ability of cells to recover from injury.

5.4.6 Nuclear Damage

The nucleus contains DNA, which stores the genetic information required for cellular structure, function, growth, and reproduction. Nuclear damage may occur due to radiation, toxic chemicals, oxidative stress, severe metabolic disturbances, and other harmful stimuli.

Mechanisms of nuclear damage:

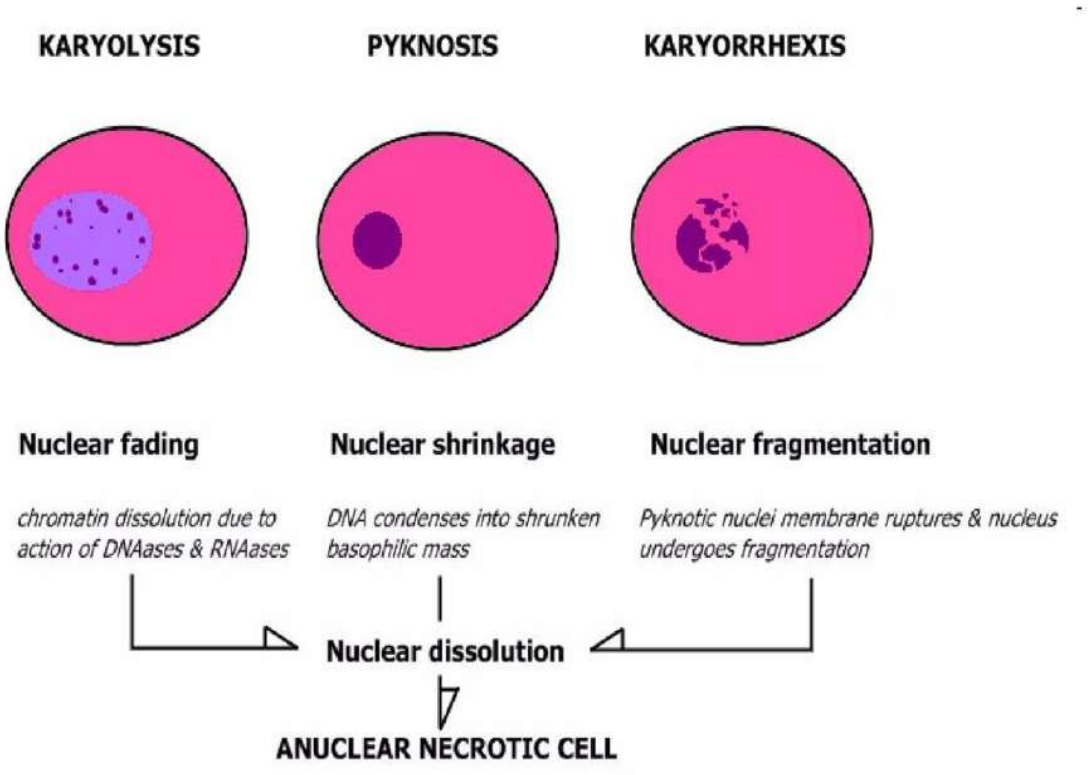
- DNA strand breaks
- DNA oxidation
- Damage to nuclear proteins
- Abnormal chromatin changes
- Disruption of DNA replication and repair
- Activation of cell death pathways

Consequences of nuclear damage:

1. Impaired DNA replication
2. Abnormal gene expression
3. Activation of DNA repair mechanisms
4. Cell cycle arrest
5. Mutations if damaged DNA is not correctly repaired
6. Activation of apoptosis when damage is severe or irreparable

In irreversible cell injury, characteristic nuclear changes may occur. These include:

- Pyknosis: Shrinkage of the nucleus with increased staining intensity due to chromatin condensation.
- Karyorrhexis: Fragmentation of the nucleus.
- Karyolysis: Dissolution or fading of the nucleus due to degradation of nuclear DNA.



5.4.7 Interrelationship of Cellular Injury Mechanisms

Cellular injury mechanisms are closely interconnected. For example, oxygen deprivation reduces ATP production, leading to failure of ion pumps and cellular swelling. It may also cause increased intracellular calcium and mitochondrial dysfunction. These changes can promote oxidative stress and membrane damage. When injury becomes severe, nuclear damage and cell death may follow.

Thus, cellular injury is not usually the result of a single isolated event. It is commonly produced by multiple interacting mechanisms.

Table 5.4: Major Cellular Targets and Consequences of Injury

Cellular target	Major mechanism of damage	Important consequences
Plasma membrane	Lipid peroxidation, phospholipid degradation, cytoskeletal damage	Increased permeability, ion imbalance, leakage of cellular contents
Mitochondria	Impaired oxidative phosphorylation, membrane permeability changes	ATP depletion, oxidative stress, activation of cell death pathways
Ribosomes	Impaired ribosomal function and detachment from rough ER	Reduced protein synthesis
Nucleus	DNA damage, chromatin changes, nuclear degradation	Cell cycle arrest, mutations, apoptosis or necrotic changes
Lysosomes	Membrane damage and enzyme release	Digestion of cellular components
Cytoskeleton	Damage to structural proteins	Loss of cell shape and mechanical stability

5.4.8 Outcome of Cellular Injury

The outcome of cellular injury depends on the severity and duration of the harmful stimulus and the ability of the cell to repair the damage.

- Recovery: If the injury is mild and the harmful stimulus is removed, the cell may return to normal.
- Reversible injury: Cellular function and structure are disturbed, but recovery remains possible.
- Irreversible injury: Severe damage prevents recovery and leads to cell death.
- Cell death: The final outcome may occur through different regulated or unregulated processes, which are discussed in Chapter 6.

Cellular adaptation is a reversible response that enables cells to survive altered conditions. When stress exceeds the adaptive capacity of a cell, cellular injury occurs. Depending on the severity and duration of the insult, injury may be reversible or irreversible. Feedback systems help maintain homeostasis through coordinated interactions among receptors, control centres, and effectors. Negative feedback opposes the initial change, whereas positive feedback amplifies it until a specific endpoint is reached.

Major causes of cellular injury include oxygen deprivation, physical agents, chemicals, infectious organisms, immunological reactions, nutritional imbalances, genetic abnormalities, and ageing. The principal mechanisms of cellular injury involve ATP depletion, mitochondrial dysfunction, increased intracellular calcium, oxidative stress, and damage to cellular structures. Injury to the plasma membrane, mitochondria, ribosomes, and nucleus may impair essential cellular activities and ultimately lead to cell death.

Chapter 6: Morphology of Cell Injury and Cellular Adaptation

6.1 Adaptive Changes

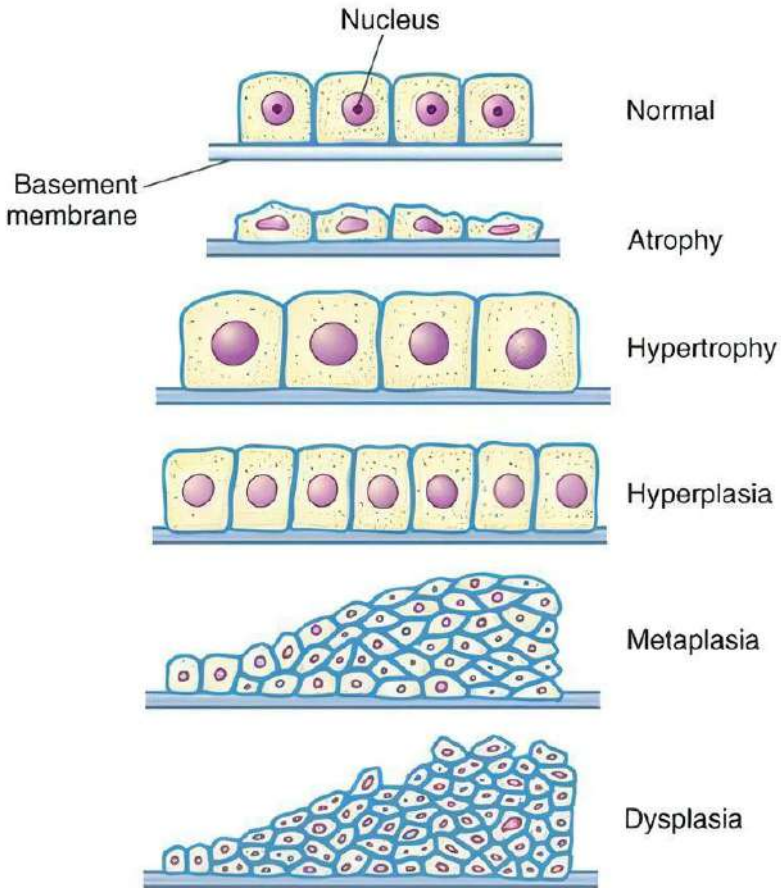
6.1.1 Introduction

Cells respond to changes in their environment through adaptive mechanisms that help maintain survival and function. These changes may involve alterations in cell size, cell number, differentiation, or growth patterns.

Cellular adaptations are generally reversible when the causative stimulus is removed. However, persistent or abnormal stimuli may lead to cellular injury and, in some cases, progression towards irreversible damage.

The major adaptive changes are:

1. Atrophy
2. Hypertrophy
3. Hyperplasia
4. Metaplasia
5. Dysplasia



6.1.2 Atrophy

Definition: Atrophy is a decrease in the size of cells, resulting in a reduction in the size of the affected tissue or organ. It may occur due to reduced functional demand, inadequate nutrition, loss of nerve supply, decreased blood supply, or ageing.

In atrophy, cells generally become smaller because of a reduction in cellular components, including proteins and organelles. In some cases, the number of cells may also decrease.

Causes of Atrophy

1. Disuse: Reduced physical activity or immobilization may cause skeletal muscle atrophy.
2. Denervation: Loss of nerve supply may result in wasting of skeletal muscle.
3. Reduced blood supply: Chronic reduction in blood flow may contribute to tissue atrophy.
4. Inadequate nutrition: Protein-calorie deficiency may lead to generalized tissue wasting.
5. Loss of hormonal stimulation: Reduced hormonal support may cause atrophy of hormone-dependent tissues.
6. Ageing: Certain tissues undergo gradual reduction in size and function with advancing age.
7. Pressure: Prolonged compression may reduce blood supply and contribute to tissue atrophy.

Mechanism of Atrophy

Atrophy occurs mainly through reduced protein synthesis and increased protein degradation. Cells may also increase autophagy, a process through which damaged or unnecessary cellular components are broken down and recycled.

Examples of Atrophy

- Skeletal muscle wasting following prolonged immobilization
- Muscle atrophy due to loss of nerve supply
- Reduction in uterine size after pregnancy
- Atrophy of tissues associated with reduced hormonal stimulation

Morphological Features

- Reduced cell size
- Decreased tissue or organ size
- Reduced cellular organelles
- Possible accumulation of residual pigments, such as lipofuscin, in some settings

6.1.3 Hypertrophy

Definition: Hypertrophy is an increase in the size of individual cells, resulting in an increase in the size of the affected tissue or organ. It occurs when cells respond to increased functional demand or hormonal stimulation.

Hypertrophy is particularly important in tissues composed of cells with limited ability to divide, such as cardiac and skeletal muscle.

Causes of Hypertrophy

- Increased workload
- Hormonal stimulation
- Increased functional demand
- Certain growth-factor-mediated signals

Types of Hypertrophy

1. Physiological hypertrophy

It occurs as a normal adaptive response.

Examples:

- Enlargement of skeletal muscles following resistance exercise
- Enlargement of uterine smooth muscle during pregnancy

2. Pathological hypertrophy

It occurs in response to abnormal or excessive stimulation.

Example:

- Enlargement of cardiac muscle cells due to chronic increased workload, such as in long-standing hypertension.

Mechanism of Hypertrophy

Increased workload or stimulation activates intracellular signalling pathways that promote the synthesis of proteins and cellular components. This results in an increase in cell size and functional capacity.

Morphological Features

- Increased cell size
- Increased amount of cytoplasm and organelles
- Increased size of the affected tissue or organ
- In muscle cells, increased contractile proteins

6.1.4 Hyperplasia

Definition: Hyperplasia is an increase in the number of cells in a tissue or organ due to increased cellular proliferation. It occurs in tissues whose cells retain the ability to divide.

Hyperplasia may occur as a normal physiological response or as a pathological response to excessive stimulation.

Types of Hyperplasia

1. Physiological hyperplasia

Physiological hyperplasia occurs under normal conditions.

It may be classified into:

- Hormonal hyperplasia: Increased cell proliferation due to hormonal stimulation. For example, glandular proliferation in the breast during pregnancy.
- Compensatory hyperplasia: Increased cell proliferation following loss or removal of part of an organ. For example, regeneration of liver tissue after partial removal.

2. Pathological hyperplasia

Pathological hyperplasia occurs due to excessive or abnormal stimulation, often involving hormones or growth factors.

Examples:

- Endometrial hyperplasia associated with prolonged oestrogen stimulation
- Benign prostatic hyperplasia

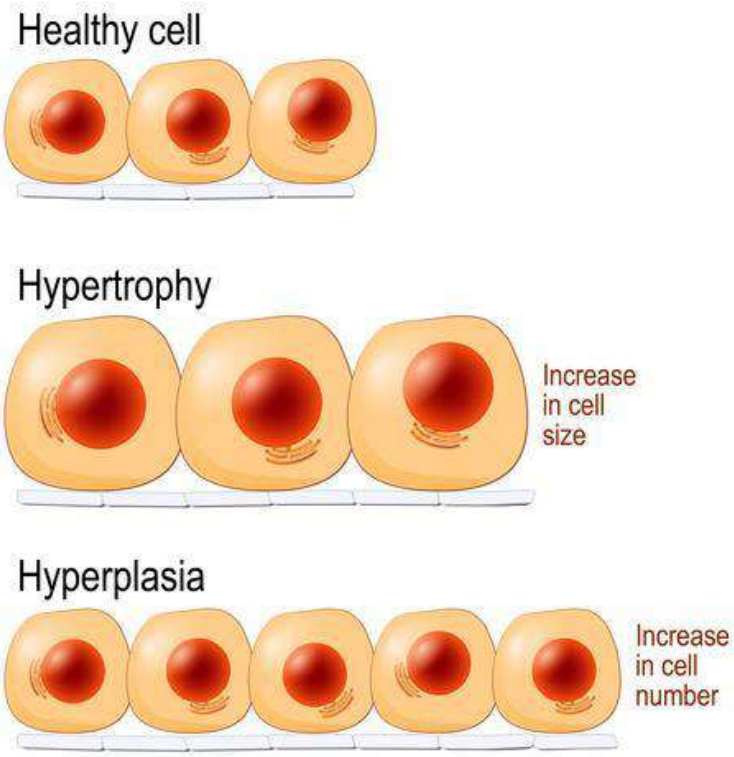
Mechanism of Hyperplasia

Growth factors and hormonal signals stimulate cells to enter the cell cycle and undergo division. The resulting increase in cell number leads to enlargement of the tissue or organ.

Morphological Features

- Increased number of cells
- Increased thickness or size of the tissue
- Increased mitotic activity in proliferating tissues
- Preservation of tissue organization in many forms of physiological hyperplasia

Important distinction: Hyperplasia involves an increase in cell number, whereas hypertrophy involves an increase in cell size. Both processes may occur together in the same tissue.



6.1.5 Metaplasia

Definition: Metaplasia is a reversible change in which one mature differentiated cell type is replaced by another mature differentiated cell type that is better able to tolerate a particular environmental stress.

Metaplasia commonly occurs in epithelial tissues, but it may also occur in connective tissue.

Causes of Metaplasia

- Chronic irritation
- Persistent inflammation
- Exposure to harmful chemicals
- Repeated physical stress
- Changes in the tissue environment

Types and Examples

1. Squamous metaplasia

In squamous metaplasia, a non-squamous epithelial cell type is replaced by stratified squamous epithelium.

Example: In the respiratory tract, prolonged exposure to cigarette smoke may cause replacement of normal ciliated columnar epithelium by squamous epithelium.

2. Columnar metaplasia

In columnar metaplasia, one epithelial cell type is replaced by a columnar epithelial type.

Example: Barrett oesophagus involves replacement of the normal squamous lining of the lower oesophagus by columnar epithelium with intestinal-type features, usually in association with chronic gastro-oesophageal reflux.

Mechanism of Metaplasia

Metaplasia generally results from reprogramming of tissue stem cells or undifferentiated precursor cells. These cells differentiate along an alternative pathway in response to changes in the local environment.

Morphological Features

- Replacement of one mature cell type by another
- Alteration in tissue architecture
- Adaptation to persistent stress
- Potential reduction in normal specialized functions

Clinical Significance

Metaplasia is often reversible if the causative stimulus is removed. However, persistent metaplastic changes may be associated with an increased risk of dysplasia and malignancy in certain tissues.

6.1.6 Dysplasia

Definition: Dysplasia is an abnormal pattern of cellular growth and maturation characterized by variations in cell size, cell shape, nuclear appearance, and tissue organization. It is commonly observed in epithelial tissues and may be associated with persistent irritation, inflammation, or infection.

Dysplasia is not the same as a normal adaptive response. It represents disordered cellular development and may be considered a precancerous change in certain contexts.

Causes and Associated Factors

- Persistent exposure to carcinogens
- Chronic inflammation
- Certain viral infections
- Long-standing epithelial injury
- Abnormal cellular growth regulation

Morphological Features of Dysplasia

1. Variation in cell size and shape, known as pleomorphism.
2. Enlarged and irregular nuclei.
3. Increased nuclear-to-cytoplasmic ratio.
4. Increased or abnormal mitotic figures.
5. Loss of normal cell polarity.
6. Disturbance of tissue architecture.
7. Abnormal maturation of epithelial cells.

Grades of Dysplasia

Dysplasia may be described as mild, moderate, or severe, depending on the degree of cellular and architectural abnormalities. In some organs, standardized grading systems are used.

Severe epithelial dysplasia involving the full thickness of the epithelium, without invasion through the basement membrane, may be classified as carcinoma in situ in appropriate clinical settings.

Clinical Significance

Dysplasia may regress, persist, or progress, depending on its cause, grade, and tissue context. Detection and appropriate follow-up are important because certain forms of dysplasia are associated with an increased risk of cancer.

6.1.7 Comparison of Cellular Adaptive Changes

Table 6.1: Comparison of Atrophy, Hypertrophy, Hyperplasia, Metaplasia and Dysplasia

Adaptive change	Definition	Main cellular change	Example
Atrophy	Reduction in cell size	Decreased cell size and cellular components	Muscle wasting after immobilization
Hypertrophy	Increase in cell size	Increased cell volume	Skeletal muscle enlargement after exercise
Hyperplasia	Increase in cell number	Increased cellular proliferation	Breast glandular proliferation during pregnancy
Metaplasia	Replacement of one mature cell type by another	Altered cellular differentiation	Squamous metaplasia in respiratory epithelium
Dysplasia	Disordered cellular growth and maturation	Abnormal cell morphology and tissue organization	Cervical epithelial dysplasia

6.2 Cell Swelling

6.2.1 Definition

Cell swelling is an increase in cell volume due to the accumulation of water within the cytoplasm. It is one of the earliest and most common morphological manifestations of reversible cell injury.

Cell swelling commonly develops when energy-dependent ion transport mechanisms fail, resulting in the accumulation of sodium and water inside the cell.

6.2.2 Causes of Cell Swelling

The major causes include:

- Hypoxia and ischaemia
- ATP depletion
- Certain chemical toxins
- Severe metabolic disturbances
- Damage to plasma membrane ion transport systems

6.2.3 Mechanism of Cell Swelling

Under normal conditions, the sodium-potassium ATPase pump maintains ionic balance by transporting sodium out of the cell and potassium into the cell. This process requires ATP.

During cellular injury, ATP production may decrease. As a result:

1. Sodium-potassium pump activity declines.
2. Sodium accumulates inside the cell.
3. Water enters the cell by osmosis.
4. Cellular volume increases.
5. Cytoplasmic organelles, particularly the endoplasmic reticulum, may become swollen.

6.2.4 Morphological Features

Cell swelling may produce the following changes:

- Increased cell size
- Pale and enlarged cytoplasm
- Small cytoplasmic vacuoles in some cells
- Swelling of mitochondria and endoplasmic reticulum
- Disturbance of normal cellular architecture

When water accumulation is prominent, the condition may be described as hydropic change or hydropic degeneration.

6.2.5 Significance of Cell Swelling

Cell swelling is generally reversible if the harmful stimulus is removed and normal energy production is restored. However, persistent injury may cause severe membrane damage and progression to irreversible injury.

6.3 Intracellular Accumulation

6.3.1 Definition

Intracellular accumulation refers to the abnormal collection of substances within the cytoplasm or cellular organelles. These substances may be produced by the cell, derived from outside the cell, or formed as a result of abnormal metabolism.

Accumulation may occur because of excessive production, inadequate removal, defective transport, or inability to metabolize a substance.

6.3.2 Causes and Mechanisms of Intracellular Accumulation

Intracellular substances may accumulate through several mechanisms:

1. Excessive production: A substance is produced in greater amounts than the cell can remove.
2. Defective metabolism: Enzyme deficiencies prevent normal breakdown of substances.
3. Impaired transport: A substance cannot be transported out of the cell.
4. Inadequate degradation: Cellular systems responsible for breakdown are unable to process the accumulated material.
5. External uptake: Substances entering from outside the cell may accumulate when they cannot be metabolized or eliminated.

6.3.3 Major Types of Intracellular Accumulation

1. Lipid Accumulation

Lipid accumulation occurs when fats, particularly triglycerides, accumulate within cells. It is commonly observed in the liver and may also occur in other tissues.

Fatty change (steatosis) refers to the abnormal accumulation of triglycerides within parenchymal cells.

Causes:

- Alcohol-related metabolic injury
- Obesity and insulin resistance
- Diabetes mellitus
- Certain drugs and toxins
- Malnutrition
- Hypoxia

Morphological features:

- Clear cytoplasmic vacuoles in routine histological sections
- Enlargement of affected cells
- Displacement of the nucleus in marked accumulation

Clinical significance: Fatty change may be reversible when the underlying cause is corrected, but persistent injury may contribute to inflammation and progressive tissue damage.

2. Protein Accumulation

Proteins may accumulate inside cells due to excessive synthesis, abnormal folding, impaired transport, or defective degradation.

Examples:

- Protein droplets in renal tubular cells following increased protein reabsorption
- Accumulation of abnormal proteins in certain inherited disorders
- Misfolded proteins in cells affected by specific degenerative conditions

Morphological features:

- Eosinophilic cytoplasmic droplets or inclusions
- Accumulation of abnormal protein material within cellular compartments

3. Glycogen Accumulation

Glycogen is the storage form of glucose. Excessive glycogen accumulation may occur in certain metabolic disorders or in conditions associated with abnormal glucose regulation.

Examples:

- Glycogen accumulation in liver cells in poorly controlled diabetes mellitus
- Glycogen storage diseases caused by inherited enzyme deficiencies

Morphological features:

- Clear or pale cytoplasmic areas in routine sections
- Positive staining with periodic acid–Schiff (PAS) stain, which may be reduced after diastase digestion

4. Pigment Accumulation

Pigments are coloured substances that may accumulate within cells. They may be endogenous, produced within the body, or exogenous, derived from outside the body.

A. Endogenous pigments

Lipofuscin: A yellow-brown pigment formed from the breakdown of cellular membrane lipids and proteins. It may accumulate in ageing or atrophic cells.

Melanin: A brown-black pigment produced by melanocytes. It contributes to skin, hair, and eye colour and provides protection against ultraviolet radiation.

Haemosiderin: An iron-containing pigment derived from haemoglobin breakdown. It may accumulate locally after bleeding or more widely in conditions involving excessive iron storage.

Bilirubin: A yellow pigment formed during haemoglobin degradation. Increased bilirubin may cause yellow discoloration of tissues, known as jaundice.

B. Exogenous pigments

Carbon pigment: Carbon particles may be inhaled and accumulate in macrophages within the lungs and lymph nodes.

Table 6.2: Important Intracellular Accumulations

Substance	Main site or example	General significance
Triglycerides	Liver cells in fatty change	May indicate metabolic or toxic injury
Proteins	Renal tubular cells and other tissues	May reflect increased uptake or defective processing
Glycogen	Liver and other tissues	May occur in metabolic disorders
Lipofuscin	Ageing or atrophic cells	Residual pigment associated with cellular wear
Melanin	Skin and other pigmented tissues	Endogenous protective pigment
Haemosiderin	Macrophages and tissues after iron accumulation	Indicates local or systemic iron deposition
Carbon	Lung macrophages	Exogenous pigment from inhaled particles

6.3.4 Clinical Significance of Intracellular Accumulation

Intracellular accumulation may be harmless, reversible, or associated with cellular dysfunction, depending on the substance and amount accumulated. Some accumulations indicate an underlying metabolic disorder, while others reflect chronic injury or ageing. Histological examination and special staining techniques may help identify the accumulated substances.

6.4 Cell Death

6.4.1 Definition

Cell death is the permanent loss of cellular viability and function. It may occur following severe injury or through regulated biological processes. Cell death is an essential part of normal development and tissue maintenance, but excessive or inappropriate cell death may contribute to disease.

The two major forms of cell death commonly studied in pathology are:

1. Necrosis
2. Apoptosis

Other regulated forms of cell death, such as necroptosis, pyroptosis, and ferroptosis, are also recognized in modern cell biology.

6.4.2 Necrosis

Definition: Necrosis is a form of cell death associated with severe cellular injury and loss of membrane integrity. It commonly occurs in living tissues following ischaemia, toxins, infections, or physical injury.

Necrotic cells undergo structural breakdown and may release intracellular contents into surrounding tissues, often producing an inflammatory response.

Causes of Necrosis

- Severe ischaemia
- Chemical toxins
- Physical injury
- Infections
- Severe burns
- Certain immune-mediated injuries

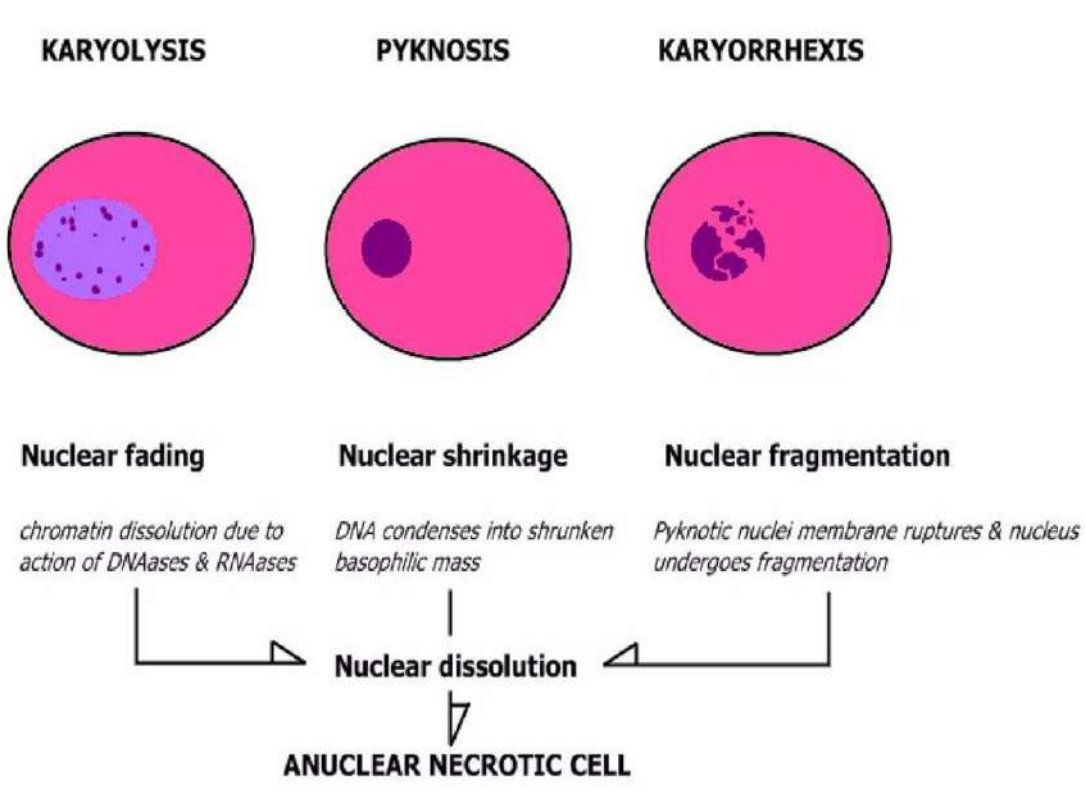
Morphological Features of Necrosis

Cytoplasmic changes:

- Increased eosinophilic staining
- Loss of normal cellular details
- Cytoplasmic vacuolation
- Breakdown of organelles
- Loss of membrane integrity

Nuclear changes:

1. Pyknosis: Nuclear shrinkage and chromatin condensation.
2. Karyorrhexis: Fragmentation of the pyknotic nucleus.
3. Karyolysis: Fading or dissolution of the nucleus.



Types of Necrosis

1. Coagulative necrosis

In coagulative necrosis, the basic tissue architecture is preserved for a period, although the cells are dead. It commonly occurs following ischaemia in solid organs, except the brain.

Example: Myocardial infarction.

2. Liquefactive necrosis

In liquefactive necrosis, enzymatic digestion causes the tissue to become soft and liquid.

Examples:

- Brain infarction
- Certain bacterial infections producing abscesses

3. Caseous necrosis

Caseous necrosis is characterized by a soft, friable, cheese-like appearance. It is classically associated with tuberculosis.

4. Fat necrosis

Fat necrosis involves the destruction of adipose tissue, often due to the action of lipases or physical injury.

Examples:

- Acute pancreatitis
- Traumatic injury to fatty tissue

5. Fibrinoid necrosis

Fibrinoid necrosis is characterized by deposition of fibrin-like material in the walls of blood vessels. It may occur in certain immune-mediated vascular injuries.

6. Gangrenous necrosis

Gangrene is a clinical term used for extensive tissue necrosis, commonly involving a limb or part of the gastrointestinal tract. It may be classified as dry, wet, or gas gangrene.

6.4.3 Apoptosis

Definition: Apoptosis is a regulated form of cell death in which cells are eliminated through an organized process involving activation of specific intracellular enzymes called caspases. It usually occurs without causing a marked inflammatory response.

Apoptosis is important during normal development, tissue turnover, and removal of damaged or potentially harmful cells.

Causes of Apoptosis

Physiological causes:

- Removal of cells during embryonic development
- Normal turnover of epithelial cells
- Elimination of cells after hormonal withdrawal
- Removal of self-reactive lymphocytes

Pathological causes:

- DNA damage
- Accumulation of misfolded proteins
- Certain viral infections
- Cell injury that activates regulated death pathways

Mechanisms of Apoptosis

Apoptosis occurs mainly through two pathways:

1. Intrinsic or mitochondrial pathway

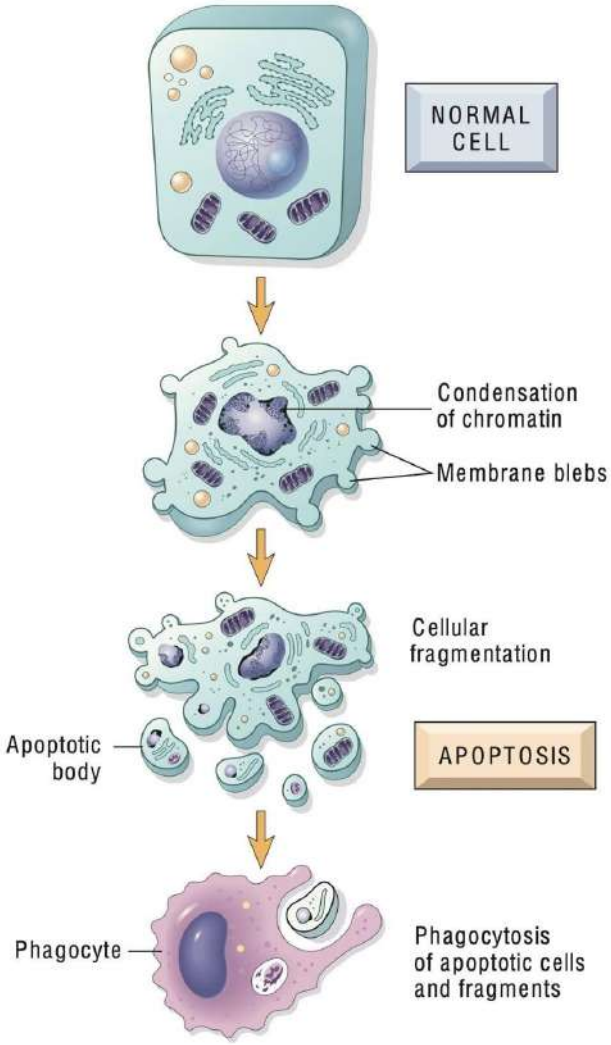
This pathway is activated by internal cellular stress, such as DNA damage or growth factor withdrawal. Changes in mitochondrial membrane permeability allow the release of cytochrome c, which contributes to the activation of caspases.

2. Extrinsic or death receptor pathway

This pathway is initiated when death ligands bind to specific cell-surface receptors. Receptor activation triggers a caspase cascade that leads to cell death.

Morphological Features of Apoptosis

- Cell shrinkage
- Chromatin condensation
- Nuclear fragmentation
- Formation of membrane-bound apoptotic bodies
- Removal of apoptotic bodies by phagocytic cells
- Generally limited inflammatory response



6.4.4 Comparison Between Necrosis and Apoptosis

Table 6.3: Differences Between Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Nature	Usually associated with severe pathological injury	Regulated cell death; may be physiological or pathological
Cell size	Cell swelling is common	Cell shrinkage is typical
Plasma membrane	Membrane integrity is lost	Membrane remains intact during early stages
Nuclear changes	Pyknosis, karyorrhexis, and karyolysis	Chromatin condensation and fragmentation
Cellular contents	May leak into surrounding tissue	Packaged into apoptotic bodies
Inflammation	Commonly associated with inflammation	Usually little or no inflammation
Extent	May affect groups of adjacent cells	Often affects individual cells
Energy requirement	Commonly associated with severe energy failure	Requires regulated biochemical processes
Physiological role	Not generally a normal physiological process	Important in development and tissue homeostasis

6.4.5 Other Regulated Forms of Cell Death

In addition to apoptosis, several regulated forms of cell death have been identified.

1. Necroptosis

Necroptosis is a regulated form of cell death that has morphological features resembling necrosis. It involves specific signalling proteins and may be associated with inflammation.

2. Pyroptosis

Pyroptosis is an inflammatory form of regulated cell death commonly associated with activation of inflammatory caspases and formation of membrane pores. It plays a role in host defence against certain infections.

3. Ferroptosis

Ferroptosis is a regulated form of cell death associated with iron-dependent lipid peroxidation and failure of antioxidant defence mechanisms that protect cellular membranes.

These forms of cell death are important areas of research in inflammation, infection, cancer, and degenerative disorders.

6.4.6 Significance of Cell Death

Cell death is necessary for normal development, tissue renewal, and removal of damaged cells. However, excessive or insufficient cell death may contribute to disease. Excessive cell death can lead to tissue loss and organ dysfunction, whereas failure to eliminate damaged or abnormal cells may contribute to uncontrolled cell survival and tumour development.

Cells respond to stress through adaptive changes such as atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia. Atrophy involves a reduction in cell size, hypertrophy involves an increase in cell size, and hyperplasia involves an increase in cell number. Metaplasia is the replacement of one mature cell type by another, whereas dysplasia is characterized by disordered cellular growth and maturation.

Cell swelling is a common feature of reversible cell injury and usually results from failure of energy-dependent ion transport. Intracellular accumulation occurs when substances build up within cells due to excessive production, impaired metabolism, defective transport, or inadequate degradation. Important accumulated substances include lipids, proteins, glycogen, and pigments.

Cell death may occur through necrosis or apoptosis. Necrosis is commonly associated with severe injury, membrane breakdown, and inflammation. Apoptosis is a regulated process involved in normal tissue development and the removal of damaged cells. Other regulated forms include necroptosis, pyroptosis, and ferroptosis.

Chapter 7: Medical Terminology

7.1 Definitions of Commonly Used Relevant Medical Terminologies

7.1.1 Introduction

Medical terminology is the specialized language used by healthcare professionals to describe the structure, function, diseases, symptoms, diagnostic procedures, and treatment of the human body. It provides a standardized method of communication among pharmacists, physicians, nurses, laboratory professionals, and other healthcare workers.

Many medical terms are formed by combining word roots, prefixes, and suffixes. Understanding these components helps students interpret unfamiliar medical terms and use them correctly in pharmaceutical and clinical settings.

7.1.2 Basic Components of Medical Terms

A medical term may contain one or more of the following components:

1. Word root

The word root provides the basic meaning of the term, often referring to a body part, organ, or system.

Examples:

- Cardi – heart
- Nephr – kidney
- Derm – skin
- Gastr – stomach
- Hepat – liver

2. Prefix

A prefix is placed at the beginning of a word and modifies its meaning.

Examples:

- Hyper- – excessive or above normal
- Hypo- – below normal or deficient
- Brady- – slow
- Tachy- – rapid
- Anti- – against

3. Suffix

A suffix is placed at the end of a word and often indicates a condition, disease, procedure, or specialist.

Examples:

- -itis – inflammation
- -osis – abnormal condition
- -ectomy – surgical removal
- -algia – pain
- -logy – study of

4. Combining vowel

A combining vowel, usually "o", is used to connect word roots or to join a root to a suffix when needed.

Example: Cardi/o/logy = study of the heart.

7.1.3 Common Medical Prefixes

Table 7.1: Common Medical Prefixes

Prefix	Meaning	Example	Definition
A-, An-	Without, absence of	Apnoea	Temporary absence of breathing
Anti-	Against	Antibiotic	Substance used against susceptible microorganisms
Auto-	Self	Autoimmune	Directed against the body's own components
Brady-	Slow	Bradycardia	Abnormally slow heart rate
Dys-	Difficult, abnormal	Dysphagia	Difficulty in swallowing
Endo-	Within	Endoscopy	Visual examination within the body
Epi-	Upon, above	Epidermis	Outer layer of skin
Hyper-	Excessive, above normal	Hypertension	Elevated blood pressure
Hypo-	Below normal, deficient	Hypoglycaemia	Low blood glucose
Inter-	Between	Intercellular	Between cells
Intra-	Within	Intracellular	Within a cell
Macro-	Large	Macrophage	Large phagocytic cell
Micro-	Small	Microorganism	Microscopic organism
Neo-	New	Neoplasm	New abnormal growth of tissue
Peri-	Around	Pericardium	Membrane around the heart
Poly-	Many, much	Polyuria	Excessive urine production
Post-	After	Postoperative	After surgery
Pre-	Before	Prenatal	Before birth
Sub-	Below, under	Subcutaneous	Beneath the skin
Tachy-	Rapid	Tachycardia	Abnormally rapid heart rate
Trans-	Across, through	Transdermal	Through the skin

7.1.4 Common Medical Suffixes

Table 7.2: Common Medical Suffixes

Suffix	Meaning	Example	Definition
-algia	Pain	Neuralgia	Pain along a nerve
-centesis	Surgical puncture	Amniocentesis	Puncture to obtain amniotic fluid
-cyte	Cell	Leukocyte	White blood cell
-ectomy	Surgical removal	Appendectomy	Surgical removal of the appendix
-emia	Blood condition	Anaemia	Reduced haemoglobin or red cell mass, depending on definition
-gram	Record or image	Electrocardiogram	Record of the heart's electrical activity
-graphy	Process of recording or imaging	Angiography	Imaging of blood vessels
-itis	Inflammation	Arthritis	Inflammation of a joint
-logy	Study of	Neurology	Study of the nervous system
-lysis	Breakdown or destruction	Haemolysis	Breakdown of red blood cells
-megaly	Enlargement	Hepatomegaly	Enlargement of the liver
-oma	Tumour or mass	Lipoma	Benign tumour of adipose tissue
-opathy	Disease	Neuropathy	Disease or dysfunction of nerves
-osis	Abnormal condition	Cyanosis	Bluish discoloration due to increased deoxygenated haemoglobin
-otomy	Incision into	Tracheotomy	Incision into the trachea
-pathy	Disease	Myopathy	Disease of muscle
-penia	Deficiency or reduction	Leukopenia	Reduced white blood cell count
-phagia	Eating or swallowing	Dysphagia	Difficulty in swallowing
-phasia	Speech	Aphasia	Impairment of language ability
-plasty	Surgical repair	Rhinoplasty	Surgical repair or reshaping of the nose
-plegia	Paralysis	Paraplegia	Paralysis affecting both lower limbs
-pnea	Breathing	Dyspnoea	Difficult or uncomfortable breathing
-scopy	Visual examination	Endoscopy	Visual examination using an instrument
-stasis	Stopping or controlling	Haemostasis	Arrest of bleeding
-therapy	Treatment	Chemotherapy	Treatment using chemical agents
-tomy	Cutting or incision	Laparotomy	Surgical incision into the abdominal wall

7.1.5 Common Medical Word Roots

Table 7.3: Common Medical Word Roots

Word root	Meaning	Example	Definition
Aden/o	Gland	Adenoma	Benign tumour of glandular tissue
Angi/o	Vessel	Angiography	Imaging of blood vessels
Arthr/o	Joint	Arthritis	Inflammation of a joint

Cardi/o	Heart	Cardiology	Study of the heart
Cephal/o	Head	Cephalic	Relating to the head
Cerebr/o	Cerebrum	Cerebral	Relating to the cerebrum
Cyt/o	Cell	Cytology	Study of cells
Derm/o	Skin	Dermatitis	Inflammation of the skin
Enter/o	Intestine	Enteritis	Inflammation of the intestine
Gastr/o	Stomach	Gastritis	Inflammation of the stomach
Haem/o, Hem/o	Blood	Haematology	Study of blood
Hepat/o	Liver	Hepatitis	Inflammation of the liver
Nephr/o	Kidney	Nephrology	Study of the kidney
Neur/o	Nerve	Neurology	Study of the nervous system
Oste/o	Bone	Osteoporosis	Condition involving reduced bone strength
Path/o	Disease	Pathology	Study of disease
Pulmon/o	Lung	Pulmonary	Relating to the lungs
Rhin/o	Nose	Rhinitis	Inflammation of the nasal mucosa
My/o	Muscle	Myopathy	Disease of muscle
Ot/o	Ear	Otitis	Inflammation of the ear
Ophthalm/o	Eye	Ophthalmology	Study of the eye
Uro/o	Urinary tract	Urology	Study of the urinary system

7.1.6 Common Medical Terminologies Related to the Human Body

Table 7.4: General Medical Terms

Term	Definition
Anatomy	Study of the structure of the body and its parts
Physiology	Study of the normal functions of the body
Pathology	Study of disease and its structural and functional changes
Pathophysiology	Study of altered physiological functions associated with disease
Histology	Study of tissues at the microscopic level
Cytology	Study of cells
Homeostasis	Maintenance of a relatively stable internal environment
Metabolism	Sum of chemical reactions occurring within the body
Aetiology	Cause or origin of a disease
Pathogenesis	Mechanism by which a disease develops
Diagnosis	Identification of a disease or condition
Prognosis	Expected course or outcome of a disease
Symptom	A subjective experience reported by a patient
Sign	An objective finding observed or measured by a healthcare professional
Syndrome	A group of signs and symptoms occurring together
Lesion	An area of abnormal tissue or structural damage
Inflammation	Protective tissue response to injury or harmful stimuli
Infection	Invasion and multiplication of microorganisms in the body
Trauma	Physical injury caused by an external force

Sequela	A condition or effect remaining after an earlier disease or injury
Remission	Reduction or disappearance of signs and symptoms of a disease
Relapse	Return of a disease or its manifestations after improvement
Acute	Rapid onset or short duration
Chronic	Long-lasting or persistent
Benign	Non-cancerous; does not invade or metastasize
Malignant	Cancerous; capable of invasion and, in many cases, metastasis
Congenital	Present at birth
Acquired	Developed after birth
Idiopathic	Of unknown cause
Iatrogenic	Resulting from medical examination or treatment
Asymptomatic	Occurring without noticeable symptoms
Symptomatic	Producing or associated with symptoms

7.1.7 Common Medical Terms Related to Symptoms and Clinical Findings

Table 7.5: Common Clinical Terms

Term	Definition
Pyrexia	Fever or elevated body temperature
Hypothermia	Abnormally low body temperature
Hypertension	Persistently elevated arterial blood pressure
Hypotension	Abnormally low blood pressure
Tachycardia	Abnormally rapid heart rate
Bradycardia	Abnormally slow heart rate
Dyspnoea	Difficult or uncomfortable breathing
Apnoea	Temporary cessation of breathing
Cyanosis	Bluish discoloration of skin or mucous membranes associated with increased deoxygenated haemoglobin
Oedema	Abnormal accumulation of fluid in tissues
Jaundice	Yellow discoloration of skin and sclera due to increased bilirubin
Pallor	Unusual paleness of skin or mucous membranes
Syncope	Temporary loss of consciousness due to reduced blood flow to the brain
Nausea	Sensation of an urge to vomit
Vomiting	Forceful expulsion of stomach contents through the mouth
Diarrhoea	Passage of loose or watery stools, usually with increased frequency
Constipation	Difficult or infrequent passage of stools
Haematuria	Presence of blood in urine
Proteinuria	Presence of excess protein in urine
Polyuria	Excessive urine production
Oliguria	Reduced urine output
Anuria	Near absence of urine production
Pruritus	Itching
Myalgia	Muscle pain
Arthralgia	Joint pain
Neuralgia	Pain along the distribution of a nerve

Fatigue	Persistent feeling of tiredness or lack of energy
Malaise	General feeling of discomfort or illness

7.1.8 Common Medical Terms Related to Diseases and Disorders

Table 7.6: Common Disease-Related Terms

Term	Definition
Anaemia	A condition characterized by reduced haemoglobin concentration or red cell mass
Atherosclerosis	Accumulation of lipid-rich plaques in the walls of arteries
Thrombosis	Formation of a blood clot within a blood vessel
Embolism	Obstruction of a blood vessel by material transported through the bloodstream
Ischaemia	Inadequate blood supply to a tissue
Infarction	Tissue necrosis caused by inadequate blood supply
Necrosis	Cell death associated with loss of membrane integrity and tissue injury
Apoptosis	Regulated form of cell death
Atrophy	Reduction in cell size and often tissue or organ size
Hypertrophy	Increase in cell size
Hyperplasia	Increase in cell number
Metaplasia	Replacement of one mature cell type by another
Dysplasia	Disordered cellular growth and maturation
Neoplasia	Abnormal, uncontrolled growth of cells
Neoplasm	An abnormal mass of tissue produced by neoplastic growth
Metastasis	Spread of malignant cells from the primary site to distant sites
Fibrosis	Excessive deposition of connective tissue
Cirrhosis	Advanced chronic liver disease characterized by fibrosis and altered liver architecture
Osteoporosis	Reduction in bone strength associated with increased fracture risk
Arthritis	Inflammation of one or more joints
Diabetes mellitus	A metabolic disorder characterized by chronic hyperglycaemia
Asthma	Chronic inflammatory airway disease associated with variable respiratory symptoms and airflow limitation
Pneumonia	Infection of lung tissue, commonly involving the alveoli
Nephritis	Inflammation of the kidney
Hepatitis	Inflammation of the liver
Dermatitis	Inflammation of the skin

7.1.9 Common Medical Terms Related to Diagnostic Procedures

Table 7.7: Diagnostic and Investigative Terms

Term	Definition
Biopsy	Removal of a tissue sample for examination
Histopathology	Microscopic examination of tissues to identify disease-related changes

Haematology	Study and investigation of blood and blood-forming tissues
Urinalysis	Laboratory examination of urine
Radiography	Imaging using X-rays
Ultrasonography	Imaging using high-frequency sound waves
Computed tomography (CT)	Imaging technique using X-rays and computer processing to produce cross-sectional images
Magnetic resonance imaging (MRI)	Imaging technique using magnetic fields and radiofrequency signals
Electrocardiography (ECG)	Recording of the electrical activity of the heart
Electroencephalography (EEG)	Recording of electrical activity of the brain
Endoscopy	Visual examination of internal structures using an endoscope
Angiography	Imaging of blood vessels
Spirometry	Measurement of lung function, particularly airflow and lung volumes
Culture	Laboratory growth of microorganisms from a clinical specimen
Serology	Study or detection of antibodies and antigens in serum
Polymerase chain reaction (PCR)	Laboratory technique used to amplify specific DNA sequences
Differential diagnosis	Consideration of alternative conditions that may explain a clinical presentation

7.1.10 Common Medical Terms Related to Treatment and Medication

Table 7.8: Treatment-Related Terminology

Term	Definition
Pharmacology	Study of drugs and their effects on living systems
Pharmacokinetics	Study of drug absorption, distribution, metabolism, and excretion
Pharmacodynamics	Study of the biochemical and physiological effects of drugs and their mechanisms of action
Therapeutics	Science and practice of treating disease
Dosage	Quantity of a medicine administered at a specified time or according to a prescribed schedule
Dose	Amount of a drug administered on a particular occasion
Route of administration	Pathway by which a medicine enters the body
Contraindication	A condition or circumstance in which a treatment should not be used, or should be used only with specific precautions
Adverse drug reaction	Harmful and unintended response to a medicine used at normally intended doses
Side effect	Secondary effect of a medicine, which may be beneficial, neutral, or harmful
Drug interaction	Change in the effect of a drug caused by another drug, food, or substance
Therapeutic effect	Intended beneficial effect of a treatment
Toxicity	Harmful effect caused by a substance or drug

Tolerance	Reduced response to a drug after repeated exposure
Dependence	Physiological or psychological adaptation associated with continued use of a substance
Half-life	Time required for the concentration or amount of a drug in the body to decrease by half under specified conditions
Bioavailability	Fraction of an administered dose that reaches systemic circulation in unchanged form
Compliance/adherence	Extent to which a patient follows an agreed treatment plan
Prophylaxis	Measures taken to prevent disease
Palliative care	Care intended to relieve suffering and improve quality of life in serious illness

7.1.11 Common Abbreviations Used in Medical Practice

Medical abbreviations are frequently used in prescriptions, medical records, and clinical communication. Their use should follow institutional standards because some abbreviations may be ambiguous.

Table 7.9: Common Medical Abbreviations

Abbreviation	Full form
BP	Blood pressure
HR	Heart rate
RR	Respiratory rate
Temp.	Temperature
CNS	Central nervous system
PNS	Peripheral nervous system
CVS	Cardiovascular system
GIT	Gastrointestinal tract
CNS	Central nervous system
ECG	Electrocardiogram
EEG	Electroencephalogram
CT	Computed tomography
MRI	Magnetic resonance imaging
CBC	Complete blood count
RBC	Red blood cell
WBC	White blood cell
Hb	Haemoglobin
TLC	Total leukocyte count
DLC	Differential leukocyte count
LFT	Liver function test
RFT	Renal function test
FBS	Fasting blood sugar
PPBS	Postprandial blood sugar
HbA1c	Glycated haemoglobin

IV	Intravenous
IM	Intramuscular
SC	Subcutaneous
ID	Intradermal
PO	By mouth
PRN	When required
BID	Twice daily
TID	Three times daily
QID	Four times daily
OD	Once daily; may be ambiguous and should be written in full
SOS	If required in an urgent or specified situation; use according to local prescribing conventions

Important note: In prescriptions and medication-related communication, ambiguous abbreviations should be avoided. Writing the complete instruction improves clarity and reduces the risk of medication errors.

7.1.12 Formation and Interpretation of Medical Terms

Understanding word components allows students to interpret medical terms more easily.

Examples:

1. Gastritis

- Gastr = stomach
- -itis = inflammation Meaning: Inflammation of the stomach.

2. Nephrology

- Nephr = kidney
- -logy = study of Meaning: Study of the kidneys.

3. Tachycardia

- Tachy- = rapid
- Cardi = heart
- -ia = condition Meaning: Abnormally rapid heart rate.

4. Hypoglycaemia

- Hypo- = low
- Glyc = sugar
- -emia = blood condition Meaning: Low blood glucose concentration.

5. Hepatomegaly

- Hepato = liver

- -megaly = enlargement Meaning: Enlargement of the liver.

6. Arthralgia

- Arthr = joint
- -algia = pain Meaning: Joint pain.

7. Intracellular

- Intra- = within
- Cellular = relating to cells Meaning: Located within a cell.

8. Subcutaneous

- Sub- = beneath
- Cutaneous = relating to skin Meaning: Beneath the skin.

7.1.13 Importance of Medical Terminology in Pharmacy

Medical terminology is particularly important for pharmacy students because pharmacists routinely communicate with patients and other healthcare professionals. Knowledge of medical terms helps in:

1. Understanding prescriptions and medical records.
2. Interpreting disease names, symptoms, and diagnostic reports.
3. Communicating accurately with physicians, nurses, and patients.
4. Understanding drug indications, contraindications, and adverse effects.
5. Supporting safe dispensing and medication counselling.
6. Recognizing medical abbreviations and avoiding errors caused by ambiguous instructions.
7. Understanding pharmacological and pathophysiological concepts.

Medical terminology is a standardized language used to describe body structures, physiological functions, diseases, diagnostic procedures, and treatments. Medical terms are commonly formed from word roots, prefixes, suffixes, and combining vowels. Knowledge of these components helps students understand complex terms by identifying their individual meanings.

Common medical terminology includes terms related to anatomy, physiology, pathology, clinical symptoms, diseases, diagnostic procedures, and drug therapy. For pharmacy students, familiarity with medical terminology supports accurate interpretation of prescriptions, effective communication, and safe medication use.

