

K Sembulingam
Prema Sembulingam

Essentials of **PHYSIOLOGY** for Dental Students

Ripped by
Dr. Prodigius

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**Essentials of
PHYSIOLOGY
for Dental Students**

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K Sembulingam PhD

Shri Sathya Sai Medical College and Research Institute
Thiruporur-Guduvancherry Main Road, Nellikuppam, Tamil Nadu, India

Formerly at

MR Medical College, Gulbarga, Karnataka, India

Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India
School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia and
Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India

Prema Sembulingam PhD

Sathyabama University Dental College and Hospital
Jeppiaar Nagar, Old Mahabalipuram Road, Chennai
Tamil Nadu, India

Formerly at

MR Medical College, Gulbarga, Karnataka, India

Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India
School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia and
Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India
Shri Sathya Sai Medical College and Research Institute, Nellikuppam, Tamil Nadu, India



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Registered office

B-3 EMCA House, 23/23B Ansari Road, Daryaganj, **New Delhi** - 110 002, India

Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021

+91-11-23245672, Rel: +91-11-32558559, Fax: +91-11-23276490, +91-11-23245683

e-mail: jaypee@jaypeebrothers.com, Website: www.jaypeebrothers.com

Offices in India

- **Ahmedabad**, Phone: Rel: +91-79-32988717, e-mail: ahmedabad@jaypeebrothers.com
- **Bengaluru**, Phone: Rel: +91-80-32714073, e-mail: bangalore@jaypeebrothers.com
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- **Kochi**, Phone: +91-484-2395740, e-mail: kochi@jaypeebrothers.com
- **Kolkata**, Phone: +91-33-22276415, e-mail: kolkata@jaypeebrothers.com
- **Lucknow**, Phone: +91-522-3040554, e-mail: lucknow@jaypeebrothers.com
- **Mumbai**, Phone: Rel: +91-22-32926896, e-mail: mumbai@jaypeebrothers.com
- **Nagpur**, Phone: Rel: +91-712-3245220, e-mail: nagpur@jaypeebrothers.com

Overseas offices

- **North America office, USA**, Ph: 001-636-6279734, e-mail: jaypee@jaypeebrothers.com, anjulav@jaypeebrothers.com
- **Central America office, Panama City, Panama**, Ph: 001-507-317-0160, e-mail: cservice@jphmedical.com Website: www.jphmedical.com
- **Europe office, UK**, Ph: +44 (0) 2031708910, e-mail: info@jpmedpub.com

Essentials of Physiology for Dental Students

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To
Our beloved students

Preface

We, the authors of *Essentials of Medical Physiology* are proud to bring out another textbook in Physiology, titled *Essentials of Physiology for Dental Students*. This is the outcome of requests, wishes and friendly orders from different category of people including the dental and paramedical students and faculties.

Physiology is different from other biomedical sciences as it deals with the functional aspects of various systems in the living body along with the emphasis on the regulatory mechanism that maintain the normalcy of the functions within narrow limits. It forms the strong foundation on which other medical fields are constructed.

The primary aim of this book is to meet the needs of the dental, paramedical and health science students precisely from the examination point of view, in getting knowledge of recent developments in the field of physiology and in knowing the important applied aspects of various topics.

The descriptive diagrams are given in such a way that the students can easily understand and reproduce them wherever necessary. The explanation of the topics is supported with the flow charts and tables which make the reading a pleasure and stress-free.

In the starting of each chapter, we have included the topics that are to be learnt in that particular chapter which will help the reader to remember the contents while revising the topic. At the end of each section, the long questions and short questions are given for the follow-up of the topics.

This venture is possible only because of blessings of professors, best wishes and cooperation of our friends and co-teachers and the students who know what they want and where to get them. We are grateful and thankful to one and all for being the well wishers of us.

We wish to continue our services to the students' community through this book. We are confident that the opinions, comments and valuable suggestions from one and all coming across this book will help us to improve it further to meet the needs of everyone who has Physiology as subject in their career.

K Sembulingam
ksembu@yahoo.com

Prema Sembulingam
premsem@yahoo.com

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SECTION 1

General Physiology

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1

Cell

- n INTRODUCTION
 - n CELL
 - n TISSUES
 - n ORGANS
 - n SYSTEMS
- n STRUCTURE OF THE CELL
- n CELL MEMBRANE
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 - n STRUCTURE
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- n ORGANELLES IN CYTOPLASM
 - n ORGANELLES WITH LIMITING MEMBRANE
 - n ORGANELLES WITHOUT LIMITING MEMBRANE
- n NUCLEUS
 - n STRUCTURE
 - n FUNCTIONS
- n CELL DEATH
 - n APOPTOSIS
 - n NECROSIS

n INTRODUCTION

n CELL

Cell is defined as the structural and functional unit of the living body because it has all the characteristics of life.

n TISSUES

The tissue is defined as the group of cells having similar function. The tissues are classified into four major types which are called the primary tissues. The primary tissues include:

1. Muscle tissue – skeletal muscle, smooth muscle and cardiac muscle
2. Nervous tissue – neurons and supporting cells
3. Epithelial tissue – squamous, columnar and cuboidal epithelial cells
4. Connective tissue – connective tissue proper, cartilage, bone and blood.

n ORGANS

An organ is defined as the structure that is formed by two or more primary tissues.

Some organs are composed of all the four types of primary tissues. The organs may be tubular like intestine or hollow like stomach.

n SYSTEMS

The system is defined as group of organs functioning together to perform a specific function of the body. For example, digestive system is made out of groups of organs like esophagus, stomach, intestine etc., which is concerned with digestion of food particles.

n STRUCTURE OF THE CELL

Each cell is formed by a cell body and a cell membrane or plasma membrane that covers the cell body. The important parts of the cell are (Fig. 1-1)

- a. Cell membrane
- b. Nucleus
- c. Cytoplasm with organelles

n CELL MEMBRANE

The cell membrane is a protective sheath that envelops the cell body. It separates the fluid outside the cell called extracellular fluid (ECF) and the fluid inside the cell called intracellular fluid (ICF). It is a semipermeable membrane and allows free exchange of certain substances between ECF and ICF (Fig. 1-2).

n COMPOSITION OF CELL MEMBRANE

The cell membrane is composed of three types of substances:

1. Proteins (55%)
2. Lipids (40%)
3. Carbohydrates (5%).

n STRUCTURE OF CELL MEMBRANE

The cell membrane is a unit membrane having the 'fluid mosaic model' i.e., the membrane is a fluid with mosaic of proteins (mosaic means pattern formed by arrangement of different colored pieces of stone, tile, glass or other such materials) lipids and carbohydrates. The electron microscopic study reveals three layers in the cell membrane namely, one electron lucent lipid layer in the center and two electron dense layers on either side of the central layer. Carbohydrate molecules are found on the surface of the cell membrane.

Lipid Layer of Cell Membrane

It is a bilayered structure formed by a thin film of lipids. It is fluid in nature and the portions of the membrane along with the dissolved substances move to all areas of the cell membrane. The major lipids are:

- a. Phospholipids
- b. Cholesterol

1. Phospholipids

The phospholipid molecules are formed by phosphorus and fatty acids. Each phospholipid molecule resembles the headed pin in shape (Fig. 1-3). The outer part of the phospholipid molecule is the head portion which is water soluble (hydrophilic) and the inner part is the tail

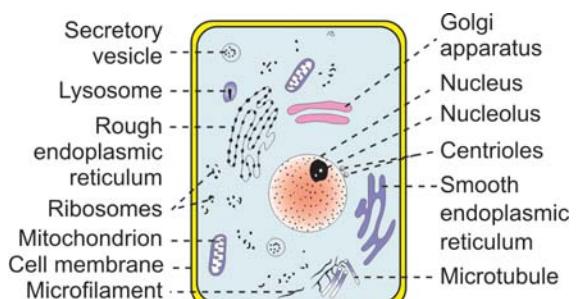


FIGURE 1-1: Structure of the cell

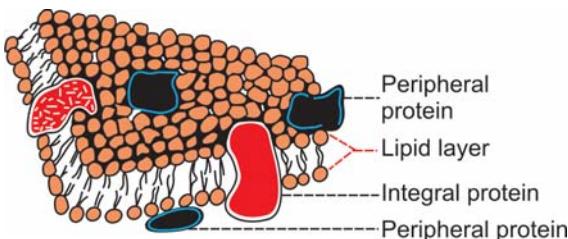


FIGURE 1-2: Diagram of the cell membrane

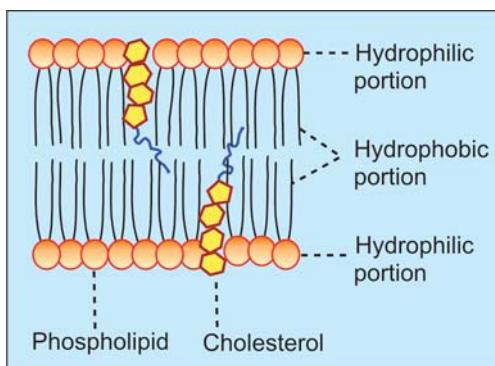


FIGURE 1-3: Lipids of the cell membrane

portion that is not soluble in water (hydrophobic). The hydrophobic tail portions meet in the center of the membrane. The hydrophilic head portions of outer layer face the ECF and those of the inner layer face the cytoplasm.

2. Cholesterol

The cholesterol molecules are arranged in between the phospholipid molecules. As phospholipids are soft and oily in nature, cholesterol helps to “pack” the phospholipids in the membrane and maintain the structural integrity of cell membrane.

Functions of lipid layer

The lipid layer is semi permeable in nature and allows only the fat soluble substances like oxygen, carbon dioxide and alcohol to pass through it. It does not allow the water soluble materials like glucose, urea and electrolytes to pass through it.

Protein Layers of the Cell Membrane

The protein layers of the cell membrane are the electron dense layers situated on either side of the central lipid layer. The protein substances present in these layers are mostly glycoproteins. These protein molecules are classified into two categories:

- Integral proteins
- Peripheral proteins

a. Integral proteins

The integral proteins, also known as transmembrane proteins, are tightly bound with the cell membrane. These protein molecules pass through the entire thickness of the cell membrane from one side to the other side.

2. Peripheral proteins

The peripheral proteins, also known as peripheral membrane proteins do not penetrate the cell membrane but are embedded partially in the outer and inner surfaces of the cell membrane. These protein molecules are loosely bound with the cell membrane and so dissociate readily from the cell membrane.

Functions of protein layers

Functionally, the proteins in the cell membrane exist in different forms such as integral proteins, channel proteins, carrier proteins etc.

- Integral proteins provide structural integrity of the cell membrane
- Channel proteins provide route for diffusion of water soluble substances like glucose and electrolytes
- Carrier proteins help in transport of substances across the cell membrane
- Receptor proteins serve as receptor sites for hormones and neurotransmitters
- Enzymes: some of the protein molecules form the enzymes which control chemical reactions within the cell membrane
- Antigens: Some proteins act as antigens and induce the process of antibody formation.

Carbohydrates of the Cell Membrane

Carbohydrate molecules form a thin loose covering over the entire surface of the cell membrane called glycocalyx. Some carbohydrate molecules are attached with proteins and form glycoproteins and some are attached with lipids and form glycolipids.

Functions of carbohydrates

1. The carbohydrate molecules are negatively charged and do not permit the negatively charged substances to move in and out of the cell.
2. The glycocalyx from the neighboring cells helps in the tight fixation of cells with one another.
3. Some of the carbohydrate molecules form the receptors for some hormones.

FUNCTIONS OF CELL MEMBRANE

1. *Protective function:* Cell membrane protects the cytoplasm and the organelles present in the cytoplasm.
2. *Selective permeability:* Cell membrane acts as a semipermeable membrane which allows only some substances to pass through it and acts as a barrier for other substances.
3. *Absorptive function:* Nutrients are absorbed into the cell through the cell membrane.
4. *Excretory function:* Metabolites and other waste products from the cell are excreted out through the cell membrane.
5. *Exchange of gases:* Oxygen enters the cell from the blood and carbon dioxide leaves the cell and enters the blood through the cell membrane.
6. *Maintenance of shape and size of the cell:* Cell membrane is responsible for the maintenance of shape and size of the cell.

CYTOPLASM

The cytoplasm is the fluid present inside the cell. It contains a clear liquid portion called cytosol which contains various substances like proteins, carbohydrates, lipids and electrolytes. Apart from

these substances, many organelles are also present in cytoplasm. The cytoplasm is distributed as peripheral ectoplasm just beneath the cell membrane and inner endoplasm between the ectoplasm and the nucleus.

ORGANELLES IN CYTOPLASM

All the cells in the body contain some common structures called organelles in the cytoplasm. Some organelles are bound by limiting membrane and others do not have limiting membrane (Table 1-1). The organelles carry out the various functions of the cell (Table 1-2).

ORGANELLES WITH LIMITING MEMBRANE

1. ENDOPLASMIC RETICULUM

Endoplasmic reticulum is made up of tubules and microsomal vesicles. These structures form an interconnected network which acts as the link between the organelles and cell membrane.

Types of Endoplasmic Reticulum

The endoplasmic reticulum is of two types namely, rough endoplasmic reticulum and smooth endoplasmic reticulum.

TABLE 1-1: Cytoplasmic organelles

The organelles with limiting membrane
1. Endoplasmic reticulum 2. Golgi apparatus 3. Lysosome 4. Peroxisome 5. Centrosome and centrioles 6. Secretory vesicles 7. Mitochondria 8. Nucleus
The organelles without limiting membrane
1. Ribosomes 2. Cytoskeleton

TABLE 1-2: Functions of cytoplasmic organelles

Organelles	Functions
Rough endoplasmic reticulum	1. Synthesis of proteins 2. Degradation of worn out organelles
Smooth endoplasmic reticulum	1. Synthesis of lipids and steroids 2. Role in cellular metabolism 3. Storage and metabolism of calcium 4. Catabolism and detoxification of toxic substances
Golgi apparatus	Processing, packaging, labeling and delivery of proteins and lipids
Lysosomes	1. Degradation of macromolecules 2. Degradation of worn out organelles 3. Removal of excess of secretory products. 4. Secretory function
Peroxisomes	1. Break down of excess fatty acids 2. Detoxification of hydrogen peroxide and other metabolic products 3. Oxygen utilization 4. Acceleration of gluconeogenesis 5. Degradation of purine to uric acid 6. Role in the formation of myelin 7. Role in the formation of bile acids
Centrosome	Movement of chromosomes during cell division
Mitochondria	1. Production of energy 2. Synthesis of ATP 3. Initiation of apoptosis
Ribosomes	Synthesis of proteins
Cytoskeleton	1. Determination of shape of the cell 2. Stability of cell shape 3. Cellular movements
Nucleus	1. Control of all activities of the cell 2. Synthesis of RNA 3. Sending genetic instruction to cytoplasm for protein synthesis 4. Formation of subunits of ribosomes 5. Control of cell division 6. Storage of hereditary information in genes (DNA)

Rough Endoplasmic Reticulum

Rough endoplasmic reticulum is the one to which the granular ribosome is attached. This gives the rough appearance and so, it is called the rough

endoplasmic reticulum. Attachment of the granular ribosome also gives the beaded or granular appearance and so it is also called granular endoplasmic reticulum (Fig. 1-4).

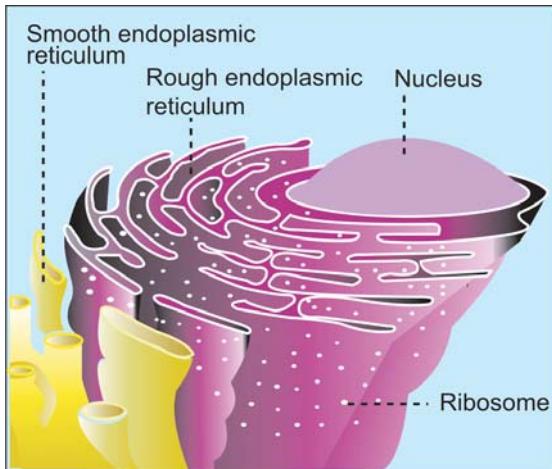


FIGURE 1-4: Endoplasmic reticulum

Functions of rough endoplasmic reticulum

It is concerned with the protein synthesis in the cell, especially those secreted from the cell such as insulin from β cells of islets of Langerhans in pancreas and antibodies in leukocytes.

It also plays an important role in degradation of worn out cytoplasmic organelles like mitochondria. It wraps itself around the worn out organelles and forms a vacuole which is often called the autophagosome. It is digested by lysosomal enzymes.

Smooth Endoplasmic Reticulum

Smooth endoplasmic reticulum is also called as agranular endoplasmic reticulum because of its smooth appearance without the attachment of ribosome. It is formed by many interconnected tubules. So, it is also called tubular endoplasmic reticulum.

Functions of smooth endoplasmic reticulum

- It is responsible for synthesis of cholesterol and steroid
- It is concerned with various metabolic processes of the cell because of the presence of many enzymes on the outer surface
- It is concerned with the storage and metabolism of calcium
- It is also concerned with catabolism and detoxification of toxic substances like some

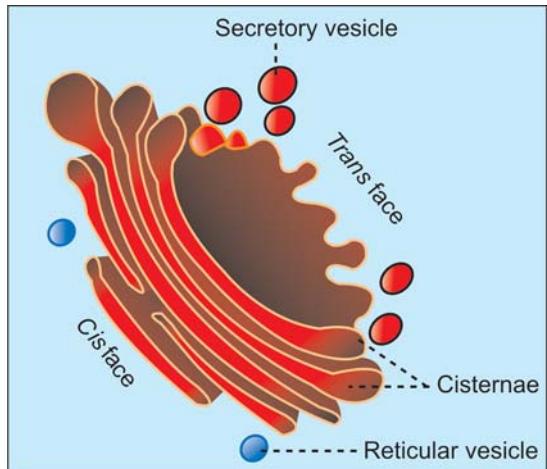


FIGURE 1-5: Golgi apparatus

drugs and carcinogens (cancer producing substances) in liver.

Rough endoplasmic reticulum and smooth endoplasmic reticulum are interconnected and continuous with one another. Depending upon the activities of the cells, the rough endoplasmic reticulum changes to smooth endoplasmic reticulum and vice versa.

2. GOLGI APPARATUS

Golgi apparatus (Golgi body or Golgi complex) is present in all the cells except red blood cells. It consists of 5 to 8 flattened membranous sacs called cisternae (Fig. 1-5).

The Golgi apparatus is situated near the nucleus. It has two ends or faces namely, *cis* face and *trans* face. The *cis* face is positioned near the endoplasmic reticulum. The reticular vesicles from endoplasmic reticulum enter the Golgi apparatus through *cis* face. The *trans* face is situated near the cell membrane. The processed substances make their exit from Golgi apparatus through *trans* face.

Functions of Golgi Apparatus

- It is concerned with the processing and delivery of substances like proteins and lipids to different parts of the cell.
- It functions like a post office because, it packs the processed materials into the secretory granules, secretory vesicles, and lysosomes

and dispatch them either out of the cell or to another part of the cell.

- iii. It also functions like a shipping department of the cell because it sorts out and labels the materials for distribution to their proper destinations.

n 3. LYSOSOMES

These are small globular structures filled with enzymes. These enzymes are synthesized in rough endoplasmic reticulum and transported to the Golgi apparatus. Here, these are processed and packed in the form of small vesicles. Then, these vesicles are pinched off from Golgi apparatus and become the lysosomes.

Types of Lysosomes

Lysosomes are of two types:

- i. Primary lysosome which is pinched off from Golgi apparatus. It is inactive in spite of having the hydrolytic enzymes.
- ii. Secondary lysosome which is active lysosome formed by the fusion of a primary lysosome with phagosome or endosome.

Functions of Lysosomes

i. *Digestion of unwanted substances*

With the help of hydrolytic enzymes like proteases, lipases, amylases and nucleases, lysosome digests and removes the unwanted substances.

ii. *Removal of excess secretory products in the cells*

Lysosomes in the cells of the secretory glands play an important role in the removal of excess secretory products by degrading the secretory granules.

iii. *Secretory function – Secretory lysosomes*

Recently, lysosomes having secretory function called secretory lysosomes are found in some of the cells, particularly in the cells of immune system. The conventional lysosomes are

modified into secretory lysosomes by combining with secretory granules

Examples of secretory lysosomes:

- a. In cytotoxic T lymphocytes and natural killer (NK) cells, lysosomes secrete perforin and granzymes which destroy both virus infected cells and tumor cells.
- b. In melanocytes, secretory lysosomes secrete melanin.
- c. In mast cells, secretory lysosomes secrete serotonin which is an inflammatory mediator

n 4. PEROXISOMES

Peroxisomes are otherwise called as micro bodies. These are pinched off from endoplasmic reticulum. Peroxisomes contain some oxidative enzymes such as catalase, urate oxidase and D-amino acid oxidase.

Functions of Peroxisomes

Peroxisomes:

- i. Degrade the toxic substances like hydrogen peroxide and other metabolic products by means of detoxification
- ii. Form the major site of oxygen utilization in the cells
- iii. Break down the excess fatty acids
- iv. Accelerate gluconeogenesis from fats
- v. Degrade purine to uric acid
- vi. Participate in the formation of myelin and bile acids.

n 5. CENTROSOME AND CENTRIOLES

The centrosome is situated near the center of the cell close to the nucleus. It consists of two cylindrical structures called centrioles which are responsible for the movement of chromosomes during cell division.

n 6. SECRETORY VESICLES

The secretory vesicles are globular structures, formed in the endoplasmic reticulum, and processed and packed in Golgi apparatus. When necessary, the secretory vesicles rupture and release the secretory substances into the cytoplasm.

n 7. MITOCHONDRION

The mitochondrion (pleural = mitochondria) is a rod or oval shaped structure with a diameter of 0.5 to 1 μ . It is covered by a double layered membrane (Fig. 1-6). The outer membrane is smooth and encloses the contents of mitochondrion. It contains various enzymes such as acetyl-CoA synthetase and glycerolphosphate acetyl-transferase.

The inner membrane forms many folds called cristae and covers the inner matrix space. The cristae also contain many enzymes and other protein molecules which are involved in respiration and ATP synthesis. Because of these functions, the enzymes and other protein molecules in cristae are collectively known as respiratory chain or electron transport system.

The mitochondria move freely in the cytoplasm of the cell and are capable of reproducing themselves. The mitochondria contain their own DNA which is responsible for many enzymatic actions.

Functions of Mitochondrion

i. Production of energy

The mitochondrion is called the 'power house of the cell' because it produces the energy required for the cellular functions. The energy is produced by oxidation of the food substances like proteins, carbohydrates and lipids by the oxidative enzymes in cristae. During oxidation, water and carbon dioxide are produced with release of energy. The released energy is stored in mitochondria and used later for synthesis of ATP.

ii. Synthesis of ATP

The components of respiratory chain in the mitochondrion are responsible for the synthesis of ATP by utilizing the energy through oxidative phosphorylation. The ATP molecules diffuse throughout the cell from mitochondrion. Whenever energy is needed for cellular activity, the ATP molecules are broken down.

iii. Apoptosis

Mitochondria are involved in apoptosis (see below) also.

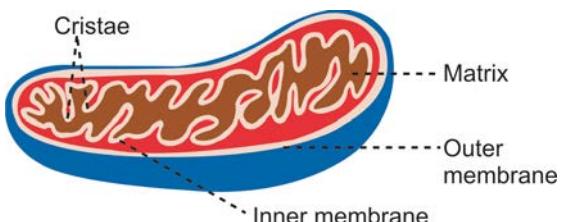


FIGURE 1-6: Structure of mitochondrion

n ORGANELLES WITHOUT LIMITING MEMBRANE

n 1. RIBOSOMES

The ribosomes are small granular structures with a diameter of 15 nm. Some ribosomes are attached to rough endoplasmic reticulum while others are present as free ribosomes in the cytoplasm. The ribosomes are made up of proteins (35%) and RNA (65%). The RNA present in ribosomes is called ribosomal RNA (rRNA).

Functions of Ribosomes

Ribosomes are called protein factories because of their role in the synthesis of proteins. Messenger RNA (mRNA) passes the genetic code for protein synthesis from nucleus to the ribosomes. The ribosomes, in turn arrange the amino acids into small units of proteins. The ribosomes attached with endoplasmic reticulum are involved in the synthesis of proteins like the enzymatic proteins, hormonal proteins, lysosomal proteins and the proteins of the cell membrane.

The free ribosomes are responsible for the synthesis of proteins in hemoglobin, peroxisome and mitochondria.

n 2. CYTOSKELETON

The cytoskeleton of the cell is a complex network that gives shape, support and stability to the cell. It is also essential for the cellular movements and the response of the cell to external stimuli. The cytoskeleton consists of three major protein components viz.

- a. Microtubules
- b. Intermediate filaments
- c. Microfilaments.

Microtubules

Microtubules are straight and hollow tubular structures formed by bundles of globular protein called α and β tubulin (Fig. 1-7 A).

Functions of microtubules

Microtubules:

- i. Determine the shape of the cell
- ii. Give structural strength to the cell
- iii. Act like conveyor belts which allow the movement of granules, vesicles, protein molecules and some organelles like mitochondria to different parts of the cell
- iv. Form the spindle fibers which separate the chromosomes during mitosis
- v. Responsible for the movements of centrioles and the complex cellular structures like cilia.

Intermediate Filaments

The intermediate filaments form a network around the nucleus and extend to the periphery of the cell. These filaments are formed by fibrous proteins (Fig. 1-7 B) and help to maintain the shape of the cell. The adjacent cells are connected by intermediate filaments by desmosomes.

Microfilaments

Microfilaments are long and fine thread like structures which are made up of non tubular contractile proteins called actin and myosin. Actin is more abundant than myosin.

Functions of microfilaments

Microfilaments:

- i. Give structural strength to the cell
- ii. Provide resistance to the cell against the pulling forces
- iii. Responsible for cellular movements like contraction, gliding and cytokinesis (partition of cytoplasm during cell division).

n NUCLEUS

Nucleus is present in those cells which divide and produce enzymes. The cells with nucleus

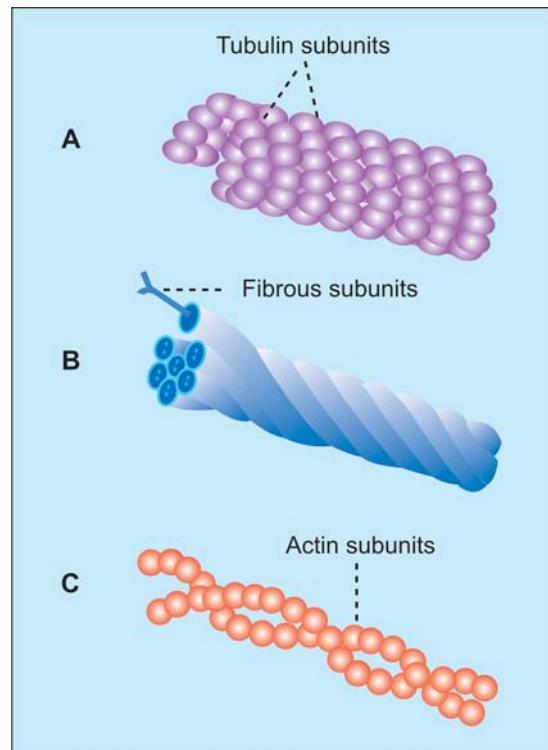


FIGURE 1-7: A = Microtubules. B = Intermediate filament. C = Microfilament of ectoplasm

are called eukaryotes and those without nucleus are known as prokaryotes (e.g. red blood cells). Prokaryotes do not divide or synthesize the enzymes.

Most of the cells have only one nucleus (uninucleated). Few types of cells like skeletal muscle cells have many nuclei (multinucleated). Generally the nucleus is located near the center of the cell. It is mostly spherical in shape. However, the shape and situation of nucleus vary in different cells.

n STRUCTURE OF NUCLEUS

Nuclear Membrane

The nucleus is covered by a double layered membrane called nuclear membrane. It encloses the fluid called nucleoplasm. Nuclear membrane is porous and permeable in nature and it allows nucleoplasm to communicate with the cytoplasm.

Nucleoplasm

It is a gel like ground substance and contains large quantities of the genetic material in the form of DNA. The DNA is made up of chromatin threads. These chromatin threads become the rod shaped chromosomes just before the cell division.

Nucleoli

One or more nucleoli are present in each nucleus. The nucleolus contains RNA and some proteins, which are similar to those found in ribosomes. The RNA is synthesized by chromosomes and stored in the nucleolus.

n FUNCTIONS OF NUCLEUS

Nucleus:

1. Controls all the activities of the cell
2. Synthesizes RNA
3. Forms subunits of ribosomes
4. Sends genetic instruction to the cytoplasm for protein synthesis through mRNA
5. Controls the cell division through genes
6. Stores the hereditary information (in genes) and transforms this information from one generation of the species to the next.

n CELL DEATH

The cell death occurs by two distinct processes:

1. Necrosis
2. Apoptosis.

n APOPTOSIS

Apoptosis is defined as the programmed cell death under genetic control. Originally apoptosis (means 'falling leaves' in Greek) refers to the process by which the leaves fall from trees in autumn. It is also called 'cell suicide' since the genes of the cell play a major role in the death.

This type of programmed cell death is a normal phenomenon and it is essential for normal development of the body.

Functional Significance of Apoptosis

The main function of apoptosis is to remove unwanted cells without causing any stress or damage to the neighboring cells. The functional significance of apoptosis:

1. Plays a vital role in cellular homeostasis. About 10 million cells are produced everyday in human body by mitosis. An equal number of cells die by apoptosis. This helps in cellular homeostasis
2. Useful for removal of a cell that is damaged by a virus or a toxin beyond repair
3. An essential event during the development and in adult stage.

Examples:

- i. A large number of neurons are produced during the development of central nervous system. But up to 50% of the neurons are removed by apoptosis during the formation of synapses between neurons
- ii. Apoptosis is responsible for the removal of tissues of webs between fingers and toes during developmental stage in fetus
- iii. It is necessary for regression and disappearance of duct systems during sex differentiation in fetus (Chapter 53)
- iv. The cell that loses the contact with neighboring cells or basal lamina in the epithelial tissue dies by apoptosis. This is essential for the death of old enterocytes shed into the lumen of intestinal glands (Chapter 31)
- v. It plays an important role in the cyclic sloughing of the inner layer of endometrium resulting in menstruation (Chapter 55)
- vi. Apoptosis removes the auto-aggressive T cells and prevents autoimmune diseases.

n NECROSIS

Necrosis (means 'dead' in Greek) is the uncontrolled and unprogrammed death of cells

due to unexpected and accidental damage. It is also called 'cell murder' because the cell is killed by extracellular or external events. After necrosis, the harmful chemical substances released from the dead cells cause damage and inflammation of neighboring tissues.

Causes for Necrosis

Common causes of necrosis are injury, infection, inflammation, infarction and cancer. Necrosis is induced by both physical and chemical events such as heat, radiation, trauma, hypoxia due to lack of blood flow, and exposure to toxins.

2

Cell Junctions

- DEFINITION AND CLASSIFICATION
- OCCLUDING JUNCTIONS
 - TIGHT JUNCTION
- COMMUNICATING JUNCTIONS
 - GAP JUNCTION
 - CHEMICAL SYNAPSE
- ANCHORING JUNCTIONS
 - ADHERENS JUNCTIONS
 - FOCAL ADHESIONS
 - DESMOSOME
 - HEMIDESMOSOME

■ DEFINITION AND CLASSIFICATION

The connection between the cells or the contact between the cell and extracellular matrix is called the cell junction. It is also called as membrane junction. It is generally classified into three types:

1. Occluding junction
2. Communicating junction
3. Anchoring junction

■ OCCLUDING JUNCTION

The junction which prevents the movement of ions and molecules from one cell to another cell is called the occluding junction. Tight junctions belong to this category.

■ TIGHT JUNCTION

It is formed by the tight fusion of the cell membranes from the adjacent cells. The area

of the fusion is very tight and forms a ridge. This type of junction is present in the apical margins of epithelial cells in intestinal mucosa, wall of renal tubule, capillary wall and choroid plexus (Fig. 2-1).

Functions of Tight Junctions

1. The tight junctions hold the neighboring cells of the tissues firmly and thus provide strength and stability to the tissues.
2. It provides the barrier or gate function by which the interchange of ions, water and macromolecules between the cells is regulated.
3. It acts like a fence by preventing the lateral movement of integral membrane proteins and lipids from cell membrane
4. By the fencing function, the tight junctions maintains the cell polarity by keeping the

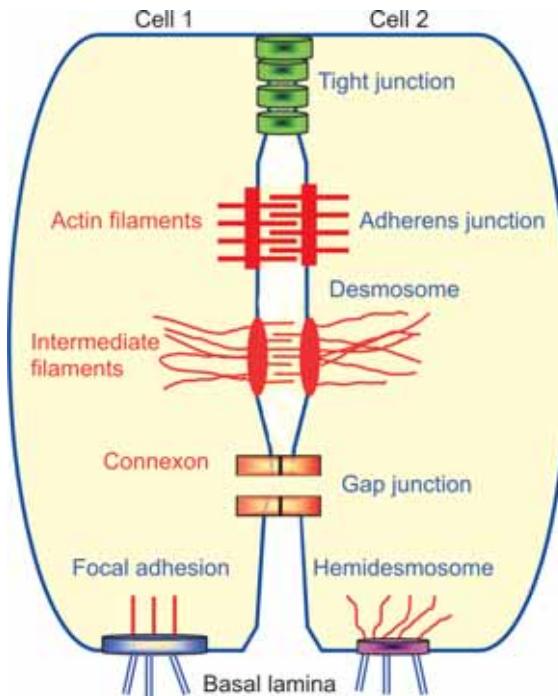


FIGURE 2-1: Different types of cell junctions

proteins in the apical region of the cell membrane.

5. Tight junctions in the brain capillaries form the blood-brain barrier (BBB) which prevents the entrance of many harmful substances from the blood into the brain tissues.

■ COMMUNICATING JUNCTIONS

The junctions, which permit the movement of ions and molecules from one cell to another cell, are called communicating junctions. Gap junction and chemical synapse are the communicating junctions.

■ GAP JUNCTION OR NEXUS

The gap junction is also called nexus. It is present in heart, basal part of epithelial cells of intestinal mucosa, etc.

Structure of Gap Junction

The membranes of the two adjacent cells lie very close to each other and the intercellular space

becomes a narrow channel. The cytoplasm of the two cells is interconnected and the molecules move from one cell to another cell through these channels without having contact with ECF. The channel is surrounded by 6 subunits of proteins which are called connexins or connexons.

Functions of Gap Junction

1. The diameter of the channel in the gap junction is about 1.5 to 3 nm. So, the substances having molecular weight less than 1000 such as glucose also can pass through this junction easily
2. It helps in the exchange of chemical messengers between the cells
3. It helps in rapid propagation of action potential from one cell to another cell.

■ CHEMICAL SYNAPSE

Chemical synapse is the junction between a nerve fiber and a muscle fiber or between two nerve fibers, through which the signals are transmitted by the release of chemical transmitter (Refer Chapter 86 for details).

■ ANCHORING JUNCTIONS

Anchoring junctions are the junctions, which provide firm structural attachment between two cells or between a cell and the extracellular matrix. There are four types of anchoring junctions

- i. Adherens junctions (cell to cell)
- ii. Focal adhesions (cell to matrix)
- iii. Desmosomes (cell to cell)
- iv. Hemidesmosomes (cell to matrix)

■ ADHERENS JUNCTIONS

These are cell to cell junctions that is the junctions found between the cells. The connection occurs through the actin filaments. Adherens junctions are present in the intercalated discs of cardiac muscles (Chapter 58) and epidermis of the skin.

■ FOCAL ADHESIONS

These are cell to matrix junctions that are junctions between the cell and the extracellular matrix. The connection occurs through the actin filaments. This type of junction is seen in epithelia of various organs.

■ DESMOSOME

Desmosome is also cell to cell junction, but here the membranes of the cells are thickened and connected by intermediate filaments. So,

desmosome functions like tight junction. This type of junction is found in areas subjected for stretching such as the skin.

■ HEMIDESMOSOME

Hemidesmosome is also cell to matrix junction and the connection is through intermediate filaments. It is like half desmosome because here, the membrane of only one cell thickens. So, this is known as hemidesmosome or half desmosome. Mostly, the hemidesmosome connects the cells with their basal lamina.

3

Transport through Cell Membrane

- INTRODUCTION
- BASIC MECHANISM OF TRANSPORT
- PASSIVE TRANSPORT
 - SIMPLE DIFFUSION
 - FACILITATED OR CARRIER MEDIATED DIFFUSION
 - FACTORS AFFECTING RATE OF DIFFUSION
 - SPECIAL TYPES OF PASSIVE TRANSPORT
 - OSMOTIC PRESSURE
- ACTIVE TRANSPORT
 - MECHANISM OF ACTIVE TRANSPORT
 - CARRIER PROTEINS
 - SUBSTANCES TRANSPORTED BY ACTIVE TRANSPORT
 - TYPES OF ACTIVE TRANSPORT
 - PRIMARY ACTIVE TRANSPORT
 - SECONDARY ACTIVE TRANSPORT
 - SPECIAL CATEGORIES OF ACTIVE TRANSPORT
 - ENDOCYTOSIS
 - EXOCYTOSIS
 - TRANSCYTOSIS

■ INTRODUCTION

Transport mechanism in the body is necessary for the supply of essential substances like nutrients, water, electrolytes, etc. to the tissues and to remove the unwanted substances like waste materials, carbon dioxide, etc. from the tissues.

■ BASIC MECHANISM OF TRANSPORT

Two basic mechanisms for the transport of substances across the cell membrane are:

1. Passive mechanism
2. Active mechanism.

■ PASSIVE TRANSPORT

The transport of the substances along the concentration gradient or electrical gradient or both (electrochemical gradient) is called passive transport. Here, the substances move from the region of higher concentration to the region of lower concentration. It is also known as diffusion or downhill movement. It does not need

energy. Diffusion or passive transport is of two types:

1. Simple diffusion
2. Facilitated diffusion.

■ SIMPLE DIFFUSION

Simple diffusion is of two types:

1. Simple diffusion through lipid layer
2. Simple diffusion through protein layer

Simple Diffusion through Lipid Layer

Lipid soluble substances like oxygen, carbon dioxide and alcohol are transported by simple diffusion through the lipid layer of the cell membrane (Fig. 3-1A).

Simple Diffusion through Protein Layer

There are specific protein channels that extend from cell membrane through which the simple diffusion takes place. Water soluble substances like electrolytes are transported through these channels. These channels are selectively permeable to only one type of ion. Accordingly, the channels are named after the ions diffusing through these channels like sodium channels, potassium channels, etc.

Protein Channels

The protein channels are of two types:

1. Ungated channels which are opened continuously
2. Gated channels which are closed all the time and are opened only when required (Fig. 3-1B).

Gated channels

The gated channels are divided into three categories:

- i. Voltage gated channels which open by change in the electrical potential (Fig. 3-1C). Examples are the calcium channels present in neuromuscular junction (Chapter 24).
- ii. Ligand gated channels that open in the presence of hormonal substances (ligand). Examples are the sodium channels which are opened by acetylcholine in neuromuscular junction.
- iii. Mechanically gated channels which are opened by some mechanical factors like pressure and force. Examples are the sodium channels in pressure receptors called Pacinian corpuscles.

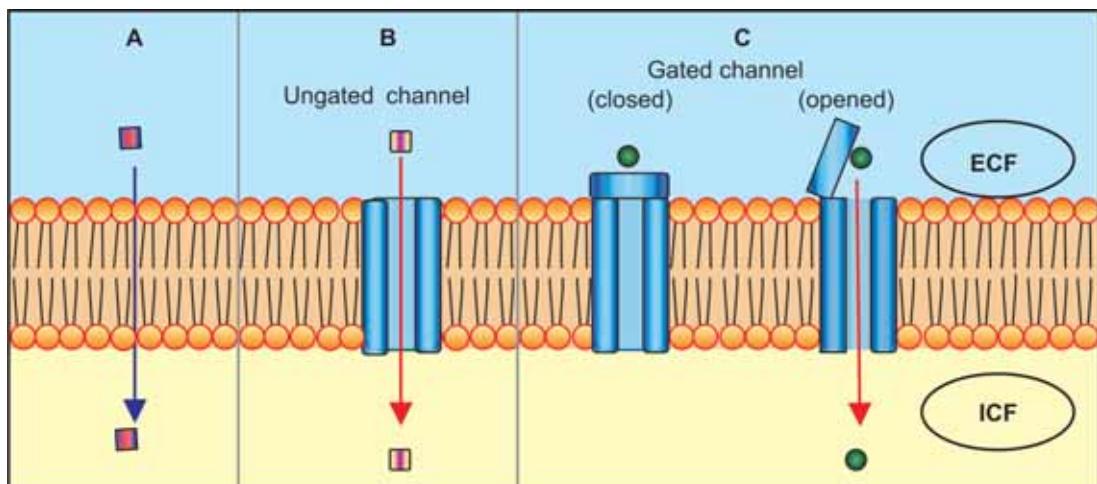


FIGURE 3-1: Hypothetical diagram of simple diffusion through the cell membrane. A = Diffusion through lipid layer. B = Diffusion through ungated channel. C = Diffusion through gated channel

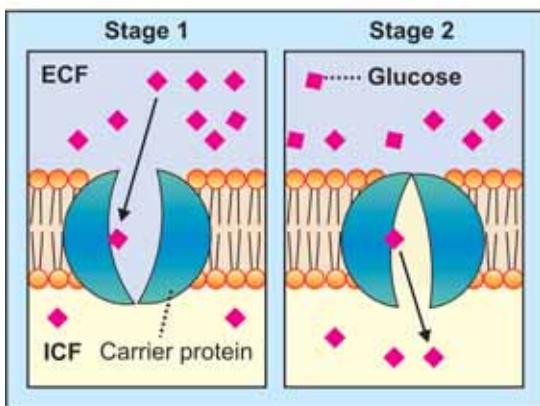


FIGURE 3-2: Hypothetical diagram of facilitated diffusion from higher concentration (ECF) to lower concentration (ICF). Stage 1: Glucose binds with carrier protein. Stage 2: Conformational change occurs in the carrier protein and glucose is released into ICF.

■ FACILITATED OR CARRIER MEDIATED DIFFUSION

In this type of diffusion, some carrier proteins help the transport of substances. The water soluble substances with larger molecules cannot pass through the protein channels by simple diffusion. Such substances are transported with the help of carrier proteins. This type of diffusion is faster than the simple diffusion. Glucose and amino acids are transported by this method (Fig. 3-2).

■ FACTORS AFFECTING RATE OF DIFFUSION

The rate of diffusion of substances through the cell membrane is directly proportional to the following factors:

1. Permeability of the cell membrane
2. Body temperature
3. Concentration gradient or electrical gradient of the substance across the cell membrane
4. Solubility of the Substance

The rate of diffusion of substances through the cell membrane is inversely proportional to the following factors:

1. Thickness of the cell membrane
2. Charge of the ions
3. Size of the molecules.

■ SPECIAL TYPES OF PASSIVE TRANSPORT

In addition to diffusion there are some special types of passive transport viz.

1. Bulk flow
2. Filtration
3. Osmosis

Bulk Flow

The diffusion of large quantity of substances from a region of high pressure to the region of low pressure is known as bulk flow. Bulk flow is due to the pressure gradient of the substance across the cell membrane. The best example for this is the exchange of gases across the respiratory membrane in lungs (Chapter 76).

Filtration

The movement of water and solutes from an area of high hydrostatic pressure to an area of low hydrostatic pressure is called filtration. The hydrostatic pressure is developed by the weight of the fluid. Filtration process is seen at the arterial end of the capillaries where movement of fluid occurs along with dissolved substances from blood into the interstitial fluid (Chapter 19). It also occurs in glomeruli of kidneys (Chapter 37).

Osmosis

Osmosis is the special type of diffusion. It is the movement of water or any other solvent from an area of lower concentration to an area of higher concentration through a semipermeable membrane (Fig. 3-3).

Osmosis is of two types:

- i. Endosmosis by which water moves into the cell
- ii. Exosmosis by which water moves outside the cell.

Osmotic Pressure

The pressure created by the solutes in a fluid is called osmotic pressure. During osmosis, when water or any other solvent moves from the area of lower concentration to the area of higher concentration, the solutes in the area of higher

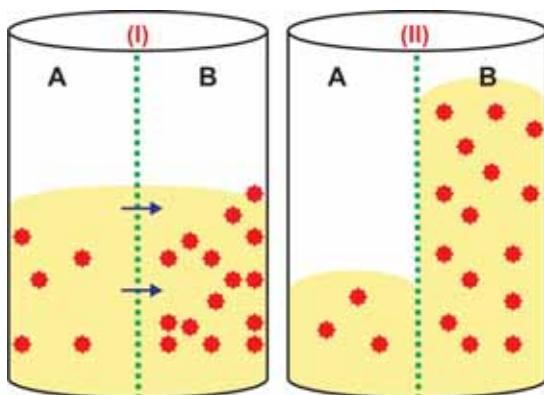


FIGURE 3-3: Osmosis. Red objects = solute. Yellow shade = water. Green dotted line = semipermeable membrane. In (I), concentration of solute is high in the compartment B and low in compartment A. So, water moves from A to B through semipermeable membrane. In (II), entrance of water into B exerts osmotic pressure

concentration get dissolved in the solvent. This creates a pressure which is known as osmotic pressure.

Colloidal Osmotic Pressure and Oncotic Pressure

The osmotic pressure exerted by the colloidal substances in the body is called the colloidal osmotic pressure. And, the osmotic pressure exerted by the colloidal substances (proteins) of the plasma is known as oncotic pressure and it is about 25 mm Hg.

■ ACTIVE TRANSPORT

Movement of substances against the chemical or electrical or electrochemical gradient is called active transport. It is also called uphill transport. Active transport requires energy which is obtained mainly by breakdown of ATP. It also needs a carrier protein.

■ MECHANISM OF ACTIVE TRANSPORT

When a substance to be transported across the cell membrane comes near the cell, it combines with the carrier protein of the cell membrane and

forms substance – protein complex. This complex moves towards the inner surface of the cell membrane. Now, the substance is released from the carrier proteins. The same carrier protein moves back to the outer surface of the cell membrane to transport another molecule of the substance.

■ CARRIER PROTEINS

There are two types of carrier proteins:

1. Uniport
2. Symport or antiport

Uniport

The carrier protein that can carry only one substance in a single direction is called uniport. It is also known as uniport pump.

Symport and antiport

The carrier protein that transports two different substances in the same direction is called symport. The carrier protein that transports two different substances in opposite directions is called antiport.

■ SUBSTANCES TRANSPORTED BY ACTIVE TRANSPORT

The actively transported substances are in ionic form and nonionic form. The substances in ionic form are sodium, potassium, calcium, hydrogen, chloride and iodide. The substances in nonionic form are glucose, amino acids and urea.

■ TYPES OF ACTIVE TRANSPORT

The active transport is of two types:

1. Primary active transport
2. Secondary active transport.

■ PRIMARY ACTIVE TRANSPORT

In primary active transport, the energy is liberated directly from the breakdown of ATP. By this method, the substances like sodium, potassium, calcium, hydrogen and chloride are transported across the cell membrane.

Primary Active Transport of Sodium and Potassium: Sodium-Potassium Pump

Sodium and potassium ions are transported across the cell membrane by sodium-potassium (Na^+ - K^+) pump which is also called Na^+ - K^+ ATPase pump. This pump is formed by a carrier protein and it is present in all cells of the body. Three sodium ions from inside and two potassium ions from outside get attached with the carrier protein (Fig. 3-4, Stage 1). Some conformational change occurs in the carrier protein by which the attachment with sodium ions faces the ECF and the attachment with potassium ions faces the ICF. Now the three sodium ions are released into ECF and two potassium ions are released into ICF (Fig. 3-4, Stage 2). It is responsible for the establishment of resting membrane potential (RMP) in the cell by distributing more sodium ions outside and more potassium ions inside. This action is called electrogenic activity of Na^+ - K^+ pump

Transport of Calcium Ions

Calcium ions are actively transported from inside to outside the cell by calcium pump with the help of a separate carrier protein. The energy is obtained from ATP.

Transport of Hydrogen Ions

Hydrogen ions are actively transported across the cell membrane by hydrogen pump with the help of another carrier protein. It also obtains energy from ATP.

■ SECONDARY ACTIVE TRANSPORT

The transport of a substance with sodium ions by a common carrier protein is called secondary active transport. It is of two types:

1. Co-transport — transport of the substance in the same direction along with sodium
2. Counter transport — transport of the substance in the opposite direction to that of sodium

Sodium Co-transport

In this, along with sodium, another substance is carried with the help of a carrier protein called

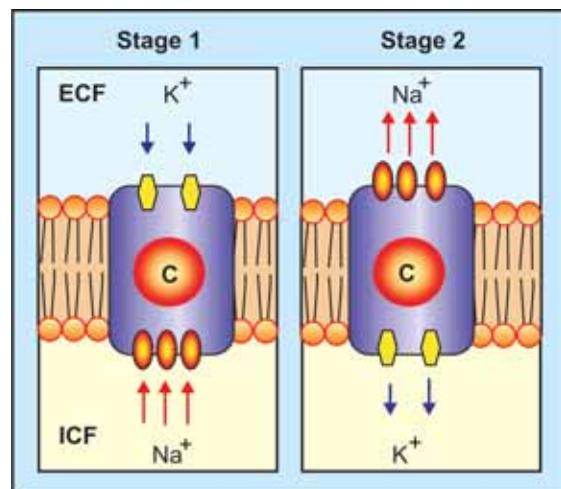


FIGURE 3-4: Hypothetical diagram of sodium-potassium pump. C = carrier protein. Stage 1: Three Na^+ from ICF and two K^+ from ECF bind with 'C'. Stage 2: Conformational change occurs in 'C' followed by release of Na^+ into ECF and K^+ into ICF

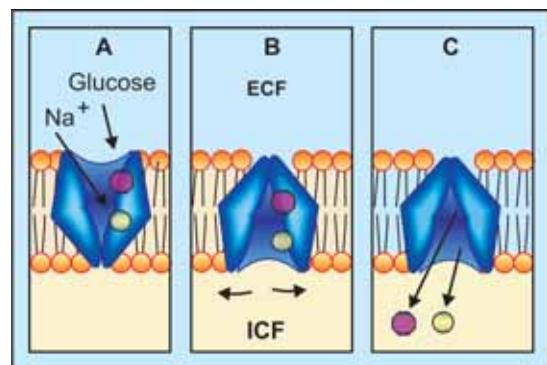


FIGURE 3-5: Sodium co-transport. A = Na^+ and glucose from ECF bind with carrier protein. B = Conformational change occurs in the carrier protein. C = Na^+ and glucose are released into ICF

symport (the protein that transports two different molecules in the same direction across the cell membrane). Glucose, amino acids, chloride, iodine, iron and urate ions are transported by this method (Fig. 3-5).

Sodium Counter Transport

In this process, the substances are transported across the cell membrane in exchange for sodium ions by the carrier protein called antiport (the

carrier protein that transports two different ions or molecules in opposite direction across the cell membrane). Examples of counter transport systems are sodium-calcium counter transport and sodium-hydrogen counter transport in the tubular cells (Figs 3-6 and 3-7).

SPECIAL CATEGORIES OF ACTIVE TRANSPORT

In addition to primary and secondary active transport systems, some special categories of active transport systems also exist in the body. The special categories of active transport are:

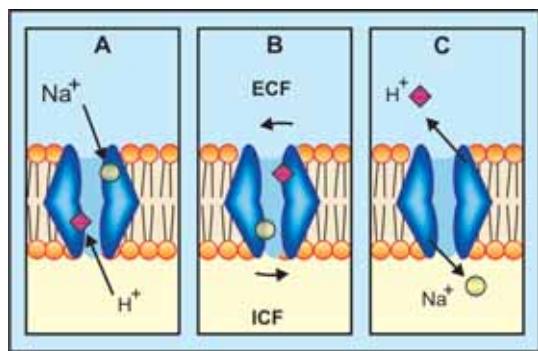


FIGURE 3-6: Sodium counter transport. A = Na^+ from ECF and H^+ from ICF bind with carrier protein. B = Conformational change occurs in the carrier protein. C = Na^+ enters ICF and H^+ enters ECF

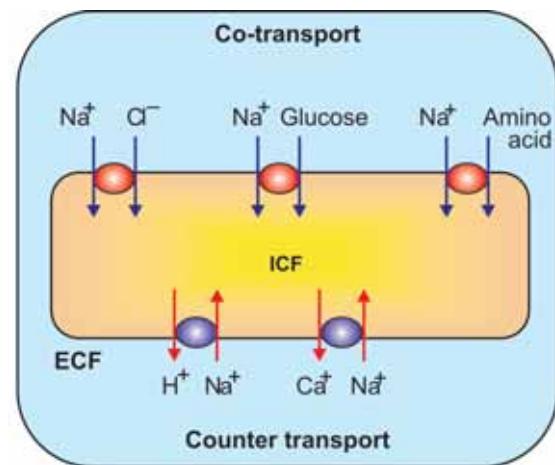


FIGURE 3-7: Sodium co-transport and counter transport by carrier proteins

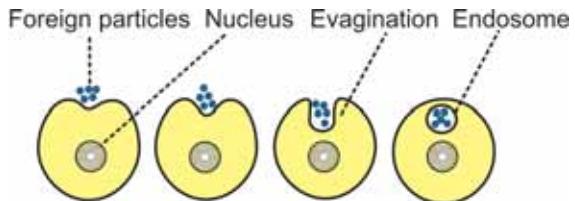


FIGURE 3-8: Process of pinocytosis

- I. Endocytosis
- II. Exocytosis
- III. Transcytosis.

ENDOCYTOSIS

Endocytosis is the transport mechanism by which the macromolecules enter the cell. The substances with larger molecules are called macromolecules and these cannot pass through the cell membrane either by active or by passive transport mechanism. Such substances are transported into the cell by endocytosis.

Endocytosis is of three types:

1. Pinocytosis
2. Phagocytosis
3. Receptor mediated endocytosis.

1. Pinocytosis

It is otherwise called the cell drinking. The macromolecules like bacteria and antigens enter the cells by pinocytosis.

Mechanism of pinocytosis

- i. The macromolecules (in the form of droplets of fluid) bind to the outer surface of the cell membrane
- ii. Now, the cell membrane evaginates and engulfs the droplets
- iv. The engulfed droplets are converted into vesicles and vacuoles, which are called endosomes (Fig. 3-8)
- v. The endosome travels into the interior of the cell
- vi. The primary lysosome in the cytoplasm fuses with the endosome and forms the secondary lysosome

- vii. Now, hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the endosomal contents.

2. Phagocytosis

The process by which the particles larger than the macromolecules are engulfed into the cells is called phagocytosis or cell eating. Larger bacteria, larger antigens and other larger foreign bodies are taken inside the cell by means of phagocytosis. Only few cells in the body like neutrophils, monocytes and the tissue macrophages show phagocytosis. Among these cells, the macrophages are the largest phagocytic cells.

Mechanism of phagocytosis

- i. When the bacteria or the foreign body enters the body, first the phagocytic cell sends cytoplasmic extension (pseudopodium) around the bacteria or the foreign body
- ii. Then, these particles are engulfed and are converted into endosome like vacuole. The vacuole is very large and it is usually called the phagosome
- iii. The phagosome travels into the interior of the cell
- iv. The primary lysosome fuses with this phagosome and forms secondary lysosome
- v. The hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the phagosomal contents (Fig. 3-9).

3. Receptor Mediated Endocytosis

Transport of macromolecules which is mediated by a receptor protein is called the receptor mediated endocytosis. The surface of cell membrane has some pits which contain a receptor protein called clathrin. Together with a receptor protein, each pit is called receptor coated pit. The coated pits are involved in the receptor mediated endocytosis.

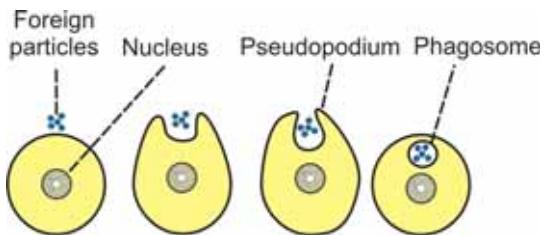


FIGURE 3-9: Process of phagocytosis

Mechanism of receptor mediated endocytosis

- i. The receptor mediated endocytosis is induced by substances like ligand (hormone) which bind to the receptors in the coated pits and form the ligand-receptor complexes
- ii. The ligand-receptor complexes get aggregated in the coated pits
- iii. Then, the pit is detached from the cell membrane and becomes the coated vesicle. This coated vesicle forms the endosome
- vi. The endosome travels into the interior of the cell (Fig. 3-10).

Receptor mediated endocytosis plays an important role in the transport of various types of macromolecules such as hormones, antibodies, lipids, growth factors, toxins, bacteria and viruses.

■ EXOCYTOSIS

Exocytosis is the process by which the substances are expelled from the cell. In this process, the substances are extruded from the cell without passing through the cell membrane. This is the reverse of endocytosis.

Mechanism of exocytosis

Secretory substances from the cells are released by exocytosis. The secretory substances of the cell are stored in the form of secretory vesicles in the cytoplasm. When required, the vesicles move towards the cell membrane and get fused with it. Later, the contents of the vesicles are released out of the cell (Fig. 3-11).

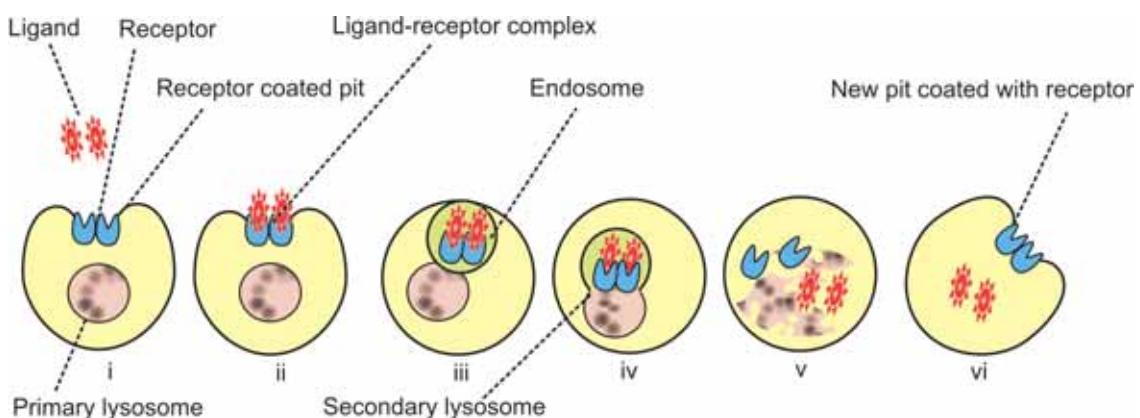


FIGURE 3-10: Mechanisms of receptor mediated endocytosis. The numbering of each figure corresponds with the numbers used in the text

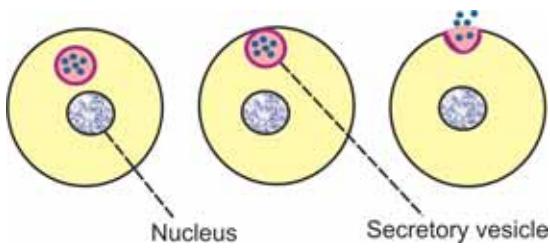


FIGURE 3-11: Exocytosis

■ TRANSCYTOSIS

Transcytosis is a transport mechanism in which an extracellular macromolecule enters through one side of a cell, migrates across cytoplasm of the cell and exits through the other side by means of exocytosis. Examples are movement of proteins and pathogens like HIV from capillary blood into interstitial fluid through endothelial cells of the capillary.

4

Homeostasis

- INTRODUCTION
- COMPONENTS OF HOMEOSTATIC SYSTEM
- HOMEOSTASIS AND VARIOUS SYSTEMS OF THE BODY
- MECHANISM OF ACTION OF HOMEOSTATIC SYSTEM

■ INTRODUCTION

"Homeostasis" means the maintenance of constant internal environment. According to Claude Bernard multicellular organisms including man live in a perfectly organized and controlled internal environment, which he called "Milieu interieur". The word 'Homeostasis' was introduced by Harvard Professor, Walter B Cannon in 1930.

The internal environment in the body is the ECF which contains nutrients, ions and all other substances necessary for the survival of the cells and in this environment the cells live. It includes the blood and interstitial fluid.

For the operation of homeostatic mechanism, the body must recognize the deviation of any physiological activity from the normal limits. Fortunately, body is provided with appropriate detectors or sensors, which recognize the deviation and alert the integrating center. The integrating center immediately sends information to the concerned effectors to either accelerate or inhibit the activity so that the normalcy is restored.

■ COMPONENTS OF HOMEOSTATIC SYSTEM

The homeostatic system in the body acts through self regulating devices, which operate in a cyclic manner (Fig. 4-1). This cycle includes three components:

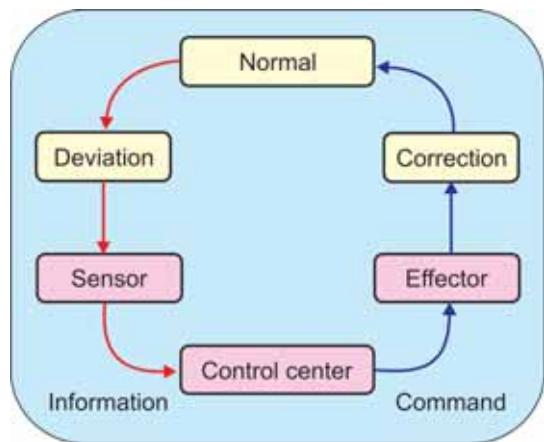


FIGURE 4-1: Components of homeostatic system

1. Detectors or sensors, which recognize the deviation
2. Control center to which the information regarding deviation is transmitted
3. Effectors which receive the information from the central control for correcting the deviation

The transmission of the message or information may be an electrical process in the form of impulses through nerves or a chemical process in the form of mainly hormones through blood and body fluids.

■ HOMEOSTASIS AND VARIOUS SYSTEMS OF THE BODY

One or more systems are involved in homeostatic mechanism of each function. Some of the functions in which the homeostatic mechanism is well established are given below.

1. The pH of the ECF has to be maintained at the critical value of 7.4. The tissues cannot survive if it is altered. Thus, the decrease in pH (acidosis) or increase in pH (alkalosis) affects the tissues markedly. The respiratory system, blood and kidney help in the regulation of pH.
2. The body temperature must be maintained at 37.5°C. Increase or decrease in temperature alters the metabolic activities of the cells. The skin, respiratory system, digestive system, excretory system, skeletal muscles and nervous system are involved in maintaining the temperature within normal limits.
3. Adequate amount of nutrients must be supplied to the cells for various activities and growth of the tissues. Digestive system and circulatory system play major roles in the supply of nutrients.
4. Adequate amount of oxygen should be supplied to the cells for the metabolic processes and the carbon dioxide and other metabolic end products must be removed from the cells. Respiratory system and excretory systems involved in these activities.

5. Many hormones are essential for the metabolism of nutrients and other substances necessary for the cells. The hormones are to be synthesized and released from the endocrine glands in appropriate quantities and, these hormones must act on the body cells appropriately. Otherwise, it leads to abnormal signs and symptoms.
6. Water and electrolyte balance should be maintained optimally. Otherwise it leads to dehydration or water toxicity and alteration in the osmolality of the body fluids. Kidneys, skin, salivary glands and gastrointestinal tract take care of this.
7. For all these functions, the blood, which forms the major part of internal environment, must be normal. It should contain required number of normal red blood cells and adequate amount of plasma with normal composition. Only then, it can transport the nutritive substances, respiratory gases, metabolic and other waste products.
8. Skeletal muscles also help in homeostasis by helping the organism to move around in search of food and protect the organism from adverse surroundings of damage and destruction.
9. The central nervous system which includes brain and spinal cord also plays an important role in homeostasis. The sensory system detects the state of the body or surroundings. The brain integrates and interprets the pros and cons of these information and commands the body to act accordingly through motor system so that, the body can avoid the damage.
10. The autonomic nervous system regulates all the vegetative functions of the body essential for homeostasis.

■ MECHANISM OF ACTION OF HOMEOSTATIC SYSTEM

The homeostatic system acts through feedback mechanism. Feedback is a process in which

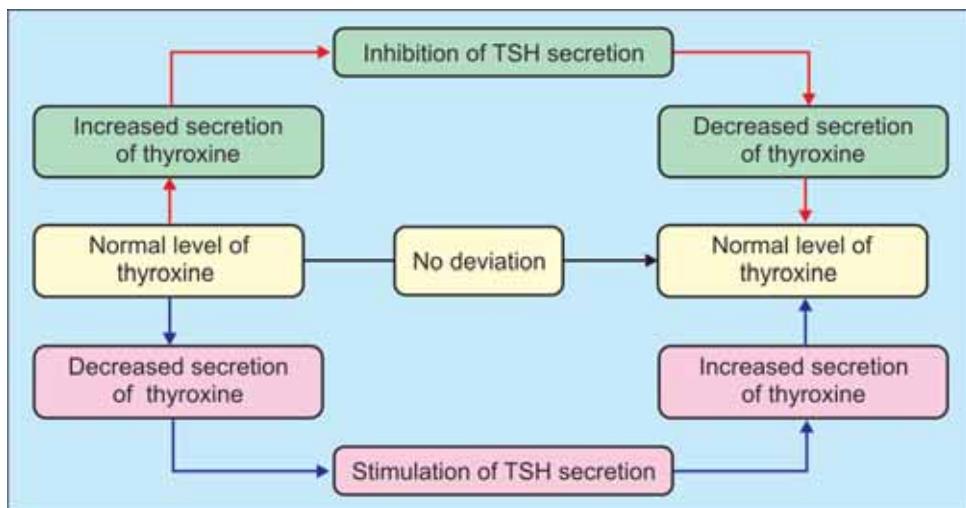


FIGURE 4-2: Negative feedback mechanism — secretion of thyroxine

some proportion of the output signal of a system is fed (passed) back to the input. There are two types of feedback mechanisms:

1. Negative feedback mechanism
2. Positive feedback mechanism

Negative Feedback Mechanism

Negative feedback mechanism is the one by which a particular system reacts in such a way as to stop the change or reverse the direction of change. After receiving a message, the effectors send the inhibitory signals back to the system. Now, the system stabilizes its own function either by stopping the signals or by reversing the signals.

For example, thyroid stimulating hormone (TSH) released from pituitary gland stimulates thyroid gland which in turn secretes thyroxine. When thyroxin level increases in blood, it inhibits the secretion of TSH from pituitary so that, the secretion of thyroxine from thyroid gland decreases (Fig. 4-2). On the other hand, if thyroxin secretion is less, it induces pituitary gland to release TSH. Now, TSH stimulates thyroid gland to secrete thyroxine (Refer Chapter 46 for details). Another example for negative feedback mechanism is maintenance of water balance in the body (Fig. 4-3).

Positive Feedback Mechanism

Positive feedback mechanism is the one in which the system reacts in such a way as to amplify (increase the intensity of) the change in the same direction. Positive feedback is less common than the negative feedback. However, it has its own significance, particularly during emergency conditions.

One of the positive feedbacks occurs during the blood clotting. Blood clotting is necessary to arrest bleeding during injury and it occurs in three stages:

- i. Formation of prothrombin activator
- ii. Conversion of prothrombin into thrombin
- iii. Conversion of fibrinogen into fibrin by thrombin.

Thrombin formed in the second stage stimulates the formation of more prothrombin activator in addition to converting fibrinogen into fibrin, (Fig. 4-4). It causes formation of more and more amount of prothrombin activator so that the blood clotting process is accelerated and blood loss is prevented quickly (Chapter 15). Other processes where positive feedback occurs are milk ejection reflex (Chapter 45) and parturition (Fig. 4-5) and both the processes involve oxytocin secretion.

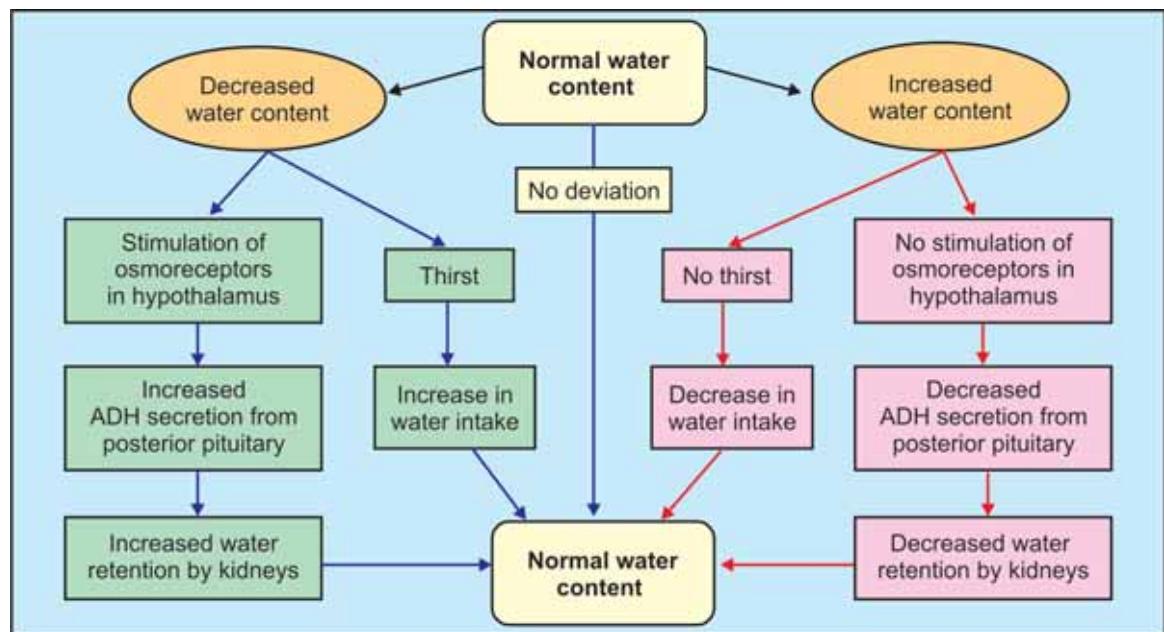


FIGURE 4-3: Negative feedback mechanism — maintenance of water balance

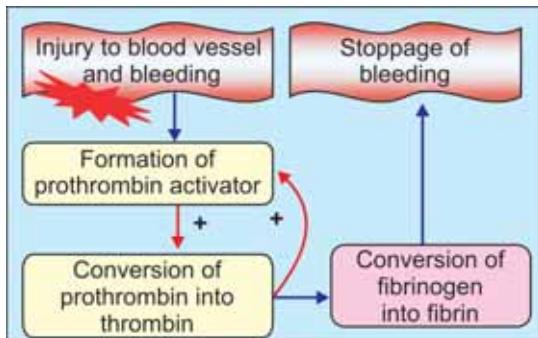


FIGURE 4-4: Positive feedback mechanism — coagulation of blood. Once formed, thrombin induces the formation of more prothrombin activator

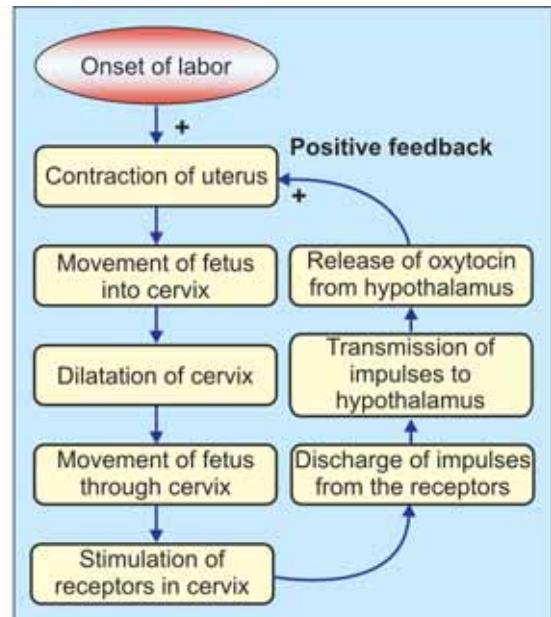


FIGURE 4-5: Positive feedback mechanism — parturition

QUESTIONS IN GENERAL PHYSIOLOGY

■ LONG QUESTIONS

1. Describe the mechanism of active transport of substances through cell membrane.
2. Describe the mechanism of passive transport of substances through cell membrane.
3. Explain the homeostasis in the body with suitable examples.

■ SHORT QUESTIONS

1. Cell membrane.
2. Proteins of cell membrane.
3. Endoplasmic reticulum.
4. Ribosomes.
5. Mitochondria.
6. Golgi apparatus

7. Apoptosis
8. Tight junctions.
9. Gap junctions.
10. Passive transport.
11. Active transport.
12. Primary active transport.
13. Secondary active transport.
14. Sodium-potassium pump.
15. Facilitated diffusion or carrier mediated diffusion.
16. Factors affecting diffusion.
17. Pinocytosis.
18. Phagocytosis.
19. Negative feedback.
20. Positive feedback

SECTION 2

Blood and Body Fluids

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5

Body Fluids

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- n COMPOSITION
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 - n INDICATOR DILUTION METHOD
 - n MEASUREMENT OF TOTAL BODY WATER
 - n MEASUREMENT OF EXTRACELLULAR FLUID VOLUME
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 - n MEASUREMENT OF BLOOD VOLUME
 - n MEASUREMENT OF INTRACELLULAR FLUID VOLUME
 - n MEASUREMENT OF INTERSTITIAL FLUID VOLUME
- n MAINTENANCE OF WATER BALANCE
- n APPLIED PHYSIOLOGY
 - n DEHYDRATION
 - n OVERHYDRATION OR WATER INTOXICATION

n INTRODUCTION

Body is formed by solids and fluids. The fluid part is more than 2/3 of the whole body. Water forms most of the fluid part of the body.

In human beings, the total body water (TBW) varies from 45 to 75% of body weight. In a normal young adult male, body contains 60 to 65% of water and 35 to 40% of solids. In a normal young adult female, the water is 50 to 55% and solids are 45 to 50%. The total quantity of body water in an average human being weighing about 70 kg is about 40 L.

n COMPARTMENTS OF BODY FLUIDS — DISTRIBUTION OF BODY FLUIDS

Compartments and distribution of body fluids with the quantity is given in Table 5-1. Water moves between different compartments (Fig. 5-1). TBW (40 L) is distributed into two major fluid compartments:

1. Intracellular fluid (ICF) forming 55% of the total body water (22 L).
2. Extracellular fluid (ECF) forming 45% of the total body water (18 L).

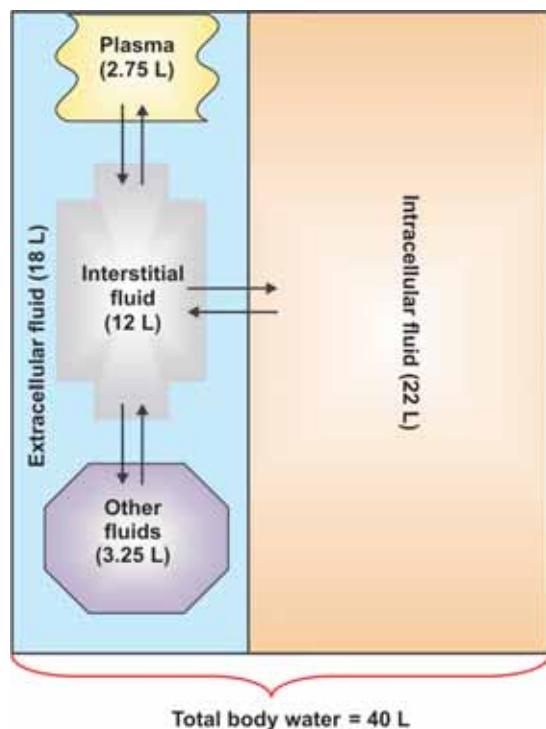


FIGURE 5-1: Body fluid compartments and movement of fluid between different compartments. Other fluids = transcellular fluid, fluid in bones and fluid in connective tissue

■ COMPOSITION OF BODY FLUIDS

Body fluids contain water and solids. Solids are organic and inorganic substances.