UNIT- II

Chapter 8: Integumentary System and Wound Healing

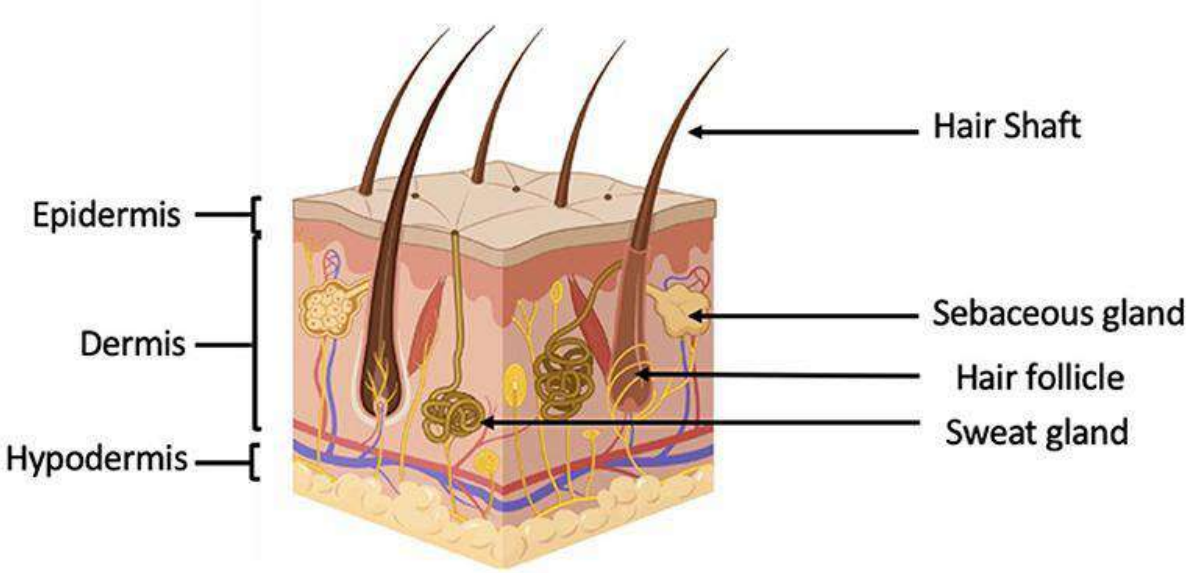
8.1 Structure and Functions of Skin

Introduction

The integumentary system is the external covering of the body and consists mainly of the skin and its associated structures, including hair, nails, sweat glands, and sebaceous glands. The skin is the largest organ of the human body and forms an important protective barrier between the internal environment and the external surroundings. It protects the body against mechanical injury, microorganisms, harmful chemicals, ultraviolet radiation, and excessive water loss. It also participates in temperature regulation, sensation, vitamin D synthesis, and immune defence.

The skin is composed of two principal layers: the epidermis and the dermis. A layer of subcutaneous tissue, also called the hypodermis, lies beneath the dermis and connects the skin to underlying structures.

8.1.1 Layers of the Skin



A. Epidermis

The epidermis is the outermost layer of the skin. It is composed of keratinized stratified squamous epithelium and does not contain blood vessels. Nutrients reach the epidermal cells by diffusion from blood vessels present in the underlying dermis.

The main cells of the epidermis are:

- Keratinocytes: These are the most abundant epidermal cells. They produce keratin, a structural protein that provides strength and helps form a protective barrier.
- Melanocytes: These cells produce melanin, the pigment responsible for skin colour and protection against ultraviolet radiation.

- Langerhans cells: These are immune cells that help recognize and process foreign substances.
- Merkel cells: These cells are associated with sensory nerve endings and contribute to touch sensation.

The epidermis is organized into several layers, known as strata. From deep to superficial, these are:

1. Stratum basale: The deepest layer, consisting mainly of actively dividing cells that replace lost epidermal cells. Melanocytes and Merkel cells are also present.
2. Stratum spinosum: Contains several layers of keratinocytes connected by strong intercellular junctions, providing mechanical strength.
3. Stratum granulosum: Contains cells with keratohyalin granules that contribute to keratin formation and the development of the skin barrier.
4. Stratum lucidum: A thin, clear layer present mainly in thick skin, such as the palms and soles.
5. Stratum corneum: The outermost layer, consisting of flattened, dead, keratin-filled cells. It forms the main protective barrier against environmental damage and water loss.

The stratum lucidum is generally absent in thin skin, such as that covering most parts of the body.

B. Dermis

The dermis lies beneath the epidermis and consists of connective tissue containing collagen and elastic fibres. It provides strength, flexibility, and nourishment to the epidermis. It also contains blood vessels, lymphatic vessels, nerves, sensory receptors, hair follicles, sweat glands, and sebaceous glands.

The dermis is divided into two layers:

1. Papillary layer: This is the superficial layer of the dermis. It consists of loose connective tissue and forms small projections called dermal papillae, which extend towards the epidermis. These projections increase the attachment between the epidermis and dermis and contain small blood vessels and sensory receptors.

2. Reticular layer: This is the deeper and thicker layer of the dermis. It consists mainly of dense irregular connective tissue containing collagen and elastic fibres. It provides tensile strength and elasticity to the skin and contains most of the skin appendages.

C. Hypodermis or Subcutaneous Tissue

The hypodermis is located beneath the dermis. Although it is not considered a true layer of the skin, it supports and connects the skin to underlying muscles and other structures. It consists mainly of loose connective tissue and adipose tissue.

Its major functions include:

- Storage of fat as an energy reserve.
- Insulation against heat loss.
- Absorption of mechanical shock.
- Providing flexibility and mobility to the skin.

- Supporting blood vessels and nerves supplying the skin.

8.1.2 Skin Appendages

Skin appendages are structures derived from the epidermis and located within or associated with the dermis.

Hair: Hair is composed mainly of keratin and grows from hair follicles. It provides protection, contributes to sensation, and helps reduce heat loss in certain body regions.

Nails: Nails are hard plates of keratin that protect the tips of fingers and toes. They also assist in grasping and manipulating small objects.

Sebaceous glands: These glands usually open into hair follicles and secrete an oily substance called sebum. Sebum lubricates the skin and hair and helps prevent excessive dryness.

Sweat glands: Sweat glands produce sweat, which contributes to thermoregulation and the removal of small quantities of waste products. Eccrine sweat glands are widely distributed and are particularly important in cooling the body. Apocrine sweat glands are found mainly in specific regions, such as the axillae and genital area.

8.1.3 Functions of the Skin

The skin performs several essential functions that maintain normal body activities.

1. Protection: The skin acts as a physical, chemical, and biological barrier against injury, microorganisms, harmful substances, and ultraviolet radiation. The keratinized epidermis also reduces water loss from the body.

2. Temperature regulation: Sweat production and changes in the diameter of cutaneous blood vessels help regulate body temperature. Sweating promotes heat loss through evaporation, while vasodilation increases heat transfer to the skin surface. Vasoconstriction reduces heat loss.

3. Sensation: Sensory receptors in the skin detect touch, pressure, vibration, pain, and temperature. These sensations help the body respond to environmental changes and potential injury.

4. Vitamin D synthesis: Ultraviolet B radiation from sunlight initiates the conversion of 7-dehydrocholesterol in the skin into vitamin D3. Further processing in the liver and kidneys produces the active form of vitamin D, which is important for calcium and phosphate regulation.

5. Excretion: Sweat contains water, salts, and small amounts of metabolic waste products. However, the kidneys are the major organs responsible for waste excretion.

6. Immune defence: The skin provides a physical barrier and contains immune cells that recognize and respond to pathogens and foreign substances.

7. Storage and insulation: Subcutaneous adipose tissue stores energy and provides insulation and cushioning against mechanical injury.

8. Wound repair: The skin has the ability to repair damaged tissue through coordinated processes involving inflammation, cell proliferation, and tissue remodeling.

8.2 Skin Disorders: Psoriasis and Dermatitis

Skin disorders may arise due to genetic factors, immune disturbances, infections, allergens, irritants, or environmental influences. Psoriasis and dermatitis are common inflammatory skin conditions. Although both may produce redness and scaling, their underlying mechanisms and clinical features differ.

8.2.1 Psoriasis

Definition

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by excessive proliferation of epidermal keratinocytes and abnormal differentiation of skin cells. It commonly presents as well-defined, raised, red plaques covered with silvery-white scales. The condition may involve the scalp, elbows, knees, lower back, and other body regions.

Psoriasis is not contagious. It may develop at any age and often follows a relapsing and remitting course.

Causes and Predisposing Factors

The exact cause of psoriasis is not completely understood. It is associated with an interaction between genetic susceptibility, immune system activation, and environmental factors.

Important predisposing or triggering factors include:

- Family history of psoriasis.
- Physical injury to the skin.
- Certain infections, particularly streptococcal throat infections in some forms of psoriasis.
- Psychological stress.
- Smoking and excessive alcohol consumption.
- Certain medicines, including some drugs that may aggravate psoriasis.
- Changes in immune regulation.

Pathophysiology

Psoriasis develops due to abnormal activation of immune pathways in the skin. Dendritic cells and other immune cells release inflammatory mediators that activate T lymphocytes. The interleukin-23 (IL-23) and T-helper 17 (Th17) pathways play important roles in the disease process.

Activated immune cells produce inflammatory cytokines, including interleukin-17 (IL-17), interleukin-22 (IL-22), and tumour necrosis factor-alpha (TNF-α). These mediators stimulate keratinocyte proliferation and alter their normal maturation.

As a result:

1. Epidermal cell proliferation increases.
2. Keratinocytes move towards the skin surface more rapidly than normal.
3. Normal epidermal maturation is disturbed.
4. Thickened epidermis and accumulation of keratinocytes produce raised plaques and scales.
5. Inflammatory changes in the dermis contribute to redness and swelling.



Clinical Features

Common clinical features include:

- Well-defined red or erythematous plaques.
- Silvery-white scaling over the affected areas.
- Itching, dryness, or discomfort.
- Cracking and occasional bleeding of the skin.
- Symmetrical involvement of the elbows, knees, scalp, and lower back.
- Nail changes, such as pitting, thickening, or separation of the nail from its bed, in some patients.

Some individuals may also develop psoriatic arthritis, an inflammatory joint condition associated with psoriasis.

Basic Principles of Management

Management depends on the type, severity, and extent of the disease. Treatment aims to reduce inflammation, slow excessive keratinocyte proliferation, control symptoms, and improve quality of life. Common approaches include topical preparations, phototherapy, and systemic medicines. Treatment should be selected according to clinical assessment.

8.2.2 Dermatitis

Definition

Dermatitis refers to inflammation of the skin characterized by redness, itching, swelling, and sometimes blistering, oozing, or scaling. It may occur due to irritants, allergens, genetic susceptibility, or disturbances in the skin barrier.

Dermatitis is a broad term that includes several conditions, such as atopic dermatitis, contact dermatitis, and seborrhoeic dermatitis.

Types of Dermatitis

1. Atopic Dermatitis: Atopic dermatitis, commonly known as eczema, is a chronic inflammatory skin condition associated with impaired skin barrier function and immune dysregulation. It often occurs in individuals with a personal or family history of allergic conditions, such as asthma or allergic rhinitis.

2. Contact Dermatitis: Contact dermatitis develops when the skin comes into contact with an irritating substance or an allergen.

- Irritant contact dermatitis results from direct damage to the skin barrier by substances such as detergents, solvents, or repeated exposure to water.
- Allergic contact dermatitis is a delayed hypersensitivity reaction caused by an immune response to a particular allergen, such as nickel or certain chemicals.

3. Seborrhoeic Dermatitis: Seborrhoeic dermatitis is a common inflammatory condition affecting areas rich in sebaceous glands, including the scalp, face, and upper chest. It is associated with inflammation, sebum-related factors, and the presence of Malassezia yeasts.

Causes and Predisposing Factors

The causes differ according to the type of dermatitis. Important factors include:

- Genetic predisposition and impaired skin barrier function.
- Exposure to irritants, such as soaps, detergents, and chemicals.
- Contact with allergens, including metals, fragrances, and cosmetics.
- Immune system disturbances.
- Dry skin and environmental changes.
- Microbial and inflammatory factors in certain forms of dermatitis.

Pathophysiology

The pathophysiology of dermatitis involves disruption of the normal skin barrier and activation of inflammatory responses.

In atopic dermatitis, genetic and environmental factors may reduce the effectiveness of the epidermal barrier. Reduced barrier function allows increased water loss and facilitates the entry of irritants, allergens, and microorganisms. This promotes immune activation and inflammation.

In allergic contact dermatitis, an allergen enters the skin and is processed by antigen-presenting cells. This initiates sensitization and the development of allergen-specific T lymphocytes. On subsequent exposure, these cells release inflammatory mediators, resulting in a delayed inflammatory reaction.

In irritant contact dermatitis, direct damage to epidermal cells and barrier lipids activates local inflammatory pathways without requiring prior allergic sensitization.

The resulting inflammation causes redness, itching, swelling, and, in some cases, fluid-filled vesicles or skin breakdown. Repeated scratching may further damage the skin barrier and increase the risk of secondary infection.



Clinical Features

The clinical features of dermatitis may include:

- Redness and inflammation.
- Itching, which may be intense.
- Dryness and scaling.
- Swelling and skin thickening in chronic cases.
- Small blisters or vesicles in acute cases.
- Oozing and crust formation when lesions are severe.
- Cracks or fissures due to dryness and repeated scratching.

The distribution of lesions depends on the type of dermatitis and the site of exposure.

Basic Principles of Management

Management focuses on identifying and avoiding triggering factors, restoring the skin barrier, and controlling inflammation. General measures include regular use of moisturizers and gentle skin cleansing. Topical anti-inflammatory medicines may be prescribed according to the type and severity of dermatitis. Persistent, severe, or infected lesions require medical assessment.

Table 8.1: Differences Between Psoriasis and Dermatitis

Feature	Psoriasis	Dermatitis
Nature	Chronic immune-mediated inflammatory disorder	Inflammatory condition caused by several mechanisms
Main pathological process	Increased keratinocyte proliferation and abnormal differentiation	Skin barrier disruption and inflammatory response
Typical appearance	Well-defined red plaques with silvery scales	Redness, itching, dryness, scaling, and sometimes vesicles
Common sites	Elbows, knees, scalp, and lower back	Depends on type; commonly flexures or areas exposed to irritants/allergens
Itching	Variable	Often prominent
Contagiousness	Not contagious	Generally not contagious
Associated factors	Genetic susceptibility, immune activation, and environmental triggers	Barrier defects, irritants, allergens, and immune factors

8.3 Pathophysiology of Leprosy

Definition

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused mainly by the bacterium Mycobacterium leprae. It primarily affects the skin and peripheral nerves but may also involve the eyes and mucous membranes of the upper respiratory tract.

The disease is characterized by a wide range of clinical manifestations depending on the immune response of the affected individual. Damage to peripheral nerves may lead to loss of sensation, muscle weakness, deformities, and secondary injuries. Leprosy is curable with multidrug therapy, and early diagnosis helps prevent permanent disability.

Causative Organism and Transmission

Mycobacterium leprae is an acid-fast, slow-growing bacterium that has a preference for cooler tissues, including the skin and peripheral nerves. It primarily infects macrophages and Schwann cells, which are the supporting cells of peripheral nerves.

Transmission is believed to occur mainly through respiratory droplets during prolonged and close contact with an untreated person with infectious leprosy. Casual contact, such as shaking hands, sharing meals, or sitting together, is not considered a typical route of transmission.

The incubation period is usually prolonged and may extend over several years.

Pathophysiology

The pathophysiology of leprosy depends largely on the interaction between the organism and the host immune response. After entering the body, M. leprae may spread to the skin and peripheral nerves. The organism has a particular ability to infect Schwann cells and macrophages.

The host immune response determines the extent of bacterial multiplication, tissue inflammation, and nerve damage.

1. Entry and Establishment of Infection

The organism generally enters through the respiratory route during prolonged exposure to an untreated infectious case. It may then spread through the body and localize in the skin and peripheral nerves. Because of its slow growth, clinical manifestations may take years to develop.

2. Infection of Schwann Cells

Schwann cells form the myelin sheath around peripheral nerve fibres and provide support for nerve function. M. leprae can enter Schwann cells and interfere with their normal function.

Infection and inflammation around peripheral nerves may cause:

- Damage to Schwann cells.
- Loss or disruption of myelin.
- Impaired nerve conduction.
- Sensory loss and, in advanced cases, motor dysfunction.

3. Role of Cell-Mediated Immunity

The immune response plays a major role in determining the clinical form of leprosy.

In individuals with a strong cell-mediated immune response, bacterial multiplication is more effectively controlled. These individuals tend to develop localized lesions with relatively few organisms.

In individuals with a weak or ineffective cell-mediated immune response, the bacteria may multiply extensively, producing widespread lesions and a higher bacterial load.

4. Inflammatory Damage to Peripheral Nerves

Inflammation within and around peripheral nerves can cause nerve swelling and compression. This may result in progressive nerve injury. Sensory impairment is particularly important because affected individuals may not recognize pain, heat, or mechanical injury.

Repeated unnoticed injuries can lead to ulcers, infections, tissue damage, and deformities. Motor nerve involvement may produce muscle weakness and loss of normal hand or foot function.

5. Spectrum of Leprosy

Leprosy is commonly described as a spectrum based on clinical findings, bacterial load, and immune response.

Tuberculoid leprosy: This form is associated with a strong cell-mediated immune response. It generally produces a small number of well-defined skin lesions with reduced sensation. Peripheral nerve involvement may be localized but can cause significant sensory or motor impairment.

Lepromatous leprosy: This form is associated with a weak cell-mediated immune response against the organism. It is characterized by numerous skin lesions, widespread involvement, and a high bacterial load. Peripheral nerve damage may be extensive.

Borderline forms: These forms show features between the tuberculoid and lepromatous ends of the spectrum. Their clinical manifestations and immune responses may vary.

Clinical Features

The major clinical features of leprosy include:

- Hypopigmented or reddish skin patches.
- Reduced or absent sensation over affected skin lesions.
- Thickening of peripheral nerves.
- Numbness, tingling, or weakness in the hands and feet.
- Muscle weakness and deformities in advanced cases.
- Non-healing ulcers due to repeated unnoticed injuries.
- Eye involvement, which may lead to visual complications.

Loss of sensation is a characteristic feature and is important in distinguishing leprosy from many other skin disorders.

Complications

If diagnosis and treatment are delayed, nerve damage may become permanent. Possible complications include:

- Loss of protective sensation.
- Repeated burns, cuts, and injuries.
- Chronic ulcers and secondary infections.
- Muscle weakness and deformities of the hands and feet.
- Eye damage and visual impairment.
- Disability affecting daily activities.

Basic Principles of Treatment and Prevention

Leprosy is treated with multidrug therapy using a combination of antimicrobial medicines. The treatment regimen depends on the classification of the disease and is provided under appropriate medical supervision. Early detection and completion of treatment reduce transmission and prevent further complications.

Prevention includes early identification of cases, treatment of affected individuals, examination of close contacts when indicated, and health education. Patients should also receive guidance on protecting areas with reduced sensation from burns and injuries.

8.4 Basic Principles of Wound Healing

Introduction

Wound healing is the biological process through which the body repairs damaged tissue following injury. It involves a coordinated sequence of cellular and biochemical events that restore tissue continuity and function. Wound healing requires interactions among blood cells, inflammatory cells, growth factors, extracellular matrix components, and tissue cells.

The healing process may occur in the skin, muscles, blood vessels, and other organs. In the skin, it aims to restore the protective barrier and close the damaged area. The final result depends on the depth and size of the wound, blood supply, infection, nutritional status, and general health of the individual.

Types of Wound Healing

Wounds may heal by different processes depending on the extent of tissue damage and whether the wound edges are brought together.

1. Healing by Primary Intention

Healing by primary intention occurs when the edges of a clean wound are closely approximated, such as in a surgical incision closed with sutures or staples. Tissue loss is minimal, and healing generally occurs with less granulation tissue formation and a smaller scar.

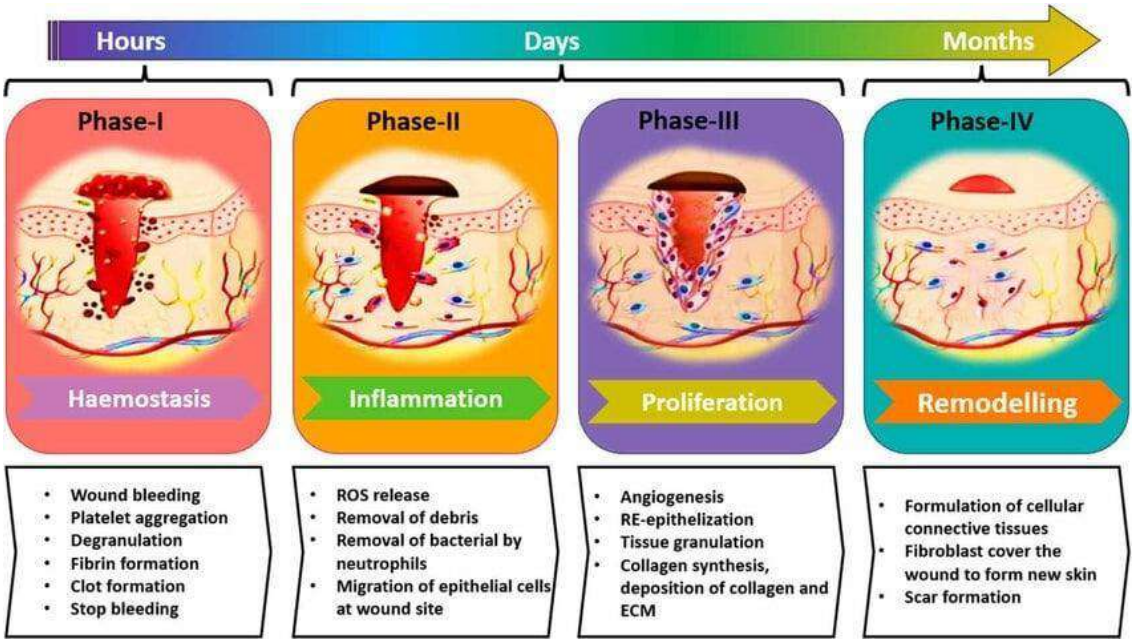
2. Healing by Secondary Intention

Healing by secondary intention occurs when the wound edges cannot be closely approximated because of extensive tissue loss, infection, or an open wound. The wound is filled gradually by granulation tissue, followed by wound contraction and epithelialization. Healing generally takes longer and produces a larger scar.

Phases of Wound Healing

Wound healing is commonly described in four overlapping phases:

1. Hemostasis
2. Inflammation
3. Proliferation
4. Remodeling or maturation



8.4.1 Hemostasis Phase

Hemostasis begins immediately after tissue injury. Its primary function is to stop bleeding and establish a temporary framework for tissue repair.

The major events include:

- Vasoconstriction: Injured blood vessels constrict to reduce blood loss.
- Platelet activation: Platelets adhere to exposed components of the damaged vessel wall and become activated.
- Platelet aggregation: Activated platelets aggregate to form a temporary platelet plug.
- Coagulation: The coagulation cascade leads to the formation of fibrin, which stabilizes the platelet plug and forms a blood clot.

The clot provides a temporary matrix for migrating cells and releases substances that participate in subsequent inflammatory and repair processes.

8.4.2 Inflammatory Phase

The inflammatory phase begins shortly after injury and is essential for removing microorganisms, damaged cells, and tissue debris.

The major events include:

- Increased blood flow to the injured area.
- Increased vascular permeability, allowing plasma proteins and immune cells to enter the tissue.
- Migration of neutrophils to the wound site.
- Recruitment of monocytes, which differentiate into macrophages.
- Removal of microorganisms and damaged tissue by phagocytosis.

Neutrophils provide early defence against infection, while macrophages play a major role in clearing debris and coordinating tissue repair. Macrophages release growth factors and cytokines that stimulate the formation of new blood vessels, fibroblast activity, and epithelial repair.

The inflammatory phase is necessary for normal healing. However, prolonged or excessive inflammation may delay wound closure and contribute to tissue damage.

8.4.3 Proliferative Phase

The proliferative phase involves the formation of new tissue to fill the wound and restore the skin surface. It commonly begins within a few days after injury and may continue for several weeks, depending on wound severity.

The major processes are:

1. Angiogenesis: Angiogenesis is the formation of new blood vessels from existing vessels. It supplies oxygen and nutrients to the healing tissue.

2. Fibroblast Proliferation: Fibroblasts migrate into the wound and produce extracellular matrix components, particularly collagen. This provides structural support for the developing tissue.

3. Granulation Tissue Formation: Granulation tissue consists of newly formed blood vessels, fibroblasts, inflammatory cells, and extracellular matrix. It appears as moist, reddish tissue and fills the wound space.

4. Re-epithelialization: Keratinocytes migrate from the wound edges and surviving skin appendages to cover the exposed surface. These cells proliferate and form a new epidermal layer.

5. Wound Contraction: Myofibroblasts help pull the wound edges towards each other, reducing the size of the wound. This process is particularly important in healing by secondary intention.

8.4.4 Remodeling or Maturation Phase

The remodeling phase involves the reorganization and strengthening of newly formed tissue. It may continue for several months or longer.

The major events include:

- Replacement and reorganization of immature collagen.
- Increased collagen cross-linking.
- Reduction in the number of newly formed blood vessels.
- Decrease in cellularity of the healing tissue.
- Improvement in tensile strength of the scar.

During this phase, the wound gradually becomes less vascular and the scar becomes flatter and paler. However, healed skin generally does not regain the full strength and structural organization of uninjured skin.

Table 8.2: Factors Affecting Wound Healing

Factors	Effect on Wound Healing
Infection	Prolongs inflammation and may cause tissue destruction
Poor blood supply	Reduces oxygen and nutrient delivery to the wound
Diabetes mellitus	May impair circulation, immune function, and tissue repair
Malnutrition	Deficiencies of protein, vitamins, and minerals can delay tissue formation
Age	Healing may be slower in older individuals due to changes in cellular activity and circulation
Smoking	Reduces tissue oxygenation and may impair blood flow
Repeated trauma	Disrupts newly formed tissue and delays wound closure
Foreign bodies	May maintain inflammation and increase the risk of infection
Excessive wound tension	Can separate wound edges and interfere with healing

Complications of Wound Healing

Abnormal wound healing may lead to several complications.

1. Wound Infection: Microorganisms may enter the wound and produce local inflammation, pus formation, tissue damage, and delayed healing.

2. Wound Dehiscence: Wound dehiscence refers to the separation of previously approximated wound edges. It may occur due to infection, excessive tension, poor tissue strength, or other factors.

3. Hypertrophic Scar: A hypertrophic scar is raised and thickened due to excessive collagen deposition but remains within the boundaries of the original wound.

4. Keloid: A keloid is an abnormal scar that extends beyond the original wound margins due to excessive scar tissue formation.

5. Chronic Wound: A chronic wound fails to progress through the normal phases of healing in an orderly and timely manner. It may be associated with poor circulation, infection, repeated pressure, or underlying systemic disease.

The integumentary system consists of the skin and its appendages and serves as a protective barrier, sensory organ, and regulator of body temperature. The skin is composed of the epidermis and dermis, with the hypodermis located beneath it. Psoriasis is an immune-mediated disorder characterized by excessive keratinocyte proliferation and plaque formation, whereas dermatitis involves skin inflammation commonly associated with barrier dysfunction, irritants, or allergens. Leprosy is a chronic infection caused by Mycobacterium leprae, primarily affecting the skin and peripheral nerves. Its manifestations depend on the host immune response, and nerve damage may lead to sensory loss and disability. Wound healing is a coordinated repair process involving hemostasis, inflammation, proliferation, and remodeling. Proper blood supply, nutrition, infection control, and protection from repeated injury are important for effective healing.

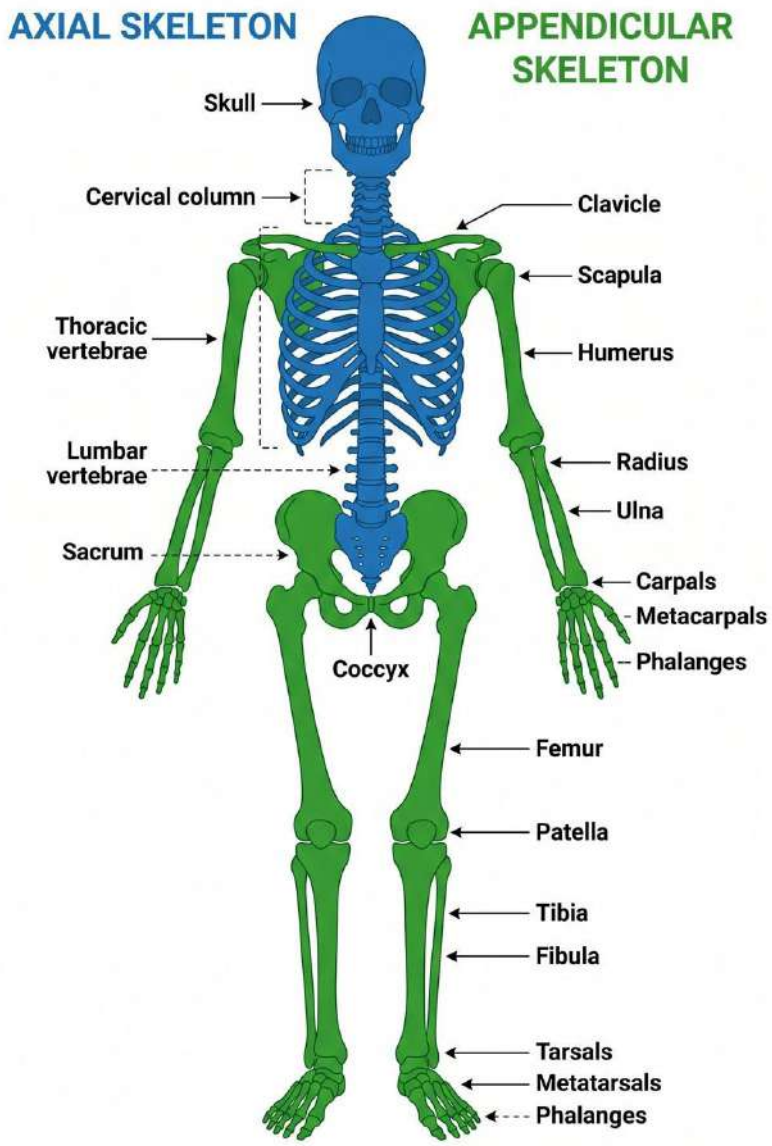
Chapter 9: Skeletal System and Joints

9.1 Divisions of Skeletal System

Introduction

The skeletal system is the supporting framework of the human body. It consists of bones, cartilages, joints, and ligaments. In an adult, the skeleton typically contains 206 bones, although the number may vary slightly among individuals due to variations in small bones and their fusion.

The skeletal system provides shape and support to the body, protects internal organs, enables movement, stores minerals, and produces blood cells. Anatomically, the human skeleton is divided into two major divisions: the axial skeleton and the appendicular skeleton.



9.1.1 Axial Skeleton

The axial skeleton forms the central axis of the body. It consists of 80 bones in the typical adult skeleton and includes the skull, vertebral column, and thoracic cage.

Its major functions are to support the head and trunk, protect the brain, spinal cord, and thoracic organs, and provide attachment sites for muscles.

The axial skeleton includes:

- **Skull:** Protects the brain and supports the structures of the face.
- **Auditory ossicles:** Three small bones in each middle ear that transmit sound vibrations.
- **Hyoid bone:** Supports the tongue and provides attachment for muscles involved in swallowing and speech.
- **Vertebral column:** Protects the spinal cord and supports the head and trunk.
- **Thoracic cage:** Consists of the ribs, sternum, and thoracic vertebrae; it protects the heart and lungs and assists in breathing.

9.1.2 Appendicular Skeleton

The appendicular skeleton consists of the bones of the upper and lower limbs and the girdles that attach them to the axial skeleton. It typically contains 126 bones in the adult body.

Its main functions are to facilitate movement, support body weight, and allow manipulation of objects and locomotion.

The appendicular skeleton includes:

- **Pectoral girdle:** Consists of the clavicles and scapulae and connects the upper limbs to the trunk.
- **Upper limbs:** Include the arm, forearm, wrist, and hand bones.
- **Pelvic girdle:** Consists of the two hip bones and connects the lower limbs to the axial skeleton.
- **Lower limbs:** Include the thigh, leg, ankle, and foot bones.

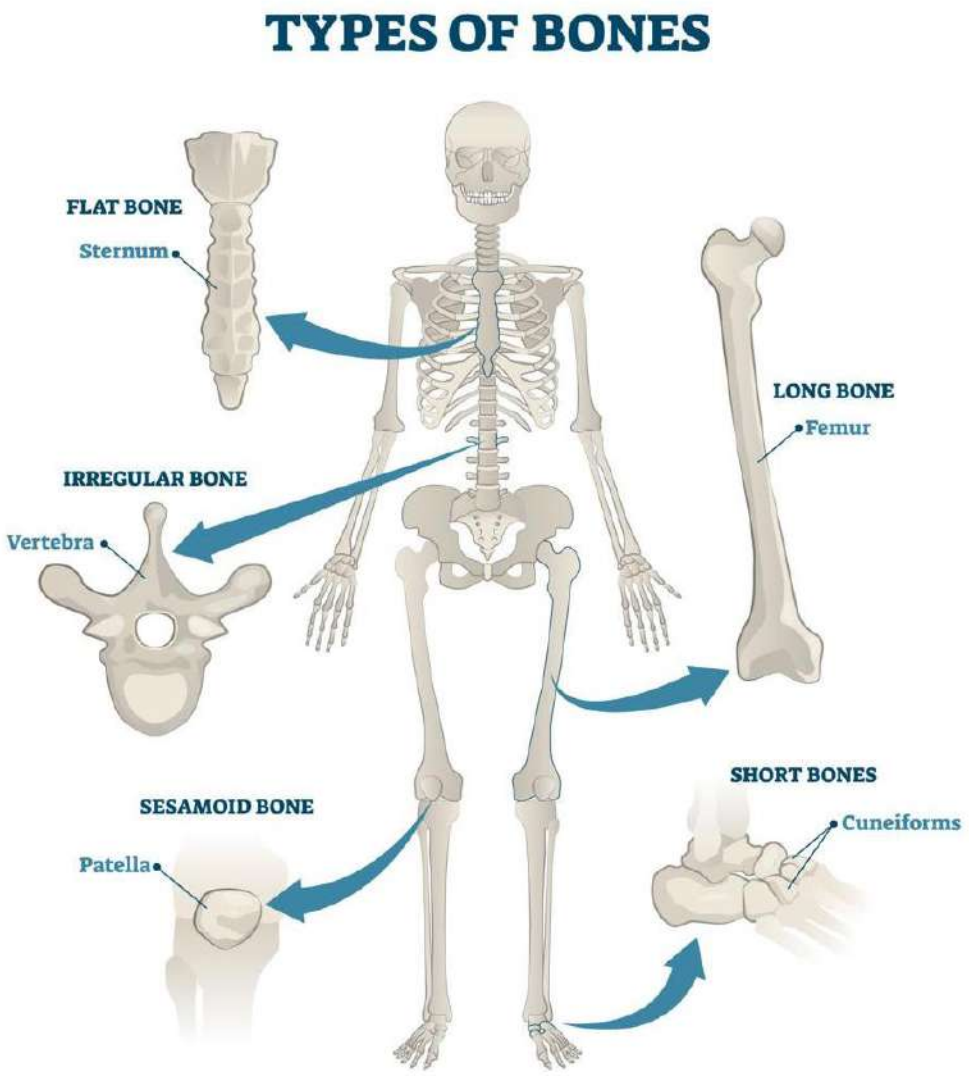
Table 9.1: Comparison of Axial and Appendicular Skeleton

Feature	Axial Skeleton	Appendicular Skeleton
Main position	Central axis of the body	Limbs and their attachment girdles
Typical number of bones	80	126
Main components	Skull, vertebral column, thoracic cage, auditory ossicles, and hyoid bone	Pectoral girdle, upper limbs, pelvic girdle, and lower limbs
Major functions	Support and protection of vital organs	Movement, locomotion, and manipulation
Examples	Cranium, ribs, sternum, vertebrae	Humerus, radius, femur, tibia, and pelvic bones

9.2 Types of Bones

Bones are living connective tissues composed of cells, collagen fibres, and mineralized extracellular matrix. They provide mechanical support, protect internal organs, act as levers for muscle movement, store minerals, and contain bone marrow involved in blood cell formation.

Bones are classified according to their shape. The major types are long, short, flat, irregular, and sesamoid bones.



9.2.1 Long Bones

Long bones are longer than they are wide and generally consist of a central shaft and two expanded ends. The shaft is called the diaphysis, while the ends are called epiphyses. The region between the diaphysis and epiphysis is known as the metaphysis.

Long bones mainly function as levers for movement and support body weight.

Examples: Femur, humerus, tibia, fibula, radius, and ulna.

9.2.2 Short Bones

Short bones are approximately equal in length, width, and thickness. They generally consist of spongy bone surrounded by a thin layer of compact bone.

They provide stability, support, and limited movement.

Examples: Carpals of the wrist and tarsals of the ankle.

9.2.3 Flat Bones

Flat bones are thin, flattened, and often slightly curved. They commonly consist of two layers of compact bone enclosing spongy bone.

They protect internal organs and provide broad surfaces for muscle attachment. Some flat bones also contain red bone marrow.

Examples: Sternum, ribs, scapulae, and cranial bones.

9.2.4 Irregular Bones

Irregular bones have complex shapes that do not fit into the other categories. Their structure is adapted to their specific functions, such as protection, support, and muscle attachment.

Examples: Vertebrae, hip bones, and certain bones of the skull.

9.2.5 Sesamoid Bones

Sesamoid bones are small, rounded bones that develop within tendons, usually near joints. They reduce friction, protect tendons, and may improve the mechanical efficiency of muscles.

Example: Patella, or kneecap.

Table 9.2: Summary of Bone Classification

Type of Bone	Main Characteristics	Examples
Long	Longer than wide; has a shaft and two ends	Femur, humerus
Short	Approximately equal dimensions	Carpals, tarsals
Flat	Thin and flattened; often protective	Sternum, ribs, cranial bones
Irregular	Complex shape	Vertebrae, hip bones
Sesamoid	Develops within a tendon	Patella

9.3 Salient Features and Functions of Bones of Axial and Appendicular Skeletal System

The bones of the axial and appendicular skeleton differ in shape, location, and function. Together, they provide support, protection, and movement.

9.3.1 Bones of the Axial Skeleton

A. Skull

The skull is the bony framework of the head. It protects the brain, supports the structures of the face, and provides attachment for muscles involved in chewing and facial expression.

The skull consists of 22 bones, excluding the auditory ossicles and hyoid bone. These are divided into cranial and facial bones.

Cranial bones: There are eight cranial bones that enclose and protect the brain.

- Frontal bone: Forms the forehead and the roof of the orbits.
- Parietal bones: Form the upper and lateral walls of the skull.
- Temporal bones: Form part of the sides and base of the skull and contain structures of the ear.
- Occipital bone: Forms the posterior and inferior part of the skull and contains the foramen magnum through which the spinal cord passes.
- Sphenoid bone: Lies at the base of the skull and contributes to the floor of the cranial cavity and the orbits.
- Ethmoid bone: Contributes to the nasal cavity, nasal septum, and medial wall of the orbit.

Facial bones: There are 14 facial bones that form the framework of the face and support the teeth and sensory structures.

Important facial bones include:

- Maxillae: Form the upper jaw and contribute to the hard palate, nasal cavity, and orbits.
- Mandible: Forms the lower jaw and is the only freely movable bone of the skull, apart from the auditory ossicles.
- Zygomatic bones: Form the cheek prominence.
- Nasal bones: Form the bridge of the nose.
- Lacrimal bones: Contribute to the medial wall of the orbit.
- Palatine bones: Form the posterior part of the hard palate.
- Vomer: Forms part of the nasal septum.
- Inferior nasal conchae: Increase the surface area inside the nasal cavity and help condition inhaled air.

B. Auditory Ossicles

The auditory ossicles are three small bones located in the middle ear on each side:

- Malleus
- Incus
- Stapes

They transmit sound vibrations from the tympanic membrane to the inner ear.

C. Hyoid Bone

The hyoid is a U-shaped bone located in the anterior neck. It does not articulate directly with another bone. It provides attachment for muscles of the tongue, pharynx, and larynx and assists in swallowing and speech.

D. Vertebral Column

The vertebral column, or backbone, forms the central supporting axis of the body. It protects the spinal cord, supports the head, and provides attachment for ribs and muscles.

In adults, it consists of 26 bones: 24 separate vertebrae, the sacrum, and the coccyx. The vertebral column is divided into five regions.

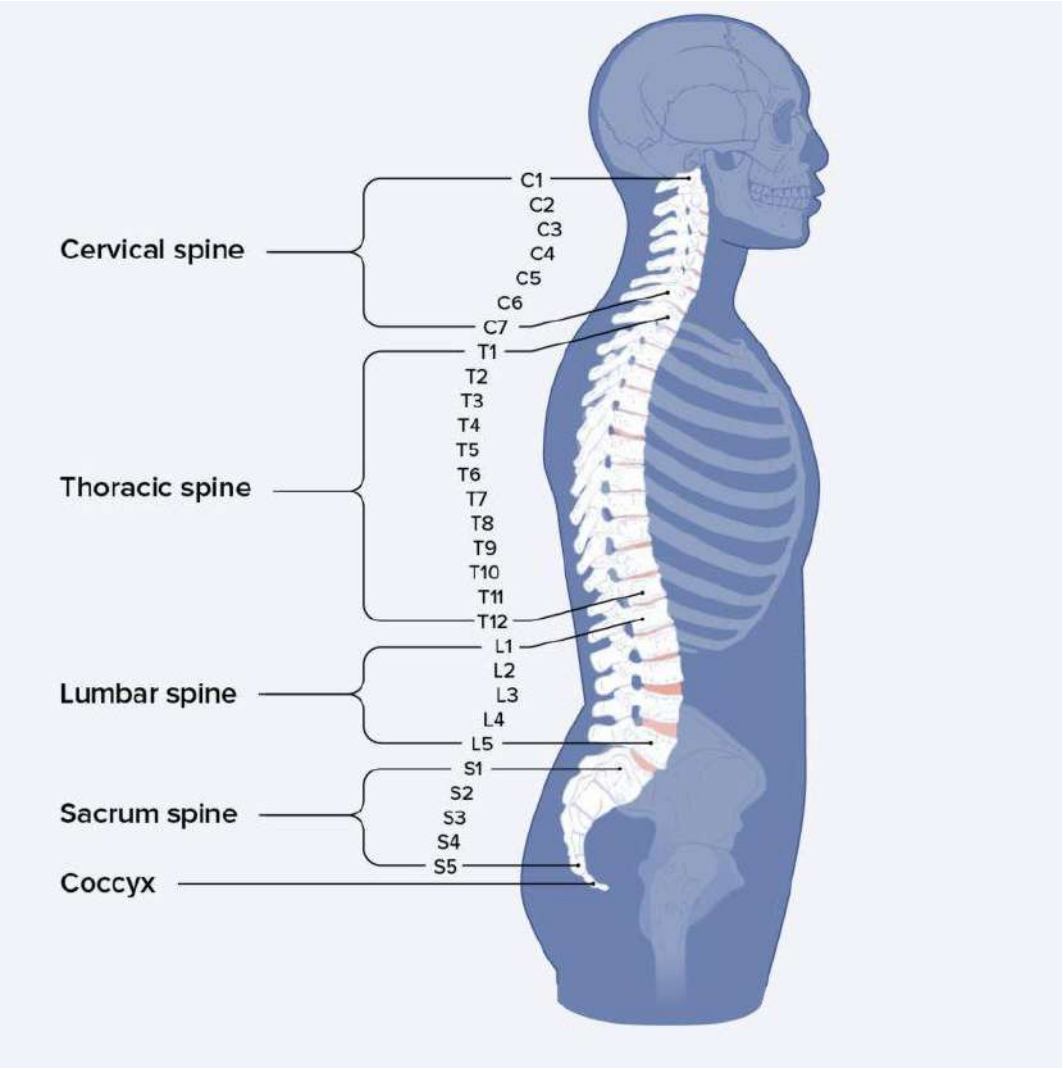


Table 9.3: Regions of the Vertebral Column, Number of Vertebrae, and Their Salient Features and Functions

Region	Number of Vertebrae	Salient Features and Functions
Cervical	7	Located in the neck; supports the head and allows a wide range of neck movement
Thoracic	12	Articulates with the ribs and contributes to the thoracic cage
Lumbar	5	Large vertebrae adapted for weight-bearing and movement of the lower back
Sacral	5 fused	Forms the sacrum and connects the vertebral column with the pelvic girdle
Coccygeal	Usually 4 fused	Forms the coccyx and provides attachment for ligaments and muscles

The first two cervical vertebrae have special features:

- Atlas (C1): Supports the skull and permits nodding movements of the head.
- Axis (C2): Contains the dens, which acts as a pivot for rotation of the head.

Between most vertebral bodies are intervertebral discs composed of fibrocartilage. These discs absorb shock, allow flexibility, and help distribute mechanical loads.

E. Thoracic Cage

The thoracic cage forms the bony framework of the chest. It consists of the sternum, 12 pairs of ribs, and 12 thoracic vertebrae.

Sternum: The sternum is a flat bone located in the anterior midline of the chest. It consists of three parts:

1. Manubrium: The upper part, which articulates with the clavicles and first pair of ribs.
2. Body: The longest part, which articulates with most of the costal cartilages.
3. Xiphoid process: The small inferior part, which provides attachment for muscles and ligaments.

Ribs: There are 12 pairs of ribs, classified according to their attachment to the sternum.

- True ribs (1–7): Attach directly to the sternum through their own costal cartilages.
- False ribs (8–10): Attach indirectly to the sternum through the cartilage of the rib above.
- Floating ribs (11–12): Do not attach to the sternum anteriorly.

The thoracic cage protects the heart and lungs and participates in respiratory movements.

9.3.2 Bones of the Appendicular Skeleton

A. Pectoral Girdle

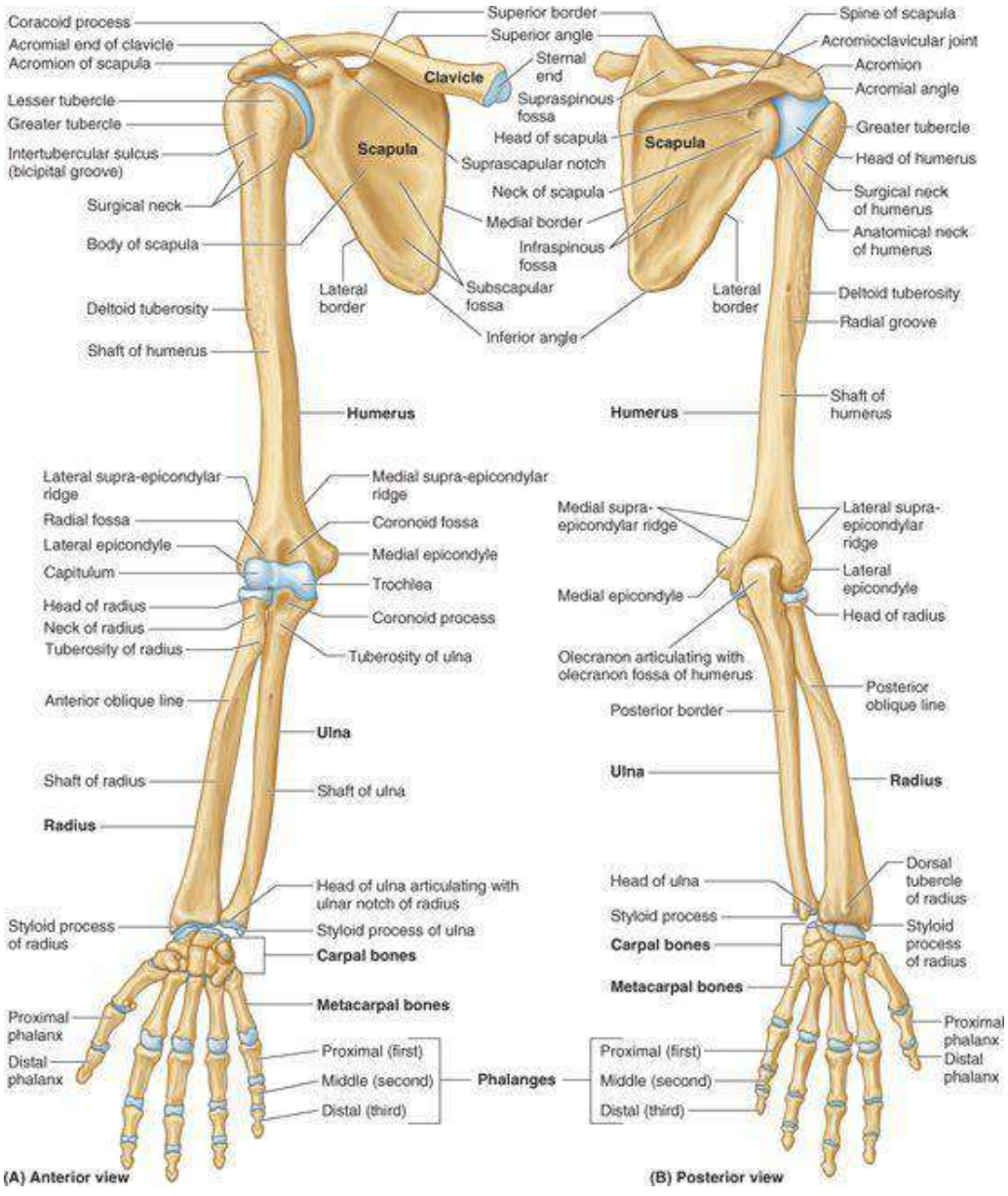
The pectoral girdle connects each upper limb to the axial skeleton. It consists of the clavicle and scapula.

Clavicle: The clavicle is an S-shaped bone located horizontally at the upper part of the chest. It connects the sternum to the scapula, supports the shoulder, and helps maintain the position of the upper limb.

Scapula: The scapula is a flat, triangular bone located on the posterior surface of the thoracic cage. It contains the glenoid cavity, which articulates with the head of the humerus to form the shoulder joint. It also provides attachment for several muscles that control shoulder and arm movement.

B. Bones of the Upper Limb

Each upper limb contains 30 bones, excluding the pectoral girdle.



Humerus: The humerus is the long bone of the arm. Its head articulates with the glenoid cavity of the scapula to form the shoulder joint. Its distal end articulates with the radius and ulna at the elbow.

Radius: The radius is located on the lateral side of the forearm in the anatomical position, on the thumb side. It participates in wrist movement and rotation of the forearm.

Ulna: The ulna is located on the medial side of the forearm, on the little-finger side. Its olecranon process forms the prominent point of the elbow and contributes to the elbow joint.

Carpal bones: The wrist contains eight carpal bones arranged in two rows. They provide flexibility and stability to the wrist.

Metacarpals: Five metacarpal bones form the framework of the palm.

Phalanges: The fingers contain 14 phalanges. The thumb has two phalanges, while each of the other fingers has three.

C. Pelvic Girdle

The pelvic girdle consists of two hip bones. Each hip bone develops from the fusion of three bones:

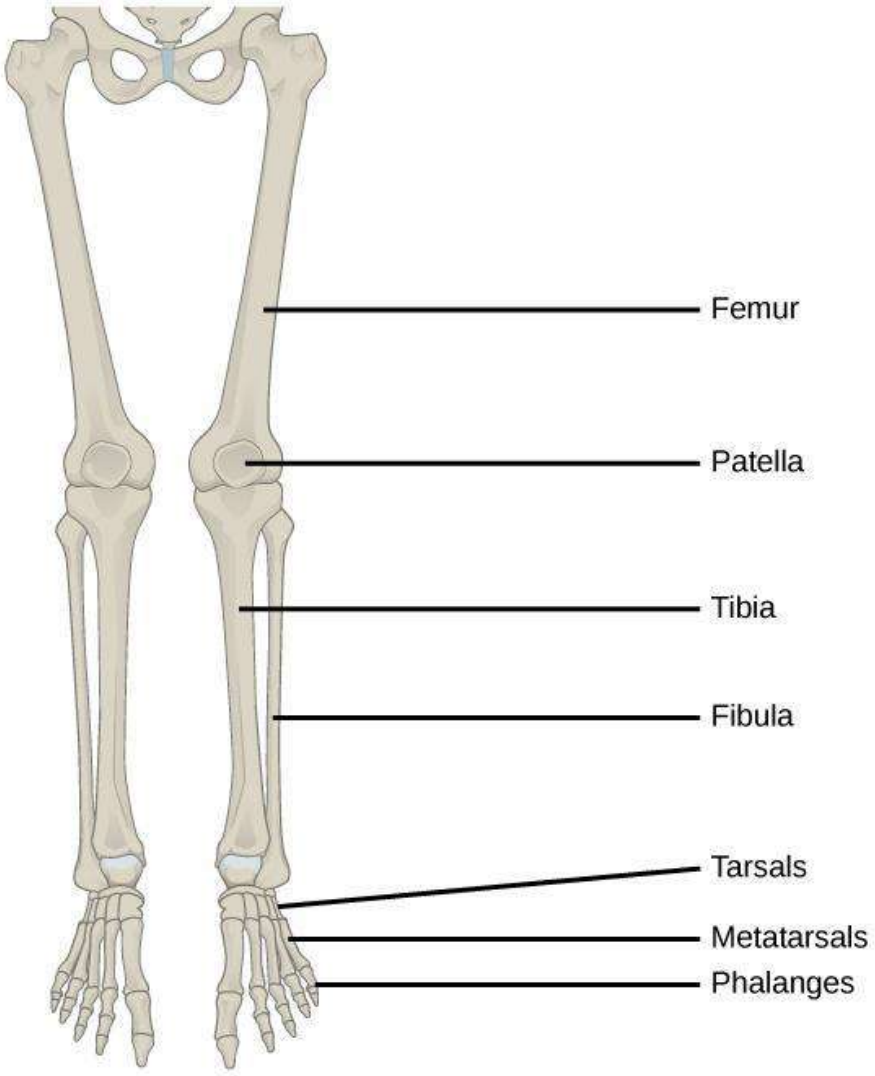
- Ilium: The broad, upper part of the hip bone.
- Ischium: The posteroinferior part that supports body weight during sitting.
- Pubis: The anterior part of the hip bone.

The three parts meet at the acetabulum, a deep socket that articulates with the head of the femur to form the hip joint.

The pelvic girdle supports the trunk, transfers body weight to the lower limbs, protects pelvic organs, and provides attachment for muscles.

D. Bones of the Lower Limb

Each lower limb contains 30 bones, excluding the pelvic girdle. These bones are adapted mainly for weight-bearing, balance, and locomotion.



Femur: The femur is the longest and strongest bone in the body. Its head articulates with the acetabulum to form the hip joint. Its distal end articulates with the tibia and patella at the knee.

Patella: The patella is a sesamoid bone located within the tendon of the quadriceps femoris muscle. It protects the anterior knee joint and improves the mechanical efficiency of knee extension.

Tibia: The tibia is the larger, medial bone of the leg. It bears most of the body weight transmitted from the femur to the ankle.

Fibula: The fibula is the slender, lateral bone of the leg. It provides attachment for muscles and contributes to the stability of the ankle, but it bears much less body weight than the tibia.