■ ORGANIC SUBSTANCES

Organic substances present in body fluids are glucose, amino acids and other proteins, fatty acids and other lipids, hormones and enzymes.

■ INORGANIC SUBSTANCES

The inorganic substances present in body fluids are sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate and sulfate. The differences between ECF and ICF are given in the Table 5-1.

TABLE 5-1: Different compartments of body fluid

Substance	ECF	ICF
Sodium	142 mEq/L	10 mEq/L
Calcium	5 mEq/L	1 mEq/L
Potassium	4 mEq/L	140 mEq/L
Magnesium	3 mEq/L	28 mEq/L
Chloride	103 mEq/L	4 mEq/L
Bicarbonate	28 mEq/L	10 mEq/L
Phosphate	4 mEq/L	75 mEq/L
Sulfate	1 mEq/L	2 mEq/L
Proteins	2 g/dL	16 g/dL
Amino acids	30 mg/dL	200 mg/dL
Glucose	90 mg/dL	0 to 20 mg/dL
Lipids	0.5 g/dL	2 to 95 g/dL
Partial pressure of oxygen	35 mm Hg	20 mm Hg
Partial pressure of carbon dioxide	46 mm Hg	50 mm Hg
Water	15 to 20 L (18)	20 to 25 L (22)
pH	7.4	7.0

■ MEASUREMENT OF BODY FLUID VOLUME

Volume of different compartments of the body fluid is measured by indicator dilution method or dye dilution method.

■ INDICATOR DILUTION METHOD

Principle

A known quantity of a substance such as a dye is administered into a specific body fluid compartment. These substances are called the marker substances or indicators. After administration into the fluid, the substance is allowed to mix thoroughly with the fluid compartment. Then, a sample of fluid is drawn and the concentration

of the marker substance is determined. The substances whose concentration can be determined by using colorimeter or radioactive substances are generally used as marker substances.

Formula to Measure the Body Fluid Volume by Indicator Dilution Method

The quantity of fluid in the compartment is measured by using the formula

$$V = \frac{M}{C}$$

V = Volume of fluid in the compartment

M = Mass or total quantity of marker substance injected

C = Concentration of the marker substance in the sample fluid

Correction factor: Some amount of marker substance is lost through urine during distribution. So, the formula is corrected as follows:

$$\text{Volume} = \frac{M - \text{Amount of substance excreted}}{C}$$

Characteristics of Marker Substances

The dye or any substance used as a marker substance should have the following qualities:

1. Must be nontoxic
2. Must mix with the fluid compartment thoroughly within reasonable time
3. Should not be excreted rapidly
4. Should be excreted from the body completely within reasonable time
5. Should not change the color of the body fluid
6. Should not alter the volume of body fluid.

n MEASUREMENT OF TOTAL BODY WATER

The marker substance for measuring TBW should be distributed through all the compartments of body fluid. Such substances are:

1. Deuterium oxide
2. Tritium oxide
3. Antipyrine.

Deuterium oxide and tritium oxide mix with fluids of all the compartments within few hours after injection. Since plasma is part of total body fluid, the concentration of marker substances can be obtained from sample of plasma. And, the formula for indicator dilution method is applied to calculate total body water.

n MEASUREMENT OF ECF VOLUME

ECF volume is measured by using the substances, which can pass through the capillary membrane freely and remain only in the ECF but not enter into the cell. Such marker substances are:

1. Radioactive sodium, chloride, bromide, sulfate and thiosulfate
2. Nonmetabolizable saccharides like inulin, mannitol, raffinose and sucrose.

When any of these substances is injected into blood, it mixes with the fluid of all subcompartments of ECF within 30 minutes to 1 hour. The indicator dilution method is applied to calculate ECF volume. Since ECF includes plasma, the concentration of marker substance can be obtained in the sample of plasma.

Some marker substances like sodium, chloride, inulin and sucrose diffuse more widely through all subcompartments of ECF. So, the measured volume of ECF by using these substances is called sodium space, chloride space, inulin space and sucrose space.

Example for Measurement of ECF Volume

Quantity of sucrose injected (M) : 150 mg

Urinary excretion of sucrose : 10 mg

Concentration of sucrose in plasma (C) : 0.01 mg/ml

$$\text{Sucrose space} = \frac{\text{Mass} - \text{Amount lost in urine}}{\text{Concentration of sucrose in plasma}}$$

$$= \frac{150 - 10 \text{ mg}}{0.01 \text{ mg/ml}} = \frac{140}{0.01}$$

$$\text{Sucrose space} = 14,000 \text{ ml}$$

Therefore, the ECF volume = 14 L.

n MEASUREMENT OF PLASMA VOLUME

The substance, which binds with plasma proteins strongly and diffuses into interstitium only in small quantities or does not diffuse at all, is used to measure plasma volume.

Measurement of Plasma Volume by Indicator or Dye Dilution Technique

The principles and other details of this technique are same as that of ECF volume. The dye which is used to measure plasma volume is Evans blue or T-1824.

Procedure: A small quantity of blood (3 to 4 ml) is drawn from the subject and a known quantity of the dye is added. This is used as control sample in the procedure. Then, a known volume of dye is injected intravenously. After 10 minutes, a sample of blood is drawn. Then, another 4 samples of blood are collected at the interval of 10 minutes. All the 5 samples are centrifuged and plasma is separated from the samples. In each sample of plasma, the concentration of the dye is measured by colorimetric method and the average concentration is found. The subject's urine is collected and the amount of dye excreted in the urine is measured.

Calculation

The plasma volume is determined by using the formula,

$$\text{Volume} = \frac{\text{Amount of dye injected} - \text{Amount excreted}}{\text{Average concentration of dye in plasma}}$$

n MEASUREMENT OF BLOOD VOLUME

Measurement of total blood volume involves two steps:

1. Determination of plasma volume
2. Determination of blood cell volume.

Plasma volume is determined by indicator dilution technique as mentioned above. Blood cell volume is determined by hematocrit value.

It is usually done by centrifuging the blood and measuring the packed cell volume (Chapter 10). PCV is expressed in percentage. If this is deducted from 100, the percentage of plasma is known. From this, and from the volume of plasma, the amount of total blood is calculated by using the formula

$$\text{Blood Volume} = \frac{100 \times \text{Amount of plasma}}{100 - \text{PCV}}$$

n MEASUREMENT OF INTRACELLULAR FLUID VOLUME

Intracellular fluid volume cannot be measured directly. It is calculated from the values of volume of total body water and ECF volume.

$$\text{ICF volume} = \text{Total fluid volume} - \text{ECF volume.}$$

n MEASUREMENT OF INTERSTITIAL FLUID VOLUME

Interstitial fluid volume also cannot be measured directly. It is calculated from the values of ICF volume and plasma volume.

$$\text{Interstitial fluid volume} = \text{ICF volume} - \text{Plasma volume.}$$

n MAINTENANCE OF WATER BALANCE

Body has several mechanisms which work together to maintain the water balance. The important mechanisms involve hypothalamus (Chapters 4 and 92) and kidneys (Chapter 34).

n APPLIED PHYSIOLOGY

n DEHYDRATION

Definition

Significant decrease in water content of the body is known as dehydration.

Classification

Basically dehydration is of three types:

1. Mild dehydration when fluid loss is about 5% of total body fluids.

2. Moderate dehydration when fluid loss is about 10%.
3. Severe dehydration when fluid loss is about 15%.

Causes

1. Severe diarrhea and vomiting
2. Excess water loss through urine
4. Insufficient intake of water
5. Excess sweating
6. Use of laxatives or diuretics.

Signs and Symptoms

Mild and moderate dehydration

1. Dryness of the mouth
2. Excess thirst
3. Decrease in sweating
4. Decrease in urine formation.

Severe dehydration

1. Decrease in blood volume
2. Decrease in cardiac output
3. Cardiac shock.

Very severe dehydration

1. Damage of organs like brain, liver and kidneys
2. Mental depression and confusion
3. Renal failure
4. Coma.

n OVERHYDRATION OR WATER INTOXICATION

Definition

Overhydration, hyperhydration, water excess or water intoxication is defined as the condition in which body has too much water.

Causes

Overhydration occurs when more fluid is taken than that can be excreted. It also develops in some conditions such as heart failure, renal disorders and hypersecretion of antidiuretic hormone.

Signs and Symptoms

1. Behavioral changes
2. Drowsiness and inattentiveness
3. Nausea and vomiting
4. Sudden loss of weight followed by weakness and blurred vision
5. Anemia, acidosis, cyanosis, hemorrhage and shock
6. Muscular weakness, cramps and paralysis
7. Severe conditions of overhydration result in:
 - i. Delirium (extreme mental condition characterized by confused state and illusion)
 - ii. Seizures (sudden uncontrolled involuntary muscular contractions)
 - iii. Coma (profound state of unconsciousness in which the person fails to respond to external stimuli and cannot perform voluntary actions).

6

Blood and Plasma Proteins

n BLOOD

n PROPERTIES

n COMPOSITION

n FUNCTIONS

n PLASMA PROTEINS

n NORMAL VALUES

n VARIATIONS IN PLASMA PROTEIN LEVEL

n ORIGIN

n PROPERTIES

n FUNCTIONS

n BLOOD

Blood is a connective tissue in fluid form. It is considered as the fluid of life because it carries oxygen from lungs to all parts of the body and carbon dioxide from all parts of the body to the lungs.

n PROPERTIES OF BLOOD

1. **Color:** Blood is red in color. Arterial blood is scarlet red because of more O₂ and venous blood is purple red because of more CO₂.
2. **Volume:** The average volume of blood in a normal adult is 5 L. In newborn baby it is 450 ml. It increases during growth and reaches 5 L at the time of puberty. In females, it is slightly less and is about 4.5 L. It is about 8% of the body weight in a normal young healthy adult weighing about 70 kg.
3. **Reaction and pH:** Blood is slightly alkaline and its pH in normal conditions is 7.4.

4. *Specific gravity:*

Specific gravity of total blood : 1.052 to 1.061

Specific gravity of blood cells : 1.092 to 1.101

Specific gravity of plasma : 1.022 to 1.026

5. **Viscosity:** Blood is five times more viscous than water. It is mainly due to red blood cells and plasma proteins.

n COMPOSITION OF BLOOD

Blood contains the blood cells which are called formed elements and the liquid portion known as plasma.

Blood Cells

Three types of cells are present in the blood:

1. Red blood cells (RBC) or erythrocytes
2. White blood cells (WBC) or leukocytes
3. Platelets or thrombocytes

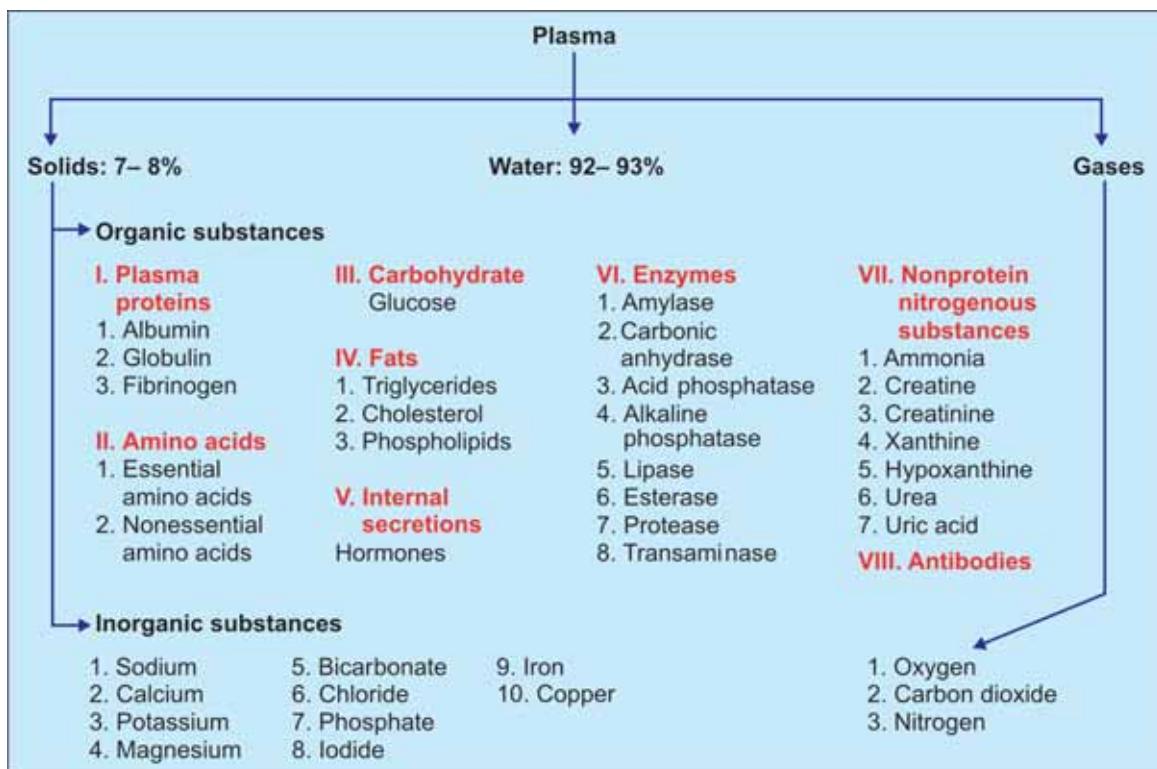


FIGURE 6-1: Composition of plasma

Plasma

Plasma is a straw colored clear liquid part of blood. It contains 91 to 92% of water and 8 to 9% of solids. The solids are the organic and inorganic substances (Fig. 6-1). Table 6-1 gives the normal values of some important substances in blood.

Serum

Serum is the clear straw colored fluid that oozes out from the clot. When the blood is shed or collected in a container, it clots because of the conversion of fibrinogen into fibrin. After about 45 minutes, serum oozes out of the clot. For clinical investigations, serum is separated from blood cells by centrifuging. Volume of the serum is almost the same as that of plasma (55%). It is different from plasma only by the absence of fibrinogen, i.e. serum contains all the other constituents of plasma except fibrinogen. Fibrinogen

TABLE 6-1: Normal values of some important substances in blood

Substance	Normal value
Glucose	100 to 120 mg/dL
Creatinine	0.5 to 1.5 mg/dL
Cholesterol	Up to 200 mg/dL
Plasma proteins	6.4 to 8.3 g/dL
Bilirubin	0.5 to 1.5 mg/dL
Iron	50 to 150 µg/dL
Copper	100 to 200 mg/dL
Calcium	9 to 11 mg/dL 4.5 to 5.5 mEq/L
Sodium	135 to 145 mEq/L
Potassium	3.5 to 5.0 mEq/L
Magnesium	1.5 to 2.0 mEq/L
Chloride	100 to 110 mEq/L
Bicarbonate	22 to 26 mEq/L

is absent in serum because it is converted into fibrin during blood clotting.

Thus, the Serum = Plasma – Fibrinogen.

n FUNCTIONS OF BLOOD

1. Nutrient Function

Nutritive substances like glucose, amino acids, lipids and vitamins derived from digested food are absorbed from gastrointestinal tract and carried by blood to different parts of the body for growth and production of energy.

2. Respiratory Function

Transport of respiratory gases is done by the blood. It carries O₂ from alveoli of lungs to different tissues and CO₂ from tissues to alveoli.

3. Excretory Function

Waste products formed in the tissues during various metabolic activities are removed by blood and carried to the excretory organs like kidney, skin, liver, etc. for excretion.

4. Transport of Hormones and Enzymes

Hormones which are secreted by ductless (endocrine) glands are released directly into the blood. The blood transports these hormones to their target organs/tissues. Blood also transports enzymes.

5. Regulation of Water Balance

Water content of the blood is freely interchangeable with interstitial fluid. This helps in the regulation of water content of the body.

6. Regulation of Acid-base Balance

The plasma proteins and hemoglobin act as buffers and help in regulation of acid-base balance.

7. Regulation of Body Temperature

Because of the high specific heat of blood, it is responsible for maintaining the thermoregulatory mechanism in the body, i.e. the balance between heat loss and heat gain in the body.

8. Storage Function

Water and some important substances like proteins, glucose, sodium and potassium are constantly required by the tissues. All these substances are present in the blood are taken by the tissues during the conditions like starvation, fluid loss, electrolyte loss, etc.

9. Defensive Function

The WBCs in the blood provide the defense mechanism and protect the body from the invading organisms. Neutrophils and monocytes engulf the bacteria by phagocytosis. Lymphocytes provide cellular and humoral immunity. Eosinophils protect the body by detoxification, disintegration and removal of foreign proteins (Chapter 12).

n PLASMA PROTEINS

The plasma proteins are:

1. Serum albumin
2. Serum globulin
3. Fibrinogen.

Globulin is of three types, α -globulin, β -globulin and γ -globulin.

n NORMAL VALUES

The normal values of the plasma proteins are:

Total proteins : 7.3 g/dL (6.4-8.3 g/dL)

Serum albumin : 4.7 g/dL

Serum globulin : 2.3 g/dL

Fibrinogen : 0.3 g/dL

Albumin/globulin Ratio

The ratio between plasma level of albumin and globulin is called Albumin/Globulin (A/G) ratio.

It is an important indicator of some liver and kidney diseases. Normal A/G ratio is 2:1.

n VARIATIONS IN PLASMA PROTEIN LEVEL

Hyperproteinemia

Hyperproteinemia is the elevation of all fractions of plasma proteins.

It occurs in the following conditions:

1. Dehydration
2. Hemolysis
3. Acute infections
4. Respiratory distress syndrome
5. Excess of glucocorticoids
6. Leukemia
7. Rheumatoid arthritis
8. Alcoholism.

Hypoproteinemia

Hypoproteinemia is the decrease in all fractions of plasma proteins.

It occurs in the following conditions:

1. Diarrhea
2. Hemorrhage
3. Burns
4. Pregnancy
5. Malnutrition
6. Prolonged starvation
7. Cirrhosis of liver
8. Chronic infections.

n ORIGIN OF PLASMA PROTEINS

In embryonic stage, the plasma proteins are synthesized by the mesenchyme cells. In adults, the plasma proteins are synthesized mainly from reticuloendothelial cells of liver and also from spleen, bone marrow, disintegrating blood cells and general tissue cells. Gamma globulin is synthesized from B lymphocytes.

n PROPERTIES OF PLASMA PROTEINS

Molecular Weight

Albumin : 69,000

Globulin : 1,56,000

Fibrinogen : 4,00,000

Specific Gravity

The specific gravity of the plasma proteins is 1.026.

Buffer Action

The acceptance of hydrogen ions is called buffer action. The plasma proteins have 1/6 of total buffering action of the blood.

n FUNCTIONS OF PLASMA PROTEINS

1. Role in Coagulation of Blood

Fibrinogen is essential for the coagulation of blood (Chapter 15).

2. Role in Defense Mechanism of Body

The gamma globulins play an important role in the defense mechanism of the body by acting as antibodies. These proteins are also called immunoglobulins (Chapter 13).

3. Role in Transport Mechanism

Plasma proteins are essential for the transport of various substances in the blood. Albumin, alpha globulin and beta globulin are responsible for the transport of the hormones, enzymes, etc. The alpha and beta globulins transport metals in the blood.

4. Role in Maintenance of Osmotic Pressure in Blood

Plasma proteins exert the colloidal osmotic (oncotic) pressure. The osmotic pressure exerted by the plasma proteins is about 25 mm Hg. Since the concentration of albumin is more than the other plasma proteins, it exerts maximum pressure.

5. Role in Regulation of Acid-base Balance

Plasma proteins, particularly the albumin, play an important role in regulating the acid-base balance in the blood. This is because of the virtue of their buffering action.

6. Role in Viscosity of Blood

The plasma proteins provide viscosity to the blood, which is important to maintain the blood pressure. Albumin provides maximum viscosity than the other plasma proteins.

7. Role in Erythrocyte Sedimentation Rate (ESR)

Globulin and fibrinogen accelerate the tendency of rouleaux formation by the red blood cells. Rouleaux formation is responsible for ESR, which is an important diagnostic and prognostic tool (Chapter 7).

8. Role in Suspension Stability of Red Blood Cells

During circulation, the red blood cells remain suspended uniformly in the blood. This property of the red blood cells is called the suspension

stability. Globulin and fibrinogen help in the suspension stability of the red blood cells.

9. Role in Production of Traphone Substances

Traphone substances are necessary for nourishment of tissue cells in culture. These substances are produced by leukocytes from the plasma proteins.

10. Role As Reserve Proteins

During fasting, inadequate food intake or inadequate protein intake, the plasma proteins are utilized by the body tissues as the last source of energy. The plasma proteins are split into amino acids by the tissue macrophages. The amino acids are taken back by blood and distributed throughout the body to form cellular protein molecules. Because of this, the plasma proteins are called the reserve proteins.

7

Red Blood Cells

- n INTRODUCTION
- n NORMAL VALUE
- n MORPHOLOGY
- n PROPERTIES
- n LIFESPAN
- n FATE
- n FUNCTIONS
- n VARIATIONS IN NUMBER
- n VARIATIONS IN SIZE
- n VARIATIONS IN SHAPE
- n HEMOLYSIS AND FRAGILITY

n INTRODUCTION

Red blood cells (RBCs), also known as erythrocytes are the non-nucleated formed elements in the blood. The red color of the RBC is due to the presence of hemoglobin.

n NORMAL VALUE

The RBC count ranges between 4 and 5.5 millions/cu mm of blood. In adult males, it is 5 millions/cu mm and in adult females it is 4.5 millions/cu mm.

n MORPHOLOGY OF RED BLOOD CELLS

n NORMAL SHAPE

Normally, the RBCs are disk-shaped and biconcave (dumbbell-shaped). The central

portion is thinner and periphery is thicker. The biconcave contour of RBCs has some mechanical and functional advantages.

Advantages of Biconcave Shape of RBCs

1. It helps in equal and rapid diffusion of oxygen and other substances into the interior of the cell.
2. Large surface area is provided for absorption or removal of different substances.
3. Minimal tension is offered on the membrane when the volume of cell alters.
4. While passing through minute capillaries, RBCs can squeeze through the capillaries easily without getting damaged.

n NORMAL SIZE

Diameter : 7.2μ (6.9 to 7.4μ).

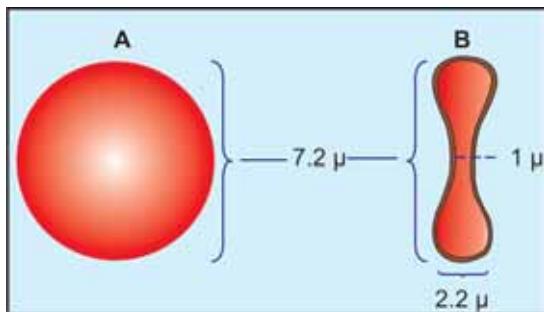


FIGURE 7-1: Dimensions of RBC. A: Surface view. B. Sectioned view



FIGURE 7-2: Rouleaux formation
(Courtesy: Dr Nivaldo Medeiros)

Thickness : At the periphery it is thicker with $2.2\text{ }\mu$ and at the center it is thinner with $1\text{ }\mu$ (Fig. 7-1). The difference in thickness is because of the biconcave shape.

Surface area : $120\text{ sq }\mu$.

Volume : 85 to $90\text{ cu }\mu$.

n NORMAL STRUCTURE

RBC is non-nucleated cell. Because of the absence of nucleus, the DNA is also absent. Other organelles such as mitochondria and Golgi apparatus also are absent in RBC. Since, mitochondria are absent, the energy is produced from glycolytic process.

n PROPERTIES OF RED BLOOD CELLS

n 1. ROULEAUX FORMATION

When blood is taken out of the blood vessel, the RBCs pile up one above another like the pile of coins. This property of the RBCs is called rouleaux (pleural = rouleau) formation (Fig. 7-2). It is accelerated by plasma proteins, namely globulin and fibrinogen.

n 2. SPECIFIC GRAVITY

The specific gravity of RBC is 1.092 to 1.101 .

n 3. PACKED CELL VOLUME

Packed cell volume (PCV) is the volume of the RBCs expressed in percentage. It is also called

hematocrit value. It is 45% of the blood and the plasma volume is 55% (Chapter 10).

n 4. SUSPENSION STABILITY

During circulation, the RBCs remain suspended or dispersed uniformly in the blood. This property of the RBCs is called the suspension stability.

n LIFESPAN OF RED BLOOD CELLS

Average lifespan of RBC is about 120 days. After the lifetime, the senile (old) RBCs are destroyed in reticuloendothelial system.

n FATE OF RED BLOOD CELLS

When the RBCs become older (120 days), the cell membrane becomes very fragile. So these cells are destroyed while trying to squeeze through the capillaries which have lesser or equal diameter as that of RBC. The destruction occurs mainly in the capillaries of spleen because these capillaries are very much narrow. So, the spleen is called graveyard of RBCs.

The destroyed RBCs are fragmented and hemoglobin is released from the fragmented parts. Hemoglobin is degraded into iron, globin and porphyrin. Iron combines with the protein called apoferritin to form ferritin, which is stored in the body and reused later. Globin enters the protein depot for later use (Fig. 7-3). The porphyrin is degraded into bilirubin which is excreted by liver through bile (Chapter 30).

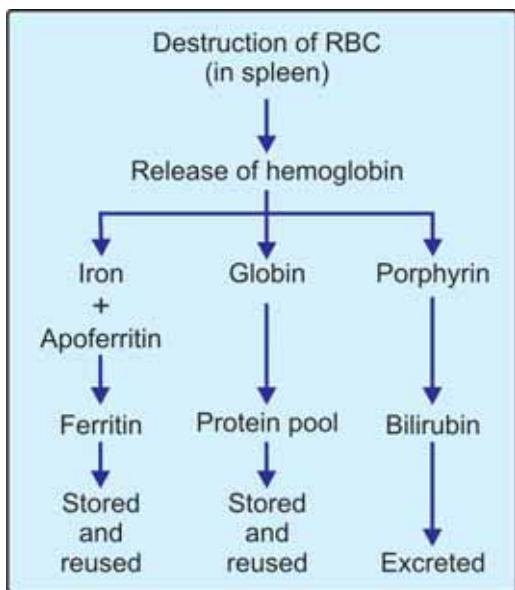


FIGURE 7-3: Fate of RBC

Daily 10% of senile RBCs are destroyed in normal young healthy adults. It causes release of about 0.6 g/dL of hemoglobin into the plasma. From this 0.9 to 1.5 mg/dL bilirubin is formed.

FUNCTIONS OF RED BLOOD CELLS

1. Transport of O_2 from the Lungs to the tissues

Hemoglobin combines with oxygen to form oxyhemoglobin (Chapter 76).

2. Transport CO_2 from the Tissues to the Lungs

Hemoglobin combines with carbon dioxide and form carbhemoglobin.

3. Buffering Action in Blood

Hemoglobin functions as a good buffer. By this action, it regulates the hydrogen ion concentration and thereby plays a role in the maintenance of acid-base balance.

4. In Blood Group Determination

RBCs carry the blood group antigens like A antigen, B antigen and Rh factor. This helps in

determination of blood group and enables to prevent the reactions due to incompatible blood transfusion (Chapter 16).

VARIATIONS IN NUMBER OF RED BLOOD CELLS

PHYSIOLOGICAL VARIATIONS

A. Increase in RBC Count — Polycythemia

Increase in the RBC count is known as polycythemia. It occurs in both physiological and pathological conditions. When it occurs in physiological conditions it is called physiological polycythemia. The increase in number during this condition is marginal and temporary. It occurs in the following conditions:

1. Age

At birth, the RBC count is 8 to 10 millions/cu mm of blood. The count decreases within 10 days after birth due to destruction of RBCs. This may cause physiological jaundice in some newborn babies. In infants and growing children, the RBC count is more than in the adults.

2. Sex

Before puberty and after menopause, in females the RBC count is similar to that in males. During reproductive period of females, the count is less than that of males (4.5 millions/cu mm).

3. High altitude

In people living in mountains (above 10,000 feet from mean sea level), the RBC count is more than 7 millions/cu mm. It is due to hypoxia (decreased oxygen supply to tissues) in high altitude. Hypoxia stimulates kidney to secrete a hormone called erythropoietin which stimulates the bone marrow to produce more RBCs (Fig. 7-4).

4. Muscular exercise

RBC count increases after muscular exercise. It is because of mild hypoxia which increases the sympathetic activity and secretion of

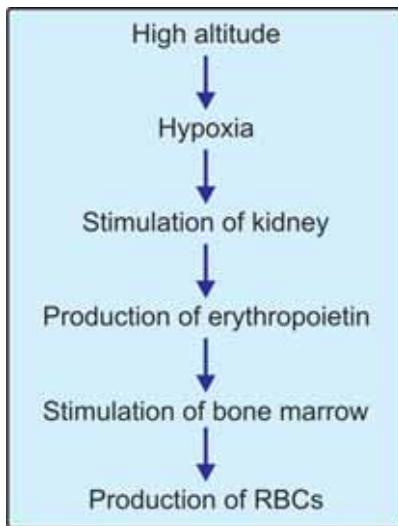


FIGURE 7-4: Physiological polycythemia in high altitude

adrenaline from adrenal medulla. Adrenaline contracts spleen and RBCs are released into blood. Hypoxia causes secretion of erythropoietin which stimulates the bone marrow to produce more RBCs

5. Emotional Conditions

The RBC count increases during the emotional conditions such as anxiety. It is because of increase in the sympathetic activity and contraction of spleen (Fig. 7-5).

6. Increased environmental temperature

Generally increased temperature increases all the activities in the body including production of RBCs.

7. After meals

There is a slight increase in the RBC count after taking meals. It is because of need for more oxygen for metabolic activities.

B. Decrease in RBC Count

Decrease in RBC count occurs in the following physiological conditions:

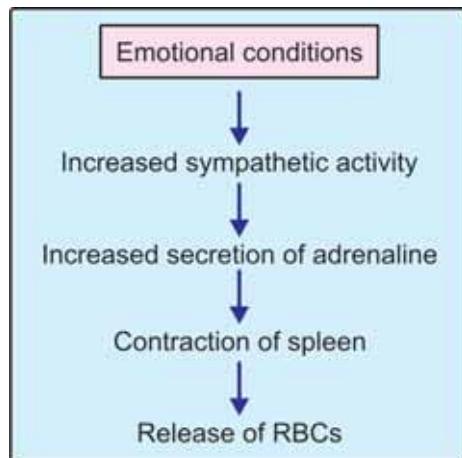


FIGURE 7-5: RBC count in emotional conditions

1. High Barometric Pressures

At high barometric pressures as in deep sea, where the oxygen tension of blood is higher, the RBC count decreases.

2. During Sleep

Generally all the activities of the body are decreased during sleep including production of RBCs.

3. Pregnancy

In pregnancy, the RBC count decreases. It is because of increase in ECF volume. Increase in ECF volume, increases the plasma volume also resulting in hemodilution. So, there is a relative reduction in the RBC count.

■ PATHOLOGICAL VARIATIONS

Pathological Polycythemia

Pathological polycythemia is the abnormal increase in the RBC count. The count increases above 7 millions/cu mm of the blood. Polycythemia is of two types, the primary polycythemia and secondary polycythemia.

Primary Polycythemia — Polycythemia Vera

Primary polycythemia is otherwise known as polycythemia vera. It is a disease characterized by

persistent increase in RBC count above 14 millions/cu mm of blood. This is always associated with increased WBC count above 24,000/cu mm of blood. Polycythemia vera occurs because of red bone marrow malignancy.

Secondary Polycythemia

It is the pathological condition in which polycytemia occurs because of diseases in some other system such as:

1. Respiratory disorders like emphysema
2. Congenital heart disease
3. Ayerza's disease — condition associated with hypertrophy of right ventricle and obstruction of blood flow to lungs
4. Chronic carbon monoxide poisoning
5. Poisoning by chemicals like phosphorus and arsenic
6. Repeated mild hemorrhages.

All these conditions lead to hypoxia which stimulates the release of erythropoietin. Erythropoietin stimulates the bone marrow resulting in increased RBC count.

Anemia

The abnormal decrease in RBC count is called anemia. This is described in Chapter 11.

n VARIATIONS IN SIZE OF RED BLOOD CELLS

Under physiological conditions, the size of RBCs in venous blood is slightly larger than those in arterial blood. In pathological conditions, the variations in size of RBCs are:

1. Microcytes — smaller cells
2. Macrocytes — larger cells
3. Anisocytosis — cells of different sizes.

Microcytes

Microcytes are present in:

- i. Iron deficiency anemia
- ii. Prolonged forced breathing
- iii. Increased osmotic pressure in blood.

Macrocytes

Macrocytes are present in:

- i. Megaloblastic anemia
- ii. Muscular exercise
- iii. Decreased osmotic pressure in blood.

Anisocytes

Anisocytes are found in pernicious anemia.

n VARIATIONS IN SHAPE OF RED BLOOD CELLS

The shape of RBCs is altered in many conditions including different types of anemia:

1. Crenation: Shrinkage as in hypertonic conditions
2. Spherocytosis: Globular form as in hypotonic conditions
3. Elliptocytosis: Elliptical shape as in certain types of anemia
4. Sickle cell: Crescentic shape as in sickle cell anemia
5. Poikilocytosis: Unusual shapes due to deformed cell membrane. The shape will be of flask, hammer or any other unusual shape.

n HEMOLYSIS AND FRAGILITY OF RBC

n DEFINITION

Hemolysis

Hemolysis is the destruction of formed elements. To define more specifically, it is the process, which involves the breakdown of RBC and liberation of hemoglobin.

Fragility

The susceptibility of RBC to hemolysis or tendency to break easily is called fragility (Fragile = easily broken).

Fragility is of two types:

- i. Osmotic fragility which occurs due to exposure to hypotonic saline.
- ii. Mechanical fragility which occurs due to mechanical trauma (wound or injury).

Normally, old RBCs are destroyed in the reticuloendothelial system. Abnormal hemolysis is the process by which even younger RBCs are destroyed in large number by the presence of hemolytic agents or hemolysins.

n PROCESS OF HEMOLYSIS

Normally, plasma and RBCs are in osmotic equilibrium. When the osmotic equilibrium is disturbed, the cells are affected. For example, when the RBCs are immersed in hypotonic saline the cells swell and rupture by bursting because of endosmosis (Chapter 3). The hemoglobin is released from the ruptured RBCs.

n CONDITIONS WHEN HEMOLYSIS OCCURS

1. Hemolytic jaundice
2. Antigen antibody reactions
3. Poisoning by chemicals or toxins.

n HEMOLYSINS

Hemolysins or hemolytic agents are the substances, which cause destruction of RBCs.

Hemolysins are of two types:

- I. Chemical substances
- II. Substances of bacterial origin or substances found in body.

n CHEMICAL SUBSTANCES

1. Alcohol
2. Benzene
3. Chloroform
4. Ether
5. Acids
6. Alkalies
7. Bile salts
8. Saponin
9. Chemical poisons like arsenic preparations, carbolic acid, nitrobenzene and resin.

n SUBSTANCES OF BACTERIAL ORIGIN OR SUBSTANCES FOUND IN BODY

1. Toxic substances or toxins from bacteria such as *streptococcus*, *staphylococcus*, *tetanus bacillus*, etc.
2. Venom of poisonous snakes like cobra
3. Hemolysins from normal tissues.

8

Erythropoiesis

- n **DEFINITION**
- n **SITE OF ERYTHROPOIESIS**
 - n **IN FETAL LIFE**
 - n **IN NEWBORN BABIES, CHILDREN AND ADULTS**
- n **PROCESS OF ERYTHROPOIESIS**
 - n **STEM CELLS**
 - n **CHANGES DURING ERYTHROPOIESIS**
 - n **STAGES OF ERYTHROPOIESIS**
- n **FACTORS NECESSARY FOR ERYTHROPOIESIS**
 - n **GENERAL FACTORS**
 - n **MATURATION FACTORS**
 - n **FACTORS NECESSARY FOR HEMOGLOBIN FORMATION**

n **DEFINITION**

Erythropoiesis is the process of the origin, development and maturation of erythrocytes. Hemopoiesis is the process of origin, development and maturation of all the blood cells.

n **SITE OF ERYTHROPOIESIS**

n **IN FETAL LIFE**

In fetal life, the erythropoiesis occurs in different sites in different periods:

1. *Mesoblastic Stage*

During the first two or three months (first trimester) of intrauterine life, the RBCs are produced from mesenchymal cells of yolk sac.

2. *Hepatic Stage*

During the next three months (second trimester) of intrauterine life, RBCs are produced mainly from the liver. Some cells are produced from the spleen and lymphoid organs also.

3. *Myeloid Stage*

During the last three months (third trimester) of intrauterine life, the RBCs are produced from red bone marrow and liver.

n **IN NEWBORN BABIES, CHILDREN AND ADULTS**

1. *Up to the age of 20 years*: RBCs are produced from red bone marrow of all bones
2. *After the age of 20 years*: RBCs are produced from all the membranous bones and ends of long bones.

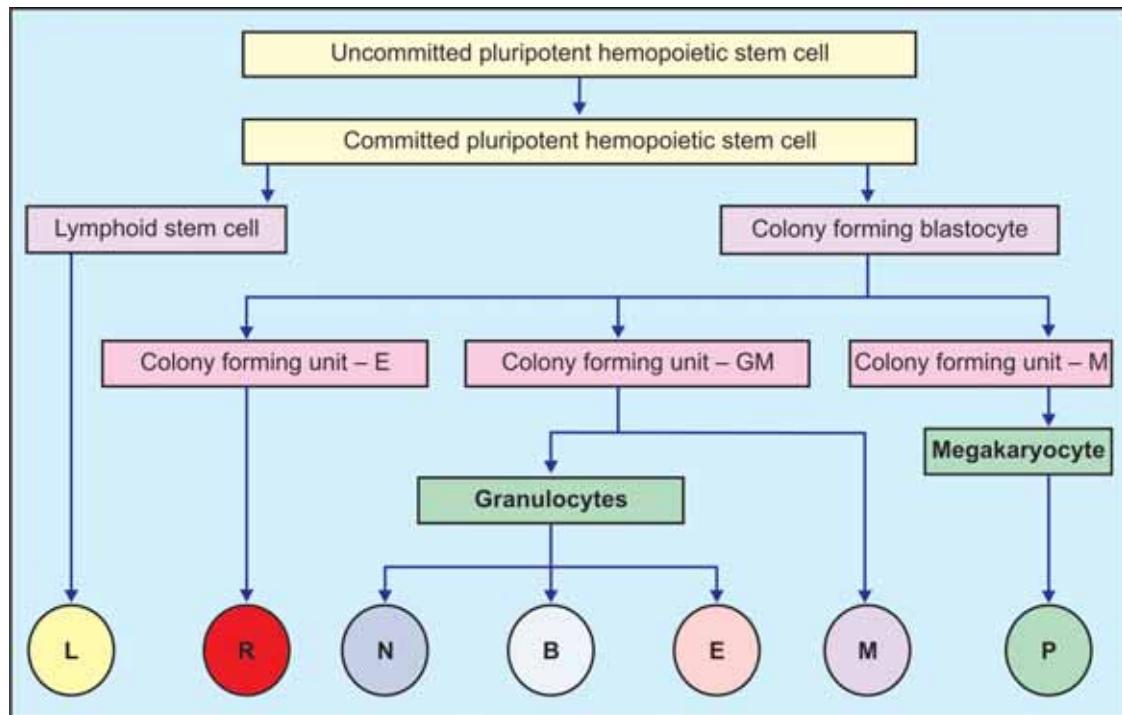


FIGURE 8-1: Stem cells. L – Lymphocyte, R – Red blood cells, N – Neutrophil, B – Basophil, E – Eosinophil, M – Monocyte, P – Platelets

n PROCESS OF ERYTHROPOIESIS

n STEM CELLS

RBCs develop from the hemopoietic stem cells in the bone marrow. These cells are called uncommitted pluripotent hemopoietic stem cells (PHSC). PHSC are not designed to form a particular type of blood cell; hence the name uncommitted PHSC. When the cells are designed to form a particular type of blood cell, the uncommitted PHSCs are called committed PHSC.

The committed PHSCs are of two types:

1. Lymphoid stem cells (LSC) which give rise to lymphocytes and natural killer (NK) cells
2. Colony forming blastocytes, which give rise to all the other blood cells except lymphocytes. When grown in cultures, these cells form colonies hence the name colony forming blastocytes.

The different units of colony forming cells are:

- i. Colony forming Unit – Erythrocytes (CFU-E) from which RBCs develop.
- ii. Colony forming Unit – Granulocytes/ Monocytes (CFU-GM) from which granulocytes (neutrophils, basophils and eosinophils) and monocytes develop.
- iii. Colony forming Unit – Megakaryocytes (CFU-M) from which platelets develop.

n CHANGES DURING ERYTHROPOIESIS

When the cells of CFU-E pass through different stages and finally become the matured RBCs, four important changes are noticed.

1. Reduction in size of the cell (from the diameter of 25 to 7.2μ)
2. Disappearance of nucleoli and nucleus
3. Appearance of hemoglobin
4. Change in the staining properties of the cytoplasm.

n STAGES OF ERYTHROPOIESIS

The various stages between CFU-E cells and matured RBC are:

1. Proerythroblast
2. Early normoblast
3. Intermediate normoblast
4. Late normoblast
5. Reticulocyte
6. Matured erythrocyte.

1. *Proerythroblast (Megaloblast)*

Proerythroblast or megaloblast is very large in size with a diameter of about $20\text{ }\mu$. A large nucleus with two or more nucleoli and a chromatin network is present. Hemoglobin is absent. The cytoplasm is basophilic in nature. The proerythroblast multiplies several times and finally forms the cell of next stage called early normoblast.

2. *Early Normoblast*

It is smaller than proerythroblast with a diameter of about $15\text{ }\mu$. The nucleoli disappear from the nucleus and condensation of chromatin network occurs. The condensed network becomes dense. The cytoplasm is basophilic in nature. So, this cell is also called basophilic erythroblast. This cell develops into the next stage called intermediate normoblast (Fig. 8-2).

3. *Intermediate Normoblast*

It is smaller than the early normoblast with a diameter of 10 to $12\text{ }\mu$. The nucleus is still present. But, the chromatin network shows further condensation. This stage is marked by the appearance of hemoglobin. Because of the presence of small quantity of acidic hemoglobin, the cytoplasm which is basophilic becomes polychromatic, i.e. both acidic and basic in nature. So this cell is called polychromophilic or polychromatic erythroblast. This cell develops into the next stage called late normoblast.

4. *Late Normoblast*

The diameter of the cell decreases further to about 8 to $10\text{ }\mu$. Nucleus becomes very small

with very much condensed chromatin network and is called ink spot nucleus. Quantity of hemoglobin increases making the cytoplasm almost acidophilic. So, the cell is now called orthochromic erythroblast. At the end of late normoblastic stage, just before it passes to the next stage, the nucleus disintegrates and disappears by the process called pyknosis. The final remnant is extruded from the cell. Late normoblast develops into the next stage called reticulocyte.

5. *Reticulocyte*

It is slightly larger than matured RBC. It is otherwise known as immature RBC. It is called reticulocyte because, the reticular network or reticulum that is formed from the disintegrated organelles are present in the cytoplasm.

In newborn babies, the reticulocyte count is 2 to 6% of RBCs, i.e. 2 to 6 reticulocytes are present for every 100 RBCs. The number of reticulocytes decreases during the first week after birth. Later, the reticulocyte count remains constant at or below 1%. The number increases whenever the erythropoietic activity increases. Reticulocytes can enter the capillaries through the capillary membrane from the site of production by diapedesis.

6. *Matured Erythrocyte*

The cell decreases in size with the diameter of $7.2\text{ }\mu$. The reticular network disappears and the cell becomes the matured RBC with biconcave shape and hemoglobin but without nucleus. It requires seven days for the proerythroblast to become fully developed and matured RBC.

n FACTORS NECESSARY FOR ERYTHROPOIESIS

Development and maturation of erythrocytes require many factors which are classified into 3 categories:

- I. General factors
- II. Maturation factors
- III. Factors necessary for hemoglobin formation.

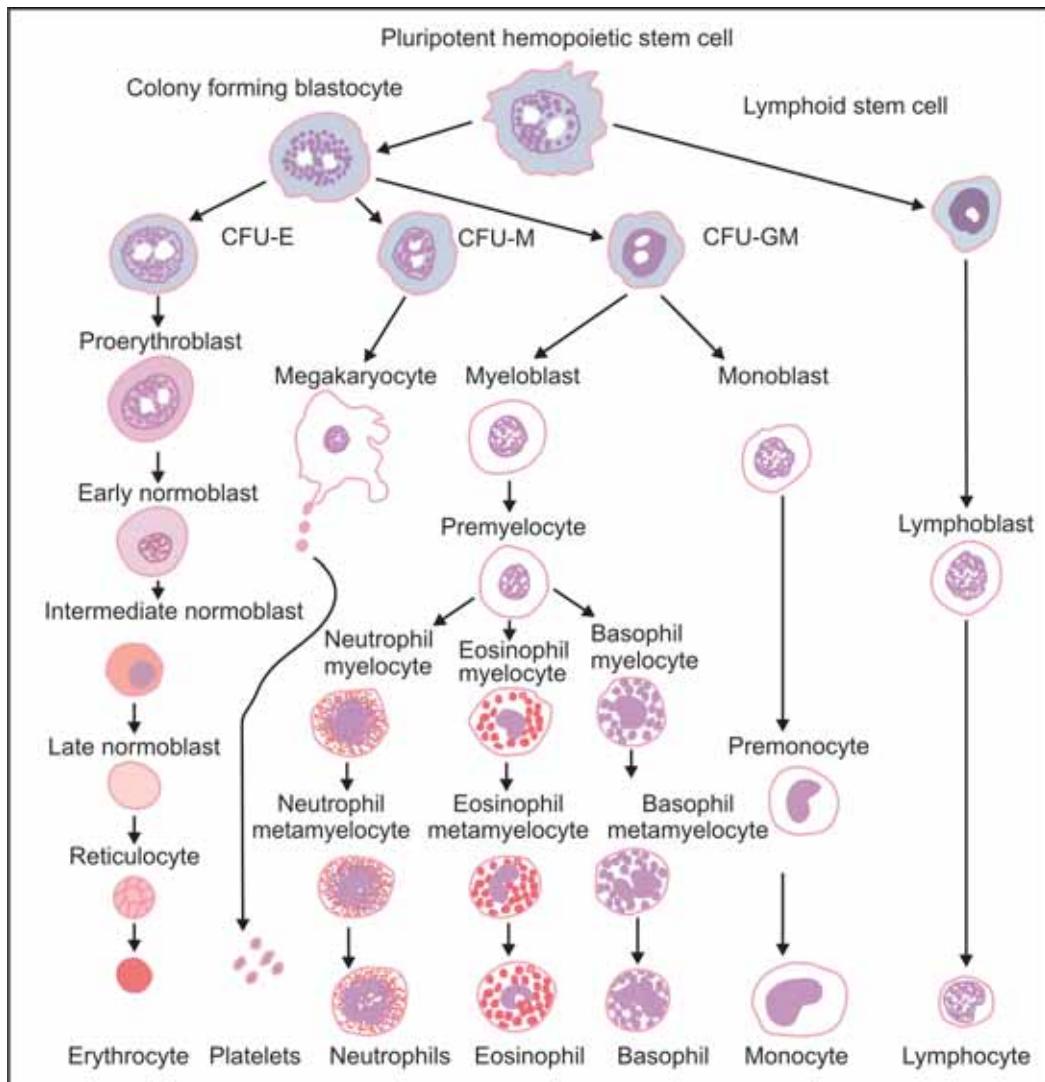


FIGURE 8-2: Stages of erythropoiesis. CFU-E = Colony forming unit – Erythrocyte, CFU-M = Colony forming unit – Megakaryocyte, CFU-GM = Colony forming unit – Granulocyte/Monocyte

n GENERAL FACTORS

1. *Erythropoietin*

Erythropoietin is a hormone secreted mainly by peritubular capillaries in the kidney and a small quantity is also secreted from the liver and the brain. Hypoxia is the stimulant for the secretion of erythropoietin.

Erythropoietin promotes the following processes:

- Production of proerythroblasts from CFU-E of the bone marrow
- Development of proerythroblasts into matured RBCs through the several stages
- Release of matured erythrocytes into blood. Some reticulocytes are also released along with matured RBCs.

2. Thyroxine

Being a general metabolic hormone, thyroxine accelerates the process of erythropoiesis at many levels.

3. Hemopoietic Growth Factors

Hemopoietic growth factors or growth inducers are the interleukins – 3, 6 and 11 and stem cell factor (steel factor). Generally these factors induce the proliferation of PHSCs.

4. Vitamins

The vitamins A, B, C, D and E are necessary for erythropoiesis. Deficiency of these vitamins causes anemia.

n MATURATION FACTORS

Vitamin B₁₂, intrinsic factor and folic acid are necessary for the maturation of RBCs.

1. Vitamin B₁₂ (Cyanocobalamin)

Vitamin B₁₂ is essential for synthesis of DNA, cell division and maturation in RBCs. It is also called extrinsic factor as it is obtained mostly from diet. It is also produced in the large intestine by the intestinal flora. It is absorbed from the small intestine in the presence of intrinsic factor of Castle. Vitamin B₁₂ is stored mostly in liver and in small quantity in muscle. Its deficiency causes pernicious anemia (macrocytic anemia) in which the cells remain larger with fragile and weak cell membrane.

2. Intrinsic Factor of Castle

It is produced in gastric mucosa by the parietal cells of the gastric glands. It is essential for the absorption of vitamin B₁₂ from intestine. Absence of intrinsic factor also leads to pernicious anemia because of failure of vitamin B₁₂ absorption. The deficiency of intrinsic factor occurs in conditions like severe gastritis, ulcer and gastrectomy.

3. Folic Acid

Folic acid is also essential for the synthesis of DNA. Deficiency of folic acid decreases the DNA synthesis causing maturation failure. Here the cells are larger and remain in megaloblastic (proerythroblastic) stage which leads to megaloblastic anemia.

n FACTORS NECESSARY FOR HEMOGLOBIN FORMATION

Various materials are essential for the formation of hemoglobin in the RBCs such as:

1. First class proteins and amino acids of high biological value — for the formation of globin.
2. Iron — for the formation of heme part of the hemoglobin.
3. Copper — for the absorption of iron from GI tract.
4. Cobalt and nickel — for the utilization of iron during hemoglobin synthesis.
5. Vitamins: Vitamin C, riboflavin, nicotinic acid and pyridoxine — for hemoglobin synthesis.

9

Hemoglobin

- INTRODUCTION
- NORMAL HEMOGLOBIN CONTENT
- FUNCTIONS
- STRUCTURE
- TYPES OF NORMAL HEMOGLOBIN
- ABNORMAL HEMOGLOBIN
- ABNORMAL HEMOGLOBIN DERIVATIVES
- SYNTHESIS
- DESTRUCTION

■ INTRODUCTION

Hemoglobin (Hb) is the iron containing coloring pigment of RBC. It forms 95% of dry weight of RBC and 30 to 34% of wet weight. The molecular weight of Hb is 68,000.

■ NORMAL HEMOGLOBIN CONTENT

Average Hb content in blood is 14 to 16 g/dL. However, it varies depending upon age and sex of the individual and the number of RBCs.

Age

At birth	: 25 g/dL
After 3rd month	: 20 g/dL
After 1 year	: 17 g/dL
From puberty onwards	: 14-16 g/dL

At the time of birth and in infants and growing children, Hb content is high because of increased number of RBCs (Chapter 7).

Sex

In adult males	: 15 g/dL
In adult females	: 14.5 g/dL

■ FUNCTIONS OF HEMOGLOBIN

■ TRANSPORT OF RESPIRATORY GASES

The main function of Hb is the transport of respiratory gases.

It transports:

- i. Oxygen from lungs to tissues
- ii. Carbon dioxide from tissues to lungs (Chapter 76).

n BUFFER ACTION

Hb acts as a buffer and plays an important role in acid-base balance.

n STRUCTURE OF HEMOGLOBIN

Hb is a conjugated protein. It consists of a protein called globin and an iron containing pigment called heme.

Iron is present in an unstable ferrous (Fe^{++}) form. Heme part is called porphyrin. It is formed by four pyrole rings (tetrapyrrole). The iron is attached to each pyrole ring and globin molecule.

Globin is made up of four polypeptide chains. Among the four polypeptide chains, two are α chains and two are β chains

n TYPES OF NORMAL HEMOGLOBIN

Hb is of two types:

1. Adult Hb (Hb A)
2. Fetal Hb (Hb F)

Both the types of Hb differ from each other structurally and functionally.

Structural Difference

In adult Hb, the globin contains two α chains and two β chains. In fetal Hb, there are two α chains and two γ chains instead of β chains.

Functional Difference

Functionally, fetal Hb has more affinity for oxygen than adult Hb. And, the oxygen hemoglobin dissociation curve of fetal blood is shifted to left (Chapter 76).

n ABNORMAL HEMOGLOBIN

The abnormal types of Hb are produced because of structural changes in the polypeptide chains caused by mutation in the genes of the globin chains. There are two categories of abnormal Hb:

- I. Hemoglobinopathies
- II. Hb in thalassemia and related disorders.

I. ***Hemoglobinopathies***

Hemoglobinopathy is a genetic disorder caused by abnormal polypeptide chains of Hb.

Some of the hemoglobinopathies are Hb S, C, E and M.

II. ***Hb in Thalassemia and Related Disorders***

In thalassemia different types of abnormal Hb are present. The polypeptide chains are decreased, absent or abnormal. (Refer Chapter 11).

n ABNORMAL HEMOGLOBIN DERIVATIVES

Abnormal Hb formed by the combination of Hb with some substances other than oxygen and carbon dioxide is called abnormal Hb derivative. Abnormal Hb derivatives are formed by carbon monoxide poisoning or due to the combination of some drugs like nitrites, nitrates and sulfonamides.

The abnormal hemoglobin derivatives are carboxyhemoglobin, methemoglobin and sulfhemoglobin. The high levels of abnormal Hb derivatives in blood produce serious effects by preventing the transport of oxygen. It results in oxygen lack in tissues which may be fatal.

n CARBOXYHEMOGLOBIN

Carboxyhemoglobin or carbon monoxyhemoglobin is the abnormal Hb derivative formed by the combination of carbon monoxide with Hb. Carbon monoxide is a colorless and odorless gas. Since Hb has 200 times more affinity for carbon monoxide than oxygen, it hinders the transport of oxygen resulting in tissue hypoxia (Chapter 78).

Some of the sources of carbon monoxide are charcoal burning, coal mines, deep wells, underground drainage system, exhaust of gasoline engines, gases from guns and other weapons, heating system with poor or improper ventilation, smoke from fire and tobacco smoking.

Signs and Symptoms of Carbon Monoxide Poisoning

1. While breathing air with less than 1% of carbon monoxide, the Hb saturation is 15 to 20% and mild symptoms like headache and nausea appear.
2. While breathing air with more than 1% carbon monoxide, the Hb saturation is 30 to 40%. It causes severe symptoms like convulsions, cardiorespiratory arrest, unconsciousness and coma.
3. When Hb saturation increase above 50%, death occurs.

n METHEMOGLOBIN

Methemoglobin is the abnormal Hb derivative formed when iron molecule of Hb is oxidized from normal ferrous state to ferric state. Methemoglobin is also called ferrihemoglobin. Normal methemoglobin level is less than 3% of total Hb.

Some of the sources of methemoglobin are contaminated well waters with nitrates and nitrites, match sticks, explosives, naphthalene balls, irritant gases like nitrous oxide, etc.

n SULFHEMOGLOBIN

Sulfhemoglobin is the abnormal Hb derivative formed by the combination of hemoglobin with hydrogen sulfide. It is caused by drugs such as sulfonamides. Normal sulfhemoglobin level is less than 1% of total Hb.

n SYNTHESIS OF HEMOGLOBIN

Synthesis of Hb actually starts in proerythroblastic stage. However, Hb appears in the intermediate normoblastic stage only. The production of the Hb is continued until the stage of reticulocyte. The heme portion of Hb is synthesized in mitochondria. And the protein part (globin) is synthesized in ribosomes.

n SYNTHESIS OF HEME

Heme is synthesized from succinyl CoA and the glycine in the mitochondria.

n FORMATION OF GLOBIN

The polypeptide chains of globin are produced in the ribosomes. There are four types of polypeptide chains namely, alpha, beta, gamma and delta chains. Each globin molecule is formed by the combination of 2 pairs of chains. Adult Hb contains two alpha chains and two beta chains. Fetal Hb contains two alpha chains and two gamma chains.

n CONFIGURATION

Each polypeptide chain combines with one heme molecule. Thus, after the complete configuration, each Hb molecule contains 4 polypeptide chains and 4 heme molecules.

n SUBSTANCES NECESSARY FOR HEMOGLOBIN SYNTHESIS

Various materials are essential for the formation of Hb in the RBC (Refer Chapter 8 for details).

n DESTRUCTION OF HEMOGLOBIN

After the lifespan of 120 days, the RBC is destroyed in the reticuloendothelial system particularly in spleen and the Hb is released into plasma. Soon, the Hb is degraded in the reticuloendothelial cells and split into globin, iron and porphyrin.

Globin is utilized for the resynthesis of Hb. Iron is stored in the body. Porphyrin is converted into biliverdin. In human being, most of the biliverdin is converted into bilirubin. Bilirubin and biliverdin are together called the bile pigments (Chapter 30).

10

Erythrocyte Sedimentation Rate and Packed Cell Volume

- n ERYTHROCYTE SEDIMENTATION RATE
 - n DEFINITION
 - n DETERMINATION
 - n NORMAL VALUES
 - n SIGNIFICANCE OF DETERMINING
 - n VARIATIONS
 - n FACTORS AFFECTING
- n PACKED CELL VOLUME
 - n DEFINITION
 - n METHOD OF DETERMINATION
 - n SIGNIFICANCE OF DETERMINING
 - n NORMAL VALUES
 - n VARIATIONS

n ERYTHROCYTE SEDIMENTATION RATE

n DEFINITION

Erythrocyte Sedimentation Rate (ESR) is the rate at which the erythrocytes settle down. Normally, when the blood is in circulation, the RBCs remain suspended uniformly. This is called suspension stability of RBCs. If blood is mixed with an anticoagulant and allowed to stand undisturbed on a vertical tube, the red cells settle down due to gravity with a supernatant layer of clear plasma.

n DETERMINATION OF ESR

There are two methods to determine ESR.

1. Westergren's method
2. Wintrobe's method.

Westergren's Method

In this method, Westergren's tube is used to determine ESR. This tube is 300 mm long and opened on both ends (Fig. 10-1A). It is marked from 0 to 200 mm from above downwards. 1.6 mL of blood is mixed with 0.4 mL of 3.8 percent sodium citrate (anticoagulant). The ratio of blood and anticoagulant is 4:1. This blood is loaded in the Westergren's tube up to 0 mark above. The tube is placed vertically in the Westergren's stand and left undisturbed. The reading is taken after one hour.

Wintrobe's Method

In this method, Wintrobe's tube is used to determine ESR. This tube is short and opened on one end and closed on the other end (Fig. 10-1B). It is 110 mm long with 3 mm bore.

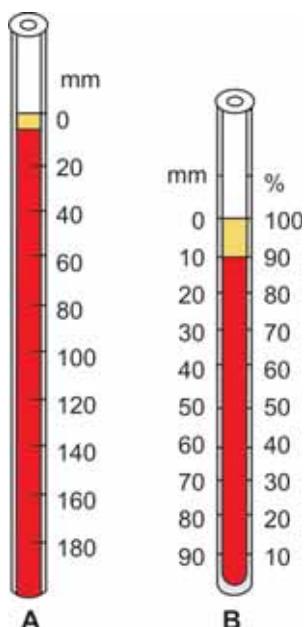


FIGURE 10-1: A = Westergren's tube
B = Wintrobe's tube

It is used for determining ESR and PCV. It is marked on both sides. On one side the marking is from 0 to 100 (for ESR) and on other side from 100 to 0 (for PCV) from above downwards.

About one mL of blood is mixed with an anticoagulant called ethylenediaminetetra acetic acid (EDTA). The blood is loaded in the tube up to '0' mark above. The tube is placed on the Wintrobe's stand and left undisturbed. The reading is taken after one hour.

n NORMAL VALUES OF ESR

By Westergren's Method

- In males : 3 to 7 mm in one hour
- In females : 5 to 9 mm in one hour
- Infants : 0 to 2 mm in one hour

By Wintrobe's Method

- In males : 0 to 9 mm in one hour
- In females : 0 to 15 mm in one hour
- Infants : 0 to 5 mm in one hour

n SIGNIFICANCE OF DETERMINING ESR

ESR is an easy and inexpensive test which helps in diagnosis as well as prognosis. Prognosis means monitoring the course of disease and response of the patient to therapy. Determination of ESR is especially helpful in assessing the progress of patients treated for certain chronic disorders such as pulmonary tuberculosis and rheumatoid arthritis.

n VARIATIONS OF ESR

Physiological Variation

1. Age: ESR is less in children and infants because of more number of RBCs
2. Sex: It is more in females than in males because of less number of RBCs
3. Menstruation: The ESR increases during menstruation because of loss of blood and RBCs
4. Pregnancy: From 3rd month to parturition, ESR increases up to 35 mm in one hour because of hemodilution.

Pathological Variation

ESR increases in the following diseases:

1. Tuberculosis
2. All types of anemia except sickle cell anemia
3. Malignant tumors
4. Rheumatoid arthritis
5. Rheumatic fever
6. Liver diseases.

ESR decreases in the following diseases:

1. Allergic conditions
2. Sickle cell anemia
3. Peptone shock
4. Polycythemia and
5. Severe leukocytosis.

n FACTORS AFFECTING ESR

Following factors increase the ESR:

1. Specific gravity of RBC
2. Rouleaux formation
3. Increase in size of RBC
4. Decrease in RBC count

Following factors decrease the ESR:

1. Viscosity of blood
2. Increase in RBC count

n PACKED CELL VOLUME

n DEFINITION

Packed cell volume (PCV) is the volume of the RBCs in the blood that is expressed in percentage. It is also called hematocrit value.

n METHOD OF DETERMINATION

Blood is mixed with the anticoagulant EDTA or heparin and filled in Wintrobe's tube up to the 100 or 0 mark above. The tube with the blood is centrifuged at a speed of 3000 revolutions per minute (rpm) for 30 minutes.

At the end of 30 minutes, the tube is taken out and the reading is noted. The RBCs are packed at the bottom and this is the PCV. The plasma remains above this. In between the RBCs and the plasma, there is a white buffy coat, which is formed by white blood cells and the platelets (see Fig. 10-2).

n SIGNIFICANCE OF DETERMINING PCV

Determination of PCV helps in:

1. Diagnosis and treatment of anemia
2. Diagnosis and treatment of polycythemia
3. Determination of severity of dehydration and recovery from dehydration after treatment
4. Decision of blood transfusion.

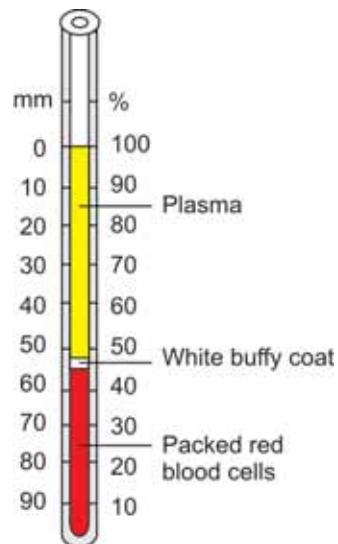


FIGURE 10-2: Packed cell volume

n NORMAL VALUES OF PCV

Normal PCV:

- In males = 40 to 45%
In females = 38 to 42%

n VARIATIONS IN PCV

PCV increases in:

1. Polycythemia
2. Dehydration

PCV decreases in:

1. Anemia
2. Cirrhosis of liver
3. Pregnancy

11

Anemia

- INTRODUCTION
- CLASSIFICATION
- SIGNS AND SYMPTOMS

■ INTRODUCTION

Anemia is the blood disorder characterized by the reduction in:

1. Red blood cell count
2. Hemoglobin content
3. Packed cell volume.

■ CLASSIFICATION OF ANEMIA

Anemia is classified by two methods:

- A. Morphological classification
- B. Etiological classification.

■ MORPHOLOGICAL CLASSIFICATION

Morphological classification depends upon the size and color of RBC. Size of RBC is expressed as mean corpuscular volume (MCV) and the color is expressed as mean corpuscular hemoglobin concentration (MCHC). By this method, the anemia is classified into four types as given in Table 11-1.

■ ETIOLOGICAL CLASSIFICATION

On the basis of the etiology (study of cause or origin), the anemia is divided into five types:

1. *Hemorrhagic Anemia*

Hemorrhage refers to excessive loss of blood (Chapter 70). Anemia due to hemorrhage is known as hemorrhagic anemia or blood loss anemia. It occurs both in acute and chronic hemorrhagic conditions.

Acute Hemorrhage

Acute hemorrhage means sudden loss of large quantity of blood as in case of accidents. The RBCs are normocytic and normochromic (Table 11-2)

TABLE 11-1: Morphological classification of anemia

Type of anemia	Size of RBC (MCV)	Color of RBC (MCHC)
Normocytic normochromic	Normal	Normal
Normocytic hypochromic	Normal	Less
Macrocytic hypochromic	Large	Less
Microcytic hypochromic	Small	Less

Chronic Hemorrhage

It refers to loss of blood over a long period of time by internal or external bleeding as in conditions like peptic ulcer, purpura, hemophilia and menorrhagia. The RBCs are microcytic and hypochromic (Table 11-2). It is because of decrease in iron content.

2. Hemolytic Anemia

Hemolysis means destruction of RBCs. Anemia due to excessive destruction of RBCs is called hemolytic anemia. Hemolysis occurs because of the following reasons (Table 11-2):

- i. Liver failure
- ii. Renal disorder
- iii. Hypersplenism
- iv. Burns
- v. Infections like hepatitis, malaria and septicemia
- vi. Drugs such as penicillin, antimalarial drugs and sulfa drugs
- vii. Poisoning by chemical substances like lead, coal and tar
- viii. Presence of isoagglutinins like anti-Rh
- ix. Autoimmune diseases such as rheumatoid arthritis and ulcerative colitis.
- x. Hereditary factors

Hereditary Disorders

Sickle cell anemia

Sickle cell anemia is an inherited blood disorder characterized by sickle shaped RBCs. It occurs when a person inherits two abnormal genes (one from each parent). It is also called hemoglobin SS disease or sickle cell disease. It is common in people of African origin.

In sickle cell anemia, hemoglobin becomes abnormal with normal α chains and abnormal β chains. Because of this, RBCs attain sickle (crescent) shape and become more fragile leading to hemolysis (Table 11-2).

Thalassemia

Thalassemia is an inherited disorder characterized by abnormal hemoglobin. In normal hemo-

globin, the number of α and β chains is equal. In thalassemia the number of these chains is not equal. This causes the precipitation of the polypeptide chains leading to defective formation of RBCs or hemolysis of the matured RBCs.

It is also known as Cooley's anemia or Mediterranean anemia. It is more common in Thailand and to some extent in Mediterranean countries.

Thalassemia is of two types:

- i. α thalassemia
- ii. β thalassemia.

The β thalassemia is very common among these two.

3. Nutrition Deficiency Anemia

Anemia that occurs due to deficiency of a nutritive substance necessary for erythropoiesis is called nutrition deficiency anemia. Such substances are iron, proteins and vitamins like C, B_{12} and folic acid. The types of nutrition deficiency anemia are:

Iron deficiency anemia

Iron deficiency anemia is the most common type of anemia. It develops due to inadequate availability of iron for hemoglobin synthesis. The RBCs are microcytic and hypochromic (Table 11-2).

Protein deficiency anemia

Protein deficiency decreases the hemoglobin synthesis and the RBCs become macrocytic and hypochromic in nature (Table 11-2).

Vitamin B_{12} deficiency — Pernicious anemia

Vitamin B_{12} is a maturation factor for RBC and deficiency of this causes pernicious anemia which is also called Addison's anemia. It occurs because of less intake of vitamin B_{12} or poor absorption of vitamin B_{12} . Vitamin B_{12} is absorbed from the stomach with the help of intrinsic factor of Castle which is secreted in the gastric mucosa. Decrease in the production of intrinsic factor causes poor absorption of vitamin B_{12} .

RBCs are macrocytic and normochromic/hypochromic (Table 11-2).

Folic acid deficiency — Megaloblastic anemia

Folic acid is necessary for the maturation of RBC. Deficiency of this leads to defective DNA synthesis making the nucleus to remain immature. The RBCs are megaloblastic and hypochromic (Table 11-2).

4. Aplastic Anemia

Aplastic anemia is due to the bone marrow disorder. The red bone marrow is reduced and

replaced by fatty tissues. In this condition, the RBCs are normocytic and normochromic (Table 11-2). It occurs in conditions such as repeated exposure to X-ray or gamma ray radiation, tuberculosis and viral infections like hepatitis and HIV infections.

5. Anemia due to Chronic Diseases

Anemia occurs due to some chronic diseases such as rheumatoid arthritis, tuberculosis and

Table 11-2: Etiological classification of anemia

Type of anemia	Causes	Morphology of RBC
Hemorrhagic anemia	1. Acute hemorrhage — acute loss of blood	Normocytic, normochromic
	2. Chronic hemorrhage — chronic loss of blood	Microcytic, hypochromic
Hemolytic anemia	1. Liver failure 2. Renal disorder 3. Hypersplenism 4. Burns 5. Infections — malaria and septicemia 6. Drugs like penicillin, antimalarial drugs and sulfa drugs 7. Poisoning by lead, coal and tar 8. Isoagglutinins — anti-Rh	Normocytic normochromic
	9. Hereditary disorders	Sickle cell anemia: Sickle shape and hypochromic Thalassemia: Small, irregular and hypochromic
Nutrition deficiency anemia	1. Iron deficiency	Microcytic, hypochromic
	2. Protein deficiency	Macrocytic, hypochromic
	3. Vitamin B ₁₂ deficiency	Macrocytic, normochromic / hypochromic
	4. Folic acid deficiency	Megaloblastic, hypochromic
Aplastic anemia	Bone marrow disorder	Normocytic, normochromic
Anemia of chronic diseases	1. Rheumatoid arthritis 2. Tuberculosis 3. Chronic renal failure	Normocytic, normochromic

chronic renal failure. RBCs are normocytic and normochromic (Table 11-2).

■ SIGNS AND SYMPTOMS OF ANEMIA

■ SKIN AND MUCOUS MEMBRANE

The color of the skin and mucous membrane becomes pale. Paleness is observed prominently in buccal cavity, pharyngeal mucous membrane, conjunctivae, lips, ear lobes, palm and nail bed. Skin also loses the elasticity and becomes thin and dry.

■ HAIR AND NAILS

Loss of hair is common with thinning and early graying. The nails become brittle and easily breakable.

■ CARDIOVASCULAR SYSTEM

There is increase in heart rate and cardiac output. Heart is dilated and cardiac murmurs are produced. The velocity of blood flow is increased.

■ RESPIRATION

Rate and force of respiration increase. Sometimes, it leads to breathlessness and dyspnea (difficulty in breathing). Oxygen hemoglobin dissociation curve is shifted to right.

■ DIGESTION

Anorexia (loss of appetite), nausea, vomiting, abdominal discomfort, and constipation are common. In pernicious anemia, there is atrophy of papillae in tongue. In aplastic anemia, necrotic lesions appear in mouth and pharynx.

■ METABOLISM

Basal metabolic rate increases in severe anemia.

■ KIDNEY

Renal function is disturbed. Albuminuria is common.

■ REPRODUCTIVE SYSTEM

In females, the menstrual cycle is disturbed. There may be menorrhagia, oligomenorrhea or amenorrhea (Chapter 55).

■ NEUROMUSCULAR SYSTEM

The common neuromuscular symptoms are headache, lack of concentration, restlessness, irritability, drowsiness, dizziness or vertigo especially when standing, increased sensitivity to cold and fainting. Muscles become weak and the patient feels lack of energy and fatigued quite often and quite easily.

12

White Blood Cells

- INTRODUCTION
- CLASSIFICATION
- MORPHOLOGY
- NORMAL COUNT
- VARIATIONS
- LIFESPAN
- PROPERTIES
- FUNCTIONS
- LEUKOPOIESIS

■ INTRODUCTION

White blood cells (WBCs) or leukocytes are the colorless and nucleated formed elements of blood (leuko = white or colorless). Compared to RBCs, the WBCs are larger in size and lesser in number. Yet functionally, these cells are as important as RBCs and play very important role in defense mechanism of body by acting like soldiers and protecting the body from invading organisms.

■ CLASSIFICATION

WBCs are classified into two groups depending upon the presence or absence of granules in the cytoplasm:

1. Granulocytes – with granules
2. Agranulocytes – without granules.

1. Granulocytes

Depending upon the staining property of granules, the granulocytes are classified into three types:

- i. Neutrophils – granules take both acidic and basic stains
- ii. Eosinophils – granules take acidic stain
- iii. Basophils – granules take basic stain.

2. Agranulocytes

Agranulocytes have plain cytoplasm without granules. Agranulocytes are of two types:

- i. Monocytes
- ii. Lymphocytes.

■ MORPHOLOGY OF WHITE BLOOD CELLS

■ NEUTROPHILS

Neutrophils are also known as polymorphonuclear leukocytes because the nucleus is multilobed. The number of lobes varies from 1 to 6 (Fig. 12-1). The granules are fine or small in size. When stained with Leishman's stain (which contains acidic eosin and basic methylene blue), the granules take both the stains equally.

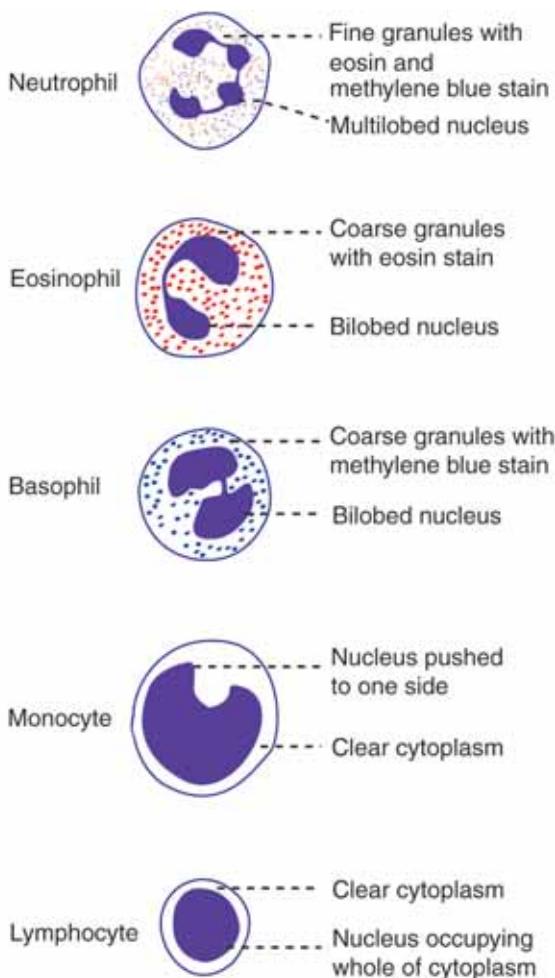


FIGURE 12-1: Diagram of the cell membrane

So, the granules appear violet in color. The diameter of cell is 10 to 12 μ . The neutrophils are ameboid and phagocytic in nature.

■ EOSINOPHILS

Eosinophils have coarse (larger) granules in the cytoplasm, which stain pink or red with eosin. Normally, the nucleus is bilobed and spectacle shaped. Rarely trilobed nucleus may be present. The diameter of the cell varies between 10 and 14 μ .

■ BASOPHILS

Basophils also have coarse granules in the cytoplasm and the granules stain purple blue with methylene blue. Nucleus is bilobed. Diameter of the cell is 8 to 10 μ .

■ MONOCYTES

Monocytes are the largest WBCs with diameter of 14 to 18 μ . The cytoplasm is clear without granules. The nucleus is round, oval, horseshoe shaped, bean shaped or kidney shaped. The nucleus is placed either in the center of the cell or pushed to one side and a large amount of cytoplasm is seen.

■ LYMPHOCYTES

Lymphocytes also do not have granules in the cytoplasm. The nucleus is oval, bean shaped or kidney shaped and occupies the whole of the cytoplasm. A rim of cytoplasm may or may not be seen.

Depending upon the size, the lymphocytes are divided into two types:

- Large lymphocytes* – younger cells with a diameter of 10 to 12 μ
- Small lymphocytes* – older cells with a diameter of 7 to 10 μ .

Depending upon the function, the lymphocytes are divided into two types:

- T lymphocytes* – concerned with cellular immunity
- B lymphocytes* – concerned with humoral immunity.

■ NORMAL LEUKOCYTE COUNT

- Total WBC count (TC): 4,000 to 11,000/ μ l of blood
- Differential WBC count (DC): Given in Table 12-1.

■ VARIATIONS IN LEUKOCYTE COUNT

WBC count varies both in physiological and pathological conditions. Increase in WBC count

TABLE 12-1: Normal values of different WBCs

Type of WBC	Percentage	Absolute value per cumm
Neutrophils	50 to 70	3000 to 6000
Eosinophils	2 to 4	150 to 450
Basophils	0 to 1	0 to 100
Monocytes	2 to 6	200 to 600
Lymphocytes	20 to 30	1500 to 2700

is called leukocytosis and decrease in the count is called leukopenia. The term leukopenia is generally used only for pathological conditions.

■ PHYSIOLOGICAL VARIATIONS

1. *Age:* In infants and children, total WBC count is more; it is about 20,000/cumm in infants and about 10,000 to 15,000/cumm of blood in children. In adults it ranges between 4000 and 11000/cumm of blood
2. *Sex:* Slightly more in males than in females
3. *Diurnal variation:* Minimum in early morning and maximum in the afternoon
4. *Exercise:* Increases slightly
5. *Sleep:* Decreases slightly
6. *Emotional conditions like anxiety:* Increases slightly
7. *Pregnancy:* Increases
8. *Menstruation:* Increases
9. *Parturition:* Increases

■ PATHOLOGICAL VARIATIONS

Leukocytosis

It occurs in the following pathological conditions:

1. Infections
2. Allergy
3. Common cold
4. Tuberculosis
5. Glandular fever.

Leukopenia

Leukopenia occurs in the following pathological conditions:

1. Anaphylactic shock

2. Cirrhosis of liver
3. Disorders of spleen
4. Pernicious anemia
5. Typhoid and paratyphoid
6. Viral infections.

Leukemia

The leukemia is the condition, which is characterized by abnormal and uncontrolled increase in WBC count more than 1,000,000/cumm. It is also called blood cancer.

However, all the WBCs may not increase at a time. Leukocytosis occurs because of increase in any one of the WBCs. The pathological variations of different types of WBCs are given in Table 12-2.

■ LIFESPAN OF WHITE BLOOD CELLS

Lifespan of WBCs is as follows:

Neutrophils	:	2 to 5 days
Eosinophils	:	7 to 12 days
Basophils	:	12 to 15 days
Monocytes	:	2 to 5 days
Lymphocytes	:	½ to 1 day

■ PROPERTIES OF WBCs

1. Diapedesis

Diapedesis is the process by which the WBCs squeeze through the narrow blood vessels.

2. Ameboid Movement

Neutrophils, monocytes and lymphocytes show amebic movement characterized by protrusion of the cytoplasm and change in the shape.

3. Chemotaxis

Chemotaxis is the attraction of WBCs towards the injured tissues by the chemical substances released at the site of injury.

4. Phagocytosis

Neutrophils and monocytes engulf the foreign bodies by means of phagocytosis (Chapter 3).

TABLE 12-2: Pathological variations in different types of WBCs

Disorder	Variation	Conditions
Neutrophilia	Increase in neutrophil count	<ol style="list-style-type: none"> 1. Acute infections 2. Metabolic disorders 3. Injection of foreign proteins 4. Injection of vaccines 5. Poisoning with drugs, chemical, etc. 6. After acute hemorrhage
Neutropenia	Decrease in neutrophil count	<ol style="list-style-type: none"> 1. Bone marrow disorders 2. Tuberculosis 3. Typhoid 4. Autoimmune diseases.
Eosinophilia	Increase in eosinophil count	<ol style="list-style-type: none"> 1. Allergic conditions like asthma 2. Blood parasitism (malaria, filariasis) 3. Intestinal parasitism 4. Scarlet fever
Eosinopenia	Decrease in eosinophil count	<ol style="list-style-type: none"> 1. Cushing's syndrome 2. Bacterial infections 3. Stress 4. Prolonged administration of drugs like steroids, ACTH and epinephrine
Basophilia	Increase in basophil count	<ol style="list-style-type: none"> 1. Smallpox 2. Chickenpox 3. Polycythemia vera
Basopenia	Decrease in basophil count	<ol style="list-style-type: none"> 1. Urticaria (skin disorder) 2. Stress 3. Prolonged exposure to chemotherapy or radiation therapy
Monocytosis	Increase in monocyte count	<ol style="list-style-type: none"> 1. Tuberculosis 2. Syphilis 3. Malaria 4. Kala-azar
Monocytopenia	Decrease in monocyte count	<ol style="list-style-type: none"> 1. Prolonged use of prednisone (immunosuppressant steroid)
Lymphocytosis	Increase in lymphocyte count	<ol style="list-style-type: none"> 1. Diphtheria 2. Infectious hepatitis 3. Mumps 4. Malnutrition 5. Rickets 6. Syphilis 7. Thyrotoxicosis 8. Tuberculosis
Lymphocytopenia	Decrease in lymphocyte count	<ol style="list-style-type: none"> 1. AIDS 2. Hodgkin's disease 3. Malnutrition 4. Radiation therapy 5. Steroid administration.

■ FUNCTIONS OF WBCs

Generally, WBCs play an important role in defense mechanism. These cells protect the body from invading organisms or foreign bodies either by destroying or inactivating them. However, in defense mechanism, each type of WBCs acts in a different way.

■ NEUTROPHILS

Along with monocytes, the neutrophils provide the first line of defense against the invading microorganisms. Neutrophils wander freely all over the body through the tissue.

Mechanism of Action of Neutrophils

Neutrophils are released in large number from the blood. At the same time, new neutrophils are also produced from the progenitor cells. All the neutrophils move by diapedesis towards the site of infection by means of chemotaxis.

The chemotaxis occurs due to the attraction by some chemical substances called chemoattractants, which are released from the infected area. After reaching the area, the neutrophils surround the area and get adhered to the infected tissues. The chemoattractants increase the adhesive nature of neutrophils so that all the neutrophils become sticky and get attached firmly to the infected area. Each neutrophil can hold about 15 to 20 microorganisms at a time. Now, the neutrophils start destroying the invaders. First, these cells engulf the bacteria and then destroy them by means of phagocytosis (Chapter 3).

Pus and Pus Cells

Pus is the whitish-yellow fluid formed in the infected tissue. During the battle against the bacteria, many WBCs are killed by the toxins released from the bacteria. The dead cells are collected in the center of infected area. The dead cells together with plasma leaked from the blood vessel, liquefied tissue cells and RBCs escaped from damaged blood vessel (capillaries) constitute the pus.

■ EOSINOPHILS

The eosinophils provide defense to the body by acting against the parasitic infections and allergic conditions like asthma. Eosinophils are responsible for detoxification, disintegration and removal of foreign proteins.

Mechanism of Action of Eosinophils

The eosinophils attack the invading organisms by secreting some special type of cytotoxic substances. These substances become lethal and destroy the parasites. Some of these substances are:

1. Eosinophil peroxidase
2. Major basic protein (MBP)
3. Eosinophil cationic protein (ECP)
4. Eosinophil derived neurotoxin
5. Interleukin-4 and interleukin-5.

■ BASOPHILS

The basophils play an important role in healing processes and acute hypersensitivity reactions (allergy).

Mechanism of Action of Basophils

The basophils execute the functions by releasing some important substances from their granules such as:

1. Heparin which is essential to prevent the intravascular blood clotting
2. Histamine, bradykinin and serotonin which produce the acute hypersensitivity reactions by causing vascular and tissue responses.
3. Proteases and myeloperoxidase that exacerbate the inflammatory responses
4. Interleukin-4 which accelerates inflammatory responses and kill the invading organisms.

Mast Cell

Mast cell is a large tissue cell resembling the basophil. Usually these cells are found along with the blood vessels and do not enter the blood stream. These cells are predominantly seen in the areas such as skin, mucosa of the lungs and digestive tract, mouth, conjunctiva and nose.

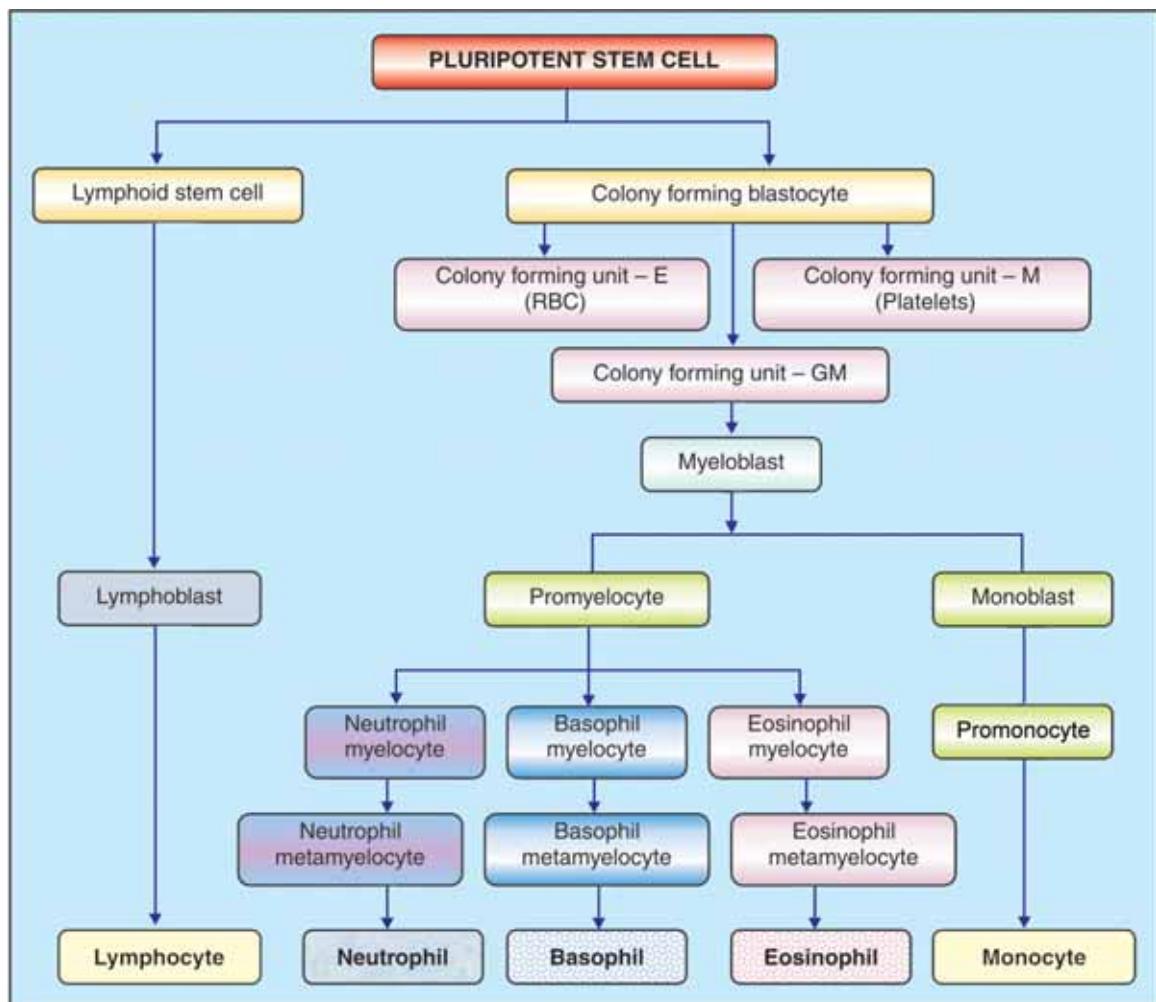


FIGURE 12-2: Leukopoiesis

Functions

The mast cells function along with basophils and produce hypersensitivity reactions like allergy and anaphylaxis. These cells act by secreting some substances like histamine, heparin, serotonin, hydrolytic enzymes, proteoglycans, chondroitin sulphates, arachidonic acid derivatives such as leukotriene C (LTC) and prostaglandin.

■ MONOCYTES

Monocytes are the largest cells among the WBCs. Like neutrophils, monocytes also are motile and phagocytic in nature. These cells wander freely through all tissues of the body and provide the first line of defense along with neutrophils.

Monocytes are the precursors of the tissue macrophages. The matured monocytes stay in

the blood only for few hours. Afterwards these cells enter the tissues from the blood and become tissue macrophages. Examples of tissue macrophages are Kupffer cells in liver, alveolar macrophages in lungs and macrophages in spleen. The functions of macrophages are discussed in Chapter 17.

Monocytes act by secreting certain substances like interleukin-1 (IL-1), colony stimulating factor (M-CSF) and platelet activating factor (PAF).

■ LYMPHOCYTES

The lymphocytes are responsible for development of immunity. Lymphocytes are classified into two categories namely T lymphocytes and B lymphocytes. The functions of these two types of lymphocytes are explained in detail in Chapter 13.

■ LEUKOPOIESIS

Leukopoiesis is the development and maturation of WBCs (Fig. 12-2).

■ STEM CELLS

The committed pluripotent stem cell gives rise to WBCs through various stages. The details are given in Chapter 8.

■ FACTORS NECESSARY FOR LEUKOPOIESIS

Leukopoiesis is influenced by hemopoietic growth factors and colony stimulating factors. Hemopoietic growth factors are discussed in Chapter 8.

Colony Stimulating Factors

The colony stimulating factors (CSF) are proteins which cause the formation of colony forming blastocytes.

Colony stimulating factors are of three types:

1. Granulocyte CSF (G-CSF) secreted by monocytes and endothelial cells
2. Granulocyte–Monocyte CSF (GM-CSF) secreted by monocytes, endothelial cells and T lymphocytes
3. Monocyte CSF (M-CSF) secreted by monocytes and endothelial cells.

13

Immunity

- DEFINITION AND TYPES OF IMMUNITY
 - INNATE IMMUNITY OR NONSPECIFIC IMMUNITY
 - ACQUIRED IMMUNITY OR SPECIFIC IMMUNITY
- DEVELOPMENT AND PROCESSING OF LYMPHOCYTES
 - T LYMPHOCYTES
 - B LYMPHOCYTES
- ANTIGENS
 - DEFINITION AND TYPES
- DEVELOPMENT OF CELL MEDIATED IMMUNITY
 - INTRODUCTION
 - ANTIGEN PRESENTING CELLS
 - ROLE OF HELPER T CELLS
 - ROLE OF CYTOTOXIC T CELLS
 - ROLE OF SUPPRESSOR T CELLS
 - ROLE OF MEMORY T CELLS
 - SPECIFICITY OF T CELLS
- DEVELOPMENT OF HUMORAL IMMUNITY
 - INTRODUCTION
 - ROLE OF ANTIGEN PRESENTING CELLS
 - ROLE OF PLASMA CELLS
 - ROLE OF MEMORY B CELLS
 - ROLE OF HELPER T CELLS
 - ANTIBODIES
- NATURAL KILLER CELL
- CYTOKINES
- IMMUNE DEFICIENCY DISEASES
 - CONGENITAL IMMUNE DEFICIENCY DISEASES
 - ACQUIRED IMMUNE DEFICIENCY DISEASES
- AUTOIMMUNE DISEASES

■ DEFINITION AND TYPES OF IMMUNITY

Immunity is defined as the capacity of the body to resist the pathogenic agents. It is the ability of the body to resist the entry of different types of foreign bodies like bacteria, virus, toxic substances, etc.

Immunity is of two types:

- I. Innate immunity
- II. Acquired immunity.

■ INNATE IMMUNITY OR NONSPECIFIC IMMUNITY

Innate immunity is the inborn capacity of the body to resist the pathogens. By chance, if the organisms enter the body, innate immunity eliminates them before the development of any disease.

This type of immunity represents the first line of defense against any type of pathogens. Therefore, it is also called nonspecific immunity. Examples of innate immunity are:

1. Destruction of toxic substances or organisms entering digestive tract through food by enzymes in digestive juices
2. Destruction of bacteria by salivary lysozyme
3. Destruction of bacteria by acidity in urine and vaginal fluid.

■ ACQUIRED IMMUNITY OR SPECIFIC IMMUNITY

Acquired immunity is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines or transplanted tissues. So, this type of immunity is also known as specific immunity.

It is the most powerful immune mechanism that protects the body from invading organisms or toxic substances. Lymphocytes are responsible for acquired immunity (Fig. 13-1).

Types of Acquired Immunity

Two types of acquired immunity develop in the body:

1. Cell mediated immunity or cellular immunity
2. Humoral immunity.

■ DEVELOPMENT AND PROCESSING OF LYMPHOCYTES

In fetus, lymphocytes develop from bone marrow. All the lymphocytes are released in the circulation and are differentiated into two categories:

1. T lymphocytes
2. B lymphocytes.

■ T LYMPHOCYTES

T lymphocytes are processed in thymus. The processing occurs mostly during the period between just before birth and few months after birth.

Thymus secretes thymosin which accelerates the proliferation and activation of lymphocytes in thymus. It also increases the activity of lymphocytes in lymphoid tissues.

Types of T Lymphocytes

During the processing, T lymphocytes are transformed into four types:

1. Helper T cells or inducer T cells
2. Cytotoxic T cells or killer T cells
3. Suppressor T cells
4. Memory T cells.

Storage of T Lymphocytes

After the transformation, all the types of T lymphocytes leave the thymus and are stored in lymphoid tissues of lymph nodes, spleen, bone marrow and the GI tract.

■ B LYMPHOCYTES

B lymphocytes were first discovered in the bursa of Fabricius in birds hence the name B lymphocytes. The bursa of Fabricius is a lymphoid organ situated near the cloaca of birds. The bursa is absent in mammals, and the processing of B lymphocytes takes place in bone marrow and liver.

Types of B Lymphocytes

After processing, the B lymphocytes are transformed into two types:

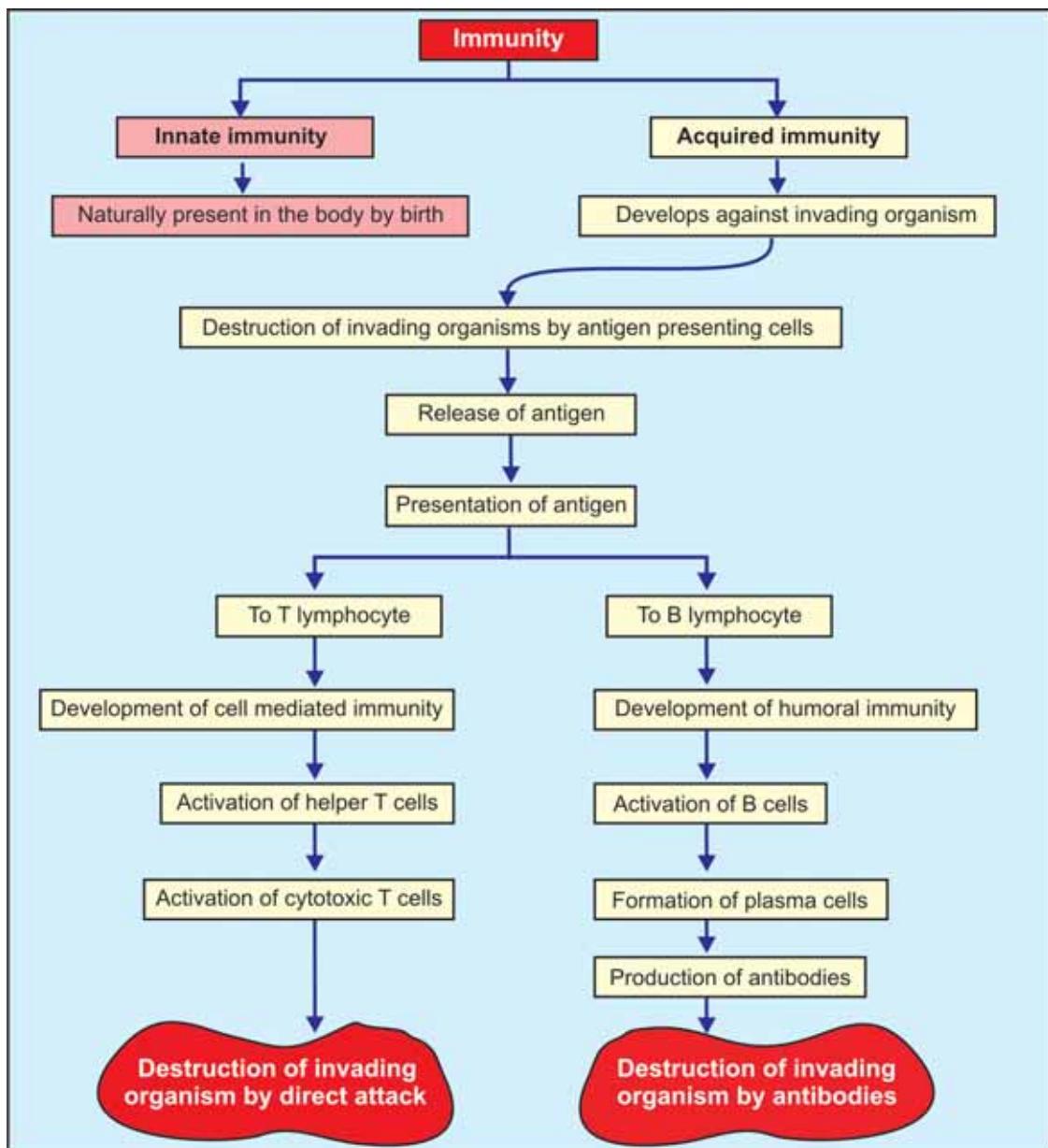


FIGURE: 13-1: Schematic diagram showing development of immunity

1. Plasma cells
2. Memory cells.

Storage of B Lymphocytes

After the transformation, B lymphocytes are stored in the lymphoid tissues of lymph nodes, spleen, bone marrow and the GI tract.

■ ANTIGENS

■ DEFINITION AND TYPES

Antigens are the substances, which induce specific immune reactions in the body. The antigens are mostly the conjugated proteins like lipoproteins, glycoproteins and nucleoproteins.

Antigens are of two types:

1. Autoantigens or self antigens which are present on the body's own cells like 'A' antigen and 'B' antigen on the RBCs.
2. Foreign antigens or nonself antigens which enter the body from outside.

■ DEVELOPMENT OF CELL MEDIATED IMMUNITY

■ INTRODUCTION

The cell mediated immunity is offered by T lymphocytes. It involves several types of cells such as macrophages, T lymphocytes and natural killer cells and hence the name cell mediated immunity. It is also called cellular immunity or T cell immunity. It does not involve antibodies.

Cellular immunity is the major defense mechanism against infections by viruses, fungi and few bacteria. It is also responsible for delayed allergic reactions and rejection of transplanted tissues.

Cell mediated immunity starts developing when T cells come in contact with the antigens. Usually, the invading microbial or nonmicrobial organisms carry the antigenic materials. These antigenic materials are released from invading organisms and are presented to the helper T cells by antigen presenting cells.

■ ANTIGEN PRESENTING CELLS

Antigen presenting cells are the special type of cells in the body which induce the release of antigenic materials from invading organisms and later present these materials to the helper T cells. Major antigen presenting cells are macrophages. Dendritic cells in spleen, lymph nodes and skin also function like antigen presenting cells.

Role of Antigen Presenting Cells

Invading foreign organisms are either engulfed by macrophages through phagocytosis or trapped by dendritic cells. Later, the antigen from these organisms is digested into small peptides. The antigenic peptide products are moved towards the surface of the antigen presenting cells and loaded on a genetic matter of the antigen presenting cells

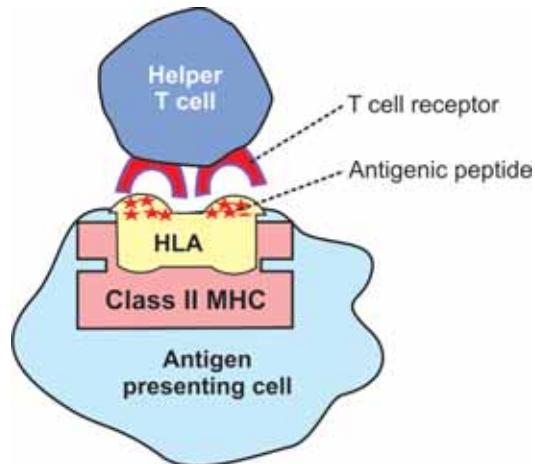


FIGURE 13-2: Antigen presentation. The antigen presenting cells present their class II MHC molecules together with antigen bound HLA to the helper T cells. MHC = Major histocompatibility complex.

called human leukocyte antigen (HLA). HLA is present in the molecule of class II major histocompatibility complex (MHC) which is situated on the surface of the antigen presenting cells.

Presentation of Antigen

The antigen presenting cells present their class II MHC molecules together with antigen bound HLA to the helper T cells. This activates the helper T cells through series of events (Fig. 13-2).

Sequence of Events during Activation of Helper T Cells

1. Helper T cell recognizes the antigen bound to class II MHC molecule which is displayed on the surface of the antigen presenting cell. It recognizes the antigen with the help of its own surface receptor protein called T cell receptor.
2. The recognition of the antigen by the helper T cell initiates a complex interaction between the helper T cell receptor and the antigen. This reaction activates helper T cells.
3. At the same time macrophages (the antigen presenting cells) release interleukin-1 which

- facilitates the activation and proliferation of helper T cells.
4. The activated helper T cells proliferate and the proliferated helper T cells enter the circulation for further actions.
 5. Simultaneously, the antigen bound to class II MHC molecules activates the B cells also resulting in development of humoral immunity (see below).

■ ROLE OF HELPER T CELLS

The helper T cells which enter the circulation activate all the other T cells and B cells. The helper T cells are of two types:

1. Helper-1 (TH1) cells
2. Helper-2 (TH2) cells.

Role of TH1 Cells

TH1 cells are concerned with cellular immunity and secrete two substances:

- i. Interleukin-2 which activates the other T cells
- ii. Gamma interferon which stimulates the phagocytic activity of cytotoxic cells, macrophages and natural killer (NK) cells.

Role of TH2 Cells

TH2 cells are concerned with humoral immunity and secrete interleukin-4 and interleukin-5 which are concerned with:

- i. Activation of B cells
 - ii. Proliferation of plasma cells
 - iii. Production of antibodies by plasma cell
- HLA = Human leukocyte antigen.

■ ROLE OF CYTOTOXIC T CELLS

The cytotoxic T cells that are activated by helper T cells circulate through blood, lymph and lymphatic tissues and destroy the invading organisms by attacking them directly.

Mechanism of Action of Cytotoxic T Cells

1. The receptors situated on the outer membrane of cytotoxic T cells bind the antigens or organisms tightly with cytotoxic T cells.

2. Then, the cytotoxic T cells enlarge and release cytotoxic substances like the lysosomal enzymes which destroy the invading organisms
3. Like this, each cytotoxic T cell can destroy a large number of microorganisms one after another.

Other Actions of Cytotoxic T Cells

1. The cytotoxic T cells also destroy cancer cells, transplanted cells such as those of transplanted heart or kidney or any other cells, which are foreign bodies
2. Cytotoxic T cells destroy even body's own tissues which are affected by the foreign bodies, particularly the viruses. Many viruses are entrapped in the membrane of affected cells. The antigen of the viruses attracts the T cells. And the cytotoxic T cells kill the affected cells also along with viruses. Because of this cytotoxic T cell is called killer cell.

■ ROLE OF SUPPRESSOR T CELLS

The suppressor T cells are also called regulatory T cells. These T cells suppress the activities of the killer T cells. Thus, the suppressor T cells play an important role in preventing the killer T cells from destroying the body's own tissues along with invaded organisms. The suppressor cells suppress the activities of helper T cells also.

■ ROLE OF MEMORY T CELLS

Some of the T cells activated by an antigen do not enter the circulation but remain in lymphoid tissue. These T cells are called memory T cells.

In later periods, the memory cells migrate to various lymphoid tissues throughout the body. When the body is exposed to the same organism for the second time, the memory cells identify the organism and immediately activate the other T cells. So, the invading organism is destroyed very quickly. The response of the T cells is also more powerful this time.

■ SPECIFICITY OF T CELLS

Each T cell is designed to be activated only by one type of antigen. It is capable of developing immunity against that antigen only. This property is called the specificity of T cells.

■ DEVELOPMENT OF HUMORAL IMMUNITY

■ INTRODUCTION

Humoral immunity is the immunity mediated by antibodies. Antibodies are secreted by B lymphocytes and released into the blood and lymph. The blood and lymph are the body fluids (humours or humors in Latin). Since the B lymphocytes provide immunity through humors, this type of immunity is called humoral immunity or B cell immunity.

The antibodies are the gamma globulins produced by B lymphocytes. These antibodies fight against the invading organisms. The humoral immunity is the major defense mechanism against the bacterial infection.

As in the case of cell mediated immunity, the macrophages and other antigen presenting cells play an important role in the development of humoral immunity also.

■ ROLE OF ANTIGEN PRESENTING CELLS

The ingestion of foreign organisms and digestion of their antigen by the antigen presenting cells are already explained.

Presentation of Antigen

The antigen presenting cells present their class II MHC molecules together with antigen bound HLA to B cells. This activates the B cells through series of events.

Sequence of Events during Activation of B Cells

1. The B cell recognizes the antigen bound to class II MHC molecule which is displayed on

the surface of the antigen presenting cell. It recognizes the antigen with the help of its own surface receptor protein called B cell receptor.

2. The recognition of the antigen by the B cell initiates a complex interaction between the B cell receptor and the antigen. This reaction activates B cells.
3. At the same time macrophages (the antigen presenting cells) release interleukin-1 which facilitates the activation and proliferation of B cells.
4. The activated B cells proliferate and the proliferated B cells carry out the further actions.
5. Simultaneously the antigen bound to class II MHC molecules activates the helper T cells also resulting in development of cell mediated immunity (already explained).

Transformation of B Cells

The proliferated B cells are transformed into two types of cells:

1. Plasma cells
2. Memory cells.

■ ROLE OF PLASMA CELLS

The plasma cells destroy the foreign organisms by producing the antibodies. Antibodies are globulin in nature. The rate of the antibody production is very high, i.e. each plasma cell produces about 2000 molecules of antibodies per second. The antibodies are also called immunoglobulins.

The antibodies are released into lymph and then transported into the circulation. The antibodies are produced until the end of lifespan of each plasma cell which may be from several days to several weeks.

■ ROLE OF MEMORY B CELLS

Memory B cells occupy the lymphoid tissues throughout the body. The memory cells are in inactive condition until the body is exposed to the same organism for the second time.

During the second exposure, the memory cells are stimulated by the antigen and produce more quantity of antibodies at a faster rate, than in the first exposure. The antibodies produced during the second exposure to the foreign antigen are also more potent than those produced during first exposure. This phenomenon forms the basic principle of vaccination against the infections.

■ ROLE OF HELPER T CELLS

Helper T cells are simultaneously activated by antigen. The activated helper T cells secrete two substances called interleukin 2 and B cell growth factor, which promote:

1. Activation of more number of B lymphocytes
2. Proliferation of plasma cells
3. Production of antibodies.

■ ANTIBODIES

An antibody is defined as a protein that is produced by B lymphocytes in response to the presence of an antigen. Antibody is globulin in nature and it is also called immunoglobulin (Ig). The immunoglobulins form 20 percent of the total plasma proteins. The antibodies enter almost all the tissues of the body.

Types of Antibodies

Five types of antibodies are identified:

1. IgA (Ig alpha)
2. IgD (Ig delta)
3. IgE (Ig epsilon)
4. IgG (Ig gamma)
5. IgM (Ig mu).

Among these antibodies, IgG forms 75 percent of the antibodies in the body.

Structure of Antibodies

Antibodies are gamma globulins and are formed by two pairs of chains namely, one pair of heavy or long chains and one pair of light or short chains.

Mechanism of Actions of Antibodies

The antibodies protect the body from the invading organisms in two ways:

1. By direct actions
2. Through complement system.

1. Direct Actions of Antibodies

Antibodies directly inactivate the invading organism by any one of the following methods:

- i. *Agglutination*: In this, the foreign bodies like RBCs or bacteria with antigens on their surfaces are held together in a clump by the antibodies.
- ii. *Precipitation*: In this, the soluble antigens toxin are converted into insoluble forms and then precipitated.
- iii. *Neutralization*: During this, the antibodies cover the toxic sites of antigenic products.
- iv. *Lysis*: In this, the antibodies rupture the cell membrane of organisms and then destroy them.

2. Actions of Antibodies through Complement System

The complement system is the one that enhances or accelerates various activities during the fight against the invading organisms. It contains plasma enzymes, which are identified by numbers from C₁ to C₉.

Functions of Different Antibodies

1. IgA plays a role in localized defense mechanism in external secretions like tear
2. IgD is involved in recognition of the antigen by B lymphocytes
3. IgE is involved in allergic reactions
4. IgG is responsible for complement fixation
5. IgM is also responsible for complement fixation.

Specificity of B Lymphocytes

Each B lymphocyte is designed to be activated only by one type of antigen. It is also capable of producing antibodies against that antigen only. This property of B lymphocyte is called specificity.

NATURAL KILLER CELL

Natural killer (NK) cell is a large granular cell with indented nucleus. It is considered as the third type of lymphocyte. It is not a phagocytic cell but its granules contain hydrolytic enzymes which causes lysis of cells of invading organisms.

Functions of NK Cell

The NK cell:

1. Destroys the viruses
2. Destroys the viral infected or damaged cells, which might form tumors
3. Destroys the malignant cells and prevents development of cancerous tumors
4. Secretes cytokines such as interleukin-2, interferons, colony stimulating factor (GM-CSF) and tumor necrosis factor- .

CYTOKINES

Cytokines are the hormone like small proteins acting as intercellular messengers (cell signaling molecules) by binding to specific receptors of target cells. These nonantibody proteins are secreted by WBCs and some other types of cells. Their major function is the activation and regulation of general immune system of the body.

Cytokines are distinct from the other cell signaling molecules such as growth factors and hormones. Cytokines are classified into several types:

1. Interleukins
2. Interferons
3. Tumor necrosis factors
4. Chemokines
5. Defensins
6. Cathelicidins
7. Platelet activating factor

IMMUNE DEFICIENCY DISEASES

Immune deficiency diseases are group of diseases in which some components of immune system is missing or defective. Normally, the defense mechanism protects the body from invading pathogenic organism. When the defense mechanism fails or becomes faulty (defective), the organisms of even low virulence produce severe disease. The organisms, which take advantage of defective defense mechanism, are called opportunists.

The immune deficiency diseases caused by such opportunists are of two types:

1. Congenital immune deficiency diseases
2. Acquired immune deficiency diseases.

CONGENITAL IMMUNE DEFICIENCY DISEASES

Congenital diseases are inherited and occur due to the defects in B cell, or T cell or both. The common examples are DiGeorge's syndrome (due to absence of thymus) and severe combined immune deficiency (due to lymphopenia or the absence of lymphoid tissue).

ACQUIRED IMMUNE DEFICIENCY DISEASES

Acquired immune deficiency diseases occur due to infection by some organisms. The most common disease of this type is acquired immune deficiency syndrome (AIDS).

Acquired Immune Deficiency Syndrome (AIDS)

It is an infectious disease caused by immune deficiency virus (HIV). AIDS is the most common problem throughout the world because of rapid increase in the number of victims. Infection occurs when a glycoprotein from HIV binds to surface receptors of T lymphocytes, monocytes, macrophages and dendritic cells leading to destruction of these cells. It causes slow progressive decrease in immune function resulting in opportunistic infections of various

types. The common opportunistic infections, which kill the AIDS patient are pneumonia and skin cancer.

■ AUTOIMMUNE DISEASES

Autoimmune disease is defined as condition in which the immune system mistakenly attacks body's own cells and tissues. Normally, an antigen induces the immune response in the body. The condition in which the immune system fails to give response to an antigen is called tolerance. This is true with respect to body's own antigens that are called self antigens or autoantigens.

Normally, body has the tolerance against self antigen. However, in some occasions, the

tolerance fails or becomes incomplete against self antigen. This state is called autoimmunity and it leads to the activation of T lymphocytes or production of autoantibodies from B lymphocytes. The T lymphocytes (cytotoxic T cells) or autoantibodies attack the body's normal cells whose surface contains the self antigen or autoantigen.

Common Autoimmune Diseases

1. Diabetes mellitus
2. Myasthenia gravis
3. Hashimoto's thyroiditis
4. Graves' disease
5. Rheumatoid arthritis.

Platelets

- INTRODUCTION
- STRUCTURE AND COMPOSITION
- NORMAL COUNT AND VARIATIONS
- PROPERTIES
- FUNCTIONS
- DEVELOPMENT
- LIFESPAN AND FATE
- APPLIED PHYSIOLOGY — PLATELET DISORDERS

■ INTRODUCTION

Platelets or thrombocytes are the formed elements of the blood. Platelets are small colorless, non nucleated and moderately refractive bodies which are considered to be the fragments of cytoplasm.

■ SIZE OF PLATELETS

Diameter : 2.5μ (2 to 4μ)
Volume : $7.5 \text{ cu}\mu$ (7 to $8 \text{ cu}\mu$).

■ SHAPE OF PLATELETS

Normally, platelets are of several shapes, viz. spherical or rod shaped and become oval or disk shaped when inactivated. Sometimes, the platelets have dumb-bell shape, comma shape, cigar shape or any other unusual shape.

■ STRUCTURE AND COMPOSITION

Platelets are constituted by cell membrane or surface membrane, microtubules and cytoplasm.

■ CELL MEMBRANE

It is 6 nm thick and contains lipids in the form of phospholipids, cholesterol and glycolipids, carbohydrates as glycocalyx, and glycoproteins and proteins.

■ MICROTUBULES

Microtubules form a ring around cytoplasm below the cell membrane. Microtubules are made up of proteins called tubulin. These tubules provide structural support for the inactivated platelets to maintain the disk-like shape.

■ CYTOPLASM

The cytoplasm of the platelets contains the cellular organelles, Golgi apparatus, endoplasmic reticulum, mitochondria, microtubule, microvessels, filaments and different types of granules.

Cytoplasm also contains some chemical substances such as:

Proteins

1. Contractile proteins
 - i. Actin and myosin which are responsible for contraction of platelets
 - ii. Thrombosthenin the third contractile protein which is responsible for clot retraction
2. *von Willebrand factor*: Responsible for adherence of platelets
3. *Fibrin stabilizing factor*: A clotting factor
4. *Platelet derived growth factor (PDGF)*: Responsible for repair of damaged blood vessels and wound healing.
5. *Platelet activating factor (PAF)*: Causes aggregation of platelets during the injury of blood vessels
6. *Vitronectin (serum spreading factor)*: Promotes adhesion of platelets and spreading of cells in culture
7. *Thrombospondin*: Inhibits angiogenesis (formation of new blood vessels).

Enzymes

1. ATPase
2. Enzymes necessary for synthesis of prostaglandins.

Hormonal Substances

1. Adrenaline
2. 5-HT (serotonin)
3. Histamine.

Other Chemical Substances

1. Glycogen
2. Substances like blood group antigens
3. Inorganic substances—calcium, copper, magnesium and iron.

Platelet Granules

Granules present in cytoplasm of platelets are of two types, alpha granules and dense granules. Alpha granules contain clotting factors V and XIII, fibrinogen and platelet derived growth factor. Dense granules contain nucleotides, serotonin, phospholipid, calcium and lysosomes.

■ NORMAL COUNT AND VARIATIONS

Normal platelet count is 2,50,000. It ranges between 2,00,000 and 4,00,000/cumm of blood.

■ PHYSIOLOGICAL VARIATIONS

1. *Age*: Platelets are less in infants (1,50,000-2,00,000/cumm) and reaches normal level at 3rd month after birth.
2. *Sex*: There is no difference in the platelet count between males and females. In females, it is reduced during menstruation.
3. *High altitude*: Platelet count increases.
4. *After meals*: After taking food, the platelet count increases.

■ PATHOLOGICAL VARIATIONS

Refer applied physiology of this chapter.

■ PROPERTIES OF PLATELETS

■ ADHESIVENESS

Adhesiveness is the property of sticking to a rough surface. While coming in contact with any rough surface the platelets are activated and stick to the surface.

■ AGGREGATION (GROUPING OF PLATELETS)

Aggregation is the grouping of platelets. Activated platelets group together and become sticky.

■ AGGLUTINATION

Agglutination is the clumping together of platelets.

■ FUNCTIONS OF PLATELETS

■ 1. ROLE IN BLOOD CLOTTING

The platelets are responsible for the formation of intrinsic prothrombin activator. This substance is responsible for the onset of blood clotting (Chapter 15).

■ 2. ROLE IN CLOT RETRACTION

In the blood clot, the blood cells including platelets are entrapped in between the fibrin

threads. The cytoplasm of platelets contains the contractile proteins namely actin, myosin and thrombosthenin which are responsible for clot retraction (Chapter 15).

■ 3. ROLE IN PREVENTION OF BLOOD LOSS (HEMOSTASIS)

Platelets accelerate hemostasis by three ways:

- i. Platelets secrete 5-HT, which causes the constriction of blood vessels
- ii. Due to the adhesive property, the platelets seal the damage in blood vessels like capillaries
- iii. By formation of temporary plug also platelets seal the damage in blood vessels (Chapter 15).

■ 4. ROLE IN REPAIR OF RUPTURED BLOOD VESSEL

The platelet derived growth factor (PDGF) formed in cytoplasm of platelets is useful for the repair of the endothelium and other structures of the ruptured blood vessels.

■ 5. ROLE IN DEFENSE MECHANISM

By the property of agglutination, platelets encircle the foreign bodies and destroy them by phagocytosis.

■ DEVELOPMENT OF PLATELETS

Platelets are formed from bone marrow. The pluripotent stem cell gives rise to the CFU-M. This develops into megakaryocyte. The cytoplasm of megakaryocyte form pseudopodium. A portion of pseudopodium is detached to form platelet, which enters the circulation (Fig. 8-2).

Production of platelets is influenced by thrombopoietin. Thrombopoietin is a glycoprotein like erythropoietin. It is secreted by liver and kidneys.

■ LIFESPAN AND FATE OF PLATELETS

Average lifespan of platelets is about 10 days. Older platelets are destroyed by tissue macrophage system in spleen.

■ APPLIED PHYSIOLOGY – PLATELET DISORDERS

■ THROMBOCYTOPENIA

Decrease in platelet count is called thrombocytopenia. It leads to thrombocytopenic purpura (Chapter 15). Thrombocytopenia occurs in the following conditions:

- i. Acute infections
- ii. Acute leukemia
- iii. Aplastic and pernicious anemia
- iv. Chickenpox
- v. Smallpox
- vi. Splenomegaly
- vii. Scarlet fever
- viii. Typhoid
- ix. Tuberculosis
- x. Purpura.

■ THROMBOCYTOSIS

The increase in platelet count is called thrombocytosis. It occurs in the following conditions:

- i. Allergic conditions
- ii. Hemorrhage
- iii. Bone fractures
- iv. Surgical operations
- v. Splenectomy
- vi. Rheumatic fever
- vii. Trauma (wound or injury or damage produced by external force).

■ THROMBOCYTHEMIA

It is the condition with persistent and abnormal increase in platelet count. It occurs in:

- i. Carcinoma
- ii. Chronic leukemia
- iii. Hodgkin's disease.

■ GLANZMANN THROMBASTHENIA

It is an inherited hemorrhagic disorder caused by structural or functional abnormality of platelets. It leads to thrombasthenic purpura (Chapter 15).

15

Hemostasis and Coagulation of Blood

- **HEMOSTASIS**
 - DEFINITION
 - STAGES OF HEMOSTASIS
- **DEFINITION OF BLOOD COAGULATION**
- **FACTORS INVOLVED IN BLOOD CLOTTING**
- **SEQUENCE OF CLOTTING MECHANISM**
 - ENZYME CASCADE THEORY
 - STAGE 1: FORMATION OF PROTHROMBIN ACTIVATOR
 - STAGE 2: CONVERSION OF PROTHROMBIN INTO THROMBIN
 - STAGE 3: CONVERSION OF FIBRINOGEN INTO FIBRIN
- **BLOOD CLOT**
 - DEFINITION
 - CLOT RETRACTION
 - FIBRINOLYSIS
- **ANTICLOTTING MECHANISM IN THE BODY**
- **ANTICOAGULANTS**
 - HEPARIN
 - COUMARIN DERIVATIVES
 - EDTA
 - OXALATE COMPOUNDS
 - CITRATES
 - OTHER SUBSTANCES
- **PHYSICAL METHODS TO PREVENT BLOOD CLOTTING**
- **PROCOAGULANTS**
- **TESTS FOR CLOTTING**
 - BLEEDING TIME
 - CLOTTING TIME
 - PROTHROMBIN TIME
- **APPLIED PHYSIOLOGY**
 - BLEEDING DISORDERS
 - THROMBOSIS

■ HEMOSTASIS

■ DEFINITION

Hemostasis is defined as arrest or stoppage of bleeding.

■ STAGES OF HEMOSTASIS

When a blood vessel is injured, the injury initiates a series of reactions resulting in hemostasis. It occurs in three stages:

1. Vasoconstriction
2. Platelet plug formation
3. Coagulation of blood.

1. Vasoconstriction

Immediately after injury, the blood vessel constricts and decreases the loss of blood from damaged portion. Usually, arterioles and small arteries constrict. The vasoconstriction is purely a local phenomenon. When the blood vessels are cut, the endothelium is damaged and the collagen is exposed. The platelets adhere to this collagen, and get activated. The activated platelets secrete serotonin and other vasoconstrictor substances which cause constriction of the blood vessels (Fig. 15-1). The adherence of platelets to the collagen is accelerated by von Willebrand factor.

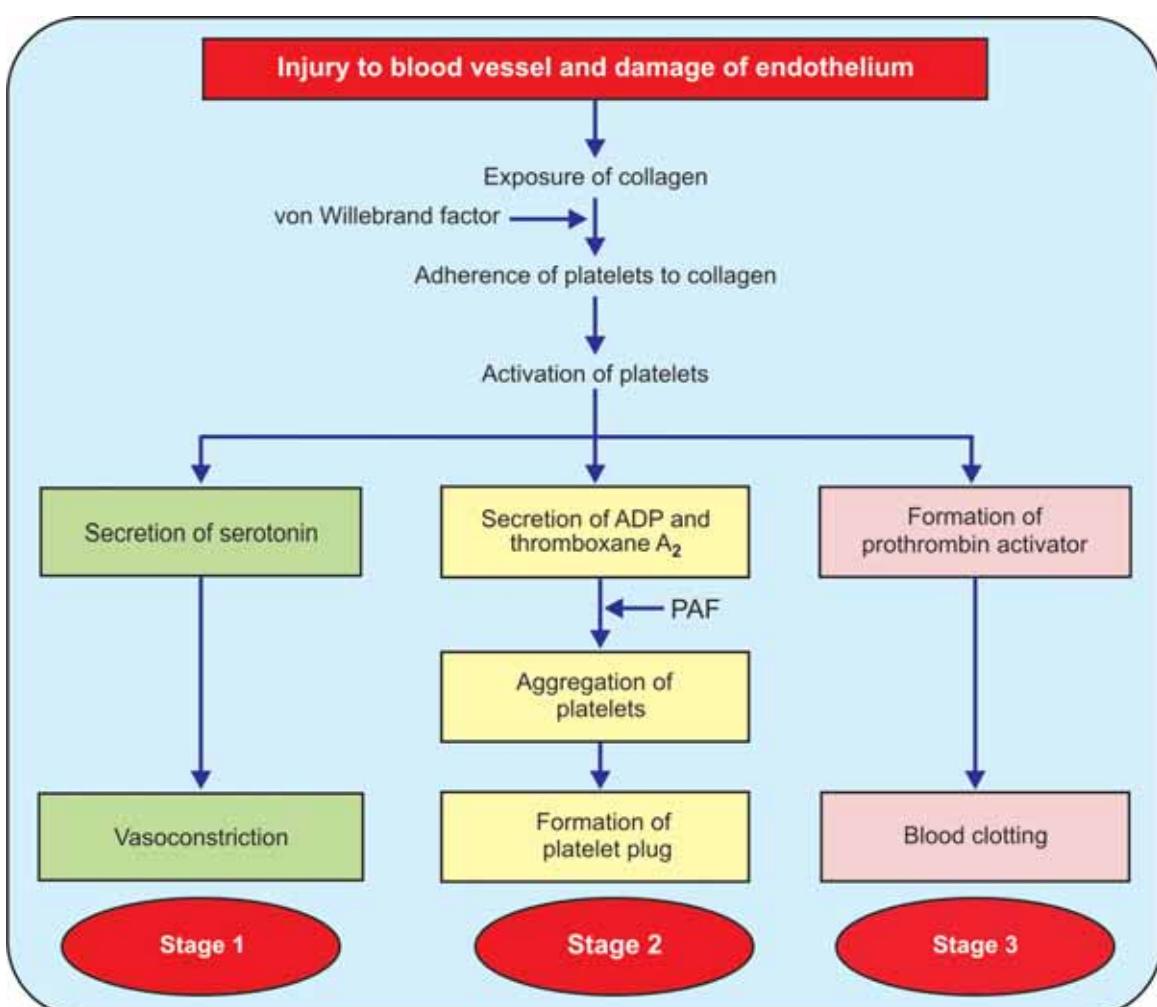


FIGURE 15-1: States of hemostasis. PAF = platelet activating factor.

2. Formation of Platelet Plug

The platelets get adhered to the collagen of ruptured blood vessel and secrete ADP and thromboxane A₂. These two substances attract more and more platelets and activate them. All these platelets aggregate together and form a loose temporary platelet plug or temporary hemostatic plug, which closes the injured part of the vessel and prevents further blood loss. The platelet aggregation is accelerated by platelet activating factor (PAF).

3. Coagulation of Blood

During this process, the fibrinogen is converted into fibrin. The fibrin threads get attached to the loose platelet plug, which blocks the ruptured part of blood vessels and prevents further blood loss completely.

■ DEFINITION OF BLOOD COAGULATION

Coagulation or clotting is defined as the process in which blood loses its fluidity and becomes a jelly like mass few minutes after it is shed out or collected in a container.

■ FACTORS INVOLVED IN BLOOD CLOTTING

Coagulation of blood occurs through a series of reactions due to the activation of a group of substances. The substances necessary for clotting are called clotting factors.

Thirteen clotting factors are identified:

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Thromboplastin (Tissue factor)
Factor IV	Calcium
Factor V	Labile factor (Proaccelerin or Accelerator globulin)
Factor VI	Presence has not been proved
Factor VII	Stable factor
Factor VIII	Antihemophilic factor (Antihemophilic globulin)
Factor IX	Christmas factor
Factor X	Stuart-Prower factor

Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor (Contact factor)
Factor XIII	Fibrin stabilizing factor (Fibrinase).

The clotting factors were named either after the scientists who discovered them or as per the activity except factor IX. Factor IX or Christmas factor was named after the patient in whom it was discovered.

■ SEQUENCE OF CLOTTING MECHANISM

■ ENZYME CASCADE THEORY

Most of the clotting factors are proteins in the form of enzymes. Normally, all the factors are present in the form of inactive proenzyme. These proenzymes must be activated into enzymes to enforce clot formation. It is carried out by series of proenzyme-enzyme conversion reactions. The first one of the series is converted into an active enzyme that activates the second one, which activates the third one; this continues till the final active enzyme thrombin is formed.

Enzyme cascade theory explains how various reactions involved in the conversion of proenzymes to active enzymes take place in the form of a cascade. Cascade refers to a process that occurs through a series of steps, each step initiating the next, until the final step is reached.

Stages of Blood Clotting

In general, blood clotting occurs in three stages:

- Formation of prothrombin activator
- Conversion of prothrombin into thrombin
- Conversion of fibrinogen into fibrin.

■ STAGE 1: FORMATION OF PROTHROMBIN ACTIVATOR

Blood clotting commences with the formation of a substance called prothrombin activator. Its formation is initiated by substances produced either within the blood itself or outside the blood.

Thus, formation of prothrombin activator occurs through two pathways:

- Intrinsic pathway
- Extrinsic pathway.

Intrinsic Pathway for the Formation of Prothrombin Activator

In this, the formation of prothrombin activator is initiated by platelets, which are within the blood itself (Fig. 15-2).

Sequence of events in intrinsic pathway

- i. During the injury, the blood vessel is ruptured. The endothelium is damaged and collagen beneath the endothelium is exposed
- ii. When platelet comes in contact with collagen of damaged blood vessel, it gets activated and releases phospholipids
- iii. When factor XII (Hegman factor) comes in contact with collagen, it is converted into activated factor XII in the presence of kallikrein and high molecular weight (HMW) kinogen
- vi. The activated factor XII converts factor XI into activated factor XI in the presence of HMW kinogen
- v. The activated factor XI activates factor IX in the presence of factor IV (calcium)
- vi. Activated factor IX activates factor X in the presence of factor VIII and calcium
- vii. Now the activated factor X reacts with platelet phospholipid and factor V to form prothrombin activator. This needs presence of calcium ions
- viii. Factor V is also activated by positive feedback effect of thrombin (see below).

Extrinsic Pathway for the Formation of Prothrombin Activator

In this, the formation of prothrombin activator is initiated by the tissue thromboplastin which is formed from the injured tissues.

Sequence of events in extrinsic pathway

- i. The tissues that are damaged during injury release factor III, i.e. tissue thromboplastin. The thromboplastin contains proteins, phospholipid and glycoprotein, which act as proteolytic enzymes

- ii. The glycoprotein and phospholipid components of thromboplastin convert factor X into activated factor X, in the presence of factor VII
- iii. The activated factor X reacts with factor V and phospholipid component of tissue thromboplastin to form prothrombin activator. This reaction requires the presence of calcium ions.

■ STAGE 2: CONVERSION OF PROTHROMBIN INTO THROMBIN

Blood clotting is all about thrombin formation. Once thrombin is formed, it definitely leads to clot formation.

Sequence of Events in Stage 2

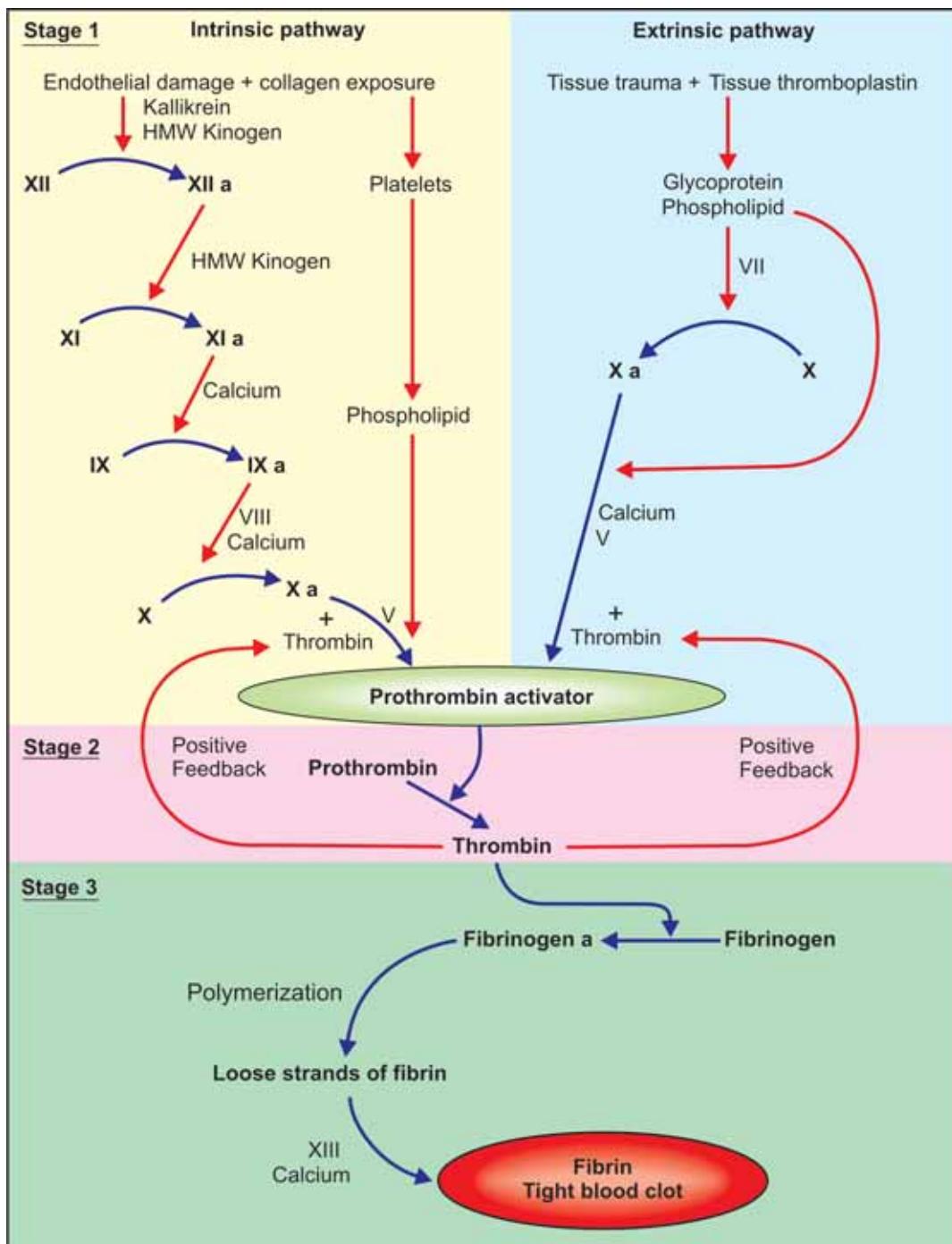
- i. Prothrombin activator that is formed in intrinsic and extrinsic pathways converts prothrombin into thrombin in the presence of calcium ions (Factor IV)
- ii. Once formed, thrombin initiates the formation of more thrombin molecules. The initially formed thrombin activates Factor V. Factor V in turn accelerates formation of both extrinsic and intrinsic prothrombin activator which converts prothrombin into thrombin. This effect of thrombin is called positive feedback effect (Fig. 15-2).

■ STAGE 3: CONVERSION OF FIBRINOGEN INTO FIBRIN

The final stage of blood clotting involves the conversion of fibrinogen into fibrin by thrombin.

Sequence of Events in Stage 3

- i. Thrombin converts fibrinogen into activated fibrinogen which is called fibrin monomer.
- ii. Fibrin monomer polymerizes with other monomer molecules and form loosely arranged strands of fibrin
- iii. Later these loose strands are modified into dense and tight fibrin threads by fibrin stabilizing factor (factor XIII) in the presence of calcium ions (Fig. 15-2). All the tight fibrin threads are aggregated to form a meshwork of stable clot.

**FIGURE 15-2:** Stages of blood coagulation.

a = activated + = thrombin induces formation of more thrombin (positive feedback)

BLOOD CLOT

DEFINITION

Blood clot is defined as the mesh of fibrin entangling RBCs, WBCs and platelets.

CLOT RETRACTION

After the formation, the blood clot starts contracting. And after about 30 to 45 minutes, the straw colored serum oozes out of the clot. The process involving the contraction of blood clot and oozing of serum is called clot retraction.

The contractile proteins namely, actin, myosin and thrombosthenin in the cytoplasm of platelets are responsible for clot retraction.

FIBRINOLYSIS

The lysis of blood clot inside the blood vessel is called fibrinolysis. It helps to remove the clot from the lumen of the blood vessel. This process requires a substance called plasmin or fibrinolysin.

Plasmin is formed from inactivated glycoprotein called plasminogen. Plasminogen is synthesized in liver and it is incorporated with other proteins in the blood clot. Plasminogen is converted into plasmin by tissue plasminogen activator (t-PA), lysosomal enzymes and thrombin.

Plasmin causes lysis of clot by dissolving and digesting the fibrin threads.

Significance of Lysis of Clot

In vital organs, particularly the heart, the blood clot obstructs the minute blood vessel leading to myocardial infarction. The lysis of blood clot allows reopening of affected blood vessels and prevents the development of infarction.

The fibrinolytic enzymes like streptokinase are used for the lysis of blood clot during the treatment in early stages of myocardial infarction.

ANTICLOTTING MECHANISM IN THE BODY

Under physiological conditions, intravascular clotting does not occur. It is because of the presence of some physicochemical factors in the body.

1. Physical Factors

- Continuous circulation of blood
- Smooth endothelial lining of the blood vessels.

2. Chemical Factors

- Presence of natural anticoagulant called heparin that is produced by the liver
- Production of thrombomodulin by endothelium of the blood vessels (except in brain capillaries). Thrombomodulin is a thrombin binding protein. It binds with thrombin and forms a thrombomodulin - thrombin complex. This complex activates protein-C. Activated protein-C along with its cofactor protein-S inactivates Factor V and Factor VIII. Inactivation of these two clotting factors prevents clot formation
- All the clotting factors are in inactive state.

ANTICOAGULANTS

The substances, which prevent or postpone coagulation of blood, are called anticoagulants.

Anticoagulants are of three types:

- Anticoagulants used to prevent blood clotting inside the body, i.e. *in vivo*
- Anticoagulants used to prevent clotting of blood that is collected from the body, i.e. *in vitro*
- Anticoagulants used to prevent blood clotting both *in vivo* and *in vitro*.

1. HEPARIN

Heparin is a naturally produced anticoagulant in the body. It is produced by mast cells which are the wandering cells situated immediately outside the capillaries in many tissues or organs that contain more connective tissue. These cells are abundant in liver and lungs. Basophils also secrete heparin.

Heparin is a conjugated polysaccharide. The commercial heparin is prepared from the liver and other organs of animals. The commercial preparation is available in liquid form or dry form as sodium, calcium, ammonium or lithium salts.

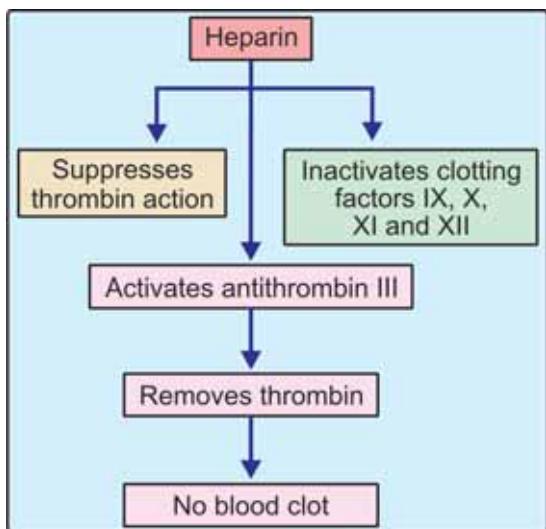


FIGURE 15-3: Mechanism of action of heparin

Mechanism of Action of Heparin

Heparin:

- Prevents blood clotting by its antithrombin activity. It directly suppresses the activity of thrombin
- Combines with antithrombin III (a protease inhibitor present in circulation) and removes thrombin from circulation
- Activates antithrombin III
- Inactivates the active form of other clotting factors like IX, X, XI and XII (Fig. 15-3).

Uses of Heparin

Heparin is used as an anticoagulant both *in vivo* and *in vitro*.

Clinical use

Intravenous injection of heparin (0.5 to 1 mg/kg body weight) postpones clotting for 3 to 4 hours (until it is destroyed by the enzyme heparinase). So, it is widely used as an anticoagulant in clinical practice for many purposes such as:

- To prevent intravascular blood clotting during surgery

- During dialysis when blood is passed through artificial kidney
- During cardiac surgery, that involves passing the blood through heart lung machine
- To preserve the blood before transfusion.

Use in the laboratory

Heparin is also used as anticoagulant *in vitro* while collecting blood for various investigations. Heparin is the most expensive anticoagulant.

■ 2. COUMARIN DERIVATIVES

Dicoumaral and warfarin are the derivatives of coumarin.

Mechanism of Action

The coumarin derivatives prevent blood clotting by inhibiting the action of vitamin K. Vitamin K is essential for the formation of various clotting factors namely, II, VII, IX and X.

Uses

Dicoumaral and warfarin are the commonly used oral anticoagulants in clinical practice (*in vivo*).

■ 3. EDTA

Ethylenediaminetetra acetic acid (EDTA) is a strong anticoagulant. It is available in two forms:

- Disodium salt (Na_2EDTA)
- Tripotassium salt (K_3EDTA).

Mechanism of Action

These substances prevent blood clotting by removing calcium from blood.

Uses

EDTA is used as an anticoagulant both *in vivo* and *in vitro*.

- It is administered intravenously in cases of lead poisoning (*in vivo*)
- It is also used as an anticoagulant in the laboratory (*in vitro*).

■ 4. OXALATE COMPOUNDS

Oxalate compounds prevent coagulation by forming calcium oxalate, which is precipitated later. Thus, these compounds reduce the blood calcium level.

Earlier sodium and potassium oxalates were used. Nowadays, mixture of ammonium oxalate and potassium oxalate in the ratio of 3:2 is used. Each salt is an anticoagulant by itself. But potassium oxalate alone causes shrinkage of RBCs. Ammonium oxalate alone causes swelling of RBCs. But together, these substances do not alter the cellular activity.

Mechanism of Action

Oxalate combines with calcium and forms insoluble calcium oxalate. Thus, oxalate removes calcium from blood and lack of calcium prevents coagulation.

Uses

Oxalate compounds are used as *in vitro* anticoagulants. Oxalate is poisonous so it cannot be used *in vivo*.

■ 5. CITRATES

Sodium, ammonium and potassium citrates are used as anticoagulants.

Mechanism of Action

Citrate combines with calcium in blood to form insoluble calcium citrate. Like oxalate, citrate also removes calcium from blood and prevents coagulation.

Uses

Citrates are used as an anticoagulant both *in vivo* and *in vitro*.

- i. Used to store blood in the blood bank. It is available in two forms:
 - a. Acid citrate dextrose (ACD)
 - b. Citrate phosphate dextrose (CPD)
- ii. Used in laboratory *in vitro* or RBC and platelet counts.

■ 6. OTHER SUBSTANCES WHICH PREVENT BLOOD CLOTTING

Peptone, proteins from venom of copperhead snake and hirudin (from leach) are the known anticoagulants.

■ PHYSICAL METHODS TO PREVENT BLOOD CLOTTING

The coagulation of blood is postponed or prevented by the following physical methods:

■ 1. COLD

Reducing the temperature to about 5°C postpones coagulation of blood.

■ 2. COLLECTING BLOOD IN A CONTAINER WITH SMOOTH SURFACE

Collecting the blood in a container with smooth surface like a silicon coated container prevents clotting. The smooth surface inhibits the activation of factor XII and platelets. So, the formation of prothrombin activator is prevented.

■ PROCOAGULANTS

Procoagulants or hemostatic agents are the substances, which accelerate the process of blood coagulation. Procoagulants are:

1. Thrombin
2. Snake venom
3. Extracts of lungs and thymus
4. Sodium or calcium alginate
5. Oxidized cellulose

■ TESTS FOR CLOTTING

■ 1. BLEEDING TIME

Bleeding time is the time interval from oozing of blood after a cut or injury till arrest of bleeding. Usually, it is determined by Duke method using blotting paper or filter paper. Its normal duration is 3-6 minutes. It is prolonged in purpura.

■ 2. CLOTTING TIME

Clotting time is the time interval from oozing of blood after a cut or injury till the formation of clot.

It is usually determined by capillary tube method. Its normal duration is 3-8 minutes. And it is prolonged in hemophilia.

■ 3. PROTHROMBIN TIME

It is the time taken by blood to clot after adding tissue thromboplastin to it. Blood is collected and oxalated so that, the calcium is precipitated and prothrombin is not converted into thrombin. Thus, the blood clotting is prevented. Then a large quantity of tissue thromboplastin with calcium is added to this blood. Calcium nullifies the effect of oxalate. The tissue thromboplastin activates prothrombin and blood clotting occurs.

During this procedure, the time taken by blood to clot after adding tissue thromboplastin is determined. Prothrombin time indicates the total quantity of prothrombin present in the blood.

The normal duration of prothrombin time is about 12 seconds. It is prolonged in deficiency of prothrombin and other factors like factors I, V, VII and X. However, it is normal in hemophilia.

■ APPLIED PHYSIOLOGY

■ BLEEDING DISORDERS

Bleeding disorders are the diseases characterized by prolonged bleeding time or clotting time. The bleeding disorders are of three types:

1. *Hemophilia*

Hemophilia is a group of sex linked inherited blood disorders characterized by prolonged clotting time. In this disorder, males are affected and the females are the carriers. Because of prolonged clotting time, even a mild trauma causes excess bleeding which can lead to death. Damage of skin while falling or extraction of a tooth may cause excess bleeding for few weeks. Easy bruising and hemorrhage in muscles and joints are also common in this disease.

Cause for hemophilia

Lack of prothrombin activator is the cause for hemophilia. The formation of prothrombin activator

is affected due to the deficiency of factor VIII, IX or XI.

Types of hemophilia

Depending upon the deficiency of the factor involved, hemophilia is classified into three types:

- i. Hemophilia A or classic hemophilia that is due to the deficiency of factor VIII. 85 percent of people with hemophilia are affected by hemophilia A.
- ii. Hemophilia B or Christmas disease which is due to the deficiency of factor IX. 15 percent of people with hemophilia are affected by hemophilia B.
- iii. Hemophilia C which is due to the deficiency of factor XI. It is a very rare blood disorder.

2. *Purpura*

It is a disorder characterized by prolonged bleeding time. However, the clotting time is normal. The characteristic feature of this disease is spontaneous bleeding under the skin from ruptured capillaries. It causes small tiny hemorrhagic spots under the skin which are called purpuric spots (purple colored patch like appearance). That is why this disease is called purpura.

Types and causes of purpura

The purpura is classified into different types depending upon the causes.

Thrombocytopenic purpura

Thrombocytopenic purpura is due to the deficiency of platelets (thrombocytopenia). In bone marrow disease, platelet production is affected leading to deficiency of platelets.

Idiopathic thrombocytopenic purpura

Purpura due to some unknown cause is called idiopathic thrombocytopenic purpura. It is believed that platelet count decreases due to the development of antibodies against platelets, which occurs after blood transfusion.

Thrombasthenic purpura

It is due to structural or functional abnormality of platelets. However, the platelet count is normal. It is characterized by normal clotting time, normal or prolonged bleeding time but defective clot retraction.

3. von Willebrand Disease

von Willebrand disease is a bleeding disorder characterized by excess bleeding even with a mild injury. It is due to inherited deficiency of von Willebrand factor which is a protein secreted by endothelium of damaged blood vessels and platelets. This protein is responsible for adherence of platelets to endothelium of blood vessels during hemostasis after an injury. It is also responsible for the survival and maintenance of factor VIII in plasma.

The deficiency of von Willebrand factor suppresses platelet adhesion. It also causes deficiency of factor VIII. This results in excess bleeding which resembles the bleeding that occurs during platelet dysfunction or hemophilia.

■ THROMBOSIS

Thrombosis or intravascular blood clotting refers to coagulation of blood inside the blood vessels. Normally, blood does not clot in the blood vessel because of some factors which are already explained. But some abnormal conditions can cause thrombosis.

Causes of Thrombosis

1. Injury to blood vessels
2. Roughened endothelial lining
3. Sluggishness of blood flow
4. Agglutination of RBCs
5. Poisons like snake venom, mercury, and arsenic compounds
6. Congenital absence of protein C.

Complications of Thrombosis

1. Thrombus

During thrombosis, lumen of blood vessels is occluded. The solid mass of platelets, red cells and/or clot, which obstructs the blood vessel, is called thrombus. The thrombus formed due to agglutination of RBC is called agglutinative thrombus.

2. Embolism and embolus

Embolism is the process in which the thrombus or part of it is detached and carried in bloodstream and occludes the small blood vessels resulting in arrests of blood flow to any organ or region of the body. Embolus is the thrombus or part of it, which arrests the blood flow. The obstruction of blood flow by embolism is common in lungs (pulmonary embolism), brain (cerebral embolism) or heart (coronary embolism).

3. Ischemia

Insufficient blood supply to an organ or area of body by the obstruction of blood vessels is called ischemia. Ischemia results in tissue damage because of hypoxia (lack of oxygen). Ischemia also causes discomfort, pain and tissue death. Death of body tissue is called necrosis.

4. Necrosis and infarction

Necrosis is a general term that refers to tissue death caused by loss of blood supply, injury, infection, inflammation, physical agents or chemical substances.

Infarction means the tissue death due to loss of blood supply. Loss of blood supply is usually caused by occlusion of an artery by thrombus or embolus and sometimes by atherosclerosis (Chapter 46). The area of tissue that undergoes infarction is called infarct. Infarction commonly occurs in heart, brain, lungs, kidneys and spleen.

16

Blood Groups and Blood Transfusion

- INTRODUCTION
- ABO BLOOD GROUPS
 - LANDSTEINER'S LAW
 - BLOOD GROUP SYSTEMS
 - ABO SYSTEM
 - DETERMINATION OF ABO GROUP
 - IMPORTANCE OF ABO GROUPS IN BLOOD TRANSFUSION
 - MATCHING AND CROSS MATCHING
 - INHERITANCE OF ABO AGGLUTINOGENS AND AGGLUTININS
 - TRANSFUSION REACTIONS DUE TO ABO INCOMPATIBILITY
- Rh FACTOR
 - INHERITANCE OF Rh ANTIGEN
 - TRANSFUSION REACTIONS DUE TO Rh INCOMPATIBILITY
 - HEMOLYTIC DISEASE OF FETUS AND NEWBORN — ERYTHROBLASTOSIS FETALIS
- OTHER BLOOD GROUPS
- IMPORTANCE OF KNOWING BLOOD GROUP
- BLOOD TRANSFUSION
 - INTRODUCTION
 - BLOOD SUBSTITUTES
 - EXCHANGE TRANSFUSION
 - AUTOLOGOUS BLOOD TRANSFUSION

■ INTRODUCTION

Blood groups are determined by the presence of antigen in RBC membrane. When blood from two individuals is mixed, sometimes clumping (agglutination) of RBCs occurs. This clumping is because of the immunological reactions. But, why clumping occurs in some cases and not in other cases remained a mystery until the discovery of

blood groups by the Austrian Scientist, Karl Landsteiner in 1901. He was honored with Nobel Prize in 1930 for this discovery.