Tarsal bones: The ankle and proximal foot contain seven tarsal bones, including the talus and calcaneus. The calcaneus forms the heel, while the talus articulates with the tibia and fibula.

Metatarsals: Five metatarsal bones form the framework of the foot.

Phalanges: The toes contain 14 phalanges. The great toe has two, while the other toes generally have three each.

9.3.3 Functions of the Skeletal System

The bones of both divisions work together to perform the following functions:

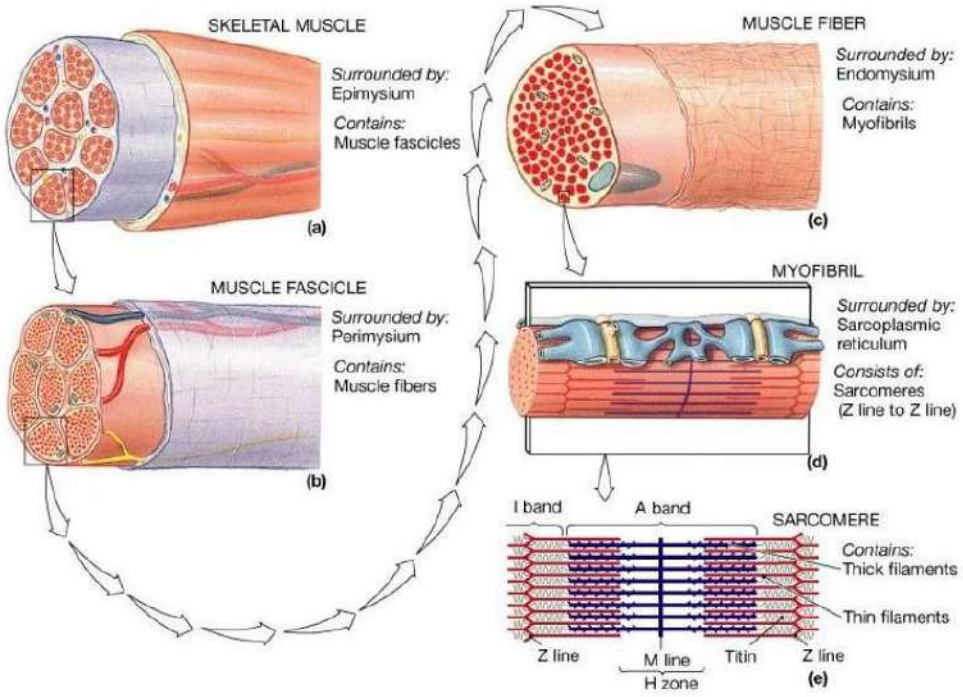
1. Support: Provide a rigid framework that maintains body shape and supports soft tissues.
2. Protection: Protect vital organs, such as the brain, spinal cord, heart, and lungs.
3. Movement: Act as levers for skeletal muscles and facilitate body movement.
4. Mineral storage: Store minerals, particularly calcium and phosphate, and release them when required.
5. Blood cell formation: Red bone marrow produces red blood cells, white blood cells, and platelets through hematopoiesis.
6. Fat storage: Yellow bone marrow stores triglycerides as an energy reserve.

9.4 Organization of Skeletal Muscle

Introduction

Skeletal muscles are voluntary muscles attached mainly to bones by tendons. They produce body movements, maintain posture, stabilize joints, and generate heat. Skeletal muscle fibres are long, cylindrical, multinucleated cells containing contractile proteins arranged in an organized pattern.

Skeletal muscle is organized at several structural levels, beginning with the whole muscle and extending to the myofilaments.



9.4.1 Connective Tissue Coverings

Each skeletal muscle is surrounded and supported by connective tissue layers.

Epimysium: The epimysium is a dense connective tissue layer that surrounds the entire muscle. It protects the muscle and helps maintain its structural organization.

Perimysium: The perimysium surrounds bundles of muscle fibres called fascicles. It carries blood vessels and nerves into the muscle.

Endomysium: The endomysium is a thin connective tissue layer surrounding each individual muscle fibre. It supports the fibres and contains small blood vessels and nerve branches.

These connective tissue layers continue into tendons, which attach muscles to bones.

9.4.2 Fascicles and Muscle Fibres

A muscle fascicle is a bundle of muscle fibres surrounded by perimysium. Each muscle fibre is a single elongated muscle cell surrounded by a cell membrane called the sarcolemma.

The sarcoplasm is the cytoplasm of the muscle fibre. It contains nuclei, mitochondria, glycogen, myoglobin, and numerous myofibrils.

Skeletal muscle fibres are multinucleated because they develop through the fusion of precursor muscle cells.

9.4.3 Myofibrils and Sarcomeres

Myofibrils are long cylindrical structures within muscle fibres. They consist of repeating contractile units called sarcomeres.

The sarcomere is the basic structural and functional unit of skeletal muscle contraction. It extends from one Z disc to the next.

Each sarcomere contains two major types of myofilaments:

- Thin filaments: Composed mainly of actin, along with the regulatory proteins troponin and tropomyosin.
- Thick filaments: Composed mainly of myosin molecules, which contain projecting heads that interact with actin during contraction.

The arrangement of thick and thin filaments produces the characteristic striated appearance of skeletal muscle.

Table 9.4: Bands and Lines of the Sarcomere

Structure	Description
Z disc	Marks the boundary of each sarcomere and anchors thin filaments
A band	Dark band corresponding to the full length of thick filaments
I band	Light band containing thin filaments without overlap with thick filaments
H zone	Central region of the A band containing thick filaments without thin filament overlap
M line	Central region that helps hold thick filaments in position

During muscle contraction, the Z discs move closer together, the I band and H zone become narrower, and the A band remains approximately constant in length. This occurs because the filaments slide past one another rather than shortening themselves.

9.4.4 Regulatory Proteins

Actin: Actin forms the main structural component of thin filaments and contains binding sites for myosin.

Myosin: Myosin forms thick filaments. Its heads bind to actin and use energy from ATP to generate force.

Tropomyosin: Tropomyosin lies along the actin filament and blocks myosin-binding sites when the muscle is relaxed.

Troponin: Troponin is a regulatory protein complex. When calcium ions bind to troponin, tropomyosin shifts and exposes the myosin-binding sites on actin.

9.4.5 Sarcoplasmic Reticulum and T-Tubules

The sarcoplasmic reticulum is a specialized membrane system that stores and releases calcium ions required for muscle contraction.

Transverse tubules (T-tubules) are inward extensions of the sarcolemma. They carry electrical signals deep into the muscle fibre and help coordinate calcium release from the sarcoplasmic reticulum.

9.5 Physiology of Muscle Contraction

Introduction

Muscle contraction is the process by which skeletal muscle develops tension and produces force. It occurs through interactions between actin and myosin filaments within sarcomeres. The accepted explanation is the sliding filament theory, according to which thin filaments slide past thick filaments, causing the sarcomere to shorten.

Muscle contraction requires electrical stimulation, calcium ions, ATP, and functional contractile proteins.

9.5.1 Sliding Filament Theory

According to the sliding filament theory, the length of actin and myosin filaments remains essentially unchanged during contraction. Instead, the thin filaments slide towards the centre of the sarcomere, increasing their overlap with thick filaments.

As the filaments slide:

- Z discs move closer together.
- The sarcomere becomes shorter.

- The I band becomes narrower.
- The H zone becomes narrower or may disappear.
- The A band remains approximately constant.

9.5.2 Excitation–Contraction Coupling

Excitation–contraction coupling is the process by which an electrical signal in a muscle fibre leads to contraction.

The major steps are:

1. A nerve impulse reaches the neuromuscular junction and stimulates the muscle fibre.
2. An action potential spreads along the sarcolemma.
3. The action potential travels into the muscle fibre through the T-tubules.
4. The electrical signal activates proteins associated with the T-tubules and sarcoplasmic reticulum.
5. Calcium ions are released from the sarcoplasmic reticulum into the sarcoplasm.
6. Calcium binds to troponin, causing a change in the position of tropomyosin.
7. Myosin-binding sites on actin become exposed, allowing cross-bridge formation.

9.5.3 Cross-Bridge Cycle

The cross-bridge cycle is the repeated interaction between myosin heads and actin filaments. It produces the sliding movement responsible for muscle contraction.

Step 1: Cross-Bridge Formation When calcium exposes the binding sites on actin, energized myosin heads attach to actin and form cross-bridges.

Step 2: Power Stroke The myosin head changes its position and pulls the actin filament towards the centre of the sarcomere. This movement is called the power stroke.

Step 3: Detachment A new ATP molecule binds to the myosin head, causing it to detach from actin.

Step 4: Reactivation of Myosin ATP is hydrolysed into ADP and inorganic phosphate. The released energy repositions the myosin head into an energized state, allowing it to bind again if calcium remains available.

The cycle continues as long as calcium and ATP are available and the binding sites on actin remain exposed.

9.5.4 Role of Calcium Ions

Calcium ions regulate the interaction between actin and myosin. In a resting muscle, the concentration of calcium in the sarcoplasm is low, and tropomyosin blocks the myosin-binding sites on actin.

When calcium is released from the sarcoplasmic reticulum, it binds to troponin. This causes tropomyosin to move away from the binding sites, allowing cross-bridge formation.

For relaxation, calcium ions are actively transported back into the sarcoplasmic reticulum by calcium pumps. The binding sites on actin become covered again, and cross-bridge cycling stops.

9.5.5 Role of ATP in Muscle Contraction

ATP is essential for both contraction and relaxation.

Its major functions include:

- Providing energy for the detachment and reactivation of myosin heads.
- Supporting the active transport of calcium ions into the sarcoplasmic reticulum.
- Maintaining ion gradients across the muscle cell membrane through membrane transport proteins.

In the absence of ATP, myosin cannot detach normally from actin. This explains the development of rigor mortis after death, when ATP production stops.

9.5.6 Muscle Relaxation

Muscle relaxation occurs when stimulation ends and calcium ions are removed from the sarcoplasm.

The major events are:

1. Motor neuron stimulation stops.
2. Acetylcholine is removed from the neuromuscular junction.
3. The muscle fibre membrane returns to its resting electrical state.
4. Calcium release from the sarcoplasmic reticulum decreases.
5. Calcium is actively transported back into the sarcoplasmic reticulum.
6. Troponin and tropomyosin return to their resting arrangement.
7. Myosin-binding sites on actin become covered, and cross-bridge cycling stops.

9.5.7 Types of Muscle Contraction

Isotonic contraction: Muscle length changes while tension is produced.

- Concentric contraction: The muscle shortens while producing force, such as during lifting a weight.
- Eccentric contraction: The muscle lengthens while producing force, such as during controlled lowering of a weight.

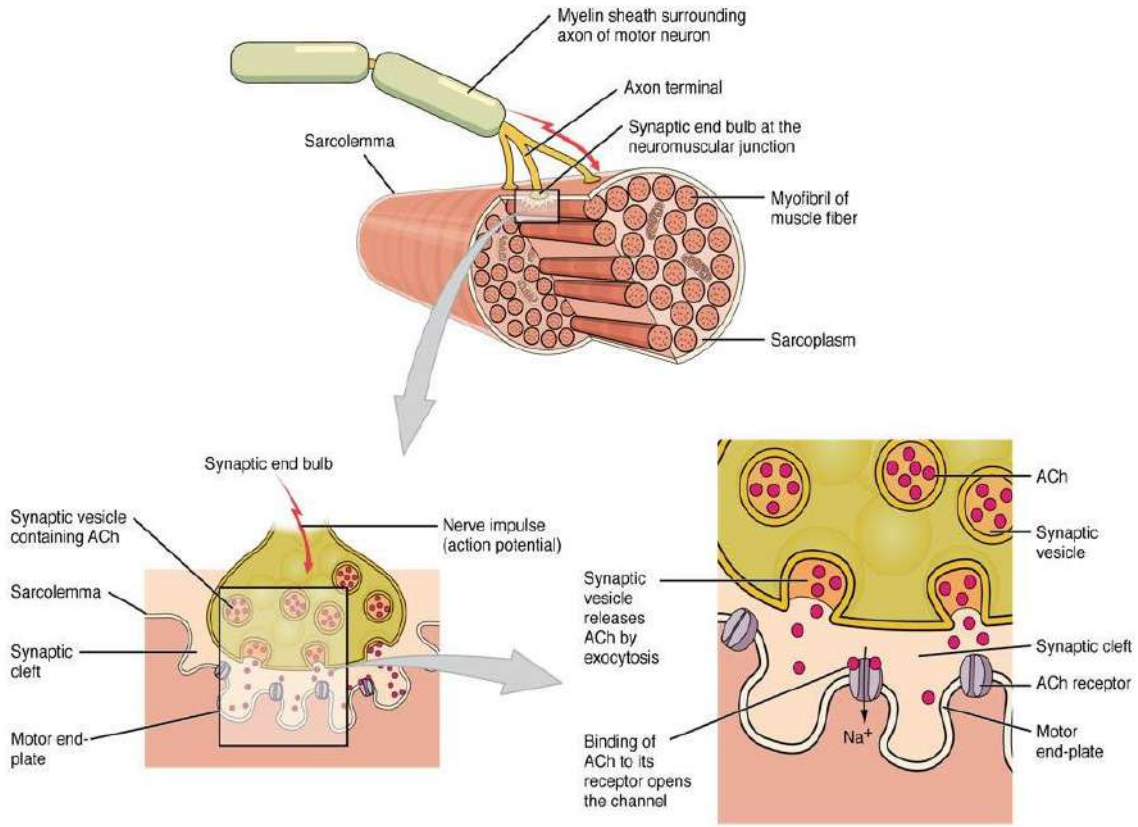
Isometric contraction: Muscle tension develops without a significant change in muscle length, such as when holding a fixed object in one position.

9.6 Neuromuscular Junction

Definition

The neuromuscular junction (NMJ) is a specialized synapse between the terminal of a motor neuron and a skeletal muscle fibre. It transmits signals from the nervous system to skeletal muscle and initiates muscle fibre contraction.

The main neurotransmitter involved in this process is acetylcholine (ACh).



9.6.1 Structure of the Neuromuscular Junction

The neuromuscular junction consists of three major components:

1. Presynaptic Terminal: The presynaptic terminal is the enlarged end of the motor neuron. It contains synaptic vesicles filled with acetylcholine and voltage-gated calcium channels.

2. Synaptic Cleft: The synaptic cleft is the narrow space between the motor neuron terminal and the muscle fibre membrane. It contains acetylcholinesterase, an enzyme responsible for breaking down acetylcholine.

3. Motor End Plate: The motor end plate is the specialized region of the muscle fibre membrane located beneath the motor neuron terminal. It contains a high concentration of nicotinic acetylcholine receptors.

9.6.2 Mechanism of Neuromuscular Transmission

Neuromuscular transmission occurs through a sequence of electrical and chemical events.

1. Arrival of nerve impulse: An action potential reaches the terminal of the motor neuron.
2. Calcium entry: Depolarization opens voltage-gated calcium channels, allowing calcium ions to enter the presynaptic terminal.
3. Release of acetylcholine: Calcium promotes the fusion of synaptic vesicles with the presynaptic membrane and the release of acetylcholine into the synaptic cleft.
4. Receptor binding: Acetylcholine diffuses across the cleft and binds to nicotinic acetylcholine receptors on the motor end plate.
5. Generation of end-plate potential: Receptor activation opens ion channels, producing a local depolarization known as the end-plate potential.
6. Muscle action potential: If the depolarization reaches threshold, an action potential is generated in the muscle fibre and spreads along the sarcolemma.
7. Initiation of contraction: The action potential travels through T-tubules and triggers calcium release from the sarcoplasmic reticulum, initiating the contraction process.

9.6.3 Role of Acetylcholinesterase

Acetylcholinesterase is an enzyme located in the synaptic cleft. It rapidly breaks down acetylcholine into acetate and choline. Choline is taken back into the presynaptic terminal and used for the synthesis of new acetylcholine.

The breakdown of acetylcholine prevents continuous stimulation of the muscle fibre and allows the neuromuscular junction to respond accurately to subsequent nerve impulses.

9.6.4 Importance of the Neuromuscular Junction

The neuromuscular junction ensures communication between the nervous system and skeletal muscles. It plays an essential role in voluntary movement, posture, and motor coordination. Normal function requires adequate release of acetylcholine, functional receptors, and effective removal of the neurotransmitter from the synaptic cleft.

9.7 Structural and Functional Classification of Joints

Introduction

A joint, also called an articulation, is the site where two or more bones meet or where bones are connected by cartilage. Joints provide stability, support, and movement. Their structure determines the degree and type of movement possible.

Joints are classified structurally according to the tissue connecting the bones and the presence or absence of a joint cavity. Functionally, they are classified according to the amount of movement they permit.

9.7.1 Structural Classification of Joints

Structurally, joints are classified into three major types:

A. Fibrous joints
B. Cartilaginous joints

C. Synovial joints

A. Fibrous Joints

In fibrous joints, bones are connected by dense fibrous connective tissue. These joints do not have a joint cavity and generally allow little or no movement.

The main types are:

Sutures: Sutures are immovable joints found between the bones of the skull. The bones are connected by a thin layer of dense connective tissue.

Syndesmoses: In syndesmoses, bones are connected by ligaments or an interosseous membrane. They permit limited movement.

Example: The distal tibiofibular joint.

Gomphoses: A gomphosis is a specialized fibrous joint in which a tooth fits into its socket in the jaw. The tooth is held in place by the periodontal ligament.

B. Cartilaginous Joints

In cartilaginous joints, bones are connected by cartilage. These joints do not contain a synovial cavity. They provide support and allow varying degrees of movement.

They are divided into two types:

Primary cartilaginous joints (synchondroses): Bones are joined by hyaline cartilage. These joints are generally temporary and may become ossified with age.

Examples: Epiphyseal growth plates and the first sternocostal joint.

Secondary cartilaginous joints (symphyses): Bones are joined by fibrocartilage, often with a thin layer of hyaline cartilage covering the articulating surfaces. These joints are strong and permit limited movement.

Examples: Intervertebral discs and the pubic symphysis.

C. Synovial Joints

Synovial joints are freely movable joints characterized by the presence of a joint cavity. The articulating bone surfaces are covered by articular cartilage, and the joint is enclosed by a capsule.

The major components include:

- Articular cartilage: Covers the ends of bones and reduces friction during movement.
- Joint cavity: A space between the articulating bones containing synovial fluid.
- Synovial fluid: Lubricates the joint and helps nourish the articular cartilage.

- Articular capsule: Encloses the joint and consists of an outer fibrous layer and an inner synovial membrane.
- Ligaments: Connect bones and help stabilize joints.

Some synovial joints also contain accessory structures, such as menisci, articular discs, bursae, and fat pads.

Table 9.5: Types of Synovial Joints

Type	Movement	Examples
Plane (gliding)	Sliding or gliding movements	Intercarpal joints
Hinge	Movement mainly in one plane, such as flexion and extension	Elbow and interphalangeal joints
Pivot	Rotation around a central axis	Atlanto-axial joint
Condyloid (ellipsoid)	Flexion, extension, abduction, and adduction	Metacarpophalangeal joints
Saddle	Movement in two planes with greater range than a plane joint	First carpometacarpal joint of thumb
Ball-and-socket	Movement in multiple directions, including rotation	Shoulder and hip joints

9.7.2 Functional Classification of Joints

Functionally, joints are classified according to the degree of movement they permit.

A. Synarthrosis

Synarthrosis refers to an immovable joint. These joints provide stability and protection.

Examples: Most sutures of the skull and gomphoses between teeth and their sockets.

B. Amphiarthrosis

Amphiarthrosis refers to a slightly movable joint. These joints provide stability while allowing limited movement.

Examples: Pubic symphysis and joints between vertebral bodies.

C. Diarthrosis

Diarthrosis refers to a freely movable joint. All synovial joints are functionally classified as diarthroses.

Examples: Shoulder, elbow, hip, knee, and wrist joints.

Table 9.6: Comparison of Structural and Functional Classification

Basis	Classification	Main Characteristics	Examples
Structural	Fibrous	Bones connected by fibrous connective	Skull sutures

		tissue; no joint cavity	
Structural	Cartilaginous	Bones connected by cartilage; no joint cavity	Pubic symphysis
Structural	Synovial	Joint cavity containing synovial fluid; freely movable	Knee and shoulder
Functional	Synarthrosis	Immovable	Skull sutures
Functional	Amphiarthrosis	Slightly movable	Pubic symphysis
Functional	Diarthrosis	Freely movable	Hip and elbow

9.7.3 Importance of Joints

Joints are essential for normal body movement and mechanical stability. They allow the skeleton to perform activities such as walking, running, grasping, and bending. The structure of each joint is adapted to its function: some joints prioritize stability and protection, while others allow a wide range of movement.

The skeletal system is divided into the axial and appendicular skeleton. The axial skeleton forms the central framework and protects vital organs, whereas the appendicular skeleton includes the limbs and their girdles and is primarily involved in movement. Bones are classified as long, short, flat, irregular, and sesamoid according to their shape. The bones of the skeleton provide support, protection, movement, mineral storage, blood cell formation, and fat storage. Skeletal muscles are organized into muscles, fascicles, muscle fibres, myofibrils, sarcomeres, and myofilaments. Muscle contraction occurs through the sliding of actin and myosin filaments and requires calcium ions and ATP. The neuromuscular junction transmits signals from motor neurons to skeletal muscle fibres through acetylcholine. Joints are structurally classified as fibrous, cartilaginous, or synovial and functionally classified as synarthroses, amphiarthroses, or diarthroses.

Chapter 10: Diseases of Bones and Joints

10.1 Pathophysiology of Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that primarily affects the synovial joints. It is characterized by persistent inflammation of the synovial membrane, progressive damage to articular cartilage, erosion of underlying bone, and, in advanced cases, joint deformity and loss of function.

Rheumatoid arthritis commonly affects the small joints of the hands, wrists, and feet. It often involves joints symmetrically, meaning that corresponding joints on both sides of the body may be affected. Although joints are the major sites of disease, RA may also involve other organs, including the skin, eyes, lungs, heart, and blood vessels.

10.1.1 Causes and Risk Factors

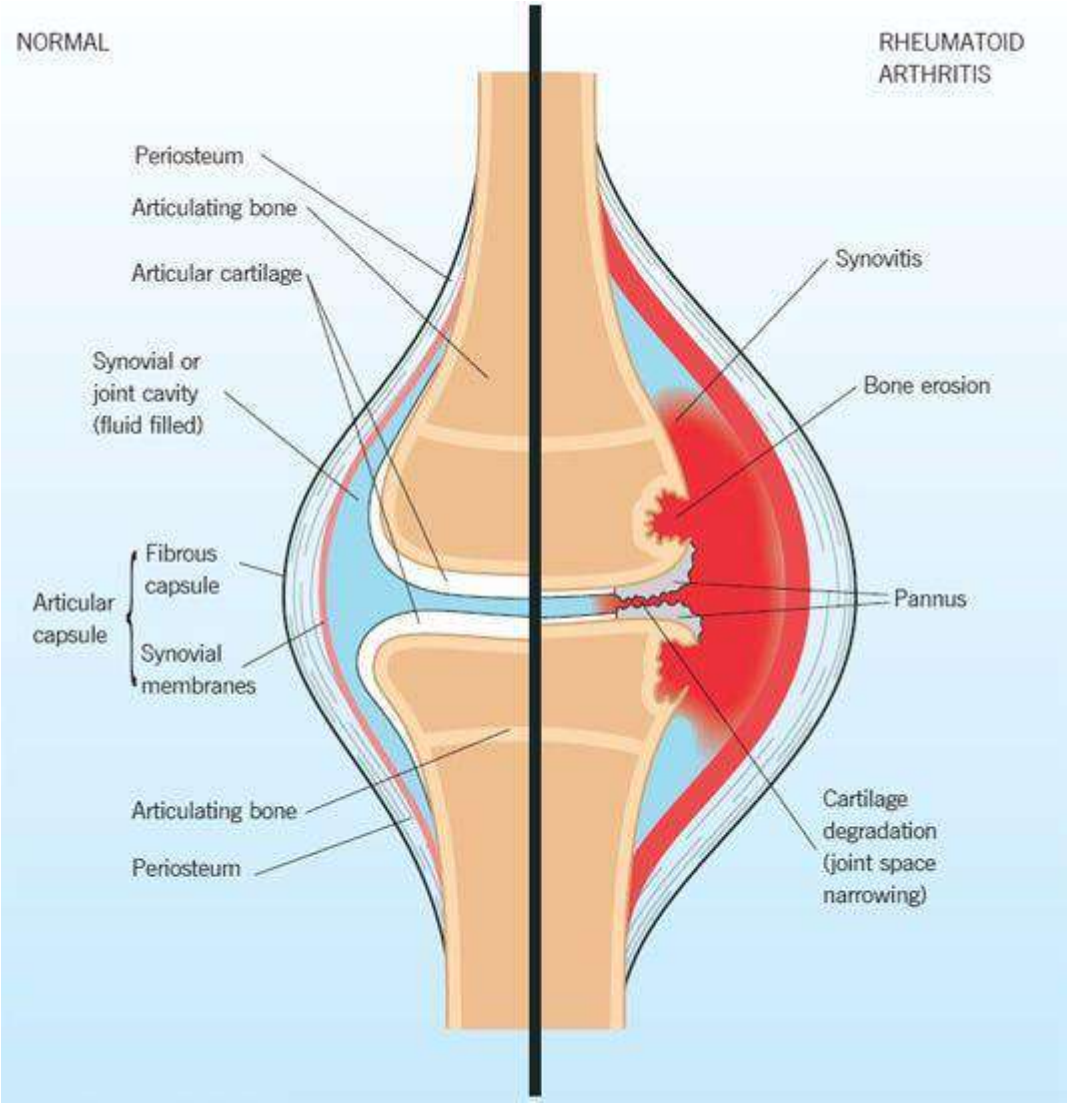
The exact cause of rheumatoid arthritis is not fully established. It is believed to develop through an interaction between genetic susceptibility, environmental influences, and abnormal immune responses.

Important risk factors include:

- Genetic factors: Certain human leukocyte antigen (HLA) variants, particularly HLA-DRB1 alleles, are associated with increased susceptibility.
- Environmental factors: Cigarette smoking is an established risk factor and may contribute to the development of autoimmunity.
- Hormonal factors: RA is more common in women than in men, suggesting that hormonal and immune-related factors may contribute.
- Immune dysregulation: Abnormal activation of immune cells leads to persistent inflammation within the synovial joints.
- Other factors: Age, family history, and certain environmental exposures may influence disease development.

10.1.2 Pathophysiology of Rheumatoid Arthritis

Rheumatoid arthritis develops due to an abnormal immune response directed against components of the body's own tissues. The synovial membrane becomes chronically inflamed, resulting in progressive destruction of joint structures.



The major pathological events are described below.

1. Initiation of Autoimmune Response

In genetically susceptible individuals, environmental factors may contribute to changes in self-proteins. These modified proteins can be recognized by the immune system, resulting in the activation of autoreactive T lymphocytes and B lymphocytes.

The immune response may lead to the production of autoantibodies, particularly:

- Rheumatoid factor (RF): An autoantibody commonly directed against the Fc portion of immunoglobulin G (IgG).
- Anti-citrullinated protein antibodies (ACPAs): Autoantibodies directed against citrullinated proteins.

These autoantibodies are important markers associated with rheumatoid arthritis, although their presence alone does not establish the diagnosis.

2. Synovial Inflammation

The synovial membrane is the tissue lining the inner surface of the joint capsule. In RA, immune cells accumulate within the synovium and release inflammatory mediators.

Activated T cells, B cells, macrophages, and other inflammatory cells contribute to the release of cytokines, including:

- Tumour necrosis factor-alpha (TNF-α)
- Interleukin-1 (IL-1)
- Interleukin-6 (IL-6)
- Interleukin-17 (IL-17)

These cytokines promote inflammation, increase the activity of synovial cells, and contribute to cartilage and bone damage.

3. Synovial Hyperplasia

Persistent inflammation causes proliferation of synovial cells and infiltration by inflammatory cells. The synovial membrane becomes thickened and develops an abnormal, highly cellular appearance.

The inflamed synovial tissue may extend over the articular cartilage and form a destructive tissue mass known as pannus.

4. Formation of Pannus

Pannus is an abnormal mass of inflamed synovial tissue containing proliferating synovial cells, inflammatory cells, fibroblasts, and newly formed blood vessels.

It grows over the articular cartilage and releases enzymes and inflammatory mediators that contribute to tissue destruction.

5. Cartilage Destruction

Inflammatory cytokines stimulate the production of enzymes, including matrix metalloproteinases (MMPs), which degrade components of the cartilage extracellular matrix.

As cartilage becomes progressively damaged, the smooth articulating surfaces of the joint are lost. This reduces normal joint movement and contributes to pain and stiffness.

6. Bone Erosion

Inflammatory cells and synovial fibroblasts stimulate the production of receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL promotes the differentiation and activation of osteoclasts, the cells responsible for bone resorption.

Increased osteoclast activity causes erosion of bone near the joint margins. Over time, cartilage loss and bone erosion may lead to joint instability, deformity, and impaired function.

7. Joint Deformity and Functional Impairment

Continuous inflammation and destruction of cartilage, bone, ligaments, and tendons may alter joint alignment. In advanced disease, deformities may develop, particularly in the hands and feet.

Chronic pain, stiffness, swelling, and reduced mobility may interfere with daily activities.

10.1.3 Clinical Features

Common clinical features of rheumatoid arthritis include:

- Pain, swelling, and tenderness of joints.
- Morning stiffness, often lasting longer than in many non-inflammatory joint conditions.
- Symmetrical involvement of joints.
- Common involvement of the metacarpophalangeal, proximal interphalangeal, wrist, and metatarsophalangeal joints.
- Reduced joint movement and grip strength.
- Fatigue and general weakness.
- Joint deformities in advanced disease.

Systemic manifestations may include rheumatoid nodules, eye inflammation, lung involvement, and anaemia of chronic inflammation.

10.1.4 Complications

If inflammation remains uncontrolled, rheumatoid arthritis may result in:

- Progressive cartilage and bone destruction.
- Joint deformity and disability.
- Tendon damage or rupture.
- Reduced mobility and muscle weakness.
- Osteoporosis, particularly around affected joints or in association with chronic inflammation.
- Extra-articular complications involving the lungs, eyes, heart, or blood vessels.

10.1.5 Basic Principles of Management

The objectives of management are to reduce inflammation, control pain, prevent joint damage, preserve mobility, and maintain quality of life. Treatment may include disease-modifying antirheumatic drugs (DMARDs), anti-inflammatory medicines, rehabilitation, and physical therapy. The selection of treatment depends on disease activity and individual clinical assessment.

10.2 Pathophysiology of Osteoporosis

Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, resulting in increased bone fragility and susceptibility to fractures. It commonly affects the hip, vertebrae, and wrist, although fractures may occur in other bones.

Bone is a dynamic tissue that undergoes continuous remodeling through the coordinated activities of osteoclasts and osteoblasts. Osteoclasts break down old bone, whereas osteoblasts form new bone. Osteoporosis develops when bone resorption exceeds bone formation over time, leading to a reduction in bone strength.

10.2.1 Causes and Risk Factors

Osteoporosis may develop due to aging, hormonal changes, nutritional deficiencies, reduced physical activity, certain diseases, or prolonged use of particular medicines.

Important risk factors include:

- Advancing age: Bone formation may become insufficient to replace the bone removed during remodeling.
- Postmenopausal estrogen deficiency: Reduced estrogen levels increase bone resorption and accelerate bone loss.
- Low calcium and vitamin D intake: These nutrients are essential for normal bone mineralization.
- Physical inactivity: Lack of weight-bearing activity may reduce the mechanical stimulation required to maintain bone mass.
- Low body weight: Lower body mass may be associated with reduced bone strength and increased fracture risk.
- Smoking and excessive alcohol consumption: These factors may negatively affect bone metabolism.
- Family history: Genetic factors contribute to differences in peak bone mass and fracture susceptibility.
- Certain medicines: Long-term use of glucocorticoids is an important cause of secondary osteoporosis.
- Underlying diseases: Endocrine, gastrointestinal, renal, and inflammatory disorders may contribute to bone loss.

10.2.2 Normal Bone Remodeling

Bone remodeling is a continuous process in which old or damaged bone is removed and replaced by new bone. It occurs in small areas throughout the skeleton.

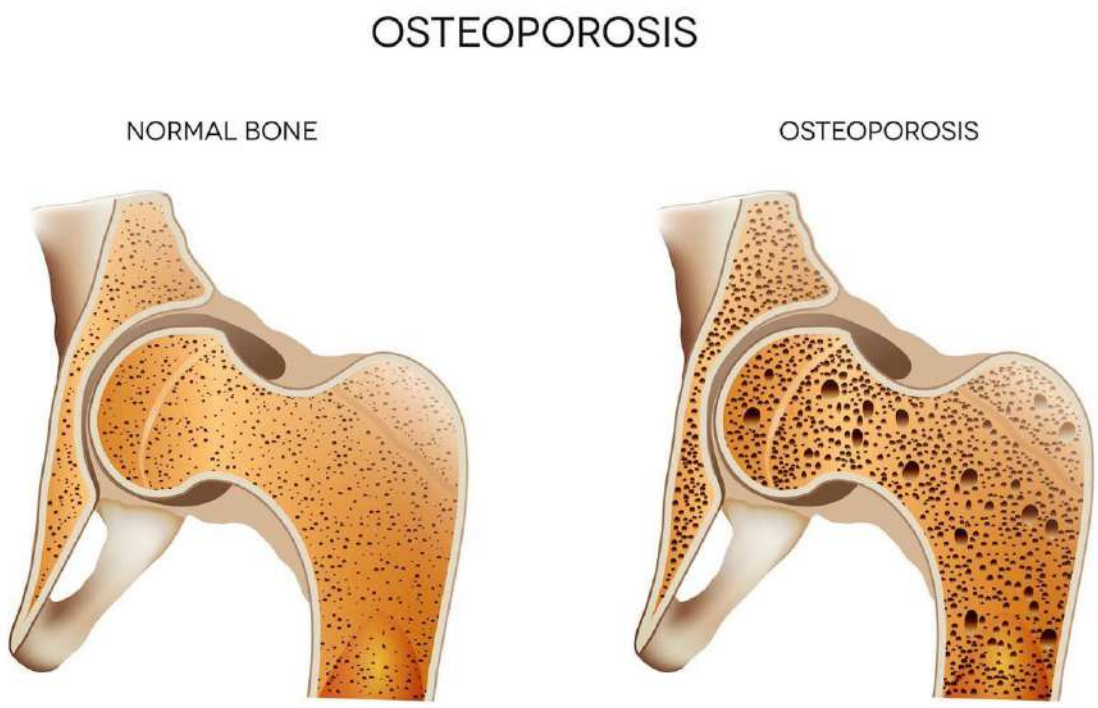
The process involves two major cell types:

Osteoclasts: These are multinucleated cells that resorb bone by dissolving mineral components and degrading the organic matrix.

Osteoblasts: These are bone-forming cells that produce osteoid, an organic matrix mainly composed of type I collagen. The osteoid subsequently becomes mineralized.

In healthy adults, bone resorption and formation remain relatively balanced. This balance maintains bone mass and structural strength.

10.2.3 Pathophysiology of Osteoporosis



Osteoporosis results from an imbalance in bone remodeling, in which bone resorption exceeds bone formation. This causes progressive loss of bone mass and deterioration of bone structure.

1. Imbalance Between Bone Resorption and Formation

Under normal conditions, osteoclast-mediated bone resorption is followed by osteoblast-mediated bone formation. In osteoporosis, this coupling becomes inadequate.

Osteoclast activity may increase, osteoblast activity may decrease, or both processes may occur together. Consequently, the amount of bone removed during each remodeling cycle is greater than the amount replaced.

2. Role of Estrogen Deficiency

Estrogen plays an important role in maintaining bone mass by limiting excessive osteoclast activity and supporting bone remodeling balance.

After menopause, estrogen levels decline. This increases the production of factors that promote osteoclast formation and activity, including RANKL, while reducing protective influences such as osteoprotegerin (OPG).

RANKL binds to its receptor RANK on osteoclast precursors and promotes their differentiation and activation. Osteoprotegerin acts as a decoy receptor that binds RANKL and limits its interaction with RANK.

When estrogen deficiency increases the RANKL-to-OPG influence, osteoclast activity rises and bone resorption accelerates.

3. Changes in Bone Microarchitecture

Continuous bone loss affects both cortical and trabecular bone.

- Trabecular bone: The trabeculae become thinner, fewer, and disconnected. This reduces the internal supporting network of bones, particularly in the vertebrae.
- Cortical bone: The outer compact layer becomes thinner and more porous, reducing resistance to mechanical stress.

These structural changes weaken the skeleton even when bone loss is not readily visible externally.

4. Reduction in Bone Mineral Density

As bone resorption exceeds formation, bone mineral density (BMD) decreases. Reduced BMD is associated with increased fracture risk.

Bone mineral density is commonly assessed using dual-energy X-ray absorptiometry (DXA). The result helps identify low bone mass and osteoporosis when interpreted according to appropriate clinical criteria.

5. Increased Bone Fragility

The combination of reduced bone mass and altered microarchitecture decreases the ability of bones to withstand normal mechanical loads. Consequently, fractures may occur after minor trauma or, in severe cases, during routine activities.

10.2.4 Types of Osteoporosis

1. Primary Osteoporosis: Primary osteoporosis develops mainly due to aging and hormonal changes without another identifiable disease being the principal cause.

- Postmenopausal osteoporosis: Commonly associated with estrogen deficiency after menopause.
- Age-related osteoporosis: Develops with advancing age in both men and women due to changes in bone formation, resorption, and calcium regulation.

2. Secondary Osteoporosis: Secondary osteoporosis develops due to an underlying disease, nutritional deficiency, or medication use.

Examples include osteoporosis associated with long-term glucocorticoid therapy, endocrine disorders, chronic kidney disease, malabsorption, and certain inflammatory conditions.

10.2.5 Clinical Features

Osteoporosis is often called a silent disorder because bone loss may occur without noticeable symptoms until a fracture develops.

Common clinical features include:

- Fragility fractures, particularly of the hip, vertebrae, and wrist.
- Back pain due to vertebral compression fractures.
- Loss of height over time.
- Increased thoracic curvature, sometimes producing a stooped posture.
- Reduced mobility and functional independence following fractures.

10.2.6 Complications

The major complications of osteoporosis include:

- Vertebral compression fractures.
- Hip fractures, which may lead to prolonged disability.
- Wrist and other fragility fractures.
- Chronic pain and reduced mobility.
- Spinal deformity and loss of height.
- Increased risk of further fractures after an initial fragility fracture.

10.2.7 Basic Principles of Prevention and Management

The main objectives are to reduce bone loss, improve bone strength, and prevent fractures. General measures include adequate calcium and vitamin D intake, regular weight-bearing and muscle-strengthening exercise, avoidance of smoking, and moderation of alcohol consumption.

Depending on fracture risk and clinical assessment, medicines may be prescribed to reduce bone resorption or increase bone formation. Fall prevention is also important, particularly in older adults.

10.3 Pathophysiology of Gout

Introduction

Gout is an inflammatory metabolic disease caused by the deposition of monosodium urate crystals in joints and surrounding tissues. It is commonly associated with hyperuricemia, which refers to an increased concentration of uric acid in the blood.

Uric acid is the final product of purine metabolism in humans. When urate concentration becomes sufficiently high, monosodium urate crystals may form and deposit in tissues. These crystals activate the innate immune system and produce episodes of acute inflammation, typically affecting one joint at a time.

The first metatarsophalangeal joint of the great toe is a common site of acute gout, although other joints may also be involved.

10.3.1 Causes and Risk Factors

Gout develops when urate production is excessive, urate excretion is reduced, or both mechanisms occur together.

Important risk factors include:

- Reduced renal excretion of urate: The kidneys are responsible for eliminating most uric acid from the body. Reduced renal clearance may increase blood urate levels.
- Increased purine metabolism: Increased breakdown of purines may raise uric acid production.
- Genetic factors: Inherited differences in urate transport and metabolism may contribute to susceptibility.
- Dietary factors: High intake of purine-rich foods, such as certain organ meats and seafood, may increase urate levels in susceptible individuals.
- Alcohol consumption: Alcohol may increase urate production or reduce its excretion.
- Metabolic conditions: Obesity, insulin resistance, and metabolic syndrome are associated with increased risk.
- Certain medicines: Some diuretics and other drugs may reduce urate excretion.
- Renal impairment: Reduced kidney function can interfere with urate elimination.

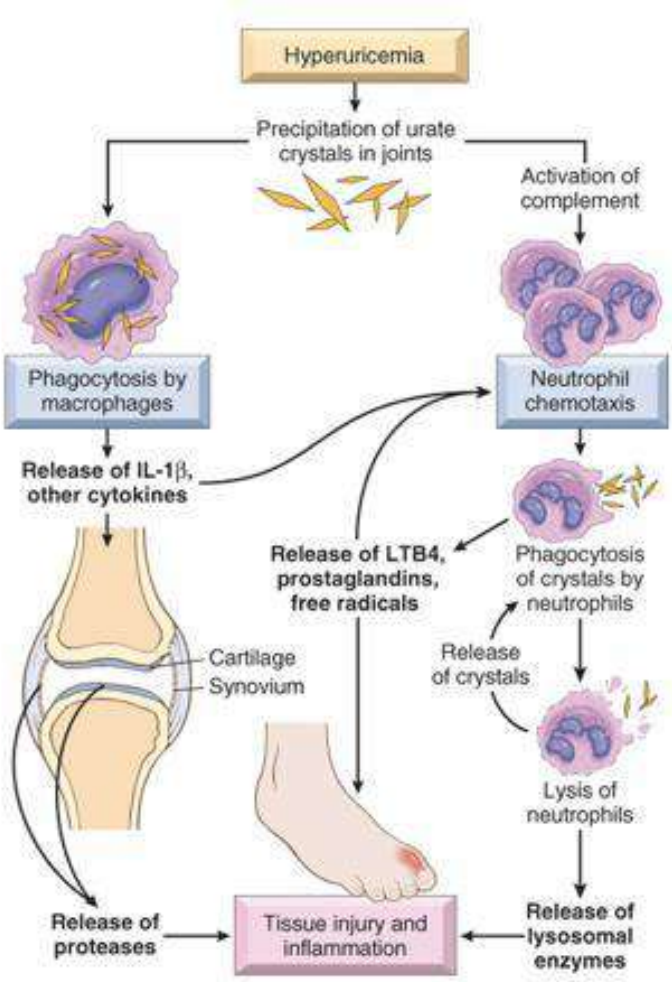
10.3.2 Purine Metabolism and Uric Acid Formation

Purines are nitrogen-containing compounds that form part of nucleic acids and other cellular molecules. They are obtained from dietary sources and are also produced during normal cellular metabolism.

Purines are degraded through a series of reactions that ultimately produce uric acid. In humans, uric acid is converted into urate at physiological pH.

Urate is eliminated mainly through the kidneys, with a smaller amount removed through the gastrointestinal tract. An imbalance between urate production and excretion may result in hyperuricemia.

10.3.3 Pathophysiology of Gout



Gout develops through the formation and deposition of monosodium urate crystals followed by an inflammatory response. The major pathological events are described below.

1. Development of Hyperuricemia

Hyperuricemia occurs when the concentration of urate in the blood becomes elevated. It most commonly results from reduced renal excretion, although increased urate production may also contribute.

Not every individual with hyperuricemia develops gout. Crystal formation depends on several factors, including urate concentration, temperature, local tissue conditions, and the presence of other substances in the joint environment.

2. Formation and Deposition of Monosodium Urate Crystals

When urate concentration exceeds its solubility under suitable conditions, monosodium urate crystals may form. These crystals can deposit in synovial joints, cartilage, tendons, bursae, and other tissues.

Peripheral joints, particularly the great toe, are frequently affected. Lower temperature in peripheral tissues may favour crystal formation.

3. Activation of the Innate Immune System

Deposited urate crystals are recognized by immune cells, especially macrophages. Crystal uptake and associated cellular signals activate the NLRP3 inflammasome, a multiprotein complex involved in inflammatory responses.

Inflammasome activation promotes the conversion of pro-interleukin-1 beta into active interleukin-1 beta (IL-1β). IL-1β is a major mediator of acute gouty inflammation.

4. Release of Inflammatory Mediators

Activated immune cells release IL-1β and other inflammatory mediators. These substances increase local inflammation and promote the recruitment of neutrophils into the affected joint.

Neutrophils migrate towards the crystals and release inflammatory substances, including enzymes and reactive oxygen species. These responses contribute to redness, warmth, swelling, and severe pain.

5. Acute Gouty Arthritis

The accumulation of inflammatory cells and mediators in the joint produces an acute attack of gouty arthritis. The affected joint becomes painful, swollen, warm, and red.

The inflammatory reaction may develop rapidly, often reaching severe intensity within a short period. Although attacks may resolve spontaneously, crystal deposits may remain and cause recurrent episodes.

6. Resolution of Acute Inflammation

Acute gout attacks may resolve as inflammatory activity decreases and crystals are cleared or become less inflammatory. However, the underlying hyperuricemia may persist. Continued crystal deposition can lead to recurrent attacks and chronic joint damage.

7. Formation of Tophi and Chronic Gout

In long-standing gout, monosodium urate crystals may accumulate in tissues and form deposits called tophi. Tophi commonly occur around joints, in the ears, and in soft tissues.

Chronic crystal deposition may produce persistent inflammation, erosion of adjacent bone, joint deformity, and restricted movement. Urate crystals may also contribute to kidney stones and other renal complications.

10.3.4 Clinical Features

The clinical manifestations of gout vary according to the stage of disease.

Acute gout attack:

- Sudden onset of severe joint pain.

- Redness, warmth, and swelling.
- Marked tenderness of the affected joint.
- Common involvement of the first metatarsophalangeal joint.
- Pain that may be severe enough to interfere with walking or movement.

Intercritical gout: This refers to the period between acute attacks. The individual may have no joint symptoms, although hyperuricemia and crystal deposits may persist.

Chronic tophaceous gout:

- Formation of visible or palpable tophi.
- Recurrent or persistent joint inflammation.
- Joint stiffness and restricted movement.
- Bone erosion and deformity in advanced disease.

10.3.5 Complications

Gout may lead to the following complications:

- Recurrent episodes of acute arthritis.
- Chronic joint inflammation and damage.
- Formation of tophi in joints and soft tissues.
- Bone erosion and joint deformity.
- Uric acid kidney stones.
- Renal complications, particularly when associated with other risk factors.

10.3.6 Basic Principles of Management

Management aims to control acute inflammation, reduce serum urate levels when indicated, prevent recurrent attacks, and limit crystal deposition. Acute attacks may be treated with anti-inflammatory medicines selected according to the patient's clinical condition. Long-term urate-lowering therapy may be prescribed for appropriate patients, along with dietary and lifestyle measures.

Adequate hydration, weight management, moderation of alcohol intake, and review of contributing medicines may form part of the overall management plan. Treatment should be individualized under medical supervision.

Table 10.1: Comparison of Rheumatoid Arthritis, Osteoporosis, and Gout

Feature	Rheumatoid Arthritis	Osteoporosis	Gout
Basic nature	Chronic autoimmune inflammatory disease	Systemic skeletal disorder with reduced bone strength	Crystal-induced inflammatory arthritis
Main tissue affected	Synovial joints	Bone	Joints and surrounding tissues
Major mechanism	Autoimmune synovitis, pannus formation, cartilage and bone	Bone resorption exceeds bone formation	Monosodium urate crystal deposition and inflammation

	erosion		
Important factors	Genetic susceptibility, immune dysregulation, environmental factors	Aging, estrogen deficiency, glucocorticoids, nutritional factors	Hyperuricemia, reduced urate excretion, increased urate production
Common sites	Hands, wrists, and feet	Hip, vertebrae, and wrist fractures	Great toe, ankle, knee, and other joints
Typical presentation	Symmetrical joint pain, swelling, and morning stiffness	Often asymptomatic until a fragility fracture occurs	Sudden episodes of severe joint pain, redness, and swelling
Major pathological change	Synovial inflammation and joint destruction	Reduced bone mass and altered microarchitecture	Urate crystal deposition and inflammatory response
Important complications	Joint deformity and systemic involvement	Fragility fractures and loss of mobility	Tophi, recurrent arthritis, and joint damage

Rheumatoid arthritis is a chronic autoimmune disease in which immune-mediated inflammation of the synovial membrane leads to synovial hyperplasia, pannus formation, cartilage destruction, and bone erosion. Osteoporosis is characterized by reduced bone mass and deterioration of bone microarchitecture due to an imbalance between bone resorption and formation. It increases the risk of fragility fractures, particularly in the hip, vertebrae, and wrist. Gout is a crystal-induced inflammatory disease associated with monosodium urate deposition in joints and tissues. Urate crystals activate the innate immune system and promote the release of inflammatory mediators, producing acute episodes of painful arthritis. Understanding the underlying pathophysiology of these disorders is important for recognizing their clinical features and principles of management.

UNIT- III

Chapter 11: Body Fluids, Blood and Lymphatic System

11.1 Body Fluids: Composition and Functions of Blood

11.1.1 Introduction to Body Fluids

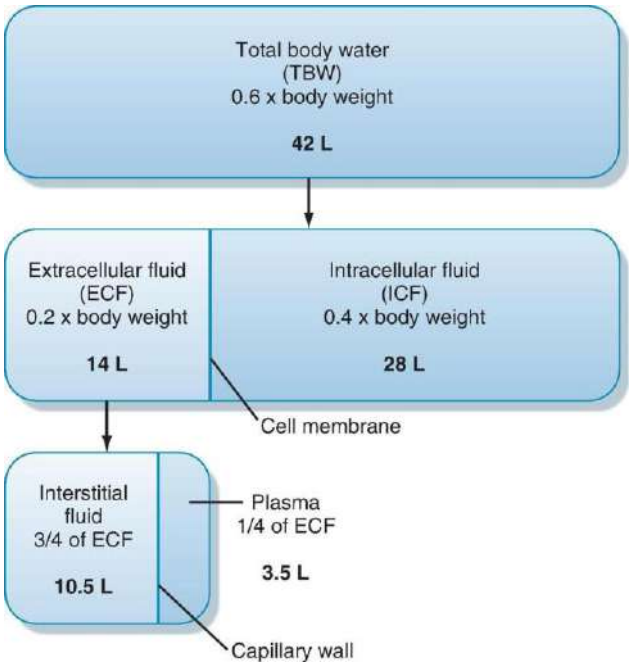
Body fluids are the water-containing solutions present inside and outside the cells of the human body. They provide the medium for metabolic reactions, transport nutrients and waste products, maintain electrolyte balance, regulate body temperature, and support the normal functioning of organs.

The total body water content varies with age, sex, and body composition. In an average adult, water constitutes approximately 50–60% of body weight. It is distributed into two major compartments:

1. **Intracellular fluid (ICF):** Fluid present inside the cells. It accounts for approximately two-thirds of total body water.
2. **Extracellular fluid (ECF):** Fluid present outside the cells. It accounts for approximately one-third of total body water.

Extracellular fluid is further divided into:

- Interstitial fluid: Fluid present in the spaces between tissue cells.
- Blood plasma: The liquid component of blood.
- Transcellular fluid: Specialized fluid found in spaces such as cerebrospinal fluid, synovial fluid, pleural fluid, and digestive secretions.



11.1.2 Composition of Body Fluids

Body fluids consist mainly of water, electrolytes, nutrients, gases, hormones, proteins, and metabolic waste products. The composition differs between intracellular and extracellular compartments.

Table 11.1: Intracellular and Extracellular Fluid Composition

Component	Intracellular Fluid	Extracellular Fluid
Major cation	Potassium (K^+)	Sodium (Na^+)
Other cations	Magnesium (Mg^{2+})	Calcium (Ca^{2+})
Major anions	Phosphate and proteins	Chloride and bicarbonate
Nutrients	Glucose, amino acids and other metabolites	Glucose, amino acids and fatty acids
Dissolved gases	Oxygen and carbon dioxide	Oxygen and carbon dioxide
Waste products	Metabolic intermediates	Urea, creatinine and other wastes

The movement of water and dissolved substances between compartments occurs through cell membranes and capillary walls. Osmosis, diffusion, filtration, and active transport are important mechanisms involved in this exchange..

11.1.3 Functions of Body Fluids

Body fluids perform several essential functions:

1. Transport: Carry oxygen, nutrients, hormones, and waste products.
2. Metabolic medium: Provide an aqueous environment for biochemical reactions.
3. Temperature regulation: Distribute heat throughout the body and support heat loss through sweating.
4. Electrolyte balance: Maintain appropriate concentrations of ions required for nerve and muscle activity.
5. Acid–base balance: Help maintain blood and tissue pH within a narrow physiological range.
6. Lubrication: Reduce friction between moving tissues and organs.
7. Protection: Cushion and protect structures such as the brain and spinal cord through cerebrospinal fluid.
8. Maintenance of cell volume: Regulate water distribution and prevent excessive cell swelling or shrinkage.

11.1.4 Blood: Introduction

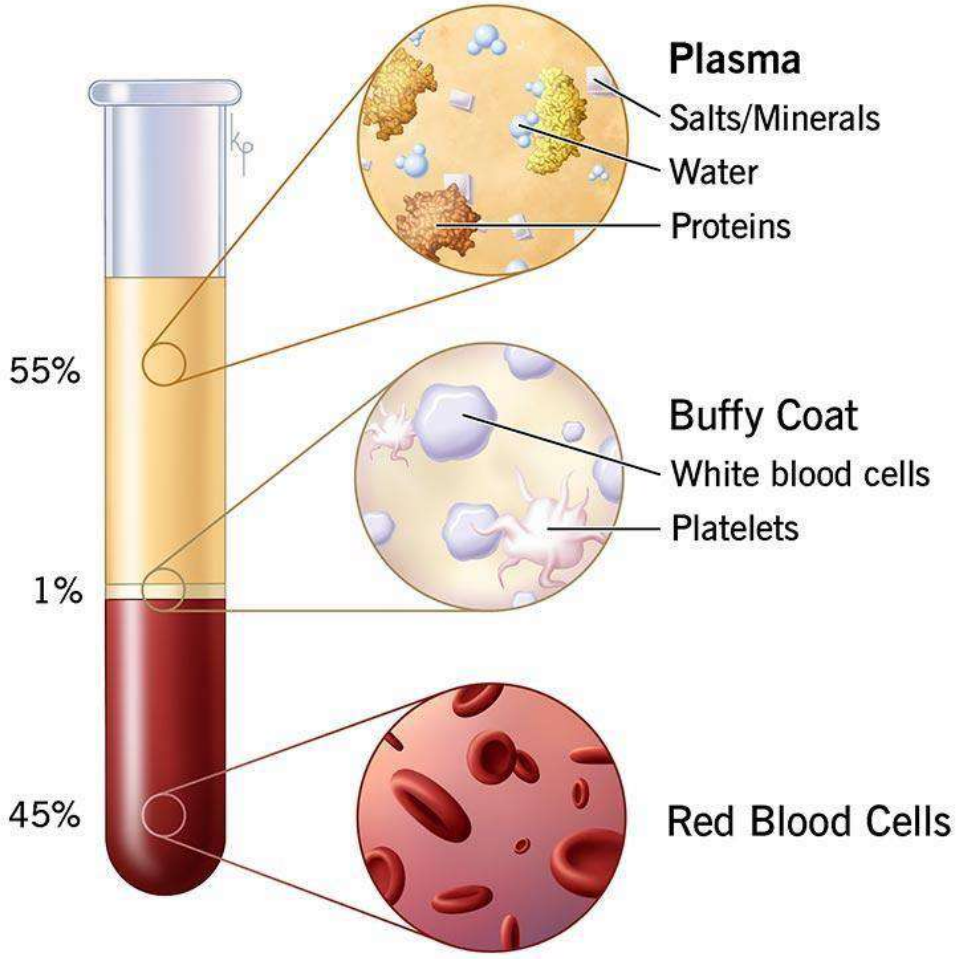
Blood is a specialized fluid connective tissue that circulates through the heart and blood vessels. It consists of a liquid component called plasma and formed elements, which include red blood cells, white blood cells, and platelets. Blood performs transport, regulatory, and protective functions and is essential for maintaining homeostasis.

In an average adult, blood volume is approximately 4.5–6 litres, although it varies with body size, sex, and physiological condition.

11.1.5 Composition of Blood

Blood is composed of two major components:

- Plasma: Approximately 55% of total blood volume.
- Formed elements: Approximately 45% of total blood volume.



A. Plasma

Plasma is the pale-yellow liquid portion of blood in which blood cells and platelets are suspended. It consists mainly of water, with dissolved proteins and other substances.

Table 11.2: Composition of plasma

Component	**Approximate proportion or examples**	**Functions**
Water	About 90–92%	Solvent and transport medium
Plasma proteins	About 6–8%	Osmotic balance, transport, immunity and clotting
Electrolytes	Sodium, potassium, calcium, chloride and bicarbonate	Fluid balance, nerve and muscle function, pH regulation
Nutrients	Glucose, amino acids, lipids and vitamins	Supply materials for cellular metabolism
Waste products	Urea, uric acid, creatinine and bilirubin	Transport to excretory organs
Hormones and	Various circulating substances	Regulation and coordination of body

enzymes		functions
Dissolved gases	Oxygen and carbon dioxide	Gas transport

Major plasma proteins

1. Albumin: The most abundant plasma protein. It maintains colloid osmotic pressure and transports substances such as fatty acids, hormones, and drugs.
2. Globulins: Include alpha, beta, and gamma globulins. They function in transport, immunity, and other physiological processes. Gamma globulins include immunoglobulins or antibodies.
3. Fibrinogen: A soluble plasma protein that is converted into fibrin during blood coagulation.

Serum is the fluid remaining after blood has clotted. It is similar to plasma but lacks fibrinogen and most clotting factors consumed during coagulation.

B. Formed Elements

The formed elements of blood are red blood cells, white blood cells, and platelets.

1. Red Blood Cells (Erythrocytes)

Red blood cells are biconcave, flexible cells that lack a nucleus and most organelles when mature. They contain haemoglobin, which enables them to transport oxygen and contributes to carbon dioxide transport.

- Normal adult RBC count is approximately 4.5–6 million cells/µL, with variation according to sex and laboratory reference range.
- Their average lifespan is about 120 days.
- They are produced in the red bone marrow.
- Old or damaged RBCs are mainly removed by macrophages in the spleen and liver.

Functions of RBCs

- Transport oxygen from the lungs to tissues.
- Assist in transporting carbon dioxide from tissues to the lungs.
- Help maintain acid–base balance through haemoglobin buffering.

2. White Blood Cells (Leukocytes)

White blood cells are nucleated blood cells involved in body defence and immunity. Their normal total count in adults is commonly around 4,000–11,000 cells/µL, depending on the laboratory reference range.

Table 11.3: Types of White Blood Cells and Their Major Features and Functions

Type	Major features and functions
Neutrophils	Engulf and destroy bacteria; important in acute inflammation
Eosinophils	Participate in defence against parasites and allergic reactions
Basophils	Release histamine and other substances involved in inflammation

Lymphocytes	Include B cells, T cells and natural killer cells; responsible for adaptive and innate immune functions
Monocytes	Enter tissues and differentiate into macrophages or related cells; perform phagocytosis and antigen presentation

3. Platelets (Thrombocytes)

Platelets are small, anucleate cell fragments formed from megakaryocytes in the bone marrow. Their normal count is approximately 150,000–450,000/µL of blood.

Functions of platelets

- Adhere to damaged blood vessel walls.
- Aggregate to form a temporary platelet plug.
- Release substances that promote haemostasis.
- Provide a surface for coagulation reactions.
- Support repair of damaged blood vessels.

11.1.6 Functions of Blood

Blood performs the following major functions:

1. Transport

- Carries oxygen from the lungs to body tissues.
- Transports carbon dioxide from tissues to the lungs.
- Delivers nutrients from the digestive tract and storage organs.
- Carries hormones to their target organs.
- Transports metabolic waste products to the kidneys, liver, lungs, and skin.

2. Regulation

- Helps maintain body temperature by distributing heat.
- Maintains acid–base balance through buffer systems.
- Supports fluid and electrolyte balance.
- Contributes to the maintenance of blood volume and osmotic pressure.

3. Protection

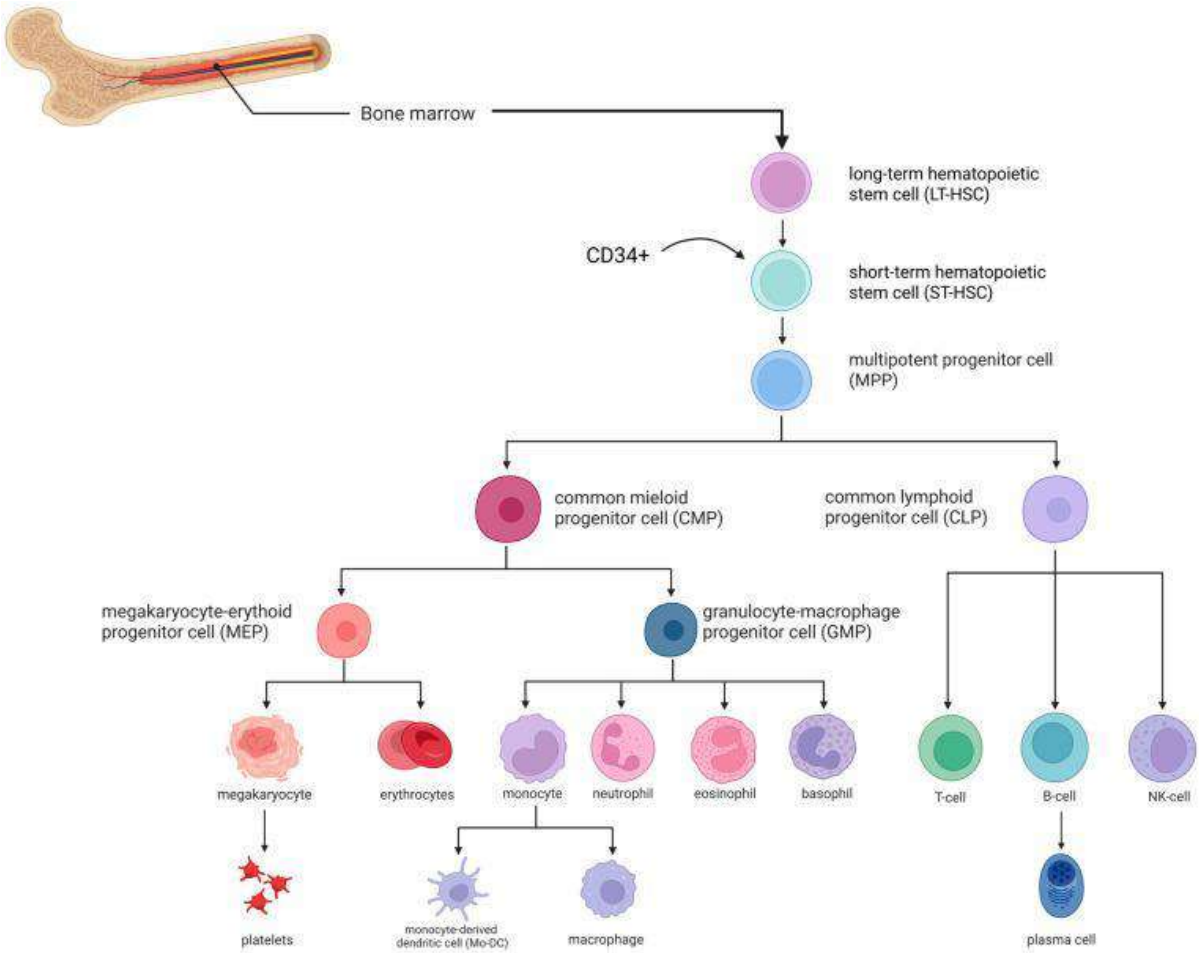
- White blood cells and antibodies protect the body against pathogens.
- Platelets and clotting factors prevent excessive blood loss.
- Immune proteins participate in inflammatory and defence reactions.

11.2 Hemopoiesis

11.2.1 Introduction

Hemopoiesis, also called haematopoiesis, is the process of formation, development, and maturation of blood cells. It produces red blood cells, white blood cells, and platelets throughout life. In adults, hemopoiesis occurs mainly in the red bone marrow.

All blood cells originate from multipotent haematopoietic stem cells (HSCs). These stem cells have two important properties: self-renewal, which maintains the stem-cell population, and differentiation, which produces specialized blood cells.



11.2.2 Sites of Hemopoiesis

The site of blood cell formation changes during development.

Table 11.4: Developmental Stages of Hemopoiesis and Major Sites of Blood Cell Formation

Developmental stage	Major site of hemopoiesis
Early embryonic stage	Yolk sac
Fetal stage	Mainly liver; also spleen and other tissues
Late fetal stage	Bone marrow becomes increasingly important
After birth	Red bone marrow
Adult life	Mainly vertebrae, ribs, sternum, skull, pelvis, and proximal ends of the femur and humerus

In certain diseases, the liver and spleen may resume blood cell production. This is called extramedullary hemopoiesis.

11.2.3 Haematopoietic Stem Cells and Cell Lineages

Haematopoietic stem cells differentiate into two major progenitor lineages:

1. Common myeloid progenitor: Gives rise to erythrocytes, megakaryocytes and platelets, granulocytes, and monocytes.
2. Common lymphoid progenitor: Gives rise to B lymphocytes, T lymphocytes, and natural killer cells.

The development of blood cells is regulated by growth factors, cytokines, and hormones. Important regulators include erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins.

11.2.4 Erythropoiesis

Erythropoiesis is the process of formation of red blood cells in the red bone marrow. It is stimulated mainly by erythropoietin, a hormone produced primarily by the kidneys in response to reduced oxygen availability.

The main stages are:

1. Haematopoietic stem cell
2. Myeloid progenitor cell
3. Erythroid progenitor cells
4. Proerythroblast
5. Basophilic erythroblast
6. Polychromatophilic erythroblast
7. Orthochromatic erythroblast
8. Reticulocyte
9. Mature erythrocyte

During maturation, the cell becomes smaller, haemoglobin content increases, and the nucleus is expelled. Reticulocytes enter the circulation and mature into erythrocytes.

Factors required for erythropoiesis

- Iron for haemoglobin synthesis.
- Vitamin B12 and folic acid for DNA synthesis and normal cell maturation.
- Amino acids for globin synthesis.
- Erythropoietin for stimulation of erythroid progenitor cells.
- Healthy bone marrow for normal cell development.

11.2.5 Leucopoiesis

Leucopoiesis is the formation of white blood cells. It occurs in the bone marrow and, for some lymphocytes, in lymphatic organs.

- Granulocytes develop through granulopoiesis.
- Monocytes develop through monocytopoiesis.
- Lymphocytes develop through lymphopoiesis.

Colony-stimulating factors and interleukins regulate the development and proliferation of different white blood cell lineages.

11.2.6 Thrombopoiesis

Thrombopoiesis is the formation of platelets from large bone marrow cells called megakaryocytes. Megakaryocytes develop from haematopoietic stem cells through the myeloid lineage. Their cytoplasm fragments into platelets, which enter the bloodstream.

Thrombopoietin, produced mainly by the liver and also by other tissues, is the principal regulator of platelet production.

11.2.7 Regulation and Importance of Hemopoiesis

Hemopoiesis is regulated according to the body's requirements. For example, reduced oxygen supply stimulates erythropoietin production and increases RBC formation. Infection and inflammation may stimulate the production of particular white blood cells, while blood loss or platelet consumption can increase the demand for platelet production.

Normal hemopoiesis is essential for:

- Oxygen delivery to tissues.
- Defence against infections.
- Prevention of excessive bleeding.
- Replacement of aged or damaged blood cells.
- Maintenance of normal blood cell counts.

11.3 Formation of Haemoglobin

11.3.1 Introduction

Haemoglobin is an iron-containing conjugated protein present in red blood cells. It is responsible mainly for transporting oxygen from the lungs to tissues and also contributes to the transport of carbon dioxide and regulation of blood pH.

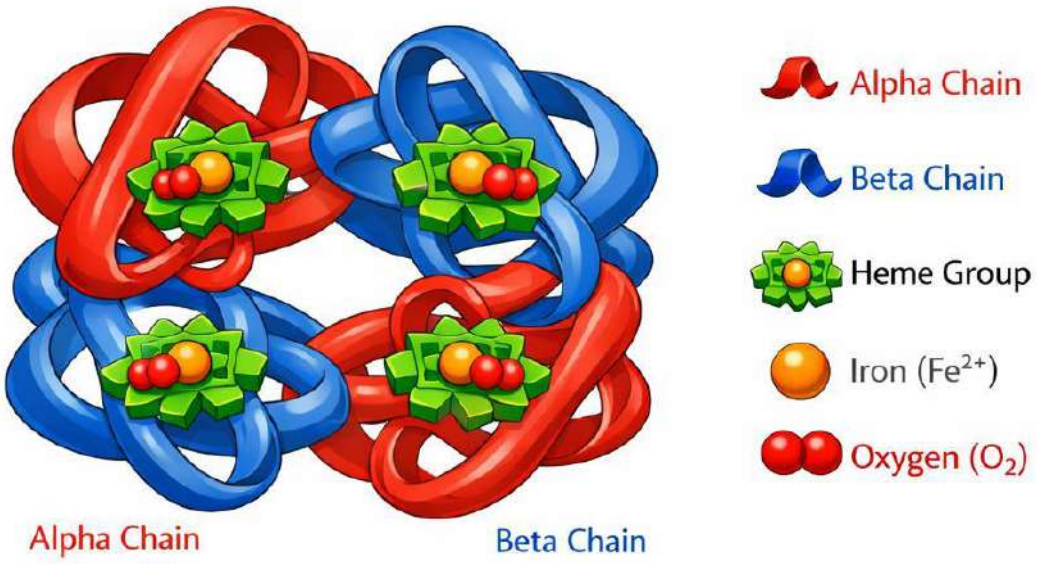
A normal adult haemoglobin molecule consists of four globin chains, each associated with one haem group. Each haem group contains a ferrous iron ion (Fe^{2+}), which can reversibly bind one oxygen molecule. Therefore, one haemoglobin molecule can carry up to four oxygen molecules.

11.3.2 Structure of Haemoglobin

Haemoglobin consists of two main components:

1. Globin: The protein portion made up of four polypeptide chains.
2. Haem: A non-protein component containing a porphyrin ring with a central ferrous iron ion.

In adult haemoglobin A (HbA), the globin chains are composed of two alpha and two beta chains ($\alpha_2\beta_2$). Other haemoglobin types include fetal haemoglobin (HbF), which contains two alpha and two gamma chains ($\alpha_2\gamma_2$), and adult haemoglobin A_2 (HbA_2), which contains two alpha and two delta chains ($\alpha_2\delta_2$).



11.3.3 Site of Haemoglobin Formation

Haemoglobin is synthesized during erythropoiesis in developing red blood cells in the red bone marrow. Haem synthesis occurs partly in mitochondria and partly in the cytoplasm, while globin chains are synthesized on ribosomes in the cytoplasm.

As erythroblasts mature, haemoglobin accumulates in their cytoplasm. Mature erythrocytes lack a nucleus and ribosomes and therefore cannot synthesize new haemoglobin.

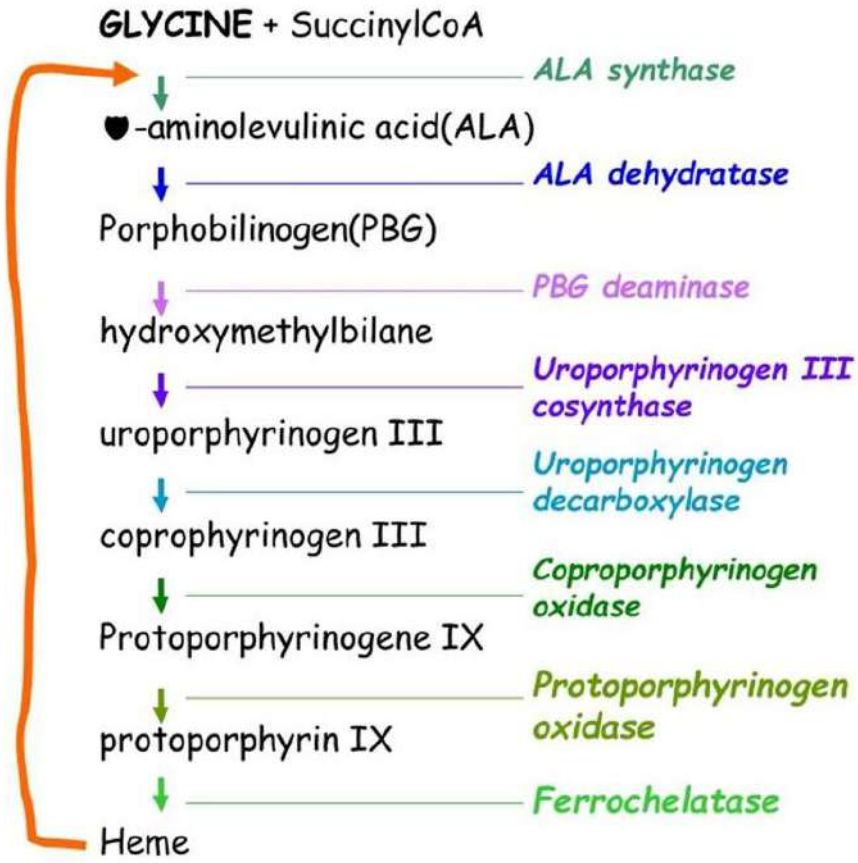
11.3.4 Synthesis of Haem

Haem is synthesized through a series of biochemical reactions involving mitochondria and cytoplasm.

Major steps in haem synthesis:

1. Formation of δ-aminolevulinic acid (ALA): Glycine combines with succinyl-CoA in the mitochondria to form ALA. This reaction is catalysed by ALA synthase and requires vitamin B6.
2. Formation of porphobilinogen: ALA is transported to the cytoplasm and converted into porphobilinogen.

3. Formation of porphyrin intermediates: Porphobilinogen is converted through several reactions into uroporphyrinogen III and then coproporphyrinogen III.
4. Formation of protoporphyrin IX: Further reactions produce protoporphyrin IX, which returns to the mitochondria.
5. Formation of haem: Ferrous iron (Fe^{2+}) is inserted into protoporphyrin IX by the enzyme ferrochelatase, forming haem.



11.3.5 Synthesis of Globin

Globin chains are synthesized on ribosomes in developing erythroblasts. The synthesis of alpha and beta globin chains is controlled by specific genes. The newly synthesized globin chains combine with haem groups to form functional haemoglobin molecules.

The balanced production of haem and globin is important. Disturbances in globin-chain synthesis can lead to disorders such as thalassemia.

Table 11.5: Factors Required for Haemoglobin Formation

Factor	Role
Iron	Required for the formation of the haem group
Glycine and succinyl-CoA	Starting materials for haem synthesis
Vitamin B6	Coenzyme for ALA synthase

Amino acids	Required for globin-chain synthesis
Vitamin B12 and folic acid	Support normal maturation of erythroid cells
Healthy bone marrow	Site of erythrocyte development
Erythropoietin	Stimulates red blood cell production

11.3.6 Functions of Haemoglobin

1. Oxygen transport: Binds oxygen in the lungs and releases it in tissues.
2. Carbon dioxide transport: Carries a portion of carbon dioxide from tissues to the lungs through binding to globin chains.
3. Buffering action: Helps maintain blood pH by binding and releasing hydrogen ions.
4. Regulation of oxygen delivery: Its oxygen-binding properties allow oxygen uptake and release according to tissue requirements.

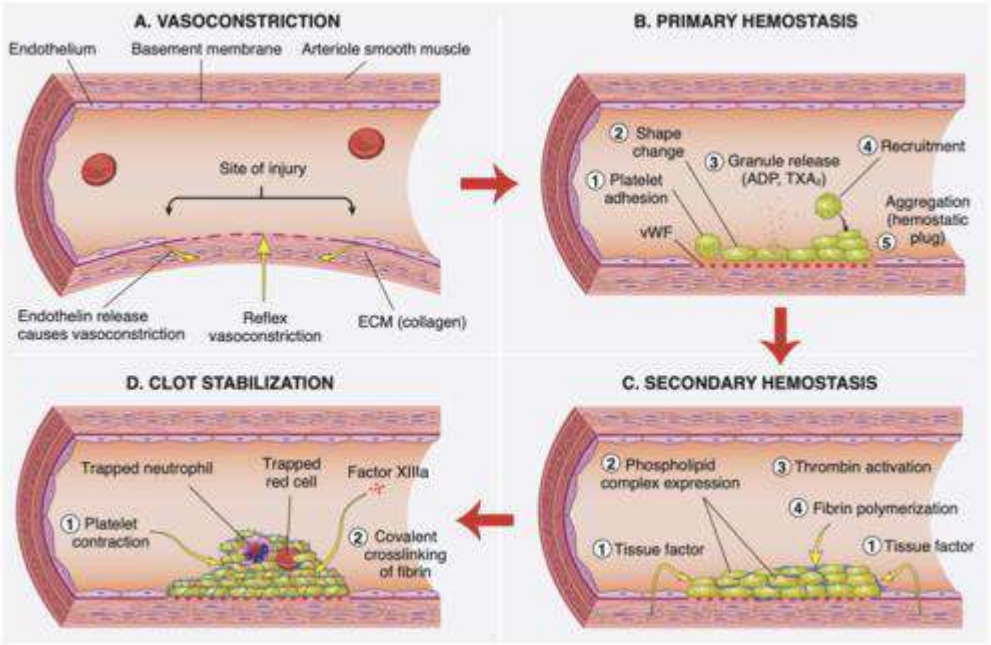
11.4 Mechanisms of Coagulation

11.4.1 Introduction

Blood coagulation is the process by which liquid blood forms a stable clot to prevent excessive blood loss following injury to a blood vessel. It is an important component of haemostasis, which includes the coordinated actions of blood vessels, platelets, and coagulation factors.

Haemostasis occurs through three closely related stages:

1. Vascular spasm.
2. Formation of a platelet plug.
3. Blood coagulation and stabilization of the clot.



11.4.2 Stages of Haemostasis

1. Vascular Spasm

Immediately after injury, the damaged blood vessel constricts. This reduces blood flow and limits blood loss. Vascular spasm is caused by local smooth muscle contraction and substances released from damaged tissues and activated platelets.

2. Platelet Plug Formation

Platelets adhere to the exposed subendothelial structures at the site of injury. Von Willebrand factor supports platelet adhesion by connecting platelets to exposed collagen. Activated platelets change shape and release chemical mediators, including ADP and thromboxane A_2, which recruit and activate additional platelets.

Platelets aggregate through glycoprotein IIb/IIIa receptors, which bind fibrinogen and connect adjacent platelets. This forms a temporary platelet plug.

3. Coagulation

Coagulation involves a series of reactions in which inactive plasma proteins called clotting factors are activated sequentially. The process leads to the conversion of soluble fibrinogen into insoluble fibrin, which strengthens and stabilizes the platelet plug.

11.4.3 Coagulation Factors

Most coagulation factors are plasma proteins produced mainly by the liver. They are commonly designated by Roman numerals.

Table 11.6: Coagulation Factors (Clotting Factors) and Their Names

Factor	Name
I	Fibrinogen
II	Prothrombin
III	Tissue factor
IV	Calcium ions
V	Proaccelerin (labile factor)
VII	Proconvertin (stable factor)
VIII	Antihaemophilic factor A
IX	Christmas factor
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor

Factor VI is not used in the current coagulation-factor numbering system.

11.4.4 Pathways of Blood Coagulation

The classical description of coagulation includes the intrinsic, extrinsic, and common pathways.

A. Intrinsic Pathway

The intrinsic pathway is initiated when blood comes into contact with negatively charged surfaces and involves factors present within the blood.

The sequence is:

- Factor XII is activated to XIIa.
- Factor XI is activated to XIa.
- Factor IX is activated to IXa.
- Factor IXa, together with factor VIIIa, calcium ions, and a phospholipid surface, activates factor X.

B. Extrinsic Pathway

The extrinsic pathway is initiated when damaged tissues expose tissue factor (factor III) to circulating blood.

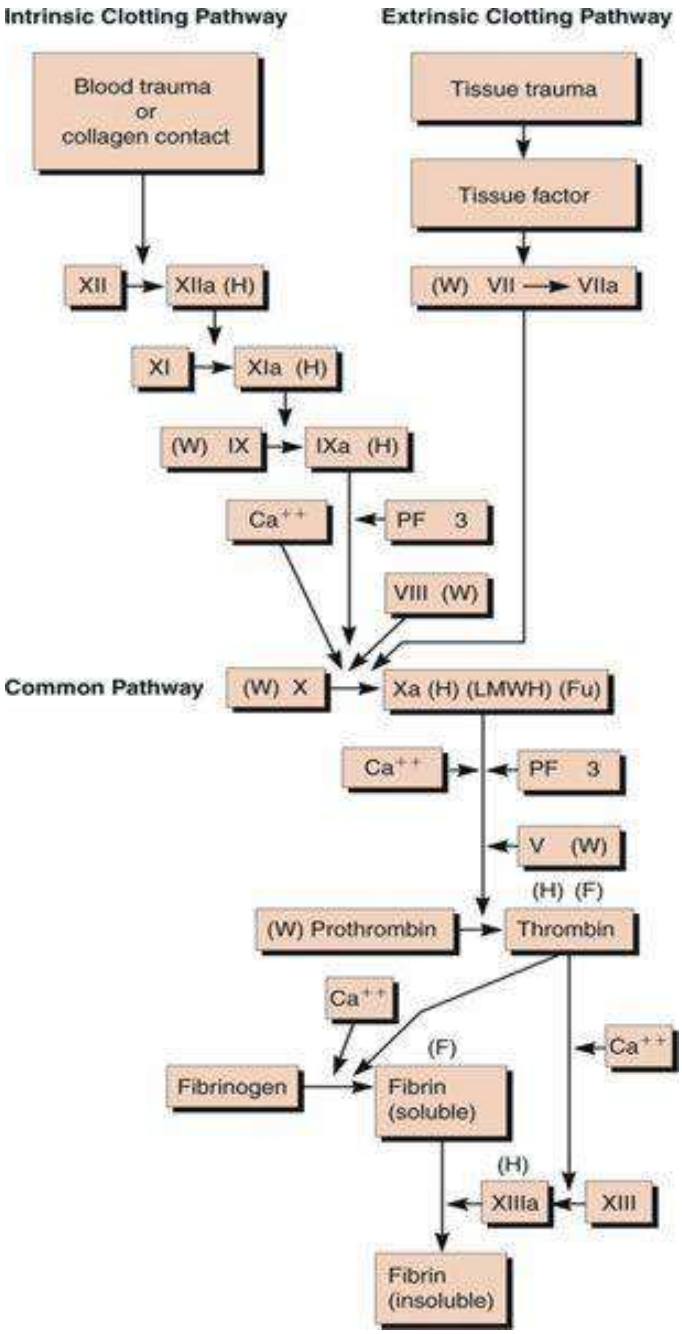
The sequence is:

- Tissue factor combines with factor VII.
- The tissue factor–VIIa complex activates factor X.
- It may also activate factor IX, linking the extrinsic and intrinsic pathways.

C. Common Pathway

Both pathways converge at the activation of factor X.

- Factor Xa combines with factor Va, calcium ions, and phospholipids to form the prothrombinase complex.
- Prothrombin (factor II) is converted into thrombin (factor IIa).
- Thrombin converts fibrinogen (factor I) into fibrin.
- Factor XIIIa cross-links fibrin strands to form a stable clot.



11.4.5 Clot Retraction and Fibrinolysis

Clot retraction: After clot formation, platelets contract through their cytoskeletal proteins and pull fibrin strands together. This reduces clot size and brings the edges of the damaged vessel closer.

Fibrinolysis: Once the vessel has been repaired, the clot is gradually removed. Plasminogen is converted into plasmin, an enzyme that breaks down fibrin into degradation products. Tissue plasminogen activator (tPA) is an important activator of plasminogen.

11.4.6 Regulation of Coagulation

Coagulation is controlled by natural anticoagulant mechanisms that prevent unnecessary clot formation.

- Antithrombin: Inhibits thrombin and several activated coagulation factors.
- Protein C and protein S: Inactivate factors Va and VIIIa.
- Tissue factor pathway inhibitor (TFPI): Limits tissue factor-initiated coagulation.
- Intact endothelium: Produces substances that inhibit platelet activation and support anticoagulant activity.

The balance between clot formation and clot removal is essential for maintaining normal circulation.

11.5 Blood Grouping, Rh Factors and Transfusion

11.5.1 Introduction to Blood Grouping

Blood grouping is the classification of blood based on the presence or absence of specific antigens on the surface of red blood cells. These antigens are inherited and are important in blood transfusion, pregnancy, and certain medical procedures.

The ABO and Rh systems are the most clinically important blood group systems.

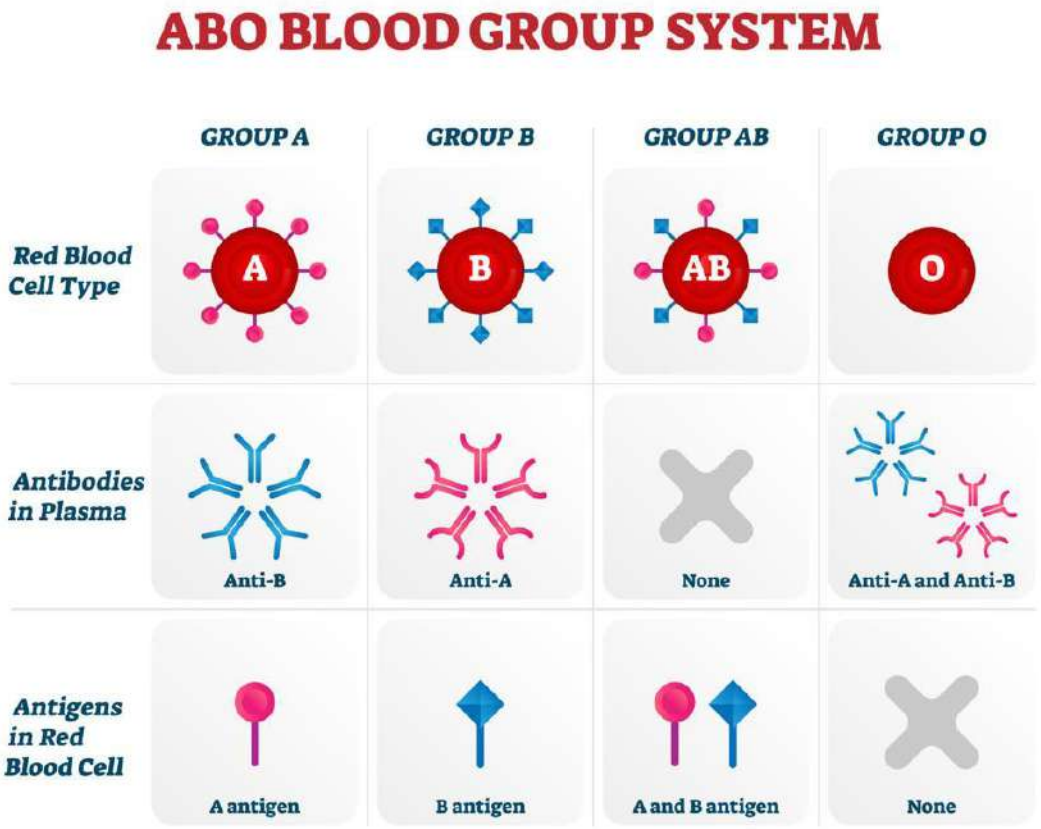
11.5.2 ABO Blood Group System

The ABO blood group system is based on the presence or absence of A and B antigens on red blood cells and the corresponding antibodies in plasma.

Table 11.7: ABO Blood Groups, Red Blood Cell Antigens, and Plasma Antibodies

Blood group	Antigen on RBCs	Antibody in plasma
A	A antigen	Anti-B
B	B antigen	Anti-A
AB	A and B antigens	Neither anti-A nor anti-B
O	Neither A nor B antigen	Anti-A and anti-B

The presence of A or B antigens determines the ABO group. Naturally occurring antibodies against the absent antigen are generally present in plasma.



11.5.3 Rh Blood Group System

The Rh blood group system includes several antigens, of which the D antigen is the most clinically significant.

- Rh-positive: D antigen is present on red blood cells.
- Rh-negative: D antigen is absent.

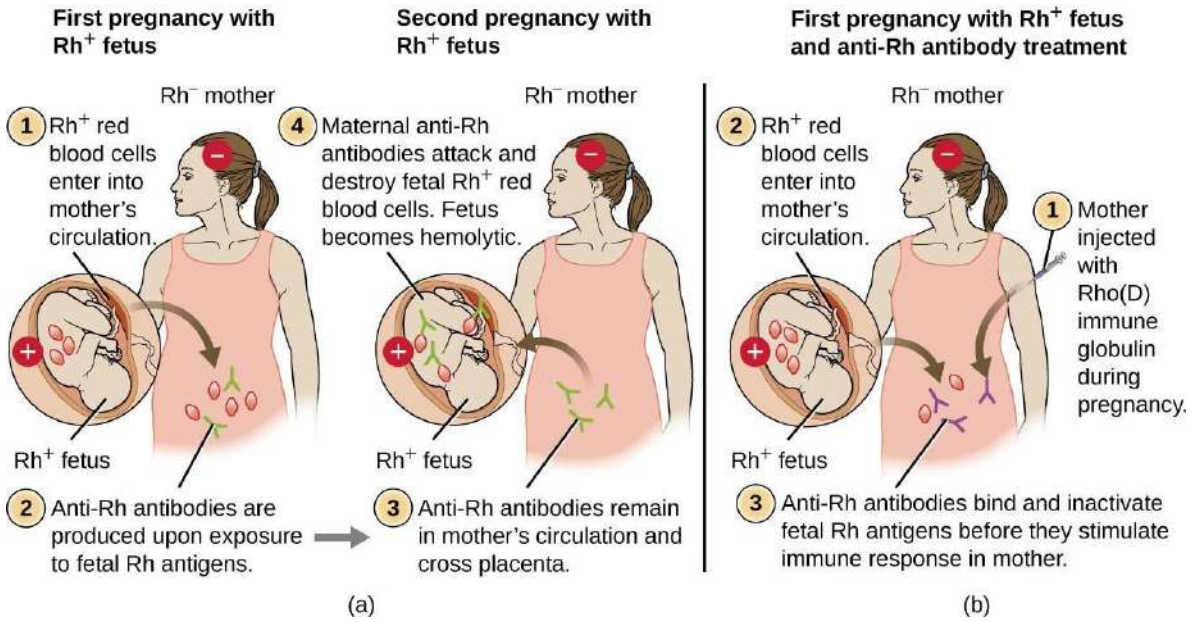
Unlike the ABO system, anti-D antibodies are not usually naturally present in Rh-negative individuals. They may develop following exposure to Rh-positive red blood cells through transfusion or pregnancy.

11.5.4 Rh Incompatibility in Pregnancy

Rh incompatibility may occur when an Rh-negative mother carries an Rh-positive fetus. Fetal red blood cells may enter the maternal circulation, particularly during delivery or certain pregnancy-related events. The mother may then become sensitized and produce anti-D antibodies.

In a subsequent pregnancy with an Rh-positive fetus, maternal IgG anti-D antibodies may cross the placenta and destroy fetal red blood cells. This can cause haemolytic disease of the fetus and newborn.

Prevention: Anti-D immunoglobulin is administered to eligible Rh-negative pregnant individuals according to clinical guidelines. It prevents maternal sensitization to the D antigen.



11.5.5 Blood Transfusion

Blood transfusion is the transfer of blood or blood components from a donor to a recipient. It is used to replace blood loss, treat severe anaemia, correct clotting-factor deficiencies, and manage certain medical conditions.

Blood may be transfused as whole blood or as specific components, such as:

- Packed red blood cells.
- Platelet concentrates.
- Fresh frozen plasma.
- Cryoprecipitate.

Component therapy allows the patient to receive the required blood component while avoiding unnecessary transfusion of other components.

11.5.6 Compatibility and Crossmatching

Before transfusion, compatibility testing is performed to reduce the risk of immune-mediated transfusion reactions.

Major compatibility checks include:

1. ABO and Rh typing: Determines the donor and recipient blood groups.
2. Antibody screening: Detects clinically significant antibodies in the recipient's plasma.
3. Crossmatching: Tests compatibility between donor red blood cells and recipient plasma, using appropriate laboratory methods.

4. Patient identification: Confirms the identity of the recipient and the blood component before administration.

For red blood cell transfusion, group O red blood cells may be used in selected emergency situations when the recipient's blood group is not yet known, according to transfusion protocols. However, compatibility testing and local clinical guidelines remain essential.

11.5.7 Transfusion Reactions

Transfusion reactions are adverse events associated with the administration of blood or blood components.

Table 11.8: Types of Blood Transfusion Reactions and Their Major Clinical Features

Type of reaction	Main features
Acute haemolytic reaction	Immune destruction of transfused red blood cells; may cause fever, chills, pain, hypotension and haemoglobinuria
Febrile non-haemolytic reaction	Fever and chills associated with inflammatory responses
Allergic reaction	Itching, urticaria or, rarely, severe allergic manifestations
Transfusion-associated circulatory overload (TACO)	Fluid overload causing respiratory distress and circulatory symptoms
Transfusion-related acute lung injury (TRALI)	Acute respiratory distress associated with transfusion
Delayed haemolytic reaction	Immune destruction of transfused red blood cells occurring days or weeks after transfusion

Any suspected transfusion reaction requires prompt clinical assessment and management according to institutional protocols.

11.5.8 Importance of Blood Grouping and Transfusion

Blood grouping and compatibility testing are essential for:

- Safe blood transfusion.
- Prevention of haemolytic transfusion reactions.
- Management of pregnancy-related Rh incompatibility.
- Selection of suitable blood components.
- Supporting emergency and surgical care.

11.6 Lymphatic Organs and Tissues

11.6.1 Introduction

The lymphatic system is a network of vessels, organs, and tissues that collects excess fluid from body tissues, returns it to the bloodstream, and contributes to immune defence. It contains lymph, a clear fluid derived from interstitial fluid, and provides pathways through which lymphocytes and other immune cells circulate.

Lymphatic organs are classified into primary and secondary lymphatic organs.

11.6.2 Primary Lymphatic Organs

Primary lymphatic organs are the sites where lymphocytes develop and mature.

1. Bone Marrow

Bone marrow is a soft tissue found within the cavities of bones. It is the site of formation of blood cells, including lymphocyte precursors. B lymphocytes mature in the bone marrow.

Functions

- Produces blood cells through hemopoiesis.
- Supports the development and maturation of B lymphocytes.
- Provides a microenvironment for haematopoietic stem cells.

2. Thymus

The thymus is a bilobed organ located in the upper part of the chest, behind the sternum. It is more active during childhood and gradually undergoes involution after puberty.

T lymphocytes develop from precursors originating in the bone marrow and mature in the thymus. During maturation, T cells undergo selection processes that help establish immune tolerance.

Functions

- Supports T-lymphocyte maturation.
- Helps develop immune tolerance.
- Produces factors that support T-cell development.

1.6.3 Secondary Lymphatic Organs and Tissues

Secondary lymphatic organs are sites where mature lymphocytes encounter antigens and initiate immune responses.

1. Lymph Nodes

Lymph nodes are small, bean-shaped structures located along lymphatic vessels. They are commonly found in the neck, armpits, groin, chest, and abdomen.

Each lymph node is surrounded by a connective tissue capsule and contains an outer cortex, paracortex, and inner medulla.

- Cortex: Contains lymphoid follicles, mainly associated with B lymphocytes.
- Paracortex: Rich in T lymphocytes.
- Medulla: Contains medullary cords and sinuses with lymphocytes, plasma cells, and macrophages.

Lymph enters through afferent lymphatic vessels and leaves through efferent lymphatic vessels at the hilum.

Functions

- Filter lymph and trap foreign particles.
- Provide sites for antigen presentation.
- Support activation and proliferation of lymphocytes.
- Participate in immune responses against infections.

2. Spleen

The spleen is the largest lymphatic organ and is located in the upper left part of the abdominal cavity. It filters blood rather than lymph.

It consists of white pulp and red pulp.

- White pulp: Contains lymphoid tissue involved in immune responses to blood-borne antigens.
- Red pulp: Removes aged or damaged red blood cells and helps store platelets.

Functions

- Filters blood.
- Removes aged and damaged erythrocytes.
- Supports immune responses against blood-borne microorganisms.
- Stores a proportion of circulating platelets.

3. Tonsils

Tonsils are collections of lymphatic tissue located around the entrance of the respiratory and digestive tracts. They include the palatine, pharyngeal, and lingual tonsils.

Functions

- Trap microorganisms entering through the mouth and nose.
- Initiate immune responses against inhaled or ingested antigens.
- Support local mucosal immunity.

4. Mucosa-Associated Lymphoid Tissue (MALT)

MALT is lymphatic tissue present in the mucosal linings of the respiratory, gastrointestinal, and genitourinary tracts. It includes structures such as Peyer's patches in the small intestine and lymphoid tissue in the appendix.

Functions

- Provides immune surveillance at mucosal surfaces.
- Detects antigens entering through mucosal routes.

- Supports local immune responses, including antibody production.

Table 11.9: Summary of Lymphatic Organs

Organ or tissue	Classification	Major function
Bone marrow	Primary	Blood cell formation and B-cell maturation
Thymus	Primary	T-cell maturation
Lymph nodes	Secondary	Filter lymph and support immune responses
Spleen	Secondary	Filter blood and respond to blood-borne antigens
Tonsils	Secondary	Protect the entrance of respiratory and digestive tracts
MALT	Secondary	Immune surveillance at mucosal surfaces

11.7 Lymphatic Vessels

11.7.1 Introduction

Lymphatic vessels are thin-walled channels that transport lymph from tissue spaces towards the venous circulation. They form an extensive network throughout the body and work alongside the cardiovascular system to maintain fluid balance and support immune defence.

Unlike blood vessels, lymphatic vessels form a one-way drainage system that begins in tissues and ultimately returns lymph to the bloodstream.

11.7.2 Types of Lymphatic Vessels

1. Lymphatic Capillaries

Lymphatic capillaries are microscopic, blind-ended vessels present in most tissues. Their endothelial cells overlap to form flap-like openings that allow interstitial fluid, proteins, and certain particles to enter.

They are highly permeable compared with blood capillaries. Specialized lymphatic capillaries called lacteals are present in the intestinal villi and absorb dietary fats.

2. Collecting Lymphatic Vessels

Lymphatic capillaries join to form larger collecting vessels. These vessels contain valves that prevent backward flow of lymph. Smooth muscle in their walls contributes to lymph movement.

3. Lymphatic Trunks

Collecting vessels unite to form larger lymphatic trunks. Major trunks include:

- Jugular trunks.
- Subclavian trunks.
- Bronchomediastinal trunks.
- Intestinal trunk.
- Lumbar trunks.

These trunks collect lymph from different regions of the body.

4. Lymphatic Ducts

The lymphatic trunks drain into two major ducts:

- Right lymphatic duct: Drains lymph from the right side of the head and neck, right upper limb, and right side of the thorax.
- Thoracic duct: Drains lymph from the remaining parts of the body. It usually begins at the cisterna chyli in the abdomen and ascends through the thorax.

Both ducts return lymph to the venous circulation near the junctions of the internal jugular and subclavian veins.

11.7.3 Structural Features of Lymphatic Vessels

Lymphatic vessels possess several features that facilitate fluid collection and movement:

- Thin walls that permit entry of interstitial fluid.
- Valves that prevent backflow.
- Overlapping endothelial cells in initial lymphatic capillaries.
- Smooth muscle in larger collecting vessels.
- Connections with lymph nodes along their course.

11.7.4 Special Lymphatic Vessels: Lacteals

Lacteals are specialized lymphatic capillaries found in the intestinal villi. They absorb dietary lipids and transport them in the form of chylomicrons. The lymph carrying absorbed fats has a milky appearance and is called chyle.

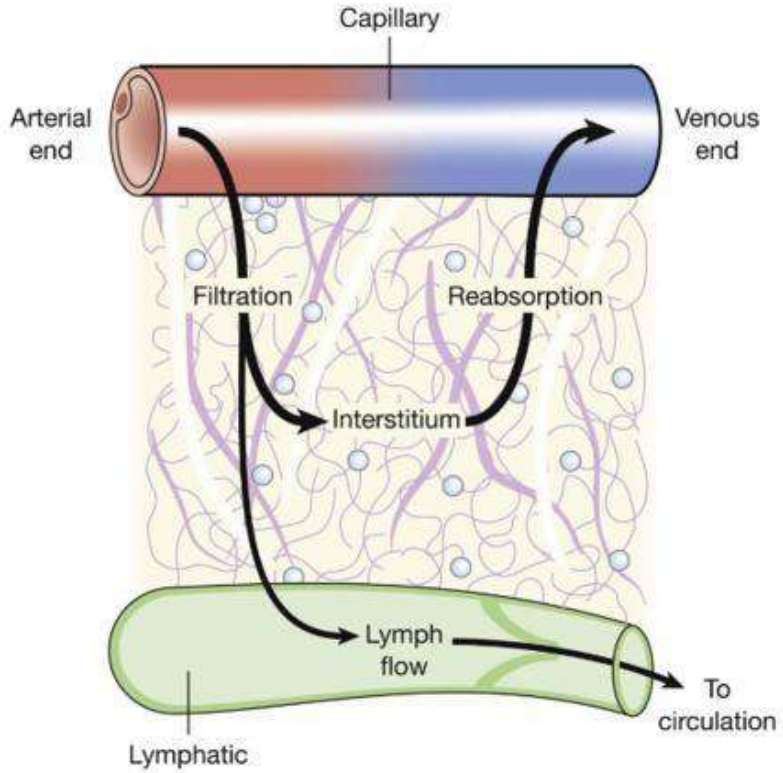
Lacteals therefore play an important role in the absorption and transport of dietary fats and fat-soluble vitamins.

11.8 Lymph Formation and Circulation

11.8.1 Formation of Lymph

Lymph is formed from interstitial fluid that enters lymphatic capillaries. Fluid continuously moves across blood capillary walls due to hydrostatic and osmotic pressure differences. Most filtered fluid is reabsorbed into blood capillaries, while the remaining fluid enters lymphatic capillaries and becomes lymph.

Lymph contains water, electrolytes, proteins, lymphocytes, and other substances collected from tissues. Its composition varies depending on the tissue from which it originates.



11.8.2 Mechanism of Lymph Formation

The formation of lymph involves the following steps:

1. Blood flows through capillaries, where some fluid moves from the blood into the surrounding interstitial spaces.
2. This fluid carries water and dissolved substances to the tissues.
3. A portion of the interstitial fluid returns to the blood circulation.
4. The remaining fluid enters the initial lymphatic capillaries through their overlapping endothelial cells.
5. Once inside lymphatic vessels, the fluid is called lymph.

The lymphatic system returns excess interstitial fluid and proteins to the circulation, helping prevent tissue fluid accumulation.

11.8.3 Circulation of Lymph

Unlike blood circulation, lymph circulation does not have a central pump such as the heart. Lymph moves through lymphatic vessels with the help of several mechanisms.

Mechanisms assisting lymph flow

1. Skeletal muscle contraction: Movement of skeletal muscles compresses lymphatic vessels and pushes lymph forward.

2. Respiratory movements: Changes in pressure during breathing assist lymph movement towards the thorax.
3. Smooth muscle contraction: Smooth muscle in larger lymphatic vessels contracts rhythmically.
4. Valves: One-way valves prevent the backward movement of lymph.
5. Arterial pulsations: Nearby arterial movements may help compress lymphatic vessels.

11.8.4 Pathway of Lymph Circulation

The general pathway of lymph circulation is:

Interstitial fluid → Lymphatic capillaries → Collecting lymphatic vessels → Lymph nodes → Lymphatic trunks → Lymphatic ducts → Subclavian veins → Blood circulation

Lymph passes through lymph nodes during its movement, allowing filtration and immune surveillance before returning to the bloodstream.

11.8.5 Intestinal Lymph Flow

Dietary fats absorbed by intestinal epithelial cells are packaged into chylomicrons. These enter lacteals and are transported through intestinal lymphatic vessels. The fat-rich lymph, called chyle, passes through the intestinal and lumbar lymphatic pathways and reaches the thoracic duct before entering the venous circulation.

11.9 Functions of the Lymphatic System

The lymphatic system performs important functions in fluid balance, fat absorption, and immune protection.

11.9.1 Maintenance of Fluid Balance

Fluid continuously leaves blood capillaries and enters tissue spaces. The lymphatic system collects excess interstitial fluid and returns it to the bloodstream. This helps maintain normal blood volume and prevents excessive accumulation of fluid in tissues.

Failure of lymphatic drainage may lead to lymphoedema, characterized by swelling due to accumulation of interstitial fluid.

11.9.2 Absorption and Transport of Dietary Fats

Lacteals in the intestinal villi absorb dietary lipids in the form of chylomicrons. These are transported through lymphatic vessels and eventually enter the blood circulation.

The lymphatic system also contributes to the absorption and transport of fat-soluble vitamins, including vitamins A, D, E, and K.

11.9.3 Immune Defence

The lymphatic system supports immune protection by transporting lymphocytes and providing sites for immune-cell activation.

Lymph nodes filter lymph and expose immune cells to antigens. The spleen performs a similar role for blood-borne antigens. Lymphatic tissues in mucosal surfaces provide protection against microorganisms entering through the respiratory, gastrointestinal, and genitourinary tracts.

11.9.4 Filtration of Lymph

Lymph passes through lymph nodes, where microorganisms, foreign particles, and cellular debris may be trapped and removed by macrophages and other immune cells. This filtration contributes to the body's defence against infection.

11.9.5 Transport of Immune Cells

Lymphatic vessels provide pathways for the movement of lymphocytes and antigen-presenting cells between tissues, lymph nodes, and the bloodstream. This movement helps coordinate immune surveillance and responses throughout the body.

11.9.6 Removal of Cellular Debris and Foreign Substances

The lymphatic system collects certain cellular debris, foreign particles, and proteins from interstitial spaces. These materials are transported to lymph nodes, where they may be processed or removed by immune cells.

Table 11.10: Summary of Functions

Function	Description
Fluid balance	Returns excess interstitial fluid and proteins to the bloodstream
Fat absorption	Absorbs and transports dietary fats through intestinal lacteals
Immune defence	Supports lymphocyte development, activation, and circulation
Lymph filtration	Removes microorganisms, foreign particles, and debris
Immune-cell transport	Provides pathways for movement of immune cells
Tissue drainage	Helps prevent excessive fluid accumulation in tissues

Body fluids are distributed between intracellular and extracellular compartments and provide the medium for transport, metabolism, and maintenance of homeostasis. Blood is a specialized connective tissue composed of plasma and formed elements. Plasma transports nutrients, hormones, gases, and waste products, while red blood cells carry oxygen, white blood cells provide immune defence, and platelets participate in haemostasis.

Hemopoiesis is the formation of blood cells from haematopoietic stem cells, mainly in the red bone marrow in adults. Haemoglobin is synthesized in developing erythrocytes through the coordinated formation of haem and globin. Blood coagulation involves platelet activation and a cascade of clotting-factor reactions that ultimately produce a stable fibrin clot. The ABO and Rh blood group systems are important in transfusion compatibility and pregnancy-related care.

The lymphatic system consists of lymphatic organs, tissues, and vessels. It collects excess interstitial fluid, transports absorbed dietary fats, filters lymph, and supports immune defence. Lymph circulates through lymphatic vessels and ducts before returning to the venous bloodstream.

Chapter 12: Basic Mechanism of Inflammation and Repair

12.1 Introduction to Inflammation

12.1.1 Definition of Inflammation

Inflammation is a protective response of vascularized tissues to injury, infection, or irritation. It involves coordinated changes in blood vessels, immune cells, and chemical mediators that help eliminate the harmful stimulus, remove damaged cells, and initiate tissue repair.

Inflammation is an essential part of the body's defence mechanism. However, when the response is excessive, prolonged, or improperly regulated, it may damage normal tissues and contribute to disease.

12.1.2 Causes of Inflammation

Inflammation may be initiated by several types of harmful stimuli.

1. Infections: Bacteria, viruses, fungi, and parasites can activate inflammatory responses.
2. Physical agents: Heat, cold, radiation, mechanical injury, and trauma may damage tissues.
3. Chemical agents: Acids, alkalis, toxins, and irritant substances can produce tissue injury.
4. Tissue necrosis: Dead or damaged cells release substances that activate inflammatory pathways.
5. Foreign bodies: Splinters, dust particles, crystals, and other foreign materials may induce inflammation.
6. Immune reactions: Allergic reactions and autoimmune responses can cause inflammation even in the absence of an external infectious agent.