■ ABO BLOOD GROUPS

Determination of blood groups depends upon the immunological reaction between antigen and antibody. Landsteiner found two antigens on the

surface of RBCs and named them as A antigen and B antigen. These antigens are also called agglutinogens because of their capacity to cause agglutination of RBCs. He noticed the corresponding antibodies or agglutinins in the plasma and named them anti A or α antibody and anti B or β antibody. However, a particular agglutinogen and the corresponding agglutinin cannot be present together. If present, it causes clumping of the blood. Based on this, Landsteiner classified the blood groups. Later it has become the "Landsteiner's law" for grouping the blood.

■ LANDSTEINER'S LAW

Landsteiner's law states that:

1. If a particular antigen (agglutinogen) is present in the RBCs, corresponding antibody (agglutinin) must be absent in the serum.
2. If a particular antigen is absent in the RBCs, the corresponding antibody must be present in the serum.

Though the second part of Landsteiner's law is a fact, it is not applicable to Rh factor.

■ BLOOD GROUP SYSTEMS

More than 20 genetically determined blood group systems are known today. But, Landsteiner discovered two blood group systems called ABO system and Rh system. These two blood group systems are the most important ones that are determined before blood transfusions.

■ ABO SYSTEM

Based on the presence or absence of antigen A and antigen B, blood is divided into four groups:

1. 'A' group
2. 'B' group
3. 'AB' group
4. 'O' group.

The blood having antigen A is called A group. This group has β antibody in the serum. The blood with antigen B and α antibody is called B group. If both the antigens are present, the blood group is called AB group and serum of this group does not contain any antibody. If both antigens are absent, the blood group is called O group and

TABLE 16-1: Antigen and antibody present in ABO blood groups

Group	Antigen in RBC	Antibody in serum
A	A	Anti B (β)
B	B	Anti A (α)
AB	A and B	No antibody
O	No antigen	Anti A and Anti B

TABLE 16-2: Percentage of people having different blood groups

Population	A	B	AB	O
Europeans	42	9	3	46
Asians	25	25	5	45

both α and β antibodies are present in the serum. The antigens and antibodies present in different groups of ABO system are given in Table 16-1. Percentage of people among Asian and European population belonging to different blood group is given in Table 16-2.

"A" group has two subgroups namely "A₁" and "A₂". Similarly, "AB" group has two subgroups namely "A₁B" and "A₂B".

■ DETERMINATION OF THE ABO GROUP

Determination of the ABO group is also called blood grouping, blood typing or blood matching.

Principle of Blood Typing — Agglutination

The blood typing is done on the basis of agglutination. Agglutination means the collection of separate particles like RBCs into clumps or masses. Agglutination occurs if an antigen is mixed with its corresponding antibody which is called isoagglutinin. Agglutination occurs when A antigen is mixed with anti A or when B antigen is mixed with anti B.

Requisites for Blood Typing

To determine the blood group of a person, a suspension of his RBC and testing antisera are

required. Suspension of RBC is prepared by mixing blood drops with isotonic saline (0.9%).

The test sera are:

1. Antiserum A, containing anti A
2. Antiserum B, containing anti B.

Procedure

1. One drop of antiserum A is placed on one end of a glass slide (or a tile) and one drop of antiserum B on the other end
2. One drop of RBC suspension is mixed with each antiserum. The slide is slightly rocked for 2 minutes. The presence or absence of agglutination is observed by naked eyes and if necessary it is confirmed by using microscope
3. Presence of agglutination is confirmed by the presence of thick masses (clumping) of RBCs
4. Absence of agglutination is confirmed by clear mixture with dispersed RBCs.

Results

1. *If agglutination occurs with antiserum A:* The antiserum A contains anti A or α antibody. The agglutination occurs if the RBC contains A antigen. So, the blood group is A (Fig. 16-1).
2. *If agglutination occurs with antiserum B:* The antiserum B contains anti B or β antibody. The agglutination occurs if the RBC contains B antigen. So, the blood group is B.
3. *If agglutination occurs with both antisera A and B:* The RBC contains both A and B antigens to cause agglutination. And, the blood group is AB.
4. *If agglutination does not occur either with antiserum A or antiserum B:* The agglutination does not occur if the RBC does not contain any antigen. The blood group is O.

■ IMPORTANCE OF ABO GROUPS IN BLOOD TRANSFUSION

During blood transfusion, only compatible blood must be used. The one who gives blood is called the donor and the one who receives the blood is called recipient.

While transfusing the blood, antigen of the donor and the antibody of the recipient are

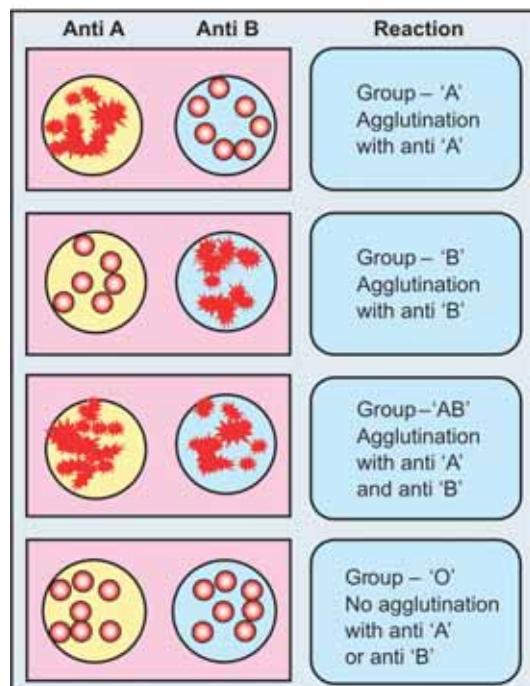


FIGURE 16-1: Determination of blood group

considered. The antibody of the donor and antigen of the recipient are ignored mostly.

Thus, RBC of "O" group has no antigen and so agglutination does not occur with any other group of blood. So, 'O' group blood can be given to any blood group persons and the people of this blood group are called universal donors.

The plasma of AB group blood has no antibody. This does not cause agglutination of RBC from any other group of blood. The people of AB group can receive blood from any blood group persons. So, people with this blood group are called universal recipients.

■ MATCHING AND CROSS MATCHING

Blood matching (typing) is a laboratory test done to determine the blood group of a person. When the person needs blood transfusion, another test called cross matching is done after the blood is typed. It is done to find out whether the person's body will accept the donor's blood or not.

For blood matching, RBC of the individual (recipient) and test sera are used. Cross matching is done by mixing the serum of the recipient and

TABLE 16-3: Inheritance of ABO group

Gene from parents	Group of the offspring	Genotype
A + A A + O	A	AA or AO
B + B B + O	B	BB or BO
A + B O + O	AB O	AB OO

the RBCs of donor. Cross matching is always done before blood transfusion. If agglutination of RBCs from a donor occurs during cross matching, the blood from that person is not used for transfusion.

Matching = Recipient's RBC + Test sera
 Cross matching = Recipient's serum +
 Donor's RBC

■ INHERITANCE OF ABO AGGLUTINOGENS AND AGGLUTININS

Blood group of a person depends upon the two genes inherited from each parent. Gene A and gene B are dominant by themselves and gene O is recessive. The inheritance of blood group is represented schematically as given in Table 16-3.

■ TRANSFUSION REACTIONS DUE TO ABO INCOMPATIBILITY

Transfusion reactions are the adverse reactions in the body which occur due to transfusion of incompatible (mismatched) blood. The reactions may vary from fever and hives (skin disorder characterized by itching) to renal failure, shock and death.

In mismatched transfusion, the transfusion reactions occur between donor's RBC and recipient's plasma. So, if the donor's plasma contains antibody against recipient's RBC, agglutination does not occur because these antibodies are diluted in recipient's blood.

But, if recipient's plasma contains antibodies against donor's RBCs, the immune system launches a response against the new blood cells. Donor RBCs are agglutinated and hemolyzed.

The hemolysis of RBCs results in release of large amount of hemoglobin into the plasma. This leads to the following complications.

1. Jaundice

Normally, hemoglobin released from destroyed RBC is degraded and bilirubin is formed from it. When the serum bilirubin level increases above 2 mg/dL jaundice occurs (Chapter 30).

2. Cardiac Shock

Simultaneously, the hemoglobin released into the plasma increases the viscosity of blood. This increases the workload on the heart leading to heart failure.

3. Renal Shutdown

Dysfunction of kidneys is called renal shutdown. The toxic substances from hemolyzed cells cause constriction of blood vessels in kidney. In addition, the toxic substances along with free hemoglobin are filtered through glomerular membrane and enter renal tubules. Because of poor rate of reabsorption from renal tubules, all these substances precipitate and obstruct the renal tubule. This suddenly stops formation of urine (anuria).

If not treated with artificial kidney, the person dies within 10-12 days because of jaundice, circulatory shock and more specifically due to renal shutdown and anuria (Fig 16-2).

■ Rh FACTOR

Rh factor is an antigen present in RBC. The antigen was discovered by Landsteiner and Wiener. It was first discovered in rhesus monkey and hence the name Rh factor. There are many Rh antigens but only the D is more antigenic in human.

The persons having D antigen are called Rh positive and those without D antigen are called

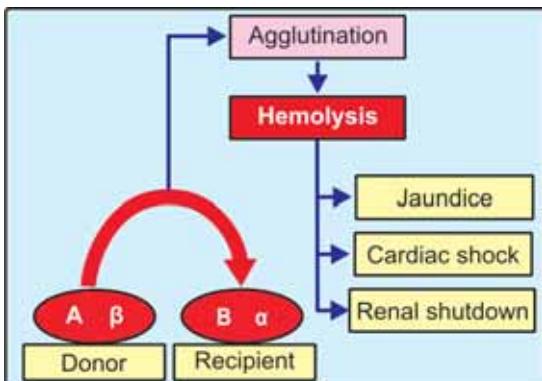


FIGURE 16-2: Complications of mismatched blood transfusion

Rh negative. Among Asian population, 85 percent of people are Rh positive and 15 percent are Rh negative.

Rh system is different from ABO group system because, the antigen D does not have corresponding natural antibody (anti D). However, if Rh positive blood is transfused to a Rh negative person for the first time, then anti D is formed in that person. On the other hand, there is no risk of complications if Rh positive person receives Rh negative blood.

■ INHERITANCE OF Rh ANTIGEN

Rhesus factor is an inherited dominant factor. It may be homozygous rhesus positive with DD or heterozygous rhesus positive with Dd (Fig. 16-3). Rhesus negative occurs only with complete absence of D (i.e. with homozygous dd).

■ TRANSFUSION REACTIONS DUE TO Rh INCOMPATIBILITY

When a Rh negative person receives Rh positive blood for the first time, he is not affected much, since the reactions do not occur immediately. But, the Rh antibodies develop within one month. The transfused RBCs, which are still present in recipient's blood are agglutinated. These agglutinated cells are lysed by macrophages. So, a delayed transfusion reaction occurs. But, it is usually mild and does

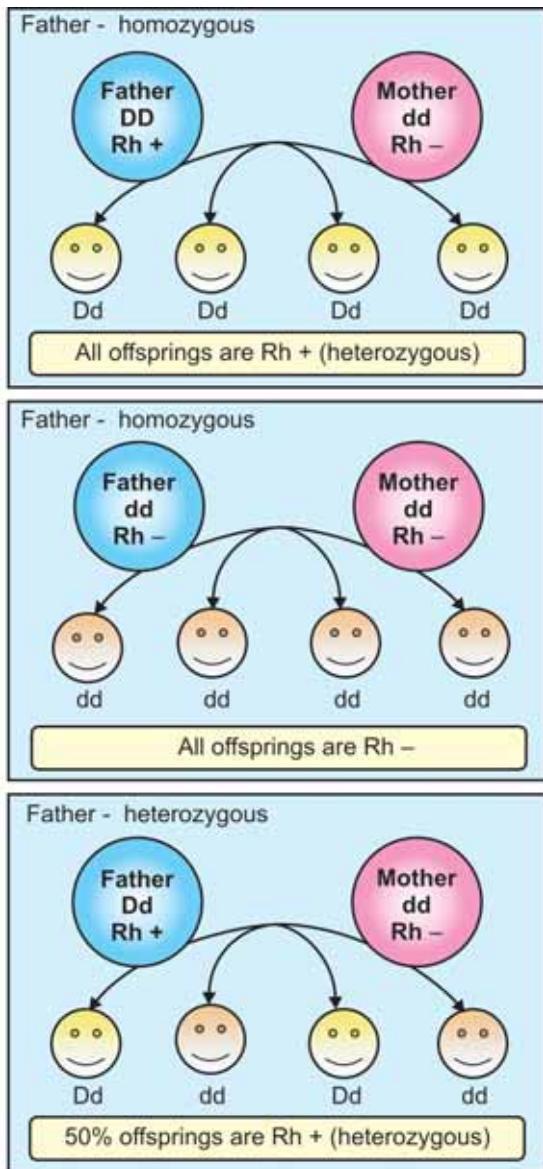


FIGURE 16-3: Inheritance of Rh antigen

not affect the recipient. However, antibodies developed in the recipient remain in the body for ever. So, when this person receives Rh positive blood for the second time, the donor RBCs are agglutinated and severe transfusion reactions occur immediately (Fig. 16-4). These reactions are similar to the reactions of ABO incompatibility (see above).

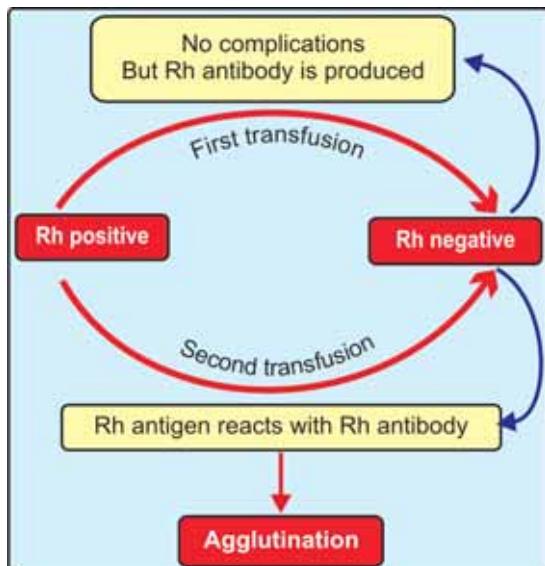


FIGURE 16-4: Rh incompatibility

■ HEMOLYTIC DISEASE OF FETUS AND NEWBORN — ERYTHROBLASTOSIS FETALIS

Hemolytic disease is the disease in fetus and newborn characterized by abnormal hemolysis of RBCs. It is due to Rh incompatibility, i.e. the difference between the Rh blood group of the mother and baby. Hemolytic disease leads to erythroblastosis fetalis.

Erythroblastosis fetalis is a disorder in fetus characterized by the presence of erythroblasts in blood. When a mother is Rh negative and fetus is Rh positive (the Rh factor being inherited from the father), usually the first child escapes the complications of Rh incompatibility. This is because the Rh antigen cannot pass from fetal blood into the mother's blood through the placental barrier.

However, at the time of parturition (delivery of the child) the Rh antigen from fetal blood may leak into mother's blood because of placental detachment. During postpartum period, i.e. within a month after delivery, the mother develops Rh antibody in her blood.

When the mother conceives for the second time and if the fetus happens to be Rh positive again, the Rh antibody from mother's blood

crosses placental barrier and enters the fetal blood. Thus, the Rh antigen cannot cross the placental barrier whereas Rh antibody can cross it.

The Rh agglutinins which enter the fetus cause agglutination of fetal RBCs resulting in hemolysis.

The severe hemolysis in the fetus causes jaundice. To compensate the hemolysis of more and more number of RBCs, there is rapid production of RBCs, not only from bone marrow, but also from spleen and liver. Now, many large and immature cells in proerythroblastic stage are released into circulation. Because of this, the disease is called erythroblastosis fetalis.

Ultimately due to excessive hemolysis severe complications develop, viz.

1. Severe anemia
2. Hydrops fetalis
3. Kernicterus.

1. Severe Anemia

Excessive hemolysis results in anemia. And the infant dies when anemia becomes severe.

2. Hydrops Fetalis

It is a serious condition in fetus characterized by edema. Severe hemolysis results in the development of edema, enlargement of liver and spleen and cardiac failure. When this condition becomes more severe it may lead to intrauterine death of fetus.

3. Kernicterus

Kernicterus is the form of brain damage in infants caused by severe jaundice. If the baby survives anemia in erythroblastosis fetalis (see above) then kernicterus develops because of high bilirubin content.

Prevention or Treatment for Erythroblastosis Fetalis

- i. If mother is found to be Rh negative and fetus is Rh positive, anti D (antibody against D antigen) should be administered to the mother at 28th and

34th weeks of gestation as prophylactic measure. If Rh negative mother delivers Rh positive baby, then anti D should be administered to the mother within 48 hours of delivery. This develops passive immunity and prevents the formation of Rh antibodies in mother's blood. So the hemolytic disease of newborn does not occur in a subsequent pregnancy.

- ii. If the baby is born with erythroblastosis fetalis, the treatment is given by means of exchange transfusion (see below). Rh negative blood is transfused into the infant replacing infant's own Rh positive blood. It will now take at least 6 months for the infant's new Rh positive blood to replace the transfused Rh negative blood. By this time all the molecules of Rh antibody derived from the mother get destroyed.

■ OTHER BLOOD GROUPS

In addition to ABO blood groups and Rh factor, many more blood group systems were found. However, these systems of blood groups do not have much clinical importance.

Other blood groups include:

1. Lewis blood group
2. MNS blood groups
3. Auber groups
4. Diego group
5. Bombay group
6. Duffy group
7. Lutheran group
8. P group
9. Kell group
10. I group
11. Kidd group
12. Sulter XG group.

■ IMPORTANCE OF KNOWING BLOOD GROUP

Nowadays, knowledge of blood group is very essential medically, socially and judicially. The importance of knowing blood group is:

1. Medically, it is important during blood transfusions and in tissue transplants

2. Socially, one should know his or her own blood group and become a member of the Blood Donor's club so that he or she can be approached for blood donation during emergency conditions
3. It is general among the couples, knowledge of blood groups helps to prevent the complications due to Rh incompatibility and save the child from the disorders like erythroblastosis fetalis
4. Judicially, it is helpful in medicolegal cases to sort out parental disputes and as a supporting evidence in identifying the criminals

■ BLOOD TRANSFUSION

■ INTRODUCTION

Blood transfusion is the process of transferring blood or blood components from one person (the donor) into the bloodstream of another person (the recipient). Transfusion may be done as a lifesaving procedure to replace blood cells or blood products lost through bleeding.

Blood transfusion is essential in the conditions like anemia, hemorrhage, trauma, burns and surgery.

Precautions to be taken Before the Transfusion of Blood

1. Donor must be healthy without any diseases like syphilis, AIDS, etc.
2. Only compatible blood must be transfused and Rh compatibility must be confirmed.
3. Both matching and cross-matching must be done.

Precautions to be taken while Transfusing Blood

1. Apparatus for transfusion must be sterile
2. The temperature of blood to be transfused must be same as body temperature
3. The transfusion of blood must be slow. The sudden rapid infusion of blood into the body increases the load on the heart resulting in many complications.

■ BLOOD SUBSTITUTES

Substances infused in the body instead of whole blood are known as blood substitutes. The commonly used blood substitutes are human plasma, 0.9 percent sodium chloride solution (saline) and 5 percent glucose.

■ EXCHANGE TRANSFUSION

Exchange transfusion is the procedure which involves removal of patient's blood and replacement with fresh donor blood or plasma.

It is otherwise known as replacement transfusion. It is carried out in conditions such as severe jaundice, sickle cell anemia, erythroblastosis fetalis, etc.

■ AUTOLOGOUS BLOOD TRANSFUSION

Autologous blood transfusion is the collection and reinfusion of patient's own blood. It is also called self blood donation. The conventional transfusion of blood that is collected from persons other than the patient is called allogeneic or heterologous blood transfusion.

17

Reticuloendothelial System and Tissue Macrophage

■ DEFINITION AND DISTRIBUTION

■ RETICULOENDOTHELIAL SYSTEM OR MACROPHAGE SYSTEM

■ MACROPHAGE

■ CLASSIFICATION OF RETICULOENDOTHELIAL CELLS

■ FIXED RETICULOENDOTHELIAL CELLS – TISSUE MACROPHAGES

■ WANDERING RETICULOENDOTHELIAL CELLS

■ FUNCTIONS OF RETICULOENDOTHELIAL SYSTEM

■ SPLEEN

■ FUNCTIONS OF SPLEEN

■ DEFINITION AND DISTRIBUTION

■ RETICULOENDOTHELIAL SYSTEM OR MACROPHAGE SYSTEM

Reticuloendothelial system or macrophage system is the system of primitive phagocytic cells which play important role in defense mechanism of the body.

■ MACROPHAGE

Macrophage is a large cell derived from monocyte. It has the property of phagocytosis. So, the macrophage is also defined as a large phagocytic cell.

■ CLASSIFICATION OF RETICULOENDOTHELIAL CELLS

The reticuloendothelial cells are classified into two types:

- a. Fixed reticuloendothelial cells or tissue macrophages
- b. Wandering reticuloendothelial cells.

■ FIXED RETICULOENDOTHELIAL CELLS – TISSUE MACROPHAGES

The fixed reticuloendothelial cells are also called the tissue macrophages or fixed histiocytes because these cells are usually located in the tissues.

The tissue macrophages are:

1. Reticuloendothelial cells in connective tissues and in serous membranes like pleura, omentum and mesentery
2. Endothelial cells of blood sinusoid in bone marrow, liver, spleen, lymph nodes, adrenal glands and pituitary glands. Kupffer's cells in liver belong to this category.
3. Cells in the reticulum of spleen, lymph node, and bone marrow

4. Meningocytes of meninges and microglia in brain
5. Alveolar cells in lungs
6. Subcutaneous tissue cells.

■ WANDERING RETICULOENDOTHELIAL CELLS

The wandering reticuloendothelial cells are also called free histiocytes. There are two types of wandering reticuloendothelial cells.

1. Free histiocytes of blood
 - i. Neutrophils
 - ii. Monocytes, which become macrophages and migrate to the site of injury or infection
2. Free histiocytes of solid tissue

During emergency, the fixed histiocytes from connective tissue and other organs become wandering cells and enter the circulation.

■ FUNCTIONS OF RETICULOENDOTHELIAL SYSTEM

Reticuloendothelial system plays an important role in the defense mechanism of the body. Most of the functions of the reticuloendothelial system are carried out by the tissue macrophages.

The functions of tissue macrophages are:

1. Phagocytic Function

Macrophages are the large phagocytic cells, which play an important role in defense of the body by phagocytosis. When any foreign body invades, macrophages ingest them by phagocytosis and liberate the antigenic products of the organism. The antigens activate the helper T lymphocytes and B lymphocytes (Refer Chapter 13 for details).

The lysosomes of macrophages contain proteolytic enzymes and lipases which digest the bacteria and other foreign bodies.

2. Secretion of Bactericidal Agents

Tissue macrophages secrete many bactericidal agents which kill the bacteria. The important bactericidal agents of macrophages are the oxidants. An oxidant is a substance that oxidizes

another substance. The oxidants secreted by macrophages are:

- i. Superoxide (O_2^-)
- ii. Hydrogen peroxide (H_2O_2)
- iii. Hydroxyl ions (OH^-).

3. Secretion of Interleukins

Tissue macrophages secrete interleukin-1, 6 and 12 which help in immunity.

4. Secretion of Tumor Necrosis Factors

Tissue macrophages secrete TNF- α and TNF- β which cause necrosis of tumor.

5. Secretion of Transforming Growth Factor

Tissue macrophages secrete transforming growth factor which plays an important role in preventing rejection of transplanted tissues or organs.

6. Secretion of Colony Stimulation Factor

Macrophages secrete the colony stimulation factor (M-CSF) which accelerates growth of granulocytes, monocytes and macrophages.

7. Secretion of Platelet Derived Growth Factor

Tissue macrophages secrete the platelet derived growth factor (PDGF), which accelerates repair of damaged blood vessel and wound healing.

8. Removal of Carbon Particles and Silicon

The macrophages ingest the substances like carbon dust particles and silicon which enter the body.

9. Destruction of Senile RBC

The reticuloendothelial cells, particularly those in spleen destroy the senile RBCs and release hemoglobin (Chapter 7).

10. Destruction of Hemoglobin

The hemoglobin released from broken senile RBCs is degraded by the reticuloendothelial cells (Chapter 9).

11. Hemopoietic Function

The reticuloendothelial cells also play an important role in the production of blood cells.

■ SPLEEN

Spleen is the largest lymphoid organ in the body and it is highly vascular. It also contains reticuloendothelial cells.

■ FUNCTIONS OF SPLEEN

1. Formation of Blood Cells

The spleen plays an important role in the hemopoietic function in embryo. During the hepatic stage, spleen produces blood cells along with liver. In myeloid stage, it produces the blood cells along with liver and bone marrow.

2. Destruction of Blood Cells

The older RBCs, lymphocytes, and thrombocytes are destroyed in the spleen. When the RBCs become old (120 days), the cell membrane

becomes more fragile. The diameter of most of the capillaries is less or equal to that of RBC. The fragile old cells are destroyed while trying to squeeze through the capillaries because these cells cannot withstand the stress of squeezing.

The destruction occurs mostly in the capillaries of spleen because the splenic capillaries have a thin lumen. So, the spleen is known as graveyard of RBCs.

3. Blood Reservoir Function

In animals, spleen stores large amount of blood. However, this function is not significant in humans. But, a large number of RBCs are stored in spleen. The RBCs are released from spleen into circulation during the emergency conditions like hypoxia and hemorrhage.

4. Role in Defense of Body

Spleen filters the blood by removing the microorganisms. The macrophages in splenic pulp destroy the micro-organisms and other foreign bodies by phagocytosis. Spleen contains about 25 percent of T lymphocytes and 15 percent of B lymphocytes and forms the site of antibody production.

18

Lymphatic System and Lymph

- LYMPHATIC SYSTEM
- LYMPH NODES
- LYMPH
 - FORMATION
 - RATE OF FLOW
 - COMPOSITION
 - FUNCTIONS

■ LYMPHATIC SYSTEM

Lymphatic system is a closed system of lymph channels or lymph vessels through which lymph flows. It is an one way system and allows the lymph flow from tissue spaces towards the blood.

■ LYMPH NODES

Lymph nodes are small glandular structures located in the course of lymph vessels. The lymph nodes are also called lymph glands or lymphatic nodes.

Each lymph node constitutes masses of lymphatic tissue covered by a dense connective tissue capsule. The structures are arranged in three layers cortex, paracortex and medulla (Fig. 18-1).

The lymph node receives lymph by one or two lymphatic vessels called afferent vessels. Afferent vessels divide into small channels. Lymph passes through afferent vessels and small channels and reaches the cortex. It circulates through cortex, paracortex and medulla of the lymph node. From medulla, the lymph leaves the node via one or two efferent vessels.

The lymph nodes are present along the course of lymphatic vessels in elbow, axilla, knee and groin. The lymph nodes are also present in certain points in abdomen, thorax and neck where many lymph vessels join.

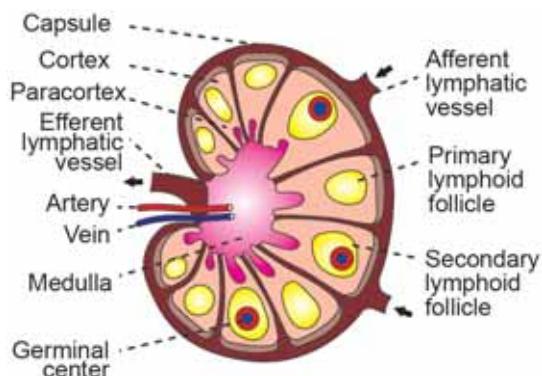


FIGURE 18-1: Structure of a lymph node

■ FUNCTIONS OF LYMPH NODES

Lymph nodes serve as filters which filter bacteria and toxic substances from the lymph. The functions of the lymph nodes are:

- When lymph passes through the lymph nodes, it is filtered, i.e. the water and electrolytes are removed. But, the proteins and lipids are retained in the lymph.
- The bacteria and other toxic substances are destroyed by macrophages of lymph nodes. Because of this, lymph nodes are called defense barriers.
- Bacteria are phagocytized by the macrophages of lymph node.

■ LYMPH

■ FORMATION

Lymph is formed from interstitial fluid, due to the permeability of lymph capillaries. When blood passes via blood capillaries in the tissues, 9/10th of fluid passes into venous end of capillaries from arterial end. And, the remaining 1/10th of

the fluid passes into lymph capillaries, which have more permeability than blood capillaries.

So, when lymph passes through lymph capillaries, the composition of lymph is more or less similar to that of interstitial fluid including protein content. Proteins present in the interstitial fluid cannot enter the blood capillaries because of their larger size. So, these proteins enter lymph vessels, which are permeable to large particles also.

■ RATE OF LYMPH FLOW

About 120 ml of lymph flows into blood per hour. Out of this, about 100 ml/hour flows through thoracic duct and 20 ml/hour flows through the right lymphatic duct.

■ COMPOSITION OF LYMPH

Usually, lymph is a clear and colorless fluid. It is formed by 96% water and 4% solids. Some blood cells are also present in lymph (Fig. 18-2).

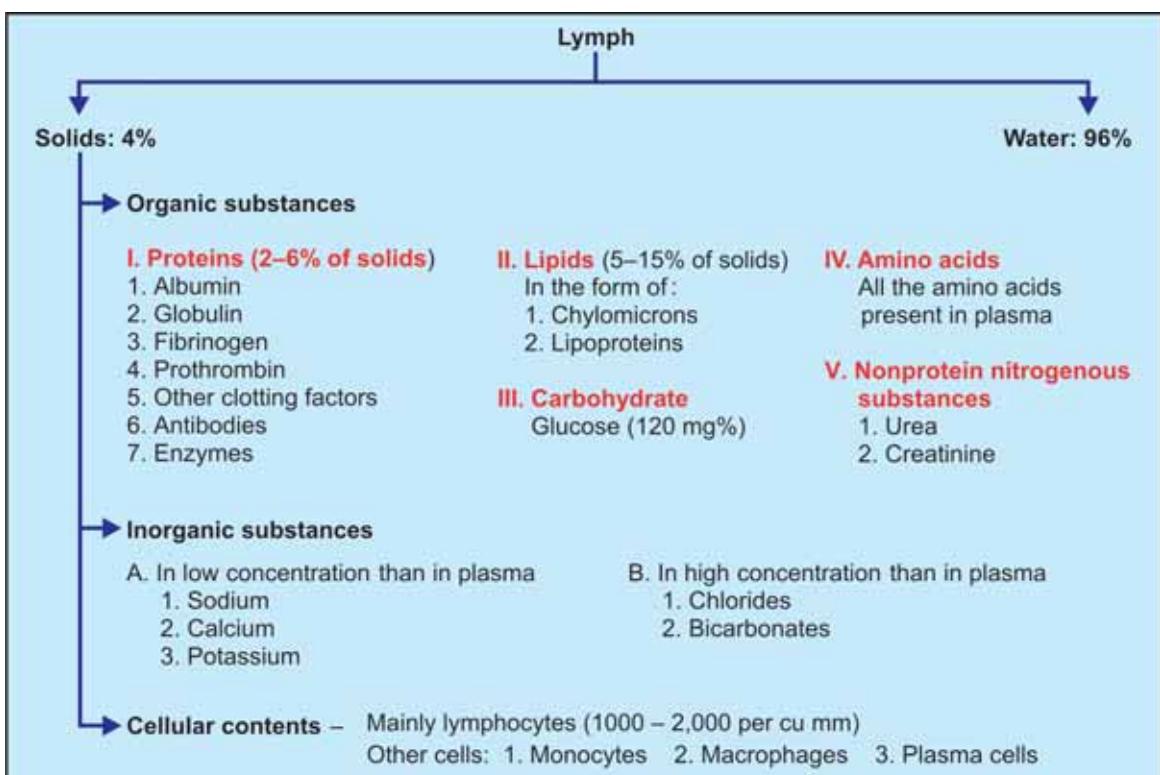


FIGURE 18-2: Composition of lymph

■ FUNCTIONS OF LYMPH

1. The important function of lymph is to return the proteins from tissue spaces into blood
2. Lymph flow plays an important role in redistribution of fluid in the body
3. Through the lymph, the bacteria, toxins and other foreign bodies are removed from tissues
4. Lymph flow is responsible for the maintenance of structural and functional integrity of tissue. Obstruction to lymph flow affects various tissues particularly myocardium, nephrons and hepatic cells
5. Lymph flow serves as an important route for intestinal fat absorption. This is the reason for the milky appearance of lymph after fatty meal
6. It plays an important role in immunity by transport of lymphocytes.

19

Tissue Fluid and Edema

- DEFINITION
- FUNCTIONS OF TISSUE FLUID
- FORMATION OF TISSUE FLUID
- APPLIED PHYSIOLOGY – EDEMA

■ DEFINITION

Tissue fluid is the medium in which cells are bathed. It is otherwise known as interstitial fluid. It forms about 20% of ECF.

■ FUNCTIONS OF TISSUE FLUID

Because of the capillary membrane, there is no direct contact between blood and cells. And, the tissue fluid acts as a medium for exchange of various substances between the cells and the blood in the capillary loop. Oxygen and nutritive substances diffuse from the arterial end of capillary through the tissue fluid and reach the cells. Carbon dioxide and waste materials diffuse from the cells into the venous end of capillary through this fluid.

■ FORMATION OF TISSUE FLUID

Formation of tissue fluid involves two processes:

1. Filtration
2. Reabsorption

■ FILTRATION

Tissue fluid is formed by the process of filtration. Normally, the blood pressure (also called hydro-

static pressure) in arterial end of the capillary is about 30 mm Hg. This hydrostatic pressure is the driving force for filtration of water and other substances from blood into tissue spaces (Fig. 19-1).

■ REABSORPTION

The fluid filtered at the arterial end of capillaries is reabsorbed back into the blood at the venous end of capillaries. Here also, the pressure gradient plays an important role. At the venous end of capillaries, the hydrostatic pressure is less (15 mm Hg) and the oncotic pressure is more (25 mm Hg). Due to the pressure gradient of 10 mm Hg, the fluid is reabsorbed along with waste materials from the tissue fluid into the capillaries. About 10% of filtered fluid enters the lymphatic vessels.

Reabsorption at the venous end helps to maintain the volume of tissue fluid.

■ APPLIED PHYSIOLOGY – EDEMA

■ DEFINITION

Edema is defined as the swelling caused by excessive accumulation of fluid in tissues. It

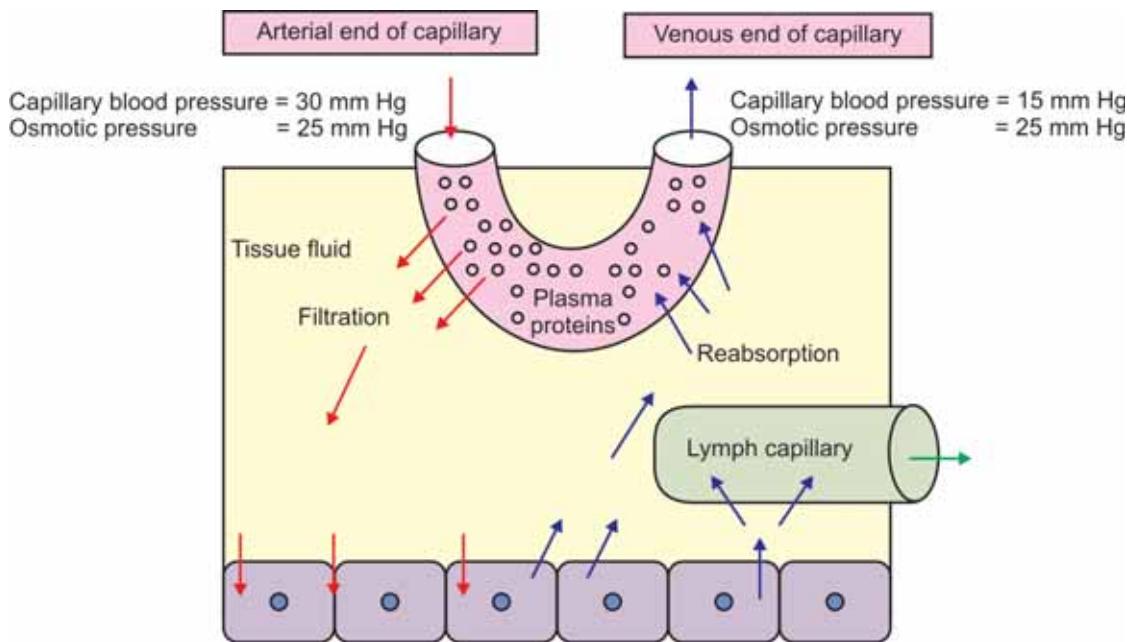


FIGURE 19-1: Formation of tissue fluid. Plasma proteins remain inside the blood capillary since the capillary membrane is not permeable to plasma proteins

may be generalized or local. Edema that involves the entire body is called generalized edema. Local edema is the one that occurs in specific areas of the body such as abdomen, lungs and extremities like feet, ankles and legs. The accumulation of fluid may be inside or outside the cell.

■ TYPES OF EDEMA

Edema is classified into two types depending upon the body fluid compartment where accumulation of excess fluid occurs:

1. Intracellular edema
2. Extracellular edema.

Intracellular Edema

Intracellular edema is the accumulation of fluid inside the cell. It occurs because of three reasons:

- i. Malnutrition
- ii. Poor metabolism
- iii. Inflammation of the tissues.

Extracellular Edema

Extracellular edema is defined as the accumulation of fluid outside the cell. It occurs because of abnormal leakage of fluid from capillaries into interstitial space and obstruction of lymphatics that prevents return of fluid from interstitial fluid back into blood.

The common conditions which leads to extracellular edema are:

1. Heart failure
2. Renal disease
3. Decreased amount of plasma proteins
4. Lymphatic obstruction
5. Increased endothelial permeability.

Pitting and Non-pitting Edema

Interstitial fluid is present in the form of a gel that is almost like a semisolid substance. It is because the interstitial fluid is not present as fluid but is bound in a proteoglycan meshwork. It does not allow any free space for the fluid movement.

When interstitial fluid volume increases, most of the fluid becomes free fluid that is not bound to proteoglycan meshwork. It flows freely through tissue spaces, producing a swelling called edema. This type of edema is known as pitting edema because, when this area is pressed with the finger, displacement of fluid occurs producing a depression or pit. When the

finger is removed, the pit remains for few seconds, sometimes as long as one minute, till the fluid flows back into that area.

Edema also develops due to swelling of the cells or clotting of interstitial fluid in the presence of fibrinogen. This is called non-pitting edema because, it is hard and a pit is not formed by pressing.

QUESTIONS IN BLOOD AND BODY FLUIDS

■ LONG QUESTIONS

1. What are the compartments of body fluid? Enumerate the differences between ECF and ICF and explain the measurement of ECF volume.
2. What is indicator dilution technique? How is it applied in the measurement of total body water? Describe dehydration briefly.
3. Give a detailed account of erythropoiesis.
4. Define erythropoiesis. List the different stages of erythropoiesis. Describe the changes, which take place in each stage and the factors necessary for erythropoiesis.
5. Describe the morphology, development and functions of leukocytes.
6. Describe the development of cellular mediated immunity.
7. Describe the development of humoral immunity.
8. Define blood coagulation. Describe the mechanisms involved in coagulation. Add a note on anticoagulants.
9. Enumerate the factors involved in blood coagulation and describe the intrinsic mechanism of coagulation.
10. Give an account of extrinsic mechanism of coagulation of blood. Give a brief description of bleeding disorders.

■ SHORT QUESTIONS

1. Dye or indicator dilution technique.
2. Measurement of total body water.
3. Measurement of ECF volume.
4. Measurement of ICF volume.
5. Measurement of blood volume.
6. Measurement of plasma volume.
7. Dehydration.
8. Water intoxication.
9. Functions of blood.

10. Plasma proteins.
11. Functions of RBCs.
12. Fate of RBCs.
13. Lifespan of RBCs.
14. Physiological variations of RBC count.
15. Polycythemia.
16. Factors necessary for erythropoiesis.
17. Destruction of hemoglobin.
18. Abnormal hemoglobin.
19. Abnormal hemoglobin derivatives.
20. Pernicious anemia.
21. Erythrocyte sedimentation rate.
22. Packed cell volume or hematocrit.
23. Anemia.
24. Hemolysins.
25. Types and morphology of WBCs.
26. Functions of WBCs.
27. T lymphocytes.
28. B lymphocytes.
29. Role of macrophages in immunity.
30. Immunoglobulins or antibodies.
31. Immune deficiency diseases.
32. Autoimmune diseases.
33. Platelets.
34. Hemostasis.
35. Fibrinolysis.
36. Tests for coagulation.
37. Anticoagulants.
38. Hemophilia.
39. Purpura.
40. Thrombosis.
41. ABO blood groups.
42. Rh factor.
43. Transfusion reactions.
44. Erythroblastosis fetalis.
45. Tissue macrophage.
46. Functions of spleen.
47. Lymph.
48. Lymph nodes.
49. Tissue fluid.
50. Edema.

SECTION 3

Muscle Physiology

CHAPTERS —

20.	Classification of Muscles	113
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23.	Electrical and Molecular Changes during Muscular Contraction	126
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20

Classification of Muscles

- DEPENDING UPON STRIATIONS
- DEPENDING UPON CONTROL
- DEPENDING UPON SITUATION

There are more than 600 muscles in our body. Muscles perform many useful functions and help us in doing everything in day to day life. Muscles are classified by three different methods based on different factors:

- I. Depending upon the presence or absence of striations
- II. Depending upon the control
- III. Depending upon the function.

■ DEPENDING UPON STRIATIONS

Depending upon the presence or absence of the cross striations, muscles are divided into two groups:

1. Striated muscle
2. Nonstriated muscle.

Striated Muscle

Striated muscle is the muscle which has a large number of cross striations (transverse lines). Skeletal muscle and cardiac muscle belong to this category.

Nonstriated Muscle

The muscle which does not have cross striations is called nonstriated muscle. It is also called plain

muscle or smooth muscle. It is found in the wall of the visceral organs.

■ DEPENDING UPON CONTROL

Depending upon control, the muscles are classified into two types:

1. Voluntary muscle
2. Involuntary muscle.

Voluntary Muscle

Voluntary muscle is the muscle that is controlled by the will. Skeletal muscles are the voluntary muscles. These muscles are innervated by somatic nerves.

Involuntary Muscle

The muscle that cannot be controlled by the will is called involuntary muscle. Cardiac muscle and smooth muscle are involuntary muscles. These muscles are innervated by autonomic nerves.

■ DEPENDING UPON SITUATION

The muscles are classified into three types depending upon the situation:

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

TABLE 20-1: Features of skeletal, cardiac and smooth muscle fibers

Features	Skeletal muscle	Cardiac muscle	Smooth muscle
Location	In association with bones	In the heart	In the visceral organs
Shape	Cylindrical and unbranched	Branched	Spindle shaped unbranched
Length	1 to 4 cm	80 to 100 μ	50 to 200 μ
Diameter	10 to 100 μ	15 to 20 μ	2 to 5 μ
No. of Nucleus	More than one	One	One
Cross striations	Present	Present	Absent
Myofibrils	Present	Present	Absent
Sarcomere	Present	Present	Absent
Troponin	Present	Present	Absent
Sarcotubular system	Well developed	Well developed	Poorly developed
'T' tubules	Long and thin	Short and broad	Absent
Depolarization	Upon stimulation	Spontaneous	Spontaneous
Fatigue	Possible	Not possible	Not possible
Summation	Possible	Not possible	Possible
Tetanus	Possible	Not possible	Possible
Resting membrane potential	Stable	Stable	Unstable
For trigger of contraction, calcium binds with	Troponin	Troponin	Calmodulin
Source of calcium	Sarcoplasmic reticulum	Sarcoplasmic reticulum	Extracellular
Speed of contraction	Fast	Intermediate	Slow
Neuromuscular junction	Well defined	Not well defined	Not well defined
Action	Voluntary action	Involuntary action	Involuntary action
Control	Only neurogenic	Myogenic	Neurogenic and myogenic
Nerve supply	Somatic nerves	Autonomic nerves	Autonomic nerves

The features of these muscles are given in Table 20-1.

Skeletal Muscle

Skeletal muscle is situated in association with bones forming the skeletal system. The skeletal muscles form 40 to 50% of body mass and are

voluntary and striated. These muscles are supplied by somatic nerves.

The fibers of the skeletal muscles are arranged in parallel. In most of the skeletal muscles, the muscle fibers are attached to tendons on either end. The skeletal muscles are anchored to the bones by the tendons.

Cardiac Muscle

Cardiac muscle forms the musculature of the heart. These muscles are striated and involuntary. Cardiac muscles are supplied by autonomic nerve fibers.

Smooth Muscle

Smooth muscle or visceral muscle is situated in association with viscera. Smooth muscle is non-striated and involuntary. Because of the absence of cross striations it is called smooth or plain muscle. It is supplied by autonomic nerve fibers.

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Structure of Skeletal Muscle

- MUSCLE MASS
- MUSCLE FIBER
- MYOFIBRIL
 - MICROSCOPIC STRUCTURE OF A MYOFIBRIL
- SARCOMERE
 - ELECTRON MICROSCOPIC STUDY OF SARCOMERE
- CONTRACTILE ELEMENTS (PROTEINS) OF MUSCLE
 - MYOSIN MOLECULE
 - ACTIN MOLECULE
 - TROPOMYOSIN
 - TROPONIN
- SARCOTUBULAR SYSTEM
- COMPOSITION OF MUSCLE

■ MUSCLE MASS

The muscle mass (or tissue) is made up of a large number of individual muscle cells or myocytes. The muscle cells are commonly called muscle fibers because these cells are long and slender in appearance. The skeletal muscle fibers are multinucleated and arranged parallel to one another with some connective tissue in between.

The muscle mass is separated from the neighboring tissues by the thick fibrous tissue layer known as fascia. Beneath the fascia, the muscle is covered by a connective tissue sheath called epimysium. In the muscle, the muscle fibers are arranged in various groups called the bundles or fasciculi. The connective tissue sheath

that covers each fasciculus is called perimysium. Each muscle fiber is covered by the connective tissue layer called the endomysium (Fig. 21-1).

■ MUSCLE FIBER

Each muscle cell or muscle fiber is cylindrical in shape. The length of the fiber is between 1 and 4 cm depending upon the length of the muscle. The diameter of the muscle fiber varies from 10 to 100 μ . The muscle fibers are attached to bone by a tough cord of connective tissue called tendon.

Each muscle fiber is enclosed by a cell membrane called plasma membrane that lies beneath the endomysium. It is also called

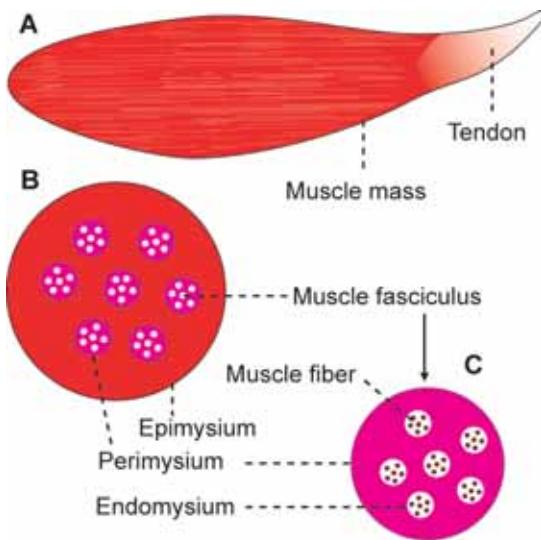


FIGURE 21-1: Diagram showing A = Skeletal muscle mass B = Cross-section of muscle C = One muscle fasciculus

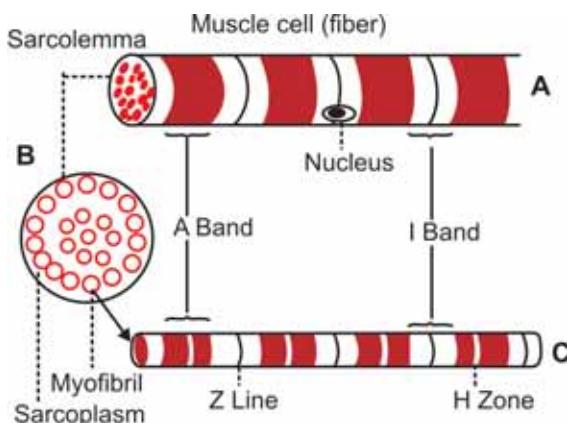


FIGURE 21-2: A = One muscle cell B = Cross-section of one muscle cell C = One myofibril

sarcolemma (Fig. 21-2). The cytoplasm of the muscle is known as sarcoplasm. Many structures are embedded within the sarcoplasm:

1. Nuclei
2. Myofibril
3. Golgi apparatus
4. Mitochondria
5. Sarcoplasmic reticulum
6. Ribosomes
7. Glycogen droplets
8. Occasional lipid droplets.

■ MYOFIBRIL

Myofibrils or myofibrillae are the special structures present only in muscle fibers. These are the fine parallel filaments present in sarcoplasm of the muscle cell. The myofibrils run through the entire length of the muscle fiber.

■ MICROSCOPIC STRUCTURE OF A MYOFIBRIL

Light microscopic studies show that, each myofibril consists of a number of two alternating bands. The two bands are:

1. Light band or 'I' band
2. Dark band or 'A' band.

Light Band or 'I' Band

The light band is called 'I' band because it is isotropic to polarized light. When the polarized light is passed through the muscle fiber at this area the light rays are refracted at the same angle.

Dark Band or 'A' Band

The dark band is called 'A' band because it is anisotropic to polarized light. When the polarized light is passed through the muscle fiber at this area, the light rays are refracted at different directions (An = not; iso = it; trop = turning).

In an intact muscle fiber, 'I' band and 'A' band of the adjacent myofibrils are placed side by side. It gives the appearance of characteristic cross striations in the muscle fiber.

I band is divided into two portions by a narrow dark line called 'Z' line or 'Z' disk (in German zwischenscheibe = between disks). The 'Z' line is formed by a protein disk which does not permit passage of light. The portion of myofibril in between two 'Z' lines is called sarcomere.

■ SARCOMERE

Definition

Sarcomere is the structural and functional unit of the skeletal muscle.

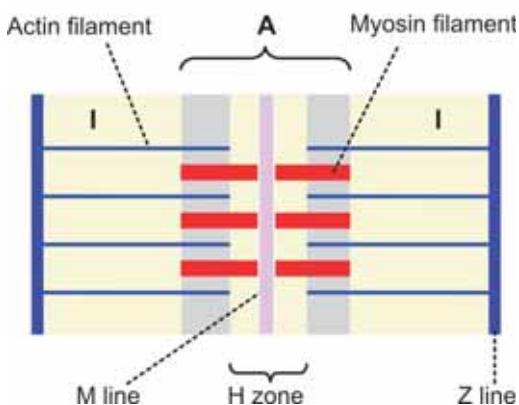


FIGURE 21-3: Sarcomere. A = A band,
I = I band

Extent

Each sarcomere extends between two 'Z' lines of myofibril. Thus, each myofibril contains many sarcomeres arranged in series throughout its length. When the muscle is in relaxed state, the average length of each sarcomere is 2-3 microns.

Components

Each myofibril consists of alternate dark 'A' band and light 'I' band (Fig. 21-3). In the middle of 'A' band, there is a light area called 'H' zone ($H = \text{hell} = \text{light}$ in German, $H = \text{Henson} - \text{discoverer}$). In the middle of 'H' zone lies the middle part of myosin filament. This is called 'M' line (in German $\text{mittel} = \text{middle}$). 'M' line is formed by myosin binding proteins.

ELECTRON MICROSCOPIC STUDY OF SARCOMERE

The electron microscopic studies reveal, that the sarcomere consists of many thread like structures called myofilaments. Myofilaments are of two types:

1. Actin filaments
2. Myosin filaments.

Actin Filaments

Actin filaments are the thin filaments that extend from either side of the 'Z' lines, run across 'I' band and enter into 'A' band up to 'H' zone.

Myosin Filaments

Myosin filaments are thick filaments and are situated in 'A' band.

Some lateral processes (projections) or cross bridges arise from myosin filaments. These bridges have enlarged structures called myosin heads at their tips. The myosin heads attach themselves to actin filaments. These heads pull the actin filaments during contraction of the muscle by means of a mechanism called sliding mechanism or ratchet mechanism (Chapter 23).

■ CONTRACTILE ELEMENTS (PROTEINS) OF MUSCLE

The myosin filaments are formed by protein molecules called myosin molecules. The actin filaments are formed by three types of proteins called actin, tropomyosin and troponin. These four proteins together constitute the muscle proteins or the contractile elements of the muscle.

In addition to the contractile proteins, the sarcomere contains some more proteins (Fig. 21-8).

■ MYOSIN MOLECULE

Each myosin filament consists of about 200 myosin molecules. Myosin is a globulin which is made up of 6 polypeptide chains. Out of these, two are heavy chains and four are light chains. The two heavy chains twist around each other to form a double helix (Fig. 21-4). At one end, the two chains remain twisted around one another and form the tail portion. At the other end, both the chains turn away in opposite directions and

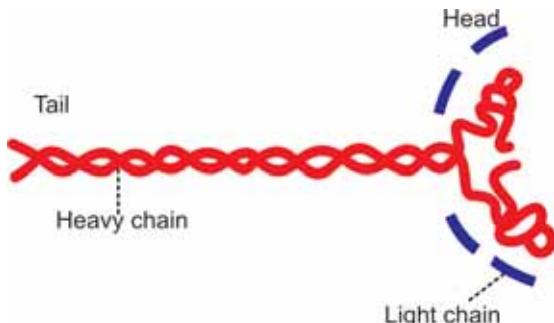


FIGURE 21-4: Myosin molecule formed by two heavy chains and four light chains of polypeptides

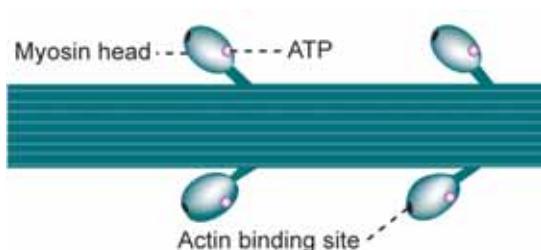


FIGURE 21-5: Diagram showing myosin filament

form the globular head portion. To each part of this head, are attached two light chains.

Each myosin head has two attachment sites. One site is for actin filament and the other one is for one ATP molecule (Fig. 21-5). In the central part of the myosin filament, i.e. in the 'H' zone, the myosin head is absent.

■ ACTIN MOLECULE

Actin molecules are the major constituents of the thin actin filaments. Each actin molecule is called F actin and it is derived from G actin. There are about 300-400 actin molecules in each actin filament. The actin molecules in the actin filament are also arranged in the form of a double helix. Each F actin molecule has an active site to which the myosin head is attached (Fig. 21-6).

■ TROPOMYOSIN

There are about 40-60 tropomyosin molecules situated along the double helix strand of actin filament. In relaxed condition of the muscle, the tropomyosin molecules cover all the active sites of F actin molecules.

■ TROPONIN

It is formed by three subunits:

1. Troponin I – attached to F actin
2. Troponin T – attached to tropomyosin
3. Troponin C – attached to calcium ions.

■ SARCOTUBULAR SYSTEM

Sarcotubular system is a system of membranous structures in the form of vesicles and tubules in the sarcoplasm of the muscle fiber. It surrounds the myofibrils embedded in the sarcoplasm.

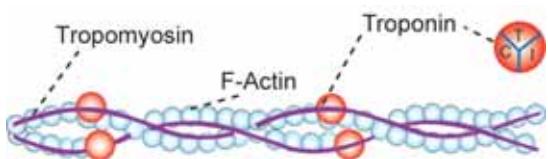


FIGURE 21-6: Part of actin filament. Troponin has three subunits, T, C and I

The sarcotubular system is formed mainly by two types of structures:

1. 'T' tubules
2. 'L' tubules or sarcoplasmic reticulum.

'T' Tubules

'T' tubules or transverse tubules are narrow tubules formed by invagination of the sarcolemma. These tubules penetrate all the way from one side of the muscle fiber to other side.

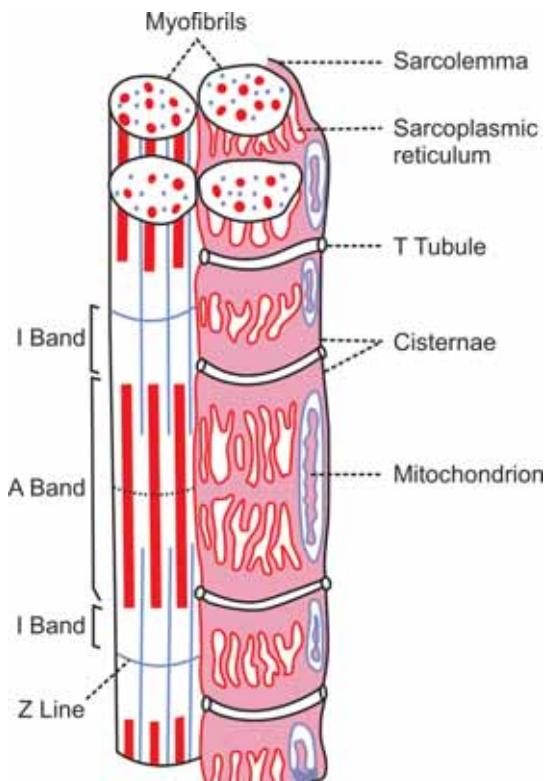


FIGURE 21-7: Diagram showing the relation between sarcotubular system and parts of sarcomere. Only few myofilaments are shown in the myofibril drawn on the right side of the diagram

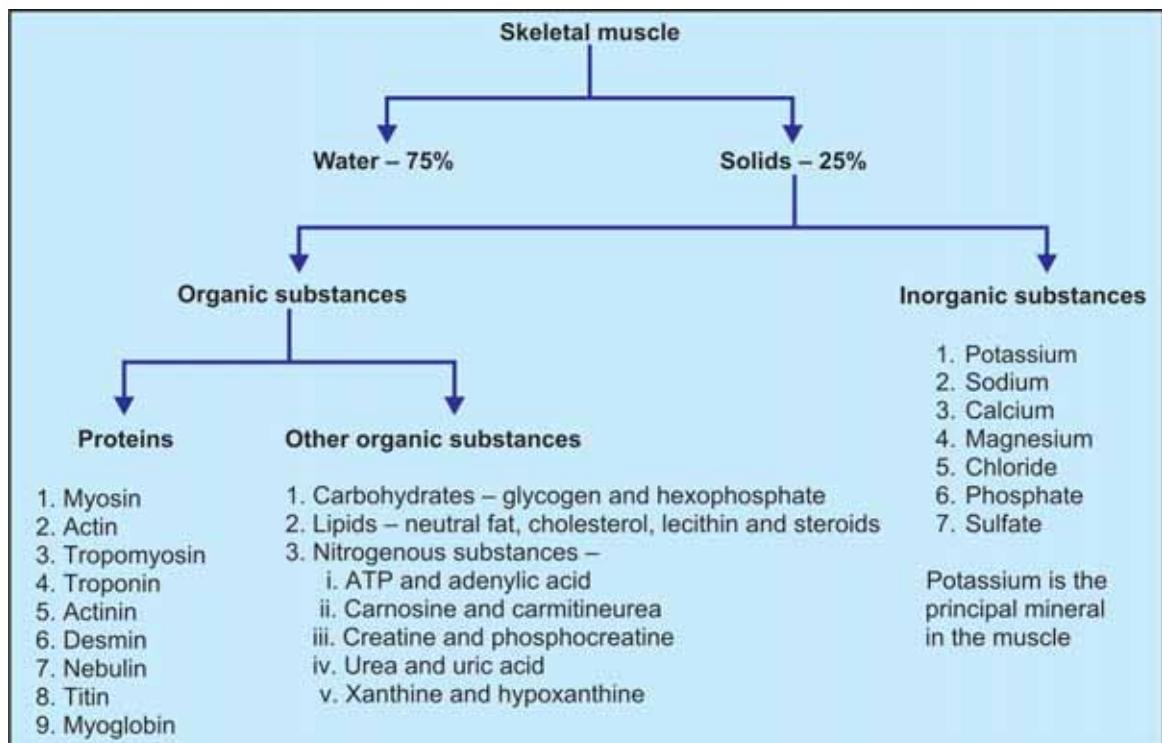


FIGURE 21-8: Composition of skeletal muscle

Because of their origin from sarcolemma, the 'T' tubules open to the exterior of the muscle cell. Therefore, the ECF runs through their lumen.

Function of 'T' Tubules

The 'T' tubules are responsible for rapid transmission of impulse in the form of action potential from sarcolemma to the myofibrils.

'L' Tubules or Sarcoplasmic Reticulum

The 'L' tubules or longitudinal tubules are the closed tubules that run in long axis of the muscle fiber forming sarcoplasmic reticulum. These tubules form a closed tubular system around each myofibril and do not open to exterior like 'T' tubules.

The 'L' tubules correspond to the endoplasmic reticulum of other cells. At regular intervals, throughout the length of the myofibrils, the 'L' tubules dilate to form a pair of lateral sacs called terminal cisternae. Each pair of terminal cisternae

is in close contact with 'T' tubule. The 'T' tubule along with the cisternae on either side is called the triad of skeletal muscle. Calcium ions are stored in 'L' tubule and the amount of calcium ions is more in cisternae (Fig. 21-7).

Functions of 'L' tubules

The 'L' tubules store a large quantity of calcium ions. When the action potential reaches the cisternae of 'L' tubule, the calcium ions are released into the sarcoplasm. The calcium ions trigger the processes involved in contraction of the muscle. The process by which the calcium ions cause contraction of muscle is called excitation contraction coupling (Chapter 23).

■ COMPOSITION OF MUSCLE

The skeletal muscle is formed by 75% of water and 25% of solids. Solids are 20% of proteins and 5% of organic substances other than proteins and inorganic substances (Fig. 21-8).

Properties of Skeletal Muscle

- EXCITABILITY
 - DEFINITION
 - STIMULUS
- CONTRACTILITY
 - TYPES OF CONTRACTION
 - RED MUSCLE AND PALE MUSCLE
 - FACTORS AFFECTING FORCE OF CONTRACTION
 - REFRACTORY PERIOD
- MUSCLE TONE
 - DEFINITION
 - MAINTENANCE OF MUSCLE TONE
- APPLIED PHYSIOLOGY— ABNORMALITIES OF MUSCLE TONE

■ EXCITABILITY

■ DEFINITION

Excitability is defined as the reaction or response of a tissue to irritation or stimulation. It is a physicochemical change.

■ STIMULUS

Stimulus is the change in environment. It is defined as an agent or influence or act, which brings about the response in an excitable tissue.

Types of Stimulus

There are four types of stimuli, which can excite a living tissue:

1. Mechanical stimulus (Pinching)
2. Electrical stimulus (Electric shock)

3. Thermal stimulus (By applying heated glass rod or icepiece)
4. Chemical stimulus (By applying chemical substances like acids).

Electrical stimulus is commonly used for experimental purposes.

Intensity of Stimulus

The intensity or strength of a stimulus is of five types:

- i. Subminimal stimulus
- ii. Minimal stimulus
- iii. Submaximal stimulus
- iv. Maximal stimulus
- v. Supramaximal stimulus.

The stimulus whose strength (or voltage) is sufficient to excite the tissue is called threshold or liminal or minimal stimulus.

■ CONTRACTILITY

Contractility is the response of the skeletal muscle to a stimulus by change in either the length or tension of the muscle fibers.

■ TYPES OF CONTRACTION

Muscular contraction is classified into two types based on change in the length of muscle fibers or tension of the muscle:

1. Isotonic contraction
2. Isometric contraction.

Isotonic Contraction

Isotonic contraction is the type of muscular contraction in which the tension remains the same and the length of the muscle fiber is altered (Iso = same; Tonic = tension). Example is the simple flexion of arm, where shortening of muscle fibers occurs but the tension does not change.

Isometric Contraction

Isometric contraction is the type of muscular contraction in which the length of muscle fibers remains the same and the tension is increased. Example is pulling any heavy object when muscles become stiff and strained with increased tension but the length does not change.

■ RED MUSCLE AND PALE MUSCLE

Based on the contraction time, the skeletal muscles are classified into two types, the red (slow) muscles and pale (fast) muscles. Similarly, the muscle fibers are also divided into two types, type I and type II fibers. Type I fibers (slow fibers or slow twitch fibers) have small diameter. Type II fibers (fast fibers or fast twitch fibers) have large diameter. Most of the skeletal muscles in human beings contain both the types of fibers.

Red Muscles

The muscles which contain large number of type I fibers are called red muscles. These muscles are also called slow muscles or slow twitch

muscles. The red muscles have longer contraction time. Back muscles and gastrocnemius muscles are red muscles.

Pale Muscles

The muscles which have large number of type II fibers are called pale muscles. These muscles are also called white muscles, fast muscles or fast twitch muscles. The pale muscles have shorter contraction time. Hand muscles and ocular muscles are pale muscles.

The characteristic features of red and pale muscles are given in Table 22-1.

■ FACTORS AFFECTING FORCE OF CONTRACTION

The force of contraction of the skeletal muscle is affected by the following factors:

- A. Strength of stimulus
- B. Number of stimulus
- C. Temperature
- D. Load.

A. Effect of Strength of Stimulus

Force of contraction is directly proportional to strength of stimulus.

B. Effect of Number of Stimulus

The response of the muscle in the form of contraction differs depending upon the number of stimuli. If a single stimulus is given, the muscle gives response only once. If two stimuli are given with sufficient time interval it gives response twice.

When a muscle is stimulated by multiple stimuli, two types of effects are obtained depending upon the frequency of stimuli:

1. Fatigue
2. Tetanus.

1. Fatigue

Definition

Fatigue is defined as the decrease in muscular activity due to repeated stimuli with low frequency. When the stimuli are applied

TABLE 22-1: Features of red and pale muscles

	Red (slow) muscle	Pale (fast) muscle
1.	Type I fibers are more	Type II fibers are more
2.	Myoglobin content is high. So, it is red	Myoglobin content is less. So, it is pale
3.	Sarcoplasmic reticulum is less extensive	Sarcoplasmic reticulum is more extensive
4.	Blood vessels are more extensive	Blood vessels are less extensive
5.	Mitochondria are more in number	Mitochondria are less in number
6.	Response is slow with long latent period	Response is rapid with short latent period
7.	Contraction is less powerful	Contraction is more powerful
8.	This muscle is involved in prolonged and continued activity as it undergoes sustained contraction	This muscle is not involved in prolonged and continued activity as it relaxes immediately.
9.	Fatigue occurs slowly	Fatigue occurs quickly.
10.	Depends upon cellular respiration for ATP production	Depends upon glycolysis for ATP production.

continuously, after some time, the muscle does not show any response to the stimulus. This condition is called fatigue.

Causes for fatigue

- i. Exhaustion of acetylcholine in motor endplate
- ii. Accumulation of metabolites like lactic acid and phosphoric acid
- iii. Lack of nutrients like glycogen
- iv. Lack of oxygen.

Site (Seat) of fatigue

In the intact body, the sites of fatigue are in the following order:

- i. Betz (pyramidal) cells in cerebral cortex
- ii. Anterior gray horn cells (motor neurons) of spinal cord
- iii. Neuromuscular junction
- iv. Muscle.

Recovery of the muscle after fatigue

The fatigue is a reversible phenomenon. The fatigued muscle recovers if given rest and nutrition.

Causes of recovery

- i. Removal of metabolites
- ii. Formation of acetylcholine at the neuromuscular junction
- iii. Re-establishment of normal polarized state of the muscle
- iv. Availability of nutrients
- v. Availability of oxygen.

In the intact body, all the processes involved in recovery are achieved by circulation itself.

2. Tetanus

Definition

Tetanus is defined as the sustained contraction of muscle due to repeated stimuli with high frequency. When the multiple stimuli are applied at a higher frequency in such a way that the successive stimuli fall during contraction period of previous twitch, the muscle remains in state of tetanus, i.e. all the contractions are fused. The muscle relaxes only after the stoppage of stimulus or when the muscle is fatigued.

If the frequency of stimuli is less, partial fusion of contractions takes place leading to incomplete tetanus or clonus.

Frequency of stimuli necessary to cause tetanus and clonus

In gastrocnemius muscle of human being, the frequency required to cause tetanus is 60/second. And for clonus, the frequency of stimuli necessary is 55/second.

C. Effect of Variations in Temperature

If the temperature of muscle is altered, the force of contraction is also affected.

Warm temperature

At warm temperature of about 40°C, the force of contraction increases because of the following reasons:

1. The excitability of muscle increases
2. The chemical processes involved in muscular contraction are accelerated
3. The viscosity of muscle decreases.

Cold temperature

At cold temperature of about 10°C, the force of contraction decreases because of the following reasons:

1. Excitability of muscle decreases
2. Chemical processes are slowed or delayed
3. Viscosity of the muscle increases.

High or hot temperature – Heat rigor

At high temperatures, heat rigor occurs in the muscle. Rigor refers to shortening and stiffening of muscle fibers. Heat rigor is the rigor that occurs due to increased temperature above 60°C. The cause of heat rigor is the coagulation of muscle proteins actin and myosin. It is an irreversible phenomenon.

Other types of rigors are:

1. Cold rigor that occurs due to the exposure to severe cold. It is a reversible phenomenon
2. Calcium rigor which is due to increased calcium content. It is also reversible
3. Rigor mortis which develops after death.

Rigor mortis

Rigor mortis refers to after death condition of the body which is characterized by stiffness of muscles and joints (Latin word rigor means stiff). It occurs due to stoppage of aerobic respiration which causes changes in the muscles.

Soon after death, the cell membrane becomes highly permeable to calcium. So a large number of calcium ions enters the muscle fibers and promotes the formation of actomyosin complex resulting in contraction of the muscles.

Few hours after death, all the muscles of body undergo severe contraction and become rigid. The joints also become stiff and locked.

Normally for relaxation, the muscle needs to drive out the calcium which requires ATP. But during continuous muscular contraction and other cellular processes after death, the ATP molecules are completely exhausted. New ATP molecules cannot be produced because of lack of oxygen. So in the absence of ATP, the muscles remain in contracted state until the onset of decomposition.

Medicolegal importance of rigor mortis

Rigor mortis is useful in determining the time of death. Onset of stiffness starts between 10 minutes and 3 hours after death depending upon the condition of the body and environmental temperature at the time of death. If the body is active or the environmental temperature is high at the time of death, the stiffness sets in quickly.

The stiffness develops first in facial muscles and then spreads to other muscles. The maximum stiffness occurs around 12 to 24 hours after death. The stiffness of muscles and joints continues for 1 to 3 days.

Afterwards, the decomposition of the general tissues starts. Now the lysosomal intracellular hydrolytic enzymes like cathepsins and calpains are released. These enzymes hydrolyze the muscle proteins, actin and myosin resulting in breakdown of actomyosin complex. It relieves the stiffness of the muscles. This process is known as resolution of rigor.

D. Effect of Load

The load acting on muscle is of two types:

1. Afterload
2. Free load.

1. Afterload

Afterload is the load, that acts on the muscle after the beginning of muscular contraction. Example of afterload is lifting any object from the ground. The load acts on muscles of arm only after lifting the object off the ground, i.e. only after beginning of the muscular contraction.

2. Free load

Free load is the load, which acts on the muscle freely, even before the onset of contraction of the muscle. It is otherwise called fore load. Example of free load is filling water from a tap by holding the bucket in hand.

Muscle in free loaded condition works better than the muscle in after loaded condition. It is because, in free loaded condition, the muscle fibers are stretched and the initial length of muscle fibers is increased. So, the force of contraction and the work done by the muscles are increased. It is in accordance with Frank-Starling law.

Frank-Starling law

Frank-Starling law states that the force of contraction is directly proportional to the initial length of muscle fibers within physiological limits.

■ REFRACtORY PERIOD

Refractory period is the period at which the muscle does not show any response to a stimulus. It is because already one action potential is in progress and the muscle is in depolarized state during this period. The muscle is unexcitable to further stimulation until it is repolarized. Refractory period is of two types:

1. Absolute refractory period
2. Relative refractory period

1. Absolute Refractory Period

Absolute refractory period is the period during which the muscle does not show any response at all, whatever may be the strength of stimulus.

2. Relative Refractory Period

Relative refractory period is the period, during which the muscle shows some response if the strength of stimulus is increased to maximum.

■ MUSCLE TONE

■ DEFINITION

Muscle tone is defined as continuous and partial contraction of the muscles with certain degree of vigor and tension. More details on muscle tone are given in Chapter 97.

■ MAINTENANCE OF MUSCLE TONE

In Skeletal Muscle

Maintenance of tone in skeletal muscle is neurogenic. It is due to continuous discharge of impulses from gamma motor neurons in anterior gray horn of spinal cord. The gamma motor neurons in spinal cord are controlled by higher centers in brain.

In Cardiac Muscle

In cardiac muscle, maintenance of tone is purely myogenic, i.e. the muscles themselves control the tone. The tone is not under nervous control in cardiac muscle.

In Smooth Muscle

In smooth muscle, tone is myogenic. It depends upon calcium level and number of cross bridges.

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF MUSCLE TONE

1. Hypertonia – increased muscle tone
2. Hypotonia – decreased muscle tone

23

Electrical and Molecular Changes during Muscular Contraction

- ELECTRICAL CHANGES DURING MUSCULAR CONTRACTION
 - RESTING MEMBRANE POTENTIAL
 - ACTION POTENTIAL
 - ACTION POTENTIAL CURVE
 - IONIC BASIS OF ELECTRICAL EVENTS
 - GRADED POTENTIAL
- MOLECULAR CHANGES DURING MUSCULAR CONTRACTION
 - ACTOMYOSIN COMPLEX
 - MOLECULAR BASIS OF MUSCULAR CONTRACTION

■ ELECTRICAL CHANGES DURING MUSCULAR CONTRACTION

When the muscle is in resting condition, the electrical potential is called resting membrane potential. When the muscle is stimulated, electrical changes occur which are collectively called action potential.

■ RESTING MEMBRANE POTENTIAL

Resting membrane potential is the electrical potential difference (voltage) across the cell membrane (between inside and outside of the cell) under resting condition. It is also called membrane potential, transmembrane potential, transmembrane potential difference or transmembrane potential gradient.

Resting muscle shows negativity inside and positivity outside. The condition of the muscle during resting membrane potential is called polarized state. In human skeletal muscle, the resting membrane potential is -90 mV.

■ ACTION POTENTIAL

Action potential is defined as a series of electrical changes that occur when the muscle or nerve is stimulated.

Action potential occurs in two phases:

1. Depolarization
2. Repolarization.

Depolarization

Depolarization is the initial phase of action potential in which the inside of the muscle becomes positive and outside becomes negative. That is, the polarized state (resting membrane potential) is abolished resulting in depolarization.

Repolarization

Repolarization is the phase of action potential when the potential inside the muscle reverses back to the resting membrane potential. That is,

TABLE 23-1: Properties of action potential and graded potential

Action potential	Graded potential
Propagative	Non-propagative
Long distance signal	Short distance signal
Both depolarization and repolarization	Only depolarization or hyperpolarization
Obeys all or none law	Does not obey all or none law
Summation is not possible	Summation is possible
Has refractory period	No refractory period

within a short time after depolarization the interior of muscle becomes negative and outside becomes positive. So, the polarized state of the muscle is re-established.

Properties of Action Potential

The properties of action potential are listed in Table 23-1.

ACTION POTENTIAL CURVE

Stimulus Artifact

The resting membrane potential is recorded as a straight baseline at -90 mV (Fig. 23-1). When a stimulus is applied, there is a slight irregular deflection of baseline for a very short period. This is called stimulus artifact. The artifact is due to leakage of current from stimulating electrode to the recording electrode. The stimulus artifact is followed by latent period.