Table 12.1: Cardinal Signs of Inflammation

The classical signs of inflammation are redness, heat, swelling, pain, and loss of function.

Sign	Description	Main mechanism
Redness (rubor)	Reddish appearance of the affected area	Increased blood flow due to vasodilation
Heat (calor)	Increased local temperature	Increased blood flow
Swelling (tumor)	Enlargement of the affected tissue	Increased vascular permeability and fluid accumulation
Pain (dolor)	Tenderness or discomfort	Chemical mediators and pressure from tissue swelling
Loss of function (functio laesa)	Reduced or impaired function	Pain, swelling, and tissue damage

12.1.3 Importance of Inflammation

Inflammation performs several protective functions:

- Helps eliminate microorganisms and other harmful agents.

- Removes dead cells and damaged tissue.
- Activates immune cells and promotes host defence.
- Initiates tissue repair and healing.
- Restricts the spread of infection or injury.

Although inflammation is protective, excessive or persistent inflammation may cause tissue destruction, fibrosis, and impaired organ function.

12.2 Classification of Inflammation

Inflammation is commonly classified according to its duration, predominant cellular response, and pathological characteristics. The two major forms are acute and chronic inflammation.

12.2.1 Acute Inflammation

Acute inflammation is a rapid and short-duration response that begins within minutes or hours after tissue injury. It is characterized mainly by fluid exudation and the migration of neutrophils into the affected tissue.

Causes

- Bacterial infections.
- Physical injury and trauma.
- Burns and chemical irritation.
- Tissue necrosis.
- Allergic reactions.

Main features

- Rapid onset.
- Short duration, usually lasting hours to days.
- Vasodilation and increased vascular permeability.
- Formation of inflammatory exudate.
- Predominant accumulation of neutrophils.

Possible outcomes

1. Complete resolution.
2. Healing by fibrosis or scar formation.
3. Progression to chronic inflammation.
4. Formation of an abscess in certain bacterial infections.

12.2.2 Chronic Inflammation

Chronic inflammation is a prolonged inflammatory response that may last for weeks, months, or years. It occurs when the causative agent persists, when acute inflammation fails to resolve, or when the immune system reacts continuously against self or environmental antigens.

Causes

- Persistent infections, such as tuberculosis.
- Autoimmune diseases, such as rheumatoid arthritis.
- Prolonged exposure to irritants or foreign materials.
- Certain metabolic and inflammatory disorders.

Main features

- Infiltration by macrophages, lymphocytes, and plasma cells.
- Ongoing tissue injury.
- Attempts at tissue repair.
- Formation of new blood vessels.
- Fibrosis and scarring in prolonged cases.

Table 12.2: Comparison Between Acute and Chronic Inflammation

Feature	Acute inflammation	Chronic inflammation
Onset	Rapid	Usually gradual or persistent
Duration	Short	Prolonged
Predominant cells	Neutrophils	Macrophages, lymphocytes and plasma cells
Vascular changes	Prominent	May be less prominent or variable
Tissue injury	Usually limited and potentially reversible	Often persistent and progressive
Repair	May result in resolution or scar formation	Repair and tissue destruction occur simultaneously
Common examples	Acute bacterial infection, injury	Tuberculosis, rheumatoid arthritis

12.2.3 Morphological Patterns of Acute Inflammation

Acute inflammation may show different patterns depending on the nature of the injury and the tissue involved.

1. Serous Inflammation

Serous inflammation is characterized by the accumulation of a thin, watery fluid containing relatively few cells. It may occur in skin blisters and certain body-cavity inflammations.

2. Fibrinous Inflammation

Fibrinous inflammation occurs when increased vascular permeability allows fibrinogen to enter tissues or body cavities, where it is converted into fibrin. It may be seen in inflammation of the pericardium or pleura.

3. Suppurative or Purulent Inflammation

This type is characterized by the formation of pus, which contains neutrophils, dead cells, tissue debris, and fluid. It is commonly associated with bacterial infections.

4. Ulcerative Inflammation

An ulcer is a local defect or excavation of a tissue surface caused by the loss of inflamed and necrotic tissue. Ulcers may occur in the skin or mucosal surfaces.

12.2.4 Granulomatous Inflammation

Granulomatous inflammation is a distinctive form of chronic inflammation characterized by collections of activated macrophages, often called epithelioid cells, with or without multinucleated giant cells. Lymphocytes may surround these collections.

Granulomas may develop in response to persistent microorganisms, foreign materials, or immune-mediated conditions. Tuberculosis is a classic example of granulomatous inflammation, although not all granulomas are caused by infection.

12.3 Pathophysiology of Inflammation

12.3.1 Introduction

The pathophysiology of inflammation involves a sequence of vascular, cellular, and biochemical events triggered by tissue injury or infection. These events are coordinated by inflammatory mediators and immune cells.

The major stages include:

1. Recognition of the harmful stimulus.
2. Vascular changes.
3. Increased vascular permeability.
4. Recruitment and activation of leukocytes.
5. Elimination of the harmful agent.
6. Resolution or progression to tissue repair and chronic inflammation.

12.3.2 Recognition of the Inflammatory Stimulus

Inflammatory responses begin when cells recognize microorganisms, damaged cells, or foreign substances.

Immune cells such as macrophages, dendritic cells, and mast cells possess pattern-recognition receptors (PRRs). These receptors detect:

- Pathogen-associated molecular patterns (PAMPs): Molecular structures commonly found in microorganisms.
- Damage-associated molecular patterns (DAMPs): Substances released from damaged or dying cells.

Recognition of these signals activates intracellular pathways that promote the production of inflammatory mediators, including cytokines and chemokines.

12.3.3 Vascular Changes

Vascular changes are among the earliest events in acute inflammation.

1. Vasodilation

Small blood vessels, particularly arterioles, dilate due to mediators such as histamine and nitric oxide. This increases blood flow to the affected tissue and produces redness and heat.

2. Increased Vascular Permeability

The endothelial barrier becomes more permeable, allowing fluid and plasma proteins to move from blood vessels into the interstitial space. This produces inflammatory exudate and tissue swelling.

3. Stasis of Blood Flow

Loss of fluid from the circulation increases blood viscosity and slows blood flow. This process, called stasis, brings leukocytes closer to the endothelial surface and facilitates their movement into tissues.

12.3.4 Cellular Events in Inflammation

Leukocytes, especially neutrophils and monocytes, are recruited from the blood into the site of injury.

1. Margination and Rolling

As blood flow slows, leukocytes move towards the vessel wall. They interact weakly with endothelial cells through selectins, producing a rolling movement.

2. Adhesion

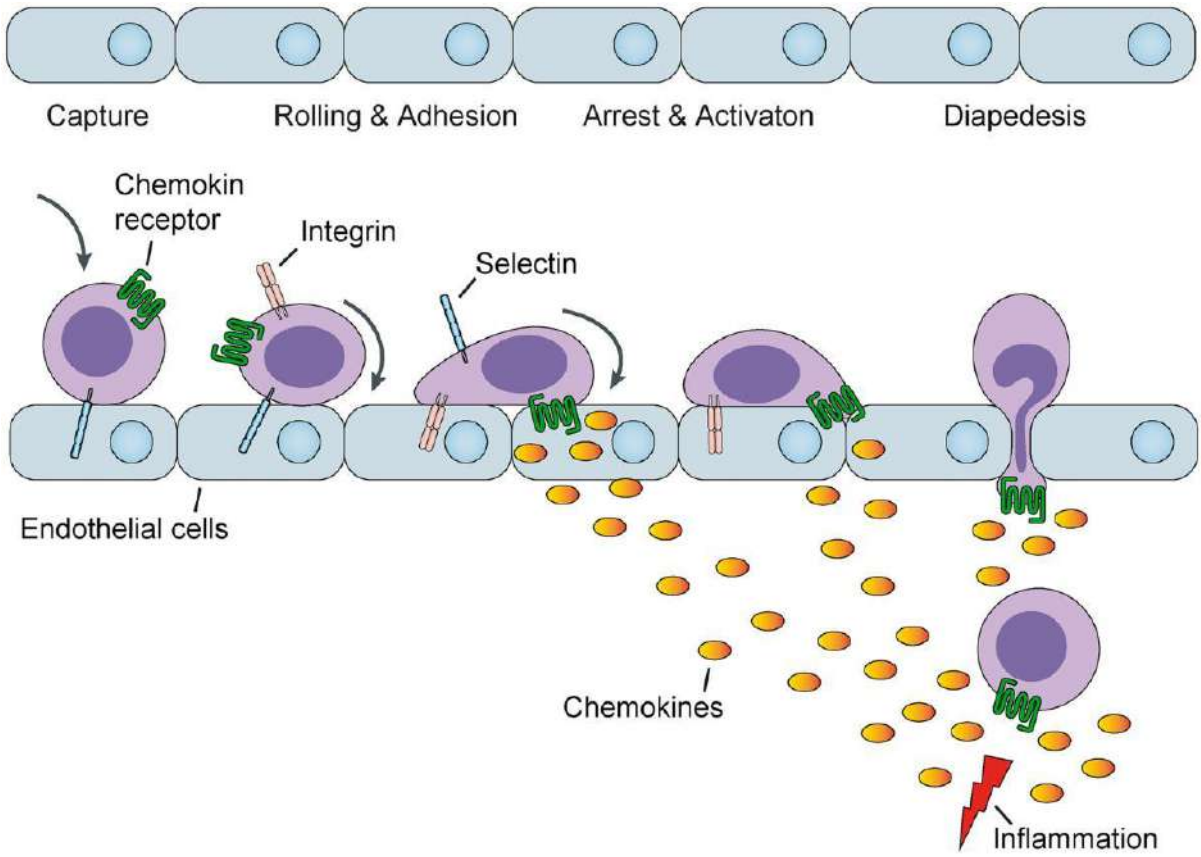
Leukocytes become firmly attached to endothelial cells through integrins and their endothelial ligands. Inflammatory cytokines increase the expression and activity of these adhesion molecules.

3. Transmigration or Diapedesis

Leukocytes pass between endothelial cells and cross the vascular basement membrane into the surrounding tissue. This process is also called extravasation.

4. Chemotaxis

Leukocytes move towards the site of inflammation along chemical concentration gradients. Important chemotactic substances include bacterial products, complement component C5a, leukotriene B4, and chemokines such as IL-8 (CXCL8).



12.3.5 Phagocytosis and Destruction of Harmful Agents

Phagocytosis is the process by which cells engulf and remove microorganisms, foreign particles, and damaged cellular material. Neutrophils and macrophages are the principal phagocytic cells in inflammation.

The process involves three main stages:

1. Recognition and attachment: Phagocytes recognize the target directly or through opsonins such as antibodies and complement proteins.
2. Engulfment: The target is enclosed within a membrane-bound vesicle called a phagosome.
3. Killing and degradation: The phagosome fuses with lysosomes to form a phagolysosome, where enzymes and reactive oxygen species help destroy and digest the material.

12.3.6 Outcomes of Inflammation

The outcome depends on the type and severity of injury, the ability to remove the harmful stimulus, and the regenerative capacity of the affected tissue.

1. Resolution

When the harmful agent is removed and tissue damage is limited, inflammatory cells and fluid are cleared, and normal tissue structure may be restored.

2. Healing by Fibrosis

When tissue damage is extensive or the affected cells have limited regenerative capacity, connective tissue may replace the damaged area, resulting in scar formation.

3. Abscess Formation

Certain infections may lead to localized collections of pus containing neutrophils, dead cells, and microorganisms.

4. Chronic Inflammation

Persistent stimuli or defective resolution may lead to chronic inflammation, characterized by continued immune-cell infiltration, tissue destruction, and repair.

12.3.7 Tissue Repair

Tissue repair is the process by which the body restores tissue integrity after injury. It may occur through regeneration, in which damaged cells are replaced by the same type of cells, or through fibrosis, in which connective tissue forms a scar.

The major stages of repair include:

1. Haemostasis: Blood clot formation limits blood loss and provides a temporary framework for repair.
2. Inflammation: Immune cells remove microorganisms and damaged tissue.
3. Proliferation: Fibroblasts produce extracellular matrix, endothelial cells form new blood vessels, and epithelial cells migrate to cover the wound.
4. Remodelling: Collagen is reorganized, excess cells and vessels are removed, and the wound gains strength.

12.3.8 Factors Affecting Tissue Repair

Tissue repair may be influenced by local and systemic factors.

Local factors

- Infection.
- Poor blood supply.
- Foreign bodies.
- Repeated mechanical stress.
- Extent and type of tissue injury.

Systemic factors

- Nutritional deficiencies, especially protein and vitamin deficiencies.
- Diabetes mellitus.
- Advanced age.
- Anaemia and impaired oxygen delivery.
- Certain medications, including corticosteroids and some immunosuppressive agents.

12.4 Mediators of Inflammation

12.4.1 Introduction

Inflammatory mediators are chemical substances that initiate, regulate, and terminate inflammatory responses. They may be derived from plasma proteins or produced by cells such as mast cells, macrophages, neutrophils, endothelial cells, and platelets.

These mediators regulate vascular changes, leukocyte recruitment, pain, fever, tissue destruction, and repair.

12.4.2 Classification of Inflammatory Mediators

Inflammatory mediators are broadly classified into:

1. Cell-derived mediators.
2. Plasma-derived mediators.

12.4.3 Cell-Derived Mediators

Cell-derived mediators are produced or released by activated cells at the site of inflammation.

1. Histamine

Histamine is stored mainly in mast cells and basophils and is released during tissue injury, allergic reactions, and immune activation.

Actions

- Causes vasodilation.
- Increases vascular permeability.
- Contributes to redness and swelling.
- Participates in allergic and inflammatory reactions.

2. Prostaglandins

Prostaglandins are lipid mediators synthesized from arachidonic acid through the cyclooxygenase (COX) pathway.

Actions

- Promote vasodilation.
- Contribute to pain and fever.
- Participate in inflammatory responses.
- Influence vascular and cellular functions.

Prostaglandin E_2 (PGE_2) is particularly important in fever and inflammatory pain.

3. Leukotrienes

Leukotrienes are lipid mediators formed from arachidonic acid through the lipoxygenase pathway.

Actions

- Promote leukocyte recruitment.
- Increase vascular permeability.
- Cause bronchoconstriction, particularly cysteinyl leukotrienes.
- Contribute to inflammatory responses in allergic and respiratory conditions.

4. Cytokines

Cytokines are signalling proteins that regulate immune and inflammatory responses.

Table 12.3: Major Cytokines and Their Functions in Inflammatory and Immune Responses

Cytokine	Major functions
Tumour necrosis factor-alpha (TNF-α)	Activates endothelium, promotes leukocyte recruitment and systemic inflammatory responses
Interleukin-1 (IL-1)	Promotes fever, endothelial activation and leukocyte recruitment
Interleukin-6 (IL-6)	Stimulates acute-phase protein production and contributes to systemic inflammation
Interleukin-8 (IL-8/CXCL8)	Attracts and activates neutrophils
Interleukin-10 (IL-10)	Suppresses several inflammatory responses and supports regulation
Transforming growth factor-beta (TGF-β)	Regulates immune responses and promotes tissue repair and fibrosis

5. Chemokines

Chemokines are a group of cytokines that guide the movement of leukocytes towards sites of inflammation. They create chemical gradients that direct immune cells to injured or infected tissues.

6. Nitric Oxide

Nitric oxide (NO) is a gaseous mediator produced by several cell types. It contributes to vasodilation and can participate in antimicrobial and inflammatory responses.

7. Reactive Oxygen Species

Reactive oxygen species (ROS), including superoxide and hydrogen peroxide, are generated by activated phagocytes and other cells. They help destroy microorganisms but may also damage host tissues when produced excessively.

8. Platelet-Activating Factor

Platelet-activating factor (PAF) is a lipid mediator produced by several inflammatory cells. It promotes platelet activation, leukocyte adhesion, vasodilation, and increased vascular permeability.

12.4.4 Plasma-Derived Mediators

Plasma-derived mediators circulate in inactive forms and are activated through enzymatic cascades.

1. Complement System

The complement system consists of plasma proteins that support immune defence and inflammation.

Important complement components include:

- C3a and C5a: Promote mast-cell activation and increased vascular permeability.
- C5a: Also acts as a powerful chemotactic factor for leukocytes.
- C3b: Acts as an opsonin and enhances phagocytosis.
- C5b–C9: Form the membrane attack complex, which can damage susceptible microbial cell membranes.

2. Kinin System

The kinin system produces bradykinin, a peptide mediator involved in inflammation.

Actions of bradykinin

- Increases vascular permeability.
- Causes vasodilation.
- Produces pain.
- Contributes to smooth muscle effects.

3. Coagulation System

The coagulation system is activated during tissue injury and produces fibrin to limit blood loss. Some activated coagulation factors and related pathways can also influence inflammatory responses.

4. Fibrinolytic System

The fibrinolytic system breaks down fibrin clots. Plasmin, the principal fibrinolytic enzyme, can also interact with inflammatory pathways and contribute to the removal of damaged tissue.

Table 12.4: Summary of Important Inflammatory Mediators

Mediator	Main source	Major action
Histamine	Mast cells, basophils	Vasodilation and increased vascular permeability
Prostaglandins	Many activated cells	Pain, fever and vasodilation
Leukotrienes	Leukocytes and other cells	Leukocyte recruitment, permeability and bronchoconstriction
TNF-α	Mainly macrophages and other immune cells	Endothelial activation and systemic inflammation
IL-1	Macrophages and other cells	Fever and endothelial activation
IL-6	Macrophages and other cells	Acute-phase response

Chemokines	Immune and tissue cells	Leukocyte migration
Nitric oxide	Endothelial and other cells	Vasodilation and immune effects
ROS	Activated phagocytes and other cells	Microbial killing and potential tissue injury
C3a and C5a	Complement cascade	Inflammatory cell activation
C3b	Complement cascade	Opsonization
Bradykinin	Kinin system	Pain, vasodilation and increased permeability
TGF-β	Many cell types	Repair, immune regulation and fibrosis

12.4.5 Regulation and Termination of Inflammation

Inflammation is normally controlled by regulatory mechanisms that limit tissue injury and promote resolution. Anti-inflammatory cytokines, lipid mediators, removal of inflammatory cells, and clearance of cellular debris contribute to termination of the response.

Failure to regulate inflammation may result in persistent tissue injury, chronic inflammatory disease, or excessive fibrosis.

Inflammation is a protective response to infection, tissue injury, and other harmful stimuli. It is characterized by vascular changes, leukocyte recruitment, and the release of chemical mediators. Acute inflammation develops rapidly and is commonly dominated by neutrophils, whereas chronic inflammation is prolonged and involves macrophages, lymphocytes, tissue destruction, and repair.

The pathophysiology of inflammation includes recognition of harmful stimuli, vasodilation, increased vascular permeability, leukocyte migration, phagocytosis, and removal of the causative agent. Tissue repair occurs through regeneration or fibrosis. Inflammatory mediators, including histamine, prostaglandins, leukotrienes, cytokines, complement proteins, and bradykinin, regulate the intensity and duration of the response.

Chapter 13: Haematological Diseases

13.1 Pathophysiology of Iron Deficiency Anaemia

13.1.1 Introduction

Iron deficiency anaemia (IDA) is a common type of anaemia caused by insufficient iron availability for haemoglobin synthesis. Iron is an essential component of haem, the oxygen-binding part of haemoglobin. When iron stores become depleted, haemoglobin production decreases, resulting in reduced oxygen-carrying capacity of blood.

Iron deficiency usually develops gradually. Initially, the body's iron stores decrease without a significant reduction in haemoglobin. With continued deficiency, iron supply becomes inadequate for erythropoiesis, and anaemia develops.

13.1.2 Causes of Iron Deficiency

The major causes of iron deficiency include:

1. Inadequate dietary intake: Insufficient consumption of iron-rich foods may lead to deficiency, particularly when nutritional requirements are increased.
2. Increased iron requirements: Pregnancy, infancy, childhood, and adolescence are periods of increased iron demand.
3. Chronic blood loss: Heavy menstrual bleeding, gastrointestinal bleeding, parasitic infections, and other sources of persistent blood loss may deplete iron stores.
4. Reduced iron absorption: Conditions affecting the stomach or small intestine, gastrointestinal surgery, and certain intestinal disorders may reduce iron absorption.
5. Increased physiological demand: Rapid growth and repeated blood donation may increase the risk of iron depletion.

13.1.3 Normal Iron Metabolism

Iron is obtained from dietary sources and absorbed mainly in the duodenum and upper small intestine. Dietary iron occurs in haem and non-haem forms. Absorbed iron enters the circulation and binds to transferrin, the principal iron-transport protein in plasma.

Iron is delivered to the bone marrow for haemoglobin synthesis or stored in the form of ferritin and haemosiderin, mainly in the liver, macrophages, and other tissues.

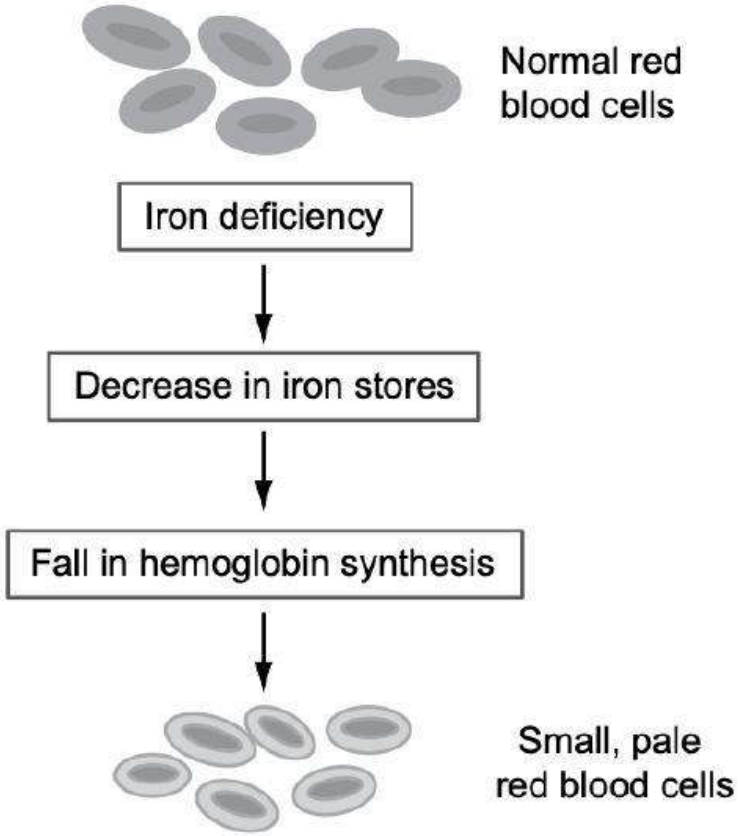
Hepcidin, a hormone produced by the liver, regulates systemic iron balance by controlling the activity of ferroportin, a protein responsible for iron export from intestinal cells and macrophages.

13.1.4 Pathophysiology of Iron Deficiency Anaemia

Iron deficiency develops when iron loss or iron requirements exceed iron intake and absorption.

The major pathological sequence is:

1. Depletion of iron stores.
2. Reduction in circulating iron availability.
3. Reduced delivery of iron to developing erythroblasts.
4. Decreased haem synthesis.
5. Formation of smaller red blood cells with reduced haemoglobin content.
6. Development of microcytic, hypochromic anaemia.



In iron deficiency, erythroblasts undergo additional cell divisions because haemoglobin accumulation is insufficient. This produces smaller-than-normal red blood cells (microcytosis). Their reduced haemoglobin content gives them a pale appearance (hypochromia).

13.1.5 Clinical Features

Common clinical features include:

- Fatigue and weakness.
- Pallor of skin and mucous membranes.
- Breathlessness on exertion.
- Dizziness and headache.
- Palpitations.
- Reduced concentration and exercise tolerance.
- Brittle nails or spoon-shaped nails (koilonychia) in some cases.
- Soreness of the tongue and cracks at the corners of the mouth.
- Pica, an unusual craving for non-food substances, in some individuals.

Table 13.1: Laboratory Findings

Parameter	Typical finding in iron deficiency anaemia
Haemoglobin	Decreased
Mean corpuscular volume (MCV)	Usually decreased
Mean corpuscular haemoglobin (MCH)	Decreased
Peripheral blood smear	Microcytic, hypochromic RBCs; anisocytosis may occur
Serum ferritin	Decreased
Serum iron	Decreased
Total iron-binding capacity (TIBC)	Usually increased
Transferrin saturation	Decreased

Serum ferritin is a useful indicator of iron stores, although it may be increased by inflammation because it is an acute-phase protein.

13.1.6 Complications and Management Principles

Untreated iron deficiency anaemia may impair physical performance, cognitive function, and quality of life. Severe anaemia may place additional stress on the cardiovascular system.

Management involves identifying and treating the underlying cause, improving iron intake, and replacing iron when indicated. Oral iron is commonly used, while intravenous iron may be considered when oral treatment is ineffective, poorly tolerated, or unsuitable.

13.2 Pathophysiology of Megaloblastic Anaemia (Vitamin B12 and Folic Acid Deficiency)

13.2.1 Introduction

Megaloblastic anaemia is a group of disorders characterized by impaired DNA synthesis in developing blood cells, resulting in abnormal maturation of the nucleus and formation of large precursor cells called megaloblasts. It is commonly caused by deficiency of vitamin B12 (cobalamin) or folic acid (folate).

Because DNA synthesis is impaired, nuclear maturation is delayed while cytoplasmic development continues. This produces large erythroid precursors and often macrocytic red blood cells in peripheral blood.

13.2.2 Causes of Vitamin B12 Deficiency

Vitamin B12 is required for normal DNA synthesis, red blood cell formation, and neurological function.

Major causes include:

1. Inadequate dietary intake: May occur in individuals consuming insufficient animal-derived foods without adequate fortified foods or supplementation.

2. Pernicious anaemia: An autoimmune condition in which intrinsic factor production or function is impaired, reducing vitamin B12 absorption.
3. Gastrointestinal disorders: Diseases or surgical procedures affecting the stomach or terminal ileum may impair absorption.
4. Intrinsic factor deficiency: Prevents normal absorption of vitamin B12.
5. Certain medications: Some medicines may interfere with vitamin B12 absorption or metabolism.

13.2.3 Causes of Folic Acid Deficiency

Folate is essential for DNA synthesis and normal cell division.

Major causes include:

- Inadequate dietary intake.
- Increased requirements during pregnancy and periods of rapid growth.
- Malabsorption disorders.
- Chronic alcohol use.
- Certain medications that interfere with folate metabolism.
- Conditions associated with increased cell turnover.

13.2.4 Normal Role of Vitamin B12 and Folic Acid

Vitamin B12 and folate participate in one-carbon metabolism, which is essential for the synthesis of nucleotides required for DNA production.

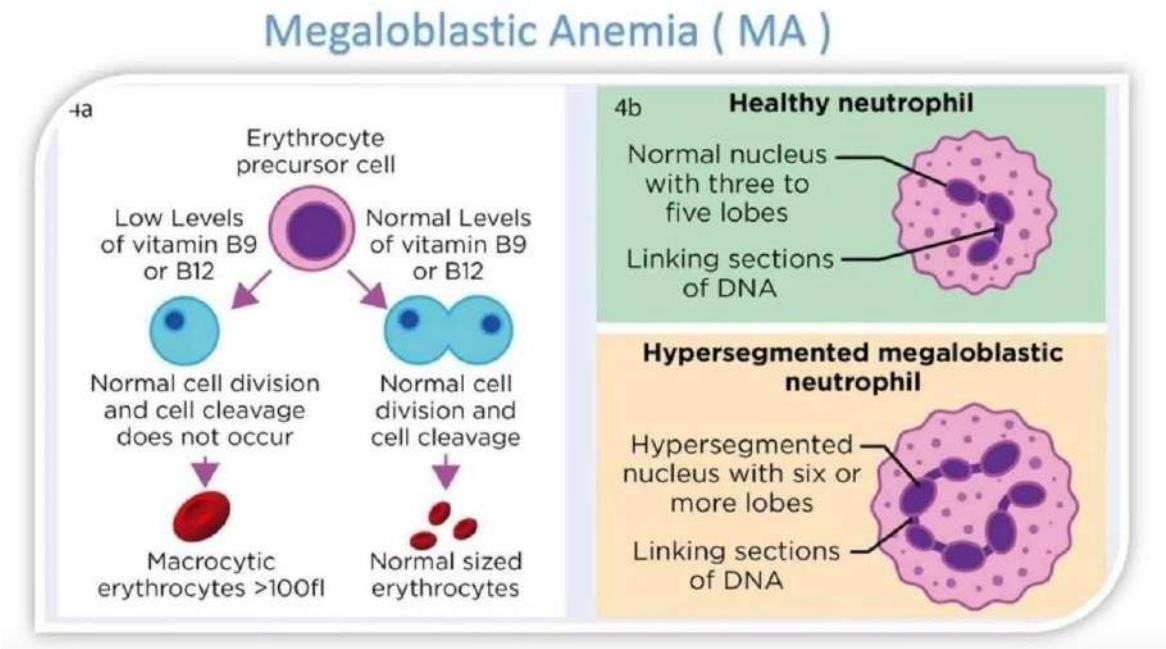
Folate is converted into metabolically active forms that donate one-carbon units during nucleotide synthesis. Vitamin B12 is required for the conversion of methyl-tetrahydrofolate to tetrahydrofolate, allowing folate to be reused in cellular reactions.

Deficiency of either nutrient impairs DNA synthesis, particularly in rapidly dividing cells such as bone marrow precursors.

13.2.5 Pathophysiology of Megaloblastic Anaemia

The central mechanism is defective DNA synthesis in haematopoietic cells.

1. Vitamin B12 or folate deficiency reduces the availability of substrates required for DNA synthesis.
2. Nuclear maturation becomes delayed.
3. Cytoplasmic development continues relatively normally.
4. Nuclear-cytoplasmic maturation becomes asynchronous.
5. Large abnormal erythroid precursors (megaloblasts) develop in the bone marrow.
6. Many abnormal cells are destroyed within the bone marrow, producing ineffective haematopoiesis.
7. Macrocytic anaemia develops, often accompanied by reduced white blood cell and platelet counts in severe cases.



13.2.6 Clinical Features

Common clinical manifestations include:

- Fatigue and weakness.
- Pallor.
- Breathlessness on exertion.
- Glossitis, characterized by a smooth, sore tongue.
- Loss of appetite and gastrointestinal discomfort.
- Mild jaundice in some cases due to ineffective erythropoiesis.

Features more commonly associated with vitamin B12 deficiency

- Numbness and tingling in the hands and feet.
- Impaired vibration and position sense.
- Difficulty walking or balance disturbances.
- Cognitive or mood-related changes in some individuals.

Neurological abnormalities are not a typical feature of isolated folate deficiency.

Table 13.2: Laboratory Findings

Parameter	Typical finding
Haemoglobin	Decreased
MCV	Increased
Peripheral blood smear	Macro-ovalocytes and hypersegmented neutrophils
Bone marrow	Megaloblastic changes
Vitamin B12	Decreased in B12 deficiency
Serum or red cell folate	May be decreased in folate deficiency

Reticulocyte count	Often low before treatment
Bilirubin	May be increased due to ineffective erythropoiesis

Table 13.3: Difference Between Vitamin B12 and Folate Deficiency

Feature	Vitamin B12 deficiency	Folate deficiency
Main role	DNA synthesis and neurological function	DNA synthesis
Common causes	Pernicious anaemia, malabsorption, inadequate intake	Poor intake, increased requirement, malabsorption, medicines
Blood picture	Megaloblastic, macrocytic anaemia	Megaloblastic, macrocytic anaemia
Neurological manifestations	May occur	Not usually present
Biochemical feature	Increased methylmalonic acid may occur	Methylmalonic acid usually remains normal
Treatment principle	Replace vitamin B12 and address cause	Replace folate and address cause

Important: Folate should not be given as the only treatment when vitamin B12 deficiency has not been excluded, because blood abnormalities may improve while neurological damage due to B12 deficiency continues.

13.3 Pathophysiology of Sickle Cell Anaemia

13.3.1 Introduction

Sickle cell anaemia is an inherited haemoglobin disorder caused by a mutation in the beta-globin gene. It leads to the production of abnormal haemoglobin known as haemoglobin S (HbS). Under conditions such as low oxygen tension, HbS molecules polymerize, causing red blood cells to become rigid and assume a sickle-like shape.

The disease is characterized by chronic haemolytic anaemia, episodes of vaso-occlusion, and progressive damage to various organs.

13.3.2 Genetic Basis

Sickle cell anaemia is inherited in an autosomal recessive pattern. The affected individual generally inherits two abnormal beta-globin alleles, one from each parent.

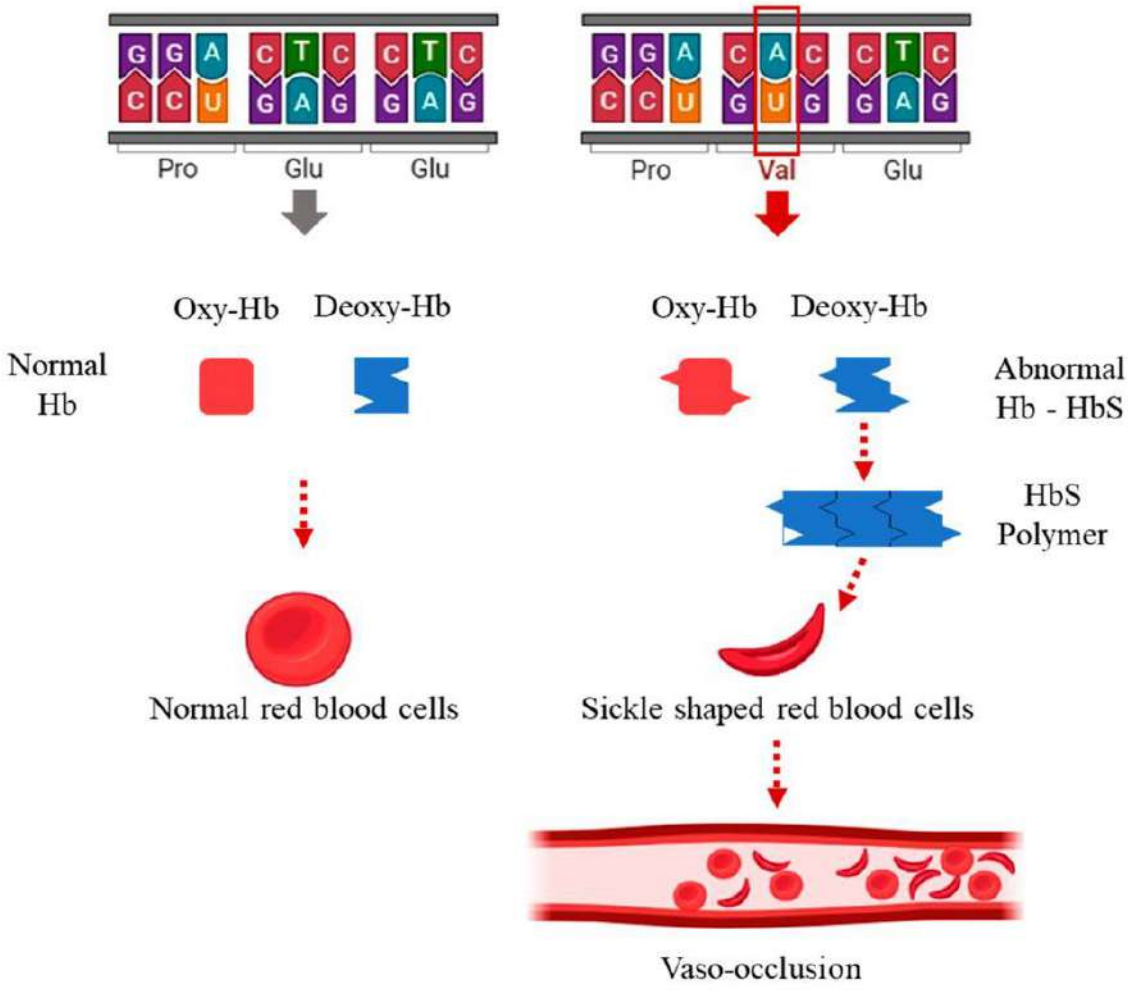
The mutation involves substitution of valine for glutamic acid at the sixth position of the beta-globin chain. This produces haemoglobin S.

Individuals who inherit one normal and one sickle haemoglobin allele are generally described as having sickle cell trait. Their clinical course differs from that of sickle cell anaemia.

13.3.3 Pathophysiology

The major pathological mechanism is polymerization of deoxygenated HbS.

1. Reduced oxygen tension causes HbS molecules to aggregate and form long polymers.
2. Polymer formation distorts red blood cells into sickle or crescent shapes.
3. Repeated sickling and unsickling damage the red cell membrane.
4. Damaged cells become rigid and less deformable.
5. Rigid cells are destroyed prematurely, causing chronic haemolytic anaemia.
6. Sickled cells obstruct small blood vessels, reducing tissue perfusion.
7. Repeated vaso-occlusion causes ischemia, inflammation, and tissue injury.



13.3.4 Major Pathological Processes

1. Chronic Haemolysis

Sickled red blood cells have a shortened lifespan. Their premature destruction produces chronic anaemia and increases bilirubin formation. Haemolysis may occur within blood vessels and through removal by macrophages.

2. Vaso-Occlusion

Rigid sickled cells interact abnormally with the vascular endothelium and other blood cells. They may obstruct small vessels, causing reduced oxygen delivery and ischemic injury.

3. Repeated Tissue Ischemia and Reperfusion

Episodes of reduced blood flow followed by restoration of circulation can promote oxidative stress and inflammation. Repeated injury may gradually damage organs.

4. Functional Asplenia

Repeated sickling and infarction of splenic tissue may cause progressive loss of splenic function, particularly during childhood. This increases susceptibility to infections caused by encapsulated bacteria.

13.3.5 Clinical Features

Clinical manifestations vary among individuals and may include:

- Chronic haemolytic anaemia.
- Fatigue and pallor.
- Painful vaso-occlusive crises.
- Swelling of hands and feet, particularly in children.
- Jaundice.
- Recurrent infections.
- Delayed growth and development.
- Acute chest syndrome.
- Stroke or other neurological complications.
- Renal, retinal, and bone complications.

Table 13.4: Laboratory Findings

Parameter	Typical finding
Haemoglobin	Decreased
Peripheral blood smear	Sickle-shaped cells, target cells and other abnormal RBCs
Reticulocyte count	Usually increased
Bilirubin	May be increased due to haemolysis
Haemoglobin analysis	HbS present; HbA absent in typical HbSS disease
Sickling or solubility tests	May detect HbS but do not reliably distinguish all genotypes

13.3.6 Complications and Management Principles

Important complications include painful crises, acute chest syndrome, stroke, infections, avascular necrosis, renal impairment, and chronic organ damage.

Management aims to prevent complications, reduce pain, treat infections, and improve quality of life. Measures may include vaccination, infection prevention, hydroxyurea in appropriate patients, transfusion in selected situations, and other specialist-directed therapies. Haematopoietic stem-cell transplantation and gene-based therapies may be considered for selected patients.

13.4 Pathophysiology of Thalassemia

13.4.1 Introduction

Thalassemia is a group of inherited disorders characterized by reduced or absent synthesis of one or more globin chains of haemoglobin. The imbalance between globin chains leads to ineffective erythropoiesis, red blood cell destruction, and anaemia.

The two major forms are alpha-thalassemia and beta-thalassemia, classified according to the affected globin chain.

13.4.2 Classification of Thalassemia

1. Alpha-Thalassemia

Alpha-thalassemia results from reduced or absent production of alpha-globin chains. Most cases are caused by deletions or other mutations affecting alpha-globin genes.

The severity depends on the number of affected alpha-globin genes.

Table 13.5: Major Cytokines and Their Functions in Inflammatory and Immune Responses

Number of affected alpha-globin genes	Common clinical description
One	Silent carrier
Two	Alpha-thalassemia trait
Three	Haemoglobin H disease
Four	Hb Bart's hydrops fetalis, usually severe and often fatal without specialized intervention

2. Beta-Thalassemia

Beta-thalassemia results from reduced or absent synthesis of beta-globin chains. It is commonly caused by mutations affecting beta-globin gene expression or processing.

It is classified according to the severity of beta-chain production:

- Beta-thalassemia minor (trait): Usually mild or asymptomatic.
- Beta-thalassemia intermedia: Variable severity, with clinical features between minor and major forms.
- Beta-thalassemia major: Severe disease that commonly presents during infancy after fetal haemoglobin levels decline.

13.4.3 Pathophysiology of Thalassemia

The main mechanism is an imbalance in globin-chain production.

1. Genetic defects reduce the synthesis of alpha- or beta-globin chains.
2. Unpaired globin chains accumulate within developing erythroid cells.
3. Excess unmatched chains damage cell membranes and promote oxidative injury.
4. Many developing erythroid cells are destroyed within the bone marrow, causing ineffective erythropoiesis.
5. Circulating red blood cells are also removed prematurely, producing haemolytic anaemia.
6. Increased erythropoietin stimulates expansion of erythroid tissue, which may cause bone changes and enlargement of the spleen and liver.
7. In transfusion-dependent forms, repeated transfusions and increased intestinal iron absorption may result in iron overload.

13.4.4 Pathophysiology of Beta-Thalassemia

In beta-thalassemia, reduced beta-chain production causes excess alpha-globin chains to accumulate in erythroid precursors. These excess chains precipitate and damage developing cells, leading to ineffective erythropoiesis.

The resulting anaemia stimulates erythropoietin production, causing expansion of the bone marrow. In severe disease, this may produce skeletal deformities and increased metabolic demand.

13.4.5 Pathophysiology of Alpha-Thalassemia

In alpha-thalassemia, reduced alpha-chain production results in excess non-alpha chains. In fetal life, excess gamma chains may form Hb Bart's, while after birth excess beta chains may form HbH.

These abnormal haemoglobin forms have altered oxygen-binding properties and may contribute to tissue hypoxia and red blood cell damage. Clinical severity depends on the number of affected alpha-globin genes.

13.4.6 Clinical Features

Clinical manifestations depend on the type and severity of thalassemia.

Mild forms

- Often asymptomatic.
- Mild microcytosis.
- Mild or no anaemia.

Severe forms

- Pallor and fatigue.
- Poor growth and delayed development.
- Jaundice.
- Enlarged liver and spleen.
- Bone changes due to marrow expansion.
- Increased susceptibility to complications associated with anaemia and iron overload.

Table 13.6: Laboratory Findings

Parameter	Typical finding
Haemoglobin	Decreased to variable degree
MCV and MCH	Usually decreased
Peripheral blood smear	Microcytosis, hypochromia, target cells and anisopoikilocytosis
Reticulocyte count	May be increased
Haemoglobin analysis	Abnormal haemoglobin fractions depending on the type
Iron studies	Usually not consistent with iron deficiency unless both conditions coexist

In beta-thalassemia trait, HbA_2 is commonly increased. In beta-thalassemia major, HbF is usually markedly increased, while HbA may be absent or very low depending on the genotype and clinical context.

13.4.7 Complications and Management Principles

Complications may include severe anaemia, growth retardation, skeletal abnormalities, splenomegaly, iron overload, endocrine dysfunction, and cardiac or liver injury.

Management depends on the type and severity. It may include regular blood transfusions, iron chelation therapy when indicated, folate supplementation in selected patients, and specialist monitoring. Haematopoietic stem-cell transplantation may offer a curative option for selected individuals.

13.5 Hereditary and Acquired Anaemia

13.5.1 Introduction

Anaemia is a condition in which the haemoglobin concentration or red blood cell mass is below the expected level for a person's age, sex, and physiological condition. It reduces the oxygen-carrying capacity of blood and may produce symptoms such as fatigue, weakness, pallor, and breathlessness.

Anaemia may be classified according to its cause as hereditary or acquired. It may also be classified morphologically as microcytic, normocytic, or macrocytic based on the mean corpuscular volume (MCV).

13.5.2 Hereditary Anaemia

Hereditary anaemias result from genetic abnormalities affecting haemoglobin production, red blood cell membrane structure, or red blood cell enzymes.

Major types include:

1. Sickle Cell Anaemia

An inherited haemoglobin disorder caused by HbS production. Red blood cells may become sickle-shaped under low-oxygen conditions, leading to haemolysis and vaso-occlusion.

2. Thalassemia

Inherited disorders caused by reduced synthesis of alpha- or beta-globin chains. They produce globin-chain imbalance, ineffective erythropoiesis, and variable degrees of anaemia.

3. Hereditary Spherocytosis

A red blood cell membrane disorder commonly caused by defects in proteins such as spectrin, ankyrin, band 3, or protein 4.2. The cells become spherical and less deformable, making them more likely to be destroyed in the spleen.

4. Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

An inherited enzyme deficiency that reduces the ability of red blood cells to protect themselves against oxidative stress. Certain infections, medicines, or foods may trigger haemolysis in affected individuals.

5. Other Inherited Red Cell Disorders

Other hereditary conditions include pyruvate kinase deficiency and certain rare haemoglobin variants. These may cause anaemia through reduced red cell survival or abnormal haemoglobin function.

13.5.3 Acquired Anaemia

Acquired anaemias develop during life due to nutritional deficiencies, blood loss, chronic diseases, bone marrow disorders, or increased red blood cell destruction.

Major types include:

1. Iron Deficiency Anaemia

Caused by inadequate iron availability for haemoglobin synthesis. It generally produces microcytic, hypochromic red blood cells.

2. Megaloblastic Anaemia

Caused mainly by vitamin B12 or folate deficiency, resulting in impaired DNA synthesis and macrocytic red blood cells.

3. Anaemia of Chronic Disease or Inflammation

Occurs in association with chronic infections, inflammatory disorders, malignancy, and other long-term conditions. Inflammatory cytokines increase hepcidin production, which reduces intestinal iron absorption and iron release from macrophages. Iron becomes less available for erythropoiesis.

4. Aplastic Anaemia

A bone marrow failure disorder characterized by reduced production of red blood cells, white blood cells, and platelets. It may be associated with immune-mediated marrow damage, certain drugs, chemicals, radiation, or infections; some cases are inherited.

5. Haemolytic Anaemia

Occurs when red blood cells are destroyed faster than they can be replaced by the bone marrow. Causes may be immune-mediated, mechanical, infectious, toxic, or related to acquired red cell abnormalities.

6. Blood-Loss Anaemia

Develops due to acute or chronic blood loss. Acute haemorrhage may cause a rapid reduction in circulating blood volume, while chronic blood loss can gradually deplete iron stores and lead to iron deficiency anaemia.

Table 13.7: Classification of Anaemia Based on Red Blood Cell Size

The MCV is used to classify anaemia according to the average size of red blood cells.

Type	MCV	Common causes
Microcytic anaemia	Below the laboratory reference range, commonly less than 80 fL in adults	Iron deficiency, thalassemia, some cases of anaemia of chronic disease, sideroblastic anaemia
Normocytic anaemia	Within the reference range, commonly 80–100 fL in adults	Acute blood loss, haemolysis, chronic kidney disease, aplastic anaemia, early anaemia of chronic disease
Macrocytic anaemia	Above the reference range, commonly greater than 100 fL in adults	Vitamin B12 or folate deficiency, alcohol use, liver disease, certain medicines, bone marrow disorders

These MCV ranges are commonly used for adults; interpretation should consider age, laboratory reference intervals, and the clinical context.

13.5.4 General Pathophysiology of Anaemia

Anaemia develops through one or more of three major mechanisms:

1. Reduced Red Blood Cell Production

This may result from nutritional deficiency, reduced erythropoietin, bone marrow failure, chronic inflammation, or genetic abnormalities affecting haemoglobin synthesis.

2. Increased Red Blood Cell Destruction

Premature destruction of red blood cells causes haemolytic anaemia. The bone marrow may increase erythrocyte production in response, but severe destruction can exceed its compensatory capacity.

3. Blood Loss

Loss of blood reduces circulating red blood cell mass. Chronic blood loss may also deplete iron stores, impairing subsequent red blood cell production.

13.5.5 Clinical Features of Anaemia

The manifestations depend on the severity, rate of development, and underlying cause.

Common features include:

- Fatigue and weakness.
- Pallor.
- Breathlessness, especially during physical activity.
- Dizziness or headache.
- Palpitations.
- Reduced exercise tolerance.
- Cold extremities.

Severe or rapidly developing anaemia may cause chest discomfort, fainting, or cardiovascular strain, particularly in individuals with pre-existing heart disease.

13.5.6 General Laboratory Evaluation

The evaluation of anaemia commonly includes:

- Complete blood count (CBC).
- Haemoglobin and haematocrit.
- Red blood cell indices, including MCV, MCH, and MCHC.
- Peripheral blood smear.
- Reticulocyte count.
- Iron studies, vitamin B12, and folate when indicated.
- Haemolysis markers, such as bilirubin, lactate dehydrogenase, and haptoglobin, when appropriate.
- Further tests based on the suspected underlying cause.

Table 13.8: Comparison Between Hereditary and Acquired Anaemia

Feature	Hereditary anaemia	Acquired anaemia
Cause	Genetic abnormalities	Develops due to nutritional, medical, environmental, or other factors
Onset	May be present from birth or become evident later	Develops during life
Examples	Sickle cell anaemia, thalassemia, hereditary spherocytosis, G6PD deficiency	Iron deficiency, megaloblastic, aplastic, chronic disease and blood-loss anaemia
Inheritance	May follow autosomal recessive, autosomal dominant, or X-linked	Usually not inherited as the anaemia itself

	patterns	
Management	Depends on the genetic disorder and complications	Depends on the underlying cause

13.6 Pathophysiology of Haemophilia

13.6.1 Introduction

Haemophilia is an inherited bleeding disorder characterized by deficiency or dysfunction of specific coagulation factors. This results in impaired formation of a stable fibrin clot and prolonged bleeding after injury. Bleeding may occur spontaneously or following minor trauma, depending on the severity of the disorder.

The two major types are haemophilia A and haemophilia B. Haemophilia A is caused by deficiency of clotting factor VIII, whereas haemophilia B is caused by deficiency of factor IX.

13.6.2 Types of Haemophilia

1. Haemophilia A

Haemophilia A is caused by reduced or absent activity of coagulation factor VIII. It is the most common form of haemophilia.

2. Haemophilia B

Haemophilia B, also known as Christmas disease, is caused by reduced or absent activity of coagulation factor IX.

3. Haemophilia C

Haemophilia C is a less common bleeding disorder caused by factor XI deficiency. It differs from haemophilia A and B in its inheritance pattern and clinical presentation.

13.6.3 Genetic Basis

Haemophilia A and B are usually inherited as X-linked recessive disorders. The genes responsible for factors VIII and IX are located on the X chromosome. Therefore, the disorders predominantly affect males, while females are commonly carriers, although some females may also have clinically significant bleeding.

Haemophilia C is generally inherited in an autosomal recessive pattern and affects males and females.

13.6.4 Pathophysiology of Haemophilia

Normal blood coagulation requires activation of a series of clotting factors that ultimately produce thrombin and fibrin. Factors VIII and IX are essential components of the intrinsic pathway and contribute to the activation of factor X.

In haemophilia A or B, deficiency of factor VIII or IX impairs the intrinsic tenase complex, reducing the activation of factor X. This decreases thrombin generation and fibrin formation, resulting in an unstable clot.

The major pathological sequence is:

1. Genetic mutation causes reduced production or function of factor VIII or IX.
2. Intrinsic coagulation pathway activity becomes impaired.
3. Activation of factor X is reduced.
4. Thrombin generation decreases.
5. Fibrin formation and clot stabilization are inadequate.
6. Bleeding becomes prolonged or may occur spontaneously in severe cases.

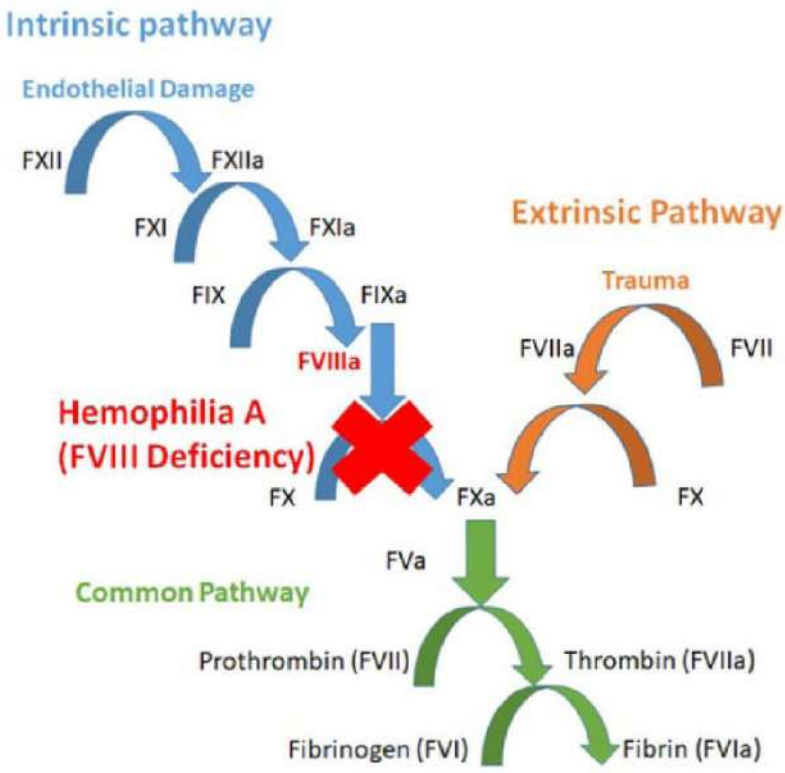


Table 13.9: Haemophilia Classification According to Severity

Haemophilia is classified according to the percentage of normal clotting-factor activity.

Severity	Clotting-factor activity	Typical clinical pattern
Severe	Less than 1%	Spontaneous bleeding, including bleeding into joints and muscles
Moderate	1–5%	Bleeding after minor injuries; occasional spontaneous bleeding
Mild	More than 5% but less than 40%	Bleeding mainly after surgery, dental procedures, or significant trauma

The clinical severity may vary between individuals, even within the same factor-activity category.

13.6.5 Clinical Features

Common clinical manifestations include:

- Prolonged bleeding after cuts or injuries.
- Excessive bleeding after surgery or dental extraction.
- Recurrent bleeding into joints (haemarthrosis).
- Muscle and soft-tissue haematomas.
- Easy bruising.
- Nosebleeds or gum bleeding in some individuals.
- Prolonged bleeding after circumcision or other procedures.
- Severe internal bleeding in serious cases.