Latent Period

This is the period when no change occurs in the electrical potential. It is a very short period with duration of 0.5 to 1 millisecond.

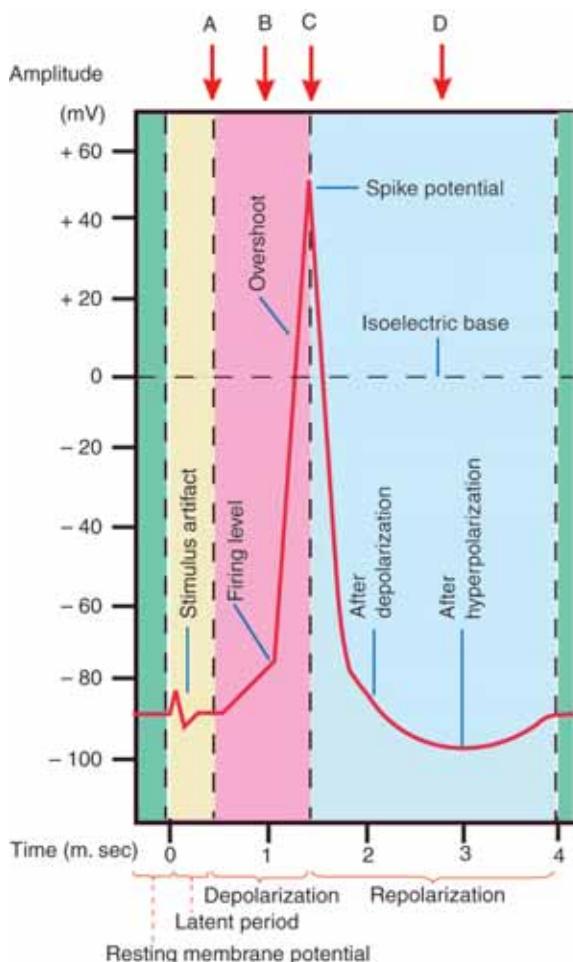
Firing Level and Depolarization

Depolarization starts after the latent period. Initially, it is very slow. After the initial slow depolarization for about 15 mV (up to -75 mV),

the rate of depolarization increases suddenly. The point at which the depolarization increases suddenly is called firing level.

Overshoot

From firing level, the curve reaches isoelectric potential (zero potential) rapidly and then shoots up (overshoots) beyond the zero potential (isoelectric base) up to +55 mV. It is called overshoot.

**FIGURE 23-1:** Action potential in a skeletal muscle

- A = Opening of few Na^+ channels
- B = Opening of many Na^+ channels
- C = Closure of Na^+ channels and opening of K^+ channels
- D = Closure of K^+ channels

Repolarization

When depolarization is completed (+55 mV), the repolarization starts. Initially, the repolarization occurs rapidly and then it becomes slow.

Spike Potential

The rapid rise in depolarization and the rapid fall in repolarization are together called spike potential. It lasts for 0.4 millisecond.

After Depolarization or Negative after Potential

The rapid fall in repolarization is followed by a slow repolarization. It is called after depolarization or negative after potential. Its duration is 2 to 4 milliseconds.

After Hyperpolarization or Positive after Potential

After reaching the resting level (-90 mV), it becomes more negative beyond resting level. This is called after hyperpolarization or positive after potential. This lasts for more than 50 milliseconds. After this, the normal resting membrane potential is restored slowly.

■ IONIC BASIS OF ELECTRICAL EVENTS

Resting Membrane Potential

The development and maintenance of resting membrane potential in a muscle fiber or a neuron are carried out by movement of ions, which produce ionic imbalance across the cell membrane. This results in the development of more positivity outside and more negativity inside the cell.

The ionic imbalance is produced by two factors:

1. Sodium-potassium pump
2. Selective permeability of cell membrane.

1. Sodium-potassium pump

Sodium and potassium ions are actively transported in opposite directions across the cell

membrane by means of an electrogenic pump called sodium-potassium pump. It moves three sodium ions out of the cell and two potassium ions inside the cell by using energy from ATP. Since more positive ions (cations) are pumped outside than inside, a net deficit of positive ions occurs inside the cell. It leads to negativity inside and positivity outside the cell. More details of this pump are given Chapter 3.

2. Selective permeability of cell membrane

The permeability of cell membrane depends largely on the transport channels. The transport channels are selective for movement of some specific ions. Most of the channels are gated channels and the specific ions can move across the membrane only when these gated channels are opened.

Channels for major anions (negatively charged substances) like proteins

However, channels for some of the negatively charged large substances such as proteins and negatively charged organic phosphate and sulfate compounds are absent or closed. So, such substances remain inside the cell and play a major role in the development and maintenance of negativity inside the cell (resting membrane potential).

Channels for ions

In addition, the channels for three important ions, sodium, chloride and potassium also play an important role in maintaining the resting membrane potential.

Action Potential

During the onset of depolarization, voltage gated Na^+ channels open resulting in slow influx of Na^+ . When depolarization reaches 7 to 10 mV, the voltage gated Na^+ channels start opening at a faster rate. It is called Na^+ channel activation. When the firing level is reached, the influx of Na^+ is very great and it leads to overshoot.

But the Na^+ transport is short-lived. This is because of rapid inactivation of Na^+ channels.

Thus, the Na^+ channels open and close quickly. At the same time, the K^+ channels start opening. This leads to efflux of K^+ out of the cell, causing repolarization.

Unlike the Na^+ channels, the K^+ channels remain open for longer duration. These channels remain opened for few more milliseconds after completion of repolarization. It causes efflux of more number of K^+ producing more negativity inside. It is the cause for hyperpolarization.

■ GRADED POTENTIAL

Graded potential is a mild local change in the membrane potential that develops in receptors, synapse or neuromuscular junction when stimulated. It is also called graded membrane potential or graded depolarization. The graded potential is distinct from the action potential and the properties of these two potentials are given in Table 23-1. In most of the cases, the graded potential is responsible for the generation of action potential. However, in some cases the graded potential hyperpolarizes the membrane potential (more negativity than resting membrane potential).

The graded potentials include:

1. End plate potential in neuromuscular junction (Chapter 24)
2. Receptor potential (Chapter 85)
4. Excitatory postsynaptic potential (Chapter 86)
5. Inhibitory postsynaptic potential (Chapter 86).

■ MOLECULAR CHANGES DURING MUSCULAR CONTRACTION

■ ACTOMYOSIN COMPLEX

In the relaxed state of the muscle, the thin actin filaments from the opposite ends of the sarcomere are away from each other leaving a broad 'H' zone.

During the contraction of the muscle, the actin (thin) filaments glide over the myosin (thick) filaments and form actomyosin complex.

■ MOLECULAR BASIS OF MUSCULAR CONTRACTION

The molecular mechanism is responsible for formation of actomyosin complex that results in muscular contraction. It includes three stages:

1. Excitation contraction coupling
2. Role of troponin and tropomyosin
3. Sliding mechanism

1. Excitation Contraction Coupling

Excitation contraction coupling is the process that occurs in between the excitation and contraction of the muscle. This process involves series of activities which are responsible for the contraction of the excited muscle.

Stages of excitation contraction coupling

When the impulse passes through a motor neuron and reaches the neuromuscular junction, acetylcholine is released from motor endplate. Acetylcholine causes opening of ligand gated sodium channels. So, sodium ions enter the neuromuscular junction. It leads to the development of endplate potential. Endplate potential causes generation of action potential in the muscle fiber.

The action potential spreads over sarcolemma and also into the muscle fiber through the 'T' tubules. The 'T' tubules are responsible for the rapid spread of action potential into the muscle fiber. When the action potential reaches the cisternae of 'L' tubules, these cisternae are excited. Now, the calcium ions stored in the cisternae are released into the sarcoplasm. The calcium ions from the sarcoplasm move towards the actin filaments to produce the contraction.

Thus, the calcium ion forms the link or coupling material between the excitation and the contraction of muscle. Hence, the calcium ions are said to form the basis of excitation contraction coupling.

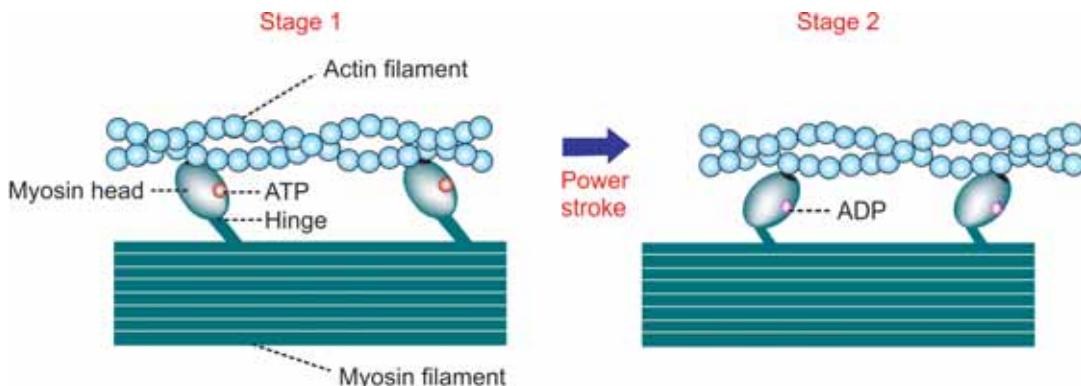


FIGURE 23-2: Diagram showing power stroke by myosin head. **Stage 1:** Myosin head binds with actin; **Stage 2:** Tilting of myosin head (power stroke) drags the actin filament

2. Role of Troponin and Tropomyosin

Normally, the head of myosin molecules has a strong tendency to get attached with active site of F actin. However, in relaxed condition, the active site of F actin is covered by the tropomyosin. Therefore, the myosin head cannot combine with actin molecule.

Large number of calcium ions, which are released from 'L' tubules during the excitation of the muscle, bind with troponin C. The loading of troponin C with calcium ions produces some change in the position of troponin molecule. It in turn, pulls tropomyosin molecule away from F actin. Due to the movement of tropomyosin, the active site of F actin is uncovered and immediately the head of myosin gets attached to the actin.

3. Sliding Mechanism and Formation of Actomyosin Complex – Sliding Theory

Sliding theory explains how the actin filaments slide over myosin filaments and form the actomyosin complex during muscular contraction. It is also called ratchet theory or walk along theory.

Each cross bridge from the myosin filaments has got three components namely, a hinge, an arm and a head.

After binding with active site of F actin, the myosin head is tilted towards the arm so that

the actin filament is dragged along with it (Fig. 23-2). This tilting of head is called power stroke. After tilting, the head immediately breaks away from the active site and returns to the original position. Now, it combines with a new active site on the actin molecule. And, tilting movement occurs again. Thus, the head of cross bridge bends back and forth and pulls the actin filament towards the center of sarcomere.

In this way, all the actin filaments of both the ends of sarcomere are pulled. So, the actin filaments of opposite sides overlap and form actomyosin complex. Formation of actomyosin complex results in contraction of the muscle.

When the muscle shortens further, the actin filaments from opposite ends of the sarcomere approach each other. So, the 'H' zone becomes narrow. And, the two 'Z' lines come closer with reduction in length of the sarcomere. However, the length of 'A' band is not altered. But, the length of 'I' band decreases.

When the muscular contraction becomes severe, the actin filaments from opposite ends overlap and, the 'H' zone disappears.

Thus, during the contraction of the muscle, the following changes occur in the sarcomere:

1. The length of all the sarcomeres decreases as the 'Z' lines come close to each other
2. The length of the 'I' band decreases since the actin filaments from opposite side overlap



FIGURE 23-3: Sequence of events during muscular contraction

3. The 'H' zone either decreases or disappears
4. The length of 'A' band remains the same.

The summary of sequence of events during muscular contraction is given in Fig. 23-3.

Energy for Muscular Contraction

The energy for movement of myosin head (power stroke) is obtained by breakdown of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and inorganic phosphate (Pi).

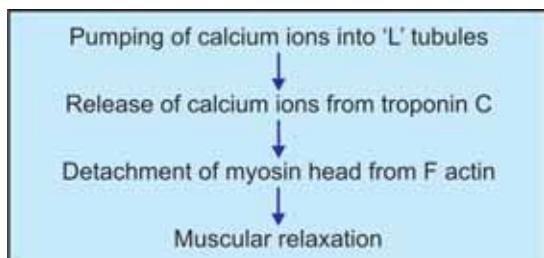


FIGURE 23-4: Sequence of events during muscular relaxation

The head of myosin has a site for ATP. Actually, the head itself can act as the enzyme ATPase and catalyze the breakdown of ATP. Even before the onset of contraction, an ATP molecule binds with myosin head.

When tropomyosin moves to expose the active sites, the head is attached to the active site. Now ATPase cleaves ATP into ADP and Pi, which remains in head itself. The energy released during this process is utilized for contraction.

When head is tilted, the ADP and Pi are released and a new ATP molecule binds with head. This process is repeated until the muscular contraction is completed.

Relaxation of the Muscle

The relaxation of the muscle occurs when the calcium ions are pumped back into the L tubules. When calcium ions enter the L tubules, calcium content in sarcoplasm decreases leading to the release of calcium ions from the troponin. It causes detachment of myosin from actin followed by relaxation of the muscle (Fig. 23-4). The detachment of myosin from actin obtains energy from breakdown of ATP. Thus, the chemical process of muscular relaxation is an active process although the physical process is said to be passive.

24

Neuromuscular Junction

- DEFINITION AND STRUCTURE
- NEUROMUSCULAR TRANSMISSION
 - RELEASE OF ACETYLCHOLINE
 - ACTION OF ACETYLCHOLINE
 - ENDPLATE POTENTIAL
 - MINIATURE ENDPLATE POTENTIAL
 - FATE OF ACETYLCHOLINE
- NEUROMUSCULAR BLOCKERS
- MOTOR UNIT
 - DEFINITION
 - NUMBER OF MUSCLE FIBERS IN MOTOR UNIT
- APPLIED PHYSIOLOGY – DISORDERS OF NEUROMUSCULAR JUNCTION

■ DEFINITION AND STRUCTURE

■ DEFINITION

Neuromuscular junction is the junction between the terminal branch of the nerve fiber and muscle fiber.

■ STRUCTURE

Skeletal muscle fibers are innervated by the motor nerve fibers. Each nerve fiber (axon) divides into many terminal branches. Each terminal branch innervates one muscle fiber through the neuromuscular junction (Fig. 24-1).

Axon Terminal and Motor Endplate

Terminal branch of nerve fiber is called axon terminal. When the axon comes close to the

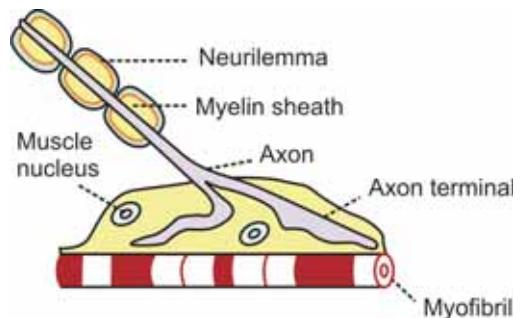


FIGURE 24-1: Longitudinal section of neuromuscular junction

muscle fiber, it loses the myelin sheath. So, the axis cylinder is exposed. This portion of the axis cylinder is expanded like a bulb which is called motor endplate.

The axon terminal contains mitochondria and synaptic vesicles. The synaptic vesicles contain the neurotransmitter substance, acetylcholine. The acetylcholine is synthesized by mitochondria present in the axon terminal and stored in the vesicles. The mitochondria contain ATP which is the source of energy for the synthesis of acetylcholine.

Synaptic Trough or Gutter

The motor endplate invaginates inside the muscle fiber and forms a depression which is known as synaptic trough or synaptic gutter. The membrane of the muscle fiber below the motor endplate is thickened.

Synaptic Cleft

The membrane of the nerve ending is called the presynaptic membrane. The membrane of the muscle fiber is called postsynaptic membrane. The space between these two is called synaptic cleft. The synaptic cleft contains basal lamina. It is a thin layer of spongy reticular matrix through which, the extracellular fluid diffuses. Large quantity of an enzyme called acetylcholinesterase is attached to the matrix of basal lamina.

Subneural Clefts

The postsynaptic membrane is the membrane of the muscle fiber. It is thrown into numerous folds called subneural clefts. The postsynaptic membrane contains the receptors called nicotinic acetylcholine receptors (Fig. 24-2).

■ NEUROMUSCULAR TRANSMISSION

Neuromuscular transmission is defined as the transfer of information from motor nerve ending to the muscle fiber through neuromuscular junction. It is the mechanism by which the motor nerve impulses initiate muscle contraction. A series of events take place in the neuromuscular junction during this process (Fig. 24-3).

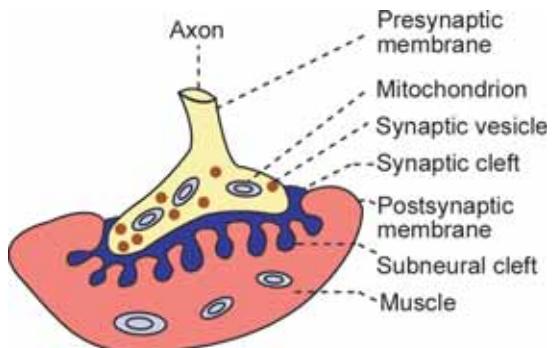


FIGURE 24-2: Structure of neuromuscular junction

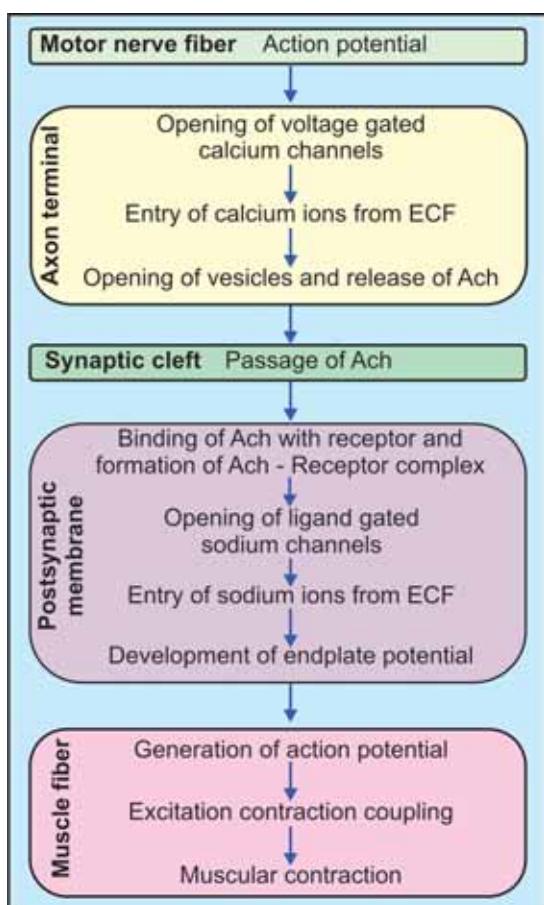


FIGURE 24-3: Sequence of events during neuromuscular transmission.

Ach = Acetylcholine. ECF = Extracellular fluid

1. Release of acetylcholine
2. Action of acetylcholine
3. Development of endplate potential
4. Development of miniature endplate potential
5. Destruction of acetylcholine.

■ 1. RELEASE OF ACETYLCHOLINE

When the action potential reaches the axon terminal, it opens the voltage gated calcium channels in the membrane of the axon terminal. Calcium ions enter the axon terminal from extracellular fluid and cause bursting of the vesicles. Now, acetylcholine is released from the vesicles and diffuses through presynaptic membrane and enters the synaptic cleft.

Each vesicle contains about 10,000 acetylcholine molecules. And, at a time, about 300 vesicles open and release acetylcholine.

■ 2. ACTION OF ACETYLCHOLINE

After entering the synaptic cleft, the acetylcholine molecules bind with nicotinic receptors present in the postsynaptic membrane and form the acetylcholine–receptor complex. It opens the ligand gated channels for sodium in the postsynaptic membrane. Now, sodium ions from extracellular fluid enter the neuromuscular junction through these channels. And there, the sodium ions produce an electrical potential called the endplate potential.

■ 3. ENDPLATE POTENTIAL

Endplate potential is the change in the resting membrane potential when an impulse reaches the neuromuscular junction. The resting membrane potential at the neuromuscular junction is -90 mV . When sodium ions enter inside, slight depolarization occurs up to -60 mV which is called endplate potential.

The endplate potential is a graded potential (Chapter 23) and it is not action potential. It is nonpropagative. But it causes the development of action potential in the muscle fiber.

■ 4. MINIATURE ENDPLATE POTENTIAL

Miniature endplate potential is a weak endplate potential in neuromuscular junction that is developed by the release of a small quantity of acetylcholine from axon terminal. And, each quantum of this neurotransmitter produces a weak miniature endplate potential. The amplitude of this potential is only up to 0.5 mV .

Miniature endplate potential cannot produce action potential in the muscle. When more and more quanta of acetylcholine are released continuously, the miniature endplate potentials are added together and finally produce endplate potential resulting in action potential in the muscle.

■ 5. FATE OF ACETYLCHOLINE

Acetylcholine released into the synaptic cleft is destroyed very quickly within one millisecond by the enzyme, acetylcholinesterase. However, the acetylcholine is so potent, that even this short duration of 1 millisecond is sufficient to excite the muscle fiber. The rapid destruction of acetylcholine is functionally significant because it prevents repeated excitation of the muscle fiber and allows the muscle to relax.

Reuptake Process

Reuptake is a process in neuromuscular junction, by which a degraded product of neurotransmitter re-enters the presynaptic axon terminal where it is reused. Acetylcholinesterase splits (degrades) acetylcholine into inactive choline and acetate. Choline is taken back into axon terminal from synaptic cleft by reuptake process. There, it is reused in synaptic vesicle to form new acetylcholine molecule.

■ NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are the drugs, which can prevent the transmission of impulses from nerve fiber to the muscle fiber through the neuro-

muscular junctions. Following are the neuromuscular blockers commonly used in surgery and in research.

1. Curare

Curare prevents the neuromuscular transmission by combining with acetylcholine receptors. So, the acetylcholine cannot combine with the receptors. And, the endplate potential cannot develop. Since curare blocks the neuromuscular transmission by acting on the acetylcholine receptors, it is called receptor blocker.

2. Bungarotoxin

It is a toxin from the venom of deadly snakes. It affects the neuromuscular transmission by blocking the acetylcholine receptors.

3. Succinylcholine and Carbamylcholine

These drugs block the neuromuscular transmission by acting like acetylcholine and keeping the muscle in a depolarized state. But, these drugs are not destroyed by cholinesterase. So, the muscle remains in a depolarized state for a long time.

4. Botulinum Toxin

It is derived from the bacteria *Clostridium botulinum*. It prevents release of acetylcholine from axon terminal into the neuromuscular junction.

■ MOTOR UNIT

■ DEFINITION

The single motor neuron, its axon terminals and the muscle fibers innervated by it are together called motor unit. Each motor neuron activates a group of muscle fibers through the axon terminals. Stimulation of a motor neuron causes contraction of all the muscle fibers innervated by that neuron.

■ NUMBER OF MUSCLE FIBERS IN MOTOR UNIT

The number of muscle fiber in each motor unit varies. The number of muscle fiber is small in the motor units of the muscles concerned with fine, graded and precise movements. Examples are:

Laryngeal muscles : 2 to 3 muscle fibers per motor unit

Pharyngeal muscles: 2 to 6 muscle fibers per motor unit

Ocular muscles : 3 to 6 muscle fibers per motor unit

The muscles concerned with crude or coarse movements have motor units with large number of muscle fibers. There are about 120 to 165 muscle fibers in each motor unit in these muscles. Examples are the muscles of leg and back.

■ APPLIED PHYSIOLOGY – DISORDERS OF NEUROMUSCULAR JUNCTION

The disorders of neuromuscular junction includes:

1. Myasthenia gravis
2. Eaton-Lambert syndrome.

■ 1. MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder of neuromuscular junction caused by antibodies to cholinergic receptors. It is characterized by grave weakness of the muscle due to the inability of neuromuscular junction to transmit impulses from nerve to the muscle.

■ 2. EATON-LAMBERT SYNDROME

Eaton-Lambert syndrome is also an autoimmune disorder of neuromuscular junction. It is caused by antibodies to calcium channels in axon terminal. This disease is characterized by features of myasthenia gravis. In addition the patients have blurred vision and dry mouth.

25

Smooth Muscle

- **DISTRIBUTION**
- **STRUCTURE**
- **TYPES**
- **ELECTRICAL ACTIVITY IN SINGLE UNIT SMOOTH MUSCLE**
- **ELECTRICAL ACTIVITY IN MULTIUNIT SMOOTH MUSCLE**
- **CONTRACTILE PROCESS**
- **CONTROL OF SMOOTH MUSCLE**

■ DISTRIBUTION OF SMOOTH MUSCLE

Smooth muscles are nonstriated (plain) and involuntary muscles present in almost all the organs in the form of sheets, bundles or sheaths around other tissues. These muscles form the major contractile tissues of various organs.

Smooth muscle fibers are present in the following structures:

- i. Wall of organs like esophagus, stomach and intestine in gastrointestinal tract
- ii. Ducts of digestive glands
- iii. Trachea, bronchial tube and alveolar ducts of respiratory tract
- iv. Ureter, urinary bladder and urethra in excretory system
- v. Wall of the blood vessels in circulatory system
- vi. Arrector pilorum of skin
- vii. Mammary glands, uterus, genital ducts, prostate gland and scrotum in reproductive system
- viii. Iris and ciliary body of the eye.

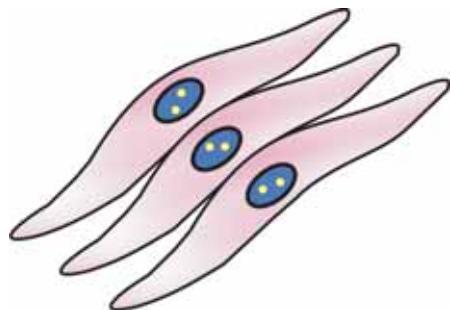


FIGURE 25-1: Smooth muscle fibers

■ STRUCTURE OF SMOOTH MUSCLE

Smooth muscle fibers are fusiform or elongated cells. The nucleus is single and elongated and it is centrally placed. Normally, two or more nucleoli are present in the nucleus (Fig. 25-1). Smooth muscle fibers are generally very small, measuring 2 to 5 μ in diameter and 50 to 200 μ in length. Smooth muscle fibers are covered by connective tissue. But the tendons are absent.

Myofibrils and Sarcomere

Well defined myofibrils and sarcomere are absent in smooth muscles. So the alternate dark and light bands are absent. Absence of dark and light bands gives the nonstriated appearance to the smooth muscle.

Myofilaments and Contractile Proteins

The contractile proteins in smooth muscle fiber are actin, myosin and tropomyosin. But troponin or tropomodulin like substance is absent.

Thick and thin filaments are present in smooth muscle. However, these filaments are not arranged in orderly fashion as in skeletal muscle. Thick filaments are formed by myosin molecules and have more number of cross bridges than in skeletal muscle. Thin filaments are formed by actin and tropomyosin molecules.

Dense Bodies

Dense bodies are the special structures of smooth muscle fibers to which the actin and tropomyosin molecules of thin filaments are attached.

Sarcotubular System

Sarcotubular system in smooth muscle fibers is in the form of network. 'T' tubules are absent and 'L' tubules are poorly developed (Table 20-1).

■ TYPES OF SMOOTH MUSCLE FIBERS

Smooth muscle fibers are of two types:

1. Single unit or visceral smooth muscle fibers
2. Multiunit smooth muscle fibers.

■ SINGLE UNIT OR VISCERAL SMOOTH MUSCLE FIBERS

Single unit smooth muscle fibers are the fibers with interconnecting gap junctions. The gap junctions allow rapid spread of action potential throughout the tissue so that all the muscle fibers show synchronous contraction as a single unit. Single unit smooth muscle fibers are also called visceral smooth muscle fibers.

The features of single unit smooth muscle fibers:

- i. The muscle fibers are arranged in sheets or bundles
- ii. The cell membrane of adjacent fibers fuses at many points to form gap junctions. Through the gap junctions, ions move freely from one cell to the other. Thus a functional syncytium is developed. The syncytium contracts as a single unit. In this way, the visceral smooth muscle resembles cardiac muscle more than the skeletal muscle.

The visceral smooth muscle fibers are in the walls of the organs such as gastrointestinal organs, uterus, ureters, respiratory tract, etc.

■ MULTIUNIT SMOOTH MUSCLE FIBERS

The multiunit smooth muscle fibers are the muscle fibers without interconnecting gap junctions. These smooth muscle fibers resemble the skeletal muscle fibers in many ways. The features of multiunit smooth muscle fibers:

- i. The muscle fibers are individual fibers
- ii. Each muscle fiber is innervated by a single nerve ending
- iii. Each muscle fiber has got an outer membrane made up of glycoprotein, which helps to insulate and separate the muscle fibers from one another
- iv. The control of these muscle fibers is mainly by nerve signals
- v. These smooth muscle fibers do not exhibit spontaneous contractions.

The multiunit muscle fibers are in ciliary muscles of the eye, iris of the eye, nictitating membrane (in cat), arrector pili, and smooth muscles of the blood vessels and urinary bladder.

■ ELECTRICAL ACTIVITY IN SINGLE UNIT SMOOTH MUSCLE

Usually 30 to 40 smooth muscle fibers are simultaneously depolarized which leads to development of self propagating action potential. It is possible because of gap junctions and syncytial arrangements of single unit smooth muscles.

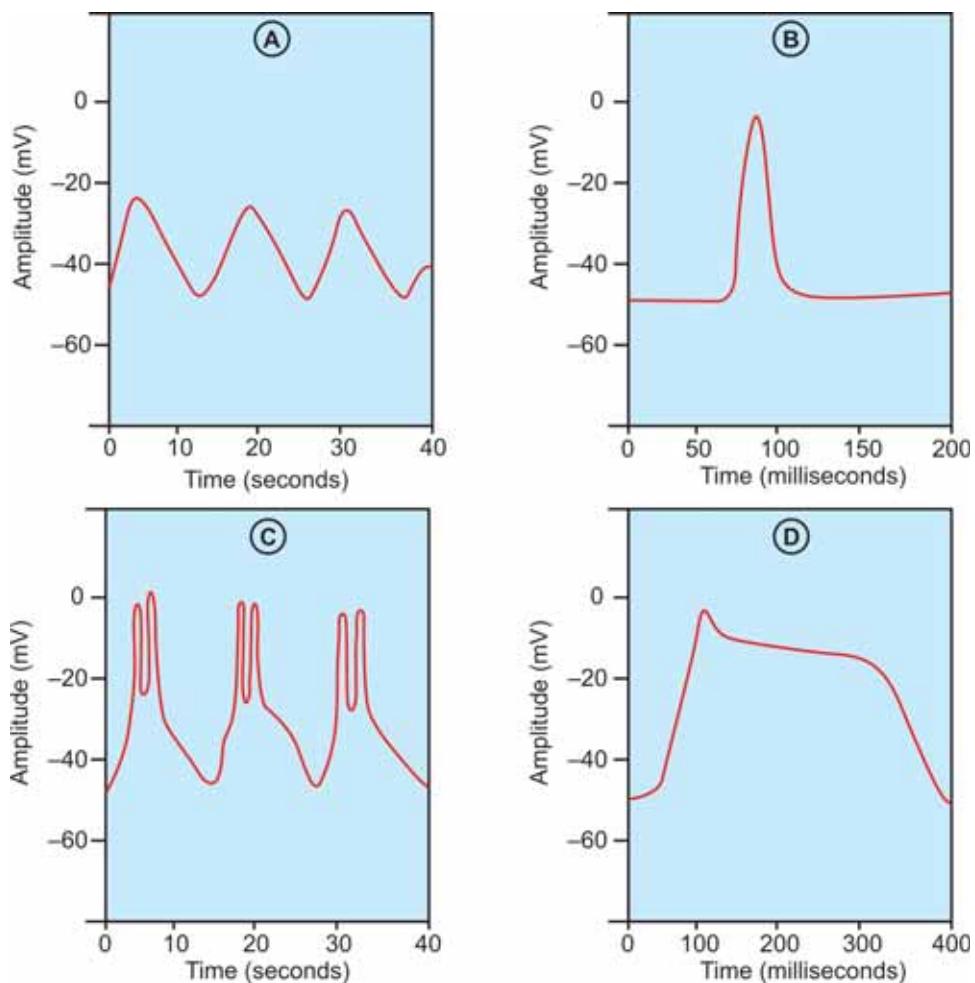


FIGURE 25-2: Electrical activities in smooth muscle

A = Slow wave rhythm of resting membrane potential. B = Spike potential
C = Spike potential initiated by slow wave rhythm. D = Action potential with plateau

■ RESTING MEMBRANE POTENTIAL

Resting membrane potential in visceral smooth muscle is very much unstable and ranges between -50 and -75 mV. Sometimes, it reaches the low level of -25 mV.

■ CAUSE FOR UNSTABLE RESTING MEMBRANE POTENTIAL – SLOW WAVE POTENTIAL

The unstable is caused by the appearance of some wave like fluctuations called slow waves. The slow waves occur in a rhythmic fashion at

a frequency of 4 to 10 per minute with the amplitude of 10 to 15 mV (Fig. 25-2). The cause of the slow wave rhythm is not known. It is suggested that it may be due to the rhythmic modulations in the activities of sodium-potassium pump. The slow wave is not action potential and it cannot cause contraction of the muscle. But it initiates the action potential (see below).

■ ACTION POTENTIAL

Three types of action potential occur in visceral smooth muscle fibers

1. Spike potential
2. Spike potential initiated by slow wave rhythm
3. Action potential with plateau.

1. Spike Potential

The spike potential in visceral smooth muscle is different from that in skeletal muscles. In smooth muscle, the average duration of spike potential varies between 30 and 50 milliseconds. Its amplitude is very low and it does not reach the isoelectric base. It is due to nervous and other stimuli and it leads to contraction of the muscle.

2. Spike Potential Initiated by Slow Wave Rhythm

Sometimes the slow wave rhythm of resting membrane potential initiates the spike potentials, which lead to contraction of the muscle. The spike potentials appear rhythmically at a rate of about one or two spikes at the peak of each slow wave. These potentials initiated by the slow wave rhythm cause rhythmic contractions of smooth muscles. This type of potentials appears mostly in smooth muscles, which are self excitatory and contract themselves without any external stimuli. So, the spike potentials initiated by slow wave rhythm are otherwise called pacemaker waves. The smooth muscles showing rhythmic contractions are present in some of the visceral organs such as intestine.

3. Action Potential with Plateau

This type of action potential starts with rapid depolarization as in the case of skeletal muscle. But, repolarization does not occur immediately. The muscle remains depolarized for long periods of about 100 to 1000 milliseconds. This type of action potential is responsible for sustained contraction of smooth muscle fibers. After the long depolarized state, slow repolarization occurs.

■ TONIC CONTRACTION OF SMOOTH MUSCLE WITHOUT ACTION POTENTIAL

The smooth muscles of some visceral organs maintain a state of partial contraction called tonus

or tone. It is due to the tonic contraction of the muscle that occurs without any action potential or any stimulus. Sometimes, the tonic contraction occurs due to the action of some hormones.

■ IONIC BASIS OF ACTION POTENTIAL

The important difference between the action potential in skeletal muscle and smooth muscle lies in the ionic basis of depolarization. In skeletal muscle, the depolarization occurs due to opening of sodium channels and entry of sodium ions from extracellular fluid into the muscle fiber. But in smooth muscle, the depolarization is due to entry of calcium ions rather than sodium ions. Unlike the fast sodium channels, the calcium channels open and close slowly. It is responsible for the prolonged action potential with plateau in smooth muscles. The calcium ions play an important role during the contraction of the muscle.

■ ELECTRICAL ACTIVITY IN MULTIUNIT SMOOTH MUSCLE

The electrical activity in multiunit smooth muscle is different from that in the single unit smooth muscle. The electrical changes leading to contraction of multiunit smooth muscle are triggered by nervous stimuli. The nerve endings secrete the neurotransmitters like acetylcholine and noradrenaline. The neurotransmitters depolarize the membrane of smooth muscle fiber slightly leading to contraction. The action potential does not develop. This type of depolarization is called local depolarization or junctional potential. The local depolarization travels throughout the entire smooth muscle fiber and causes contraction. The local depolarization is developed because the multiunit smooth muscle fibers are too small to develop action potential.

■ CONTRACTILE PROCESS IN SMOOTH MUSCLE

Compared to skeletal muscles, in smooth muscles, the contraction and relaxation processes are slow.

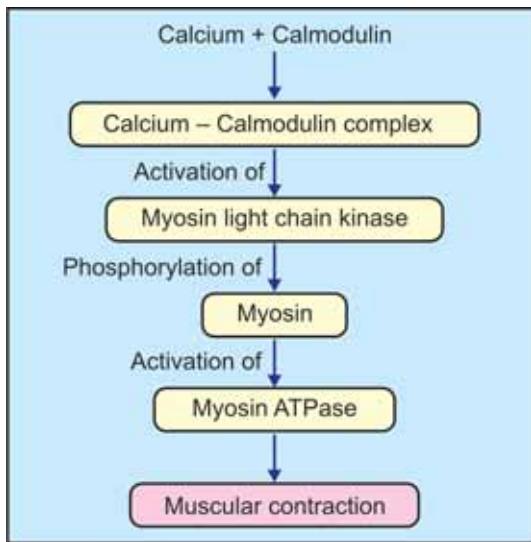


FIGURE 25-3: Molecular basis of smooth muscle contraction

■ MOLECULAR BASIS OF SMOOTH MUSCLE CONTRACTION

The process of excitation and contraction is very slow in smooth muscles because of poor development of L tubules (sarcoplasmic reticulum). So, the calcium ions, which are responsible for excitation contraction coupling, must be obtained from the extracellular fluid. It makes the process of excitation contraction coupling slow.

Calcium–Calmodulin Complex

The stimulation of ATPase activity of myosin in smooth muscle is different from that in the skeletal muscle. In smooth muscle, the myosin has to be phosphorylated for the activation of myosin ATPase. The phosphorylation of myosin occurs in the following manner (Fig. 25-3). Calcium which enters the sarcoplasm from the extracellular fluid combines with a protein called calmodulin and forms calcium–calmodulin complex. It activates an enzyme called calmodulin – dependent myosin light chain kinase. This enzyme in turn causes phosphorylation of

myosin followed by activation of myosin ATPase. Now, the sliding of actin filaments starts.

The phosphorylated myosin gets attached to the actin molecule for longer period. It is called latch bridge mechanism and it is responsible for the sustained contraction of the muscle with expenditure of little energy.

The relaxation of the muscle occurs due to the dissociation of calcium–calmodulin complex.

Length-Tension Relationship – Plasticity

Smooth muscle fibers have the property of plasticity. Plasticity is the adaptability of smooth muscle fibers to a wide range of lengths. If the smooth muscle fiber is stretched, it adapts to this new length and contracts when stimulated. This adaptability exists to a wide range of lengths. Because of this property, tension produced in the muscle fiber is not directly proportional to resting length of the muscle fiber. In other words, Starling's law is not applicable to smooth muscle. In skeletal and cardiac muscles, Starling's law is applicable and the tension or force of contraction is directly proportional to initial length of the muscle fibers.

■ CONTROL OF SMOOTH MUSCLE

Smooth muscle fibers are controlled by:

- Nervous factors
- Humoral factors.

■ NERVOUS FACTORS

Smooth muscles are supplied by both sympathetic and parasympathetic nerves, which act opposite to each other in controlling the activities of smooth muscles. However, these nerves are not responsible for the initiation of any activity in smooth muscle.

■ HUMORAL FACTORS

The activity of smooth muscle is also controlled by humoral factors which include hormones, neurotransmitters and other humoral factors.

QUESTIONS IN MUSCLE PHYSIOLOGY

■ LONG QUESTIONS

1. Explain the molecular basis of muscular contraction.
2. Describe the electrical changes during muscular contraction.
3. Explain the ionic basis of electrical events during contraction of skeletal muscle.
4. Describe the neuromuscular junction with a suitable diagram. Add a note on neuromuscular transmission.

■ SHORT QUESTIONS

1. Compare skeletal muscle and cardiac muscle.
2. Compare skeletal muscle and smooth muscle.
3. Sarcomere.
4. Contractile elements of the muscle.
5. Muscle proteins.
6. Sarcotubular system.
7. Sarcoplasmic reticulum.
8. Composition of muscle.
9. Differences between pale and red muscles.

10. Heat rigor/rigor mortis.
11. Effects of repeated stimuli on skeletal muscle.
12. Fatigue.
13. Tetanus.
14. Starling's law of muscle.
15. Refractory period.
16. Muscle tone.
17. Resting membrane potential.
18. Action potential.
19. Graded potential.
20. Actomyosin complex.
21. Excitation contraction coupling.
22. Sliding theory of muscular contraction.
23. Electrical activity in smooth muscle.
24. Molecular basis of smooth muscular contraction.
25. Neuromuscular junction.
26. Neuromuscular transmission.
27. Endplate potential.
28. Neuromuscular blockers.
29. Motor unit.
30. Myasthenia gravis.

SECTION 4

Digestive System

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26

Introduction to Digestive System

- INTRODUCTION
- FUNCTIONAL ANATOMY
- WALL OF GASTROINTESTINAL TRACT
 - MUCUS LAYER
 - SUBMUCUS LAYER
 - MUSCULAR LAYER
 - SEROUS OR FIBROUS LAYER
- NERVE SUPPLY TO GASTROINTESTINAL TRACT
 - INTRINSIC NERVE SUPPLY
 - EXTRINSIC NERVE SUPPLY

■ INTRODUCTION

Digestion is defined as the process by which food is broken down into simple chemical substances that can be absorbed and used as nutrients by the body. Most of the substances in the diet cannot be utilized as such. These substances must be broken into smaller particles. Then only these substances can be absorbed into blood and distributed to various parts of the body for utilization. The digestive system is responsible for these functions.

■ FUNCTIONAL ANATOMY OF THE DIGESTIVE SYSTEM

Digestive system is made up of gastrointestinal tract (GI tract) or alimentary canal and accessory organs, which help in the process of digestion and absorption (Fig. 26-1). GI tract is a tubular structure extending from the mouth up to anus

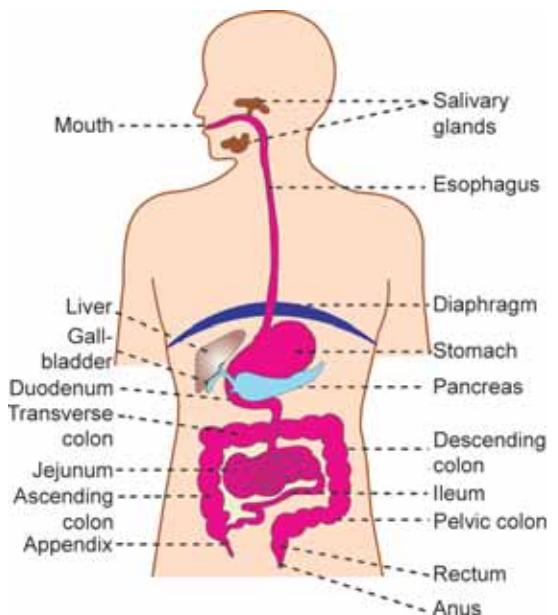


FIGURE 26-1: Gastrointestinal tract

with a length of about 30 feet. It opens to the external environment on both ends. GI tract is formed by two types of organs:

1. Primary digestive organs
2. Accessory digestive organs.

1. Primary Digestive Organs

Primary digestive organs are the organs where actual digestion takes place. These organs are:

1. Mouth
2. Pharynx
3. Esophagus
4. Stomach
5. Small intestine
6. Large intestine.

2. Accessory Digestive Organs

Accessory digestive organs are the organs which help the primary digestive organs in the process of digestion. These organs are:

1. Teeth
2. Tongue
3. Salivary glands
4. Exocrine part of pancreas
5. Liver
6. Gallbladder.

■ WALL OF GASTROINTESTINAL TRACT

In general, the wall of the GI tract is formed by four layers which are from inside out:

1. Mucus layer
2. Submucus layer
3. Muscular layer
4. Serous or fibrous layer.

■ 1. MUCUS LAYER

The mucus layer is the innermost layer of the wall of GI tract. It is also called gastrointestinal mucosa or mucous membrane. It faces the cavity of GI tract.

The mucosa has three layers of structures:

- i. Epithelial lining which is in contact with contents of GI tract

- ii. Lamina propria formed by connective tissue
- iii. Muscularis mucosa formed by smooth muscle fibers.

■ 2. SUBMUCUS LAYER

This is present in all parts of GI tract except mouth and pharynx. This layer contains loose collagen fibers, elastic fibers, reticular fibers and few cells of connective tissue. Blood vessels, lymphatic vessels and nerve plexus are present in this layer.

■ 3. MUSCULAR LAYER

This layer in lips, cheeks and wall of pharynx have skeletal muscle fibers. The esophagus has both skeletal and smooth muscle fibers. Wall of the stomach and intestine is formed by smooth muscle fibers.

The smooth muscle fibers in stomach are arranged in three layers:

- i. Inner oblique layer
- ii. Middle circular layer
- iii. Outer longitudinal layer.

The smooth muscle fibers in the intestine are arranged in two layers:

- i. Inner circular layer
- ii. Outer longitudinal layer.

The smooth muscle fibers present in inner circular layer of anal canal constitute internal anal sphincter. The external anal sphincter is formed by skeletal muscle fibers.

■ 4. SEROUS OR FIBROUS LAYER

Outermost layer of the wall of GI tract is either serous or fibrous in nature. The serous layer is formed by connective tissue and mesoepithelial cells. It is also called serosa or serous membrane. It covers stomach, small intestine and large intestine.

The fibrous layer is otherwise called fibrosa. It is formed by connective tissue. It covers pharynx and esophagus.

■ NERVE SUPPLY TO GASTROINTESTINAL TRACT

GI tract has two types of nerve supply:

- I. Intrinsic nerve supply
- II. Extrinsic nerve supply.

■ INTRINSIC NERVE SUPPLY – ENTERIC NERVOUS SYSTEM

The enteric nervous system is present within the wall of GI tract from esophagus to anus. The nerve fibers of this system are interconnected and form two major networks called

1. Auerbach's plexus
2. Meissner's plexus.

These nerve plexus contain nerve cell bodies, processes of nerve cells and the receptors. The receptors in the GI tract are stretch receptors and chemoreceptors. The enteric nervous system is controlled by extrinsic nerves.

Auerbach's Plexus

It is also known as myenteric nerve plexus. It is present in between the inner circular muscle layer and the outer longitudinal muscle layer (Fig. 26-2).

Functions of Auerbach's Plexus

The major function of this plexus is to regulate the movements of GI tract. Some nerve fibers of this plexus accelerate the movements by secreting the excitatory neurotransmitter sub-

stances like acetylcholine, serotonin and substance P. Other fibers of this plexus inhibit the GI motility by secreting the inhibitory neurotransmitters such as vasoactive intestinal polypeptide (VIP), neurotensin and enkephalin.

Meissner's Nerve Plexus

Meissner's plexus is otherwise called submucous nerve plexus. It is situated in between the muscular layer and submucosal layer of GI tract.

Functions of Meissner's Plexus

The function of Meissner's plexus is the regulation of secretory functions of GI tract. And these nerve fibers cause constriction of blood vessels of GI tract.

■ EXTRINSIC NERVE SUPPLY

The extrinsic nerves that control the enteric nervous system are from autonomic nervous system. Both sympathetic and parasympathetic divisions of autonomic nervous system innervate the GI tract (Fig. 26-3).

Sympathetic Nerve Fibers

Preganglionic sympathetic nerve fibers to GI tract arise from lateral horns of spinal cord between fifth thoracic and second lumbar segments (T5 – L2). From here, the fibers leave the spinal cord, pass through the ganglia of sympathetic chain without having any synapse and then terminate in the celiac and mesenteric ganglia. The postganglionic fibers from these ganglia are distributed throughout the GI tract.

Functions of sympathetic nerve fibers

Sympathetic nerve fibers inhibit the movements and decrease the secretions of GI tract by secreting the neurotransmitter noradrenaline. It also causes constriction of sphincters.

Parasympathetic Nerve Fibers

Parasympathetic nerve fibers to GI tract pass through some of the cranial nerves and sacral

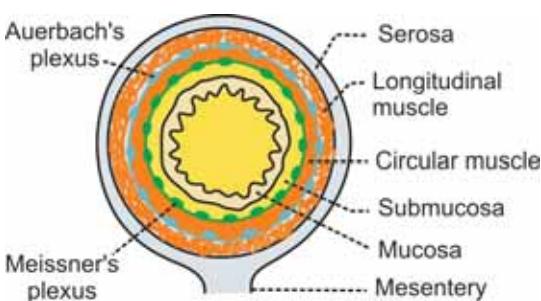


FIGURE 26-2: Structure of intestinal wall with intrinsic nerve plexus

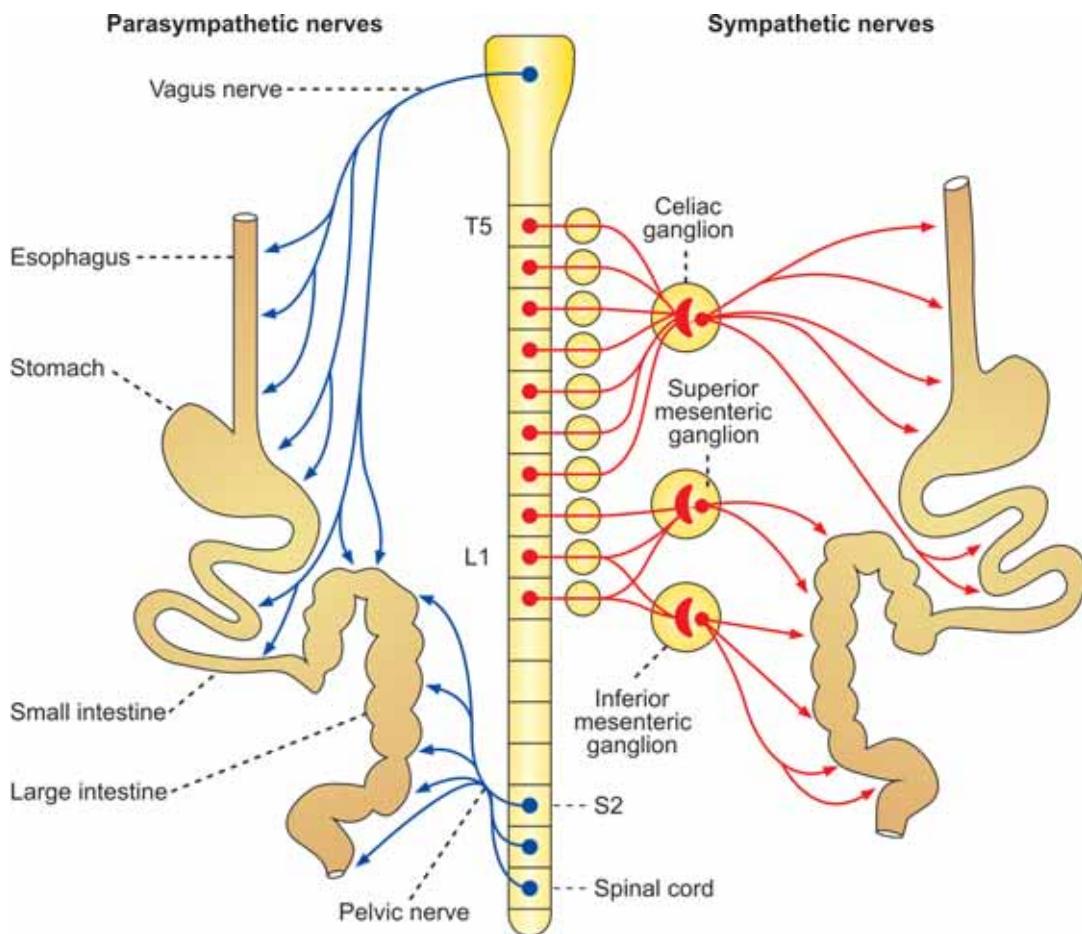


FIGURE 26-3: Extrinsic nerve supply to GI tract. T5 = 5th thoracic segment of spinal cord.
L1 = 1st lumbar segment of spinal cord; S2 = 2nd sacral segment of spinal cord

nerves. The preganglionic and postganglionic parasympathetic nerve fibers to mouth and salivary glands pass through facial and glossopharyngeal nerves.

The preganglionic parasympathetic nerve fibers to esophagus, stomach, small intestine and upper part of large intestine pass through vagus nerve. The preganglionic nerve fibers to lower part of large intestine arise from second, third and fourth sacral segments (S1, S2 and S3) of

spinal cord and pass through pelvic nerve. All these preganglionic parasympathetic nerve fibers synapse with the postganglionic nerve cells in the myenteric and submucous plexus.

Functions of parasympathetic nerve fibers

Parasympathetic nerve fibers accelerate movements and increase the secretions of GI tract. The neurotransmitter secreted by the parasympathetic nerve fibers is acetylcholine.

27

Mouth and Salivary Glands

- **FUNCTIONAL ANATOMY OF MOUTH**
- **FUNCTIONS OF MOUTH**
- **SALIVARY GLANDS**
- **PROPERTIES AND COMPOSITION OF SALIVA**
- **FUNCTIONS OF SALIVA**
- **REGULATION OF SALIVARY SECRETION**
- **EFFECTS OF DRUGS AND CHEMICALS ON SALIVARY SECRETION**
- **APPLIED PHYSIOLOGY**

■ **FUNCTIONAL ANATOMY OF MOUTH**

The mouth is otherwise known as oral cavity or buccal cavity. It is formed by cheeks, lips and palate. It encloses the teeth, tongue and salivary glands. It opens anteriorly to the exterior through lips and posteriorly through fauces into the pharynx.

Digestive juice present in the mouth is saliva which is secreted by the salivary glands.

■ **FUNCTIONS OF MOUTH**

The primary function of mouth is eating. It has few other important functions also. The functions of the mouth are:

1. Ingestion of food materials.
2. Chewing the food and mixing it with saliva.
3. Appreciation of the taste.
4. Transfer of food (bolus) to the esophagus by swallowing.

5. Role in speech.
6. Social functions such as smiling and other expressions.

■ **SALIVARY GLANDS**

In humans, the saliva is secreted by three pairs of major (larger) salivary glands and some minor (small) salivary glands in the oral and pharyngeal mucous membrane. The major glands are:

1. Parotid glands
2. Submaxillary or submandibular glands
3. Sublingual glands.

■ **PAROTID GLANDS**

Parotid glands are the largest of all salivary glands situated at the side of the face just below and in front of the ear. Secretions from these glands are emptied into the oral cavity by Stensen's duct that opens inside the cheek against the upper second molar tooth (Fig. 27-1).

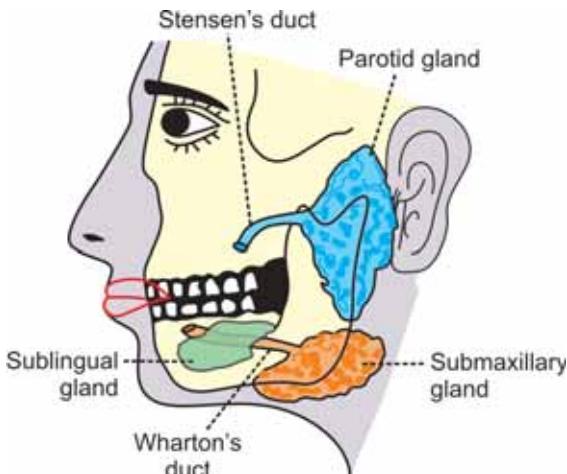


FIGURE 27-1: Major salivary glands

■ SUBMAXILLARY GLANDS

Submaxillary glands or submandibular glands are located in submaxillary triangle medial to mandible. Saliva from these glands is emptied into the oral cavity by Wharton's duct. The duct opens at the side of frenulum of tongue by means of a small opening on the summit of papilla called caruncula sublingualis.

■ SUBLINGUAL GLANDS

Sublingual glands are the smallest salivary glands situated in the mucosa at floor of mouth. Saliva from these glands is poured into 5-15 small ducts called ducts of Ravidus. These ducts open on small papillae beneath the tongue. One of the ducts is larger and it is called Bartholin's duct (Table 27-1). It drains the anterior part of the gland and opens on caruncula sublingualis near the opening of submaxillary duct.

TABLE 27-1: Ducts of major salivary glands

Gland	Duct
Parotid gland	Stensen's duct
Submaxillary gland	Wharton's duct
Sublingual gland	Ducts of Ravidus/Bartholin's duct

■ MINOR SALIVARY GLANDS

1. Lingual mucus glands situated in posterior 1/3 of the tongue, behind circum vallate papillae and at the tip and margins of tongue.
2. Lingual serous glands located near circum vallate papillae and foliform papillae.
3. Buccal glands present between the mucous membrane and buccinator muscle. Four to five of these are larger and situated outside buccinator around terminal part of parotid duct. These glands are called molar glands.
4. Labial glands situated beneath the mucous membrane around the orifice of mouth.
5. Palatal glands found beneath the mucous membrane of the soft palate.

■ CLASSIFICATION OF SALIVARY GLANDS

Salivary glands are classified into three types based on the type of secretion.

1. Serous Glands

This type of gland is predominantly made up of serous cells. These glands secrete thin and watery saliva. Parotid glands and lingual serous glands are serous glands.

2. Mucus Glands

This type of glands is made up of mainly the mucus cells. These glands secrete thick, viscous saliva with high mucin content. Lingual mucus glands, buccal glands and palatal glands belong to this type.

3. Mixed Glands

Mixed glands are made up of both serous and mucus cells. Submandibular, sublingual and labial glands are the mixed glands.

■ STRUCTURE AND DUCT SYSTEM OF SALIVARY GLANDS

Salivary glands are made up of acini or alveoli. Each acinus is formed by a small group of cells which surround a central globular cavity. The

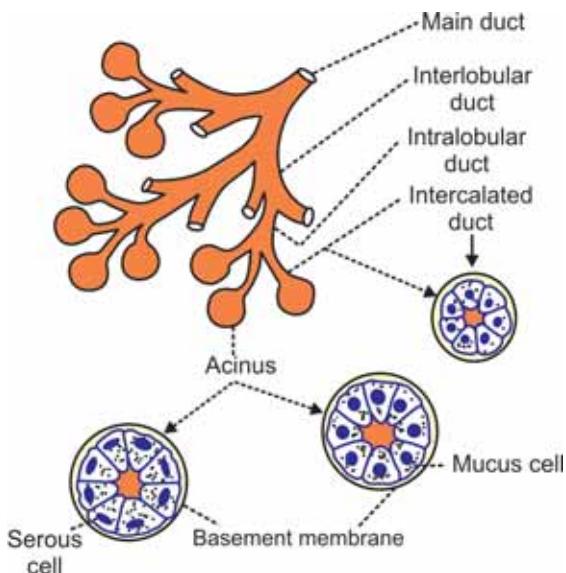


FIGURE 27-2: Diagram showing acini and duct system in salivary glands

central cavity of each acinus is continuous with the lumen of the duct. The fine duct draining each acinus is called intercalated duct. Many intercalated ducts join together to form intralobular duct. Few intralobular ducts join to form interlobular ducts, which unite to form the main duct of the gland (Fig. 27-2). The gland with this type of structure and duct system is called racemose type (racemose = bunch of grapes).

■ PROPERTIES AND COMPOSITION OF SALIVA

Properties of Saliva

1. **Volume:** 1000 to 1500 mL of saliva is secreted per day and, it is approximately about 1 mL/minute. Contribution by each major salivary gland is:
 - i. Parotid glands: 25%
 - ii. Submaxillary glands: 70%
 - iii. Sublingual glands: 5%.
2. **Reaction:** Mixed saliva from all the glands is slightly acidic with pH of 6.35 to 6.85.
3. **Specific gravity:** It ranges between 1.002 and 1.012.
4. **Tonicity:** Saliva is hypotonic to plasma.

Composition of Saliva

Mixed saliva contains 99.5% water and 0.5% solids. Composition of saliva is given in Figure 27-3.

■ FUNCTIONS OF SALIVA

Saliva is a very essential digestive juice. Since it has many functions, its absence leads to many inconveniences.

■ 1. PREPARATION OF FOOD FOR SWALLOWING

When food is taken into the mouth, it is moistened and dissolved by saliva. The mucous membrane of mouth is also moistened by saliva. It facilitates chewing. By the movement of the tongue, the moistened and masticated food is rolled into a bolus. The mucin of saliva lubricates the bolus and facilitates the swallowing.

■ 2. APPRECIATION OF TASTE

Taste is a chemical sensation. Saliva by its solvent action dissolves the solid food substances, so that the dissolved substances can stimulate the taste buds. The stimulated taste buds recognize the taste.

■ 3. DIGESTIVE FUNCTION

Saliva has three digestive enzymes namely, salivary amylase, maltase and lingual lipase (Table 27-2).

Salivary Amylase

Salivary amylase is a carbohydrate digesting (amylolytic) enzyme. It acts on cooked or boiled starch and converts it into dextrin and maltose. Though starch digestion starts in the mouth, major part of it occurs in the stomach because, food stays only for a short time in the mouth.

The optimum pH necessary for the activation of salivary amylase is 6. The salivary amylase cannot act on cellulose. The enzyme maltase is present only in traces in human saliva. It converts maltose into glucose.

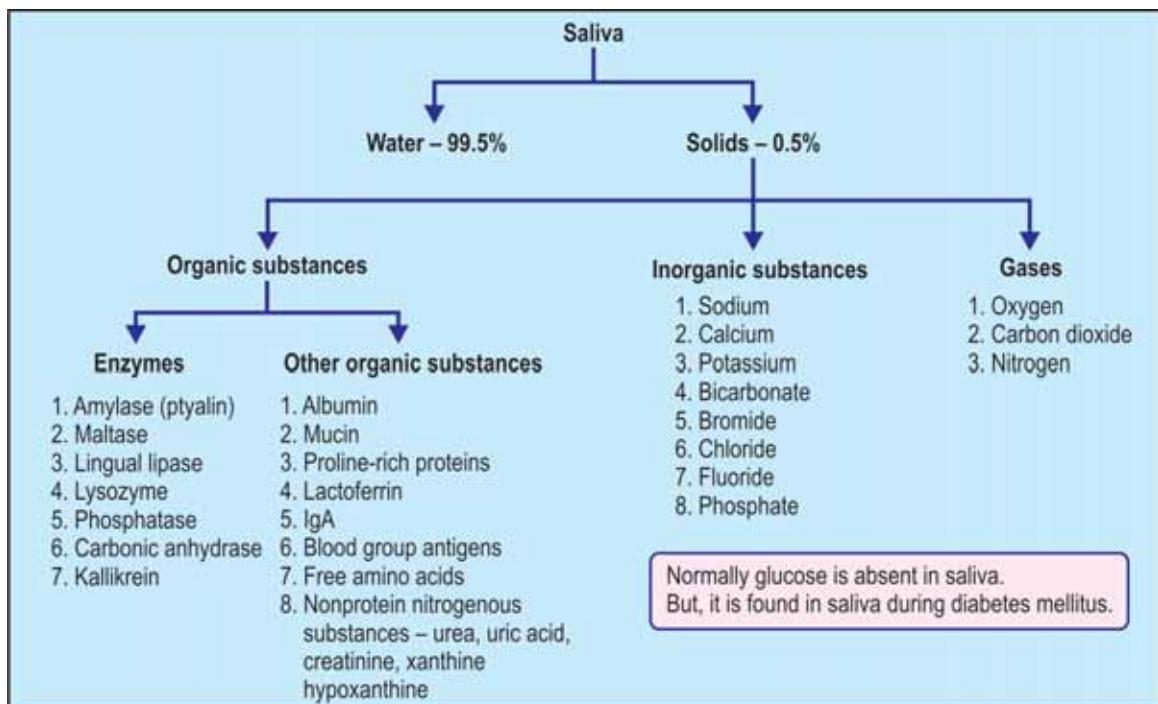


FIGURE 27-3: Composition of saliva

TABLE 27-2: Digestive enzymes of saliva

Enzyme	Source of secretion	Activator	Action
1. Salivary amylase	All salivary glands	Acid medium	Converts cooked starch into maltose
2. Maltase	Major salivary glands	Acid medium	Converts maltose into glucose
3. Lingual lipase	Lingual glands	Acid medium	Converts triglycerides of milk fat into fatty acids and diacylglycerol

Lingual Lipase

Lingual lipase is lipid digesting (lipolytic) enzymes. It digests milk fats (pre-emulsified fats). It hydrolyzes triglycerides into fatty acids and diacylglycerol (Table 27-2).

■ 4. CLEANSING AND PROTECTIVE FUNCTIONS

- Due to the constant secretion of saliva, the mouth and teeth are rinsed and kept free off food debris, shed epithelial cells and foreign particles. In this way, saliva prevents bacterial growth by removing

materials, which may serve as culture media for the bacterial growth

- The enzyme lysozyme of saliva kills some bacteria such as *staphylococcus*, *streptococcus*, and *brucella*
- The proline-rich proteins and lactoferrin present in saliva possess antimicrobial property. These proteins also protect the teeth by stimulating enamel formation
- Saliva also contains secretory immunoglobulin IgA which has antibacterial and antiviral actions
- Mucin present in the saliva protects the mouth by lubricating the mucous membrane of the mouth.

■ 5. ROLE IN SPEECH

By moistening and lubricating soft parts of mouth and lips, saliva helps in speech. If the mouth becomes dry, articulation and pronunciation become difficult.

■ 6. EXCRETORY FUNCTION

Many substances, both organic and inorganic, are excreted in saliva. It excretes substances like mercury, potassium iodide, lead, and thiocyanate. Saliva also excretes some viruses such as those causing rabies and mumps.

In some pathological conditions, saliva excretes certain substances, which are not found in saliva under normal conditions such as glucose in diabetes mellitus. In certain conditions, some of the normal constituents of saliva are excreted in large quantities. For example, excess urea is excreted in saliva during nephritis, and excess calcium is excreted during hyperparathyroidism.

■ 7. REGULATION OF BODY TEMPERATURE

In dogs and cattle, excessive dripping of saliva during panting helps in loss of heat and regulation of body temperature. However, in human being sweat glands play major role in temperature regulation and saliva does not play any role in this function.

■ 8. REGULATION OF WATER BALANCE

When the body water content decreases, salivary secretion also decreases. This causes dryness of the mouth and induces thirst. When the water is taken, it quenches the thirst and restores the body water content.

■ REGULATION OF SALIVARY SECRETION

Salivary secretion is regulated only by nervous mechanism. Autonomic nervous system is involved in the regulatory function.

■ NERVE SUPPLY TO SALIVARY GLANDS

Salivary glands are supplied by parasympathetic and sympathetic divisions of autonomic nervous system.

■ PARASYMPATHETIC FIBERS

Parasympathetic Fibers to Submandibular and Sublingual Glands

The parasympathetic preganglionic fibers to submandibular and sublingual glands arise from the superior salivatory nucleus situated in pons. After taking origin from this nucleus, the preganglionic fibers run through nervus intermedius of Wrisberg, geniculate ganglion, the motor fibers of facial nerve, chorda tympani branch of facial nerve and lingual branch of trigeminal nerve and finally reach the submaxillary ganglion (Fig. 27-4).

The postganglionic fibers arise from this ganglion and supply the submaxillary and sublingual glands.

Parasympathetic Fibers to Parotid Gland

The parasympathetic preganglionic fibers to parotid gland arise from inferior salivatory nucleus situated in the upper part of medulla oblongata. From here, the fibers pass through the tympanic branch of glossopharyngeal nerve, tympanic plexus and lesser petrosal nerve and end in otic ganglion (Fig. 27-5).

The postganglionic fibers arise from otic ganglion and reach the parotid gland by passing through the auriculotemporal branch in mandibular division of trigeminal nerve.

Function of Parasympathetic Fibers

When the parasympathetic fibers of salivary glands are stimulated, a large quantity of watery saliva is secreted with less amount of organic constituents. It is because the parasympathetic fibers activate the acinar cells and dilate the blood vessels of salivary glands. The neurotransmitter is acetylcholine.

■ SYMPATHETIC FIBERS

The sympathetic preganglionic fibers to salivary glands arise from the lateral horns of first and second thoracic segments of spinal cord. The fibers leave the cord through the anterior nerve roots and end in superior cervical ganglion of the sympathetic chain.

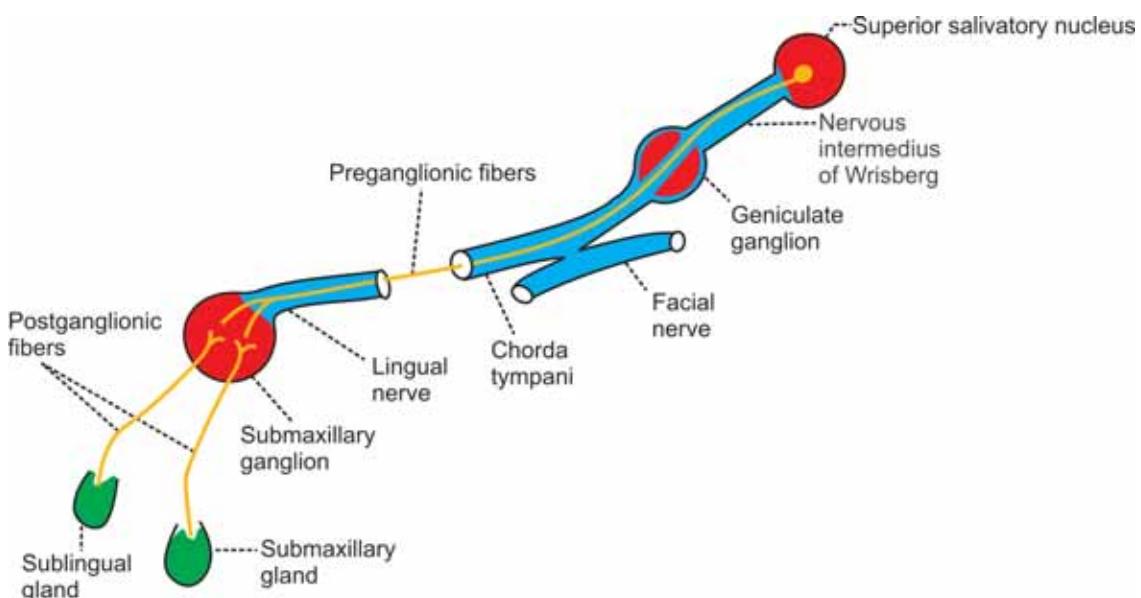


FIGURE 27-4: Parasympathetic nerve supply to submaxillary and sublingual glands

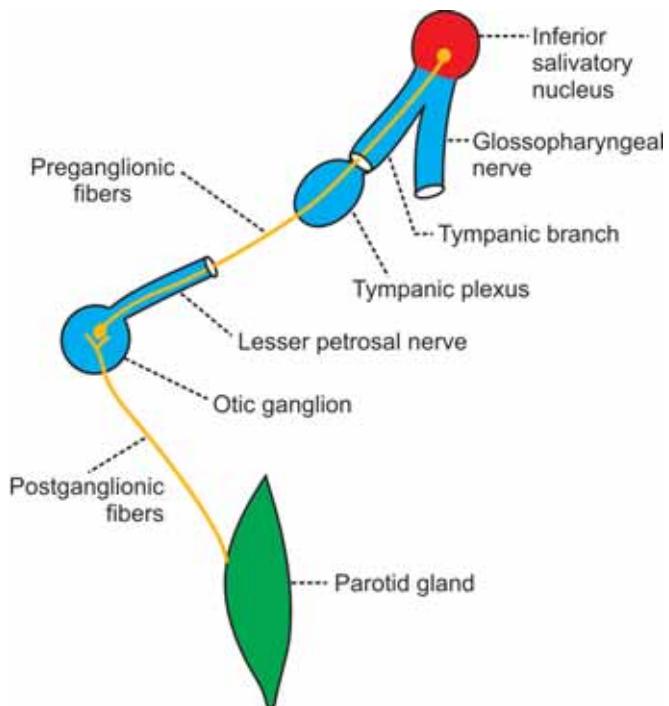


FIGURE 27-5: Parasympathetic nerve supply to parotid gland

The postganglionic fibers from this ganglion are distributed to the salivary glands along the nerve plexus around the arteries supplying the glands.

Function of Sympathetic Fibers

The stimulation of sympathetic fibers causes less secretion of saliva, which is thick and rich in

mucus. It is because these fibers activate the acinar cells and cause vasoconstriction by secreting noradrenaline.

■ REFLEX REGULATION OF SALIVARY SECRETION

Salivary secretion is regulated by nervous mechanism through reflex action. Salivary reflexes are of two types:

1. Unconditioned reflex
2. Conditioned reflex.

1. Unconditioned Reflex

Unconditioned reflex is the inborn reflex that is present since birth. It does not need any previous experience. This reflex induces salivary secretion when any substance is placed in the mouth. It is due to the stimulation of nerve endings in the mucous membrane of the oral cavity.

Examples:

- i. When food is taken
- ii. When any unpleasant or unpalatable substance enters the mouth
- iii. When the oral cavity is handled with instruments by dentists.

2. Conditioned Reflex

Conditioned reflex is the one that is acquired by experience and it needs previous experience (Chapter 101). Presence of food in the mouth is not necessary to elicit this reflex. The stimulus for this reflex is the sight, smell, hearing or thought of food. It is due to the impulses arising from eyes, nose, ear, etc.

■ EFFECT OF DRUGS AND CHEMICALS ON SALIVARY SECRETION

Substances which Increase the Salivary Secretion

1. Sympathomimetic drugs like adrenaline and ephedrine
2. Parasympathomimetic drugs like acetylcholine, pilocarpine, muscarine and physostigmine
3. Histamine.

Substances which Decrease the Salivary Secretion

1. Sympathetic depressants like ergotamine and dibenamine
2. Parasympathetic depressants like atropine, and scopolamine.

■ APPLIED PHYSIOLOGY

■ HYPOSALIVATION

The reduction in the secretion of saliva is called hyposalivation. It is of two types, namely, the temporary hyposalivation and the permanent hyposalivation.

1. Temporary hyposalivation occurs in:
 - i. Emotional conditions like fear
 - ii. Fever
 - iii. Dehydration.
2. Permanent hyposalivation occurs in:
 - i. Obstruction of salivary duct (sialolithiasis)
 - ii. Congenital absence or hypoplasia of salivary glands
 - iii. Paralysis of facial nerve (Bell's palsy).

■ HYPERSALIVATION

The excess secretion of saliva is known as hypersalivation. The physiological condition when hypersalivation occurs is pregnancy. Hypersalivation in pathological conditions is called ptyalism, sialorrhea, sialism or sialosis.

Hypersalivation occurs in the following conditions:

1. Decay of tooth or neoplasm (abnormal new growth or tumor) in mouth or tongue – due to continuous irritation of nerve endings in the mouth
2. Disease of esophagus, stomach and intestine
3. Neurological disorders such as mental retardation, cerebral stroke and parkinsonism
4. Some psychological and psychiatric conditions
5. Nausea and vomiting.

■ OTHER DISORDERS

In addition to hyposalivation and hypersalivation, salivary secretion is affected by other disorders also which include:

1. Xerostomia

Xerostomia means dry mouth. It is also called pasties or cottonmouth. It is due to hyposalivation or absence of salivary secretion (ptyalism). The causes of this disease are:

- i. Dehydration or renal failure
- ii. Sjögren's syndrome (see below)
- iii. Radiotherapy
- iv. Trauma to salivary gland or their ducts
- v. Side effect of drugs like antihistamines, antidepressants, and, antiparkinsonian drugs
- vi. Shock
- vii. After smoking marijuana (psychoactive compound from the plant cannabis).