Repeated bleeding into joints may cause chronic synovial inflammation, cartilage damage, joint deformity, and reduced mobility. This condition is known as haemophilic arthropathy.

Table 13.10: Laboratory Findings

Investigation	Typical finding in haemophilia A or B
Platelet count	Usually normal
Bleeding time	Usually normal
Prothrombin time (PT)	Usually normal
Activated partial thromboplastin time (aPTT)	Prolonged
Factor VIII activity	Decreased in haemophilia A
Factor IX activity	Decreased in haemophilia B
Mixing study	Usually corrects prolonged aPTT in factor deficiency; failure to correct may suggest an inhibitor

Specific factor assays are required to confirm the diagnosis and identify the type of haemophilia.

13.6.6 Complications

Major complications include:

1. Haemarthrosis: Repeated bleeding into joints may cause chronic joint damage.
2. Muscle haematomas: Bleeding into muscles can cause pain, swelling, and pressure on surrounding structures.
3. Intracranial haemorrhage: A serious complication that may occur spontaneously or after trauma.
4. Chronic pain and disability: Repeated joint bleeding can result in permanent functional impairment.
5. Inhibitor development: Some individuals develop antibodies against infused clotting factors, reducing treatment effectiveness.

13.6.7 Management Principles

Management aims to prevent and control bleeding, preserve joint function, and reduce complications.

- Factor replacement therapy: Replaces the deficient factor VIII or IX.
- Non-factor therapies: Certain medicines improve haemostasis through mechanisms other than direct factor replacement.
- Desmopressin: May be used in selected patients with mild haemophilia A because it increases the release of stored factor VIII and von Willebrand factor.
- Antifibrinolytic agents: May be used in selected mucosal bleeding situations.
- Physiotherapy and joint care: Help maintain mobility and reduce disability.
- Avoidance of unnecessary trauma: Helps reduce bleeding episodes.
- Genetic counselling: Supports informed family planning and understanding of inheritance.

Treatment should be individualized according to the type and severity of haemophilia, bleeding history, and presence of inhibitors.

Haematological diseases affect the production, structure, function, or survival of blood cells and coagulation components. Iron deficiency anaemia develops when iron availability becomes inadequate for haemoglobin synthesis, producing microcytic and hypochromic red blood cells. Megaloblastic anaemia results from impaired DNA synthesis, most commonly due to vitamin B12 or folate deficiency, and is characterized by macrocytosis and abnormal maturation of blood-cell precursors. Sickle cell anaemia is an inherited haemoglobin disorder caused by haemoglobin S, which polymerizes under low-oxygen conditions and produces red blood cell sickling, haemolysis, and vaso-occlusion. Thalassemia results from reduced synthesis of alpha- or beta-globin chains, leading to ineffective erythropoiesis and haemolysis. Hereditary anaemias arise from genetic abnormalities, whereas acquired anaemias develop due to nutritional deficiencies, blood loss, chronic disease, bone marrow disorders, or increased red blood cell destruction. Haemophilia is an inherited coagulation disorder caused mainly by factor VIII or factor IX deficiency. Impaired coagulation results in reduced thrombin and fibrin formation, leading to prolonged bleeding and, in severe cases, spontaneous bleeding into joints and muscles.

UNIT- IV

Chapter 14: Peripheral Nervous System

14.1 Classification of the Peripheral Nervous System

Introduction

The nervous system is the control and communication system of the human body. It receives information from internal and external environments, processes this information, and produces appropriate responses. Anatomically, the nervous system is divided into two major parts: the central nervous system (CNS) and the peripheral nervous system (PNS).

The central nervous system consists of the brain and spinal cord, whereas the peripheral nervous system includes all nervous tissue located outside the brain and spinal cord. It connects the CNS with different organs, muscles, glands, and sensory receptors throughout the body.

The peripheral nervous system consists mainly of cranial nerves, spinal nerves, ganglia, and sensory receptors. It carries sensory information towards the CNS and transmits motor commands from the CNS to muscles and glands.

Components of the Peripheral Nervous System

The major components of the PNS are:

1. **Cranial nerves:** Twelve pairs of nerves that arise from the brain or brainstem. They mainly supply the head and neck, although some also extend to thoracic and abdominal organs.
2. **Spinal nerves:** Thirty-one pairs of nerves that arise from the spinal cord and supply the trunk and limbs.
3. **Ganglia:** Collections of neuronal cell bodies located outside the CNS. They may be sensory or autonomic.
4. **Sensory receptors:** Specialized structures that detect stimuli such as touch, pain, temperature, pressure, light, sound, and chemical changes.

Classification of the Peripheral Nervous System

The PNS can be classified according to the direction of nerve impulses and the type of activity controlled.

A. Based on the Direction of Nerve Impulses

1. Sensory (Afferent) Division

The sensory division carries nerve impulses from sensory receptors towards the CNS. It provides information about the external environment and the internal condition of the body.

Sensory information may arise from:

- Skin receptors detecting touch, pressure, pain, and temperature.
- Proprioceptors detecting body position and movement.

- Visceral receptors monitoring internal organs, blood pressure, and chemical conditions.
- Special sensory receptors responsible for vision, hearing, smell, taste, and balance.

2. Motor (Efferent) Division

The motor division carries impulses from the CNS to effectors such as muscles and glands. It is further divided into the somatic and autonomic nervous systems.

B. Based on the Type of Response

1. Somatic Nervous System

The somatic nervous system controls voluntary movements and carries sensory information from the skin, skeletal muscles, and joints. It supplies skeletal muscles through motor neurons and is responsible for activities such as walking, writing, and maintaining posture.

The somatic motor pathway generally consists of a single motor neuron extending from the CNS to the skeletal muscle. The neurotransmitter released at the neuromuscular junction is acetylcholine.

Functions of the Somatic Nervous System

- Controls voluntary movements of skeletal muscles.
- Transmits sensory information from the skin and musculoskeletal system.
- Helps maintain posture and body balance.
- Participates in spinal reflexes, such as the withdrawal reflex.

2. Autonomic Nervous System

The autonomic nervous system (ANS) regulates involuntary activities of internal organs. It controls smooth muscle, cardiac muscle, and glands and helps maintain homeostasis.

The autonomic motor pathway generally consists of two neurons:

- Preganglionic neuron: Its cell body is located in the CNS, and its axon extends to an autonomic ganglion.
- Postganglionic neuron: Its cell body is located in the autonomic ganglion, and its axon extends to the target organ.

The autonomic nervous system is divided into:

- Sympathetic nervous system.
- Parasympathetic nervous system.

Both divisions usually supply the same organs but produce different, often opposing, effects. Their coordinated activity maintains normal physiological function.

Table 14.1: Comparison of Somatic and Autonomic Nervous Systems

Feature	Somatic nervous system	Autonomic nervous system
Main control	Voluntary and reflex skeletal muscle activity	Involuntary visceral activity
Effectors	Skeletal muscles	Smooth muscle, cardiac muscle and glands
Motor pathway	Usually one neuron	Usually two neurons
Ganglia	No peripheral motor ganglion in the pathway	Autonomic ganglia are present
Neurotransmitter at effector	Acetylcholine	Acetylcholine or noradrenaline, depending on the pathway
Main function	Movement and posture	Regulation of internal organs and homeostasis

Functions of the Peripheral Nervous System

The major functions of the PNS include:

1. Sensory communication: Carries information from receptors to the CNS.
2. Motor communication: Transmits commands from the CNS to muscles and glands.
3. Coordination: Connects the CNS with different parts of the body.
4. Reflex activity: Participates in rapid, automatic responses to stimuli.
5. Homeostasis: Regulates involuntary functions such as heart rate, digestion, glandular secretion, and blood vessel diameter.

14.2 Structure and Functions of the Sympathetic Nervous System

Introduction

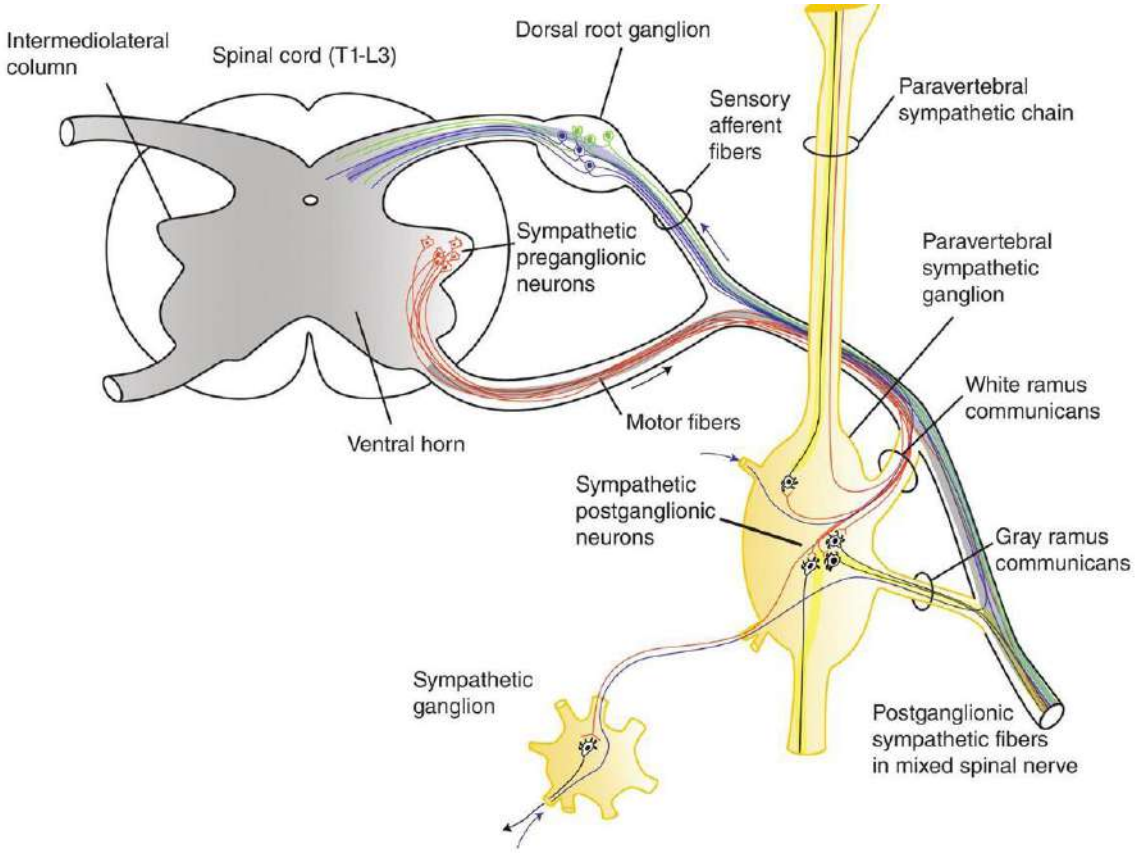
The sympathetic nervous system is a division of the autonomic nervous system. It prepares the body to respond to stressful or demanding situations, including physical activity, fear, excitement, and emergencies. Its overall response is commonly described as the “fight-or-flight” response.

It increases the availability of energy and modifies the activity of several organs to support rapid action. It also contributes to normal body functions, including the regulation of blood vessel tone and internal organ activity.

Structure of the Sympathetic Nervous System

The sympathetic nervous system is also known as the thoracolumbar division because its preganglionic neurons originate mainly from the thoracic and upper lumbar segments of the spinal cord, generally T1–L2.

Its motor pathway consists of two neurons: preganglionic and postganglionic neurons.



1. Preganglionic Neurons

The cell bodies of sympathetic preganglionic neurons are located in the lateral horn (intermediolateral cell column) of the spinal cord from approximately T1 to L2. Their axons leave the spinal cord through the ventral roots, enter the spinal nerves, and pass through the white rami communicantes to reach sympathetic ganglia.

Preganglionic fibres are generally short because many sympathetic ganglia are located close to the spinal cord.

2. Sympathetic Ganglia

Sympathetic ganglia contain the cell bodies of postganglionic neurons. They are of two major types:

A. Paravertebral Ganglia

These ganglia are arranged on both sides of the vertebral column and form the sympathetic trunks or sympathetic chains. They extend from the cervical region to the sacral region.

Preganglionic fibres may synapse at the level where they enter the sympathetic chain, ascend or descend before synapsing, or pass through the chain without synapsing.

B. Prevertebral (Collateral) Ganglia

These ganglia are located anterior to the vertebral column, mainly around major abdominal arteries. Examples include:

- Coeliac ganglia.
- Superior mesenteric ganglia.
- Inferior mesenteric ganglia.

They mainly supply abdominal and pelvic viscera.

3. Postganglionic Neurons

The cell bodies of postganglionic neurons are located in sympathetic ganglia. Their axons travel to target organs, where they release neurotransmitters.

Most sympathetic postganglionic neurons release noradrenaline (norepinephrine). An important exception is the sympathetic supply to most sweat glands, where acetylcholine is released.

4. Adrenal Medulla

The adrenal medulla is functionally related to the sympathetic nervous system. Preganglionic sympathetic fibres directly stimulate chromaffin cells of the adrenal medulla. These cells release adrenaline (epinephrine) and noradrenaline into the bloodstream, producing widespread and relatively prolonged effects.

Neurotransmitters of the Sympathetic Nervous System

The principal neurotransmitters are:

- Acetylcholine: Released by sympathetic preganglionic neurons at autonomic ganglia.
- Noradrenaline: Released by most sympathetic postganglionic neurons at target organs.
- Adrenaline and noradrenaline: Released into the blood by the adrenal medulla.

Table 14.2: Functions of the Sympathetic Nervous System

The sympathetic nervous system produces coordinated changes in different organs.

Organ or system	Sympathetic effect
Eye	Dilates the pupil (mydriasis)
Heart	Increases heart rate and force of contraction
Blood vessels	Produces vasoconstriction in many vascular beds; effects vary according to receptor type and tissue
Lungs	Dilates bronchi and bronchioles
Gastrointestinal tract	Generally decreases motility and secretion
Liver	Promotes glycogen breakdown and glucose release
Adipose tissue	Promotes breakdown of stored fat
Sweat glands	Increases sweating
Urinary bladder	Relaxes the detrusor muscle and promotes urinary storage
Skin	Produces piloerection and regulates vascular tone

Adrenal medulla	Stimulates release of adrenaline and noradrenaline

Physiological Significance

During stressful conditions, sympathetic activation increases blood supply to tissues required for immediate activity, supports oxygen delivery, and mobilizes energy reserves. For example, increased heart rate and bronchodilation help meet the increased metabolic demands of skeletal muscles.

Sympathetic activity is not limited to emergencies. It also contributes to maintaining blood pressure, regulating body temperature through sweating and vascular responses, and controlling the distribution of blood flow.

14.3 Structure and Functions of the Parasympathetic Nervous System

Introduction

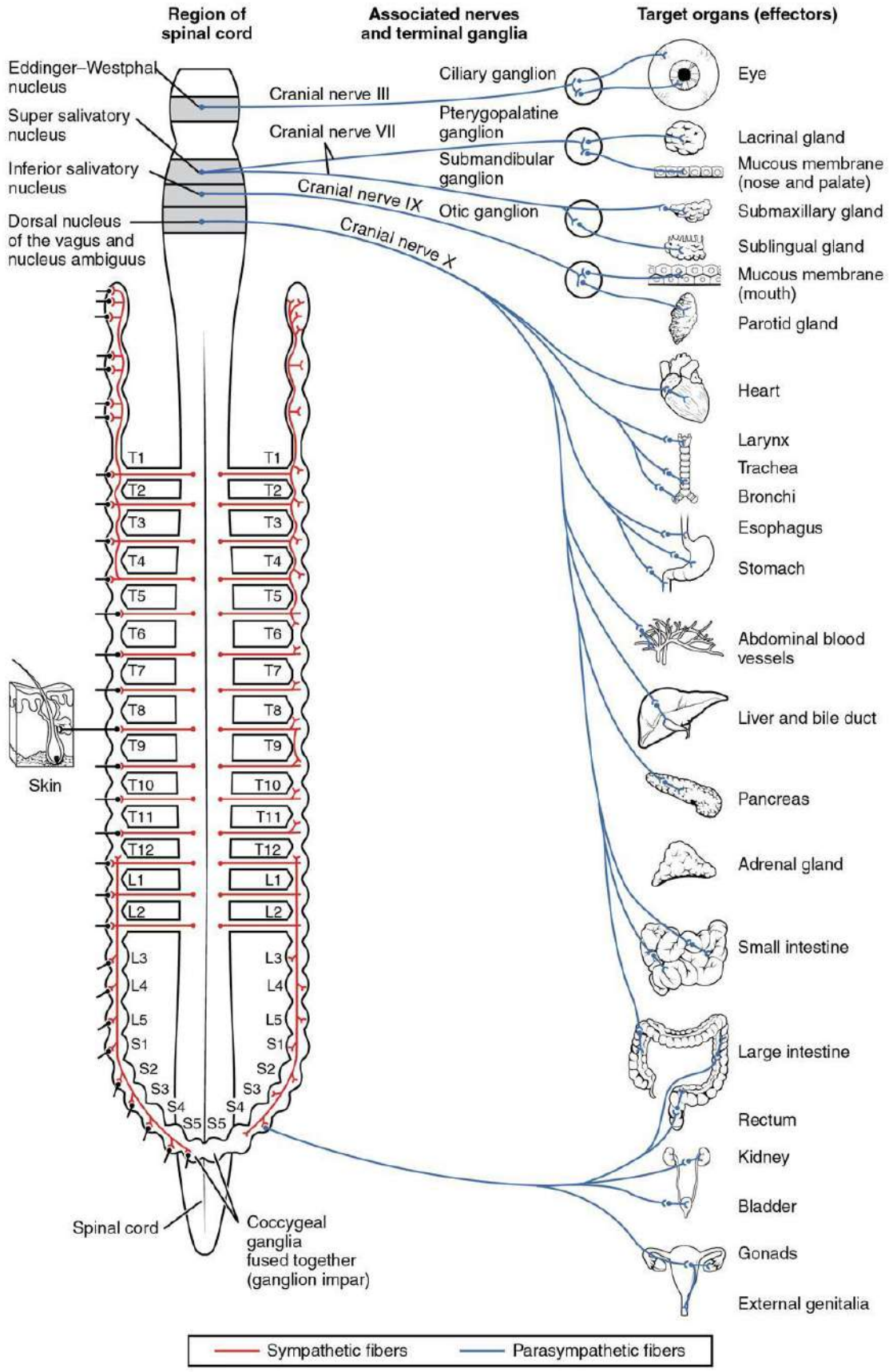
The parasympathetic nervous system is the second major division of the autonomic nervous system. It is commonly described as the "rest-and-digest" system because it supports energy conservation, digestion, nutrient absorption, and routine maintenance of body functions.

It generally promotes activities that restore and conserve energy, including slowing the heart rate, stimulating gastrointestinal activity, and facilitating urination and defecation.

Structure of the Parasympathetic Nervous System

The parasympathetic nervous system is also called the craniosacral division because its preganglionic neurons originate from specific cranial nerves and the sacral region of the spinal cord.

Its pathway consists of preganglionic and postganglionic neurons. In most organs, the preganglionic fibres are long, while the postganglionic fibres are short.


Region of spinal cord
Associated nerves and terminal ganglia
Target organs (effectors)
Eddinger–Westphal nucleus
Super salivatory nucleus
Inferior salivatory nucleus
Dorsal nucleus of the vagus and nucleus ambiguus
Cranial nerve III
Cranial nerve VII
Cranial nerve IX
Cranial nerve X
Ciliary ganglion
Pterygopalatine ganglion
Submandibular ganglion
Otic ganglion
Eye
Lacrinal gland
Mucous membrane (nose and palate)
Submaxillary gland
Sublingual gland
Mucous membrane (mouth)
Parotid gland
Heart
Larynx
Trachea
Bronchi
Esophagus
Stomach
Abdominal blood vessels
Liver and bile duct
Pancreas
Adrenal gland
Small intestine
Large intestine
Rectum
Kidney
Bladder
Gonads
External genitalia
Skin
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Spinal cord
Coccygeal ganglia fused together (ganglion impar)
Sympathetic fibers
Parasympathetic fibers

1. Cranial Outflow

The cranial component arises from the brainstem and travels through four cranial nerves:

- Oculomotor nerve (III): Carries parasympathetic fibres to the ciliary ganglion, which supplies the sphincter pupillae and ciliary muscle.
- Facial nerve (VII): Carries fibres to the pterygopalatine and submandibular ganglia, contributing to lacrimal, nasal, submandibular, and sublingual glandular secretion.
- Glossopharyngeal nerve (IX): Carries fibres to the otic ganglion, which supplies the parotid gland.
- Vagus nerve (X): Supplies many thoracic and abdominal organs, including the heart, lungs, and gastrointestinal tract up to the proximal two-thirds of the transverse colon.

2. Sacral Outflow

The sacral component arises from the spinal cord segments S2–S4. Its preganglionic fibres travel through the pelvic splanchnic nerves and supply pelvic organs, including the urinary bladder, distal large intestine, and reproductive organs.

3. Parasympathetic Ganglia

Parasympathetic ganglia are located close to or within the walls of target organs. Examples include:

- Ciliary ganglion.
- Pterygopalatine ganglion.
- Submandibular ganglion.
- Otic ganglion.
- Terminal or intramural ganglia associated with visceral organs.

Because the ganglia are located near the target organs, parasympathetic preganglionic fibres are generally long and postganglionic fibres are short.

Neurotransmitters of the Parasympathetic Nervous System

Acetylcholine is the principal neurotransmitter at both stages of the parasympathetic pathway:

1. Preganglionic neurons release acetylcholine at nicotinic receptors in the ganglia.
2. Postganglionic neurons release acetylcholine at muscarinic receptors on target organs.

Table 14.3: Functions of the Parasympathetic Nervous System

Organ or system	Parasympathetic effect
Eye	Constricts the pupil (miosis) and promotes accommodation for near vision
Heart	Decreases heart rate
Lungs	Produces bronchoconstriction and increases bronchial secretion
Salivary glands	Stimulates watery salivary secretion
Lacrimal glands	Stimulates tear secretion

Gastrointestinal tract	Increases motility and secretion
Urinary bladder	Contracts the detrusor muscle and facilitates urination
Rectum	Supports defecation
Reproductive organs	Contributes to erection and genital vasodilation

Physiological Significance

The parasympathetic nervous system is particularly active during resting conditions. It supports digestion, absorption, glandular secretion, and elimination of waste. Its activity helps conserve energy and maintain normal functioning of internal organs.

Table 14.4: Comparison of Sympathetic and Parasympathetic Nervous Systems

Feature	**Sympathetic nervous system**	**Parasympathetic nervous system**
Alternative name	Thoracolumbar division	Craniosacral division
Origin	T1–L2 spinal cord segments	Brainstem and S2–S4 spinal cord segments
Ganglia	Near the spinal cord or in prevertebral locations	Near or within target organs
Preganglionic fibres	Generally short	Generally long
Postganglionic fibres	Generally long	Generally short
Preganglionic neurotransmitter	Acetylcholine	Acetylcholine
Main postganglionic neurotransmitter	Usually noradrenaline	Acetylcholine
General role	Fight-or-flight response	Rest-and-digest response
Heart	Increases heart rate	Decreases heart rate
Pupil	Dilates	Constricts
Gastrointestinal activity	Generally decreases	Generally increases
Urinary bladder	Promotes storage	Promotes emptying

The sympathetic and parasympathetic divisions work together rather than functioning as completely independent systems. Their balanced activity helps regulate internal organs and maintain homeostasis.

14.4 Origin and Functions of Spinal Nerves

Introduction

Spinal nerves are part of the peripheral nervous system. They connect the spinal cord with different regions of the body and carry sensory information towards the CNS and motor commands away from it. They are mixed nerves because they contain both sensory and motor fibres.

There are 31 pairs of spinal nerves in the human body. Each spinal nerve is formed by the union of a dorsal root and a ventral root arising from the spinal cord.

Origin of Spinal Nerves

The spinal nerves originate from the spinal cord and are grouped according to the region from which they emerge.

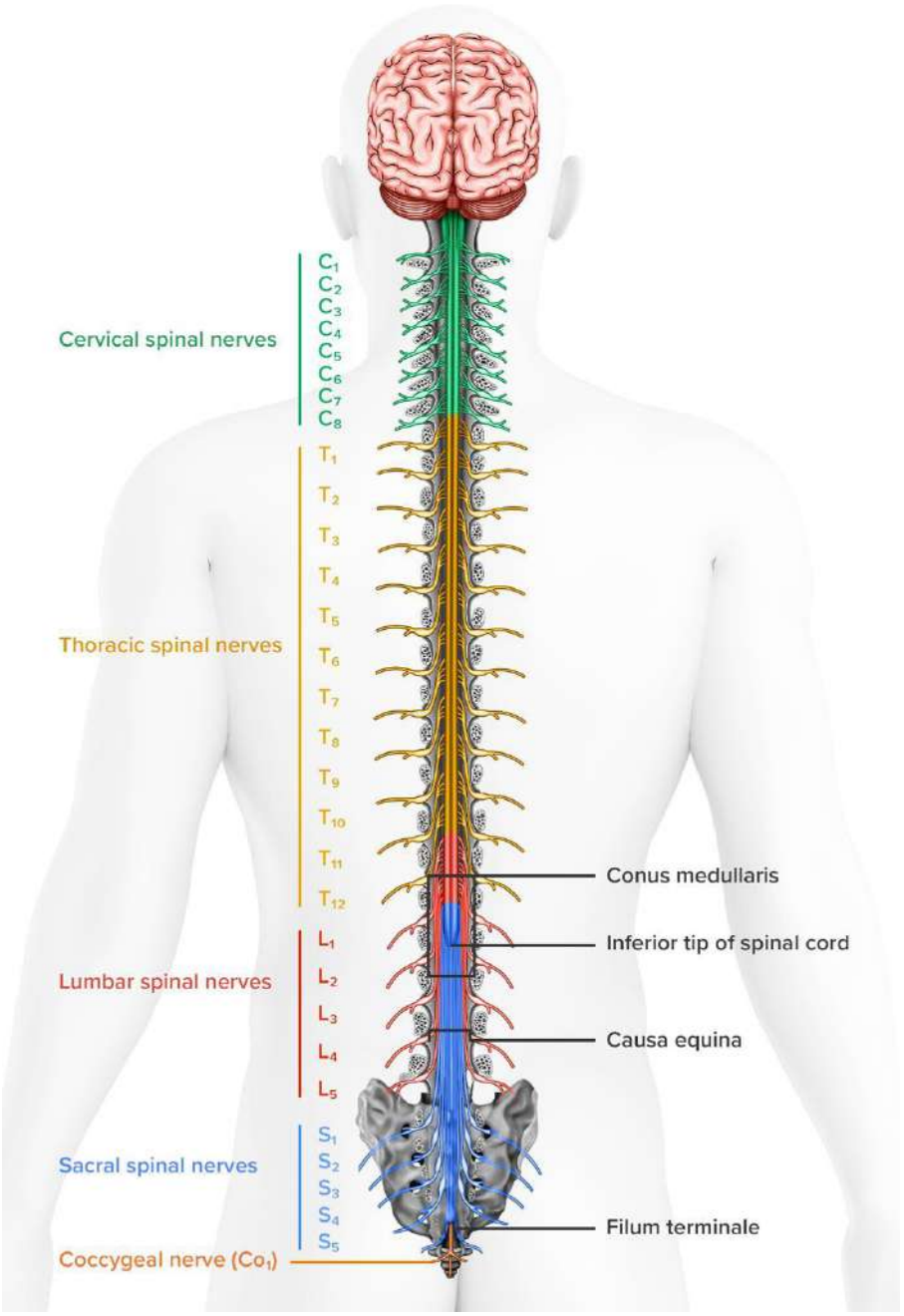


Table 14.5: 31 pairs pairs of spinal nerves

Region	Number of pairs	Spinal nerves
Cervical	8	C1–C8
Thoracic	12	T1–T12
Lumbar	5	L1–L5
Sacral	5	S1–S5

Coccygeal	1	Co1
Total	31	

Although there are seven cervical vertebrae, there are eight pairs of cervical spinal nerves. The first seven cervical nerves exit above their corresponding vertebrae, while C8 exits between the C7 and T1 vertebrae. From T1 onwards, spinal nerves generally exit below their corresponding vertebrae.

Formation of Spinal Nerves

Each spinal nerve is formed by the joining of two roots:

1. Dorsal (Posterior) Root

The dorsal root carries sensory (afferent) impulses from the body towards the spinal cord.

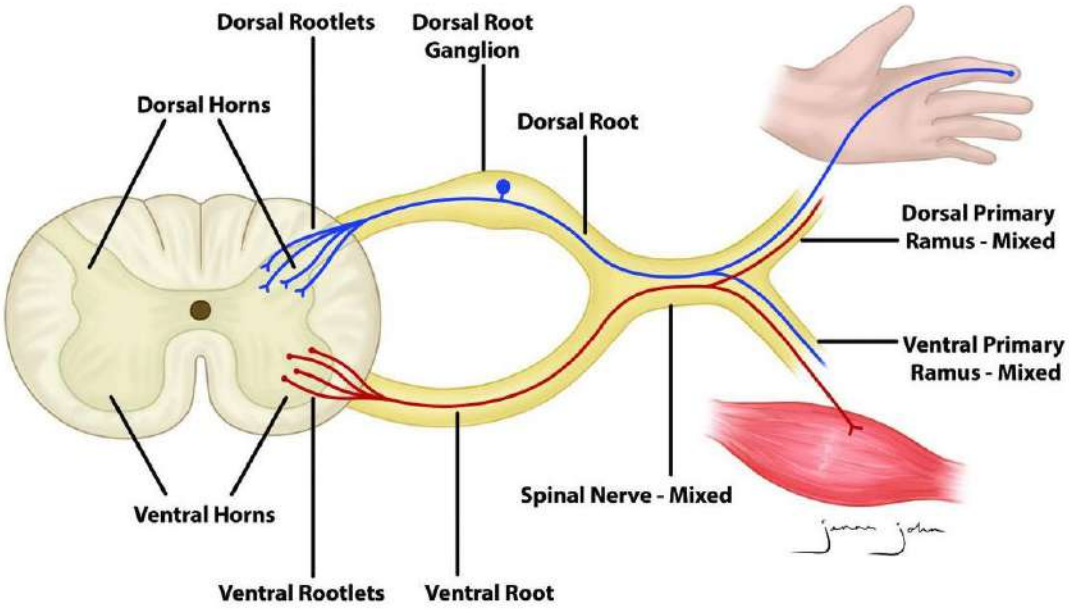
- It contains sensory nerve fibres.
- The cell bodies of sensory neurons are located in the dorsal root ganglion.
- Sensory impulses enter the spinal cord through this root.

2. Ventral (Anterior) Root

The ventral root carries motor (efferent) impulses from the spinal cord towards muscles and other effectors.

- It contains motor nerve fibres.
- The cell bodies of somatic motor neurons are located in the anterior horn of the spinal cord.
- Autonomic preganglionic motor fibres also leave the spinal cord through the ventral roots at their respective levels.

The dorsal and ventral roots unite near the intervertebral foramen to form a mixed spinal nerve.



Branches of Spinal Nerves

After emerging from the intervertebral foramen, each spinal nerve divides into branches called rami.

1. Dorsal Ramus

The dorsal ramus supplies the deep muscles of the back, joints of the vertebral column, and skin over the back. It contains both sensory and motor fibres.

2. Ventral Ramus

The ventral ramus supplies the anterolateral trunk and limbs. In most regions, ventral rami form nerve plexuses, where fibres from different spinal nerves combine and redistribute.

Important nerve plexuses include:

- Cervical plexus: Formed mainly by C1–C4; supplies structures of the neck and contributes to the phrenic nerve.
- Brachial plexus: Formed by C5–T1; supplies the shoulder and upper limb.
- Lumbar plexus: Formed mainly by L1–L4; supplies parts of the abdominal wall and lower limb.
- Sacral plexus: Formed mainly by L4–S4; supplies the pelvis, buttock, and much of the lower limb.

The thoracic ventral rami generally remain separate and form the intercostal nerves.

3. Meningeal Branch

A small recurrent branch returns to the vertebral canal and supplies structures such as the meninges, ligaments, and blood vessels within the vertebral canal.

4. Rami Communicantes

These branches connect spinal nerves with the sympathetic trunk. White rami communicantes carry preganglionic sympathetic fibres and are present mainly from T1 to L2. Gray rami communicantes carry postganglionic sympathetic fibres and are associated with spinal nerves throughout the body.

Functions of Spinal Nerves

The major functions of spinal nerves are:

1. Sensory function: Carry sensations such as pain, temperature, touch, pressure, and proprioception from the body to the spinal cord.
2. Motor function: Carry impulses from the spinal cord to skeletal muscles, enabling voluntary movements.
3. Autonomic function: Carry autonomic fibres involved in regulating blood vessels, sweat glands, and visceral organs.

4. Reflex function: Participate in spinal reflexes by carrying sensory information to the spinal cord and transmitting motor responses to effectors.
5. Regional supply: Provide communication between the spinal cord and specific regions of the trunk, limbs, and parts of the head and neck.

Clinical Significance

Damage to a spinal nerve or its roots may cause pain, numbness, altered sensation, muscle weakness, or loss of reflexes in the affected region. Compression of spinal nerve roots, such as in intervertebral disc herniation, may produce radiating pain and sensory or motor disturbances. The pattern of symptoms depends on the spinal level and the structures affected.

14.5 Origin and Functions of Cranial Nerves

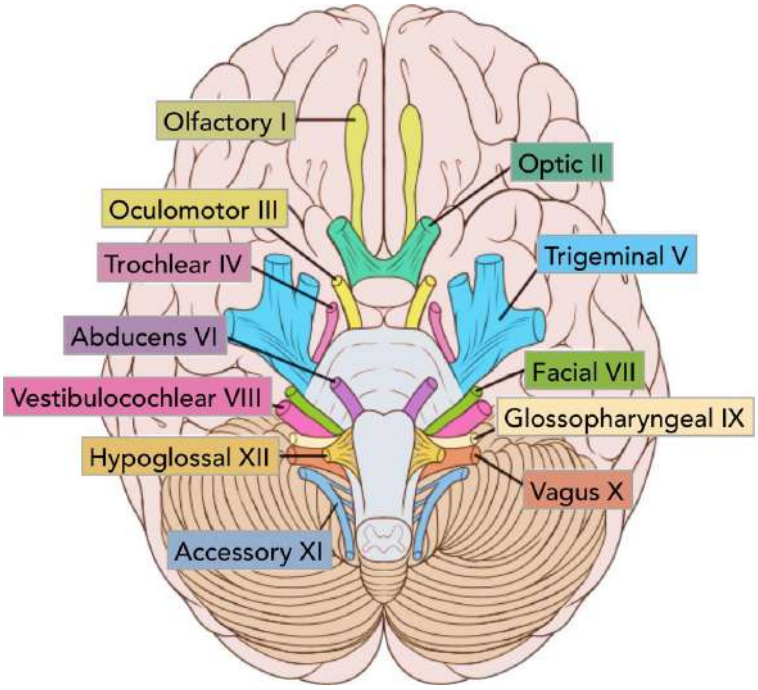
Introduction

Cranial nerves are twelve pairs of nerves that arise from the brain or brainstem and form an important part of the peripheral nervous system. They mainly supply the head and neck, but the vagus nerve also supplies organs in the thorax and abdomen.

Cranial nerves may be sensory, motor, or mixed. They transmit information related to special senses, general sensation, muscle movement, and autonomic regulation.

Origin of Cranial Nerves

Most cranial nerves arise from the brainstem. The olfactory and optic nerves are associated with the forebrain and diencephalon, respectively. Cranial nerves are numbered I to XII according to their order of emergence from the brain.



Classification of Cranial Nerves

Cranial nerves are classified according to their functional components.

1. Sensory Cranial Nerves

These nerves mainly carry sensory information from receptors to the brain.

- Olfactory nerve (I)
- Optic nerve (II)
- Vestibulocochlear nerve (VIII)

2. Motor Cranial Nerves

These nerves mainly carry motor impulses to muscles.

- Oculomotor nerve (III)
- Trochlear nerve (IV)
- Abducens nerve (VI)
- Accessory nerve (XI)
- Hypoglossal nerve (XII)

3. Mixed Cranial Nerves

These nerves contain both sensory and motor fibres.

- Trigeminal nerve (V)
- Facial nerve (VII)
- Glossopharyngeal nerve (IX)
- Vagus nerve (X)

Table 14.6: Origin and Functions of Individual Cranial Nerves

Cranial nerve	Type	Origin	Main functions
I. Olfactory	Sensory	Olfactory receptors in the nasal cavity; fibres pass to the olfactory bulb	Sense of smell
II. Optic	Sensory	Retina; fibres pass to the optic chiasm and visual pathways	Vision
III. Oculomotor	Motor with parasympathetic fibres	Midbrain	Controls most eye movements, raises the upper eyelid, constricts the pupil, and helps in accommodation
IV. Trochlear	Motor	Midbrain	Supplies the superior oblique muscle and helps move the eye

			downward when it is adducted
V. Trigeminal	Mixed	Pons	Sensation from the face, cornea, oral and nasal cavities; motor supply to muscles of mastication
VI. Abducens	Motor	Pontomedullary junction	Supplies the lateral rectus muscle and abducts the eye
VII. Facial	Mixed with parasympathetic fibres	Pontomedullary junction	Controls muscles of facial expression; carries taste from the anterior two-thirds of the tongue; stimulates lacrimal and salivary secretion
VIII. Vestibulocochlear	Sensory	Pontomedullary junction	Hearing and balance
IX. Glossopharyngeal	Mixed with parasympathetic fibres	Medulla oblongata	Taste and sensation from the posterior one-third of the tongue; assists swallowing; stimulates parotid secretion
X. Vagus	Mixed with parasympathetic fibres	Medulla oblongata	Supplies pharynx and larynx; carries visceral sensory information; regulates many thoracic and abdominal organs
XI. Accessory	Motor	Medulla and upper cervical spinal cord	Supplies sternocleidomastoid and trapezius muscles; assists head movement and shoulder elevation
XII. Hypoglossal	Motor	Medulla oblongata	Controls movements of the tongue

Important Functions of Cranial Nerves

1. Sensory Functions

Cranial nerves transmit sensory information from the head and neck to the brain. They are responsible for special senses such as smell, vision, hearing, taste, and balance. They also carry general sensations, including touch, pain, and temperature, from the face and oral cavity.

2. Motor Functions

Several cranial nerves control the muscles of the eyes, face, tongue, pharynx, and neck. These functions are essential for eye movement, facial expression, chewing, swallowing, speech, and head movement.

3. Autonomic Functions

Some cranial nerves contain parasympathetic fibres that regulate involuntary activities, including pupil constriction, tear production, salivary secretion, and the activity of thoracic and abdominal organs.

Clinical Significance of Cranial Nerves

Damage to cranial nerves can produce characteristic signs and symptoms depending on the nerve involved. Examples include:

- Olfactory nerve damage: Reduced or complete loss of smell.
- Optic nerve damage: Visual impairment or loss of vision.
- Oculomotor nerve damage: Drooping of the upper eyelid, abnormal eye movement, and possible pupil dilation.
- Trigeminal nerve damage: Facial sensory disturbances or weakness of mastication.
- Facial nerve damage: Weakness or paralysis of facial muscles.
- Vestibulocochlear nerve damage: Hearing loss, tinnitus, or balance disturbances.
- Glossopharyngeal or vagus nerve damage: Difficulty in swallowing and altered gag reflex.
- Hypoglossal nerve damage: Weakness and deviation of the tongue.

The peripheral nervous system connects the central nervous system with the rest of the body. It is divided functionally into sensory and motor divisions, while the motor division includes the somatic and autonomic nervous systems. The autonomic nervous system consists of sympathetic and parasympathetic divisions, which regulate involuntary activities and maintain internal balance.

The sympathetic nervous system arises from the thoracolumbar region and prepares the body for increased activity. The parasympathetic nervous system arises from cranial and sacral regions and supports resting, digestion, and energy conservation. The PNS also includes 31 pairs of spinal nerves and 12 pairs of cranial nerves, which carry sensory, motor, and autonomic information.

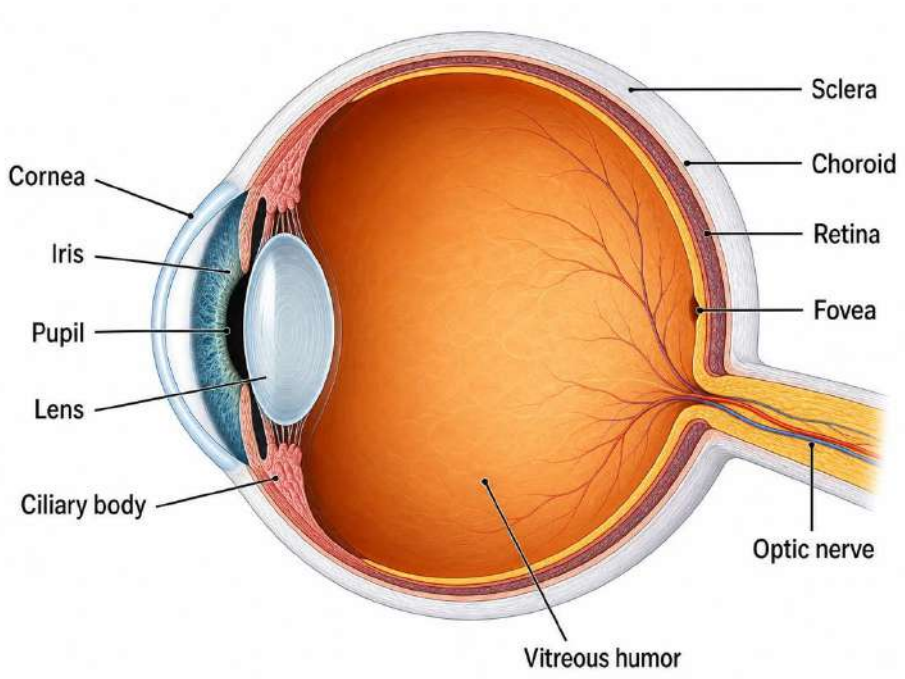
Chapter 15: Special Senses

15.1 Structure and Functions of the Eye

Introduction

The eye is a specialized sensory organ responsible for vision. It detects light and converts it into electrical signals that are transmitted to the brain through the optic nerve. The brain interprets these signals to produce visual perception, including the recognition of shape, colour, movement, distance, and depth.

The eyeball is located within the bony orbit of the skull. It is protected by the eyelids, eyelashes, conjunctiva, and tear-producing structures. The eye contains transparent refractive media that allow light to reach the retina, where photoreceptors initiate the visual process.



Structure of the Eye

The eyeball is approximately spherical and consists of three main layers: the fibrous layer, vascular layer, and nervous layer.

1. Fibrous Layer

The outermost layer provides protection and maintains the shape of the eyeball. It consists of the sclera and cornea.

A. Sclera

The sclera is the tough, white outer covering of the eye. It is composed mainly of dense connective tissue.

Functions:

- Protects the internal structures of the eye.
- Maintains the shape of the eyeball.
- Provides attachment for the extraocular muscles.

B. Cornea

The cornea is the transparent, curved anterior portion of the fibrous layer. It allows light to enter the eye and provides most of the eye's refractive power.

Functions:

- Transmits incoming light.
- Refracts light towards the retina.
- Provides a protective barrier against external injury and microorganisms.

2. Vascular Layer (Uvea)

The middle layer is rich in blood vessels and contains the choroid, ciliary body, and iris.

A. Choroid

The choroid is a highly vascular, pigmented layer located between the sclera and retina.

Functions:

- Supplies oxygen and nutrients to the outer retina.
- Absorbs excess light and reduces internal reflection.

B. Ciliary Body

The ciliary body is located behind the iris. It contains the ciliary muscle and ciliary processes.

Functions:

- Produces aqueous humour through the ciliary processes.
- Changes the curvature of the lens during accommodation.
- Helps maintain the position of the lens through the suspensory ligaments.

C. Iris

The iris is the coloured part of the eye surrounding the pupil. It contains smooth muscles that regulate pupil diameter.

Functions:

- Controls the amount of light entering the eye.
- Constricts the pupil in bright light.
- Dilates the pupil in dim light.

3. Nervous Layer (Retina)

The retina is the innermost layer of the eye and contains photoreceptor cells that detect light.

It contains two major types of photoreceptors:

A. Rods

Rods are highly sensitive to low-intensity light and are mainly responsible for dim-light and peripheral vision. They do not provide colour discrimination.

B. Cones

Cones function best in bright light and are responsible for colour vision and high visual acuity. They are concentrated in the macula, particularly in the fovea centralis.

Other important retinal structures include:

- Macula lutea: The central retinal region responsible for detailed central vision.
- Fovea centralis: A small depression in the macula containing a high concentration of cones and providing the sharpest vision.
- Optic disc: The region where the optic nerve exits the eye. It lacks photoreceptors and forms the physiological blind spot.

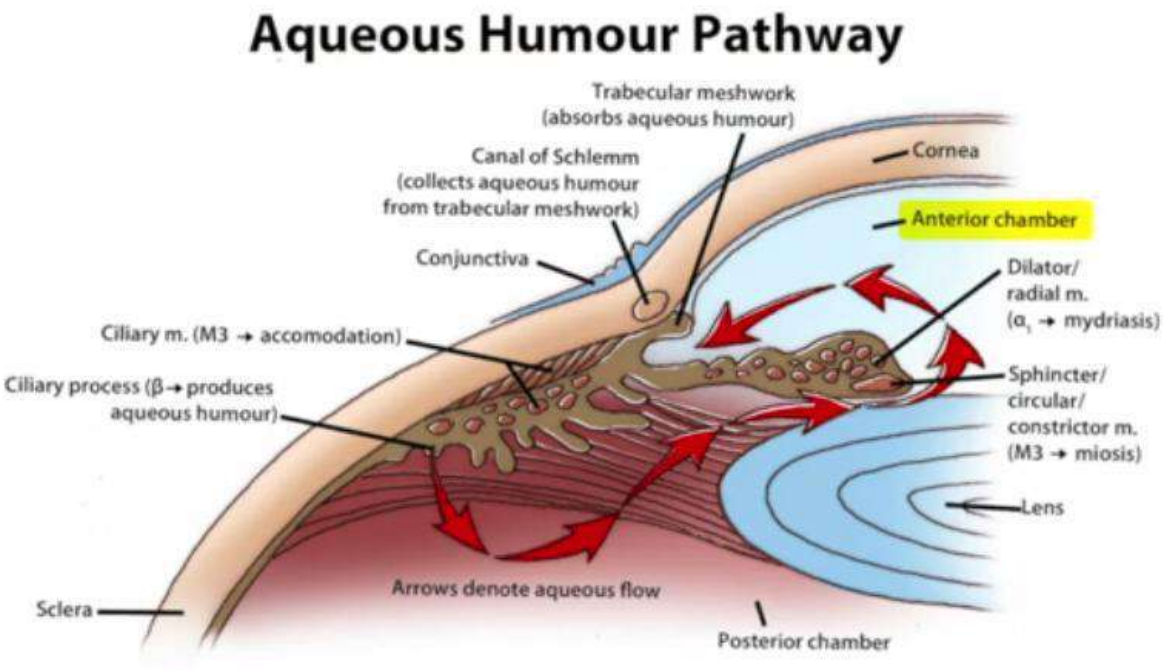
Refractive Media of the Eye

Light passes through four main transparent structures before reaching the retina:

1. Cornea: Provides most of the refractive power.
2. Aqueous humour: Clear fluid present in the anterior and posterior chambers of the anterior segment.
3. Lens: A transparent, flexible structure that fine-tunes the focus of light.
4. Vitreous humour: A transparent gel that fills the posterior cavity and helps maintain the shape of the eyeball.

Aqueous Humour and Its Circulation

Aqueous humour is produced by the ciliary processes. It flows from the posterior chamber through the pupil into the anterior chamber and drains mainly through the trabecular meshwork into Schlemm's canal and the venous circulation. A smaller proportion drains through the uveoscleral pathway.



Normal production and drainage of aqueous humour help maintain intraocular pressure and support the avascular structures of the anterior eye.

Functions of the Eye

The major functions of the eye include:

1. Vision: Detects light and enables perception of the environment.
2. Refraction: Focuses incoming light on the retina.
3. Accommodation: Changes lens curvature to focus on near and distant objects.
4. Regulation of light entry: Adjusts pupil diameter according to light intensity.
5. Colour discrimination: Cones enable recognition of different colours.
6. Dim-light vision: Rods support vision under low-light conditions.
7. Protection: Eyelids, eyelashes, tears, and the corneal surface protect the eye from injury and foreign particles.

Mechanism of Vision

Light enters through the cornea, passes through the aqueous humour, pupil, lens, and vitreous humour, and reaches the retina. The lens adjusts its shape to focus the image on the retina.

Photoreceptors convert light energy into electrical signals. These signals pass through retinal neurons and leave the eye through the optic nerve. Visual information travels through the optic chiasm and optic tracts to the lateral geniculate nucleus of the thalamus and then to the visual cortex in the occipital lobe, where it is processed and interpreted.

Accommodation

Accommodation is the ability of the eye to adjust its focusing power for objects at different distances.

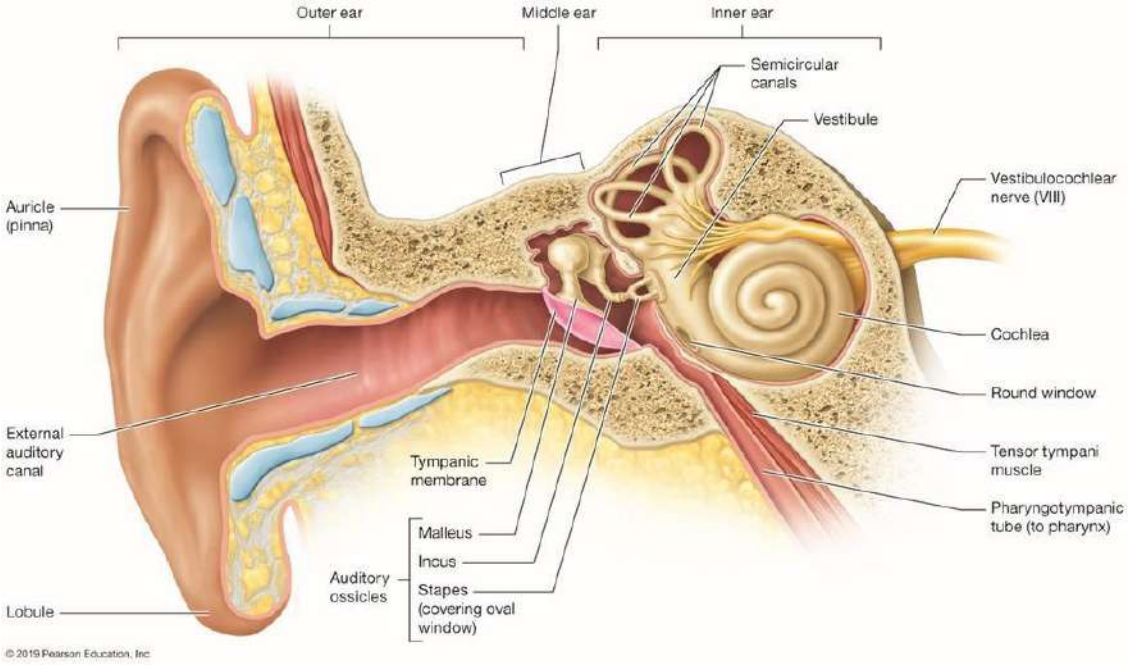
- For distant vision: The ciliary muscle relaxes, the suspensory ligaments become taut, and the lens becomes flatter.
- For near vision: The ciliary muscle contracts, the suspensory ligaments become less taut, and the lens becomes more convex.

Accommodation is accompanied by convergence of the eyes and pupillary constriction during near vision.

15.2 Structure and Functions of the Ear

Introduction

The ear is the sensory organ responsible for hearing and maintaining balance. It detects sound waves and converts them into nerve impulses. It also contains vestibular structures that provide information about head position and movement. Anatomically, the ear is divided into three regions: external ear, middle ear, and inner ear.



Structure of the Ear

1. External Ear

The external ear collects sound waves and directs them towards the tympanic membrane.

It consists of:

A. Pinna (Auricle)

The pinna is the visible part of the ear, composed mainly of elastic cartilage covered by skin.

Functions:

- Collects sound waves.
- Helps localize the direction of sound.
- Directs sound into the external auditory canal.

B. External Auditory Canal

The external auditory canal extends from the pinna to the tympanic membrane. It contains hairs and ceruminous glands that produce earwax.

Functions:

- Conducts sound waves towards the tympanic membrane.
- Provides protection through hairs and cerumen.
- Helps prevent entry of foreign particles and microorganisms.

C. Tympanic Membrane

The tympanic membrane, or eardrum, separates the external ear from the middle ear. It vibrates in response to sound waves.

2. Middle Ear

The middle ear is an air-filled cavity located within the temporal bone. It contains three small auditory ossicles.

A. Malleus

The malleus is attached to the tympanic membrane and transmits its vibrations to the incus.

B. Incus

The incus is the middle ossicle and transmits vibrations from the malleus to the stapes.

C. Stapes

The stapes is the smallest bone in the human body. Its footplate is attached to the oval window of the inner ear.

Together, the ossicles transmit and amplify mechanical vibrations from the tympanic membrane to the inner ear.

D. Eustachian Tube

The auditory or Eustachian tube connects the middle ear with the nasopharynx.

Functions:

- Equalizes air pressure on both sides of the tympanic membrane.

- Allows drainage of middle-ear secretions.
- Helps maintain normal vibration of the tympanic membrane.

3. Inner Ear

The inner ear is located within the temporal bone and contains the structures responsible for hearing and balance. It consists of the cochlea, vestibule, and semicircular canals.

A. Cochlea

The cochlea is a spiral-shaped structure responsible for hearing. It contains the organ of Corti, which includes sensory hair cells.

Functions:

- Converts mechanical vibrations into electrical signals.
- Detects sound frequency and intensity.
- Transmits auditory information through the cochlear division of the vestibulocochlear nerve.