Xerostomia causes difficulties in mastication, swallowing and speech. It also causes halitosis (bad breath).

2. Drooling

Uncontrolled flow of saliva outside the mouth is called drooling. It is often called ptyalism.

Drooling occurs because of excess production of saliva in association with inability to retain saliva within the mouth.

Drooling occurs in the following conditions:

- i. During teeth eruption in children
- ii. Upper respiratory tract infection or nasal allergies in children
- iii. Difficulty in swallowing
- iv. Tonsillitis
- v. Peritonsillar abscess.

3. Chorda Tympani Syndrome

Chorda tympani syndrome is the condition characterized by sweating while eating. During trauma or surgical procedure some of the parasympathetic nerve fibers to salivary glands may be severed. And, during the regeneration some of these nerve fibers, which run along with chorda tympani branch of facial nerve may deviate and join with the nerve fibers supplying sweat glands. When the food is placed in the mouth, salivary secretion is associated with sweat secretion.

4. Mumps

Mumps is the acute viral infection affecting the parotid glands. The virus causing this disease is paramyxovirus. It is common in children who are not immunized. It occurs in adults also. Features of mumps are puffiness of cheeks (due to swelling of parotid glands), fever, sore throat and weakness. Mumps affects meninges, gonads and pancreas also.

5. Sjögren's Syndrome

It is an autoimmune disorder in which the immune cells destroy exocrine glands such as lacrimal glands and salivary glands. Common symptoms of this syndrome are dryness of the mouth due to lack of saliva (xerostomia), persistent cough and dryness of eyes. In severe conditions the organs like kidneys, lungs, liver, pancreas, thyroid, blood vessels and brain are affected.

28

Stomach

- FUNCTIONAL ANATOMY OF STOMACH
- GLANDS OF STOMACH
- FUNCTIONS OF STOMACH
- PROPERTIES AND COMPOSITION OF GASTRIC JUICE
- FUNCTIONS OF GASTRIC JUICE
 - DIGESTIVE FUNCTION
 - HEMOPOIETIC FUNCTION
 - PROTECTIVE FUNCTION – FUNCTION OF MUCUS
 - FUNCTIONS OF HYDROCHLORIC ACID
- SECRETION OF GASTRIC JUICE
 - SECRETION OF PEPSINOGEN
 - SECRETION OF HYDROCHLORIC ACID
- REGULATION OF GASTRIC SECRETION
 - METHODS OF STUDY
 - PHASES OF GASTRIC SECRETION
- APPLIED PHYSIOLOGY
 - GASTRITIS
 - GASTRIC ATROPHY
 - PEPTIC ULCER

■ FUNCTIONAL ANATOMY OF STOMACH

Stomach is a hollow organ situated just below the diaphragm on the left side in the abdominal cavity. Volume of empty stomach is 50 ml. Under normal conditions, it can expand to accommodate 1 to 1.5 liters of solids and

liquids. However, it is capable of expanding still further up to 4 liters.

■ PARTS OF STOMACH

In humans, stomach has four parts:

1. Cardiac region
2. Fundus

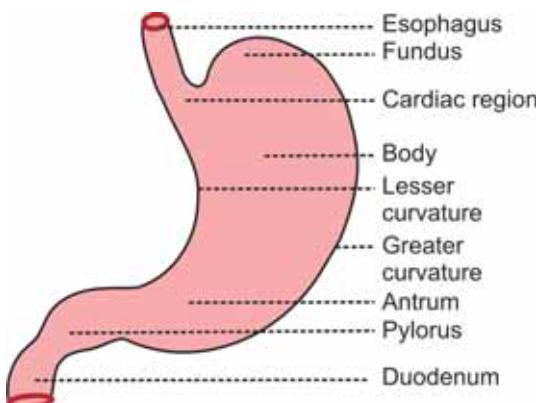


FIGURE 28-1: Parts of stomach

3. Body or corpus
4. Pyloric region.

1. Cardiac Region

It is the upper part of the stomach where esophagus opens. The opening is guarded by a sphincter called cardiac sphincter which opens only towards stomach. This portion is also known as cardiac end.

2. Fundus

It is a small dome shaped structure. It is elevated above the level of esophageal opening.

3. Body or Corpus

It is the largest part of stomach forming about 75 to 80% of the whole stomach. It extends from just below the fundus up to the pyloric region (Fig. 28-1).

4. Pyloric Region

The pyloric region has two parts, antrum and pyloric canal. The body of the stomach ends in antrum. The junction between body and antrum is marked by an angular notch called incisura angularis. Antrum is continued as the narrow canal which is called pyloric canal or pyloric end. Pyloric canal opens into first part of small intestine called duodenum. The opening of pyloric canal is guarded by a sphincter called pyloric sphincter. It opens towards duodenum.

Stomach has two curvatures. The one on the right side is lesser curvature and the one on the left side is greater curvature.

■ STRUCTURE OF STOMACH WALL

The wall of the stomach is formed by four layers of structures:

1. Outer serous layer formed by peritoneum
2. Muscular layer made up of three layers of smooth muscle fibers namely, inner oblique, middle circular and outer longitudinal layers
3. Submucous layer formed by areolar tissue, blood vessels and lymph vessels
4. Inner mucus layer lined by mucus secreting columnar epithelial cells. The gastric glands are situated in this layer. The inner surface of mucus layer is covered by 2 mm thick mucus.

■ GLANDS OF STOMACH

Glands of the stomach or gastric glands are tubular structures made up of different types of cells. These glands open into the stomach cavity through gastric pits.

■ CLASSIFICATION OF GLANDS OF THE STOMACH

Gastric glands are classified into three types depending upon their situation:

1. Fundic glands situated in body and fundus of stomach. Fundic glands are also called main gastric glands or oxytic glands
2. Pyloric glands present in the pyloric part of the stomach
3. Cardiac glands located in the cardiac region of the stomach.

All the gastric glands open into the cavity of stomach through gastric pits.

■ STRUCTURE OF GASTRIC GLANDS

Fundic Glands

The fundic glands are considered as the typical gastric glands (Fig. 28-2). These glands are long and tubular glands. Each gland has three parts viz. body, neck and isthmus.

The cells present in the fundic glands are:

1. Chief cells or pepsinogen cells
2. Parietal cells or oxytic cells
3. Mucus neck cells
4. Enterochromaffin (EC) cells
5. Enterochromaffin-like (ECL) cells.

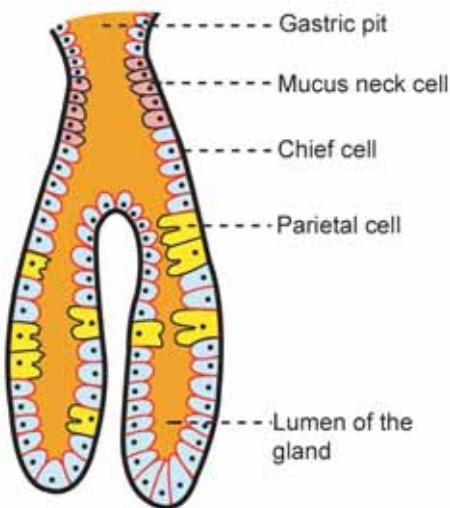


FIGURE 28-2: Gastric glands

Secretions of these cells are given in Table 28-1.

Parietal cells are different from other cells of the gland because of the presence of canaliculi (singular = canaliculus). The parietal cells empty their secretions into the lumen of the gland

TABLE 28-1: Secretory functions of cells in gastric glands

Cell	Secretory products
Chief cells	Pepsinogen Rennin Lipase Gelatinase Urase
Parietal cells	Hydrochloric acid Intrinsic factor of Castle
Mucus neck cells	Mucin
G cells	Gastrin
Enterochromaffin (EC) cells	Serotonin
Enterochromaffin-like (ECL) cells	Histamine

through the canaliculi, whereas other cells empty their secretions directly into lumen of the gland.

Pyloric Glands

The pyloric glands are short and tortuous in nature. The cells that form the pyloric glands are G cells, mucus cells, EC cells and ECL cells.

Cardiac Glands

Cardiac glands are also short and tortuous in structure with many mucus cells. EC cells, ECL cells and chief cells are also present in the cardiac glands.

Enteroendocrine Cells

Enteroendocrine cells are the hormone secreting cells present in the glands or mucosa of gastrointestinal tract particularly stomach and intestine. The enteroendocrine cells present in gastric glands are G cells, enterochromaffin cells and enterochromaffin like cells.

FUNCTIONS OF STOMACH

■ 1. MECHANICAL FUNCTION

i. Storage Function

The food is stored in the stomach for a long period, i.e. for 3 to 4 hours and emptied into the intestine slowly. The maximum capacity of stomach is up to 1.5 L. The slow emptying of stomach provides enough time for proper digestion and absorption of food substances in the small intestine.

ii. Formation of Chyme

The peristaltic movements of stomach mix the bolus with gastric juice and convert it into the semisolid material known as chyme.

■ 2. DIGESTIVE FUNCTION

Refer functions of gastric juice.

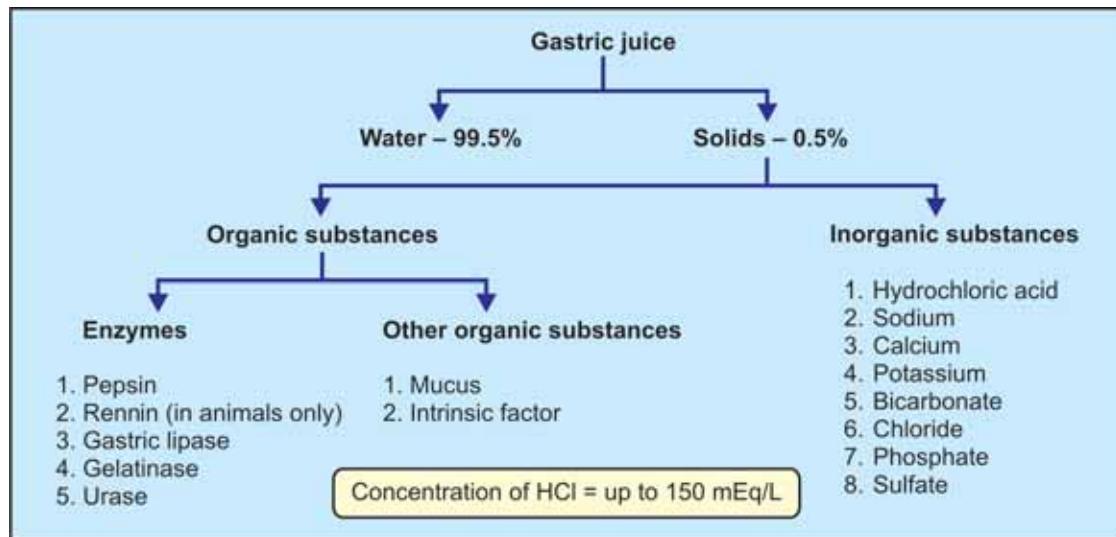


FIGURE 28-3: Composition of gastric juice

■ 3. PROTECTIVE FUNCTION

Refer functions of gastric juice.

■ 4. HEMOPOIETIC FUNCTION

Refer functions of gastric juice.

■ 5. EXCRETORY FUNCTION

Many substances like toxins, alkaloids and metals are excreted through gastric juice.

■ PROPERTIES AND COMPOSITION OF GASTRIC JUICE

Gastric juice is the mixture of secretions from different gastric glands.

Properties of Gastric Juice

- | | |
|------------------|---|
| Volume | : 1200 to 1500 mL/day |
| Reaction | : Gastric juice is highly acidic with pH of 0.9 to 1.2 due to hydrochloric acid |
| Specific gravity | : 1.002 to 1.004 |

Composition of Gastric Juice

Gastric juice contains 99.5% of water and 0.5% solids. The solids are organic and inorganic

substances. Refer Figure 28-3 for composition of gastric juice.

■ FUNCTIONS OF GASTRIC JUICE

■ 1. DIGESTIVE FUNCTION

The gastric juice acts mainly on proteins. The proteolytic enzymes of the gastric juice are pepsin and rennin (Table 28-2). Gastric juice also contains some other enzymes like gastric lipase, gelatinase, urease and gastric amylase.

Pepsin

Pepsin is secreted as inactive pepsinogen. Pepsinogen is converted into pepsin by hydrochloric acid which is secreted by parietal cells. The optimum pH for activation of pepsinogen is below 6.

Action of pepsin

Pepsin converts proteins into proteoses, peptones and polypeptides. Pepsin also causes curdling and digestion of milk (casein).

Gastric Lipase

Gastric lipase is a weak lipolytic enzyme. It needs acidic medium with pH between 4 and 5 for

TABLE 28-2: Digestive enzymes of gastric juice

Enzyme	Activator	Acts on	End products
1. Pepsin	Hydrochloric acid	Proteins	Proteoses, peptones and poly-peptides
2. Gastric lipase	Acid medium	Triglycerides of butter	Fatty acids and glycerols
3. Gastric amylase	Acid medium	Starch	Dextrin and maltose (negligible action)
4. Gelatinase	Acid medium	Gelatin and collagen of meat	Peptides
5. Urase	Acid medium	Urea	Ammonia

its action. But it becomes inactive when the pH falls below 2.5. Gastric lipase acts on tributyrin (butter fat) and hydrolyzes it into fatty acids and glycerols.

Actions of Other Enzymes of Gastric Juice

- i. Gelatinase degrades gelatin and collagen into peptides
- ii. Urase acts on urea and produces ammonia
- iii. Gastric amylase degrades starch (but its action is insignificant)
- iv. Rennin curdles milk (present in animals only).

■ 2. HEMOPOIETIC FUNCTION

The intrinsic factor of Castle secreted by parietal cells of gastric glands plays an important role in erythropoiesis. It is necessary for absorption of vitamin B₁₂ (which is called extrinsic factor) from GI tract into the blood. Vitamin B₁₂ is an important maturation factor during erythropoiesis. Absence of intrinsic factor in gastric juice causes deficiency of vitamin B₁₂ leading to pernicious anemia (Chapter 11).

■ 3. PROTECTIVE FUNCTION – FUNCTION OF MUCUS

The mucus present in the gastric juice protects gastric wall as mentioned below.

Mucus:

- i. Protects the stomach wall from irritation or mechanical injury by virtue of its high viscosity
- ii. Prevents the digestive action of pepsin on gastric mucosa
- iii. Protects the gastric mucosa from hydrochloric acid of gastric juice because of its alkaline nature and its acid combining power.

■ 4. FUNCTIONS OF HYDROCHLORIC ACID

Hydrochloric acid present in the gastric juice:

- i. Activates pepsinogen into pepsin
- ii. Kills some of the bacteria entering the stomach along with food substances – this action is called bacteriolytic action
- iii. Provides acid medium which is necessary for the actions of the hormones.

■ SECRETION OF GASTRIC JUICE

■ SECRETION OF PEPSINOGEN

Pepsinogen is synthesized from amino acids in the ribosomes attached to endoplasmic reticulum in chief cells. The pepsinogen molecules are packed into zymogen granules by Golgi apparatus.

When zymogen granule is secreted into stomach from chief cells, the granule is dissolved and pepsinogen is released into gastric juice.

Pepsinogen is activated into pepsin by hydrochloric acid.

■ SECRETION OF HYDROCHLORIC ACID

Hydrochloric acid secretion is an active process that takes place in the canaliculi of parietal cells in gastric glands. The energy for this is derived from oxidation of glucose.

In the parietal cells, the carbon dioxide is formed from metabolic activity. It is also derived from blood. Carbon dioxide combines with water to form carbonic acid in the presence of carbonic anhydrase. This enzyme is present in high concentration in parietal cells. Carbonic acid is the most unstable compound and, immediately it splits into hydrogen ion and bicarbonate ion. The hydrogen ion is actively pumped into the canalculus of parietal cell.

Simultaneously, the chloride ion is also pumped into canalculus actively. The chloride is derived from sodium chloride in the blood. Now, the hydrogen ion combines with chloride ion to form hydrochloric acid. To compensate the loss of chloride ion, the bicarbonate ion from parietal cell enters the blood and combines with sodium to form sodium bicarbonate. Thus, the entire process is summarized as (Fig. 28-4):

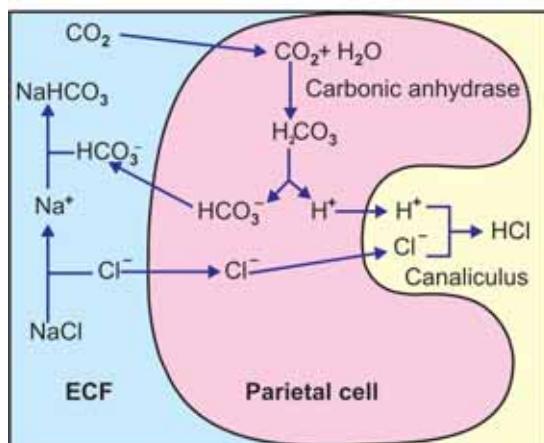
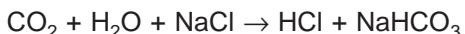


FIGURE 28-4: Secretion of hydrochloric acid in parietal cell of gastric gland

■ REGULATION OF GASTRIC SECRETION

Regulation of gastric secretion and intestinal secretion is studied by some experimental procedures.

■ METHODS OF STUDY

1. Pavlov's Pouch

Pavlov's pouch is a small part of the stomach that is incompletely separated from the main portion and made into a small bag like pouch (Fig. 28-5). Pavlov's pouch was designed by the Russian scientist Pavlov in dog during his studies on conditioned reflexes.

Procedure

To prepare a Pavlov's pouch, stomach of an anesthetized dog is divided into a larger part and a smaller part by making an incomplete incision. The mucous membrane is completely divided. A small part of muscular coat called isthmus is retained. The isthmus connects the two parts.

The cut edges of major portions are stitched. The smaller part is also stitched, leaving a small outlet. This outlet is brought out through the abdominal wall and used to drain the pouch.

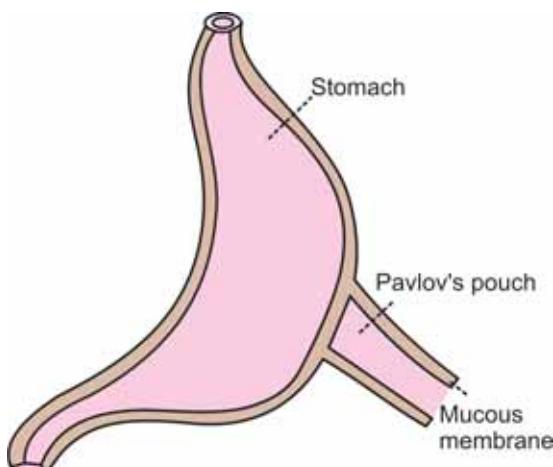


FIGURE 28-5: Pavlov's pouch

Nerve supply of Pavlov's pouch

Pavlov's pouch receives parasympathetic (vagus) nerve fibers through isthmus and sympathetic fibers through blood vessels.

Use of Pavlov's pouch

Pavlov's pouch is used to demonstrate the different phases of gastric secretion particularly the cephalic phase and used to demonstrate the role of vagus in cephalic phase.

2. Farrel and Ivy Pouch

This pouch is prepared by removing the part of Pavlov's pouch from the stomach and transplanting it in the subcutaneous tissue of abdominal wall or thoracic wall in the same animal. It is used for experimental purpose, when the new blood vessels are developed.

Uses of Farrel and Ivy pouch

This pouch is useful to study the role of hormones during gastric and intestinal phases of gastric secretion.

3. Sham Feeding

Sham feeding means the false feeding. It is another experimental procedure devised by Pavlov to demonstrate the regulation of gastric secretion.

Procedure

- i. A hole is made in the neck of an anesthetized dog
- ii. Esophagus is transversely cut. The cut ends are drawn out through the hole in the neck
- iii. When the dog eats food, it comes out through the cut end of the esophagus
- iv. But the dog has the satisfaction of eating the food. It is called sham feeding.

This experimental procedure is supported by the preparation of Pavlov's pouch with a fistula from the stomach. The fistula opens to the exterior and it is used to observe the gastric secretion. The animal is used for experimental

purpose after a week's time when healing is completed.

Advantage of sham feeding

It is useful to demonstrate the secretion of gastric juice during cephalic phase. In the same animal after vagotomy, sham feeding does not induce gastric secretion. It proves the role of vagus nerve during cephalic phase.

■ PHASES OF GASTRIC SECRETION

Gastric juice is secreted in three different phases:

- I. Cephalic phase
- II. Gastric phase
- III. Intestinal phase.

In human beings, a fourth phase called interdigestive phase exists. All the phases are regulated by neural mechanism or hormonal mechanism or both.

■ CEPHALIC PHASE

Secretion of gastric juice by the stimuli arising from head region (cephalus) is called cephalic phase (Fig. 28-6). This phase is regulated by nervous mechanism.

During this phase, the gastric secretion occurs even without the presence of food in the stomach. The quantity of the juice is less but it is rich in enzymes and hydrochloric acid.

The nervous mechanism that regulates cephalic phase operates through reflex action. Two types of reflexes occur:

1. Unconditioned reflex
2. Conditioned reflex.

Unconditioned Reflex

Unconditioned reflex is the inborn reflex. When food is placed in the mouth, it induces salivary secretion (Chapter 27). Simultaneously, gastric secretion also occurs.

Stages of the reflex action

- i. The presence of food in the mouth stimulates the taste buds and other receptors in the mouth

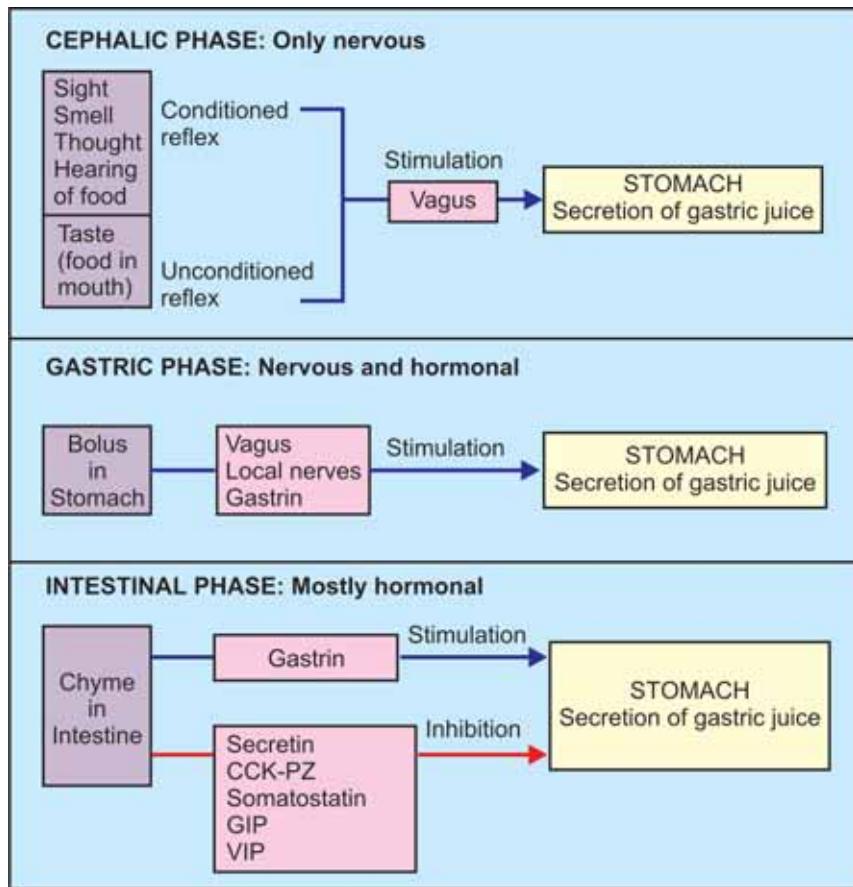


FIGURE 28-6: Schematic diagram showing the regulation of gastric secretion

- The sensory (afferent) impulses from mouth pass via afferent nerve fibers of glossopharyngeal and facial nerves to appetite center present in amygdala and hypothalamus
- From here, efferent impulses pass through dorsal nucleus of vagus and vagal efferent nerve fibers to the wall of the stomach
- Acetylcholine is secreted at the vagal efferent nerve endings stimulates gastric glands to increase the secretion.

This is experimentally proved by Pavlov's pouch and sham feeding.

Conditioned Reflex

Conditioned reflex is the reflex response acquired by previous experience (Chapter 101). Presence

of food in the mouth is not necessary to elicit this reflex. The sight, smell, hearing or thought of food which induce salivary secretion also induce gastric secretion.

Stages of reflex action

- Impulses from the special sensory organs (eye, ear and nose) pass through afferent fibers of neural circuits to the cerebral cortex. Thinking of food stimulates the cerebral cortex directly
- From cerebral cortex the impulses pass through dorsal nucleus of vagus and vagal efferents and reach stomach wall
- The vagal nerve endings secrete acetylcholine. It stimulates the gastric glands to increase its secretion.

Conditioned reflex of gastric secretion is proved by Pavlov's pouch and bell dog experiment (Chapter 101).

■ GASTRIC PHASE

The secretion of gastric juice when the food enters the stomach is called gastric phase. This phase is regulated by both nervous and hormonal mechanisms. The gastric juice secreted during this phase is rich in pepsinogen and hydrochloric acid. The mechanisms involved in this phase are:

1. Nervous mechanism through local myenteric reflex and vagovagal reflex
2. Hormonal mechanism through gastrin.

1. Nervous Mechanism

Local myenteric reflex

Local myenteric reflex is elicited by stimulation of myenteric nerve plexus in stomach wall. After entering stomach, the food particles stimulate the local nerve plexus (Chapter 26) present in the wall of the stomach. These nerve fibers release acetylcholine, which stimulates the gastric glands to secrete a large quantity of gastric juice. Simultaneously, acetylcholine stimulates G cells to secrete gastrin (see below).

Vagovagal reflex

Vagovagal reflex is the reflex in which both afferent and efferent vagal fibers are involved. Presence of food in stomach stimulates the sensory (afferent) nerve endings of vagus which generate sensory impulses. The sensory impulses are transmitted to the brainstem via sensory fibers of vagus. Brainstem in turn sends efferent impulses through the motor (efferent) fibers of vagus back to stomach and cause secretion of gastric juice. Since, both afferent and efferent impulses pass through vagus, this reflex is called vagovagal reflex.

2. Hormonal Mechanism – Gastrin

Gastrin is a gastrointestinal hormone secreted by the G cells which are present in pyloric glands of stomach. Small amount of gastrin is also

secreted in mucosa of upper small intestine. Gastrin is a polypeptide containing G14, G17 or G34 amino acids.

Gastrin is released when food enters stomach. The mechanism involved in the release of gastrin may be the local nervous reflex or vagovagal reflex. The nerve endings release the neurotransmitter called gastrin releasing peptide which stimulates the G cells to secrete gastrin.

Actions of gastrin on gastric secretion

Gastrin stimulates the secretion of pepsinogen and hydrochloric acid by the gastric glands.

Experimental evidences of gastric phase

The nervous mechanism of gastric secretion during gastric phase is proved by Pavlov's pouch. Hormonal mechanism of gastric secretion is proved by Farrel and Ivy pouch (see above).

■ INTESTINAL PHASE

Intestinal phase is the secretion of gastric juice when chyme enters the intestine. When chyme enters the intestine initially the gastric secretion increases and later it stops. Intestinal phase of gastric secretion is under both nervous and hormonal control.

Initial stage of intestinal phase

The chyme entering intestine stimulates the duodenal mucosa to release gastrin which is transported to stomach through blood. There, it increases gastric secretion.

Later stage of intestinal phase

After the initial increase, there is decrease or complete stoppage of secretion of gastric juice. Two factors are responsible for the inhibition:

1. Enterogastric reflex
2. GI hormones.

1. Enterogastric reflex

It is a reflex that inhibits the secretion and movements of stomach due to the distention or

irritation of intestinal mucosa. It is mediated by myenteric nerve (Auerbach's) plexus and vagus.

2. GI hormones

The presence of chyme in the intestine stimulates the secretion of many GI hormones from intestinal mucosa and other structures. All these hormones inhibit the gastric secretion. Some of these hormones inhibit the gastric motility also.

GI hormones which inhibit gastric secretion:

- i. *Secretin*: Secreted by the presence of acid chyme in the intestine
- ii. *Cholecystokinin*: Secreted by the presence of chyme containing fats and amino acids in intestine
- iii. *Gastric inhibitory peptide (GIP)*: Secreted by the presence of chyme containing glucose and fats in the intestine
- iv. *Vasoactive intestinal polypeptide (VIP)*: Secreted by the presence of acidic chyme in intestine
- v. *Peptide YY*: Secreted by the presence of fatty chyme in intestine.

In addition to these hormones, pancreas also secretes a hormone called somatostatin during intestinal phase. It also inhibits gastric secretion.

The intestinal phase of gastric secretion is demonstrated by Farrel and Ivy pouch.

■ INTERDIGESTIVE PHASE

Secretion of small amount of gastric juice in between meals (or during period of fasting) is called interdigestive phase. Gastric secretion during this phase is mainly due to the hormones like gastrin. This phase of gastric secretion is demonstrated by Farrel and Ivy pouch.

■ APPLIED PHYSIOLOGY

■ 1. GASTRITIS

Inflammation of gastric mucosa is called gastritis. It may be acute or chronic.

Causes of Gastritis

- i. Infection with bacterium *Helicobacter pylori*
- ii. Excess consumption of alcohol
- iii. Excess or long term administration nonsteroidal anti-inflammatory drugs (NSAIDs)
- iv. Trauma by nasogastric tubes
- v. Autoimmune disease.

Features

Features of gastritis are:

- i. Abdominal upset or pain
- ii. Nausea
- iii. Vomiting
- iv. Anorexia (loss of appetite)
- iv. Indigestion
- v. Discomfort or feeling of fullness in the epigastric region
- vi. Belching (process to relieve swallowed air that is accumulated in stomach).

■ 2. GASTRIC ATROPHY

Gastric atrophy is the condition in which the muscles of the stomach shrink and become weak. The gastric glands also shrink resulting in the deficiency of gastric juice.

Cause

Gastric atrophy is caused by chronic gastritis and autoimmune disease.

Features

Gastric atrophy causes achlorhydria (absence of hydrochloric acid in gastric juice) and pernicious anemia. Some patients develop gastric cancer.

■ 3. PEPTIC ULCER

Ulcer means the erosion of the surface of any organ due to shedding or sloughing of inflamed necrotic tissue that lines the organ. Peptic ulcer means an ulcer in the wall of stomach or duodenum caused by digestive action of gastric juice. If peptic ulcer is found in stomach, it is called gastric ulcer and if found in duodenum it is called duodenal ulcer.

Causes

- i. Increased peptic activity due to excessive secretion of pepsin in gastric juice
- ii. Hyperacidity of gastric juice
- iii. Reduced alkalinity of duodenal content
- iv. Decreased mucus content in gastric juice or decreased protective activity in stomach or duodenum
- v. Constant physical or emotional stress
- vi. Food with excess spices or smoking (classical causes of ulcers)
- vii. Long term use of NSAIDs (see above) such as aspirin, ibuprofen, and naproxen
- viii. Chronic inflammation due to *Helicobacter pylori*.

Features

The most common feature of peptic ulcer is severe burning pain in epigastric region. In gastric ulcer, pain occurs while eating or drinking. In duodenal ulcer, pain is felt 1 or 2 hours after food intake and during night.

Other symptoms accompanying pain are:

- i. Nausea
- ii. Vomiting
- iii. Hematemesis (vomiting blood)
- iv. Heartburn (burning pain in chest due to regurgitation of acid from stomach into esophagus)
- v. Anorexia (loss of appetite)
- vi. Loss of weight.

- FUNCTIONAL ANATOMY AND NERVE SUPPLY OF PANCREAS
- PROPERTIES AND COMPOSITION OF PANCREATIC JUICE
- FUNCTIONS OF PANCREATIC JUICE
- NEUTRALIZING ACTION OF PANCREATIC JUICE
- REGULATION OF PANCREATIC SECRETION
- APPLIED PHYSIOLOGY

■ FUNCTIONAL ANATOMY AND NERVE SUPPLY OF PANCREAS

Pancreas is a dual organ having two functions, the endocrine function and the exocrine function. The endocrine function is concerned with production of the hormones (Chapter 48). The exocrine function is concerned with secretion of digestive juice called pancreatic juice.

■ FUNCTIONAL ANATOMY OF EXOCRINE PART OF PANCREAS

Exocrine part of pancreas is made up of acini or alveoli like salivary glands. Each acinus has a single layer of acinar cells with a lumen in the center. The acinar cells contain zymogen granules, which possess digestive enzymes.

A small duct arises from lumen of each alveolus. Some of these ducts from neighboring alveoli unite to form intralobular duct. All the intralobular ducts unite to form the main duct of pancreas called Wirsung's duct. Wirsung's duct joins common bile duct to form ampulla of Vater which opens into duodenum (see Fig. 30-3).

■ NERVE SUPPLY TO PANCREAS

Pancreas is supplied by both sympathetic and parasympathetic fibers. The sympathetic fibers are supplied through splanchnic nerve and parasympathetic fibers are supplied through vagus nerve.

■ PROPERTIES AND COMPOSITION OF PANCREATIC JUICE

Properties of Pancreatic Juice

Volume	: 500 to 800 mL/day
Reaction	: Highly alkaline with pH of 8 to 8.3
Specific gravity	: 1.010 to 1.018

Composition of Pancreatic Juice

Pancreatic juice contains 99.5% of water and 0.5% of solids. The solids are the organic and inorganic substances. Composition of pancreatic juice is given in Fig. 29-1.

The bicarbonate content is very high in pancreatic juice. It is about 110 to 150 mEq/L

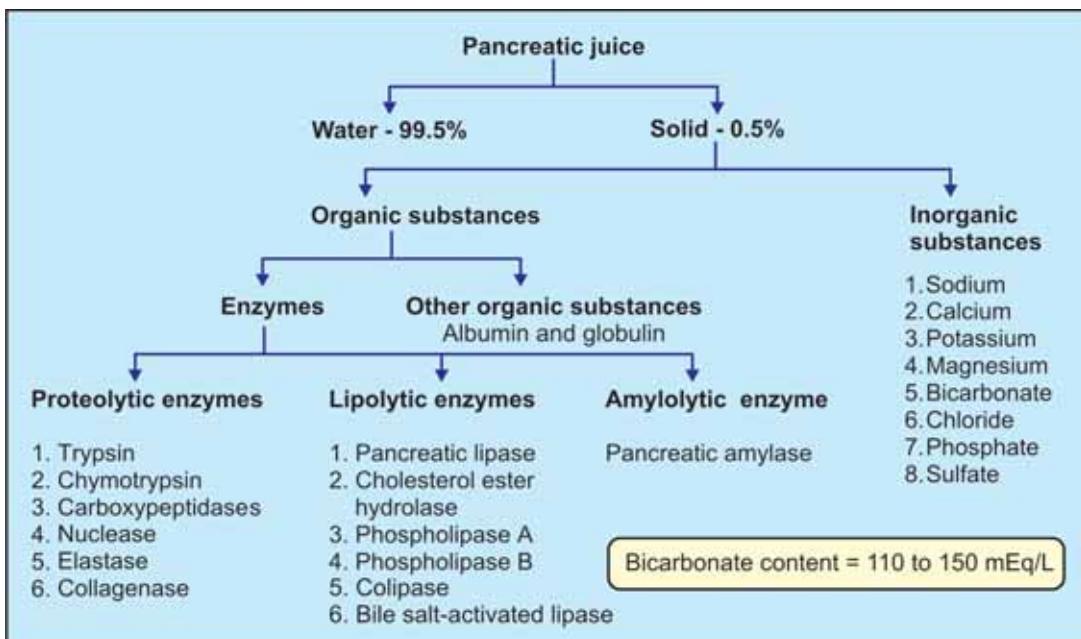


FIGURE 29-1: Composition of pancreatic juice

against the concentration of 24 mEq/L in plasma. This high concentration of bicarbonate is responsible for the alkalinity of pancreatic juice.

■ FUNCTIONS OF PANCREATIC JUICE

Pancreatic juice has digestive functions and the neutralizing action.

■ DIGESTIVE FUNCTIONS OF PANCREATIC JUICE

Pancreatic juice plays an important role in the digestion of proteins and lipids. It also has mild action on carbohydrate digestion.

■ DIGESTION OF PROTEINS

The major proteolytic enzymes of pancreatic juice are trypsin and chymotrypsin. Other proteolytic enzymes are carboxypeptidases, nuclease, elastase and collagenase.

1. Trypsin

Trypsin is a single polypeptide with a molecular weight of 25,000. It contains 229 amino acids.

It is secreted as inactive trypsinogen which is converted into active trypsin by enterokinase. Enterokinase is also called enteropeptidase and it is secreted by the brush bordered cells of duodenal mucous membrane. Once formed, trypsin itself activates trypsinogen by means of autocatalytic or autoactive action.

Actions of trypsin

- Digestion of proteins: Trypsin is the most powerful proteolytic enzyme. It is an endopeptidase and breaks the interior bonds of the protein molecules. And it converts proteins into proteoses and polypeptides
- Curdling of milk – it converts caseinogens in the milk into casein
- It accelerates blood clotting
- It activates other enzymes of pancreatic juice:
 - Chymotrypsinogen into chymotrypsin
 - Procarboxypeptidases into carboxypeptidases
 - Proelastase into elastase
 - Procolipase into colipase
- Trypsin also activates collagenase, phospholipase A and phospholipase B.

- vi. Autocatalytic action — once formed, trypsin itself converts trypsinogen into trypsin.

2. Chymotrypsin

Chymotrypsin is a polypeptide with a molecular weight of 25,700 and 246 amino acids. It is secreted as inactive chymotrypsinogen and activated into chymotrypsin by trypsin.

Actions of chymotrypsin

- Digestion of proteins:* Chymotrypsin is also an endopeptidase and it breaks the proteins into polypeptides
- Digestion of milk:* Chymotrypsin digests casein faster than trypsin. The combination of both enzymes causes more rapid digestion of milk.
- On blood clotting – no action.

3. Carboxypeptidases

The two carboxypeptidases are carboxypeptidase A and carboxypeptidase B. These are secreted as procarboxypeptidase A and procarboxypeptidase B. The inactive procarboxypeptidases are activated into carboxypeptidases by trypsin.

Actions of carboxypeptidases

Carboxypeptidases are exopeptidases and split the polypeptides and other proteins into amino acids.

4. Nucleases

The nucleases of pancreatic juice are ribonuclease and deoxyribonuclease, which are responsible for the digestion of nucleic acids. These enzymes convert the ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) into mononucleotides.

5. Elastase

Elastase is secreted as inactive proelastase and is activated into active elastase by trypsin. It digests the elastic fibers.

6. Collagenase

Collagenase is secreted as inactive procollagenase and is activated into active collagenase by trypsin. It digests collagen.

■ DIGESTION OF LIPIDS

The lipolytic enzymes present in pancreatic juice are pancreatic lipase, cholesterol ester hydrolase, phospholipase A, phospholipase B and a coenzyme called colipase.

1. Pancreatic Lipase

Pancreatic lipase is a powerful lipolytic enzyme. It digests the triglycerides into monoglycerides and fatty acids. The activity of pancreatic lipase is accelerated in the presence of bile. The optimum pH required for activity of this enzyme is 7 to 9.

Digestion of fat by pancreatic lipase requires two more factors:

- Bile salts which are responsible for the emulsification of fat prior to their digestion
- Colipase which is a coenzyme necessary for the pancreatic lipase to hydrolyze the dietary lipids. Colipase is secreted as an inactive procolipase which activated into colipase by trypsin.

About 80% of fat is digested by pancreatic lipase. The deficiency or absence of this enzyme leads to excretion of undigested fat in feces (see below).

2. Cholesterol Ester Hydrolase

Cholesterol ester hydrolase or cholesterol esterase converts cholesterol ester into free cholesterol and fatty acid by hydrolysis.

3. Phospholipase A

It is activated by trypsin. Phospholipase A digests phospholipids namely lecithin and cephalin and converts them into lysolecithin and lysocephalin.

4. Phospholipase B

Phospholipase B is also activated by trypsin. This enzyme converts lysolecithin and lysocephalin into phosphoryl choline and free fatty acids.

5. Colipase

Colipase is a small coenzyme which facilitates the hydrolysis of fats by pancreatic lipase.

6. Bile Salt-activated Lipase

This enzyme has a weak lipolytic action. It digests a variety of lipids like phospholipids, cholesterol esters and triglycerides. Since it is activated bile salt, it is known as bile salt-activated lipase (Table 29-1).

■ DIGESTION OF CARBOHYDRATES

Pancreatic amylase is the amylolytic enzyme present in pancreatic juice. Like salivary amylase,

the pancreatic amylase also converts starch into dextrin and maltose.

■ NEUTRALIZING ACTION OF PANCREATIC JUICE

When acid chyme enters intestine from stomach, pancreatic juice with large quantity of bicarbonate is released into intestine. Presence of large quantity of bicarbonate ions makes the pancreatic juice highly alkaline. This alkaline pancreatic juice neutralizes acidity of chyme in the intestine.

Neutralizing action is an important function of pancreatic juice, because, it protects the intestine from the destructive action of acid in the chyme.

TABLE 29-1: Digestive enzymes of pancreatic juice

Enzyme	Activator	Acts on	End products
1. Trypsin	Enterokinase Trypsin	Proteins	Proteoses and Polypeptides
2. Chymotrypsin	Trypsin	Proteins	Polypeptides
3. Carboxypeptidases	Trypsin	Polypeptides	Amino acids
4. Nucleases	Trypsin	RNA and DNA	Mononucleotides
5. Elastase	Trypsin	Elastin	Amino acids
6. Collagenase	Trypsin	Collagen	Amino acids
7. Pancreatic lipase	Alkaline medium	Triglycerides	Monoglycerides and fatty acids
8. Cholesterol ester hydrolase	Alkaline medium	Cholesterol ester	Cholesterol and fatty acids
9. Phospholipase A	Trypsin	Phospholipids	Lysophospholipids
10. Phospholipase B	Trypsin	Lysophospholipids	Phosphoryl choline and free fatty acids
11. Colipase	Trypsin	Facilitates action of trypsin	- - -
12. Bile salt – activated lipase	Trypsin	Phospholipids	Lysophospholipids
		Cholesterol esters	Cholesterol and fatty acids
		Triglycerides	Monoglycerides and fatty acids
13. Pancreatic amylase	- - -	Starch	Dextrin and maltose

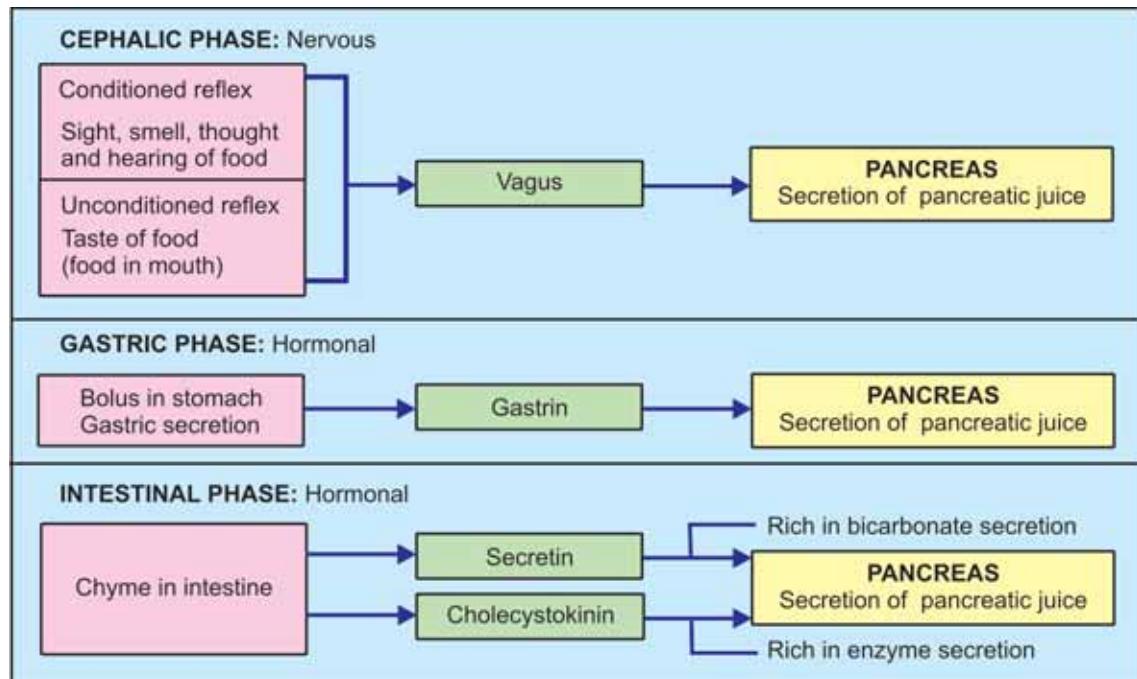


FIGURE 29-2: Schematic diagram showing the regulation of pancreatic secretion

■ REGULATION OF PANCREATIC SECRETION

The pancreatic secretion occurs in three stages:

1. Cephalic phase
2. Gastric phase
3. Intestinal phase.

Each phase is regulated by nervous mechanism or hormonal mechanism or both.

■ 1. CEPHALIC PHASE

As in case of gastric secretion, the cephalic phase of pancreatic secretion is regulated by nervous mechanism through reflex action. Two types of reflexes occur:

1. Unconditioned reflex
2. Conditioned reflex.

Unconditioned Reflex

Unconditioned reflex is the inborn reflex. When food is placed in the mouth, it induces salivary secretion (Chapter 27), gastric secretion (Chapter 28). Simultaneously it induces pancreatic secretion also.

Conditioned Reflex

Conditioned reflex is the reflex response acquired by previous experience (Chapter 101). Presence of food in the mouth is not necessary to elicit this reflex. The sight, smell, hearing or thought of food which induce salivary secretion and gastric secretion also induces pancreatic secretion (Fig. 29-2).

The impulses from mouth (during unconditioned reflex) or from the cerebral cortex (during conditioned reflex) reach the dorsal nucleus of vagus. From the dorsal nucleus of vagus, the efferent impulses reach the pancreas via efferent fibers of vagus nerve. The vagal nerve endings release acetylcholine which stimulates the acinar cells to release the enzymes.

■ 2. GASTRIC PHASE

Secretion of pancreatic juice when food enters the stomach is known as gastric phase. This phase of pancreatic secretion is under hormonal control. The hormone involved is gastrin.

When food enters stomach, gastrin is secreted from stomach (Chapter 28). When gastrin is transported to pancreas through blood, it stimulates the pancreatic secretion. The pancreatic juice secreted during gastric phase is rich in enzymes.

■ 3. INTESTINAL PHASE

Intestinal phase is the secretion of pancreatic juice when the chyme enters the intestine. This phase is also under hormonal control.

When chyme enters the intestine, many hormones are released. Some hormones stimulate the pancreatic secretion and some hormones inhibit the pancreatic secretion.

Hormones Stimulating Pancreatic Secretion

- i. Secretin
- ii. Cholecystokinin.

Secretin

Secretin is produced by S cells of mucous membrane in duodenum and jejunum. It is produced in an inactive prosecretin which is activated into secretin by acid chyme.

The stimulant for the release and activation of prosecretin is the acid chyme entering intestine. The products of protein digestion also stimulate the hormonal secretion.

Action of secretin

Secretin stimulates the secretion of watery pancreatic juice which contains high concentration of bicarbonate ion.

Cholecystokinin

Cholecystokinin (CCK) is also called cholecystokinin-pancreozymin (CCK-PZ). It is secreted by I cells in duodenal and jejunal mucosa. The stimulant for the release of this hormone is the chyme containing digestive products such as fatty acids, peptides and amino acids.

Action of cholecystokinin

Cholecystokinin stimulates the secretion of pancreatic juice rich in enzyme and less in volume.

Hormones Inhibiting Pancreatic Secretion

- i. Pancreatic polypeptide – secreted by PP cells in islets of Langerhans of pancreas
- ii. Somatostatin – secreted by D cells in islets of Langerhans of pancreas
- iii. Peptide YY – secreted by intestinal mucosa
- iv. Peptides like ghrelin and leptin.

■ APPLIED PHYSIOLOGY

■ PANCREATITIS

Pancreatitis is the inflammation of pancreatic acini.

Causes of Pancreatitis

- i. Long-time consumption of low alcohol
- ii. Congenital abnormalities of pancreatic duct
- iii. Malnutrition (poor nutrition; mal = bad)
- iv. Heavy alcohol intake
- v. Gallstones.

Features of Pancreatitis

- i. Absence of pancreatic enzymes
- ii. Steatorrhea
- iii. Severe abdominal pain
- iv. Nausea and vomiting
- v. Loss of appetite and weight
- vi. Fever
- vii. Shock

■ STEATORRHEA

Steatorrhea is the formation of bulky, foul smelling, frothy and clay colored stools with large quantity of undigested fat because of impaired digestion and absorption of fat.

Causes of Steatorrhea

1. Lack of pancreatic lipase
2. Liver disease affecting secretion of bile
3. Atrophy of intestinal villi.

30

Liver and Gallbladder

- FUNCTIONAL ANATOMY OF LIVER AND BILIARY SYSTEM
- BLOOD SUPPLY TO LIVER
- PROPERTIES AND COMPOSITION OF BILE
- FORMATION OF BILE
- STORAGE OF BILE
- BILE SALTS
- BILE PIGMENTS
- FUNCTIONS OF BILE
- FUNCTIONS OF LIVER
- GALLBLADDER
- REGULATION OF BILE SECRETION
- APPLIED PHYSIOLOGY

■ FUNCTIONAL ANATOMY OF LIVER AND BILIARY SYSTEM

Liver is a dual organ having both secretory and excretory functions. It is the largest gland in the body weighing about 1.5 kg in man. It is located in the upper and right side of the abdominal cavity immediately beneath diaphragm.

■ LIVER

Liver is made up of many lobes called hepatic lobes (Fig. 30-1). Each lobe consists of many lobules called hepatic lobules.

The hepatic lobule is the structural and functional unit of liver. It is a honeycomb like structure and it is made up of liver cells called hepatocytes. Hepatocytes are arranged in hepatic plates. Each plate is made up of two columns

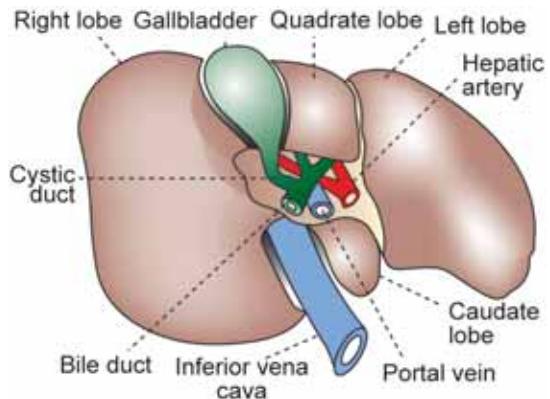


FIGURE 30-1: Posterior surface of liver

of cells. In between the two columns of each plate lies a bile canaliculus (Fig. 30-2).

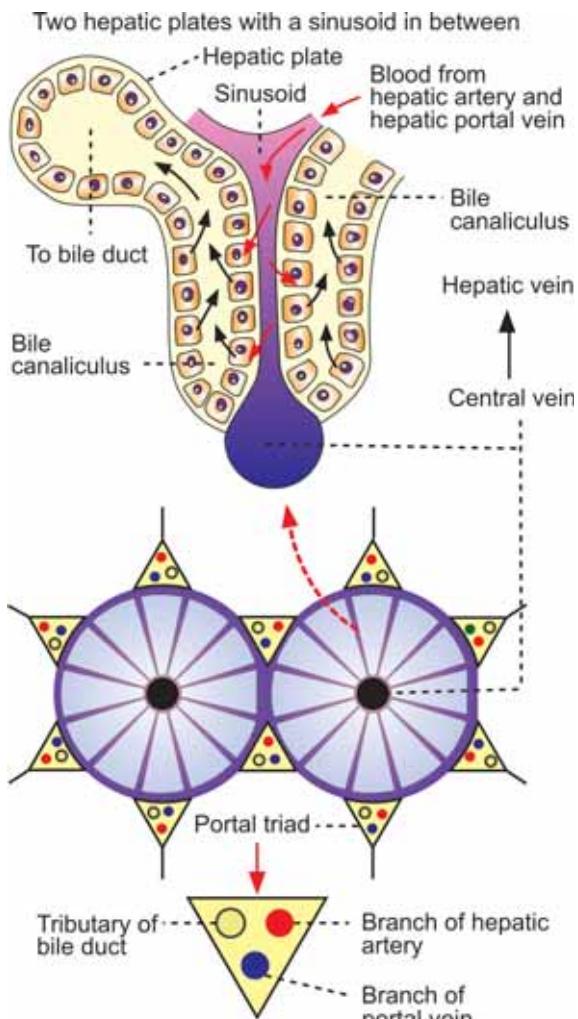


FIGURE 30-2: Hepatic lobule

In between the neighboring plates a blood space called sinusoid is present. Sinusoid is lined by the endothelial cells. In between the endothelial cells some special macrophages called Kupffer's cells are present.

Portal Triads

Each lobule is surrounded by many portal triads. Each portal triad consists of three vessels:

1. A branch of hepatic artery
2. A branch of portal vein
3. A tributary of bile duct.

The branches of hepatic artery and portal vein open into the sinusoid. Sinusoid opens into the

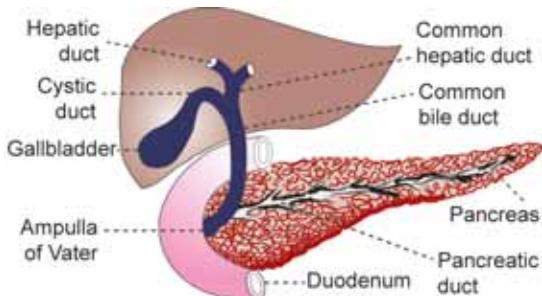


FIGURE 30-3: Biliary system

central vein. Central vein empties into hepatic vein.

Bile is secreted by hepatic cells and emptied into bile canaliculus. From canaliculus, the bile enters the tributary of bile duct. The tributaries of bile duct from canaliculi of neighboring lobules unite to form small bile ducts. These small bile ducts join together and finally form left and right hepatic ducts which emerge out of liver.

■ BILIARY SYSTEM

Biliary system is also known as extrahepatic biliary apparatus. It is formed by gallbladder and the extrahepatic bile ducts (bile ducts outside the liver). The right and left hepatic bile ducts which come out of liver join to form common hepatic duct. It unites with the cystic duct from gallbladder to form common bile duct (Fig. 30-3).

The common bile duct unites with pancreatic duct to form the common hepatopancreatic duct or ampulla of Vater which opens into the duodenum.

There is a sphincter called sphincter of Oddi at the lower part of common bile duct before it joins the pancreatic duct. It is formed by smooth muscle fibers of common bile duct. It is normally kept closed; so the bile secreted from liver enters gallbladder where it is stored. Upon appropriate stimulation the sphincter opens and allows flow of bile from gallbladder into the intestine.

■ BLOOD SUPPLY TO LIVER

Liver receives the maximum blood supply of about 1500 mL/min. It receives blood from two sources namely the hepatic artery and portal vein (Fig. 30-4).

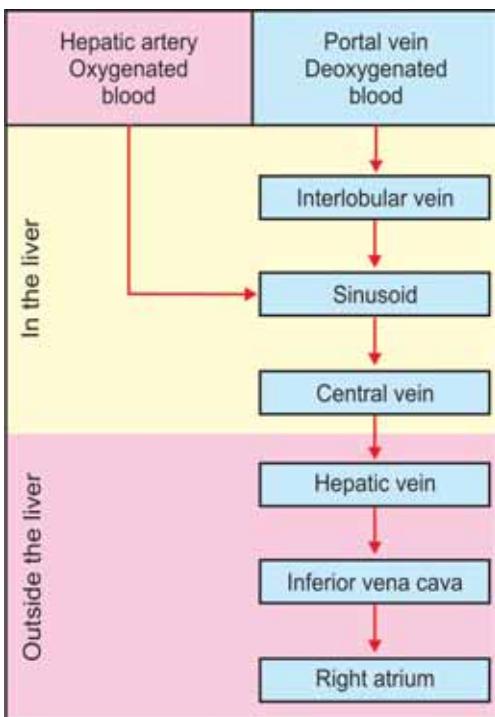


FIGURE 30-4: Schematic diagram of blood flow through liver

■ HEPATIC ARTERY

The hepatic artery arises directly from aorta and supplies oxygenated blood to liver. After entering the liver, the hepatic artery divides into many branches. Each branch enters a portal triad.

■ PORTAL VEIN

The portal vein is formed by superior mesenteric vein and splenic vein. It brings deoxygenated blood from stomach, intestine, spleen and pancreas. The portal blood is rich in monosaccharides and amino acids. It also contains bile salts, bilirubin, urobilinogen and GI hormones. However, the oxygen content is less in portal blood.

The flow of blood from intestine to liver through portal vein is known as enterohepatic circulation (Fig. 30-5).

The blood from hepatic artery mixes with blood from portal vein in the hepatic sinusoids. The hepatic cells obtain oxygen and nutrients from the sinusoid.

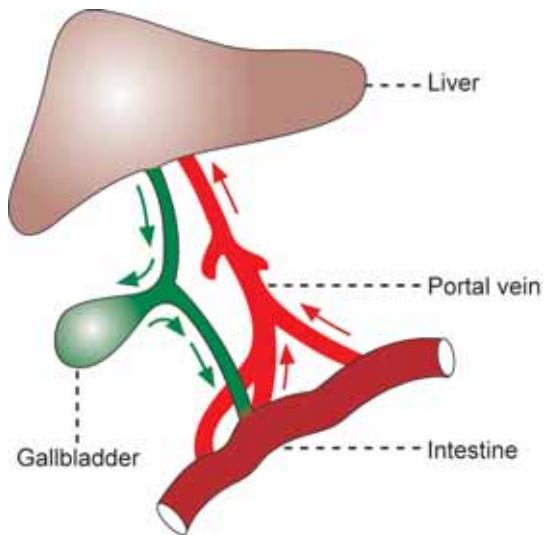


FIGURE 30-5: Enterohepatic circulation

■ HEPATIC VEIN

The substances synthesized by hepatic cells, the waste products and carbon dioxide are discharged into sinusoids. The sinusoids drain them into the central vein of the lobule. The central veins from many lobules unite to form bigger veins which ultimately form hepatic veins (right and left) which open into inferior vena cava.

■ PROPERTIES AND COMPOSITION OF BILE

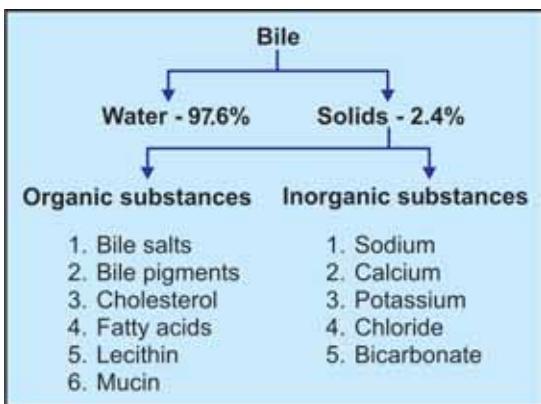
Bile is a golden yellow or greenish fluid. It enters the digestive tract along with pancreatic juice through the common opening called ampulla of Vater.

Properties of Bile

Volume	: 800 to 1200 mL/day
Reaction	: Alkaline
pH	: 8 to 8.6
Specific gravity	: 1.010 to 1.011

Composition of Bile

Bile contains 97.6% of water and 2.4% of solids. Solids include organic and inorganic substances. Refer Fig. 30-6 for details.

**FIGURE 30-6:** Composition of bile

■ FORMATION OF BILE

Bile is secreted by hepatocytes. The initial bile secreted by hepatocytes contains large quantity of bile acids, bile pigments, cholesterol, lecithin and fatty acids. From hepatocytes, bile passes through canaliculi and hepatic ducts to reach common hepatic duct. From here it may enter the intestine or gallbladder.

Sodium, bicarbonate and water are added to bile when it passes through the ducts. These substances are secreted by the epithelial cells of the ducts. The addition of sodium, bicarbonate and water increases the total quantity of bile (Fig. 30-8).

■ STORAGE OF BILE

Most of the bile from liver enters the gallbladder where it is stored. It is released from gallbladder into the intestine whenever it is required. When bile is stored in gallbladder, it undergoes many changes both in quality and quantity such as:

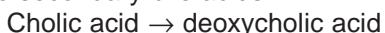
1. Volume is reduced because of absorption of large amount of water and electrolytes (except calcium and potassium)
2. Concentration of bile salts, bile pigments, cholesterol, fatty acids and lecithin is increased because of absorption of water
2. The pH is slightly decreased
3. Specific gravity is increased
4. Mucin is added (Table 30-1).

■ BILE SALTS

Bile salts are the sodium and potassium salts of bile acids, which are conjugated with glycine or taurine. Bile salts are formed in liver.

■ FORMATION OF BILE SALTS

Bile salts are formed from the primary bile acids namely cholic acid and chenodeoxycholic acid which are formed in liver and enter the intestine through bile. Due to the bacterial action in the intestine these primary bile acids are converted into secondary bile acids:



Secondary bile acids from intestine are transported back to liver through enterohepatic circulation. In the liver the secondary bile acids are conjugated with glycine or taurine and form conjugated bile acids namely glycocholic acid and taurocholic acids. These bile acids combine with sodium or potassium ions to form the salts, sodium or potassium glycocholate and sodium or potassium taurocholate.

■ ENTEROHEPATIC CIRCULATION OF BILE SALTS

Enterohepatic circulation is the transport of substances from small intestine to liver through portal vein. About 90 to 95% of bile salts from intestine are transported to liver through enterohepatic circulation. The remaining 5 to 10% of the bile salts enter large intestine. Here the bile salts are converted into deoxycholate and lithocholate and excreted in feces.

■ FUNCTIONS OF BILE SALTS

The bile salts are required for digestion and absorption of fats in the intestine. The functions of bile salts are:

1. *Emulsification of Fats*

Emulsification is the process by which the fat globules are broken down into minute droplets and made in the form of a milky fluid called emulsion. Emulsification of fats occurs in small intestine by the action of bile salts.

TABLE 30-1: Differences between liver bile and gallbladder bile

Types of entities	Liver bile	Gallbladder bile
pH	8 to 8.6	7 to 7.6
Specific gravity	1010 to 1011	1026 to 1032
Water content	97.6%	89%
Solids	2.4%	11%
Organic substances		
Bile salts	0.5 g/dL	6.0 g/dL
Bile pigments	0.05 g/dL	0.3 g/dL
Cholesterol	0.1 g/dL	0.5 g/dL
Fatty acids	0.2 g/dL	1.2 g/dL
Lecithin	0.05 g/dL	0.4 g/dL
Mucin	Absent	Present
Inorganic substances		
Sodium	150 mEq/L	135 mEq/L
Calcium	4 mEq/L	22 mEq/L
Potassium	5 mEq/L	12 mEq/L
Chloride	100 mEq/L	10 mEq/L
Bicarbonate	30 mEq/L	10 mEq/L

Fats cannot be digested directly by lipolytic enzymes of GI tract, because the fats are insoluble in water due to the surface tension. The bile salts reduce the surface tension of the fats due to their detergent action. Because of this, the lipid granules are broken into minute particles which can be easily digested by lipolytic enzymes. The emulsification of fats by bile salts needs the presence of lecithin from bile.

2. Absorption of Fats

Bile salts help in the absorption of digested fats from intestine into blood. The bile salts combine with fats and make complexes of fats called micelles. The fats in the form of micelles can be absorbed easily.

3. Choleretic Action

Bile salts stimulate the secretion of bile from liver. This action is called choleretic action.

4. Cholagogue Action

Cholagogue is an agent, which causes contraction of gallbladder and release of bile into the intestine. Bile salts act as cholagogues indirectly by stimulating the secretion of hormone cholecystokinin. This hormone causes contraction of gallbladder resulting in release of bile.

5. Laxative Action

Laxative is an agent which induces defecation. Bile salts act as laxatives by stimulating peristaltic movements of the intestine.

6. Prevention of Gallstone Formation

Bile salts prevent the formation of gallstone by keeping the cholesterol and lecithin in solution. In the absence of bile salts, cholesterol precipitates along with lecithin and forms gallstone.

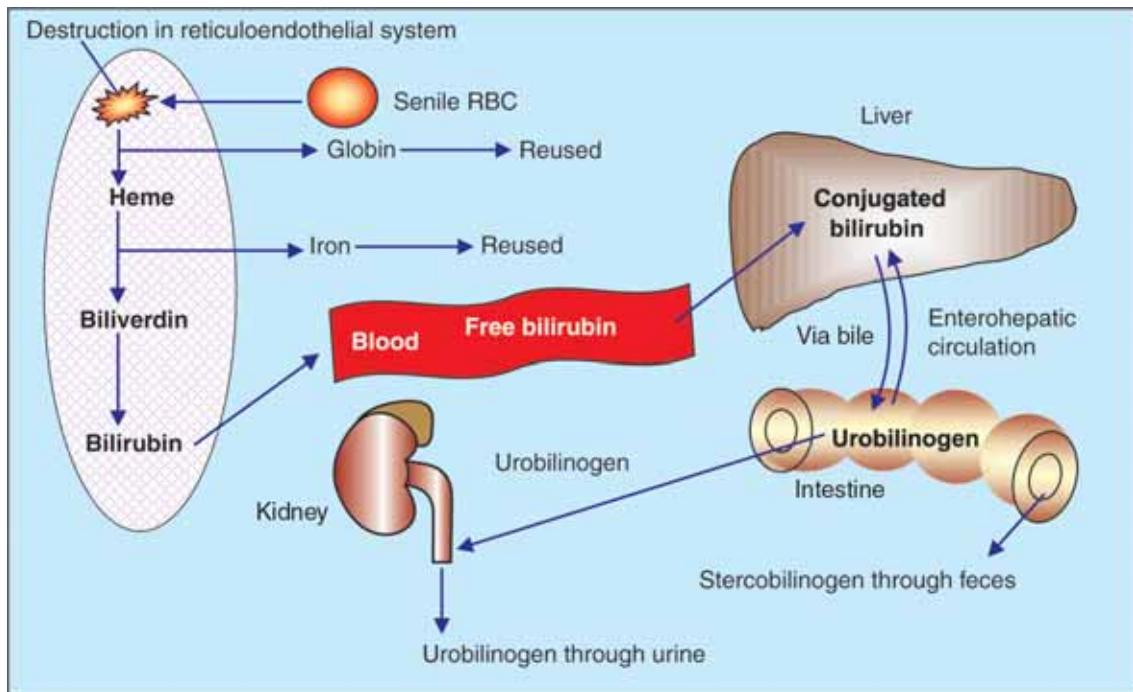


FIGURE 30-7: Formation and circulation of bile pigments

BILE PIGMENTS

Bile pigments are the excretory products in bile. Bilirubin and biliverdin are the two bile pigments and bilirubin is the major bile pigment in human being.

The bile pigments are formed during the breakdown of hemoglobin, which is released from the destroyed RBCs in the reticuloendothelial system (Fig. 30-7).

FORMATION AND EXCRETION OF BILE PIGMENTS

Stages of formation and circulation of bile pigments:

1. The senile erythrocytes are destroyed in reticuloendothelial system and hemoglobin is released from them
2. The hemoglobin is broken into globin and heme
3. Heme is split into iron and the pigment biliverdin
4. The iron goes to iron pool and is reused

5. The first formed pigment biliverdin is reduced to bilirubin
6. The bilirubin is released into blood from reticuloendothelial cells
7. The bilirubin circulating in the blood is called free bilirubin or unconjugated bilirubin
8. Within few hours the free bilirubin is taken up by the liver cells
9. In the liver, it is conjugated with glucuronic acid to form conjugated bilirubin
10. Conjugated bilirubin is then excreted into intestine through bile.

FATE OF CONJUGATED BILIRUBIN

Stages of excretion of conjugated bilirubin:

1. In the intestine 50% of the conjugated bilirubin is converted into urobilinogen by intestinal bacteria. First the conjugated bilirubin is deconjugated into free bilirubin which is later reduced into urobilinogen.
2. Remaining 50% of conjugated bilirubin from intestine enters the liver through

- enterohepatic circulation. From liver, it is re-excreted in bile
3. Most of the urobilinogen from intestine enters liver via enterohepatic circulation. Later, it is re-excreted through bile
 4. About 5% of urobilinogen is excreted by kidney through urine. In urine, due to the exposure to air, the urobilinogen is converted into urobilin by oxidation
 5. Some of the urobilinogen is excreted in feces as stercobilinogen. In feces, stercobilinogen is oxidized to stercobilin.

■ NORMAL PLASMA LEVELS OF BILIRUBIN

The normal bilirubin (Total bilirubin) content in plasma is 0.5 to 1.5 mg/dL. When it exceeds 1 mg/dL, the condition is called hyperbilirubinemia. When it exceeds 2 mg/dL, jaundice occurs.

■ FUNCTIONS OF BILE

Most of the functions of bile are due to the bile salts.

■ 1. DIGESTIVE FUNCTIONS

Refer functions of bile salts.

■ 2. ABSORPTIVE FUNCTIONS

Refer functions of bile salts.

■ 3. EXCRETORY FUNCTIONS

Bile pigments are the major excretory products of the bile. The other substances excreted in bile are:

- i. Heavy metals like copper and iron
- ii. Some bacteria like typhoid bacteria
- iii. Some toxins
- iv. Cholesterol
- v. Lecithin
- vi. Alkaline phosphatase.

■ 4. LAXATIVE ACTION

Bile salts act as laxatives (see above).

■ 5. ANTISEPTIC ACTION

Bile inhibits the growth of certain bacteria in the lumen of intestine by its natural detergent action.

■ 6. CHOLERETIC ACTION

Bile salts have the choleric action (see above).

■ 7. MAINTENANCE OF pH IN GASTROINTESTINAL TRACT

As the bile is highly alkaline, it neutralizes acid chyme which enters the intestine from stomach. Thus, an optimum pH is maintained for the action of digestive enzymes.

■ 8. PREVENTION OF GALLSTONE FORMATION

Refer function of bile salts.

■ 9. LUBRICATION FUNCTION

The mucin in bile acts as a lubricant for the chyme in intestine.

■ 10. CHOLAGOGUE ACTION

Bile salts act as cholagogues (see above).

■ FUNCTIONS OF LIVER

Liver is the largest gland and one of the vital organs of the body. It performs many vital metabolic and homeostatic functions, which are summarized below.

■ 1. METABOLIC FUNCTION

Liver is the organ where maximum metabolic reactions are carried out such as metabolism of carbohydrates, proteins, fats, vitamins and many hormones.

■ 2. STORAGE FUNCTION

Many substances like glycogen, amino acids, iron, folic acid and vitamins A, B₁₂, and D are stored in liver.

■ 3. SYNTHETIC FUNCTION

Liver produces glucose by gluconeogenesis. It synthesizes all the plasma proteins and other proteins (except immunoglobulins) such as clotting factors, complement factors, and hormone binding proteins. It also synthesizes steroids, somatomedin and heparin.

■ 4. SECRETION OF BILE

Liver secretes bile, which contains bile salts, bile pigments, cholesterol, fatty acids and lecithin.

The functions of bile are mainly due to the bile salts. The bile salts are required for digestion and absorption of fats in the intestine. Bile helps to carry away waste products and breakdown fats, which are excreted through feces or urine.

■ 5. EXCRETORY FUNCTION

Liver excretes cholesterol, bile pigments, heavy metals (like lead, arsenic and bismuth), toxins, bacteria and virus (like that of yellow fever) through bile.

■ 6. HEAT PRODUCTION

Liver is the organ where maximum heat is produced because of the metabolic reactions.

■ 7. HEMOPOIETIC FUNCTION

In fetus (hepatic stage), liver produces the blood cells (Chapter 8). It stores vitamin B₁₂ necessary for erythropoiesis and iron necessary for synthesis of hemoglobin. Liver produces thrombopoietin that promotes production of thrombocytes.

■ 8. HEMOLYTIC FUNCTION

The senile RBCs after the lifespan of 120 days are destroyed by reticuloendothelial cells (Kupffer's cells) of liver.

■ 9. INACTIVATION OF HORMONES AND DRUGS

Liver catabolizes the hormones such as growth hormone, parathormone, cortisol, insulin,

glucagon and estrogen. It also inactivates the drugs particularly the fat soluble drugs. The fat soluble drugs are converted into water soluble substances, which are excreted through bile or urine.

■ 10. DEFENSIVE AND DETOXIFICATION FUNCTIONS

The reticuloendothelial cells (Kupffer's cells) of the liver play an important role in the defense of the body. Liver is also involved in the detoxification of the foreign bodies.

- i. The foreign bodies such as bacteria or antigens are swallowed and digested by reticuloendothelial cells of liver by means of phagocytosis
- ii. The reticuloendothelial cells of liver are also involved in production of some substances like interleukins and tumor necrosis factors, which activate the immune system of the body (Chapter 13).
- iii. Liver cells are involved in removal of toxic property of various harmful substances. The removal of toxic property of the harmful agent is known as detoxification.

■ GALLBLADDER

The bile secreted from liver is stored in gallbladder. The capacity of gallbladder is approximately 50 mL. The gallbladder is not essential for life. The removal of gallbladder (cholecystectomy) is often done in patients suffering from gallbladder dysfunction. After cholecystectomy, patients do not suffer from any major disadvantage. In some species, gallbladder is absent.

■ FUNCTIONS OF GALLBLADDER

The major functions of gallbladder are the storage and concentration of bile.

1. Storage of Bile

Bile is continuously secreted from liver. But it is released into intestine only intermittently and most of the bile is stored in gallbladder till it is required.