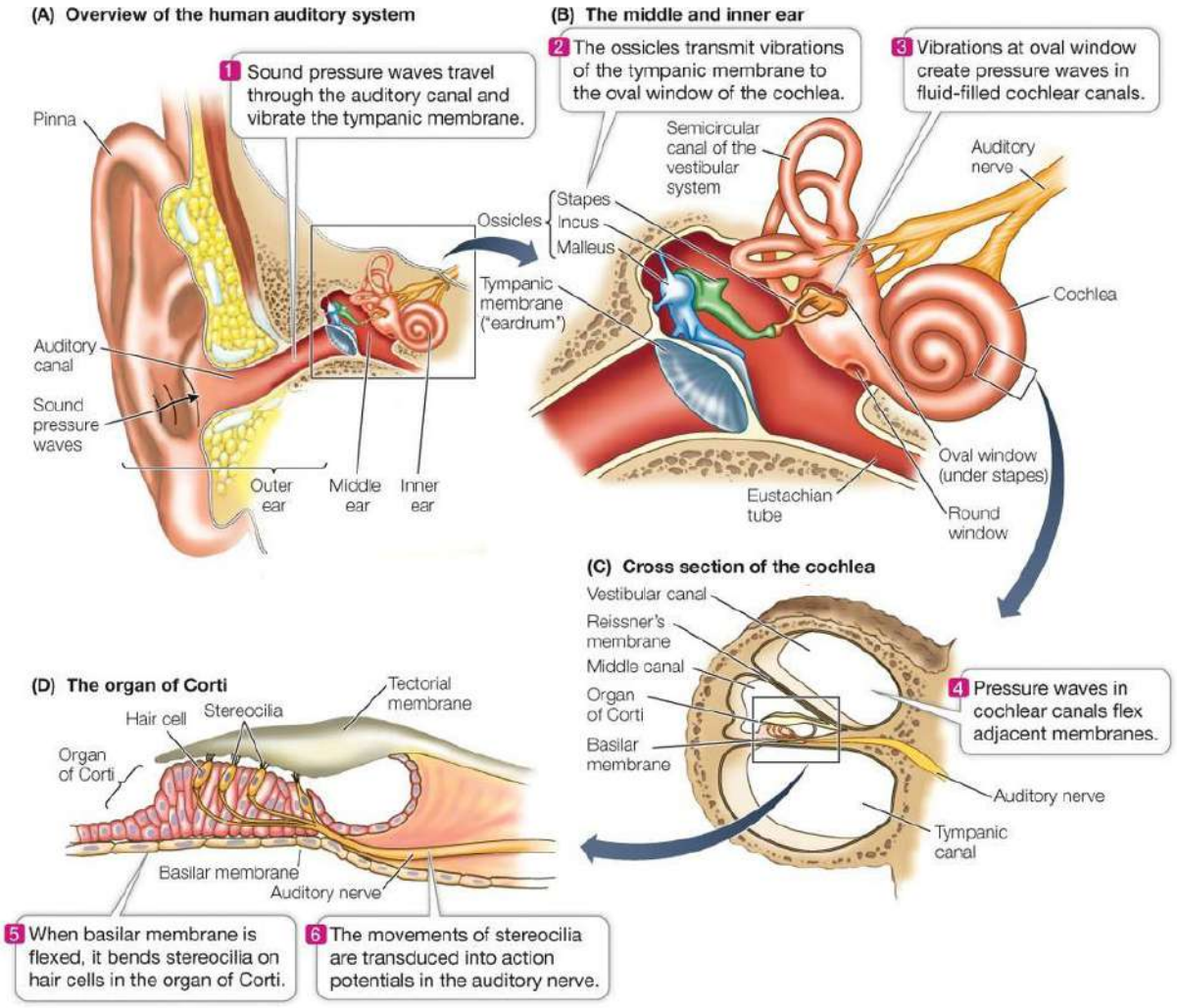
B. Vestibule

The vestibule contains the utricle and saccule. These structures detect linear acceleration and the position of the head relative to gravity.

C. Semicircular Canals

Three semicircular canals are arranged approximately at right angles to each other. They detect angular or rotational movements of the head.

Mechanism of Hearing



The mechanism of hearing occurs in the following sequence:

1. Sound waves are collected by the pinna and travel through the external auditory canal.
2. Sound waves cause vibration of the tympanic membrane.
3. Vibrations are transmitted through the malleus, incus, and stapes.
4. Movement of the stapes at the oval window generates pressure waves in the cochlear fluids.
5. Fluid movement causes displacement of the basilar membrane.
6. Hair cells in the organ of Corti bend against the tectorial membrane, producing receptor potentials.
7. Electrical signals are transmitted through the cochlear nerve to the brainstem and auditory pathways.
8. Auditory information reaches the auditory cortex in the temporal lobe, where sound is perceived.

Mechanism of Balance

Balance is maintained through the combined activity of the vestibular system, vision, and proprioceptive receptors.

- The semicircular canals detect rotational movements of the head.

- The utricle and saccule detect linear acceleration and head position relative to gravity.
- Vestibular signals travel through the vestibular division of cranial nerve VIII to the brainstem and cerebellum.
- The brain integrates vestibular information with visual and proprioceptive input to maintain posture, equilibrium, and coordinated eye movements.

Functions of the Ear

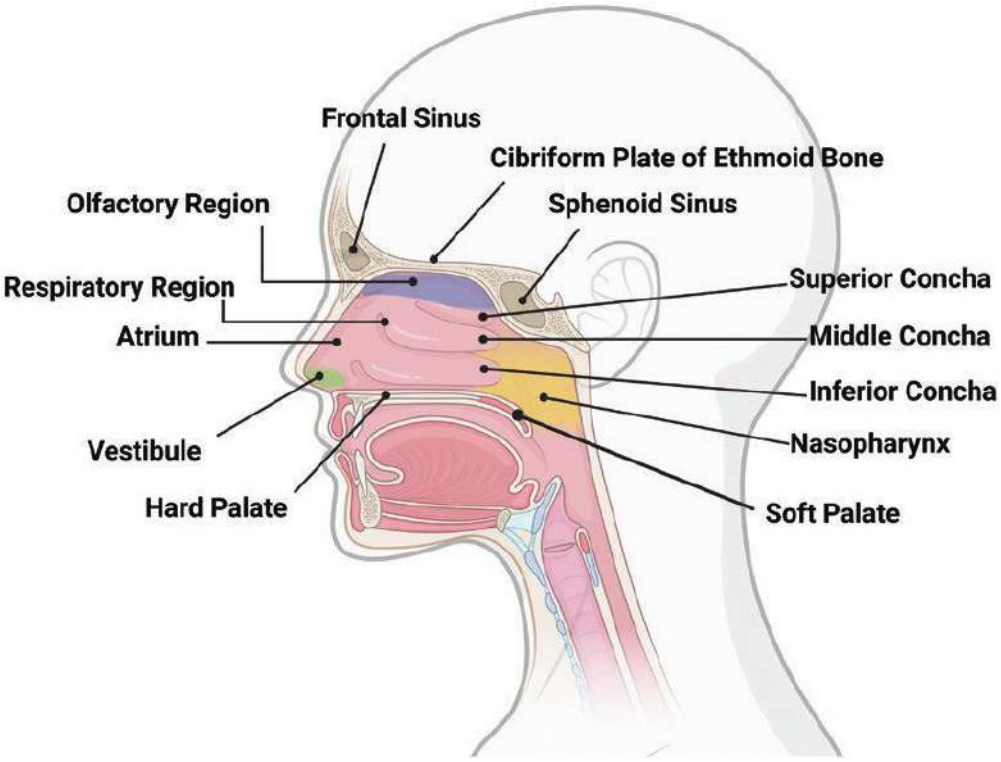
1. Hearing: Detects sound and enables communication.
2. Sound localization: Helps determine the direction of sound.
3. Balance: Detects head position and movement.
4. Postural control: Provides information required for maintaining body posture.
5. Protection: Cerumen, hairs, and the external auditory canal help protect the ear from foreign materials.

15.3 Structure and Functions of the Nose

Introduction

The nose is the primary organ of smell and also forms the initial passageway for air entering the respiratory system. It detects airborne chemicals through specialized olfactory receptors and contributes to the perception of flavour.

The nose consists of external structures and an internal nasal cavity. The nasal cavity is divided into right and left halves by the nasal septum and is lined mainly by respiratory mucosa, with specialized olfactory epithelium in its upper region.



Structure of the Nose

1. External Nose

The external nose is formed by bone and cartilage and includes the root, bridge, dorsum, apex, and nostrils.

Functions:

- Provides an entrance for inspired air.
- Helps direct airflow into the nasal cavity.
- Contributes to facial appearance.

2. Nasal Cavity

The nasal cavity extends from the nostrils to the posterior openings called choanae, which communicate with the nasopharynx. It is divided into two halves by the nasal septum.

The lateral walls contain three nasal conchae:

- Superior nasal concha.
- Middle nasal concha.
- Inferior nasal concha.

These structures increase the surface area of the nasal cavity and create airflow patterns that improve air conditioning.

3. Nasal Mucosa

The nasal cavity is lined by mucous membrane. Most of it is respiratory mucosa, containing ciliated epithelial cells and mucus-secreting cells.

Functions:

- Traps dust and microorganisms.
- Warms and humidifies inspired air.
- Helps remove particles through mucociliary clearance.

4. Olfactory Epithelium

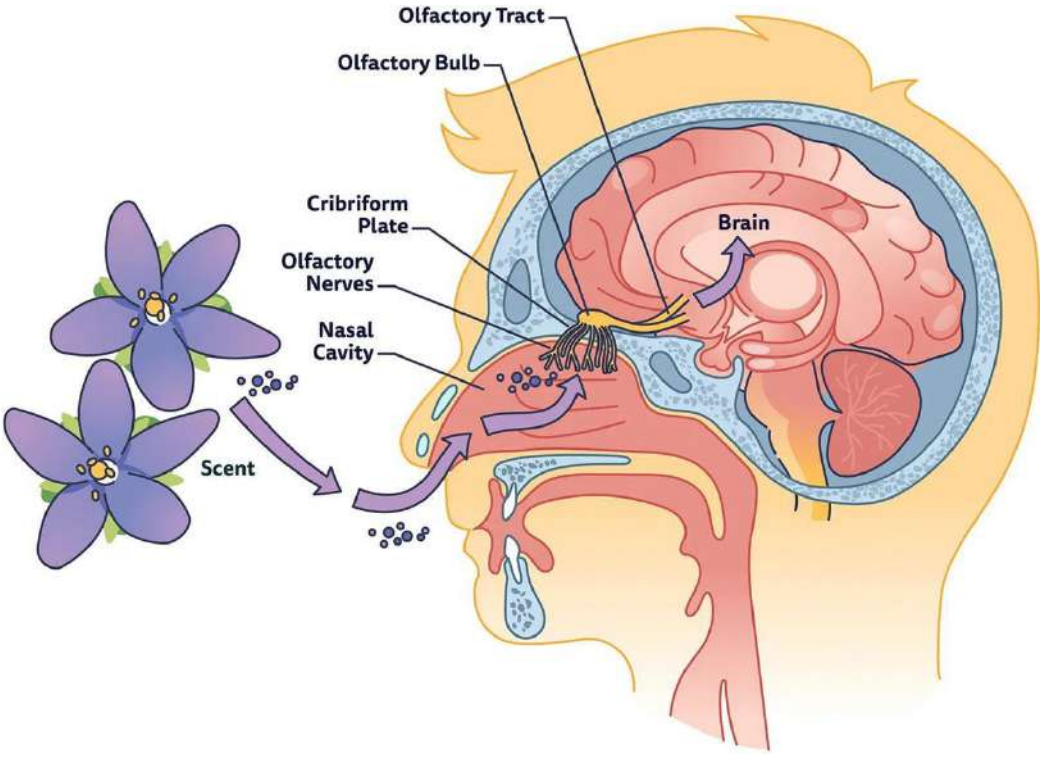
The olfactory epithelium is located mainly in the roof of the nasal cavity, superior nasal concha, and upper part of the nasal septum.

It contains:

- Olfactory receptor neurons: Detect odorant molecules and generate electrical signals.
- Supporting cells: Provide structural and metabolic support.
- Basal cells: Act as stem cells and help replace olfactory receptor neurons.

- Olfactory glands: Produce secretions that help dissolve and remove odorant molecules.

Mechanism of Smell (Olfaction)



The process of smell occurs as follows:

1. Odorant molecules enter the nasal cavity during breathing.
2. Odorants dissolve in the mucus covering the olfactory epithelium.
3. They bind to receptors on the cilia of olfactory receptor neurons.
4. Receptor activation produces electrical signals in the olfactory neurons.
5. Axons of these neurons pass through the cribriform plate of the ethmoid bone.
6. They reach the olfactory bulb, where they synapse with neurons in olfactory glomeruli.
7. Signals travel through the olfactory tract to olfactory regions of the brain.
8. The brain interprets the signals as specific smells.

Functions of the Nose

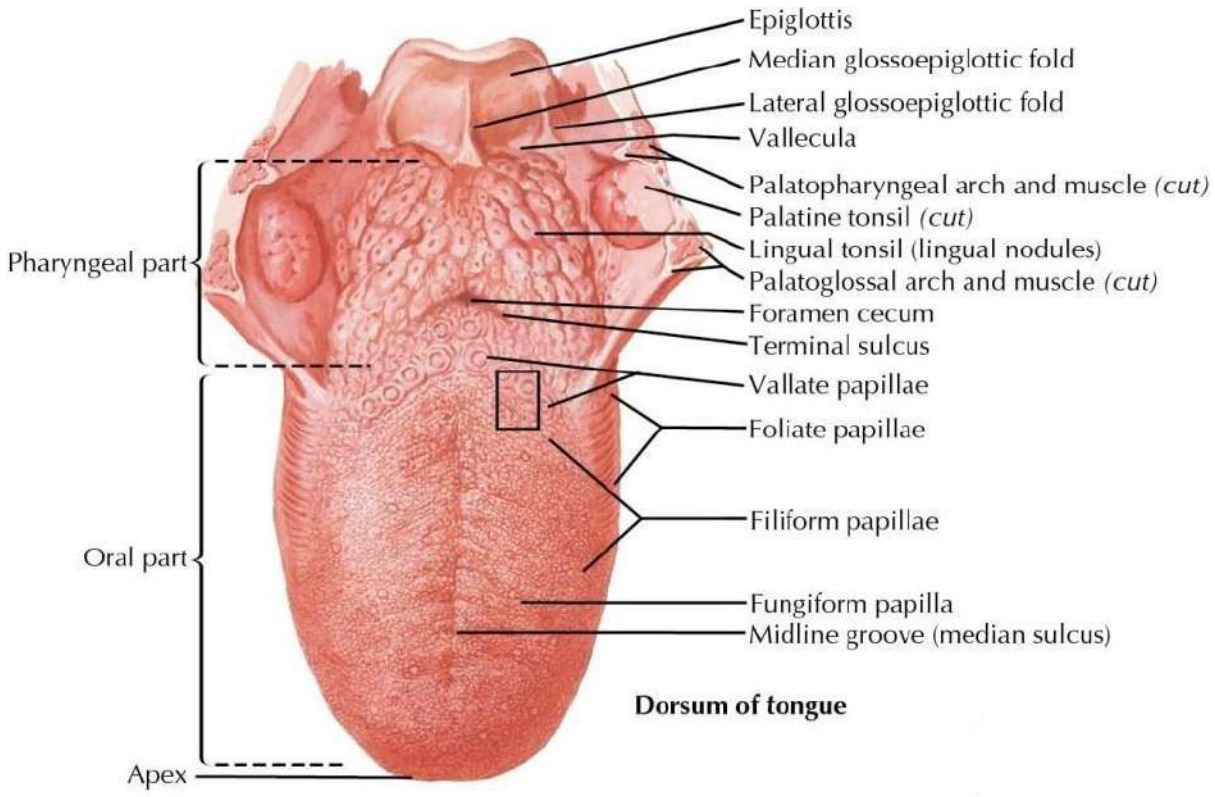
1. Olfaction: Detects and identifies different odours.
2. Air filtration: Traps dust and foreign particles in mucus and nasal hairs.
3. Warming of air: Rich blood supply helps warm inspired air.
4. Humidification: Moistens air before it reaches the lower respiratory tract.
5. Contribution to taste: Smell contributes significantly to flavour perception.
6. Voice resonance: The nasal cavity contributes to the resonance of speech.
7. Protection: Mucociliary clearance and local immune mechanisms help defend the respiratory tract.

15.4 Structure and Functions of the Tongue

Introduction

The tongue is a muscular organ located in the oral cavity. It plays an important role in taste, speech, mastication, swallowing, and manipulation of food. Its surface contains specialized structures called papillae, some of which contain taste buds.

The tongue is composed of skeletal muscles covered by a mucous membrane. Its muscles allow complex movements required for oral functions.



Structure of the Tongue

The tongue is divided into:

- Anterior two-thirds (oral part): Located within the oral cavity.
- Posterior one-third (pharyngeal part): Located towards the oropharynx.

The two parts are separated by a V-shaped groove called the sulcus terminalis.

Muscles of the Tongue

The tongue contains intrinsic and extrinsic skeletal muscles.

1. Intrinsic Muscles

Intrinsic muscles are located entirely within the tongue. They change its shape, helping in speech and food manipulation.

2. Extrinsic Muscles

Extrinsic muscles originate outside the tongue and attach to it. They move the tongue in different directions.

Important extrinsic muscles include:

- Genioglossus.
- Hyoglossus.
- Styloglossus.
- Palatoglossus.

Most tongue muscles are supplied by the hypoglossal nerve (cranial nerve XII), while the palatoglossus is supplied by the vagus nerve through the pharyngeal plexus.

Papillae of the Tongue

The dorsal surface of the tongue contains four major types of papillae.

A. Filiform Papillae

These are the most numerous papillae. They are slender and provide friction that helps move food during chewing. They generally do not contain taste buds.

B. Fungiform Papillae

These are mushroom-shaped papillae, distributed mainly near the tip and sides of the tongue. Many contain taste buds.

C. Circumvallate Papillae

These are large papillae arranged in a V-shaped row near the posterior part of the oral tongue. They contain numerous taste buds along their sides.

D. Foliate Papillae

These are located along the posterolateral borders of the tongue and contain taste buds, particularly in early life.

Taste Buds

Taste buds are sensory structures present mainly in fungiform, foliate, and circumvallate papillae. Each taste bud contains specialized taste receptor cells, supporting cells, and basal cells.

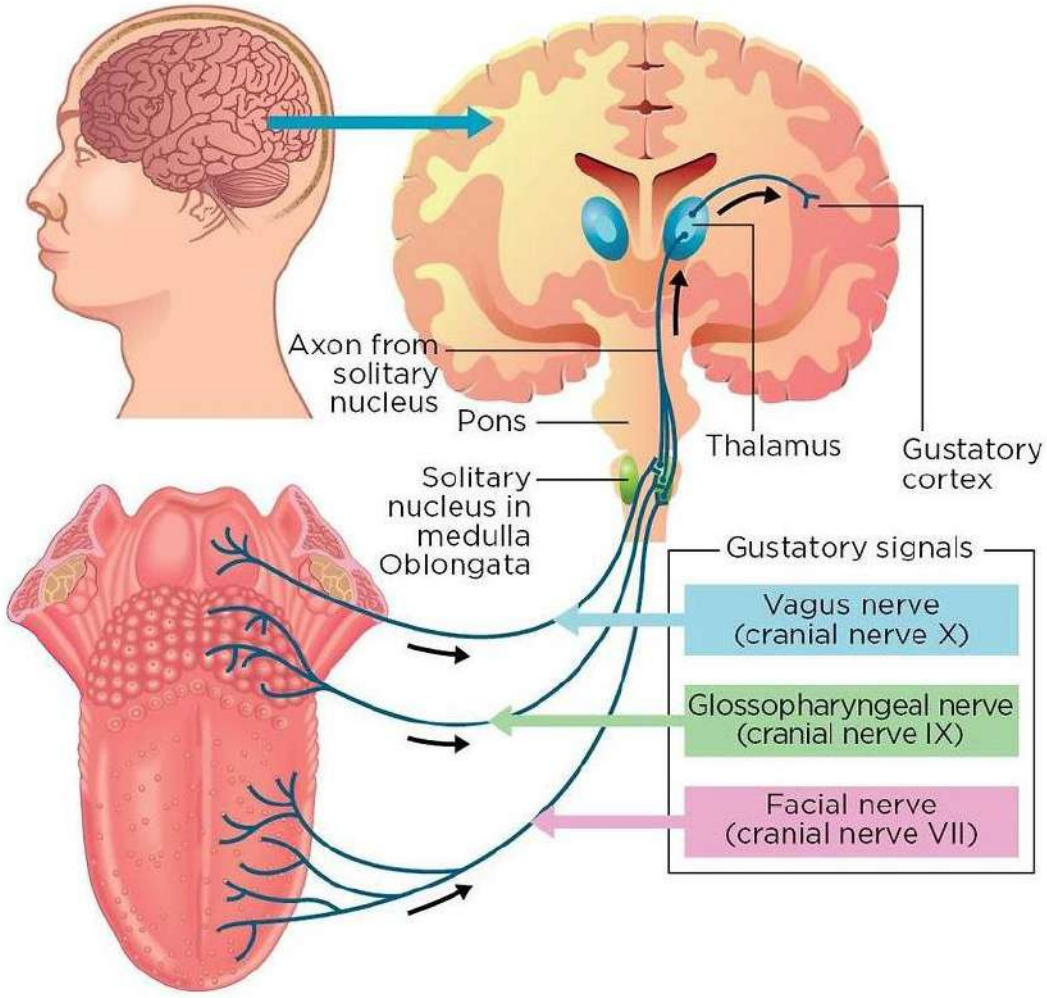
Taste receptor cells respond to chemicals dissolved in saliva. Their activation produces signals that are transmitted through sensory nerves to the brain.

The five commonly recognized basic taste qualities are:

1. Sweet.
2. Sour.
3. Salty.
4. Bitter.
5. Umami (savoury).

Taste perception is not restricted to separate regions of the tongue. Most regions containing taste buds can respond to several taste qualities, although sensitivity may vary.

Mechanism of Taste (Gustation)



The process of taste occurs as follows:

1. Food chemicals dissolve in saliva.
2. Dissolved substances enter the taste pore and interact with receptor cells.
3. Taste receptor cells generate electrical signals.
4. Sensory information is transmitted through:
    - Facial nerve (VII): anterior two-thirds of the tongue.
    - Glossopharyngeal nerve (IX): posterior one-third of the tongue.
    - Vagus nerve (X): taste from a small region near the epiglottis and pharynx.

5. Signals reach the nucleus of the solitary tract in the brainstem.
6. Information is relayed through the thalamus to the gustatory cortex, where taste is perceived.

Functions of the Tongue

1. Taste: Detects dissolved chemical substances in food.
2. Mastication: Moves food during chewing and mixes it with saliva.
3. Swallowing: Helps form and propel the food bolus towards the pharynx.
4. Speech: Assists in producing clear speech sounds.
5. Oral sensation: Detects texture, temperature, and other sensory properties of food.
6. Cleaning: Helps remove food particles from the oral cavity.

15.5 Pathophysiology of Glaucoma

Introduction

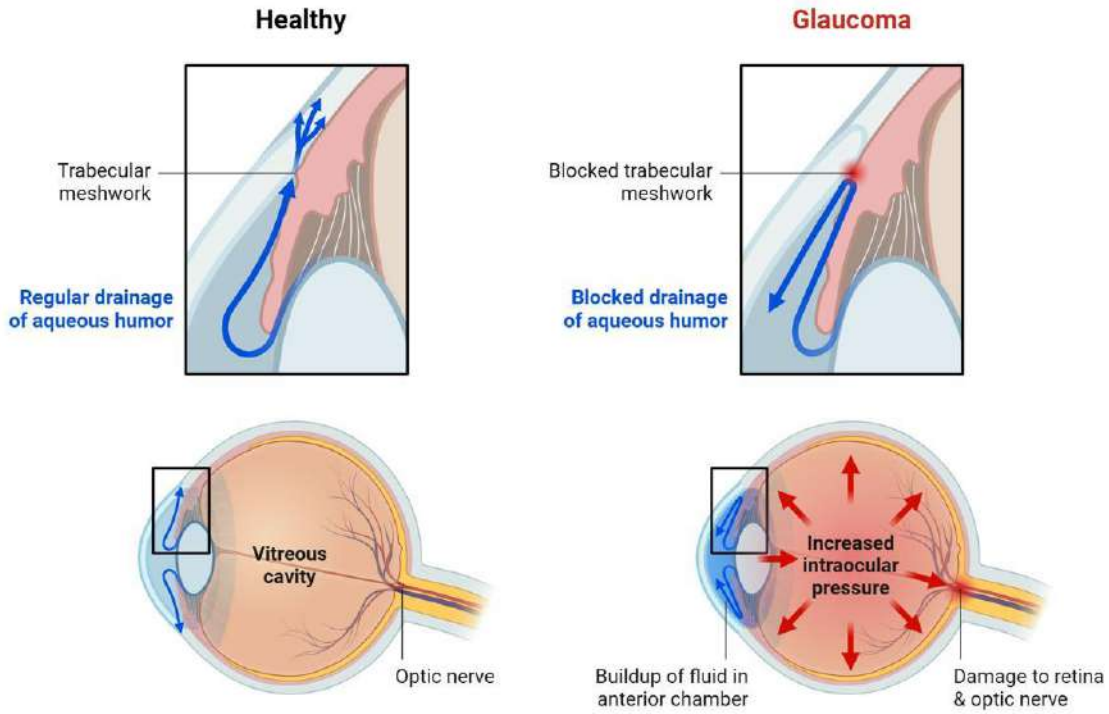
Glaucoma is a group of eye disorders characterized by progressive damage to the optic nerve, often associated with increased intraocular pressure (IOP). It can cause gradual loss of peripheral vision and may lead to irreversible blindness if not detected and treated.

Increased IOP is an important risk factor, but glaucoma can also occur in individuals with statistically normal IOP. The essential pathological feature is characteristic optic nerve damage, often involving loss of retinal ganglion cells and their axons.

Normal Intraocular Pressure Regulation

Intraocular pressure is maintained by a balance between the production and drainage of aqueous humour.

Aqueous humour is produced by the ciliary processes, enters the posterior chamber, passes through the pupil into the anterior chamber, and drains mainly through the trabecular meshwork and Schlemm's canal.



Pathophysiology

The pathophysiology of glaucoma involves impaired aqueous humour drainage or other mechanisms that result in optic nerve injury.

1. Aqueous humour is continuously produced by the ciliary processes.
2. In certain types of glaucoma, drainage through the trabecular meshwork is reduced or the drainage angle becomes obstructed.
3. Reduced outflow may increase intraocular pressure.
4. Elevated pressure and other associated factors contribute to mechanical stress and impaired blood supply at the optic nerve head.
5. Retinal ganglion cells and their axons undergo progressive damage.
6. Loss of nerve fibres produces characteristic optic disc changes and visual field defects.
7. Untreated disease may progress to severe visual impairment and blindness.

Types of Glaucoma

1. Primary Open-Angle Glaucoma

In primary open-angle glaucoma, the anterior chamber angle remains anatomically open, but aqueous humour drainage through the trabecular meshwork becomes inefficient. The condition is usually chronic and develops gradually.

2. Angle-Closure Glaucoma

In angle-closure glaucoma, the drainage angle between the iris and cornea becomes narrowed or blocked. This prevents normal aqueous humour outflow and may cause a rapid rise in intraocular pressure.

Acute angle closure is an ophthalmic emergency.

3. Secondary Glaucoma

Secondary glaucoma develops due to another ocular or systemic condition, trauma, inflammation, or certain medications, such as prolonged corticosteroid use.

4. Congenital Glaucoma

Congenital glaucoma results from abnormal development of the aqueous humour drainage system. It may present during infancy or early childhood.

Clinical Features

The manifestations depend on the type and severity of glaucoma.

- Gradual loss of peripheral vision in chronic open-angle glaucoma.
- Difficulty adapting to changes in lighting.
- Blurred vision in some cases.
- Severe eye pain, redness, headache, nausea, and blurred vision in acute angle-closure glaucoma.
- Optic disc cupping and visual field defects on examination.

Diagnosis

Diagnosis may involve:

- Measurement of intraocular pressure (tonometry).
- Examination of the optic nerve head.
- Visual field testing.
- Gonioscopy to assess the anterior chamber angle.
- Optical coherence tomography to evaluate retinal nerve fibre and ganglion cell layers.

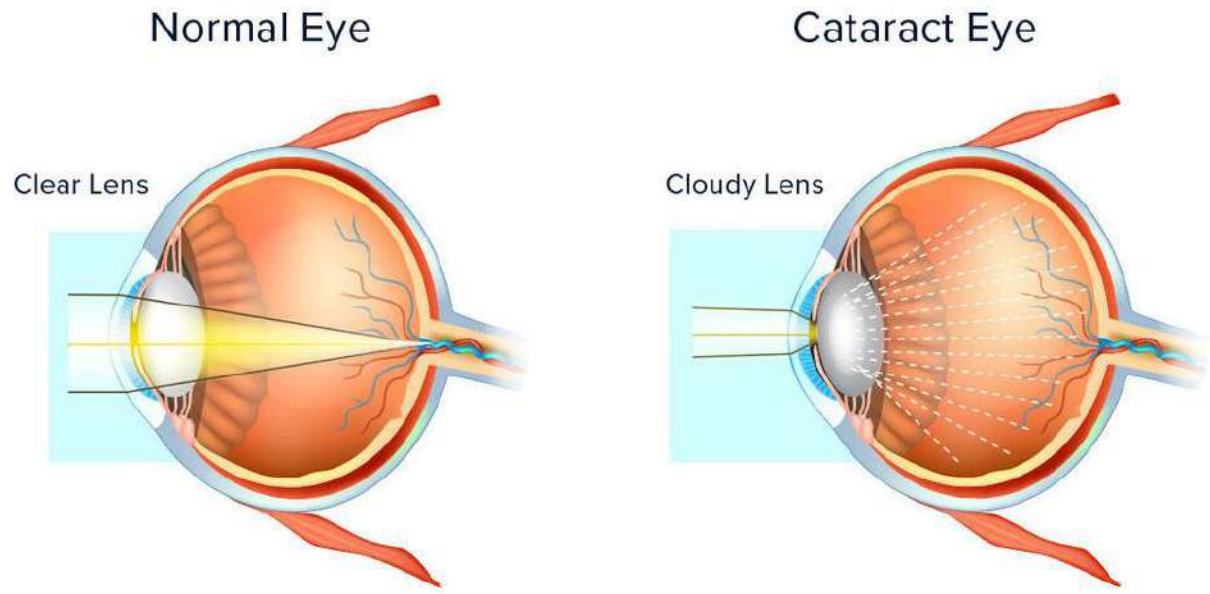
Treatment Principles

Treatment aims to reduce intraocular pressure and prevent further optic nerve damage. It may include topical medicines that reduce aqueous humour production or increase its outflow, laser procedures, and surgery when required. Established optic nerve damage is generally irreversible, making early detection important.

15.6 Pathophysiology of Cataract

Introduction

A cataract is the clouding or loss of transparency of the crystalline lens of the eye. It interferes with the passage of light through the lens and causes progressive visual impairment. Cataract is commonly associated with ageing, but it may also occur due to congenital conditions, trauma, metabolic disorders, or medication exposure.



Normal Lens Structure and Function

The crystalline lens is a transparent, biconvex structure located behind the iris. It consists of:

- Lens capsule.
- Lens epithelial cells.
- Lens fibres.
- Crystallin proteins.

The highly organized arrangement of lens fibres and crystallin proteins maintains lens transparency. The lens refracts light and changes its curvature during accommodation.

Pathophysiology of Cataract

Cataract develops when the normal arrangement and transparency of lens proteins and fibres are disturbed.

1. Ageing, oxidative stress, metabolic changes, or injury affects lens cells and proteins.
2. Crystallin proteins undergo structural changes, aggregation, or degradation.
3. Damage to lens cell membranes and changes in ion and water balance may occur.
4. The orderly arrangement of lens fibres is disrupted.
5. Light scattering increases as the lens becomes opaque.
6. Less focused light reaches the retina, resulting in blurred or reduced vision.

Oxidative stress is an important mechanism in age-related cataract. Reduced antioxidant protection, particularly involving glutathione, may contribute to lens protein damage.

Types of Cataract

1. Nuclear Cataract

Nuclear cataract affects the central nucleus of the lens. It is commonly associated with ageing and may cause gradual blurring, reduced contrast, and changes in refractive power.

2. Cortical Cataract

Cortical cataract affects the peripheral lens cortex. It often appears as spoke-like or wedge-shaped opacities extending towards the centre.

3. Posterior Subcapsular Cataract

This type develops near the posterior surface of the lens. It may cause marked difficulty with reading and vision in bright light.

4. Congenital Cataract

Congenital cataract is present at birth or develops during early childhood. It may result from genetic factors, intrauterine infections, or metabolic disorders.

5. Secondary Cataract

Secondary cataract may develop in association with diabetes, ocular inflammation, trauma, or prolonged use of certain medications.

Clinical Features

- Painless, gradual blurring of vision.
- Increased sensitivity to glare.
- Difficulty seeing at night.
- Faded or altered colour perception.
- Frequent changes in spectacle prescription.
- Double vision in one eye in some cases.

Diagnosis

Diagnosis is based on visual assessment and examination of the lens, commonly using slit-lamp biomicroscopy. Visual acuity testing helps determine the degree of functional impairment.

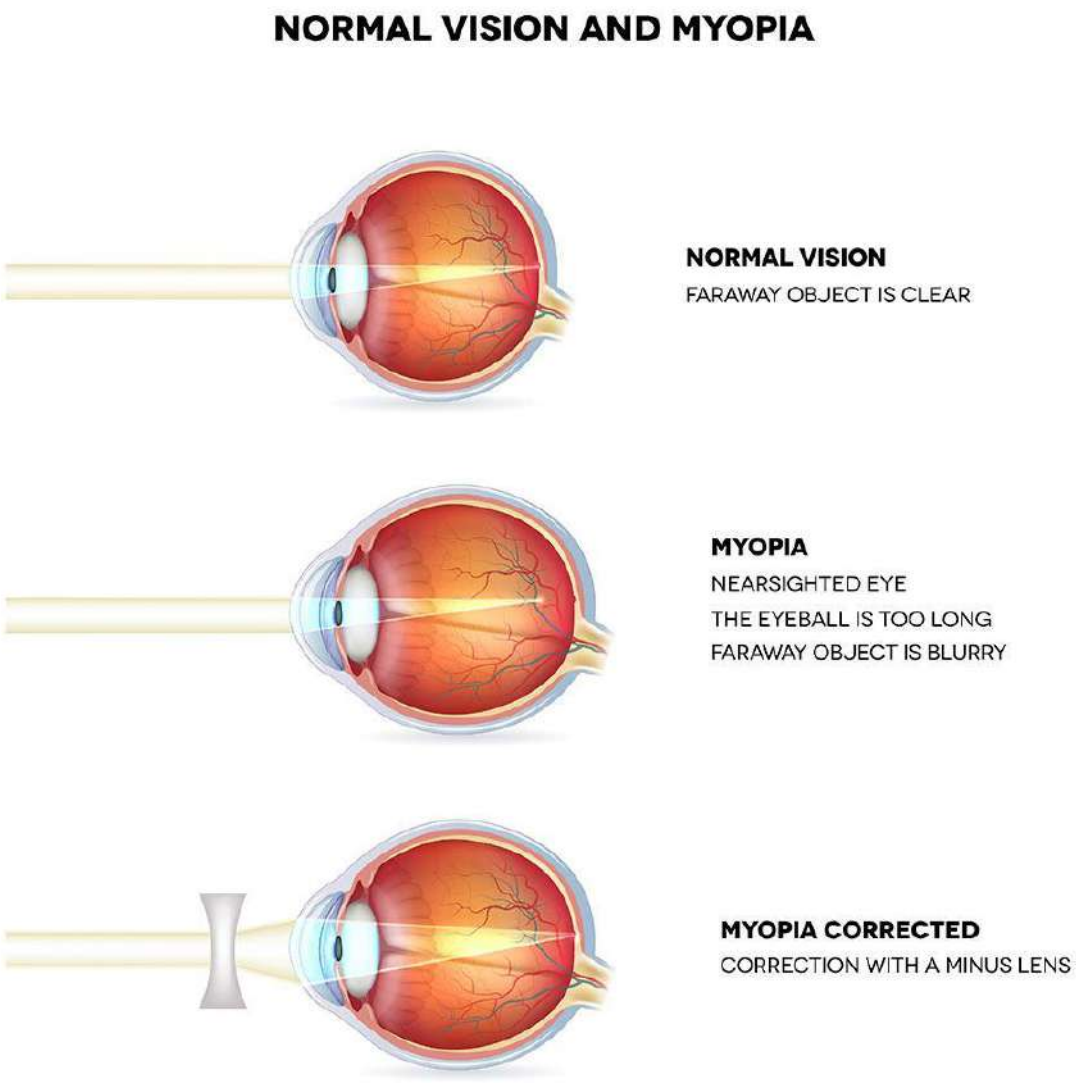
Treatment Principles

The definitive treatment for visually significant cataract is surgical removal of the cloudy lens, usually followed by implantation of an artificial intraocular lens. Management depends on the severity of visual impairment and its effect on daily activities.

15.7 Pathophysiology of Myopia

Introduction

Myopia, commonly known as short-sightedness or near-sightedness, is a refractive error in which distant objects appear blurred while near objects are seen more clearly. It occurs when light from distant objects is focused in front of the retina rather than directly on it.



Normal Refraction

In a normal eye, the cornea and lens refract incoming light so that it focuses on the retina. This produces a clear image that can be processed by the visual pathways.

Pathophysiology of Myopia

Myopia develops when the optical power of the eye is too strong relative to its axial length, or when the eyeball is longer than normal.

The major mechanisms include:

1. Axial Myopia

Axial myopia occurs when the anteroposterior length of the eyeball is increased. As a result, light rays from distant objects focus in front of the retina.

2. Refractive Myopia

Refractive myopia occurs when the refractive power of the cornea or lens is greater than normal, causing excessive bending of light.

Mechanism

1. Parallel light rays enter the eye from a distant object.
2. The cornea and lens refract the rays.
3. Due to increased axial length or excessive refractive power, the rays converge before reaching the retina.
4. The image becomes blurred on the retinal surface.
5. The person experiences difficulty seeing distant objects clearly.

Types of Myopia

1. Simple Myopia

Simple myopia is a common form that generally develops during childhood or adolescence and often stabilizes in early adulthood.

2. Pathological Myopia

Pathological or high myopia is associated with excessive elongation of the eyeball and structural changes in the retina, choroid, and optic nerve. It may increase the risk of retinal detachment, myopic macular degeneration, and other ocular complications.

3. Congenital Myopia

Congenital myopia is present at birth and may be associated with developmental or genetic factors.

Clinical Features

- Blurred distance vision.
- Squinting to see distant objects.
- Eye strain or headache in some individuals.
- Difficulty seeing classroom boards or distant signs.
- In high myopia, increased risk of retinal and other ocular complications.

Diagnosis

Diagnosis is based on visual acuity testing and refraction. An eye examination helps determine the degree of myopia and assess associated ocular changes.

Treatment Principles

Myopia is commonly corrected using:

- Concave (minus-power) lenses: Diverge incoming light rays so that the image focuses on the retina.
- Contact lenses: Provide optical correction directly on the eye.
- Refractive surgery: May be considered for suitable individuals after clinical assessment.

Children and adolescents may benefit from specific myopia-control approaches prescribed by an eye-care professional.

15.8 Pathophysiology of Otitis Externa

Introduction

Otitis externa is inflammation or infection of the external auditory canal, the passage extending from the pinna to the tympanic membrane. It is commonly known as swimmer's ear because prolonged exposure to water can increase the risk of infection. The condition may be acute or chronic and is frequently associated with bacterial infection.

Causes and Risk Factors

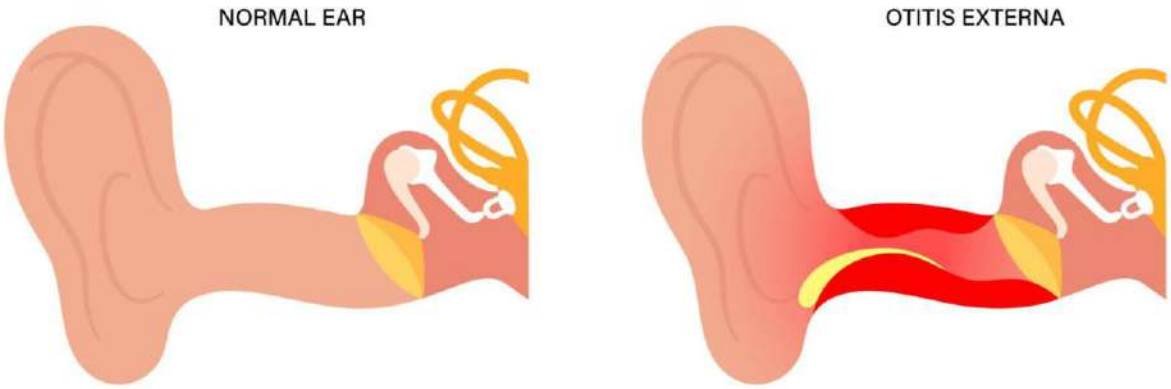
Common causes and predisposing factors include:

- Excessive moisture in the external auditory canal.
- Frequent swimming or prolonged water exposure.
- Trauma caused by cotton buds, fingernails, or other objects.
- Removal of protective earwax.
- Skin conditions such as eczema or dermatitis.
- Use of hearing aids or earplugs that irritate the canal.
- Bacterial infection, commonly involving Pseudomonas aeruginosa or Staphylococcus aureus.

Fungal infections, particularly those caused by Aspergillus or Candida species, may also occur.

Pathophysiology

The external auditory canal is normally protected by intact skin and cerumen. Cerumen provides a protective barrier and helps maintain an acidic environment that limits microbial growth.



The development of otitis externa generally involves the following sequence:

1. Moisture, trauma, or skin inflammation damages the protective epithelial barrier of the external auditory canal.
2. Removal or alteration of cerumen reduces the canal's natural antimicrobial protection.
3. Microorganisms multiply within the moist and damaged canal.
4. Local inflammation develops, producing redness, swelling, and increased secretion.
5. Swelling narrows the external auditory canal and may interfere with sound conduction.
6. In severe cases, infection may extend to surrounding tissues.

Clinical Features

Common clinical manifestations include:

- Ear pain, often increased by pulling the pinna or pressing the tragus.
- Itching inside the ear.
- Redness and swelling of the external auditory canal.
- Ear discharge.
- A feeling of fullness in the ear.
- Temporary hearing reduction when swelling or discharge obstructs the canal.

Diagnosis

Diagnosis is generally based on history and examination using an otoscope. The external auditory canal may appear red, swollen, and tender, with possible discharge. Culture testing may be considered in persistent, recurrent, or severe infections.

Treatment Principles

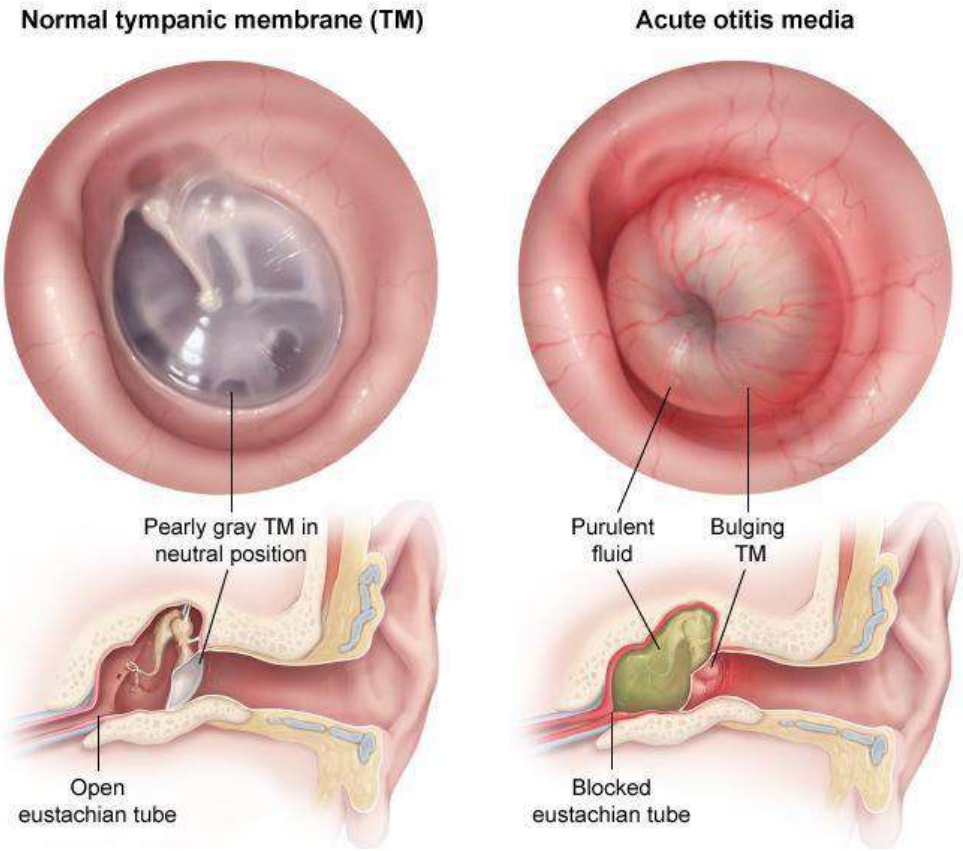
Treatment aims to control infection, reduce inflammation, and restore the protective condition of the external auditory canal. It may include topical antimicrobial preparations, sometimes combined with corticosteroids, and appropriate pain relief. Keeping the ear dry and avoiding instrumentation are important supportive measures. Severe or complicated infections require medical assessment.

15.9 Pathophysiology of Otitis Media

Introduction

Otitis media refers to inflammation of the middle ear, the air-filled cavity located behind the tympanic membrane. It is particularly common in children and may occur as acute otitis media, otitis media with effusion, or chronic otitis media.

The condition is frequently associated with dysfunction of the Eustachian tube, which connects the middle ear to the nasopharynx and helps equalize pressure and drain middle-ear secretions.



Causes and Risk Factors

Common factors include:

- Viral upper respiratory tract infections.
- Bacterial infection, commonly involving Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.
- Eustachian tube dysfunction.
- Enlarged adenoids.
- Exposure to tobacco smoke.
- Anatomical and developmental factors, particularly in children.
- Allergic or inflammatory conditions affecting the nasopharynx.

Pathophysiology

The Eustachian tube normally ventilates the middle ear and allows fluid to drain into the nasopharynx. Dysfunction of this tube can contribute to the development of otitis media.

1. A respiratory infection or inflammation causes swelling around the opening of the Eustachian tube.
2. The tube becomes obstructed or fails to open normally.
3. Air within the middle ear is gradually absorbed, producing negative pressure.
4. Fluid may accumulate in the middle-ear cavity.
5. Microorganisms from the nasopharynx may enter the middle ear and multiply in the accumulated fluid.
6. Inflammatory responses produce swelling, fluid accumulation, and sometimes pus formation.
7. Pressure on the tympanic membrane causes pain and may impair its movement.
8. Reduced movement of the tympanic membrane and ossicles produces conductive hearing loss.

Types of Otitis Media

1. Acute Otitis Media

Acute otitis media is characterized by rapid onset of middle-ear inflammation, often with fluid accumulation and signs of acute infection. It may follow an upper respiratory tract infection.

2. Otitis Media with Effusion

This condition involves fluid accumulation in the middle ear without the typical acute signs of infection. It may persist after an acute infection or develop due to ongoing Eustachian tube dysfunction. Persistent effusion can cause temporary conductive hearing impairment.

3. Chronic Otitis Media

Chronic otitis media involves long-standing inflammation or infection of the middle ear. It may be associated with persistent tympanic membrane perforation and recurrent ear discharge.

Clinical Features

- Ear pain.
- Fever, particularly in acute infection.
- Reduced hearing.
- Feeling of fullness or pressure in the ear.
- Irritability and disturbed sleep in children.
- Ear discharge if the tympanic membrane perforates.
- In some cases, nausea or balance-related symptoms.

Complications

Possible complications include:

- Persistent middle-ear effusion.

- Conductive hearing loss.
- Tympanic membrane perforation.
- Mastoiditis.
- Chronic suppurative otitis media.
- Rarely, spread of infection to intracranial structures.

Diagnosis

Diagnosis is based on clinical history and examination of the tympanic membrane. Otoscopy may reveal a bulging, opaque, or poorly mobile tympanic membrane in acute otitis media. Pneumatic otoscopy or tympanometry may help identify middle-ear fluid.

Treatment Principles

Treatment depends on the patient's age, severity, duration of symptoms, and clinical findings. Management may include pain relief, observation in selected cases, and antimicrobial therapy when indicated. Persistent middle-ear effusion or recurrent disease may require specialist evaluation.

15.10 Pathophysiology of Vertigo

Introduction

Vertigo is a false sensation of movement, commonly described as spinning, tilting, or rotation of the person or surroundings. It is a symptom rather than a disease and usually results from dysfunction of the vestibular system, which helps maintain balance and spatial orientation.

The vestibular system includes the semicircular canals, utricle, and saccule of the inner ear, along with the vestibular nerve and central pathways in the brainstem and cerebellum.

Normal Physiology of Balance

The vestibular system detects head movement and position.

- The semicircular canals detect angular acceleration or rotational movement.
- The utricle and saccule detect linear acceleration and head position relative to gravity.
- Vestibular signals travel through the vestibular nerve to the brainstem and cerebellum.
- The brain integrates vestibular information with visual and proprioceptive information to maintain posture and coordinate eye movements.

Normal balance depends on accurate and coordinated input from these systems.

Pathophysiology of Vertigo

Vertigo develops when there is abnormal or unequal activity in the vestibular pathways.

1. A disorder affects the inner ear, vestibular nerve, brainstem, or cerebellar pathways.
2. Vestibular signals become abnormal or differ between the two sides.
3. The brain receives conflicting information about head position and movement.

4. This mismatch produces a false perception of movement.
5. Abnormal vestibulo-ocular reflex activity may cause involuntary rhythmic eye movements called nystagmus.
6. Associated autonomic responses may produce nausea, vomiting, and sweating.

Common Causes of Vertigo

1. Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is a common peripheral vestibular disorder. It occurs when small calcium carbonate particles, called otoconia, become displaced from the utricle and enter a semicircular canal, most commonly the posterior canal.

During certain head movements, the displaced particles move within the canal and abnormally stimulate sensory receptors. This produces brief episodes of positional vertigo.

2. Ménière's Disease

Ménière's disease is associated with abnormal fluid regulation within the inner ear, commonly described as endolymphatic hydrops. It may cause recurrent vertigo, fluctuating hearing loss, tinnitus, and a feeling of fullness in the affected ear.

3. Vestibular Neuritis

Vestibular neuritis involves inflammation or dysfunction of the vestibular nerve. It may produce sudden, prolonged vertigo, often without hearing loss.

4. Labyrinthitis

Labyrinthitis involves inflammation of the inner ear structures responsible for hearing and balance. It may cause vertigo along with hearing impairment.

5. Central Vertigo

Central vertigo results from disorders involving the brainstem or cerebellum. Causes may include stroke, multiple sclerosis, and other neurological conditions. Central causes require careful clinical evaluation, particularly when symptoms begin suddenly or are accompanied by neurological signs.

Clinical Features

- Sensation of spinning or movement.
- Nausea and vomiting.
- Imbalance or unsteadiness.
- Nystagmus.
- Sweating and pallor.
- Tinnitus or hearing changes in some inner-ear disorders.

Diagnosis

Evaluation includes a detailed history, neurological and ear examination, assessment of eye movements, and positional testing when appropriate. Hearing tests and vestibular investigations may be used depending on the suspected cause. Imaging may be required when a central neurological cause is suspected.

Treatment Principles

Treatment depends on the underlying cause. BPPV may respond to specific repositioning manoeuvres. Other conditions may require medicines for short-term symptom relief, vestibular rehabilitation, or disease-specific treatment. Persistent or sudden severe vertigo, particularly with weakness, speech difficulty, double vision, severe headache, or difficulty walking, requires urgent medical assessment.

15.11 Pathophysiology of Anosmia

Introduction

Anosmia is the complete loss of the sense of smell. It may occur due to damage or dysfunction of the olfactory epithelium, olfactory nerve fibres, olfactory bulb, or central olfactory pathways.

Smell contributes to the perception of flavour, detection of environmental hazards, and quality of life. Loss of smell may therefore affect food enjoyment, appetite, safety, and emotional experiences.

Causes of Anosmia

Common causes include:

- Viral upper respiratory tract infections.
- Nasal obstruction due to inflammation or swelling.
- Chronic rhinosinusitis.
- Nasal polyps.
- Head injury affecting olfactory nerve fibres.
- Certain neurological disorders.
- Exposure to toxic chemicals.
- Congenital absence or abnormal development of olfactory structures.
- Some medications and medical treatments.

Pathophysiology

The mechanism of anosmia depends on the site of damage.

1. Conductive Anosmia

Conductive anosmia occurs when odorant molecules cannot reach the olfactory epithelium because of obstruction or inflammation.

Examples include nasal polyps, severe nasal congestion, and chronic rhinosinusitis.

Mechanism:

1. Nasal inflammation or obstruction develops.
2. Airflow carrying odorant molecules is reduced or altered.
3. Fewer odorant molecules reach the olfactory receptors.
4. Olfactory receptor activation decreases.
5. The perception of smell becomes reduced or absent.

2. Sensorineural Anosmia

Sensorineural anosmia results from damage to olfactory receptor neurons, their axons, or associated neural structures.

Mechanism:

1. Infection, trauma, toxins, or other factors damage olfactory receptor cells or nerve fibres.
2. Odorant detection and signal generation become impaired.
3. Fewer or no signals reach the olfactory bulb.
4. The brain receives insufficient olfactory information.
5. Smell perception is reduced or lost.

3. Central Anosmia

Central anosmia occurs when structures involved in olfactory processing, such as the olfactory bulb, olfactory tract, or higher brain regions, are affected.

Possible causes include head trauma, neurological disorders, and lesions involving olfactory pathways.

Clinical Features

- Complete loss of smell.
- Reduced ability to detect food odours.
- Reduced flavour perception.
- Decreased appetite or changes in eating habits.
- Inability to detect hazards such as smoke, gas leaks, or spoiled food.
- Possible reduction in quality of life.

Diagnosis

Diagnosis involves clinical history and examination of the nasal cavity. Smell identification or threshold tests may be used to assess olfactory function. Nasal endoscopy may help identify obstruction or inflammation. Imaging may be considered when structural or neurological causes are suspected.

Treatment Principles

Treatment depends on the underlying cause. Nasal obstruction or inflammation may require appropriate medical management. Olfactory training, involving repeated exposure to selected odours, may be recommended in certain cases, particularly after post-viral smell loss. Recovery varies according to the cause and extent of neural injury.

Special senses enable the body to detect and interpret specific environmental stimuli. The eye is responsible for vision, the ear for hearing and balance, the nose for smell, and the tongue for taste. Each organ contains specialized sensory structures that convert physical or chemical stimuli into electrical signals transmitted to the central nervous system. Glaucoma involves progressive optic nerve damage, often associated with increased intraocular pressure. Cataract results from loss of lens transparency, while myopia occurs when light focuses in front of the retina. Otitis externa affects the external auditory canal, whereas otitis media involves inflammation of the middle ear. Vertigo is a false sensation of movement commonly associated with vestibular dysfunction, and anosmia refers to complete loss of smell due to dysfunction of the olfactory system.

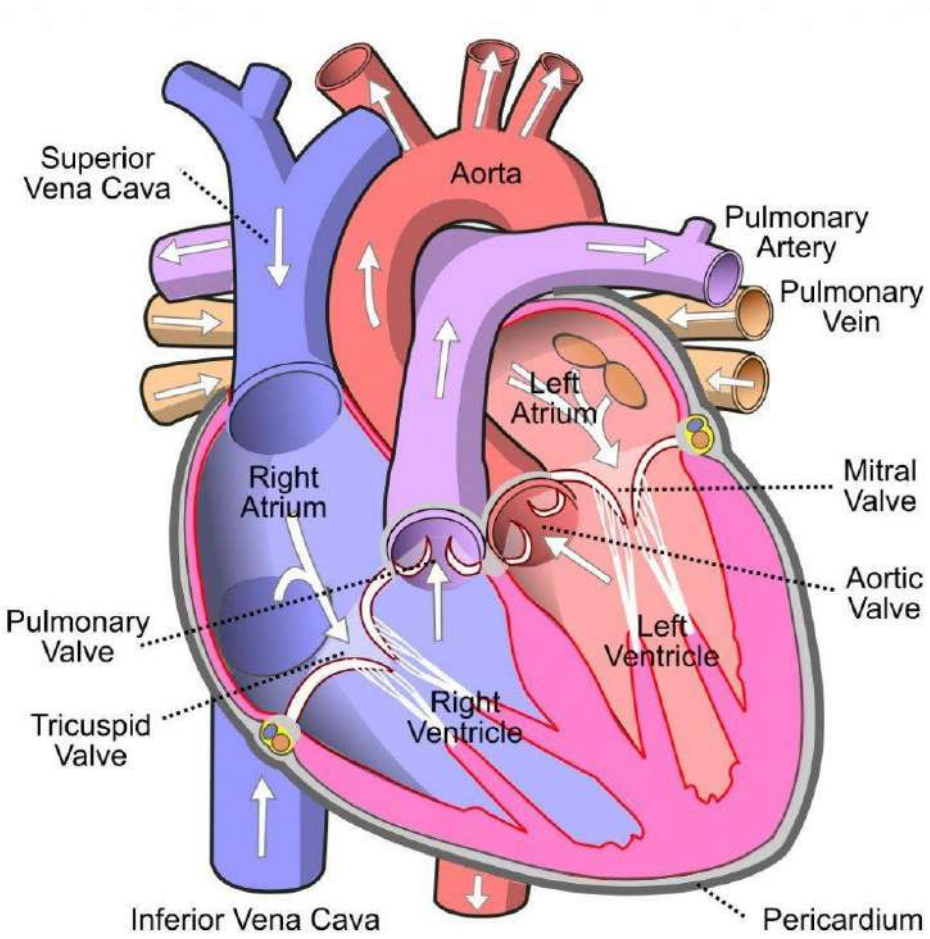
UNIT- V

Chapter 16: Cardiovascular System

The cardiovascular system is responsible for the continuous circulation of blood throughout the body. It supplies oxygen, nutrients and hormones to tissues and removes carbon dioxide and metabolic waste products. It also helps maintain body temperature, fluid balance and acid–base balance. The system consists of the heart, blood and blood vessels. The heart acts as a muscular pump, while blood vessels form a closed network through which blood circulates.

16.1 Anatomy of the Heart

The heart is a hollow, muscular organ situated in the thoracic cavity between the lungs, in a region called the mediastinum. It lies behind the sternum and above the diaphragm. Approximately two-thirds of the heart lies to the left of the midline. The size of the heart is generally comparable to that of a closed fist.



External Structure

The heart is enclosed by a double-walled sac called the pericardium. It consists of:

1. Fibrous pericardium: The tough outer layer that protects the heart, prevents excessive expansion and anchors it within the thoracic cavity.

2. Serous pericardium: The inner membrane, which has a parietal layer and a visceral layer. The visceral layer is also known as the epicardium.
3. Pericardial cavity: The space between the serous layers, containing a small amount of lubricating fluid that reduces friction during heart movements.

The pointed lower end of the heart is called the apex, which is directed downward and to the left. The broader upper portion is called the base.

Table 16.1: Layers of the Heart Wall

The wall of the heart consists of three layers:

Layer	Description and function
Epicardium	Outermost layer; protects the heart and contains blood vessels, nerves and adipose tissue.
Myocardium	Middle muscular layer; responsible for contraction and pumping of blood. It is thickest in the left ventricle.
Endocardium	Smooth inner lining of the chambers and valves; reduces friction as blood flows through the heart.

Chambers of the Heart

The heart is divided into four chambers: two upper atria and two lower ventricles. The right side receives and pumps deoxygenated blood, whereas the left side receives and pumps oxygenated blood.

Right atrium: Receives deoxygenated blood from the superior vena cava, inferior vena cava and coronary sinus. It transfers blood to the right ventricle through the tricuspid valve.

Right ventricle: Receives blood from the right atrium and pumps it to the lungs through the pulmonary trunk and pulmonary arteries. The pulmonary valve prevents backflow into the ventricle.

Left atrium: Receives oxygenated blood from the pulmonary veins and transfers it to the left ventricle through the mitral valve.

Left ventricle: Pumps oxygenated blood into the aorta for distribution to the body. Its wall is the thickest among the four chambers because it must generate sufficient pressure to maintain systemic circulation.

Table 16.2: Valves of the Heart

Heart valves maintain one-way blood flow and prevent backflow during the cardiac cycle. There are four major valves.

Valve	Location	Function
Tricuspid valve	Between right atrium and right ventricle	Prevents backflow into the right atrium during ventricular contraction.
Pulmonary valve	Between right ventricle and pulmonary trunk	Prevents backflow from the pulmonary trunk into the right ventricle.

Mitral (bicuspid) valve	Between left atrium and left ventricle	Prevents backflow into the left atrium during ventricular contraction.
Aortic valve	Between left ventricle and aorta	Prevents backflow from the aorta into the left ventricle.

The tricuspid and mitral valves are called atrioventricular valves, while the pulmonary and aortic valves are called semilunar valves. The atrioventricular valves are supported by chordae tendineae, which attach to papillary muscles and help prevent valve prolapse during ventricular contraction.

Major Blood Vessels Associated with the Heart

- Superior vena cava: Returns deoxygenated blood from the upper part of the body to the right atrium.
- Inferior vena cava: Returns deoxygenated blood from the lower part of the body to the right atrium.
- Pulmonary trunk and pulmonary arteries: Carry deoxygenated blood from the right ventricle to the lungs.
- Pulmonary veins: Carry oxygenated blood from the lungs to the left atrium.
- Aorta: Carries oxygenated blood from the left ventricle to the systemic circulation.
- Coronary arteries: Supply oxygenated blood to the myocardium.
- Coronary veins and coronary sinus: Return deoxygenated blood from the myocardium to the right atrium.

Septa of the Heart

The right and left sides of the heart are separated by septa, which prevent mixing of oxygenated and deoxygenated blood.

- Interatrial septum: Separates the two atria.
- Interventricular septum: Separates the two ventricles.

The muscular structure of the heart, its valves and septa together ensure efficient and unidirectional blood circulation.

16.2 Blood Circulation

Blood circulation refers to the continuous movement of blood through the heart and blood vessels. It transports oxygen, nutrients and hormones to tissues and carries carbon dioxide and waste products away from them.

In humans, circulation is double circulation, because blood passes through the heart twice during one complete circuit: once through the pulmonary circulation and once through the systemic circulation.

Pulmonary Circulation

Pulmonary circulation carries deoxygenated blood from the right side of the heart to the lungs and returns oxygenated blood to the left side of the heart.

Route:

Right ventricle → Pulmonary valve → Pulmonary trunk → Pulmonary arteries → Lung capillaries → Pulmonary veins → Left atrium

In the pulmonary capillaries, carbon dioxide diffuses from the blood into the alveoli, while oxygen diffuses from the alveoli into the blood. The blood becomes oxygenated and returns to the left atrium through the pulmonary veins.

Systemic Circulation

Systemic circulation carries oxygenated blood from the left side of the heart to the body tissues and returns deoxygenated blood to the right side of the heart.

Route:

Left ventricle → Aortic valve → Aorta → Arteries → Arterioles → Tissue capillaries → Venules → Veins → Superior and inferior vena cava → Right atrium

At the tissue capillaries, oxygen and nutrients move from blood into the cells, while carbon dioxide and metabolic waste products enter the blood.

Coronary Circulation

Coronary circulation supplies blood to the heart muscle itself. The right and left coronary arteries arise from the base of the aorta. Their branches supply oxygen and nutrients to the myocardium. Venous blood from the heart muscle drains mainly into the coronary sinus, which opens into the right atrium.

Coronary circulation is essential because the myocardium has a high metabolic requirement and cannot obtain sufficient oxygen directly from the blood inside the heart chambers.

16.3 Blood Vessels: Structure and Functions of Arteries, Veins and Capillaries

Blood vessels form a continuous network that transports blood between the heart and body tissues. They are classified into arteries, arterioles, capillaries, venules and veins.

General Structure of Blood Vessels

Most arteries and veins consist of three basic layers, also called tunics:

1. Tunica intima: The innermost layer, consisting mainly of endothelium and supporting connective tissue. It provides a smooth surface for blood flow.
2. Tunica media: The middle layer, composed mainly of smooth muscle and elastic fibres. It regulates vessel diameter and blood flow.
3. Tunica externa (adventitia): The outer connective tissue layer that supports and protects the vessel.

The relative thickness of these layers differs according to the function of the vessel.

Arteries

Arteries carry blood away from the heart. Most arteries transport oxygenated blood, except the pulmonary arteries and certain fetal vessels, which carry deoxygenated blood.

Structure:

- Thick, strong and elastic walls.
- Well-developed tunica media containing smooth muscle and elastic fibres.
- Relatively narrow lumen compared with veins of similar size.
- Usually lack valves.

Functions:

- Carry blood away from the ventricles.
- Maintain blood pressure through elastic recoil.
- Distribute blood to different organs.
- Regulate tissue blood supply by vasoconstriction and vasodilation.

Arteries divide into smaller vessels called arterioles. Arterioles are important resistance vessels because changes in their diameter strongly influence peripheral resistance and blood pressure.

Veins

Veins carry blood towards the heart. Most veins transport deoxygenated blood, except pulmonary veins, which carry oxygenated blood from the lungs to the left atrium.

Structure:

- Thinner walls than arteries.
- Less smooth muscle and elastic tissue in the tunica media.
- Wider lumen.
- Many veins, particularly in the limbs, contain valves that prevent backflow.

Functions:

- Return blood to the heart.
- Act as blood reservoirs because they contain a large proportion of the circulating blood volume.
- Assist venous return through skeletal muscle contraction and respiratory movements.
- Maintain one-way blood flow with the help of valves.

Capillaries

Capillaries are microscopic blood vessels that connect arterioles with venules. Their walls consist mainly of a single layer of endothelial cells and a basement membrane.

Functions:

- Allow exchange of oxygen and carbon dioxide between blood and tissues.
- Facilitate movement of nutrients, hormones and metabolic waste products.
- Participate in fluid exchange between blood and interstitial spaces.
- Provide a large surface area for exchange due to their extensive branching network.

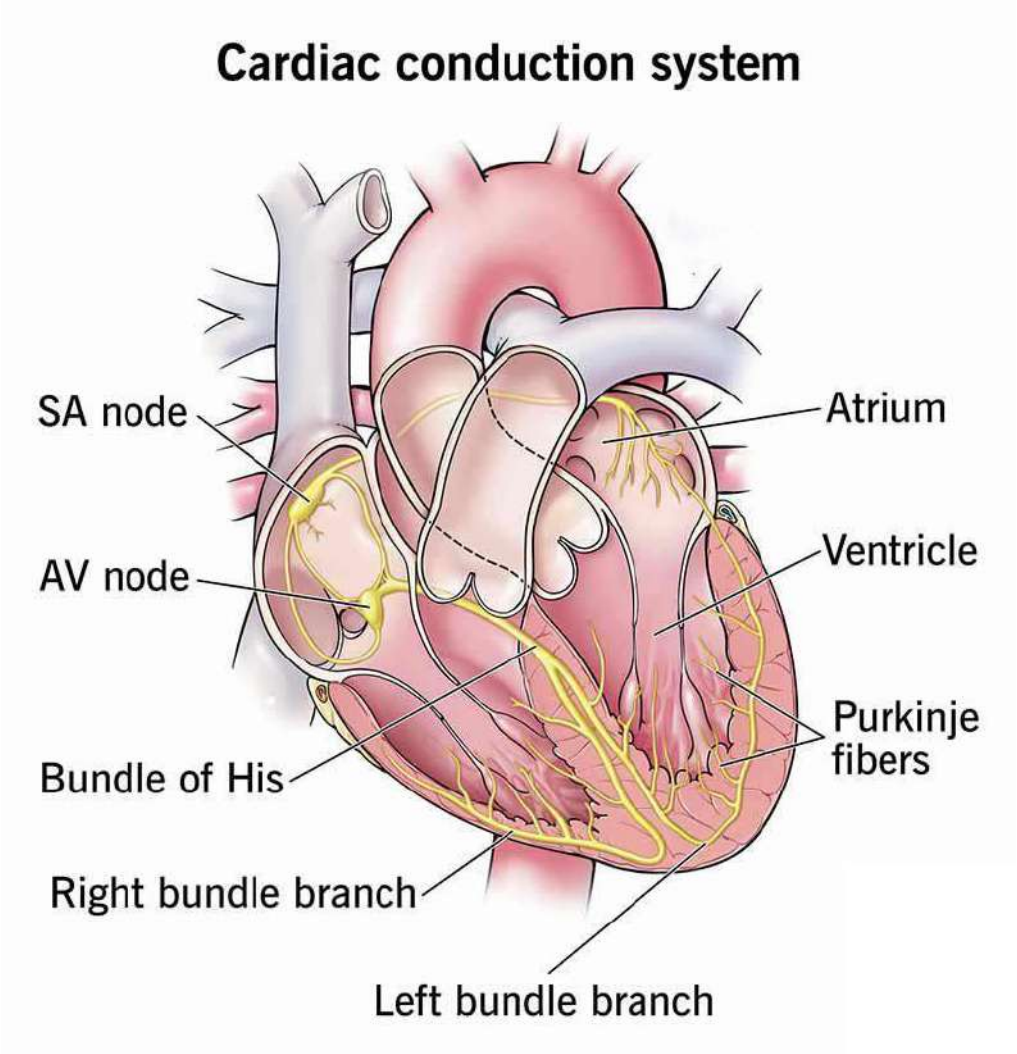
Exchange across capillary walls occurs through diffusion, filtration, reabsorption and, for some substances, vesicular transport.

Table 16.3: Comparison of Arteries, Veins and Capillaries

Feature	Arteries	Veins	Capillaries
Direction of flow	Away from heart	Towards heart	Connect arterioles and venules
Wall	Thick and elastic	Thin and less elastic	One endothelial cell layer
Lumen	Relatively narrow	Relatively wide	Very narrow
Pressure	High	Low	Low to moderate, varies along the capillary
Valves	Generally absent	Present in many veins	Absent
Main function	Distribution of blood	Return and storage of blood	Exchange of substances
Pulse	Usually palpable in large arteries	Not normally palpable	Not palpable

16.4 Elements of the Conduction System of the Heart and Heartbeat

The conduction system of the heart is a specialized network of cardiac cells that generates and conducts electrical impulses. These impulses coordinate atrial and ventricular contraction, enabling the heart to pump blood efficiently.



Components of the Conduction System

1. Sinoatrial (SA) node

The SA node is located in the wall of the right atrium near the opening of the superior vena cava. It is the normal pacemaker of the heart because it spontaneously generates electrical impulses at the highest intrinsic rate under normal conditions. The impulse spreads through the atrial myocardium and causes atrial contraction.

2. Atrioventricular (AV) node

The AV node is located in the lower part of the interatrial septum near the opening of the coronary sinus. It receives impulses from the atria and briefly delays their transmission. This delay allows the ventricles sufficient time to fill with blood before they contract.

3. Atrioventricular bundle (Bundle of His)

The Bundle of His conducts impulses from the AV node into the interventricular septum. It is the normal electrical connection between the atria and ventricles.

4. Right and left bundle branches

The Bundle of His divides into right and left bundle branches, which conduct impulses along the interventricular septum towards the apex of the heart.

5. Purkinje fibres

Purkinje fibres distribute electrical impulses rapidly throughout the ventricular myocardium, producing coordinated ventricular contraction.

Sequence of Electrical Conduction

SA node → Atrial myocardium → AV node → Bundle of His → Right and left bundle branches → Purkinje fibres → Ventricular myocardium

Heartbeat

A heartbeat is one complete cycle of contraction and relaxation of the heart. The contraction phase is called systole, while the relaxation phase is called diastole.

- Atrial systole: The atria contract and push the remaining blood into the ventricles.
- Ventricular systole: The ventricles contract and eject blood into the pulmonary trunk and aorta.
- Complete cardiac relaxation: The atria and ventricles relax and fill with blood.

The normal resting heart rate in adults is commonly about 60–100 beats per minute, although it varies with age, physical fitness, activity, emotions and health status.

16.5 Regulation of Heartbeat by the Autonomic Nervous System

The autonomic nervous system regulates heart rate, conduction and the force of cardiac contraction. It has two main divisions: the sympathetic and parasympathetic nervous systems. These divisions generally exert opposing effects on cardiac activity.

Sympathetic Regulation

Sympathetic nerve fibres arise mainly from the upper thoracic spinal cord and supply the SA node, AV node and myocardium. They release noradrenaline, which acts primarily on β_1-adrenergic receptors.

Stimulation of the sympathetic nervous system produces:

- Increased heart rate (positive chronotropic effect).
- Increased force of myocardial contraction (positive inotropic effect).
- Increased conduction velocity through the AV node (positive dromotropic effect).
- Increased cardiac output, particularly during exercise or stress.

Adrenaline released from the adrenal medulla also stimulates cardiac β_1 receptors and contributes to these effects.

Parasympathetic Regulation

Parasympathetic control of the heart is mainly mediated by the vagus nerve (cranial nerve X). Vagal nerve endings release acetylcholine, which acts on muscarinic M_2 receptors, particularly in the SA and AV nodes.

Parasympathetic stimulation produces:

- Decreased heart rate.
- Slower conduction through the AV node.
- A reduction in cardiac activity, especially at rest.

Its direct effect on ventricular contractility is relatively limited compared with sympathetic stimulation.

Table 16.4: Comparison of Autonomic Effects

Feature	Sympathetic nervous system	Parasympathetic nervous system
Main neurotransmitter at heart	Noradrenaline	Acetylcholine
Main receptor	β_1-adrenergic	Muscarinic M_2
Heart rate	Increases	Decreases
AV nodal conduction	Increases	Decreases
Contractility	Increases, especially in ventricles	Limited direct effect on ventricles
Overall effect	Increases cardiac activity	Reduces cardiac activity

The resting heart rate reflects the balance between sympathetic and parasympathetic influences, with substantial resting vagal tone in many healthy adults.

16.6 Cardiac Output

Cardiac output is the volume of blood pumped by each ventricle per minute. It is an important measure of the pumping efficiency of the heart and depends mainly on heart rate and stroke volume.

$$\text{Cardiac Output (CO)} = \text{Heart Rate (HR)} \times \text{Stroke Volume (SV)}$$

Where:

- Heart rate (HR): Number of heartbeats per minute.
- Stroke volume (SV): Volume of blood ejected by one ventricle during each heartbeat.

For example, if the heart rate is 70 beats/minute and stroke volume is 70 mL/beat:

$$CO = 70 \times 70 = 4900 \text{ mL/min}$$

Thus, the cardiac output is approximately 4.9 L/min.

Factors Affecting Cardiac Output

1. Heart rate: An increase in heart rate generally increases cardiac output, provided ventricular filling remains adequate. Very rapid heart rates may reduce filling time and lower stroke volume.

2. Preload: Preload refers to the degree of ventricular stretching at the end of diastole. It is influenced by venous return and ventricular filling. Within physiological limits, increased preload increases the force of contraction and stroke volume through the Frank–Starling mechanism.

3. Contractility: Contractility is the intrinsic strength of myocardial contraction at a given preload. Sympathetic stimulation and circulating catecholamines increase contractility and stroke volume.

4. Afterload: Afterload is the resistance or pressure against which the ventricles must pump. Increased afterload can reduce stroke volume if the heart cannot compensate.

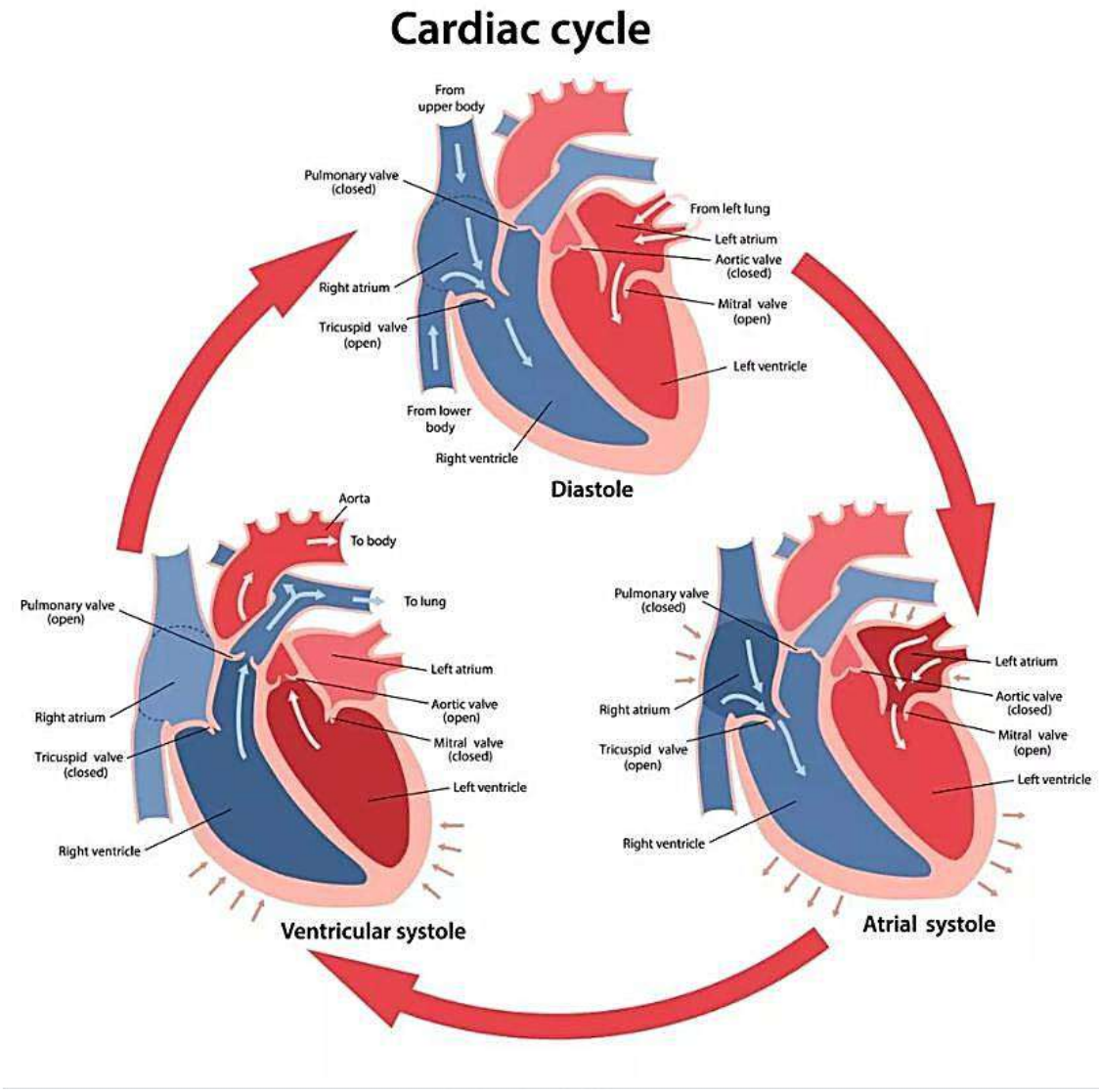
5. Venous return: Venous return determines the amount of blood returning to the heart and influences ventricular filling and stroke volume.

Significance of Cardiac Output

Cardiac output helps maintain adequate blood flow to body tissues. It increases during exercise, pregnancy and other conditions with increased metabolic demand. It may decrease in severe dehydration, blood loss, myocardial dysfunction and certain cardiac disorders.

16.7 Cardiac Cycle

The cardiac cycle refers to the sequence of electrical and mechanical events occurring during one complete heartbeat. It includes atrial systole, ventricular systole and diastole. At a heart rate of approximately 75 beats per minute, one cardiac cycle lasts about 0.8 seconds.



Phases of the Cardiac Cycle

1. Atrial systole

Atrial contraction pushes the remaining blood into the ventricles. The atrioventricular valves are open, while the semilunar valves are closed. This phase completes ventricular filling.

2. Isovolumetric ventricular contraction

The ventricles begin to contract, causing ventricular pressure to rise. The mitral and tricuspid valves close, producing the first heart sound (S_1). All four valves are briefly closed, so ventricular volume remains unchanged while pressure increases.

3. Ventricular ejection

When ventricular pressure exceeds pressure in the pulmonary trunk and aorta, the pulmonary and aortic valves open. Blood is ejected from the right and left ventricles into pulmonary and systemic circulation, respectively.

4. Isovolumetric ventricular relaxation

The ventricles relax and their pressure decreases. The semilunar valves close, producing the second heart sound (S_2). All valves are briefly closed, and ventricular volume remains constant while pressure falls.

5. Ventricular filling

When ventricular pressure becomes lower than atrial pressure, the atrioventricular valves open and blood flows from the atria into the ventricles. Filling is initially rapid and then slows during diastasis. The next atrial systole completes the cycle.

Heart Sounds

The normal heart sounds are mainly produced by closure and vibration of the cardiac valves and associated structures.

- First heart sound (S_1): Mainly due to closure of the mitral and tricuspid valves at the beginning of ventricular systole.
- Second heart sound (S_2): Mainly due to closure of the aortic and pulmonary valves at the beginning of ventricular diastole.

Additional heart sounds may occur in certain physiological or pathological conditions.

Table 16.5: Summary of the Cardiac Cycle

Phase	Main event	AV valves	Semilunar valves
Atrial systole	Atria contract; ventricles complete filling	Open	Closed
Isovolumetric contraction	Ventricular pressure rises	Closed	Closed
Ventricular ejection	Blood leaves ventricles	Closed	Open
Isovolumetric relaxation	Ventricular pressure falls	Closed	Closed
Ventricular filling	Blood enters ventricles	Open	Closed

16.8 Regulation of Blood Pressure

Blood pressure is the force exerted by circulating blood against the walls of blood vessels, particularly arteries. Arterial blood pressure is usually expressed as systolic pressure over diastolic pressure and is measured in millimetres of mercury (mmHg).

- Systolic blood pressure: Maximum arterial pressure during ventricular contraction.
- Diastolic blood pressure: Minimum arterial pressure during ventricular relaxation.

Blood pressure is influenced by cardiac output, peripheral resistance, blood volume, arterial elasticity and blood viscosity.

Relationship Between Blood Pressure, Cardiac Output and Peripheral Resistance

$$\text{Mean Arterial Pressure (MAP)} \approx \text{Cardiac Output (CO)} \times \text{Total Peripheral Resistance}$$

This relationship indicates that blood pressure is affected by both the amount of blood pumped by the heart and the resistance offered by systemic blood vessels.

Mechanisms of Blood Pressure Regulation

Blood pressure is regulated by rapid neural mechanisms and slower hormonal and renal mechanisms.

1. Baroreceptor reflex

Baroreceptors are stretch-sensitive receptors located mainly in the carotid sinus and aortic arch. They detect changes in arterial pressure and transmit signals to cardiovascular centres in the medulla oblongata.

- When blood pressure rises, baroreceptor firing increases, leading to reduced sympathetic and increased parasympathetic activity. Heart rate and vascular resistance decrease.
- When blood pressure falls, baroreceptor firing decreases, leading to increased sympathetic activity. Heart rate, contractility and vascular resistance increase.

2. Chemoreceptor reflex

Chemoreceptors in the carotid and aortic bodies respond to changes in oxygen, carbon dioxide and hydrogen ion concentration. They influence respiratory and cardiovascular centres and may contribute to blood pressure regulation, particularly during significant changes in blood gas levels.

3. Renin–angiotensin–aldosterone system (RAAS)

When renal blood flow or sodium delivery to the kidney decreases, renin release increases. Renin initiates the formation of angiotensin II, which:

- Produces vasoconstriction.
- Stimulates aldosterone secretion.
- Promotes sodium and water retention indirectly through aldosterone.
- Supports maintenance of blood volume and arterial pressure.

4. Antidiuretic hormone (ADH)

ADH, also called vasopressin, is released from the posterior pituitary in response to increased plasma osmolality or reduced effective circulating volume. It increases water reabsorption in the kidneys and, at higher concentrations, can cause vasoconstriction.

5. Renal regulation

The kidneys regulate long-term blood pressure by controlling sodium and water excretion. Increased blood volume can increase venous return and cardiac output, whereas reduced blood volume can lower cardiac output and blood pressure.

6. Local regulation of blood vessels

Local metabolic factors, endothelial substances and tissue signals regulate vascular tone. Nitric oxide causes vasodilation, while endothelin promotes vasoconstriction. These mechanisms help match blood flow to tissue requirements.

Factors Affecting Blood Pressure

- Cardiac output.
- Peripheral vascular resistance.
- Blood volume.
- Elasticity of arterial walls.
- Blood viscosity.
- Autonomic nervous system activity.
- Renal function and hormonal regulation.

16.9 Pulse

Pulse is the rhythmic expansion and recoil of an artery produced by the pressure wave generated when the left ventricle ejects blood into the aorta. It can be felt at superficial arteries located near the skin.

Characteristics of Pulse

1. Rate: Number of pulse beats per minute.
2. Rhythm: Regularity of intervals between successive beats.
3. Volume or amplitude: Strength of the pulse wave.
4. Character: Nature of the pulse wave, including its rise and fall.
5. Equality: Comparison of pulse strength on both sides of the body.

The normal resting adult pulse rate is commonly about 60–100 beats per minute. It may vary with age, physical activity, emotions, body temperature, medication and health status.

Table 16.6: Common Sites for Pulse Examination

Pulse site	Artery
Temporal	Superficial temporal artery
Carotid	Common carotid artery
Brachial	Brachial artery
Radial	Radial artery
Femoral	Femoral artery
Popliteal	Popliteal artery
Posterior tibial	Posterior tibial artery
Dorsalis pedis	Dorsalis pedis artery

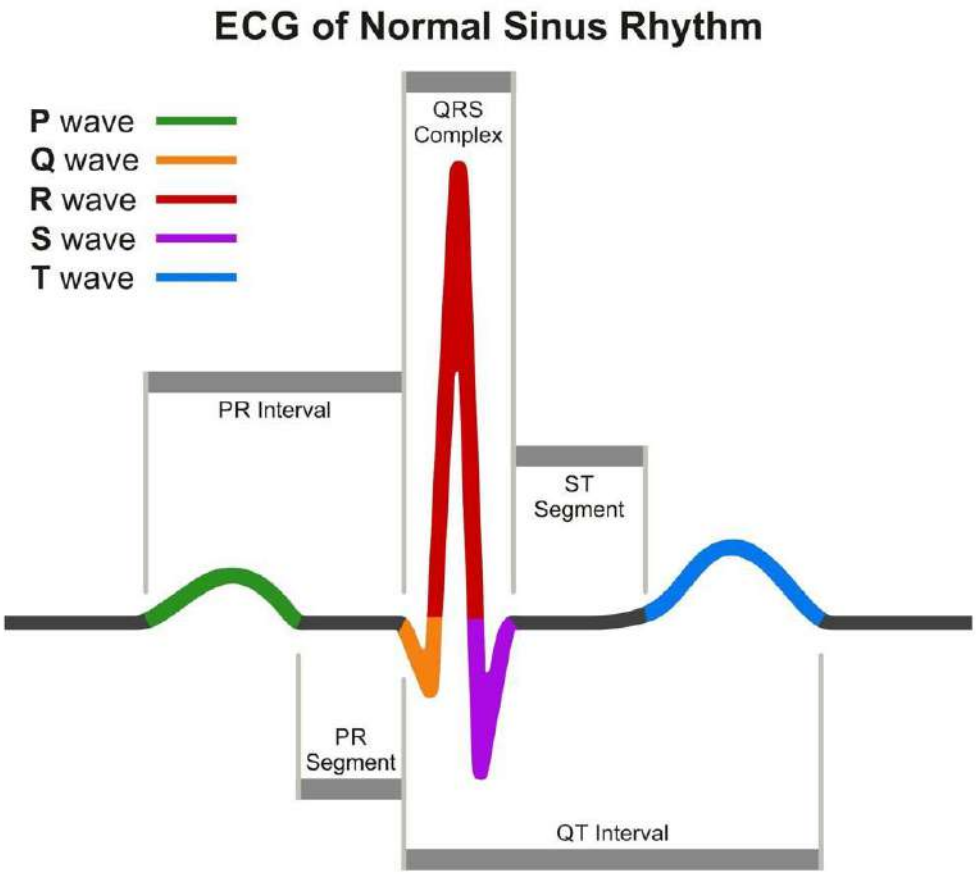
Measurement of Pulse

The pulse is commonly measured by placing the index and middle fingers over an accessible artery and applying gentle pressure. The pulse may be counted for 30 seconds and multiplied by two when regular; counting for a full minute is preferable when the rhythm is irregular or an accurate rate is required.

The thumb is generally avoided because it has its own palpable pulse. Pulse assessment provides information about heart rate, rhythm and peripheral circulation.

16.10 Electrocardiogram

An electrocardiogram (ECG or EKG) is a graphic recording of the electrical activity of the heart obtained from electrodes placed on the skin. It provides information about cardiac rhythm, electrical conduction and certain abnormalities of the myocardium.



Principle of ECG

During cardiac activity, electrical impulses spread through the myocardium and produce changes in electrical potential. Electrodes placed on the body detect these potential differences, which are recorded as waves on an ECG tracing.

A standard 12-lead ECG uses ten electrodes to record electrical activity from twelve different lead perspectives.

Main Components of a Normal ECG

1. P wave

The P wave represents atrial depolarization, which initiates atrial contraction.

2. PR interval

The PR interval extends from the beginning of the P wave to the beginning of the QRS complex. It represents the time taken for the electrical impulse to travel from the atria through the AV node and conduction system to the ventricles.

3. QRS complex

The QRS complex represents ventricular depolarization. Atrial repolarization occurs at approximately the same time and is usually hidden within the QRS complex.

4. ST segment

The ST segment extends from the end of the QRS complex to the beginning of the T wave. It normally lies close to the baseline and represents the period when the ventricles are depolarized.

5. T wave

The T wave represents ventricular repolarization.

6. QT interval

The QT interval extends from the beginning of the QRS complex to the end of the T wave. It represents the total duration of ventricular depolarization and repolarization and varies with heart rate.

ECG Paper and Calibration

A standard ECG is commonly recorded at a paper speed of 25 mm/second and calibration of 10 mm/mV.

- One small horizontal square represents 0.04 seconds.
- One large horizontal square represents 0.20 seconds.
- Five large squares represent 1 second.
- One small vertical square represents 0.1 mV under standard calibration.

Clinical Significance of ECG

ECG is used to assess:

- Heart rate and rhythm.
- Conduction abnormalities.
- Evidence suggestive of myocardial ischemia or infarction.

- Chamber enlargement patterns.
- Effects of electrolyte disturbances and certain drugs.
- Some forms of pericardial and other cardiac disorders.

ECG findings must be interpreted along with symptoms, physical examination and other investigations because a normal ECG does not exclude all forms of heart disease.

Chapter 17: Pathophysiology of Cardiovascular Disorders

Cardiovascular disorders affect the heart and blood vessels and may interfere with blood flow, oxygen delivery and normal cardiac function. Common disorders include hypertension, cardiac arrhythmias, congestive heart failure and ischemic heart disease. Their development often involves interactions among genetic, metabolic, vascular, neural and environmental factors.

17.1 Pathophysiology of Hypertension

Hypertension is a chronic condition characterized by persistently elevated arterial blood pressure. It increases the workload of the heart and can progressively damage blood vessels and target organs such as the brain, kidneys, retina and heart.

Regulation of Normal Blood Pressure

Blood pressure depends mainly on cardiac output and total peripheral resistance:

$$\text{Blood Pressure} \propto \text{Cardiac Output} \times \text{Total Peripheral Resistance}$$

Cardiac output is determined by heart rate and stroke volume. Peripheral resistance is influenced largely by the diameter of small arteries and arterioles, as well as vascular tone and blood viscosity.

Classification of Hypertension

1. Primary (essential) hypertension

Primary hypertension is elevated blood pressure without a single identifiable cause. It is associated with multiple genetic and environmental factors, including excess dietary sodium, obesity, physical inactivity, ageing, alcohol consumption and altered renal or vascular regulation.

2. Secondary hypertension

Secondary hypertension results from an identifiable underlying condition or cause. Examples include renal disease, endocrine disorders, obstructive sleep apnoea and certain medications.

Pathophysiology of Primary Hypertension

Primary hypertension develops through complex interactions among the kidneys, blood vessels, nervous system and hormonal pathways.

1. Increased peripheral vascular resistance

Persistent narrowing of small arteries and arterioles increases resistance to blood flow. This raises arterial pressure and increases the workload of the left ventricle.

2. Renal sodium and water retention

Reduced ability of the kidneys to excrete sodium at normal pressure can lead to increased extracellular fluid volume. This increases venous return and cardiac output, contributing to elevated blood pressure.

3. Increased sympathetic activity

Increased sympathetic nervous system activity can raise heart rate, myocardial contractility and peripheral vasoconstriction. It may also stimulate renin release from the kidneys.

4. Activation of the RAAS

Increased activity of the renin–angiotensin–aldosterone system promotes vasoconstriction and sodium and water retention. Angiotensin II also contributes to vascular remodelling and cardiac hypertrophy.

5. Endothelial dysfunction

The endothelium regulates vascular tone through substances such as nitric oxide and endothelin. Reduced nitric oxide availability and increased vasoconstrictor activity can impair vasodilation and increase vascular resistance.

6. Vascular remodelling

Long-term elevation of blood pressure can cause thickening of arterial walls, increased stiffness and narrowing of the vascular lumen. These changes further increase peripheral resistance and sustain hypertension.

Pathophysiology of Secondary Hypertension

Secondary hypertension may arise from:

- Renal disorders that impair sodium and water regulation.
- Endocrine conditions that increase hormonal effects on vascular tone or fluid balance.
- Obstructive sleep apnoea associated with intermittent hypoxia and sympathetic activation.
- Drugs or substances that raise blood pressure.

Complications of Hypertension

Persistent hypertension can cause:

- Heart: Left ventricular hypertrophy, coronary artery disease and heart failure.
- Brain: Stroke and vascular cognitive impairment.
- Kidneys: Chronic kidney disease and progressive renal damage.
- Eyes: Hypertensive retinopathy.
- Blood vessels: Atherosclerosis, arterial stiffness and increased risk of vascular events.

The complications result from prolonged pressure-related injury, endothelial dysfunction and structural changes in blood vessels.

17.2 Pathophysiology of Cardiac Arrhythmias

Cardiac arrhythmias are abnormalities in the rate, rhythm or sequence of electrical activation of the heart. They may occur when impulse formation, impulse conduction or both are disturbed.

Normal Electrical Activity

Under normal conditions, the SA node initiates impulses that spread through the atria, AV node, Bundle of His, bundle branches and Purkinje fibres. This coordinated electrical activation produces effective atrial and ventricular contraction.

Mechanisms of Arrhythmia

1. Abnormal automaticity

Automaticity is the ability of certain cardiac cells to generate spontaneous electrical impulses. Abnormal changes in automaticity may cause a pacemaker focus to fire too rapidly, too slowly or at an inappropriate site.

2. Triggered activity

Triggered activity occurs when abnormal after-depolarizations develop during or after the cardiac action potential. These electrical disturbances may initiate premature beats or sustained arrhythmias.

3. Re-entry

Re-entry occurs when an electrical impulse repeatedly circulates through a pathway in the heart tissue rather than terminating after one activation. It may occur when conduction is slowed and tissue has recovered excitability, allowing the impulse to re-enter previously activated tissue.

4. Conduction block

A conduction block occurs when electrical impulses are delayed or fail to pass through part of the conduction system. Depending on the site and severity, it may produce bradycardia or abnormal coordination of contraction.

Table 17.1: Classification of Arrhythmias

Arrhythmias may be classified according to heart rate and the site of origin.

Type	Description
Tachyarrhythmia	Abnormally rapid cardiac rhythm
Bradyarrhythmia	Abnormally slow cardiac rhythm
Supraventricular arrhythmia	Originates above the ventricles, commonly in the atria or AV junction
Ventricular arrhythmia	Originates in the ventricles
Atrial fibrillation	Disorganized atrial electrical activity causing an irregular ventricular response

Atrial flutter	Rapid, organized atrial electrical activity
Ventricular tachycardia	Rapid rhythm originating in the ventricles
Ventricular fibrillation	Disorganized ventricular electrical activity with ineffective pumping

Causes and Predisposing Factors

- Ischemic heart disease and myocardial infarction.
- Structural heart disease and heart failure.
- Electrolyte disturbances, particularly changes in potassium, magnesium or calcium.
- Hypoxia and acid–base disturbances.
- Thyroid disorders.
- Certain medicines and stimulants.
- Congenital abnormalities of cardiac conduction pathways.

Effects of Arrhythmias

Arrhythmias may reduce cardiac output by interfering with ventricular filling or coordinated contraction. Rapid rhythms shorten diastolic filling time, while very slow rhythms may reduce the number of effective contractions per minute. Some arrhythmias cause palpitations, dizziness, breathlessness or syncope. Severe ventricular arrhythmias can result in cardiac arrest.

Atrial fibrillation may lead to blood stasis in the atria, increasing the risk of thrombus formation and embolic stroke.

17.3 Pathophysiology of Congestive Heart Failure

Congestive heart failure (CHF), commonly described as heart failure with congestion, is a clinical syndrome in which the heart is unable to pump blood adequately to meet the body's needs or can do so only at increased filling pressures. It may result from impaired contraction, impaired relaxation or a combination of both.

Types of Heart Failure

1. Left-sided heart failure

Left-sided heart failure occurs when the left ventricle cannot pump blood effectively or fill normally. Blood pressure rises in the left atrium and pulmonary veins, causing pulmonary congestion and, in severe cases, pulmonary oedema.

2. Right-sided heart failure

Right-sided heart failure occurs when the right ventricle cannot pump blood effectively into the pulmonary circulation. This causes systemic venous congestion, which may produce peripheral oedema, raised jugular venous pressure and enlargement of the liver.

3. Heart failure with reduced ejection fraction (HFrEF)

In HFrEF, the left ventricular ejection fraction is reduced, usually due to impaired systolic contraction.

4. Heart failure with preserved ejection fraction (HFpEF)

In HFpEF, the ejection fraction is preserved, but ventricular filling is impaired, often due to reduced ventricular compliance and abnormal relaxation. The heart may have difficulty filling without an increase in filling pressure.

Pathophysiology of Heart Failure

Heart failure commonly begins with an injury or condition that impairs cardiac function, such as myocardial infarction, hypertension, valvular disease or cardiomyopathy.

1. Reduced cardiac performance

Damage to cardiac muscle or increased ventricular workload can reduce the ability of the heart to eject blood or fill adequately. This may decrease cardiac output and increase cardiac filling pressures.

2. Activation of the sympathetic nervous system

Reduced effective circulation stimulates sympathetic activity. Increased heart rate and contractility initially help maintain cardiac output. However, prolonged sympathetic activation increases myocardial oxygen demand and contributes to adverse cardiac remodelling.

3. Activation of the RAAS

Reduced renal perfusion stimulates renin release, leading to increased angiotensin II and aldosterone activity. These hormones promote vasoconstriction and sodium and water retention. Initially, this helps maintain blood pressure and circulating volume, but persistent activation increases preload and afterload and worsens congestion.

4. Ventricular remodelling

Chronic pressure or volume overload and neurohormonal activation can produce changes in ventricular size, shape and structure. These include hypertrophy, dilation, fibrosis and changes in myocardial function. Remodelling may progressively reduce pumping efficiency.

5. Increased venous pressure and fluid accumulation

Elevated cardiac filling pressures are transmitted backward into the pulmonary or systemic venous circulation. Increased hydrostatic pressure promotes fluid movement into tissues, causing pulmonary or peripheral oedema.

Clinical Manifestations

- Breathlessness, particularly during exertion.
- Orthopnoea (breathlessness when lying flat).

- Paroxysmal nocturnal dyspnoea.
- Fatigue and reduced exercise tolerance.
- Peripheral oedema.
- Raised jugular venous pressure.
- Pulmonary crackles in patients with pulmonary congestion.
- Rapid weight gain due to fluid retention.

Complications

Heart failure may lead to recurrent hospitalisation, renal dysfunction, electrolyte disturbances, arrhythmias, thromboembolic events and progressive impairment of cardiac function.

17.4 Pathophysiology of Ischemic Heart Disease

Ischemic heart disease (IHD), also called coronary heart disease, occurs when blood supply to the myocardium is insufficient to meet its oxygen requirements. It most commonly results from narrowing or obstruction of the coronary arteries due to atherosclerosis. The imbalance between myocardial oxygen supply and demand can produce myocardial ischemia, angina or myocardial infarction.

Myocardial Oxygen Supply and Demand

Myocardial oxygen supply depends on coronary blood flow, oxygen content of blood and the ability of coronary vessels to dilate. Myocardial oxygen demand depends mainly on heart rate, contractility and ventricular wall stress.

Ischemia develops when oxygen supply becomes inadequate relative to demand. It may be caused by reduced coronary blood flow, increased myocardial workload or both.

Major Forms and Related Conditions

Ischemic heart disease includes several related conditions:

- Angina pectoris.
- Myocardial infarction.
- Atherosclerosis of coronary arteries.
- Coronary artery disease.

Angina

Angina pectoris is chest discomfort or pain caused by transient myocardial ischemia without myocardial cell death. It occurs when oxygen supply is insufficient for the metabolic needs of the myocardium.

Pathophysiology

Atherosclerotic narrowing of a coronary artery can limit the increase in blood flow required during exercise or emotional stress. The resulting oxygen supply–demand mismatch causes ischemia.

Ischemic myocardial tissue releases metabolites and activates sensory nerve endings, producing chest discomfort.

Types of Angina

1. Stable angina: Usually occurs predictably during exertion or emotional stress and is associated with fixed coronary narrowing. It generally improves with rest or appropriate anti-anginal treatment.
2. Unstable angina: Occurs with new, worsening or resting symptoms and is commonly associated with disruption of an atherosclerotic plaque and formation of a non-occlusive thrombus. It is part of the acute coronary syndrome spectrum and requires urgent assessment.
3. Vasospastic angina: Results from transient coronary artery spasm, which reduces myocardial blood flow. It may occur at rest.

Clinical Features

- Pressure, tightness or discomfort in the chest.
- Pain may radiate to the shoulder, arm, neck, jaw or back.
- Breathlessness, sweating or nausea may occur.
- Symptoms may be triggered by exertion, stress or occur at rest depending on the type.

Angina does not itself indicate myocardial cell death; however, new, severe or persistent chest pain may indicate an acute coronary syndrome and requires emergency medical evaluation.

Myocardial Infarction

Myocardial infarction (MI) is irreversible death of a portion of the heart muscle due to prolonged ischemia. It most commonly occurs when an atherosclerotic plaque in a coronary artery ruptures or erodes, leading to thrombus formation and acute reduction or interruption of blood flow.

Pathophysiology

1. An atherosclerotic plaque develops within the coronary artery wall.
2. The plaque surface may rupture or erode, exposing thrombogenic material to circulating blood.
3. Platelets adhere, activate and aggregate at the site.
4. The coagulation cascade promotes thrombus formation.
5. The thrombus partially or completely obstructs coronary blood flow.
6. Prolonged ischemia causes depletion of cellular energy, impaired membrane function and irreversible myocardial cell injury.
7. Necrotic tissue is gradually removed and replaced by fibrous scar tissue during healing.

The extent of myocardial damage depends on the duration and severity of ischemia, the size of the affected coronary territory and the availability of collateral circulation.

Clinical Features

- Persistent chest pain or pressure, often lasting longer than typical stable angina.

- Pain may radiate to the arm, jaw, neck or back.
- Breathlessness, sweating, nausea or vomiting.
- Weakness, dizziness or syncope.
- Some patients, including older adults and people with diabetes, may have atypical or less prominent symptoms.

Complications

- Cardiac arrhythmias.
- Acute heart failure and cardiogenic shock.
- Mechanical complications, such as rupture of cardiac structures.
- Pericarditis.
- Ventricular remodelling and chronic heart failure.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of medium-sized and large arteries characterized by the formation of lipid-rich plaques within the arterial wall. It is a major underlying cause of coronary artery disease, stroke and peripheral arterial disease.

Pathophysiology

1. Endothelial dysfunction

Risk factors such as elevated LDL cholesterol, smoking, hypertension and diabetes impair endothelial function. The endothelium becomes more permeable and expresses adhesion molecules that facilitate the entry of inflammatory cells.

2. Lipoprotein accumulation and modification

Low-density lipoprotein (LDL) particles enter the arterial intima and may undergo oxidation or other modifications. Modified LDL contributes to inflammation and attracts monocytes.

3. Monocyte migration and foam cell formation

Monocytes enter the arterial wall and differentiate into macrophages. Macrophages take up modified LDL and become lipid-laden foam cells. Accumulation of foam cells produces fatty streaks, an early visible lesion of atherosclerosis.

4. Smooth muscle cell migration and proliferation

Vascular smooth muscle cells migrate from the media into the intima, proliferate and produce extracellular matrix components, including collagen. These processes contribute to the formation of a fibrous cap over the lipid-rich core.

5. Plaque formation

A mature atherosclerotic plaque contains a lipid-rich necrotic core, inflammatory cells and a fibrous cap. Plaques may progressively narrow the arterial lumen and restrict blood flow.

6. Plaque rupture or erosion

Some plaques develop a thin or weakened fibrous cap. Rupture or erosion exposes thrombogenic material to blood, promoting platelet activation and thrombus formation. This can cause sudden arterial obstruction and acute ischemic events.

Risk Factors for Atherosclerosis

Non-modifiable risk factors:

- Increasing age.
- Family history of premature cardiovascular disease.
- Certain inherited lipid disorders.

Modifiable risk factors:

- Elevated LDL cholesterol.
- Hypertension.
- Diabetes mellitus.
- Tobacco use.
- Obesity and physical inactivity.
- Unhealthy dietary patterns.

Coronary Artery Disease

Coronary artery disease (CAD) refers to disease of the coronary arteries, most commonly due to atherosclerotic plaque formation. It may reduce blood flow to the myocardium and cause ischemia, angina, myocardial infarction or, in some cases, sudden cardiac death.

Pathophysiology

1. Atherosclerotic lesions develop in the coronary artery wall.
2. Progressive plaque growth narrows the arterial lumen and limits coronary blood flow, especially during increased myocardial demand.
3. Endothelial dysfunction may impair normal coronary vasodilation.
4. Plaque rupture or erosion can trigger platelet aggregation and thrombus formation.
5. Partial obstruction may produce unstable angina or non-ST-elevation myocardial infarction, while sustained complete obstruction may produce ST-elevation myocardial infarction, depending on the clinical and anatomical circumstances.

Coronary blood flow is especially important during ventricular diastole, when much of the left ventricular myocardial perfusion occurs. Tachycardia can reduce diastolic filling time and may further compromise myocardial oxygen supply.

Table 17.2: Relationship Between Atherosclerosis, CAD, Angina and MI

Condition	Basic mechanism	Main consequence
Atherosclerosis	Lipid accumulation and inflammation in arterial walls, leading to plaque formation	Arterial narrowing and risk of thrombosis
Coronary artery disease	Atherosclerotic or other disease affecting coronary arteries	Reduced myocardial blood supply
Angina	Transient myocardial ischemia without myocardial necrosis	Chest discomfort due to oxygen supply–demand mismatch
Myocardial infarction	Prolonged ischemia causing irreversible myocardial cell death	Necrosis of heart muscle

The cardiovascular system consists of the heart, blood and blood vessels and is responsible for maintaining blood circulation throughout the body. The heart has four chambers and four valves that ensure unidirectional blood flow. Pulmonary circulation carries blood between the heart and lungs, while systemic circulation supplies the body tissues. Arteries distribute blood, veins return it to the heart and capillaries facilitate exchange of substances. The cardiac conduction system generates and transmits electrical impulses to coordinate the heartbeat. The autonomic nervous system regulates heart rate, conduction and contractility. Cardiac output is the product of heart rate and stroke volume. The cardiac cycle includes atrial systole, ventricular systole and diastole. Blood pressure is regulated by neural, hormonal, renal and local vascular mechanisms. Pulse reflects the arterial pressure wave, while ECG records the electrical activity of the heart. Hypertension involves persistent elevation of arterial pressure due to changes in cardiac output, vascular resistance and regulatory mechanisms. Cardiac arrhythmias arise from abnormal impulse formation or conduction. Heart failure results from impaired cardiac pumping or filling and may cause pulmonary or systemic congestion. Ischemic heart disease occurs when myocardial oxygen supply is inadequate. Atherosclerosis is a major cause of coronary artery disease and may lead to angina or myocardial infarction.

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