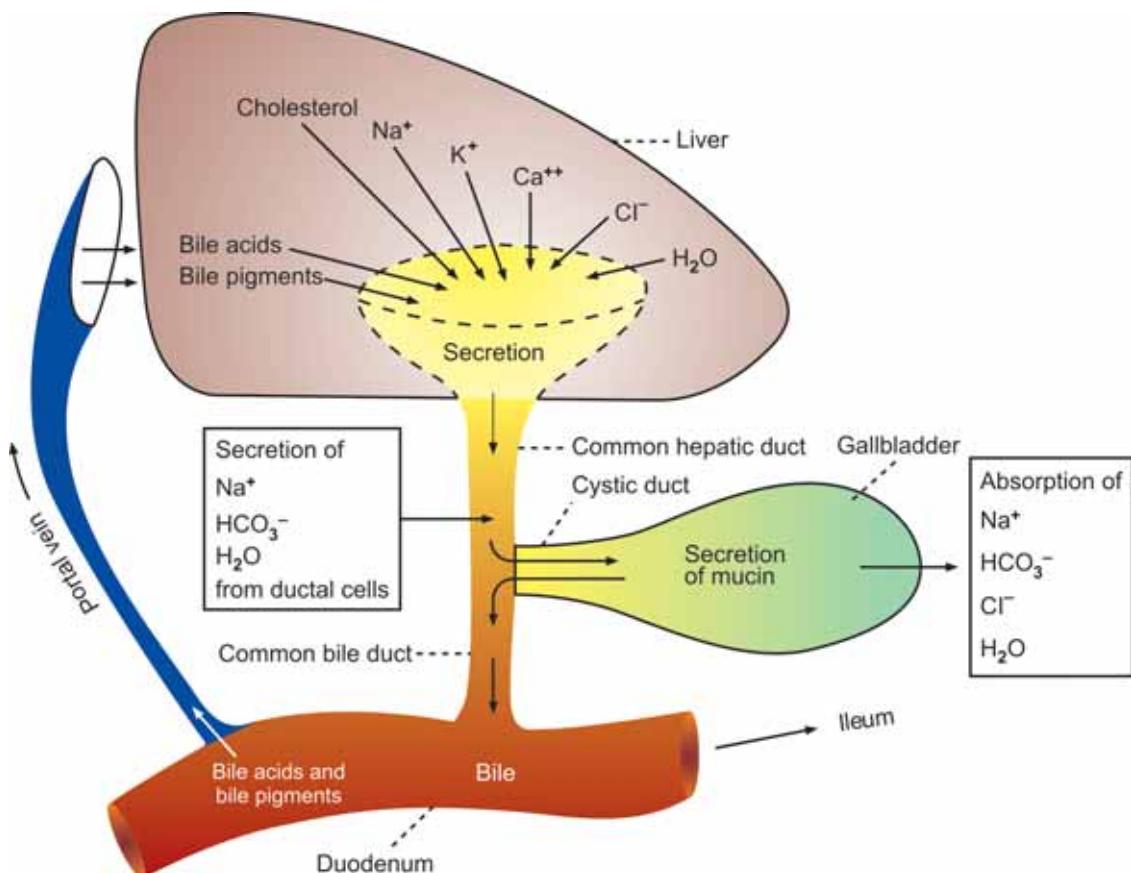


FIGURE 30-8: Diagram showing the formation of bile from liver and changes taking place in the composition of gallbladder bile

2. Concentration of Bile

Bile is concentrated while it is stored in gallbladder. The mucosa of gallbladder rapidly reabsorbs water and electrolytes except calcium and potassium. But the bile salts, bile pigments, cholesterol and lecithin are not reabsorbed. So, the concentration of these substances in bile increases 5 to 10 times.

3. Alteration of pH of Bile

The pH of bile decreases from 8 to 8.6 to 7 to 7.6 and it becomes less alkaline when it is stored in gallbladder.

4. Secretion of Mucin

Gallbladder secretes mucin into the bile. Mucin acts as a lubricant for movement of chyme in the intestine.

5. Maintenance of Pressure in Biliary System

Due to the concentrating capacity, gallbladder maintains a pressure of about 7 cm H_2O in biliary system. This pressure in the biliary system is essential for the release of bile into the intestine.

■ REGULATION OF BILE SECRETION

Bile secretion is a continuous process though the amount may be less during fasting. It starts increasing three hours after meals. The secretion of bile from the liver and release of bile from the gallbladder are influenced by some chemical factors which are categorized into three groups:

1. Choleretics
2. Cholagogue
3. Hydrocholeretic agents.

1. Choleretics

Substances, which increase the secretion of bile from liver, are known as choleretics. The effective choleretic agents are:

- i. Acetylcholine
- ii. Secretin
- iii. Cholecystokinin
- iv. Acid chyme in intestine
- v. Bile salts.

2. Cholagogues

Cholagogue is an agent, which increases the release of bile from gallbladder into the intestine by contracting the gallbladder. The common cholagogues are:

- i. Bile salts
- ii. Calcium
- iii. Fatty acids
- iv. Amino acids
- v. Inorganic acids.

All these substances stimulate the secretion of cholecystokinin, which, in turn causes contraction of gallbladder and flow of bile into intestine.

3. Hydrocholeretic Agents

Hydrocholeretic agent is a substance, which causes secretion of bile from liver with large amount of water and less amount of solids. Hydrochloric acid is a hydrocholeretic agent.

■ APPLIED PHYSIOLOGY

■ JAUNDICE OR ICTERUS

Jaundice or icterus is the condition characterized by yellow coloration of the skin, mucous membrane and deeper tissues due to increased bilirubin level in blood. The word jaundice is derived from the French word "jaune" meaning yellow.

The normal serum bilirubin level is 0.5 to 1.5 mg/dL. Jaundice occurs when bilirubin level exceeds 2 mg/dL.

Types of Jaundice

Jaundice is classified into three types:

1. Prehepatic or hemolytic jaundice
2. Hepatic or hepatocellular jaundice
3. Posthepatic or obstructive jaundice.

1. Prehepatic or Hemolytic Jaundice

Hemolytic jaundice is the type of jaundice that occurs because of excessive destruction of RBCs resulting in increased blood level of free (unconjugated) bilirubin. The function of liver is normal. Since the quantity of bilirubin increases enormously, the liver cells cannot excrete that much bilirubin rapidly. So, it accumulates in the blood resulting in jaundice.

Causes

Any condition that causes hemolytic anemia can lead to hemolytic jaundice. The common causes of hemolytic jaundice are:

- i. Liver failure
- ii. Renal disorder
- iii. Hypersplenism
- iv. Burns
- v. Infections such as malaria
- vi. Hemoglobin abnormalities such as sickle cell anemia or thalassemia
- vii. Drugs or chemical substances causing red cell damage
- viii. Autoimmune diseases.

2. Hepatic or Hepatocellular or Cholestatic Jaundice

This is the type of jaundice that occurs due to the damage of hepatic cells. Because of the damage, the conjugated bilirubin from liver cannot be excreted and it returns to blood.

Causes

- i. Hepatitis or cirrhosis of liver
- ii. Alcoholism
- iii. Exposure to toxic materials.

TABLE 30-2: Features of different types of jaundice

Features	Prehepatic jaundice (Hemolytic)	Hepatic jaundice (hepatocellular)	Posthepatic jaundice (Obstructive)
Cause	Excess breakdown of RBCs	Liver damage	Obstruction of bile ducts
Type of bilirubin in blood	Unconjugated	Conjugated and unconjugated	Conjugated
Urinary excretion of urobilinogen	Increases	Decreases	Decreases Absent in severe obstruction
Fecal excretion of stercobilinogen	Increases	Decreases (pale feces)	Absent (clay colored feces)
van den Bergh's reaction	Indirect – positive	Biphasic	Direct – positive
Liver functions	Normal	Abnormal	Exaggerated
Blood picture	Anemia Reticulocytosis Abnormal RBC	Normal	Normal
Plasma albumin and globulin	Normal	Albumin – increases Globulin – increases A : G ratio – decreases	Normal
Hemorrhagic tendency	Absent	Present due to lack of vitamin K	Present due to lack of vitamin K

3. Posthepatic or Obstructive or Extrahepatic Jaundice

This type of jaundice occurs because of the obstruction of bile flow at any level of the biliary system. The bile cannot be excreted into small intestine. So, bile salts and bile pigments enter the circulation. The blood contains more amount of conjugated bilirubin (Table 30-2).

Causes

- i. Gallstones
- ii. Cancer of biliary system or pancreas.

■ HEPATITIS

Hepatitis is the liver damage characterized by swelling and inadequate functioning of liver. It

is caused by several factors such as viral infection, bacterial infection and excess alcohol.

Common features of hepatitis are fever, nausea, vomiting, diarrhea, loss of appetite, jaundice. Liver failure and death occur in severe conditions.

■ CIRRHOSIS OF LIVER

Cirrhosis of liver refers to inflammation and damage of parenchyma of liver resulting in degeneration of hepatic cells and dysfunction of liver. It is caused by infection, obstruction of biliary system and liver enlargement due to intoxication.

Features of cirrhosis of liver are fever, nausea and vomiting, jaundice, portal hypertension, muscular weakness and wasting of muscles. Coma occurs in advanced stages.

■ GALLSTONES

Definitions

Gallstone is a solid crystal deposit that is formed by cholesterol, calcium ions and bile pigments in the gallbladder or bile duct. Cholelithiasis is the presence of gallstones in gallbladder.

Formation of Gallstones

Normally, cholesterol is water soluble. Under some abnormal conditions, it precipitates resulting in the formation of crystals in the mucosa of gallbladder. Bile pigments and calcium are attached to these crystals resulting in formation of gallstones.

Causes for Gallstone Formation

1. Reduction in bile salts
2. Excess of cholesterol or disturbed cholesterol metabolism
4. Excess of calcium ions due to increased concentration of bile
5. Damage or infection of gallbladder epithelium
6. Obstruction of bile flow from the gallbladder.

Features

The common feature of gallstone is the pain in stomach area or in upper right part of the belly under the ribs. Other features include nausea, vomiting, abdominal bloating and indigestion.

31

Small Intestine

- FUNCTIONAL ANATOMY
- INTESTINAL VILLI AND GLANDS
- PROPERTIES AND COMPOSITION OF SUCCUS ENTERICUS
- FUNCTIONS OF SUCCUS ENTERICUS
- FUNCTIONS OF SMALL INTESTINE
- REGULATION OF SECRETION OF SUCCUS ENTERICUS
- APPLIED PHYSIOLOGY

■ FUNCTIONAL ANATOMY

Small intestine is the part of GI tract extending between the pyloric sphincter of stomach and ileocecal valve, which opens into large intestine. It is called small intestine because of its small diameter compared to that of large intestine. But it is longer than large intestine. Its length is about 6 meters.

The functional importance of small intestine is absorption. Maximum absorption of digested food products takes place in small intestine.

Small intestine consists of three portions:

1. Proximal part known as duodenum
2. Middle part known as jejunum
3. Distal part known as ileum.

■ INTESTINAL VILLI AND GLANDS OF SMALL INTESTINE

■ INTESTINAL VILLI

The mucous membrane of small intestine is covered by minute projections called villi. The

villi are lined by columnar cells, which are called enterocytes. Each enterocyte gives rise to hair like projections called microvilli. Within each villus, there is a central channel called lacteal. The lacteal opens into lymphatic vessels. It contains blood vessels also.

■ CRYPTS OF LIEBERKÜHN OR INTESTINAL GLANDS

The crypts of Lieberkühn or intestinal glands are simple tubular glands of intestine. These glands open into lumen of intestine between the villi. The intestinal glands are lined by columnar cells. The lining of each gland is continuous with epithelial lining of the villi (Fig. 31-1).

Epithelial cells lining the intestinal glands undergo division by mitosis at a faster rate. The newly formed cells push the older cells upward over the lining of villi. The cells which move to villi are called enterocytes. The enterocytes secrete the enzymes. The old enterocytes are continuously shed into lumen along with enzymes.

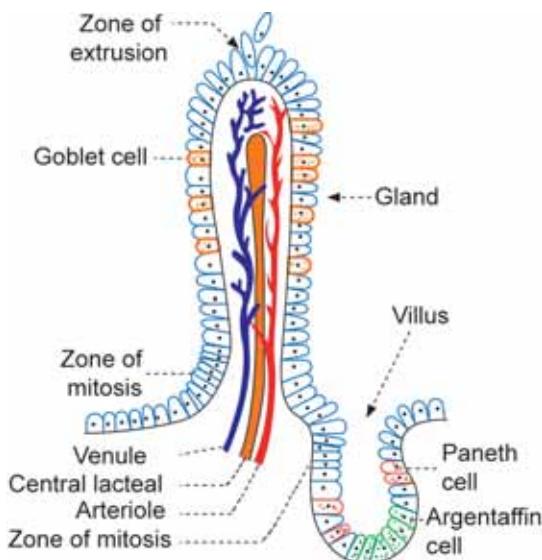


FIGURE 31-1: Intestinal gland and villus

Three types of cells are interposed between columnar cells of the glands:

1. Argentaffin cells which are otherwise known as enterochromaffin cells. These cells secrete intrinsic factor that is essential for the absorption of vitamin B₁₂
2. Goblet cells which secrete mucus
3. Paneth cells which secrete the cytokines called defensins.

■ BRUNNER'S GLANDS

In addition to intestinal glands, the first part of duodenum contains some mucus glands, which are called Brunner's glands. Brunner's gland secretes mucus and traces of enzymes.

■ PROPERTIES AND COMPOSITION OF SUCCUS ENTERICUS

Secretion from small intestine is called succus entericus.

Properties of Succus Entericus

Volume	:	1800 mL/day
Reaction	:	Alkaline
pH	:	8.3

Composition of Succus Entericus

The succus entericus contains water (99.5%) and solids (0.5%). Solids include organic and inorganic substances (Fig. 31-2). The bicarbonate concentration is slightly high in succus entericus.

■ FUNCTIONS OF SUCCUS ENTERICUS

■ 1. DIGESTIVE FUNCTION

The enzymes of succus entericus act on the partially digested food and convert them into final digestive products.

Proteolytic Enzymes

The proteolytic enzymes in succus entericus are the peptidases which convert peptides into amino acids (Fig. 31-2).

Amylolytic Enzymes

The carbohydrate splitting enzymes of succus entericus are listed in Figure 31-2. Lactase, sucrase and maltase convert the disaccharides (lactose, sucrose and maltose) into two molecules of monosaccharides (Table 31-1).

Dextrinase converts dextrin, maltose and maltriose into glucose. Trehalase or trehalose glucohydrolase causes hydrolysis of trehalose (carbohydrate present in mushrooms and yeast) and converts it into glucose.

Lipolytic Enzyme

Intestinal lipase acts on triglycerides and converts them into fatty acids.

■ 2. PROTECTIVE FUNCTION

- i. The mucus present in the succus entericus protects the intestinal wall from the acid chyme, which enters the intestine from stomach; thereby it prevents the intestinal ulcer
- ii. Paneth cells of intestinal glands secrete defensins which are the antimicrobial peptides.

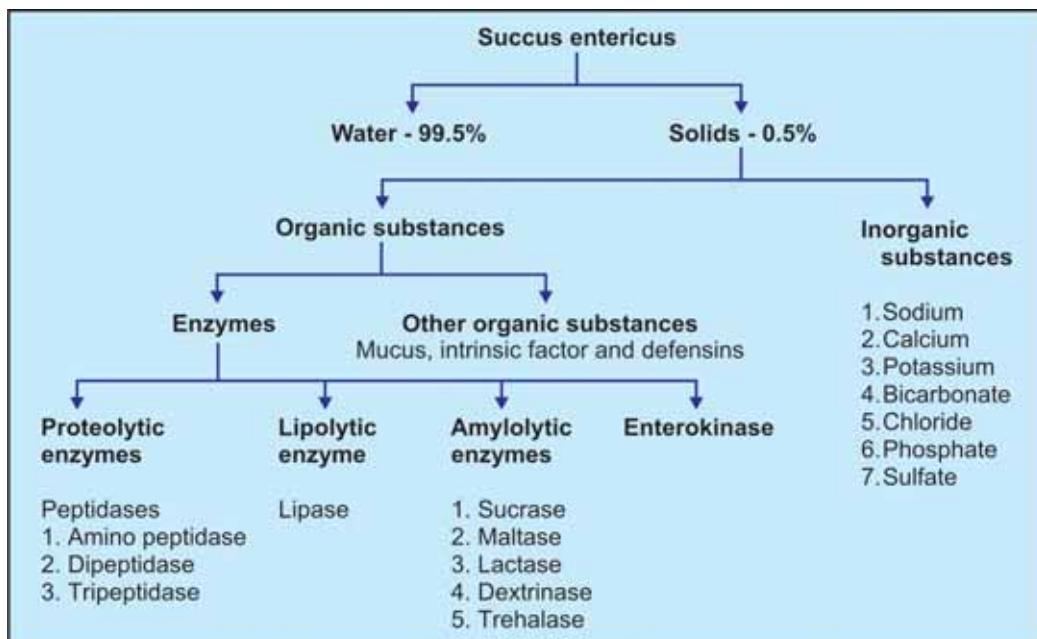


FIGURE 31-2: Composition of succus entericus

TABLE 31-1: Digestive enzymes of succus entericus

Enzyme	Substrate	End products
1. Peptidases	Peptides	Amino acids
2. Sucrase	Sucrose	Fructose and glucose
3. Maltase	Maltose and maltroiose	Glucose
4. Lactase	Lactose	Galactose and glucose
5. Dextrinase	Dextrin, maltose and maltroiose	Glucose
6. Trehalase	Trehalose	Glucose
7. Intestinal lipase	Triglycerides	Fatty acids

■ 3. ACTIVATOR FUNCTION

The enterokinase present in intestinal juice activates trypsinogen into trypsin. Trypsin, in turn activates other enzymes (Chapter 29).

■ 4. HEMOPOIETIC FUNCTION

The intrinsic factor of Castle, which is present in the intestine, plays an important role in erythropoiesis (Chapter 8).

■ 5. HYDROLYTIC PROCESS

Intestinal juice helps in all the enzymatic reactions of digestion.

■ FUNCTIONS OF SMALL INTESTINE

■ 1. MECHANICAL FUNCTION

The mixing movements of small intestine help in the thorough mixing of chyme with the digestive juices like succus entericus, pancreatic juice and bile.

■ 2. SECRETORY FUNCTION

Small intestine secretes succus entericus, enterokinase and the GI hormones.

■ 3. HORMONAL FUNCTION

Small intestine secretes many GI hormones such as secretin, cholecystokinin, etc. These hormones regulate the movement of GI tract and secretory activities of small intestine and pancreas.

■ 4. DIGESTIVE FUNCTION

Refer functions of succus entericus.

■ 5. ACTIVATOR FUNCTION

Refer functions of succus entericus.

■ 6. HEMOPOIETIC FUNCTION

Refer functions of succus entericus.

■ 7. HYDROLYTIC FUNCTION

Refer functions of succus entericus.

■ 8. ABSORPTIVE FUNCTIONS

The presence of villi and microvilli in small intestinal mucosa increases the surface area of the mucosa. This facilitates the absorptive function of intestine.

The digested products of foodstuffs, proteins, carbohydrates, fats and other nutritive substances such as vitamins, minerals and water are absorbed mostly in small intestine. From the lumen of intestine, these substances pass through lacteal of villi, cross the mucosa and enter the blood directly or through lymphatics.

■ REGULATION OF SECRETION OF SUCCUS ENTERICUS

The secretion of succus entericus is regulated by both the nervous and hormonal mechanisms.

■ NERVOUS REGULATION

Stimulation of parasympathetic nerves causes vasodilatation and increases the secretion of succus entericus. Stimulation of sympathetic nerves causes vasoconstriction and decreases the secretion of succus entericus. But, the role of these nerves in the regulation of intestinal secretion in physiological conditions is uncertain.

However, the local nervous reflexes play an important role in increasing the secretion of intestinal juice. When chyme enters the small intestine, the mucosa is stimulated by tactile stimuli or irritation. It causes development of local nervous reflexes, which stimulate the glands of intestine.

■ HORMONAL REGULATION

When the chyme enters the small intestine, the intestinal mucosa secretes enterocrinin, secretin and cholecystokinin which promote the secretion of succus entericus by stimulating the intestinal glands.

■ APPLIED PHYSIOLOGY – MALABSORPTION

Malabsorption is difficulty in the digestion or absorption of nutrients from small intestine. It may be the failure to absorb either the specific substances such as proteins, carbohydrates, fats and vitamins or some general nonspecific substances of food. Malabsorption affects growth and development of the body.

Large Intestine

- FUNCTIONAL ANATOMY
- SECRETIONS OF LARGE INTESTINE
- FUNCTIONS OF LARGE INTESTINE
- APPLIED PHYSIOLOGY

■ FUNCTIONAL ANATOMY OF LARGE INTESTINE

The large intestine is also known as colon. It extends from ileocecal valve up to anus (Fig. 26-1). It consists of seven portions:

1. Cecum with appendix
2. Ascending colon
3. Transverse colon
4. Descending colon
5. Sigmoid colon or pelvic colon
6. Rectum
7. Anal canal.

The wall of large intestine is formed by four layers of structures like any other part of the gut.

■ SECRETIONS OF LARGE INTESTINE

The large intestinal juice is a watery fluid with pH of 8.0.

■ COMPOSITION OF LARGE INTESTINAL JUICE

The large intestinal juice contains 99.5% of water and 0.5% of solids (Fig. 32-1). Digestive enzymes are absent and concentration of bicarbonate is high in large intestinal juice.

■ FUNCTIONS OF LARGE INTESTINAL JUICE

Neutralization of Acids

Strong acids formed by bacterial action in large intestine are neutralized by the alkaline nature of large intestinal juice. The alkalinity of this juice is mainly due to the presence of large quantity of bicarbonate.

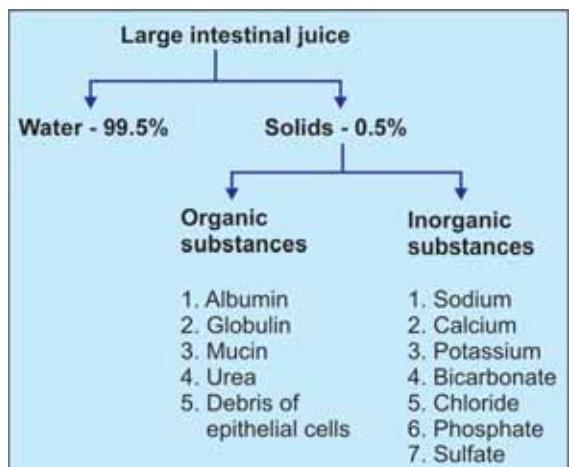


FIGURE 32-1: Composition of large intestinal juice

Lubrication Activity

The mucin present in secretion of large intestine lubricates the mucosa of large intestine and the bowel contents, so that, the movement of bowel is facilitated.

The mucin also protects the mucous membrane of large intestine by preventing the damage caused by mechanical injury or chemical substances.

■ FUNCTIONS OF LARGE INTESTINE

■ 1. ABSORPTIVE FUNCTION

Large intestine plays an important role in the absorption of various substances such as water, electrolytes, organic substances like glucose, alcohol and drugs like anesthetic agents, sedatives and steroids.

■ 2. FORMATION OF FECES

After the absorption of nutrients, water and other substances, the unwanted substances in the large intestine form feces. This is excreted out.

■ 3. EXCRETORY FUNCTION

Large intestine excretes heavy metals like mercury, lead, bismuth and arsenic through feces.

■ 4. SECRETORY FUNCTION

Large intestine secretes mucin and inorganic substances like chlorides and bicarbonates.

■ 5. SYNTHETIC FUNCTION

The bacterial flora of large intestine synthesizes folic acid, vitamin B₁₂ and vitamin K. By this function large intestine contributes in erythropoietic activity and blood clotting mechanism.

■ APPLIED PHYSIOLOGY

■ DIARRHEA

Diarrhea is the frequent and profuse discharge of intestinal contents in loose and fluid form. It

occurs due to the increased movement of intestine. It may be acute or chronic.

Causes

1. Intake of contaminated water or food, artificial sweeteners found in food, spicy food, etc.
2. Indigestion
3. Infections by bacteria, viruses and parasites
4. Reaction to medicines such as antibiotics, laxatives.
5. Intestinal diseases.

Features

Severe diarrhea results in loss of excess water and electrolytes leading to dehydration and electrolyte imbalance. Chronic diarrhea results in hypokalemia and metabolic acidosis. Other features of diarrhea are abdominal pain, nausea and bloating (a condition in which the subject feels the abdomen full and tight due to excess intestinal gas).

■ CONSTIPATION

Failure of voiding of feces, which produces discomfort, is known as constipation. It is due to the lack of movements necessary for defecation (Chapter 33). Due to the absence of mass movement in colon, feces remain in the large intestine for a long-time resulting in absorption of fluid. So the feces become hard and dry.

Causes

1. Lack of fiber or lack of liquids in diet
2. Irregular bowel habit
3. Spasm of sigmoid colon
4. Many types of diseases
5. Drugs like diuretics, pain relievers, antihypertensive drugs, antiparkinson drugs, antidepressants and anticonvulsants
6. Dysfunction of myenteric plexus in large intestine called megacolon

Megacolon is the condition characterized by distension and hypertrophy of colon associated with constipation. It is caused by the absence

or damage of ganglionic cells in myenteric plexus which causes dysfunction of myenteric plexus. It leads to accumulation of large quantity of feces in colon. The colon is distended to a diameter of 4-5 inches. It also results in hypertrophy of colon.

■ APPENDICITIS

Appendix is a small, finger-like pouch projecting from cecum of ascending colon. The inflammation of appendix is known as appendicitis. The cause for appendicitis is not known. It may occur by viral infection of the GI tract or if the connection between appendix and large intestine is blocked.

Features

1. The main symptom of appendicitis is the pain, which starts around the umbilicus and then spreads to the lower right side of the abdomen. The pain becomes severe within 6 to 12 hours
2. Nausea and vomiting
3. Constipation
4. Diarrhea
5. Low fever
6. Abdominal swelling
7. Loss of appetite

If not treated immediately, the appendix may rupture and the inflammation will spread to the whole body leading to severe complications, sometimes even death.

33

Movements of Gastrointestinal Tract

- MASTICATION
- DEGLUTITION
- MOVEMENTS OF STOMACH
- FILLING AND EMPTYING OF STOMACH
- VOMITING
- MOVEMENTS OF SMALL INTESTINE
- MOVEMENTS OF LARGE INTESTINE
- DEFECATION

■ MASTICATION

Mastication or chewing is the first mechanical process in the GI tract by which the food substances are torn or cut into small particles and crushed or ground into a soft bolus.

The significances of mastication:

1. Breakdown of foodstuffs into smaller particles
2. Mixing of saliva with food substances thoroughly
3. Lubrication and moistening of dry food by saliva so that, the bolus can be easily swallowed
4. Appreciation of taste of the food.

■ MUSCLES AND THE MOVEMENTS OF MASTICATION

Muscles of mastication:

1. Masseter muscle
2. Temporal muscle
3. Pterygoid muscles
4. Buccinator muscle.

Movements involved in mastication:

1. Opening and closure of mouth
2. Rotational movements of jaw
3. Protraction and retraction of jaw.

■ CONTROL OF MASTICATION

Action of mastication is mostly a reflex process. It is carried out voluntarily also. The center for mastication is situated in medulla and cerebral cortex. The muscles of mastication are supplied by mandibular division of V cranial (trigeminal) nerve.

■ DEGLUTITION

Definition

Deglutition or swallowing is the process by which food passes from mouth into stomach.

Stages of Deglutition

Deglutition occurs in three stages:

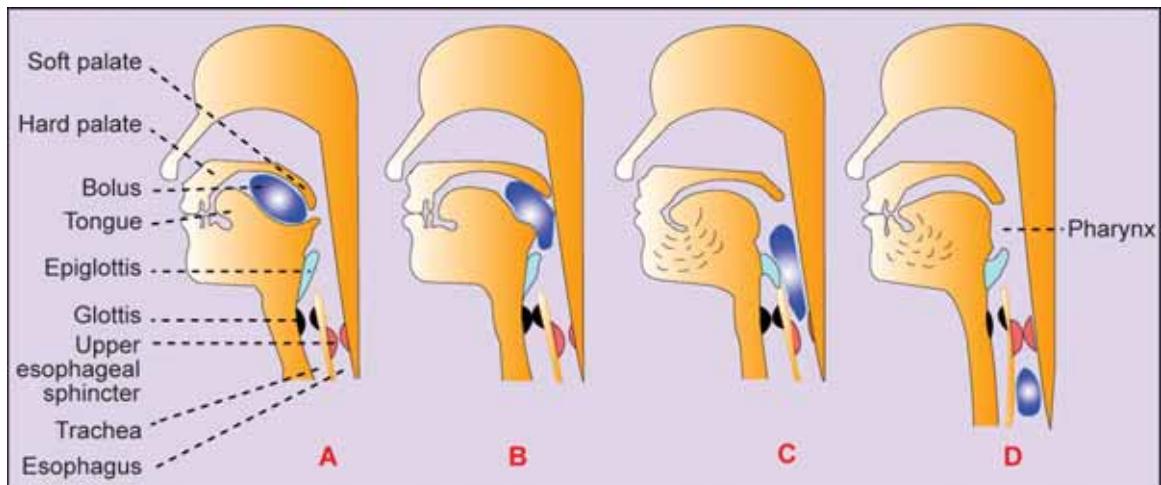


FIGURE 33-1: Stages of deglutition. A = Preparatory stage, B = Oral stage, C = Pharyngeal stage, D = Esophageal stage

- I. Oral stage when food moves from mouth to pharynx
- II. Pharyngeal stage when food moves from pharynx to esophagus
- III. Esophageal stage when food moves from esophagus to stomach.

■ ORAL STAGE OR FIRST STAGE

Oral stage is a voluntary stage. In this stage of swallowing, the bolus from oral cavity passes into the pharynx by means of series of actions such as:

1. The bolus is placed over posterodorsal surface of the tongue. It is called the preparatory position
2. The anterior part of tongue is retracted and depressed
3. The posterior part of tongue is elevated and retracted against hard palate. This pushes the bolus backwards into the pharynx
4. The forceful contraction of tongue against the palate produces a positive pressure in the posterior part of oral cavity. This pressure in the oral cavity also pushes the food into pharynx (Fig. 33-1).

■ PHARYNGEAL STAGE OR SECOND STAGE

Pharyngeal stage is an involuntary stage. In this stage, the bolus is pushed from pharynx into the

esophagus. The pharynx is a common passage for food and air. It divides into larynx and esophagus. Larynx lies anteriorly and continues as respiratory passage. Esophagus lies behind the larynx and continues as GI tract. Since pharynx communicates with mouth, nose, larynx and esophagus, during this stage of deglutition, the bolus from the pharynx can enter into four paths:

1. It can come back into mouth
2. It can go upwards into nasopharynx
3. It can move forwards into larynx
4. It can move downwards into esophagus.

However, due to various coordinated movements, bolus is made to enter only into the esophagus. The entrance of bolus through other paths is prevented as follows:

1. Back into Mouth

Return of bolus back into the mouth is prevented by:

- i. The position of tongue against the soft palate (roof of the mouth)
- ii. The high intraoral pressure developed by the movement of tongue.

2. Upward into Nasopharynx

The movement of bolus into the nasopharynx from pharynx is prevented by elevation of soft palate along with its extension called uvula.

3. Forward into Larynx

The movement of bolus into the larynx is prevented by the following actions:

- i. Approximation of the vocal cords
- ii. Forward and upward movement of larynx
- iii. The backward movement of epiglottis to seal the opening of the larynx (glottis)
- iv. All these movements arrest respiration for a few seconds. It is called deglutition apnea.

Deglutition apnea

Apnea refers to temporary arrest of breathing. Deglutition apnea or swallowing apnea is the arrest of breathing during deglutition.

4. Entrance of Bolus into Esophagus

Since the other three paths are closed for the bolus, it has to pass only through the esophagus. It occurs by the combined effects of various factors:

- i. The upward movement of the larynx stretches the opening of the esophagus
- ii. Simultaneously, the upper 3 to 4 cm of esophagus relaxes. This part of the esophagus is formed by the cricopharyngeal muscle and it is called upper esophageal sphincter or pharyngoesophageal sphincter
- iii. At the same time, the peristaltic contractions start in the pharynx due to the contraction of pharyngeal muscles
- iv. Elevation of larynx also lifts the glottis away from the food passage.

All the factors mentioned above act together so that the bolus moves easily into the esophagus. The whole process takes place within 1 to 2 seconds. And this process is purely involuntary.

■ ESOPHAGEAL STAGE OR THIRD STAGE

It is also an involuntary stage. In esophageal stage, food from stomach enters esophagus. The function of esophagus is to transport the bolus from the pharynx to the stomach. The movements of esophagus are specifically

organized for this function and the movements are called peristaltic waves. Peristalsis means a wave of contraction followed by the wave of relaxation of muscle fibers of GI tract, which travel in aboral direction (away from mouth). By this type of movement, the contents are propelled down along the GI tract.

Role of Lower Esophageal Sphincter

The distal 2 to 5 cm of esophagus acts like a sphincter and it is called lower esophageal sphincter. It is constricted always. When bolus enters this part of the esophagus, this sphincter relaxes so that the contents enter the stomach. After the entry of bolus into the stomach, the sphincter constricts and closes the lower end of esophagus. The relaxation and constriction of sphincter occur in sequence with the arrival of peristaltic contractions of esophagus.

■ DEGLUTITION REFLEX

Though the beginning of swallowing is a voluntary act, later it becomes involuntary and is carried out by a reflex action called deglutition reflex. It occurs during the pharyngeal and esophageal stages.

Stimulus

When the bolus enters the oropharyngeal region, the receptors present in this region are stimulated.

Afferent Fibers

Afferent impulses from the oropharyngeal receptors pass via the glossopharyngeal nerve fibers to the deglutition center.

Center

The deglutition center is at the floor of the fourth ventricle in medulla oblongata of brain.

Efferent Fibers

The impulses from deglutition center travel through glossopharyngeal and vagus nerves

(parasympathetic motor fibers) and reach soft palate, pharynx and esophagus. The glossopharyngeal nerve is concerned with pharyngeal stage of swallowing. The vagus nerve is concerned with esophageal stage.

Response

The reflex causes upward movement of soft palate to close nasopharynx and upward movement of larynx to close respiratory passage so that bolus enters the esophagus. Now the peristalsis occurs in esophagus pushing the bolus into stomach.

■ MOVEMENTS OF STOMACH

The movements of the stomach are:

1. Hunger contractions
2. Receptive relaxation
3. Peristalsis.

■ HUNGER CONTRACTIONS

Hunger contractions are the movements of empty stomach. These contractions are related to the sensations of hunger.

Hunger contractions are the peristaltic waves superimposed over the contractions of gastric smooth muscle as a whole. This type of peristaltic waves is different from the digestive peristaltic contractions. The digestive peristaltic contractions usually occur in body and pyloric parts of the stomach. But, the peristaltic contractions of empty stomach involve the entire stomach.

■ RECEPTIVE RELAXATION

Receptive relaxation is the relaxation of the upper portion of the stomach when bolus enters the stomach from esophagus. It involves the fundus and upper part of the body of stomach. Its significance is to accommodate the food easily without much increase in pressure inside the stomach. This process is called accommodation of stomach.

■ PERISTALSIS OF STOMACH

When the food enters the stomach, the peristaltic contraction or peristaltic wave appears with a frequency of 3 per minute. It starts from the lower part of the body of stomach, passes through the pylorus till the pyloric sphincter.

Initially, the contraction appears as a slight indentation on the greater and lesser curvatures and travels towards pylorus. The contraction becomes deeper while traveling. Finally, it ends with the constriction of pyloric sphincter. Some of the waves disappear before reaching the sphincter. Each peristaltic wave takes about one minute to travel from the point of origin to the point of ending.

This type of peristaltic contraction is called digestive peristalsis because it is responsible for the grinding of food particles and mixing them with gastric juice for digestive activities.

■ FILLING AND EMPTYING OF STOMACH

■ FILLING OF STOMACH

While taking food, the food arranges itself in the stomach in different layers. The first eaten food is placed against the greater curvature in the fundus and body of the stomach. The successive layers of food particles lie nearer the lesser curvature until the last portion of food eaten lies near the upper end of lesser curvature adjacent to cardiac sphincter.

■ EMPTYING OF STOMACH

Gastric emptying is the process by which the chyme from stomach is emptied into intestine. The food that is swallowed enters the stomach and remains there for about 3 hours. During this period, digestion takes place. The partly digested food becomes the chyme.

Chyme

Chyme is the semisolid mass of partially digested food that is formed in the stomach. It is acidic in

nature. The acid chyme is emptied from stomach into the intestine slowly with the help of peristaltic contractions. It takes about 3 to 4 hours for emptying of the chyme. This slow emptying is necessary to facilitate the final digestion and maximum (about 80%) absorption of the digested food materials from small intestine. Gastric emptying occurs due to the peristaltic waves in the body and pyloric part of the stomach and simultaneous relaxation of pyloric sphincter.

The gastric emptying is influenced by various factors of the gastric content and food. The factors which affect gastric emptying are:

1. Volume of Gastric Content

Gastric emptying is directly proportional to the volume. If the content of stomach is more, a large amount is emptied into the intestine rapidly.

2. Consistency of Gastric Content

Emptying of the stomach depends upon the consistency (degree of density) of the contents. Liquids, particularly the inert liquids like water (which do not stimulate the stomach) leave the stomach rapidly. Solids move out of stomach only after being converted into fluid or semifluid. Undigested solid particles are not easily emptied.

3. Chemical Composition

The chemical composition of the food also plays an important role in the emptying of the stomach. Carbohydrates are emptied rapidly than the proteins. Proteins are emptied rapidly than the fats.

4. pH of the Gastric Content

Gastric emptying is directly proportional to pH of the chyme.

5. Osmolar Concentration of Gastric Content

The gastric content, which is isotonic to blood, leaves the stomach rapidly than the hypotonic or hypertonic content.

■ VOMITING

Vomiting or emesis is the abnormal emptying of stomach and upper part of intestine through esophagus and mouth.

■ CAUSES OF VOMITING

1. The presence of irritating contents in GI tract
2. Mechanical stimulation of pharynx
3. Pregnancy
4. Excess intake of alcohol
5. Nauseating sight, odor or taste
6. Unusual stimulation of labyrinthine apparatus as in the case of sea sickness, air sickness, car sickness or swinging
7. Abnormal stimulation of sensory receptors in other organs like kidney, heart, semicircular canals or uterus
8. Drugs like antibiotics, opiates, etc.
9. Any GI disorder
10. Acute infection like urinary tract infection, influenza, etc.
11. Metabolic disturbances like carbohydrate starvation and ketosis (pregnancy), uremia, ketoacidosis (diabetes) and hypercalcemia.

■ MECHANISM OF VOMITING

Nausea

Vomiting is always preceded by nausea. Nausea is unpleasant sensation which induces the desire for vomiting. It is characterized by secretion of large amount of saliva containing more amount of mucus.

Retching

Strong involuntary movements in the GI tract start even before actual vomiting and intensify the feeling of vomiting. This condition is called retching (try to vomit). And, vomiting occurs few minutes after this.

Act of Vomiting

Act of vomiting involves series of movements that takes place in GI tract.

The sequence of events:

1. Beginning of antiperistalsis which runs from ileum towards the mouth through the intestine pushing the intestinal contents into the stomach within few minutes
2. Deep inspiration followed by temporary cessation of breathing
3. Closure of glottis
4. Upward and forward movement of larynx and hyoid bone
5. Elevation of soft palate
6. Contraction of diaphragm and abdominal muscles with a characteristic jerk resulting in elevation of intra-abdominal pressure
7. Compression of the stomach between diaphragm and abdominal wall leading to rise in intragastric pressure
8. Simultaneous relaxation of lower esophageal sphincter, esophagus and upper esophageal sphincter
9. Forceful expulsion of gastric contents (vomitus) through esophagus, pharynx and mouth.

All the movements during the act of vomiting throw the vomitus (materials ejected during vomiting) to the exterior through mouth. Some of the movements play important roles by preventing the entry of vomitus through other routes and thereby prevent the adverse effect of the vomitus on many structures.

Such movements are:

1. Closure of glottis and cessation of breathing prevent entry of vomitus into the lungs
2. Elevation of soft palate prevents entry of vomitus into the nasopharynx
3. Larynx and hyoid bone move upward and forward and are placed in this position rigidly. This causes the dilatation of throat which allows free exit of vomitus.

■ VOMITING REFLEX

Vomiting is a reflex act. The sensory impulses for vomiting arise from the irritated or distended part of GI tract or other organs and are transmitted to the vomiting center through vagus and sympathetic fibers.

The vomiting center is situated bilaterally in medulla oblongata near the nucleus tractus solitarius.

Motor impulses from the vomiting center are transmitted through V, VII, IX, X and XII cranial nerves to the upper part of GI tract; and through spinal nerves to diaphragm and abdominal muscles.

■ MOVEMENTS OF SMALL INTESTINE

The movements of small intestine are essential for mixing the chyme with digestive juices, propulsion of food and absorption.

Four types of movements occur in small intestine:

1. Mixing movements:
 - i. Segmentation movements
 - ii. Pendular movements
2. Propulsive movements:
 - i. Peristaltic movements
 - ii. Peristaltic rush
3. Peristalsis in fasting – Migrating motor complex
4. Movements of villi.

■ MIXING MOVEMENTS

The mixing movements of small intestine are responsible for proper mixing of chyme with digestive juices like pancreatic juice, bile and intestinal juice. The mixing movements of small intestine are segmentation contractions and pendular movements.

Segmentation Contractions

The segmentation contractions are the common type of movements of small intestine, which occur regularly or irregularly but in a rhythmic fashion. So, these movements are also called rhythmic segmentation contractions.

The contractions occur at regularly spaced intervals along a section of intestine. The segment of the intestine involved in each contraction is about 1 to 5 cm long. The segments of intestine in between the contracted segments are relaxed. The length of the relaxed

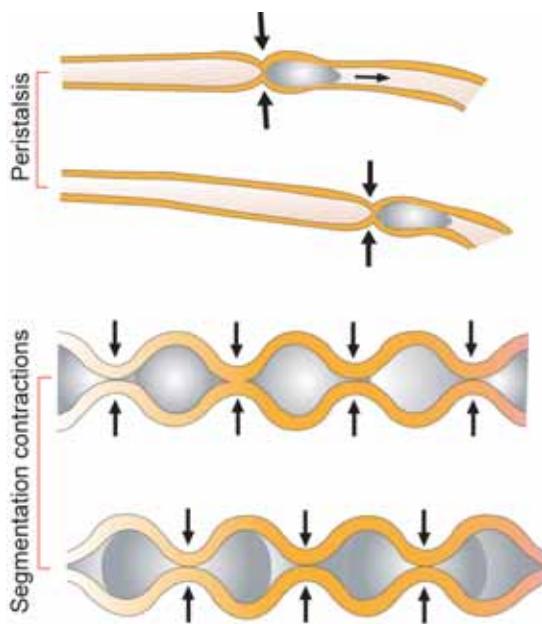


FIGURE 33-2: Movements of small intestine

segments is same as that of the contracted segments. These alternate segments of contraction and relaxation give appearance of rings resembling the chain of sausages.

After sometime, the contracted segments are relaxed and the relaxed segments are contracted (Fig. 33-2). Therefore, the segmentation contractions chop the chyme many times. This helps in mixing of chyme with digestive juices.

Pendular Movement

Pendular movement is the sweeping movement of small intestine resembling the movements of pendulum of clock. Small portions of intestine (loops) sweep forward and backward or upward and downward. It is a type of mixing movement noticed only by close observation.

It helps in mixing of chyme with digestive juices.

■ PROPULSIVE MOVEMENTS

Propulsive movements are the movements of small intestine which push the chyme in the aboral direction through intestine. The propulsive

movements are peristaltic movements and peristaltic rush.

Peristaltic Movements

Peristalsis is defined as the wave of contraction followed by wave of relaxation, which travels in aboral direction. The stimulation of smooth muscles of intestine initiates the peristalsis. It travels from point of stimulation in both directions. But under normal conditions, the progress of contraction in an oral direction is inhibited quickly and the contractions disappear. Only the contraction that travels in an aboral direction persists.

Peristaltic Rush

Sometimes, the small intestine shows a powerful peristaltic contraction. It is caused by excessive irritation of intestinal mucosa or extreme distention of the intestine. This type of powerful contraction begins in duodenum and passes through entire length of small intestine and reaches the ileocecal valve within few minutes. This is called peristaltic rush or rush waves.

The peristaltic rush sweeps the contents of intestine into the colon. Thus, it relieves the small intestine off either irritants or excessive distention.

■ PERISTALSIS IN FASTING – MIGRATING MOTOR COMPLEX

It is a type of peristaltic contraction, which occurs in stomach and small intestine during the periods of fasting for several hours. It is different from the regular peristalsis because, a large portion of stomach or intestine is involved in the contraction. The contraction extends to about 20 to 30 cm of the stomach or intestine. This type of movement occurs once in every 1½ to 2 hours.

It starts as a moderately active peristalsis in the body of stomach and runs through the entire length of small intestine. It travels at a velocity of 6 to 12 cm/min. Thus, it takes about 10 minutes to reach the colon after taking origin from stomach.

Significance of Peristalsis in Fasting

The migrating motor complex sweeps the excess digestive secretions into the colon and prevents the accumulation of the secretions in stomach and intestine. It also sweeps the residual indigested materials into colon.

■ MOVEMENTS OF VILLI

The intestinal villi also shows movements simultaneously along with intestinal movements. It is because of the extension of smooth muscle fibers of the intestinal wall into the villi.

The movements of villi are shortening and elongation, which occur alternatively and help in emptying lymph from the central lacteal into the lymphatic system. The surface area of villi is increased during elongation. This helps absorption of digested food particles from the lumen of intestine.

Movements of villi are caused by local nervous reflexes, which are initiated by the presence of chyme in small intestine.

■ MOVEMENTS OF LARGE INTESTINE

Large intestine shows sluggish movements. Still, these movements are important for mixing, propulsive and absorptive functions. Large intestine shows two types of movements:

1. Mixing movements – Segmentation contractions
2. Propulsive movements – Mass peristalsis.

■ MIXING MOVEMENTS – SEGMENTATION CONTRACTIONS

Large circular constrictions, which appear in the colon, are called mixing segmentation contractions. The contractions occur at regular distance in colon. The length of the portion of colon involved in each contraction is nearly about 2.5 cm.

■ PROPULSIVE MOVEMENTS – MASS PERISTALSIS

Mass peristalsis or mass movement propels the feces from colon towards anus. Usually, this movement occurs only a few times every day.

The duration of the mass movement is about 10 minutes in the morning before or after breakfast. This is because of the neurogenic factors like gastrocolic reflex (see below) and parasympathetic stimulation.

■ DEFECATION

Voiding of feces is known as defecation. Feces is formed in the large intestine and stored in sigmoid colon. By the influence of an appropriate stimulus, it is expelled out through the anus. This is prevented by tonic constriction of anal sphincters in the absence of the stimulus.

■ DEFECATION REFLEX

The mass movement drives the feces into sigmoid or pelvic colon. In the sigmoid colon the feces is stored. The desire for defecation occurs when some feces enters rectum due to the mass movement. Usually, the desire for defecation is elicited by an increase in the intrarectal pressure to about 20 to 25 cm H₂O.

The usual stimulus for defecation is intake of liquid like coffee or tea or water. But it differs from person to person.

Act of Defecation

The act of defecation is preceded by voluntary efforts like assuming an appropriate posture, voluntary relaxation of external sphincter and the compression of abdominal contents by voluntary contraction of abdominal muscles.

Usually, the rectum is empty. During the development of mass movement, the feces is pushed into rectum and the defecation reflex is initiated. The process of defecation involves the contraction of rectum and relaxation of internal and external anal sphincters.

The internal anal sphincter is made up of smooth muscle and it is innervated by parasympathetic nerve fibers via pelvic nerve. The external anal sphincter is composed of skeletal muscle and it is controlled by somatic nerve fibers, which pass through pudendal nerve. The pudendal nerve always keeps the external sphincter constricted and the sphincter can relax only when the pudendal nerve is inhibited.

Gastrocolic Reflex

Gastrocolic reflex is the contraction of rectum followed by desire for defecation caused by distention of stomach by food. It is mediated by intrinsic nerve fibers of GI tract.

This reflex causes only a weak contraction of rectum. But, it initiates defecation reflex.

■ PATHWAY FOR DEFECATION REFLEX

When rectum is distended due to the entry of feces by mass movement, sensory nerve endings are stimulated. The impulses from the nerve endings are transmitted via afferent fibers of pelvic nerve to the defecation center situated in sacral segments (center) of spinal cord.

The center, in turn, sends motor impulses to the descending colon, sigmoid colon and rectum via efferent nerve fibers of pelvic nerve. The motor impulses cause strong contraction of descending colon, sigmoid colon and rectum and relaxation of internal sphincter.

Simultaneously, voluntary relaxation of external sphincter occurs. It is due to the inhibition of pudendal nerve by impulses arising from cerebral cortex (Fig. 33-3).

Failure of voiding of feces is called constipation (Chapter 32).

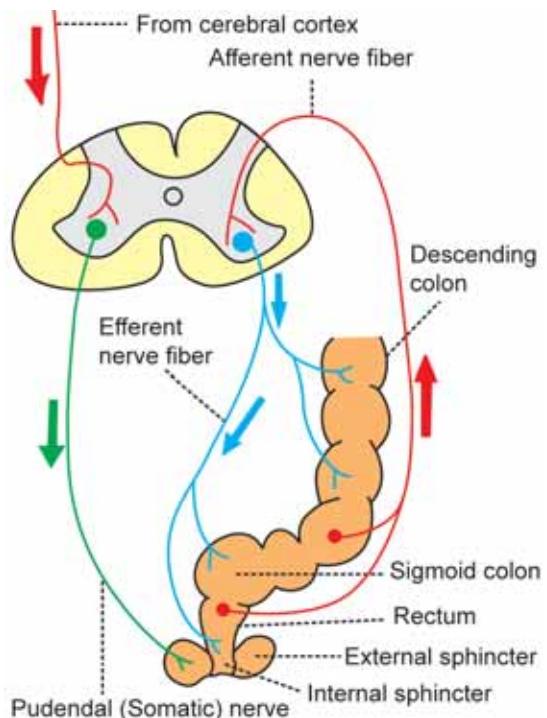


FIGURE 33-3: Defecation reflex. Afferent and efferent fibers of the reflex pass through pelvic (parasympathetic) nerve. Voluntary control of defecation is by pudendal (somatic) nerve. Defecation center is in the sacral segments of spinal cord

QUESTIONS IN DIGESTIVE SYSTEM

■ LONG QUESTIONS

1. What are the different types of salivary glands? Describe the composition, functions and regulation of secretion of saliva.
2. Describe the different phases of gastric secretion with experimental evidences.
3. Explain the composition, functions and regulation of secretion of pancreatic juice.
4. Describe the composition, functions and regulation of secretion of bile. Enumerate the differences between the liver bile and gallbladder bile. Add a note on enterohepatic circulation.

■ SHORT QUESTIONS

1. Properties and composition of saliva.
2. Functions of saliva.
3. Nerve supply to salivary glands.
4. Gastric glands.
5. Functions of stomach.
6. Properties and composition of gastric juice.
7. Functions of gastric juice
8. Mechanism of secretion of hydrochloric acid in stomach.
9. Pavlov's pouch.
10. Sham feeding.
11. Cephalic phase of gastric secretion.
12. Gastrin.
13. Peptic ulcer.

14. Properties and composition of pancreatic juice.
15. Functions of pancreatic juice.
16. Regulation of exocrine function of pancreas.
17. Steatorrhea.
18. Secretin.
19. Cholecystokinin.
20. Composition of bile.
21. Functions of bile.
22. Bile salts/bile pigments.
23. Enterohepatic circulation.
24. Functions of liver.
25. Differences between liver bile and gallbladder bile.
26. Functions of gallbladder.
27. Jaundice.
28. Succus entericus.
29. Functions of small intestine.
30. Functions of large intestine.
31. Mastication.
32. Swallowing.
33. Movements of stomach.
34. Filling and emptying of stomach.
35. Vomiting.
36. Movements of small intestine.
37. Movements of large intestine.
38. Defecation.
39. Constipation.
40. Diarrhea.

SECTION 5

Renal Physiology and Skin

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- INTRODUCTION
- FUNCTIONS OF KIDNEY
- FUNCTIONAL ANATOMY OF KIDNEY

■ INTRODUCTION

Excretion is the process by which the unwanted substances and metabolic wastes are eliminated from the body.

Although various organs such as GI tract, liver, skin and lungs are involved in removal of wastes from the body, their excretory capacity is limited. But, the renal system or urinary system has maximum capacity of excretory function.

Renal system includes:

1. A pair of kidneys
2. Ureters
3. Urinary bladder
4. Urethra.

Kidneys produce the urine. Ureters transport the urine to urinary bladder. Urinary bladder stores urine until it is voided (emptied). Urine is voided from bladder through urethra (Fig. 34-1).

■ FUNCTIONS OF KIDNEY

Kidneys perform several vital functions besides formation of urine. By excreting urine, kidneys play the principal role in homeostasis. Thus, the functions of kidneys are:

■ 1. ROLE IN HOMEOSTASIS

The primary function of kidneys is homeostasis. It is accomplished by the formation of urine.

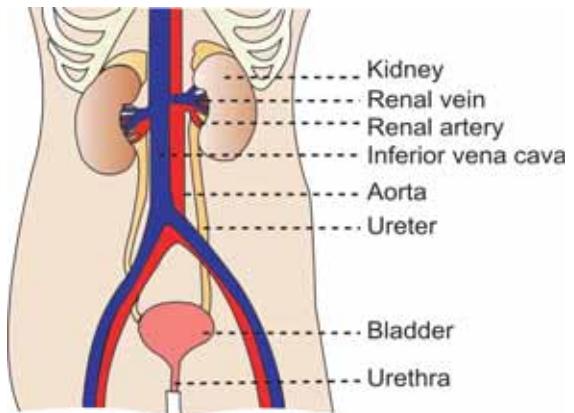


FIGURE 34-1: Urinary system

During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis such as:

i. Excretion of Waste Products

Kidneys excrete the unwanted waste products which are formed during metabolic activities:

- a. Urea – end product of amino acid metabolism
- b. Uric acid – end product of nucleic acid metabolism
- c. Creatinine – end product of metabolism in muscles
- d. Bilirubin – end product of hemoglobin degradation

- e. Products of metabolism of other substances
- f. Harmful foreign chemical substances like toxins, drugs, heavy metals, pesticides, etc.

ii. Maintenance of Water Balance

Kidneys maintain the water balance in the body by conserving water when it is decreased and excreting water when it is excess in the body. Refer Chapter 4 for details.

iii. Maintenance of Electrolyte Balance

Maintenance of electrolyte balance, especially sodium is in relation to water balance. Kidneys retain sodium if the osmolarity of body water decreases and eliminate sodium when osmolarity increases.

iv. Maintenance of Acid–Base Balance

The pH of the blood and body fluids should be maintained within narrow range for healthy living. It is achieved by the function of kidneys (Chapter 39). Body is under constant threat to develop acidosis, because of production of lot of acids during metabolic activities. However, it is prevented by kidneys, lungs and blood buffers, which eliminate these acids. Among these organs, kidneys play major role in preventing acidosis.

■ 2. HEMOPOIETIC FUNCTION

Kidneys stimulate the production of erythrocytes by secreting erythropoietin. Erythropoietin is the important stimulating factor for erythropoiesis (Chapter 8). Kidney also secretes another factor called thrombopoietin, which stimulates the production of thrombocytes (Chapter 14).

■ 3. ENDOCRINE FUNCTION

Kidneys secrete many hormonal substances in addition to erythropoietin and thrombopoietin (Chapter 51). The hormones secreted by kidneys are:

- i. Erythropoietin
- ii. Thrombopoietin
- iii. Renin

- iv. 1, 25-dihydroxycholecalciferol (calcitriol)
- v. Prostaglandins.

■ 4. REGULATION OF BLOOD PRESSURE

Kidneys play an important role in long-term regulation of arterial blood pressure (Chapter 65) by two ways: by regulating ECF volume and through renin-angiotensin mechanism.

■ 5. REGULATION OF BLOOD CALCIUM LEVEL

Kidneys play a role in the regulation of blood calcium level by activating 1, 25-dihydroxycholecalciferol into vitamin D. Vitamin D is necessary for the absorption of calcium from intestine (Chapter 51).

■ FUNCTIONAL ANATOMY OF KIDNEY

Kidney is a compound tubular gland covered by a connective tissue capsule. There is a depression on the medial border of kidney called hilum, through which renal artery, renal veins, nerves and ureter pass.

■ DIFFERENT LAYERS OF KIDNEY

The components of kidney are arranged in three layers (Fig. 34-2).

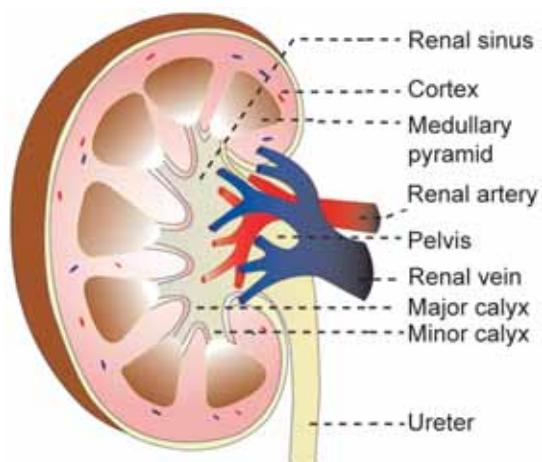


FIGURE 34-2: Longitudinal section of kidney

1. Outer cortex
2. Inner medulla
3. Renal sinus.

1. Outer Cortex

Cortex is dark and granular in appearance. It contains renal corpuscles and convoluted tubules. At intervals, cortical tissue penetrates medulla in the form of columns, which are called renal columns or columns of Bertini.

2. Inner Medulla

Medulla contains tubular and vascular structures arranged in parallel radial lines. It is divided into 8 to 18 medullary or Malpighian pyramids.

3. Renal Sinus

Renal sinus consists of the following structures:

- i. Upper expanded part of ureter called renal pelvis

- ii. Subdivisions of pelvis – 2 or 3 major calyces and about 8 minor calyces
- iii. Branches of nerves and arteries and tributaries of veins
- iv. Loose connective tissues and fat.

■ PARENCHYMA OF KIDNEY

Parenchyma of kidney is made up of tubular structures called uriniferous tubules. The uriniferous tubules are of two types:

1. Terminal or secretary tubules called nephrons, which are concerned with formation of urine
2. Collecting ducts or tubules which are concerned with transport of urine from nephrons to pelvis of ureter.

The collecting ducts unite to form ducts of Belini, which open into minor calyces through papilla. Other details are given in Chapter 35.

35

Nephron and Juxtaglomerular Apparatus

- INTRODUCTION
- RENAL CORPUSCLE
 - SITUATION OF RENAL CORPUSCLE AND TYPES OF NEPHRON
 - STRUCTURE OF RENAL CORPUSCLE
- TUBULAR PORTION OF NEPHRON
 - PROXIMAL CONVOLUTED TUBULE
 - LOOP OF HENLE
 - DISTAL CONVOLUTED TUBULE
- COLLECTING DUCT
- JUXTAGLOMERULAR APPARATUS
 - DEFINITION
 - STRUCTURE
 - FUNCTIONS

■ INTRODUCTION

Nephron is defined as the structural and functional unit of kidney. Each kidney consists of 1 to 1.3 millions of nephrons. The number of nephrons decreases in old age.

Each nephron is formed by two parts (Fig. 35-1):

1. A blind end called renal corpuscle or Malpighian corpuscle
2. A tubular portion called renal tubule.

■ RENAL CORPUSCLE

The renal corpuscle is also known as Malpighian corpuscle. It is a spheroidal and slightly flattened structure with a diameter of about $200\ \mu$. The function of the renal corpuscle is the filtration of blood which forms the first phase of urine formation.

■ SITUATION OF RENAL CORPUSCLE AND TYPES OF NEPHRON

Renal corpuscle is situated in the cortex of the kidney either near the periphery or near the medulla. Based on the situation of renal corpuscle, the nephrons are classified into two types:

1. Cortical nephrons or superficial nephrons
2. Juxtamedullary nephrons.

1. *Cortical Nephrons*

Cortical nephrons are the nephrons, which have their corpuscles in the outer cortex of the kidney near the periphery (Fig. 35-2). In human kidneys 85% nephrons are cortical nephrons.

2. *Juxtamedullary Nephrons*

Juxtamedullary nephrons are the nephrons which have their corpuscles in the inner cortex

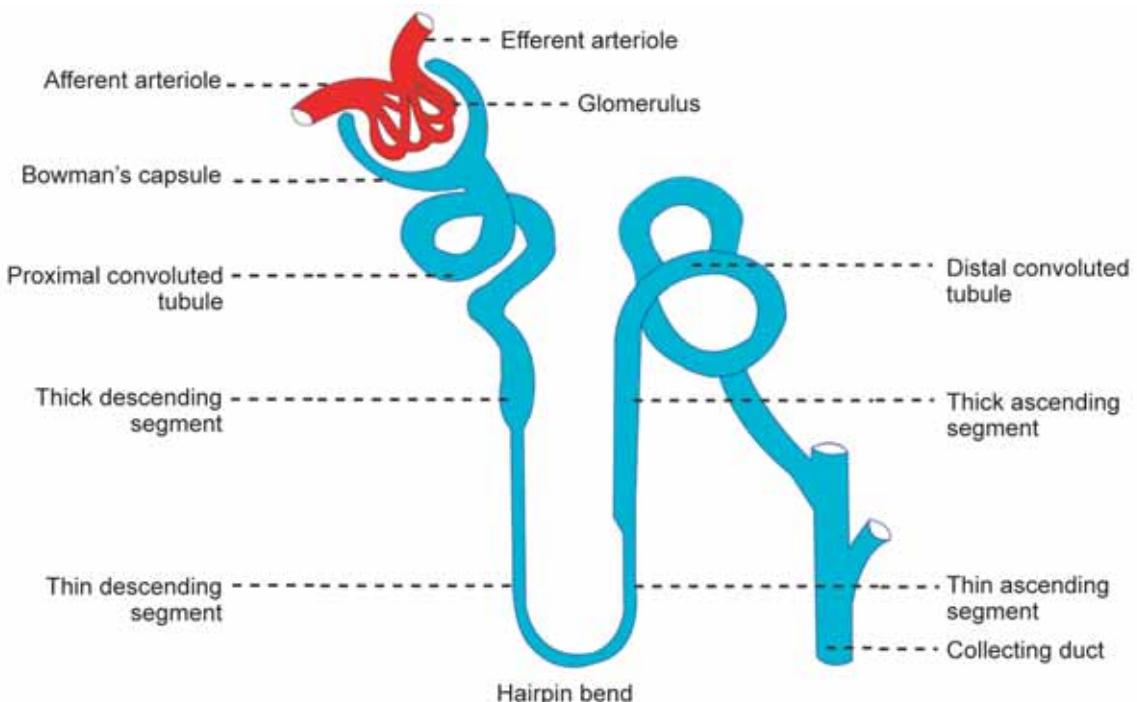


FIGURE 35-1: Structure of nephron

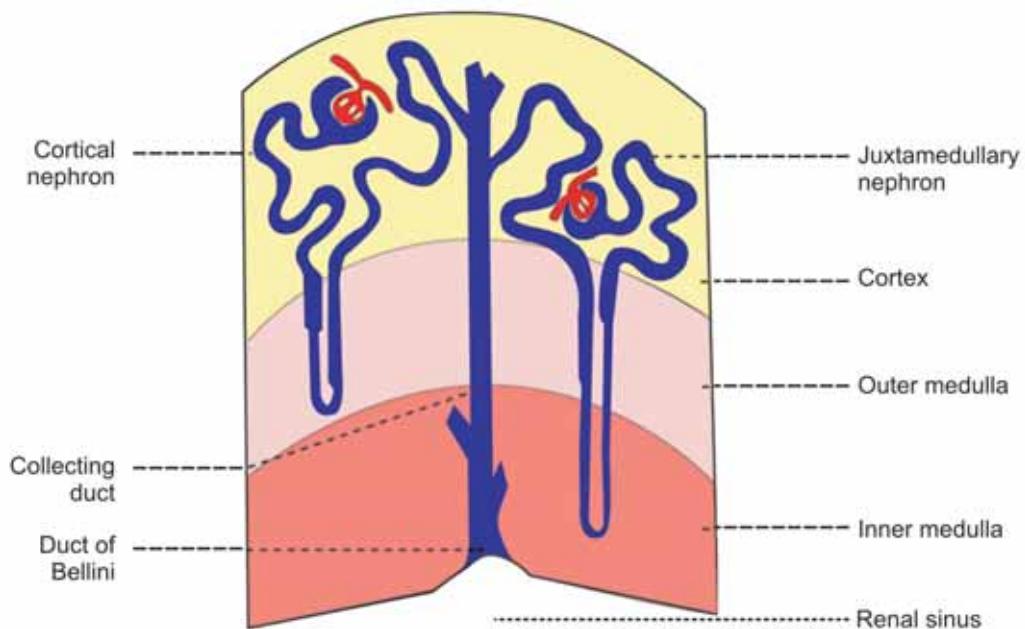


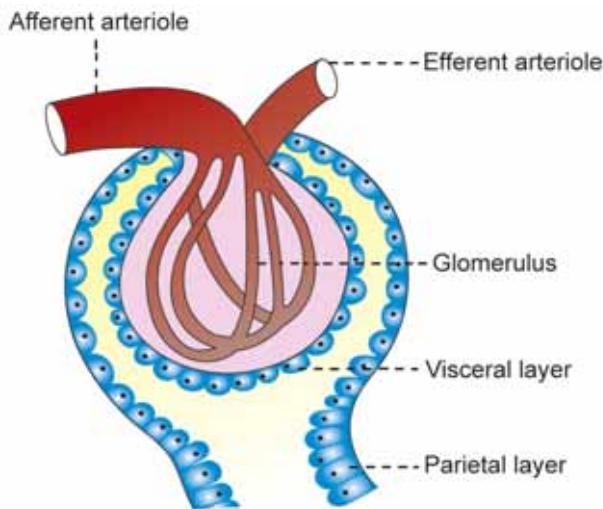
FIGURE 35-2: Types of nephron

near medulla or corticomedullary junction (Fig. 35-2).

The features of the two types of nephrons are given in Table 35-1.

TABLE 35-1: Features of two types of nephron

Features	Cortical nephron	Juxtamedullary nephrons
Situation of renal corpuscle	Outer cortex near the periphery	Inner cortex near medulla
Loop of Henle	Short	Long
	Hairpin bend penetrates only up to outer zone of medulla	Hairpin bend penetrates up to the tip of papilla
Blood supply to tubule	Peritubular capillaries	Vasa recta
Function	Formation of urine	Mainly the concentration of urine and formation of urine

**FIGURE 35-3:** Renal corpuscle

■ STRUCTURE OF RENAL CORPUSCLE

The renal corpuscle is formed by two portions:

1. Glomerulus
2. Bowman's capsule

1. Glomerulus

Glomerulus is a tuft of capillaries enclosed by Bowman's capsule. These capillaries are disposed between afferent arteriole and efferent arteriole. Thus, the vascular system in the glomerulus is purely arterial (Fig. 35-3).

The glomerular capillaries arise from the afferent arteriole. After entering the Bowman's capsule, the afferent arteriole divides into many small capillaries. These small capillaries are arranged in irregular loops and form anastomosis. All the smaller capillaries finally reunite to form the efferent arteriole which leaves the Bowman's capsule.

The diameter of the efferent arteriole is less than that of afferent arteriole. This difference in diameter has functional significance.

The capillaries are made up of single layer of endothelial cells which are attached to a basement membrane. The endothelium has many pores called fenestra or filtration pores. The diameter of each pore is 0.1μ . The presence of the fenestra is the evidence of the filtration function of the glomerulus.

2. Bowman's Capsule

Bowman's capsule encloses the glomerulus. The structure of Bowman's capsule is like a funnel with filter paper. Its diameter is 200μ .

It is formed by two layers:

1. The inner visceral layer
2. The outer parietal layer.

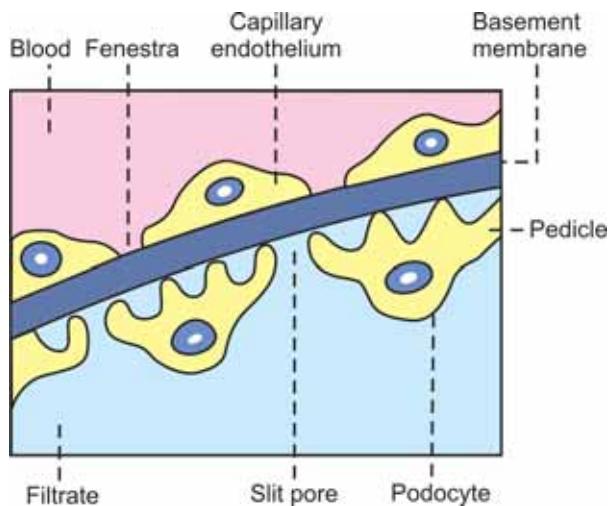


FIGURE 35-4: Filtering membrane in renal corpuscle. It is formed by capillary endothelium on one side (pink) and visceral layer of Bowman's capsule (light blue) on the other side

Visceral layer covers the glomerular capillaries. It is continued as the parietal layer at the visceral pole. The parietal layer is continued with the wall of the tubular portion of nephron. The cleft like space between the visceral and parietal layers is continued as the lumen of the tubular portion.

Histology

Both the layers of Bowman's capsule are composed of a single layer of flattened epithelial cells resting on a basement membrane. The basement membrane of the visceral layer fuses with the basement membrane of glomerular capillaries on which the capillary endothelial cells are arranged. Thus, the basement membranes, which are fused together, form the separation between the glomerular capillary endothelium and the epithelium of visceral layer of Bowman's capsule.

The epithelial cells of the visceral layer fuse with the basement membrane but the fusion is not complete. Each cell is connected with the basement membrane by cytoplasmic extensions of epithelial cells called pedicles or feet. These pedicles are arranged in an interdigitating manner leaving small cleft like spaces in between. The

cleft like space is called slit pore. The epithelial cells with pedicles are called podocytes (Fig. 35-4).

■ TUBULAR PORTION OF NEPHRON

The tubular portion of nephron is the continuation of Bowman's capsule. It is made up of three parts:

1. The proximal convoluted tubule
2. Loop of Henle
3. The distal convoluted tubule

■ PROXIMAL CONVOLUTED TUBULE

It is the coiled portion arising from Bowman's capsule. It is situated in the cortex. It is continued as descending limb of loop of Henle. Length of proximal convoluted tubule is 14 mm and the diameter is 55 μ .

Histology

Proximal convoluted tubule is formed by single layer of cuboidal epithelial cells. The special feature of these cells is the presence of hair like projections directed towards the lumen of the tubule. Because of the presence of these projections, the epithelial cells are called brush bordered cells.

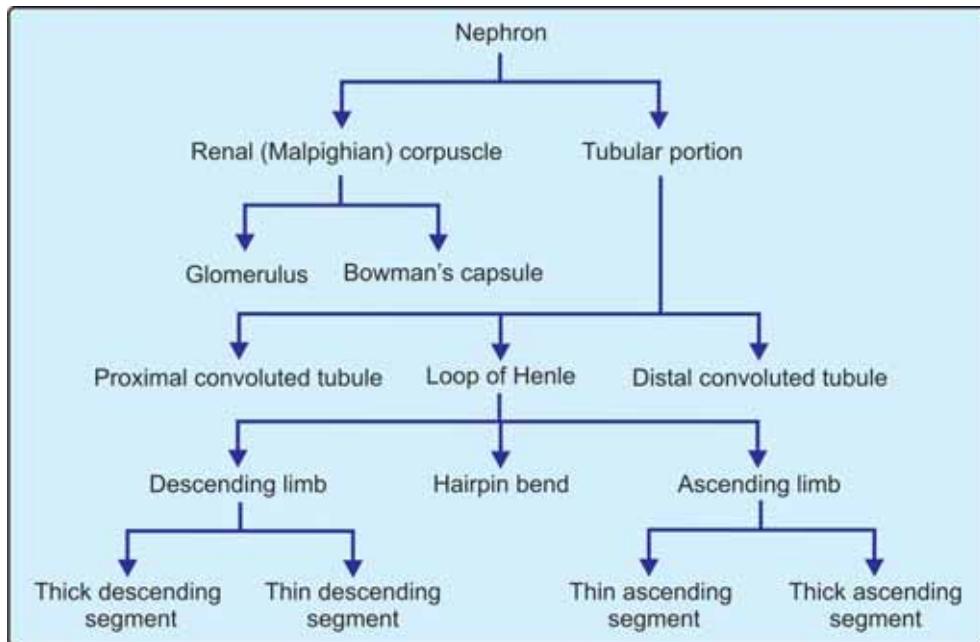


FIGURE 35-5: Parts of nephron

■ LOOP OF HENLE

Loop of Henle consists of:

- Descending limb
- Hairpin bend
- Ascending limb

Descending Limb

Descending limb of loop of Henle is made up of thick descending segment and thin descending segment. The thick descending segment is the direct continuation of the proximal convoluted tubule. It descends down into medulla. It has a length of 6 mm and a diameter of 55 μ . The thick descending segment of Henle's loop is continued as thin descending segment (Fig. 35-5).

Hairpin Bend

The thin descending segment is continued as hairpin bend of the loop. The hairpin bend is continued as the ascending segment of loop of Henle.

Ascending Limb

Ascending limb of Henle's loop has two parts, thin ascending segment and thick ascending segment. Thin ascending segment is the continuation of hairpin bend.

The total length of thin descending segment, hairpin bend and thin ascending segment of Henle's loop 10 to 15 mm and the diameter is 15 μ .

The thin ascending segment is continued as thick ascending segment. It is about 9 mm long with a diameter of 30 μ . Thick ascending segment ascends to the cortex and continues as distal convoluted tubule.

Length and Extent of Loop of Henle

The length and the extent of the loop of Henle vary in different nephrons.

- In cortical nephrons, it is short and the hairpin bend penetrates only up to outer medulla

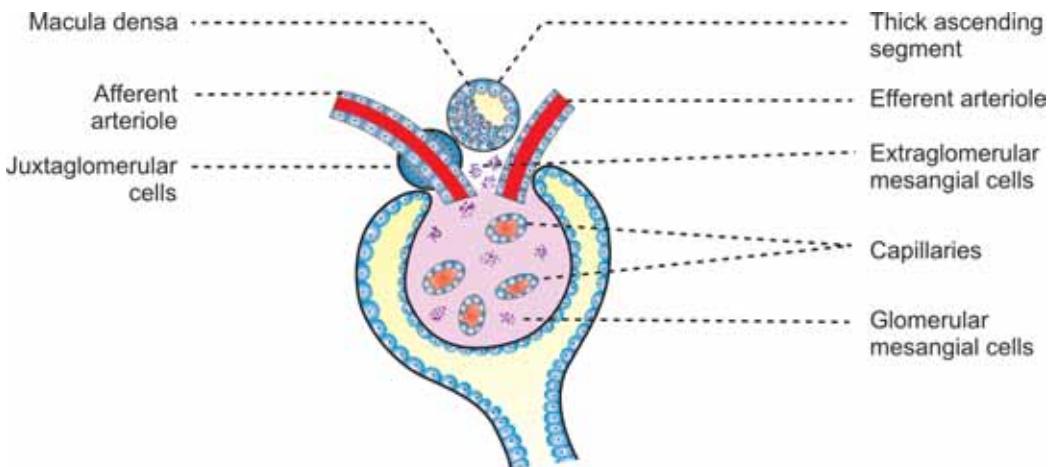


FIGURE 35-6: Juxtaglomerular apparatus

2. In juxtapamedullary nephrons, this is long and the hairpin bend extends deep into the inner medulla. In some nephrons it even runs up to the papilla.

Histology

Thick descending segment is formed by brush bordered cuboidal epithelial cells.

Thin descending segment, hairpin bend and thin ascending segment are lined by flattened epithelial cells without brush border. Thick ascending segment is lined by cuboidal epithelial cells without brush border.

The terminal portion of thick ascending segment which runs between the afferent and efferent arterioles of the same nephrons forms the macula densa. Macula densa is the part of juxtaglomerular apparatus (See below).

DISTAL CONVOLUTED TUBULE

It is the continuation of thick ascending segment and occupies the cortex of kidney. It is continued as collecting duct. The length of the distal convoluted tubule is 14.5 to 15 mm. It has a diameter of 22 to 50 μ .

Histology

Distal convoluted tubule is lined by single layer of cuboidal epithelial cells without brush border.

The epithelial cells in distal convoluted tubule are called intercalated cells (I cells).

COLLECTING DUCT

The distal convoluted tubule continues as the initial or arched collecting duct, which is in cortex. The lower part of the collecting duct lies in medulla. Seven to ten initial collecting ducts unite to form the straight collecting duct, which passes through medulla.

The length of the collecting duct is 20 to 22 mm. The diameter of collecting duct varies between 40 and 200 μ .

Histology

The collecting duct is formed by cuboidal or columnar epithelial cells. The epithelial cells of collecting duct are of two types:

1. The principal or P cells
2. Intercalated or I cells.

Passage of Urine

At the inner zone of medulla, the straight collecting ducts from each medullary pyramid unite to form papillary ducts or ducts of Bellini, which open into the papilla. Papilla collects the urine from each medullary pyramid and drains into a minor calyx. Three or four minor calyces unite to form one major calyx. Each kidney has

got about 8 minor calyces and 2 to 3 major calyces. The major calyces open into the pelvis of the ureter. The pelvis is the expanded portion of ureter present in the renal sinus. Through ureter, urine enters the urinary bladder.

■ JUXTAGLOMERULAR APPARATUS

■ DEFINITION

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

■ STRUCTURE OF JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus is formed by three different structures (Fig. 35-6):

1. Macula densa
2. Extraglomerular mesangial cells
3. Juxtaglomerular cells.

1. *Macula Densa*

Macula densa is the terminal portion of thick ascending segment of Henle's loop that runs in between afferent and efferent arterioles of the same nephron. Actually, it is very close to afferent arteriole. In this part of thick ascending segment, the cuboidal epithelial cells are tightly packed.

2. *Extraglomerular Mesangial Cells*

These cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells.

Glomerular mesangial cells

Glomerular mesangial cells or intraglomerular mesangial cells are situated in between the glomerular capillaries and form a cellular network which supports the capillary loops. These cells are contractile in nature and play an important role in regulating the glomerular filtration.

The glomerular mesangial cells are also phagocytic and secrete matrix of glomerular interstitium, prostaglandins and cytokines.

3. *Juxtaglomerular Cells*

Juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman's capsule. This part of the afferent arteriole is thickened like a cuff and it is called polar cushion or polkissen. Because of the presence of secretory granules in their cytoplasm, the juxtaglomerular cells are also called granular cells.

■ FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

The primary function of juxtaglomerular apparatus is the secretion of hormonal substances. It also regulates the glomerular blood flow and glomerular filtration rate.

1. *Secretion of Renin*

The juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin – angiotensin system which is a hormone system that plays an important role in the maintenance of blood pressure (Chapter 65).

Renin–Angiotensin system

When renin is released into the blood, it acts on angiotensinogen and converts it into angiotensin I. Angiotensin I is converted into angiotensin II by the activity of angiotensin converting enzyme (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs.

Angiotensin II has a short half-life of about 1-2 minutes. Then it is degraded into angiotensin III by angiotensinases which are present in RBCs and vascular beds in many tissues. Finally, angiotensin III is converted into angiotensin IV.

Actions of angiotensins

Angiotensin I

It is physiologically inactive and serves only as the precursor of angiotensin II.

Angiotensin II

Angiotensin II is the most active form. Its actions are:

1. Angiotensin II increases arterial blood pressure by causing vasoconstriction and inhibiting baroreceptor reflex
2. It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone
3. Angiotensin II regulates glomerular filtration
4. It increases sodium reabsorption from renal tubules
5. It increases water intake by stimulating the thirst center
6. It increases secretion of antidiuretic hormone (ADH) from hypothalamus.

Angiotensin III

Angiotensin III increases the blood pressure and stimulates aldosterone secretion from adrenal cortex.

Angiotensin IV

It also has adrenal cortical stimulating and vasopressor activities.

2. Secretion of Other Substances

The extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin (Chapter 51). *In vitro* secretion of cytokines like IL-2 and TNF by the mesangial cells is observed recently. Macula densa secretes thromboxane A₂.

3. Regulation of Glomerular Blood Flow and Glomerular Filtration Rate

Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate (Refer Chapter 37 for details).

Renal Circulation

- INTRODUCTION
- RENAL BLOOD VESSELS
- MEASUREMENT OF RENAL BLOOD FLOW
- REGULATION OF RENAL BLOOD FLOW
- SPECIAL FEATURES OF RENAL CIRCULATION

■ INTRODUCTION

Blood vessels of kidneys are highly specialized to facilitate the functions of the nephrons in the formation of urine. Renal arteries supply the blood to the kidneys.

In the adults, during resting conditions both the kidneys receive 1,300 mL of blood per minute or about 26% of the cardiac output. Kidneys are the second organs to receive maximum blood flow, the first organ being the liver which receives 1,500 mL per minute. The maximum blood supply to kidneys has got the functional significance.

■ RENAL BLOOD VESSELS

Renal artery arises directly from abdominal aorta and enters the kidney through the hilus. While passing through renal sinus, the renal artery divides into many segmental arteries, which subdivide into interlobar arteries (Fig. 36-1).

Each interlobar artery passes in between the medullary pyramids. At the base of the pyramid, it turns and runs parallel to the base of pyramid forming arcuate artery.

Each arcuate artery gives rise to interlobular arteries. The interlobular arteries run through the

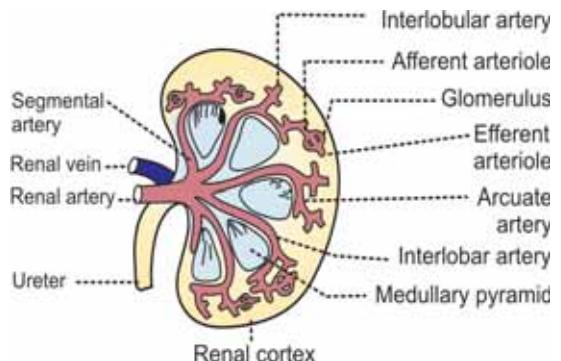


FIGURE 36-1: Renal blood vessels

renal cortex perpendicular to arcuate artery. From each interlobular artery, numerous afferent arterioles arise.

The afferent arteriole enters the Bowman's capsule and forms glomerular capillary tuft. The afferent arteriole divides into 4 or 5 large capillaries. Each large capillary divides into small capillaries, which form the loops. And, the capillary loops unite to form the efferent arteriole, which leaves the Bowman's capsule.

The efferent arterioles form a second capillary network called peritubular capillaries which surround the tubular portions of the nephrons.

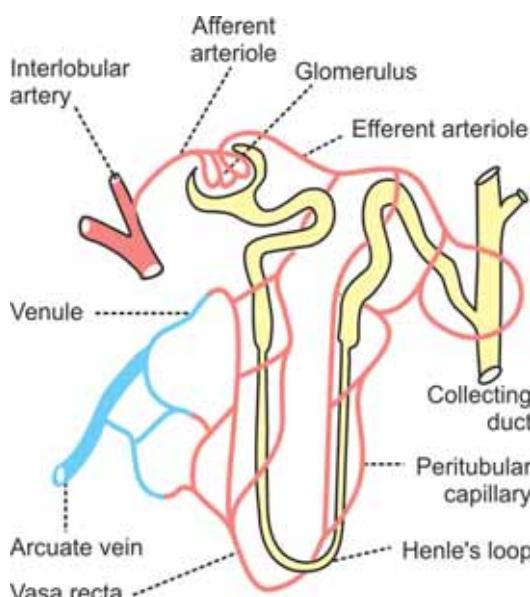


FIGURE 36-2: Renal capillaries

Thus, the renal circulation forms a portal system by the presence of two sets of capillaries – glomerular capillaries and peritubular capillaries.

The peritubular capillaries are found around the tubular portion of cortical nephrons only. The tubular portion of juxtamedullary nephrons are supplied by some specialized capillaries called vasa recta. Vasa recta arise directly from the efferent arteriole of the juxtamedullary nephrons and run parallel to the renal tubule into the medulla and ascend up towards the cortex (Fig. 36-2).

The peritubular capillaries and vasa recta drain into the venous system. Venous system starts with peritubular venules and continues as interlobular veins, arcuate veins, interlobar veins, segmental veins and finally the renal vein (Fig. 36-3).

Renal vein leaves the kidney through the hilus and joins inferior vena cava.

MEASUREMENT OF RENAL BLOOD FLOW

The blood flow to kidneys is measured by using plasma clearance of para-aminohippuric acid (Refer Chapter 40).

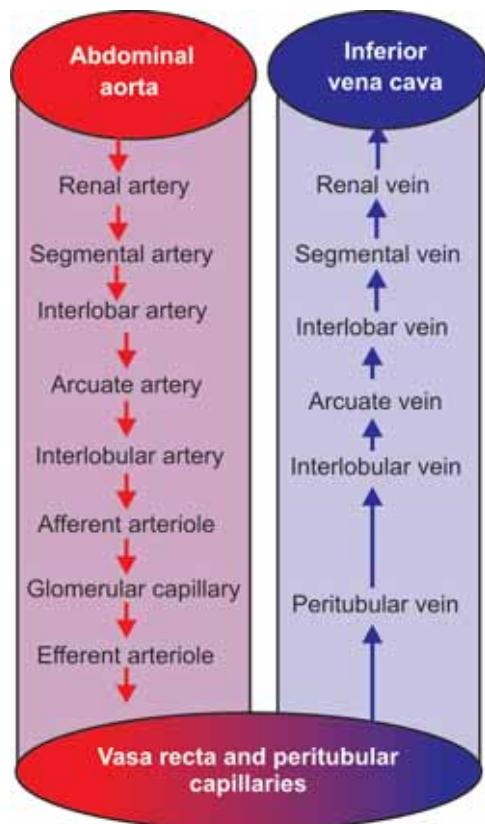


FIGURE 36-3: Schematic diagram showing renal blood flow

REGULATION OF RENAL BLOOD FLOW

The regulation of renal blood flow is mostly by autoregulation. The nerves innervating renal blood vessels have no significant role in this.

AUTOREGULATION

The intrinsic ability of an organ to regulate its own blood flow is called autoregulation. Autoregulation is present in some vital organs in the body such as brain, heart and kidneys. It is highly significant and more efficient in kidneys.

Renal Autoregulation

Renal autoregulation is important to maintain the glomerular filtration rate (GFR). Blood flow to kidneys remains normal even when the mean

arterial blood pressure vary widely between 60 and 180 mm Hg. This helps to maintain normal GFR.

Two mechanisms are involved in renal autoregulation:

1. Myogenic response
2. Tubuloglomerular feedback.

1. Myogenic Response

Whenever the blood flow to kidneys increases, it stretches the elastic wall of the afferent arteriole. Stretching of vessel wall increases the flow of calcium ions from extracellular fluid into the cells. The influx of calcium ions leads to the contraction of smooth muscles in afferent arteriole which causes constriction of afferent arteriole. So, the blood flow is decreased.

2. Tubuloglomerular Feedback

Macula densa plays an important role in tubuloglomerular feedback which controls the renal blood flow and GFR. Refer Chapter 37 for details.

SPECIAL FEATURES OF RENAL CIRCULATION

The renal circulation has some special features to cope up with the functions of the kidneys. Such special features are:

1. The renal arteries arise directly from the aorta. So the pressure in aorta is very high

and it facilitates a high blood flow to the renal parenchyma.

2. Kidneys receive about 1,300 mL of blood per minute, i.e. about 26% of cardiac output. Kidneys are the second organs to receive maximum blood flow, the first organ being the liver which receives 1,500 mL per minute, i.e. about 30% of cardiac output.
3. Whole amount of blood which flows to kidney has to pass through the glomerular capillaries before entering the venous system. Because of this, the blood is completely filtered at the renal glomeruli.
4. Renal circulation has a portal system, i.e. a double network of capillaries namely glomerular capillaries and peritubular capillaries.
5. Renal glomerular capillaries form high pressure bed with a pressure of 60 to 70 mm Hg. It is much greater than the capillary pressure elsewhere in the body, which is only about 25 to 30 mm Hg. High pressure is maintained in the glomerular capillaries because the diameter of afferent arteriole is more than that of efferent arteriole. The high capillary pressure augments glomerular filtration.
6. The peritubular capillaries form a low pressure bed with a pressure of 8 to 10 mm Hg. This low pressure helps tubular reabsorption.
7. The autoregulation of renal blood flow is well established.

Urine Formation

- INTRODUCTION
- GLOMERULAR FILTRATION
 - INTRODUCTION
 - GLOMERULAR FILTRATION RATE (GFR)
 - FILTRATION FRACTION
 - PRESSURES DETERMINING FILTRATION
 - FACTORS REGULATING (AFFECTING) GFR
- TUBULAR REABSORPTION
 - INTRODUCTION
 - SELECTIVE REABSORPTION
 - MECHANISM OF REABSORPTION
 - SITE OF REABSORPTION
 - REGULATION OF TUBULAR REABSORPTION
 - TRANSPORT MAXIMUM – T_m VALUE
 - RENAL THRESHOLD
 - REABSORPTION OF IMPORTANT SUBSTANCES
- TUBULAR SECRETION
 - INTRODUCTION
 - SUBSTANCES SECRETED IN DIFFERENT SEGMENTS OF RENAL TUBULES
- SUMMARY OF URINE FORMATION

■ INTRODUCTION

Urine formation is a blood cleansing function. Normally, about 26% of cardiac output enters the kidneys to get rid of unwanted substances. Kidneys excrete the unwanted substances in urine.

Normally, about 1 to 1.5 L of urine is formed every day.

The mechanism of urine formation includes three processes:

- I. Glomerular filtration
- II. Tubular reabsorption
- III. Tubular secretion.

Among these three processes filtration is the function of the glomerulus. Reabsorption and secretion are the functions of tubular portion of the nephron (Fig. 37-1).

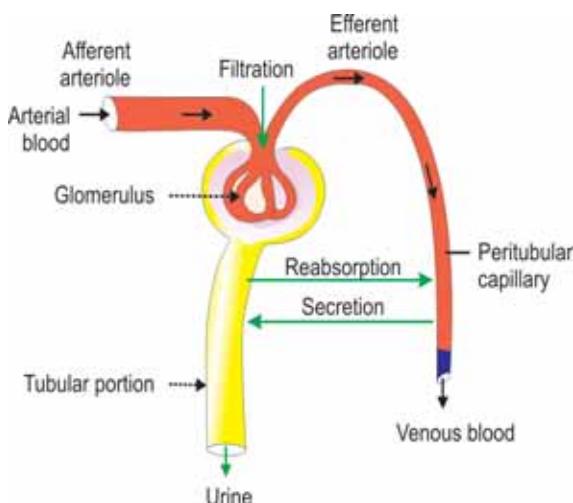


FIGURE 37-1: Events of urine formation

■ GLOMERULAR FILTRATION

■ INTRODUCTION

Glomerular filtration is the process by which the blood that passes through glomerular capillaries is filtered through the filtration membrane. It is the first process of urine formation. The structure of filtration membrane is well suited for this.

Filtration Membrane

It is formed by three layers:

1. The glomerular capillary membrane
2. Basement membrane
3. Visceral layer of Bowman's capsule.

1. Glomerular Capillary Membrane

The glomerular capillary membrane is formed by single layer of endothelial cells which are attached to the basement membrane. The capillary membrane has many pores called fenestra or filtration pores with a diameter of 0.1μ .

2. Basement Membrane

The basement membrane of glomerular capillaries fuses with the basement membrane of visceral layer of Bowman's capsule. The basement membrane separates the endothelium of

glomerular capillary and the epithelium of visceral layer of Bowman's capsule.

3. Visceral Layer of Bowman's Capsule

This is composed of a single layer of flattened epithelial cells resting on a basement membrane. Each cell is connected with the basement membrane by cytoplasmic extensions called pedicles or feet. The pedicles are arranged in an interdigitating manner leaving small cleft like spaces in between. The cleft like space is called slit pore. Filtration takes place through these slit pores. The epithelial cells with pedicles are called podocytes (Fig. 35-4).

Process of Glomerular Filtration

When the blood passes through the glomerular capillaries, the plasma is filtered into the Bowman's capsule. All the substances of plasma are filtered except plasma proteins. The filtered fluid is called glomerular filtrate.

Ultrafiltration

The glomerular filtration is called ultrafiltration because even the minute particles are filtered. But, the plasma proteins are not filtered due to their large molecular size. The protein molecules are larger than the slit pores present in the endothelium of capillaries. Thus, the glomerular filtrate contains all the substances of plasma except the plasma proteins.

■ GLOMERULAR FILTRATION RATE (GFR)

Glomerular filtration rate (GFR) is defined as the total quantity of filtrate formed in all nephrons of both the kidneys in the given unit of time.

The normal GFR is 125 mL per minute or about 180 L per day.

■ FILTRATION FRACTION

Filtration fraction is the fraction (portion) of the renal plasma which becomes the filtrate. It is the ratio between renal plasma flow and glomerular filtration rate. It is expressed in percentage.

The normal filtration fraction varies from 15-20%.

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{Renal plasma flow}} \times 100$$

$$= \frac{125 \text{ ml/min}}{650 \text{ ml/min}} \times 100$$

$$= 19.2\%.$$

The normal filtration fraction varies from 15 to 20%.

■ PRESSURES DETERMINING FILTRATION

The pressures, which determine the GFR, are:

1. Glomerular capillary pressure
2. Colloidal osmotic pressure in the glomeruli
3. Hydrostatic pressure in the Bowman's capsule.

1. Glomerular Capillary Pressure

It is the pressure exerted by the blood in glomerular capillaries. It is about 60 mm Hg and, varies between 45 and 70 mm Hg. Glomerular capillary pressure is the highest capillary pressure in the body. This pressure favors glomerular filtration.

2. Colloidal Osmotic Pressure

It is exerted by plasma proteins in the glomeruli. The plasma proteins are not filtered through the glomerular capillaries and remain in the glomerular capillaries. These proteins develop the colloidal osmotic pressure which is about 25 mm Hg. It opposes glomerular filtration.

3. Hydrostatic Pressure in Bowman's Capsule

It is the pressure exerted by the filtrate in Bowman's capsule. It is also called capsular pressure. It is about 15 mm Hg. It also opposes glomerular filtration.

Net Filtration Pressure

Net filtration pressure is the balance between pressure favoring filtration and pressures

opposing filtration. It is otherwise known as effective filtration pressure or essential filtration pressure.

The net filtration pressure =

$$\text{Glomerular capillary pressure} - \left\{ \begin{array}{l} \text{Colloidal osmotic pressure} \\ + \text{Hydrostatic pressure in Bowman's capsule} \end{array} \right\}$$

$$= 60 - (25 + 15) = 20 \text{ mm Hg.}$$

Normal net filtration pressure is about 20 mm Hg, and, it varies between 15 and 20 mm Hg.

■ FACTORS REGULATING (AFFECTING) GFR

1. Renal Blood Flow

It is the most important factor that is necessary for glomerular filtration. GFR is directly proportional to renal blood flow. The renal blood flow itself is controlled by autoregulation. Refer previous chapter for details.

2. Tubuloglomerular Feedback

Tubuloglomerular feedback is the mechanism that regulates GFR through renal tubule and macula densa (Fig. 37-2). Macula densa of

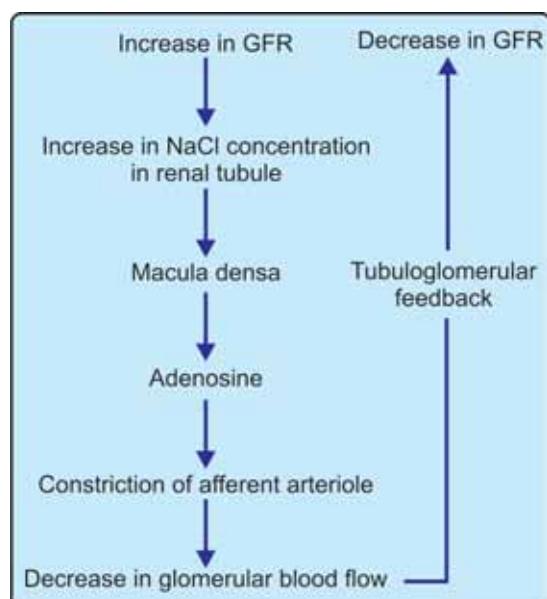


FIGURE 37-2: Tubuloglomerular feedback

juxtaglomerular apparatus in the terminal portion of thick ascending limb is sensitive to the sodium chloride in the tubular fluid.

When glomerular filtrate passes through the terminal portion of thick ascending segment, macula densa acts like a sensor. It detects the concentration of sodium chloride in the tubular fluid and accordingly alters the glomerular blood flow and GFR.

When the Concentration of Sodium Chloride Increases in the Filtrate

When the concentration of sodium chloride increases in the filtrate, macula densa releases adenosine from ATP. Adenosine causes constriction of afferent arteriole. So the blood flow through glomerulus decreases leading to decrease in GFR.

When the Concentration of Sodium Chloride Decreases in the Filtrate

When the concentration of sodium chloride decreases in the filtrate, macula densa secretes prostaglandin (PGE_2), bradykinin and renin.

PGE_2 and bradykinin cause dilatation of afferent arteriole. Renin induces the formation of angiotensin II which causes constriction of efferent arteriole. The dilatation of afferent arteriole and constriction of efferent arteriole leads to increase in glomerular blood flow and GFR.

3. Glomerular Capillary Pressure

The GFR is directly proportional to glomerular capillary pressure. The capillary pressure, in turn depends upon the renal blood flow and arterial blood pressure.

4. Colloidal Osmotic Pressure

The GFR is inversely proportional to colloidal osmotic pressure which is exerted by plasma proteins in the glomerular capillary blood. When colloidal osmotic pressure increases as in case of dehydration or increased plasma protein level, GFR decreases. During hypoproteinemia, colloidal osmotic pressure is low and GFR increases.

5. Hydrostatic Pressure in Bowman's Capsule

GFR is inversely proportional to this. The hydrostatic pressure in Bowman's capsule increases in conditions like obstruction of urethra and edema of kidney beneath renal capsule.

6. Constriction of Afferent Arteriole

The constriction of afferent arteriole reduces the blood flow to the glomerular capillaries which in turn reduces GFR.

7. Constriction of Efferent Arteriole

If efferent arteriole is constricted, initially the GFR increases because of stagnation of blood in the capillaries. Later when all the substances are filtered from this blood, further filtration does not occur because, the efferent arteriolar constriction prevents outflow of blood from glomerulus and no fresh blood enters the glomerulus for filtration.

8. Systemic Arterial Pressure

Renal blood flow or GFR are not affected till the mean arterial blood pressure is between 60 and 180 mm Hg. It is due to the autoregulatory mechanism (Chapter 36). Variation in pressure above 180 mm Hg or below 60 mm Hg affects the renal blood flow and GFR accordingly because the autoregulatory mechanism fails beyond this range.

9. Sympathetic Stimulation

Afferent and efferent arterioles are supplied by sympathetic nerves. The mild or moderate stimulation of sympathetic nerves does not cause any significant change either in renal blood flow or GFR.

Strong sympathetic stimulation causes severe constriction of the blood vessels by releasing the neurotransmitter substance, noradrenaline. The effect is more severe on the efferent arterioles than on the afferent arterioles. So, initially there is increase in filtration but later it decreases.

However, if the stimulation is continued for more than 30 minutes, there is recovery of both renal blood flow and GFR. It is because of reduction in sympathetic neurotransmitter.

10. Surface Area of Capillary Membrane

GFR is directly proportional to the surface area of the capillary membrane.

If the glomerular capillary membrane is affected as in the cases of some renal diseases, the surface area for filtration decreases. So there is reduction in GFR.

11. Permeability of Capillary Membrane

GFR is directly proportional to the permeability of glomerular capillary membrane. In many abnormal conditions like hypoxia, lack of blood supply, presence of toxic agents, etc. the permeability of the capillary membrane increases. In such conditions, even plasma proteins are filtered and excreted in urine.

12. Contraction of Glomerular Mesangial Cells

Glomerular mesangial cells are situated in between the glomerular capillaries. Contraction of these cells decreases surface area of capillaries resulting in reduction in GFR.

13. Hormonal and Other Factors

Many hormones and other secretory factors alter GFR by affecting the blood flow through glomerulus.

Factors increasing GFR by vasodilatation

- i. Atrial natriuretic peptide
- ii. Brain natriuretic peptide
- iii. cAMP
- iv. Dopamine
- v. Endothelial derived nitric oxide
- vi. Prostaglandin (PGE₂).

Factors decreasing GFR by vasoconstriction

- i. Angiotensin II

- ii. Endothelins
- iii. Noradrenaline
- iv. Platelet activating factor
- v. Platelet-derived growth factor
- vi. Prostaglandin (PGF₂).

■ TUBULAR REABSORPTION

■ INTRODUCTION

Tubular reabsorption is the process by which water and other substances are transported from renal tubules back to the blood. When the glomerular filtrate flows through the tubular portion of nephron, both quantitative and qualitative changes occur. Large quantity of water (more than 99%), electrolytes and other substances are reabsorbed by the tubular epithelial cells. The reabsorbed substances move into the interstitial fluid of renal medulla. And, from here, the substances move into the blood in peritubular capillaries.

Since the substances are taken back into the blood from the glomerular filtrate, the entire process is called tubular reabsorption.

■ SELECTIVE REABSORPTION

Tubular reabsorption is known as selective reabsorption because the tubular cells reabsorb only the substances necessary for the body. Essential substances such as glucose, amino acids and vitamins are completely reabsorbed from renal tubule. Whereas the unwanted substances like metabolic waste products are excreted through urine.

■ MECHANISM OF REABSORPTION

The basic transport mechanisms involved in tubular reabsorption are of two types:

1. Active reabsorption
2. Passive reabsorption.

1. Active Reabsorption

Active reabsorption is the movement of molecules against the electrochemical (uphill) gradient. It needs liberation of energy which is derived from ATP.

Substances reabsorbed actively

The substances reabsorbed actively from the renal tubule are sodium, calcium, potassium, phosphates, sulfates, bicarbonates, glucose, amino acids, ascorbic acid, uric acid and ketone bodies.

2. Passive Reabsorption

Passive reabsorption is the movement of molecules along the electrochemical (downhill) gradient. This process does not need energy.

Substances reabsorbed passively

The substances reabsorbed by passively are chloride, urea and water.

SITE OF REABSORPTION

The reabsorption of the substances occurs in almost all the segments of tubular portion of nephron.

1. Substances Reabsorbed from Proximal Convoluted Tubule

About 7/8 of the filtrate (about 88%) is reabsorbed in proximal convoluted tubule. The brush border of the epithelial cell in proximal convoluted tubule increases the surface area and facilitates reabsorption.

Substances reabsorbed from proximal convoluted tubule are glucose, amino acids, sodium, potassium, calcium, bicarbonates, chlorides, phosphates, uric acid and water.

2. Substances Reabsorbed from Loop of Henle

The substances reabsorbed from loop of Henle are sodium and chloride.

3. Substances Reabsorbed from Distal Convolute Tubule

Sodium, calcium, bicarbonate and water are reabsorbed from distal convoluted tubule.

■ REGULATION OF TUBULAR REABSORPTION

Tubular reabsorption is regulated by three factors:

1. Glomerulotubular balance
2. Hormonal factors
3. Nervous factors.

1. Glomerulotubular Balance

Glomerulotubular balance is the balance between the filtration and reabsorption of solutes and water in kidney. When GFR increases, the tubular load of solutes and water in the proximal convoluted tubule is increased. It is followed by increase in the reabsorption of solutes and water. This process helps in the constant reabsorption of solute particularly sodium and water from renal tubule.

Mechanism of Glomerulotubular Balance

Glomerulotubular balance occurs because of osmotic pressure in the peritubular capillaries. When GFR increases, more amount of plasma proteins accumulate in the glomerulus. Consequently, the osmotic pressure increases in the blood by the time it reaches efferent arteriole and peritubular capillaries. The elevated osmotic pressure in the peritubular capillaries increases reabsorption of sodium and water from the tubule into the capillary blood.

2. Hormonal Factors

The hormones which regulate GFR are listed in Table 37-1.

3. Nervous Factor

Activation of sympathetic nervous system increases the tubular reabsorption (particularly of sodium) from renal tubules. It also increases the tubular reabsorption indirectly by stimulating secretion of renin from juxtaglomerular cell. Renin causes formation of angiotensin II which increases the sodium reabsorption (Chapter 35).

TABLE 37-1: Hormones regulating tubular reabsorption

Hormone	Action
Aldosterone	Increases sodium reabsorption in ascending limb, distal convoluted tubule and collecting duct
Angiotensin II	Increases sodium reabsorption in proximal tubule, thick ascending limb, distal tubule and collecting duct (mainly in proximal convoluted tubule)
Antidiuretic hormone	Increases water reabsorption in distal convoluted tubule and collecting duct
Atrial natriuretic factor	Decreases sodium reabsorption
Brain natriuretic factor	Decreases sodium reabsorption
Parathormone	Increases reabsorption of calcium, magnesium and hydrogen Decreases phosphate reabsorption
Calcitonin	Decreases calcium reabsorption

■ TRANSPORT MAXIMUM – Tm VALUE

Tubular transport maximum or Tm is the rate at which a substance is reabsorbed from the renal tubule. For example, the transport maximum for glucose, (TmG) is 375 mg/minute in adult males and about 300 mg/minute in adult females.

■ RENAL THRESHOLD

Renal threshold is the plasma concentration at which a substance appears first in urine. Every substance has a threshold level in plasma or blood. Below that threshold level, the substance is completely reabsorbed and does not appear in urine. When the concentration of that substance reaches the threshold, the excess amount is not reabsorbed and, so it appears in urine. This level is called the renal threshold of that substance.

For example, the renal threshold for glucose is 180 mg/dL. That is, glucose is completely reabsorbed from tubular fluid if its concentration in blood is below 180 mg/dL. So, the glucose

does not appear in urine. When the blood level of glucose reaches 180 mg/dL it is not reabsorbed completely and appears in urine.

■ REABSORPTION OF IMPORTANT SUBSTANCES

Reabsorption of Sodium

From the glomerular filtrate, 99% of sodium is reabsorbed. Two-thirds of sodium is reabsorbed in proximal convoluted tubule and remaining one-third in other segments (except descending limb) and collecting duct.

Sodium reabsorption occurs:

- In exchange for hydrogen ion by antiport (sodium counterport protein) – in proximal convoluted tubules
- Along with other substances like glucose and amino acids by symport (sodium co-transport protein) – in other segments and collecting duct.

Reabsorption of Water

Reabsorption of water occurs from proximal and distal convoluted tubules and in collecting duct.

Reabsorption of Water from Proximal Convoluted Tubule – Obligatory Water Reabsorption

Obligatory reabsorption is the type of water reabsorption in proximal convoluted tubule, which is secondary to sodium reabsorption. When sodium is reabsorbed from the tubule, the osmotic pressure decreases. It causes osmosis of water from renal tubule.

Reabsorption of Water from Distal Convoluted Tubule and Collecting Duct – Facultative Water Reabsorption

Facultative reabsorption is the type of water reabsorption in distal convoluted tubule and collecting duct that occurs by the activity of antidiuretic hormone (ADH). Normally, the distal convoluted tubule and the collecting duct are not permeable to water. But in the presence of antidiuretic hormone (ADH), these segments become permeable to water and so it is reabsorbed.

Mechanism of Action of Antidiuretic Hormone

ADH combines with V_2 receptors in the tubular epithelial membrane and activates adenyl cyclase, to form cyclic AMP. This cyclic AMP increases the permeability of the tubules for water by activating aquaporins which form the water channels.

Aquaporins

Aquaporins (AQP) are the membrane proteins which function as water channels. ADH increases water reabsorption in distal convoluted tubules and collecting ducts by regulating the aquaporins.

Reabsorption of Glucose

Glucose is completely reabsorbed in the proximal convoluted tubule. It is transported by secondary active transport (sodium co-transport) mechanism. Glucose and sodium bind to a common carrier protein in the luminal membrane of tubular epithelium and enter the cell. The carrier protein is called sodium-dependant glucose transporter 2 (SGLT 2). From tubular cell glucose is transported into medullary interstitium by another carrier protein called glucose transporter 2 (GLUT 2).

Renal Threshold for Glucose

Renal threshold for glucose is 180 mg/dL in venous blood. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.

Tubular Maximum for Glucose (TmG)

In adult male TmG is 375 mg/minute and in adult females it is about 300 mg/minute (see above).

Reabsorption of Bicarbonates

Bicarbonate is reabsorbed actively, mostly in proximal tubule. It is reabsorbed in the form of carbon dioxide.

Bicarbonate is mostly present as sodium bicarbonate in the filtrate. Sodium bicarbonate dissociates into sodium and bicarbonate ions in the tubular lumen.

Sodium diffuses into tubular cell in exchange of hydrogen. Bicarbonate combines with hydrogen to form carbonic acid. Carbonic acid dis-

sociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into hydrogen and bicarbonate. Bicarbonate from the tubular cell enters the interstitium. There it combines with sodium to form sodium bicarbonate.

■ TUBULAR SECRETION

■ INTRODUCTION

Tubular secretion is the process by which the substances are transported from blood into renal tubules. It is also called tubular excretion.

■ SUBSTANCES SECRETED IN DIFFERENT SEGMENTS OF RENAL TUBULES

1. Potassium is secreted actively by sodium-potassium pump in proximal and distal convoluted tubules and collecting ducts.
2. Ammonia is secreted in the proximal convoluted tubule.
3. Hydrogen ions are secreted in the proximal and distal convoluted tubules. Maximum hydrogen ion secretion occurs in proximal tubule.

Thus, urine is formed in the nephron by the processes of glomerular filtration, selective reabsorption and tubular secretion.

■ SUMMARY OF URINE FORMATION

Urine formation takes place in three processes.

Glomerular Filtration

Plasma is filtered in glomeruli and the substances reach the renal tubules along with water as filtrate.

Tubular Reabsorption

Ninety nine percent of filtrate is reabsorbed in different segments of renal tubules.

Tubular Secretion

Some substances are secreted from blood into the renal tubule.

With all these changes filtrate becomes urine.

38

Concentration of Urine

■ INTRODUCTION

- FORMATION OF DILUTE URINE
 - FORMATION OF CONCENTRATED URINE
- ## ■ MEDULLARY GRADIENT
- MEDULLARY HYPEROSMOLARITY
 - DEVELOPMENT AND MAINTENANCE OF MEDULLARY GRADIENT
- ## ■ COUNTERCURRENT MECHANISM
- COUNTERCURRENT FLOW
 - COUNTERCURRENT MULTIPLIER
 - COUNTERCURRENT EXCHANGER
- ## ■ ROLE OF ADH
- ## ■ SUMMARY OF URINE CONCENTRATION

■ INTRODUCTION

Osmolarity of glomerular filtrate is same as that of plasma and it is 300 mOsm/L. But, normally urine is concentrated and its osmolarity is four times more than that of plasma, i.e. 1200 mOsm/L. Osmolarity of urine depends upon two factors:

1. Water content in the body
2. Antidiuretic hormone.

■ FORMATION OF DILUTE URINE

Mechanism of urine formation is the same for dilute urine and concentrated urine till the fluid reaches the distal convoluted tubule. Whether it has to be excreted as dilute urine or concentrated urine depends upon the water content of the body.

If water content in body is more, kidney excretes excess water making the urine dilute. It is achieved by the inhibition of ADH secretion.

ADH is secreted by posterior pituitary (Chapter 45). The stimulus for its secretion is the decreased body fluid volume and/or increased sodium concentration (hyperosmolarity). ADH increases the water reabsorption from distal convoluted tubule and collecting duct resulting in concentration of urine.

But when, the volume of body fluid increases or the osmolarity of body fluid decreases, ADH secretion stops. So water reabsorption from renal tubules does not take place (see Fig. 38-3). This leads to excretion of large amount of water in urine making the urine dilute. It brings back the normalcy of water content and osmolarity of body fluids.

■ FORMATION OF CONCENTRATED URINE

When the water content in body decreases, kidney retains water and excretes concentrated urine. Formation of concentrated urine is not as simple as that of dilute urine. It involves two important processes:

- I. Medullary gradient
- II. Secretion of ADH.

■ MEDULLARY GRADIENT

■ MEDULLARY HYPEROSMOLARITY

The osmolarity of the cortical interstitial fluid is isotonic, i.e. similar to that of plasma and it is 300 mOsm/L.

The osmolarity of medullary interstitial fluid near the cortex also is 300 mOsm/L. However, while proceeding from outer part towards the inner part of medulla, it increases gradually and, reaches the maximum at the inner most part of medulla near renal sinus. Here, it is 1200 mOsm/L (Fig. 38-1).

This type of gradual increase in the osmolarity of the medullary interstitial fluid is called the medullary gradient. It plays an important role in the concentration of urine.

■ DEVELOPMENT AND MAINTENANCE OF MEDULLARY GRADIENT

Kidney has some unique anatomical arrangements called countercurrent system, which are responsible for the development and maintenance of medullary gradient and hyperosmolarity of interstitial fluid in the inner medulla.

■ COUNTERCURRENT MECHANISM

■ COUNTERCURRENT FLOW

A countercurrent system is a system of 'U' shaped tubules (tubes) in which, the flow of fluid is in opposite direction in two limbs of the 'U' shaped tubules.

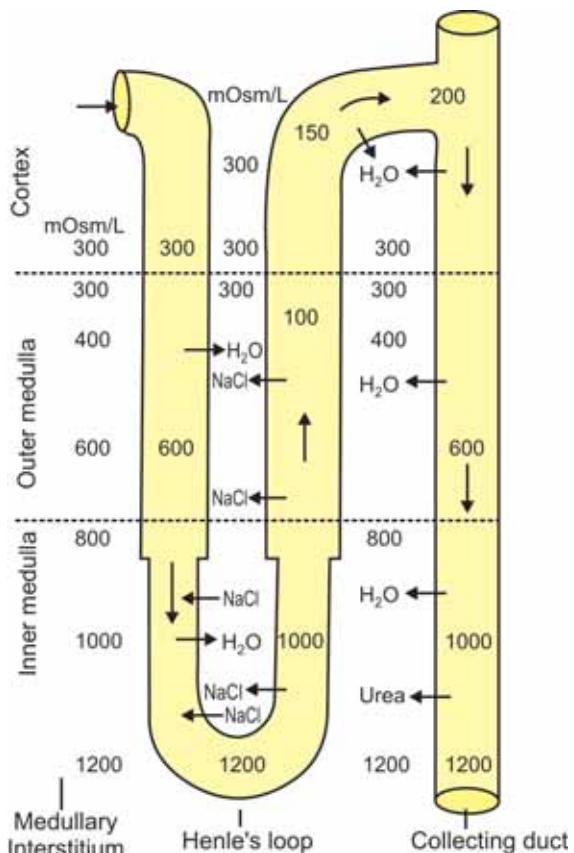


FIGURE 38-1: Countercurrent multiplier.
Numerical indicate osmolarity (mOsm/L)

In kidney, the structures, which form the counter current system, are the loop of Henle and the vasa recta. In both, the direction of flow of fluid in the descending limb is just opposite to that in the ascending limb.

The loop of Henle forms the countercurrent multiplier and, the vasa recta forms the countercurrent exchanger.

■ COUNTERCURRENT MULTIPLIER

Loop of Henle

Loop of Henle functions as countercurrent multiplier. It is responsible for the development of hyperosmolarity of medullary interstitial fluid and medullary gradient.

Role of Loop of Henle in Development of Medullary Gradient

The loop of Henle of juxamedullary nephrons plays a major role as countercurrent multiplier. It is because the loop of juxamedullary nephrons is long and extends up to the deeper parts of medulla.

The major cause for the hyperosmolarity of medullary interstitial fluid is the active reabsorption of sodium, chloride and other solutes from ascending limb of Henle's loop into the medullary interstitium. These solutes accumulate in the medullary interstitium and increase the osmolarity.

Now, due to the concentration gradient, the sodium and chloride ions diffuse from medullary interstitium into the descending limb of Henle's loop and reach the ascending limb again via hairpin bend.

Thus, the sodium and chloride ions are repeatedly recirculated between the descending limb and ascending limb of Henle's loop through medullary interstitial fluid leaving a small portion to be excreted in the urine.

Apart from this there is regular addition of more and more new sodium and chloride ions into descending limb by constant filtration. Thus, the reabsorption of sodium chloride from ascending limb and addition of new sodium chloride ions into the filtrate increase or multiply the osmolarity of medullary interstitial fluid and medullary gradient. Hence, it is called countercurrent multiplier.

Other Factors Responsible for Hyperosmolarity of Medullary Interstitial Fluid

In addition to countercurrent multiplier action provided by the loop of Henle, two more factors are involved in hyperosmolarity of medullary interstitial fluid.

1. Reabsorption of sodium from medullary part of collecting duct into the medullary interstitium, which adds to the osmolarity.
2. Urea recirculation: Urea is completely filtered in the glomeruli. As it is a waste product, it is

not reabsorbed from the renal tubule. So, all the filtered urea reach collecting duct. Now, due to concentration gradient, urea diffuses from the collecting duct into the inner medullary interstitium. So, the osmolarity increases in the inner medulla.

Due to the continuous diffusion, the concentration of urea increases in the medullary interstitium. Again, by concentration gradient, urea enters the ascending limb. From here, it passes through distal convoluted tubule and reaches the collecting duct. From here, urea enters the medullary interstitium and the cycle repeats. By this way urea recirculates repeatedly, and helps to maintain the hyperosmolarity in the inner medullary interstitium. Only a small amount of urea is excreted in urine.

■ COUNTERCURRENT EXCHANGER

Vasa Recta

Vasa recta functions as countercurrent exchanger. It is responsible for the maintenance of the hyperosmolarity of medullary interstitial fluid and the medullary gradient developed by countercurrent multiplier (Fig. 38-2).

Role of Vasa Recta in the Maintenance of Medullary Gradient

Vasa recta acts like countercurrent exchanger because of its position. It is also 'U' shaped tubule with a descending limb, hairpin bend and an ascending limb. Vasa recta runs parallel to loop of Henle. Its descending limb runs along the ascending limb of Henle's loop and its ascending limb runs along with descending limb of Henle's loop.

The sodium chloride reabsorbed from ascending limb of Henle's loop enters the medullary interstitium. From here it enters the descending limb of vasa recta. Simultaneously water diffuses from descending limb of vasa recta into medullary interstitium.

The blood flows very slowly through vasa recta. So, a large quantity of sodium chloride

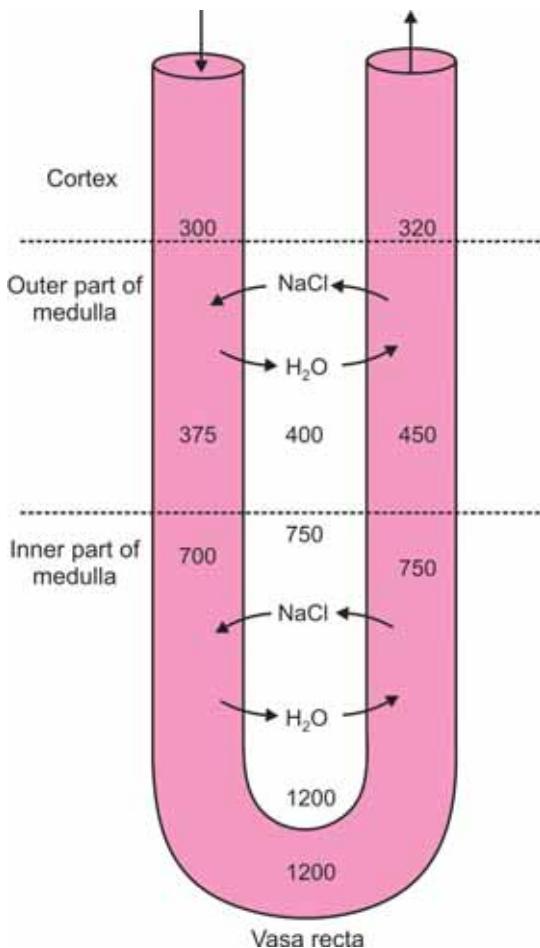


FIGURE 38-2: Countercurrent exchanger.
Numerical indicate osmolarity (mOsm/L)

accumulates in descending limb of vasa recta and flows slowly towards ascending limb. By the time the blood reaches the ascending limb of vasa recta, the concentration of sodium chloride increases very much. This causes diffusion of sodium chloride into the medullary interstitium. Water from medullary interstitium enters the ascending limb of vasa recta and the cycle is repeated.

Thus, vasa recta retains sodium chloride in the medullary interstitium and removes water from it. So, the hyperosmolarity of medullary interstitium is maintained.

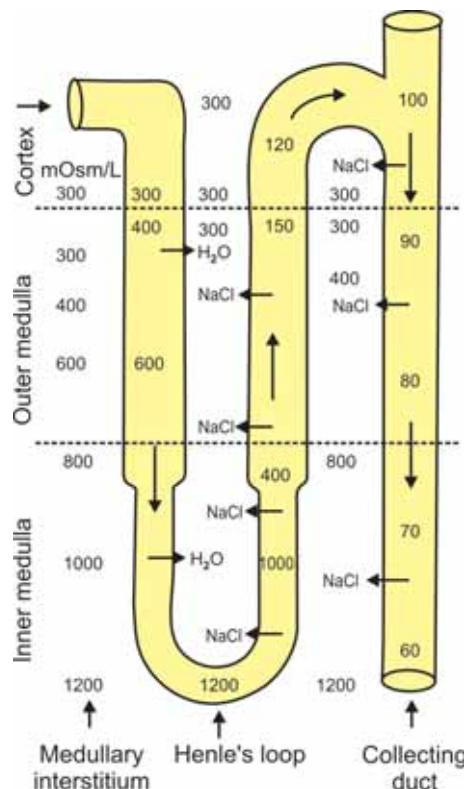


FIGURE 38-3: Mechanism for the formation of dilute urine. Numerical indicate osmolarity (mOsm/L)

Recycling of urea also occurs through vasa recta. From medullary interstitium, along with sodium chloride, urea also enters the descending limb of vasa recta. When blood passes through ascending limb of vasa recta, urea diffuses back into the medullary interstitium along with sodium chloride.

Thus, sodium chloride and urea are exchanged for water between the ascending and descending limbs of vasa recta, hence this system is called countercurrent exchanger.

■ ROLE OF ADH

The final concentration of urine is achieved by ADH. Normally, the distal convoluted tubule and the collecting duct are not permeable to water. In the presence of ADH, distal convoluted tubule

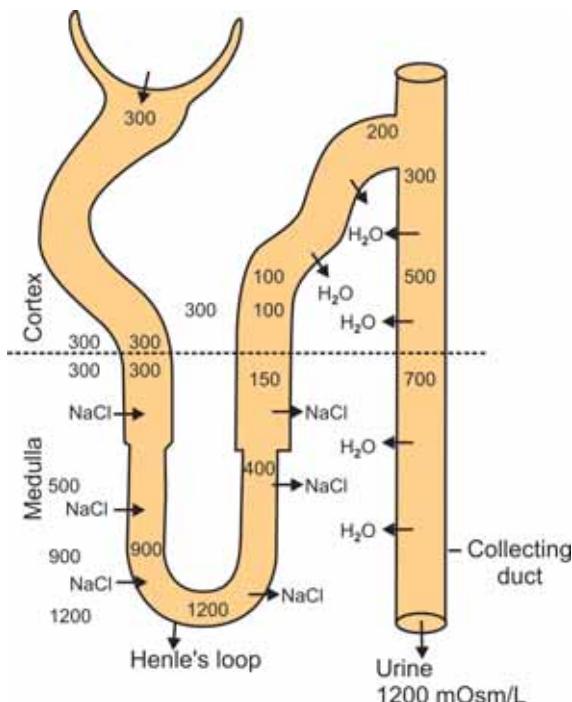


FIGURE 38-4: Role of ADH in the formation of concentrated urine. ADH increases the permeability for water in distal convoluted tubule and collecting duct

and collecting duct become permeable to water resulting in water reabsorption. The water reabsorption induced by ADH is called facultative reabsorption of water (Refer Chapter 45 for details).

A large quantity of water is removed from the fluid while passing through distal convoluted tubule and collecting duct. So, the urine becomes hypertonic with an osmolarity of 1200 mOsm/L (Fig. 38-4).

■ SUMMARY OF URINE CONCENTRATION

When the glomerular filtrate passes through renal tubule, its osmolarity is altered in different segments as described below.

■ 1. BOWMAN'S CAPSULE

The glomerular filtrate collected at the Bowman's capsule is isotonic to plasma. This is because it contains all the substances of plasma except proteins. The osmolarity of the filtrate at Bowman's capsule is 300 mOsm/L.

■ 2. PROXIMAL CONVOLUTED TUBULE

When the filtrate flows through proximal convoluted tubule, there is active reabsorption of sodium and chloride followed by obligatory reabsorption of water. So, the osmolarity of fluid remains the same as in the case of Bowman's capsule, i.e. 300 mOsm/L. Thus, in proximal convoluted tubules, the fluid is isotonic to plasma.

■ 3. THICK DESCENDING SEGMENT

When the fluid passes from proximal convoluted tubule into the thick descending segment, water is reabsorbed from the tubule into outer medullary interstitium by means of osmosis. It is due to the increased osmolarity in the medullary interstitium, i.e. outside the thick descending tubule. The osmolarity of the fluid inside this segment is between 450 and 600 mOsm/L. That means the fluid is slightly hypertonic to plasma.

■ 4. THIN DESCENDING SEGMENT OF HENLE'S LOOP

As the thin descending segment of Henle's loop passes through the inner medullary interstitium (which is increasingly hypertonic) more water is reabsorbed.

This segment is highly permeable to water, and so the osmolarity of tubular fluid becomes equal to that of the surrounding medullary interstitium.

In the short loops of cortical nephrons, the osmolarity of fluid at the hairpin bend of loop becomes 600 mOsm/L. And, in the long loops of juxamedullary nephrons, at the hairpin bend, the osmolarity is 1200 mOsm/L. Thus in this segment, the fluid is hypertonic to plasma.

■ 5. THIN ASCENDING SEGMENT OF HENLE'S LOOP

When the thin ascending segment of the loop ascends upwards through the medullary region, osmolarity decreases gradually.

Due to concentration gradient, sodium chloride diffuses out of tubular fluid and osmolarity decreases to 400 mOsm/L. The fluid in this segment is slightly hypertonic to plasma.

■ 6. THICK ASCENDING SEGMENT

This segment is impermeable to water. But there is active reabsorption of sodium and chloride

from this. Reabsorption of sodium decreases the osmolarity of tubular fluid to a greater extent. The osmolarity is between 150 and 200 mOsm/L. The fluid inside becomes hypotonic to plasma.

■ 7. DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

In the presence of ADH, distal convoluted tubule and collecting duct become permeable to water resulting in water reabsorption and final concentration of urine.

Reabsorption of large quantity of water increases the osmolarity to 1200 mOsm/L (Fig. 34-4). The urine becomes hypertonic to plasma.

Acidification of Urine and Role of Kidney in Acid–Base Balance

- INTRODUCTION
- SECRETION OF HYDROGEN IONS
- REMOVAL OF HYDROGEN IONS AND ACIDIFICATION OF URINE
 - BICARBONATE MECHANISM
 - PHOSPHATE MECHANISM
 - AMMONIA MECHANISM

■ INTRODUCTION

Kidney plays an important role in maintenance of acid–base balance by excreting hydrogen ions and retaining bicarbonate ions.

Normally, urine is acidic in nature with a pH of 4.5 to 6. The metabolic activities in the body produce lot of acids (with lot of hydrogen ions) which threaten to push the body towards acidosis. However, kidneys prevent this by excreting hydrogen ions (H^+) and conserving bicarbonate ions (HCO_3^-).

About 4320 mEq of HCO_3^- is filtered by the glomeruli everyday. It is called filtered load of HCO_3^- . Excretion of this much HCO_3^- through urine will affect the acid–base balance of body fluids. So, HCO_3^- must be taken back from the renal tubule by reabsorption.

The reabsorption of filtered HCO_3^- occurs by the secretion of H^+ in the renal tubules. About 4380 mEq of H^+ appear everyday in the renal tubule by means of filtration and secretion. Not all the H^+ are excreted in urine. Out of 4380 mEq, about 4280 to 4330 mEq of H^+ is utilized for the

reabsorption of filtered HCO_3^- . Only the remaining 50 to 100 mEq is excreted. It results in the acidification of urine.

■ SECRETION OF HYDROGEN IONS

H^+ is secreted in proximal convoluted tubule, distal convoluted tubule and collecting duct. Secretion of H^+ into the renal tubules occurs by the formation of carbonic acid. Carbon dioxide formed in the tubular cells combines with water to form carbonic acid. Carbon dioxide enters the cells from tubular fluid also. Carbonic anhydrase is essential for the formation of carbonic acid. This enzyme is available in large quantities in the epithelial cells of the renal tubules. The carbonic acid immediately dissociates into H^+ and HCO_3^- (Fig. 39-1). H^+ from the tubular cells is secreted into proximal convoluted tubule, distal convoluted tubule and collecting duct.

The distal convoluted tubule and collecting duct have a special type of cells called intercalated cells (I cells) that are involved in handling hydrogen and bicarbonate ions.

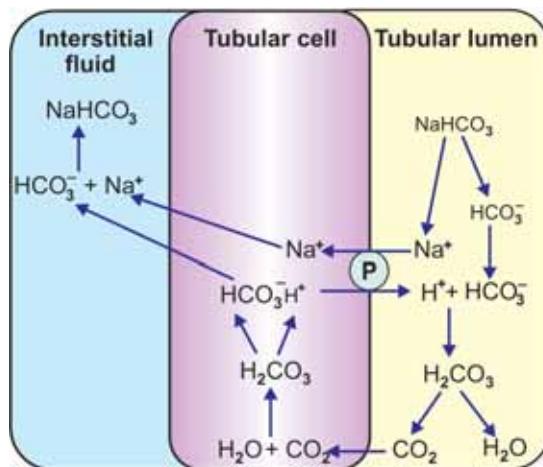


FIGURE 39-1: Reabsorption of bicarbonate ions by secretion of hydrogen ions in renal tubule. P = Sodium-Hydrogen antiport pump

TABLE 39-1: Secretion and removal of hydrogen ions in renal tubule

Mechanism	Segment of renal tubule
Sodium-hydrogen pump	Distal convoluted tubule
ATP driven proton pump	Distal convoluted tubule Collecting duct
Bicarbonate mechanism	Proximal convoluted tubule Henle's loop Distal convoluted tubule
Phosphate mechanism	Distal convoluted tubule Collecting duct
Ammonia mechanism	Proximal convoluted tubule

There are two mechanisms for the secretion of H^+ :

1. Sodium-Hydrogen antiport pump
2. ATP driven proton pump.

■ SODIUM-HYDROGEN ANTIPORT PUMP

When sodium ion (Na^+) is reabsorbed from the tubular fluid into the tubular cell, H^+ is secreted

from the cell into the tubular fluid in exchange for Na^+ . The sodium-hydrogen antiport pump present in the tubular cells is responsible for the exchange of Na^+ and H^+ . This type of sodium-hydrogen counter transport occurs predominantly in distal convoluted tubule (Table 39-1).

■ ATP DRIVEN PROTON PUMP

This is an additional mechanism of H^+ secretion in distal convoluted tubule and collecting duct. This pump is operated by obtaining energy from ATP.

■ REMOVAL OF HYDROGEN IONS AND ACIDIFICATION OF URINE

Role of Kidney in Preventing Metabolic Acidosis

Kidney plays an important role in preventing metabolic acidosis by excreting H^+ . The excretion of H^+ occurs by three mechanisms:

1. Bicarbonate mechanism
2. Phosphate mechanism
3. Ammonia mechanism.

■ BICARBONATE MECHANISM

All the HCO_3^- filtered into the renal tubules is reabsorbed. About 80% of it is reabsorbed in proximal convoluted tubule; 15% in Henle's loop and 5% in distal convoluted tubule and collecting duct. The reabsorption of HCO_3^- utilizes the H^+ secreted into the renal tubules.

The H^+ secreted into the renal tubule, combines with filtered HCO_3^- forming carbonic acid. Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^- . HCO_3^- from the tubular cell enters the interstitium. Simultaneously Na^+ is reabsorbed from the renal tubule under the influence of aldosterone. HCO_3^- combines with Na^+ to form $NaHCO_3$. Now, the H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 39-1).

Thus, for every hydrogen ion secreted into lumen of tubule, one bicarbonate ion is reabsorbed from the tubule. In this way, kidneys conserve the HCO_3^- . The reabsorption of filtered HCO_3^- is an important factor in maintaining pH of the body fluids.

■ PHOSPHATE MECHANISM

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^- . HCO_3^- from the tubular cell enters the interstitium. Simultaneously, Na^+ is reabsorbed from renal tubule under the influence of aldosterone. Na^+ enters the interstitium and combines with HCO_3^- . The H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 39-2).

The H^+ , which is secreted into renal tubules, reacts with phosphate buffer system. It combines with sodium hydrogen phosphate to form sodium dihydrogen phosphate. Sodium dihydrogen phosphate is excreted in urine. The H^+ , which is added to urine, makes it acidic. It happens mainly in distal tubule and collecting duct because of the presence of large quantity of sodium hydrogen phosphate in these segments.

■ AMMONIA MECHANISM

This is the most important mechanism by which kidneys excrete H^+ and make the urine acidic. In the tubular epithelial cells, ammonia is formed when the amino acid glutamine is converted into glutamic acid in the presence of the enzyme glutaminase. Ammonia is also formed by the deamination of some of the amino acids such as glycine and alanine (Fig. 39-3).

The ammonia (NH_3) formed in tubular cells is secreted into tubular lumen in exchange for sodium ion. Here, it combines with H^+ to form ammonium (NH_4). The tubular cell membrane is not permeable to ammonium. Therefore, it remains in the lumen and combines with sodium acetoacetate to form ammonium acetoacetate. Ammonium acetoacetate is excreted through urine. Thus, H^+ is added to urine in the form of ammonium compounds resulting in acidification of urine.

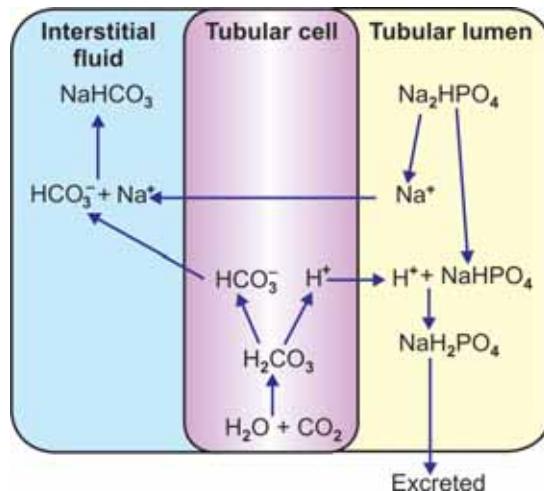


FIGURE 39-2: Excretion of hydrogen ions in combination with phosphate ions

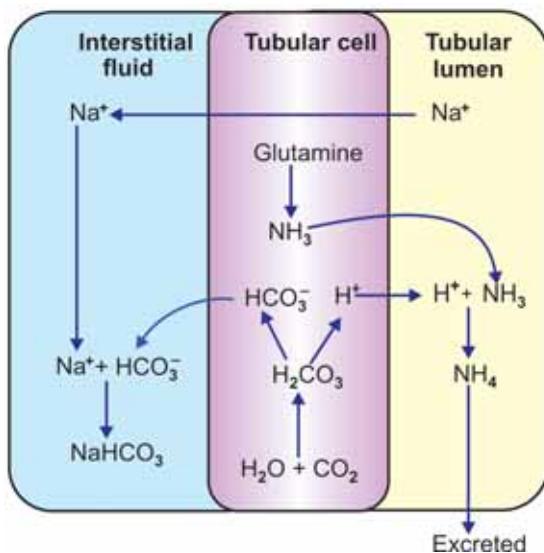


FIGURE 39-3: Excretion of hydrogen in combination with ammonia

This process takes place mostly in the proximal convoluted tubule because glutamine is converted into ammonia in the cells of this segment.

Thus, by excreting H^+ and conserving HCO_3^- , kidneys produce acidic urine and help to maintain the acid–base balance of body fluids.

- PROPERTIES AND COMPOSITION OF NORMAL URINE
- RENAL FUNCTION TESTS
- EXAMINATION OF URINE
- EXAMINATION OF BLOOD
- EXAMINATION OF BLOOD AND URINE

■ PROPERTIES AND COMPOSITION OF NORMAL URINE

■ PROPERTIES OF URINE

Volume: 1000 to 1500 mL/day

Reaction: Slightly acidic with pH of 4.5 to 6

Specific gravity: 1.010 to 1.025

Color: Normally, urine is straw colored

Odor: Fresh urine has light aromatic odor. If stored for some time, the odor becomes stronger due to bacterial decomposition.

■ COMPOSITION OF URINE

Urine consists of water and solids. Solids include organic and inorganic substances (Fig. 40-1).

■ RENAL FUNCTION TESTS

Renal function tests are the group of tests that are performed to assess the functions of kidney. The renal function tests are of three types:

- I. Examination of urine alone
- II. Examination of blood alone
- III. Examination of blood and urine.

■ EXAMINATION OF URINE — URINANALYSIS

Routine Examination of Urine

During the routine examination of urine, the following are determined:

- i. Specific gravity: Normally it is 1.010 to 1.025. But, in some conditions like chronic nephritis, it is decreased.
- ii. Presence of normal constituents of urine in abnormal quantity: Normally, substances like water, salt, amino acids and creatinine are excreted in urine either in greater or lesser amount. But, if abnormally large amount is excreted, it suggests some abnormal functional status of kidney. If 4 to 5 liters of water is excreted consistently per day, it is suggestive of diabetes insipidus. Abnormally low amount of water excretion indicates nephritis. Abnormal amount of salts or nutritive substances like amino acids appear in urine during congenital tubular defects.

Abnormal albumin excretion occurs in defective filtration. Abnormal amount of glucose is excreted in diabetes mellitus.

Solids excreted in urine			
Organic substances		Inorganic substances	
1. Urea	- 400	1. Sodium	- 200
2. Uric acid	- 4	2. Potassium	- 50
3. Creatinine	- 10	3. Calcium	- 5
4. Ammonia	- 40	4. Chloride	- 200
		5. Phosphate	- 25
		6. Sulfate	- 50

FIGURE 40-1: Quantity of solids excreted in urine (mMols/day)

- iii. Microscopic examination: This reveals the presence of red blood cells, pus cells, epithelial cells, casts and crystals which suggests the renal pathology.

■ EXAMINATION OF BLOOD

The level of plasma proteins, urea, uric acid and creatinine are determined in blood. The blood level of these substances is altered in renal failure.

■ EXAMINATION OF BLOOD AND URINE

Plasma Clearance

Plasma clearance is defined as the amount of plasma that is cleared off a substance in a given unit of time. It is also known as renal clearance. It is based on Fick's principle.

The determination of clearance value for certain substances helps in assessing the following renal functions:

1. Glomerular filtration rate
2. Renal plasma flow
3. Renal blood flow.

To determine the plasma clearance of a particular substance, measurement of the following factors is required:

1. Volume of urine excreted
2. Concentration of the substance in urine
3. The concentration of the substance in blood.

The formula to calculate clearance value is

$$C = \frac{UV}{P}$$

Where

C = Clearance

U = Concentration of the substance in urine

V = Volume of urine flow and

P = Concentration of the substance in plasma.

1. Measurement of Glomerular Filtration Rate

A substance that is completely filtered but neither reabsorbed nor secreted should be used to measure glomerular filtration rate (GFR). Inulin is a substance that is completely filtered. And, it is neither reabsorbed nor secreted. So, inulin is the ideal substance used to measure GFR.

Inulin clearance

A known amount of inulin is injected into the body. After sometime, the concentration of inulin in plasma and urine and the volume of urine excreted are estimated.

For example, the concentration of inulin in urine is 125 mg/dL. The plasma concentration is 1 mg/dL. The volume of urine output is 1 mL/min.

Thus,

$$\begin{aligned} \text{Glomerular filtration rate} &= \frac{UV}{P} \\ &= \frac{125 \times 1}{1} \\ &= 125 \text{ mL/min} \end{aligned}$$

2. Measurement of Renal Plasma Flow

To measure renal plasma flow, a substance, which is filtered and secreted but not reabsorbed, should be used. Such a substance is para-aminohippuric acid (PAH). PAH clearance indicates the amount of plasma passed through kidneys.

A known amount of PAH is injected into the body. After sometime, the concentration of PAH

in plasma and urine and the volume of urine excreted are estimated.

For example, the concentration of PAH in urine is 66 mg/dL. The plasma concentration is 0.1 mg/dL. The volume of urine output is 1 mL/min. Thus,

$$\begin{aligned}\text{Renal plasma flow} &= \frac{UV}{P} \\ &= \frac{66 \times 1}{0.1} \\ &= 660 \text{ mL/min}\end{aligned}$$

3. Measurement of Renal Blood Flow

To determine renal blood flow, value of two factors is necessary:

- i. Renal plasma flow
- ii. Percentage of plasma volume in the blood.

i. Renal plasma flow

Renal plasma flow is measured by using PAH clearance.

ii. Percentage of plasma volume in the blood

The percentage of plasma volume is indirectly determined by using PCV. For example, if PCV is 45%, the plasma volume in the blood is $100 - 45 = 55\%$, i.e. 55 mL of plasma is present in every 100 mL of blood.

Renal blood flow is calculated with the values of renal plasma volume and % of plasma in blood by using a formula given below.

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{\% \text{ of plasma in blood}}$$

For example,

Renal plasma flow is 660 mL/min
Amount of plasma in blood is 55%

$$\begin{aligned}\text{Renal blood flow} &= \frac{660}{55/100} \\ &= \frac{660 \times 100}{55} \\ &= 1200 \text{ mL/min}\end{aligned}$$

41

Micturition

- INTRODUCTION
- FUNCTIONAL ANATOMY OF URINARY BLADDER
- NERVE SUPPLY TO URINARY BLADDER AND SPHINCTER
 - SYMPATHETIC NERVE SUPPLY
 - PARASYMPATHETIC NERVE SUPPLY
 - SOMATIC NERVE SUPPLY
- FILLING OF URINARY BLADDER
 - PROCESS OF FILLING
 - CYSTOMETROGRAM
- MICTURITION REFLEX
- APPLIED PHYSIOLOGY

■ INTRODUCTION

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. The functional anatomy and nerve supply of urinary bladder are essential for the process of micturition.

■ FUNCTIONAL ANATOMY OF URINARY BLADDER

Urinary bladder consists of the body, neck and internal urethral sphincter. The smooth muscle forming the body of bladder is called detrusor muscle. At the posterior surface of the bladder wall, there is a triangular area called trigone. At the upper angles of this trigone, two ureters enter the bladder.

The lower part of the bladder is narrow and forms the neck. The distal end of the bladder is

guarded by internal urethral sphincter. This sphincter is made up of detrusor muscle. It opens towards urethra. At the distal end of urethra, there is external urethral sphincter. It is made up of skeletal muscle fibers. Therefore, it is responsible for voluntary control of micturition.

■ NERVE SUPPLY TO URINARY BLADDER AND SPHINCTERS

Urinary bladder and the internal sphincter are supplied by sympathetic and parasympathetic divisions of autonomic nervous system whereas, the external sphincter is supplied by the somatic nerve fibers (Fig. 41-1).

■ SYMPATHETIC NERVE SUPPLY

Preganglionic fibers of sympathetic nerve arise from first two lumbar segments (L_1 and L_2) of spinal cord. After leaving spinal cord, the fibers

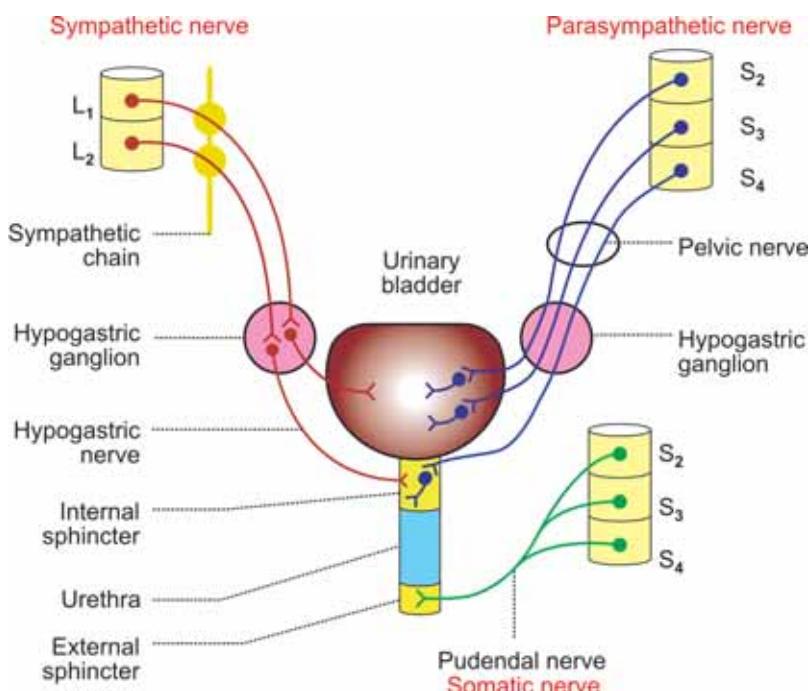


FIGURE 41-1: Nerve supply to urinary bladder and urethra

pass through lateral sympathetic chain without any synapse in the sympathetic ganglia and finally terminate in hypogastric ganglion. The postganglionic fibers arising from this ganglion form the hypogastric nerve, which supplies the detrusor muscle and internal sphincter.

Function of Sympathetic Nerve

The stimulation of sympathetic nerve causes relaxation of detrusor muscle and constriction of the internal sphincter. It results in filling of urinary bladder and so, the sympathetic nerve is called nerve of filling.

■ PARASYMPATHETIC NERVE SUPPLY

The preganglionic fibers of parasympathetic nerve form the pelvic nerve or nervus erigens. Pelvic nerve fibers arise from second, third and fourth sacral segments (S₂, S₃ and S₄) of spinal cord. These fibers run through hypogastric ganglion and synapse with postganglionic neurons situated in close relation to urinary bladder and internal sphincter (Table 41-1).

Function of Parasympathetic Nerve

The stimulation of pelvic (parasympathetic) nerve causes contraction of detrusor muscle and

TABLE 41-1: Functions of nerves supplying urinary bladder and sphincters

Nerve	On detrusor muscle	On internal sphincter	On external sphincter	Function
Sympathetic nerve	Relaxation	Constriction	Not supplied	Filling of urinary bladder
Parasympathetic nerve	Contraction	Relaxation	Not supplied	Emptying of urinary bladder
Somatic nerve	Not supplied	Not supplied	Constriction	Voluntary control of micturition

relaxation of the internal sphincter leading to emptying of urinary bladder. So, the parasympathetic nerve is called the nerve of emptying or nerve of micturition.

The pelvic nerve has also the sensory fibers which carry impulses from stretch receptors present on the wall of the urinary bladder and urethra to the central nervous system.

■ SOMATIC NERVE SUPPLY

The external sphincter is innervated by the somatic nerve called the pudendal nerve. It arises from second, third and fourth sacral segments of the spinal cord.

Function of Pudendal Nerve

It maintains the tonic contraction of the skeletal muscle fibers of the external sphincter and keeps the external sphincter constricted always.

During micturition, this nerve is inhibited. It causes relaxation of external sphincter leading to voiding of urine. Thus, the pudendal nerve is responsible for voluntary control of micturition.

■ FILLING OF URINARY BLADDER

■ PROCESS OF FILLING

Urine is continuously formed in the nephrons and it is transported drop by drop through the ureters into the urinary bladder. When urine collects in the pelvis of ureter, the contraction sets up in pelvis. The contraction is transmitted through rest of the ureter in the form of peristaltic wave up to trigone of the urinary bladder. The peristaltic wave moves the urine into the bladder.

A reasonable volume of urine can be stored in urinary bladder without any discomfort and without much increase in pressure inside the bladder (intravesical pressure). It is due to the adaptation of detrusor muscle. The relationship between the volume of urine and pressure in urinary bladder is studied by cystometrogram.

■ CYSTOMETROGRAM

Definition

Cystometrogram is the graphical registration (recording) of pressure changes in urinary

bladder in relation to volume of urine collected in it.

Method of Recording Cystometrogram

A double lumen catheter is introduced into the urinary bladder. One of the lumen is used to infuse fluid into the bladder and the other one is used to record the pressure changes by connecting it to a suitable recording instrument.

First, the bladder is emptied completely. Then, a known quantity of fluid is introduced into the bladder at regular intervals. The intravesical pressure developed by the fluid is recorded continuously. A graph is obtained by plotting all the values of volume and the pressure. This graph is the cystometrogram (Fig. 41-2).

Description of Cystometrogram

Cystometrogram shows three segments.

Segment I

Initially, when the urinary bladder is empty, the intravesical pressure is 0. When about 100 mL of fluid is collected, the pressure rises sharply to about 10 cm H₂O.

Segment II

This segment shows the plateau, i.e. the intravesical pressure remains more or less at

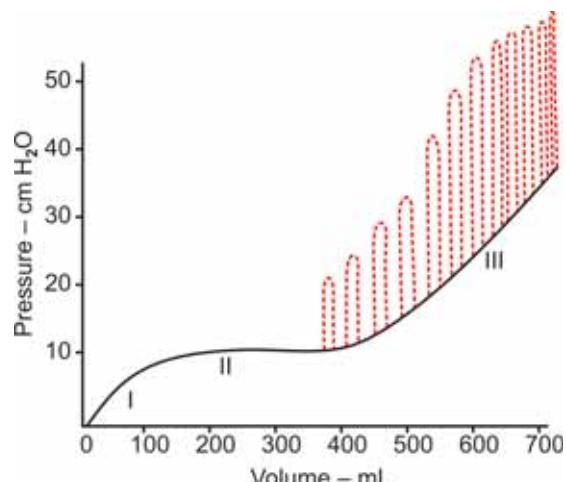


FIGURE 41-2: Cystometrogram. Dotted lines indicate the contraction of detrusor muscle

10 cm H₂O (level of segment I) without any change even after introducing 300 to 400 mL of fluid. It is because of adaptation of urinary bladder by relaxation. It is in accordance with law of Laplace.

Law of Laplace

According to this law, the pressure in a spherical organ is inversely proportional to its radius, the tone remaining constant. That is, if radius is more, the pressure is less and if radius is less the pressure is more, provided the tone remains constant.

Urinary bladder obeys Laplace law. In the bladder, the tension increases as the urine is filled. At the same time, the radius also increases due to relaxation of detrusor muscle. Because of this, the pressure rise is almost zero.

When about 100 mL of urine is collected, the pressure rises to about 10 cm H₂O and now, the desire for micturition occurs. The desire for micturition is associated with a vague feeling in the perineum. An additional volume of about 200 to 300 mL of urine can be collected in bladder without much increase in pressure. However, when total volume rises beyond 400 mL, the pressure rises sharply and the urge for micturition starts. Still voluntary control of micturition is possible. And, beyond 600 to 700 mL of urine, voluntary control starts failing.

Segment III

As the pressure increases with collection of 300–400 mL of fluid, the contraction of detrusor muscle becomes intense, increasing the consciousness and the urge for micturition. Still, voluntary control is possible. The voluntary control is possible up to volume of 600 to 700 mL at which the pressure rises to about 35 to 40 cm H₂O.

When the intravesical pressure rises above 40 cm water, the contraction of detrusor muscle becomes still more intense. And, voluntary control of micturition is not possible. Now, pain sensation develops and micturition should take place.

■ MICTURITION REFLEX

It is the reflex by which micturition occurs. This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, the pressure inside the bladder increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

The sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. The motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. The motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder (Fig. 41-3).

Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. These impulses inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs.

Once a micturition reflex begins, it is self-regenerative, i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely.

During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

Higher Centers for Micturition

Spinal centers for micturition are present in sacral and lumbar segments. These spinal centers are regulated by higher centers which are of two types:

1. Inhibitory centers which are situated in midbrain and cerebral cortex
2. Facilitatory centers which are situated in pons and cerebral cortex.

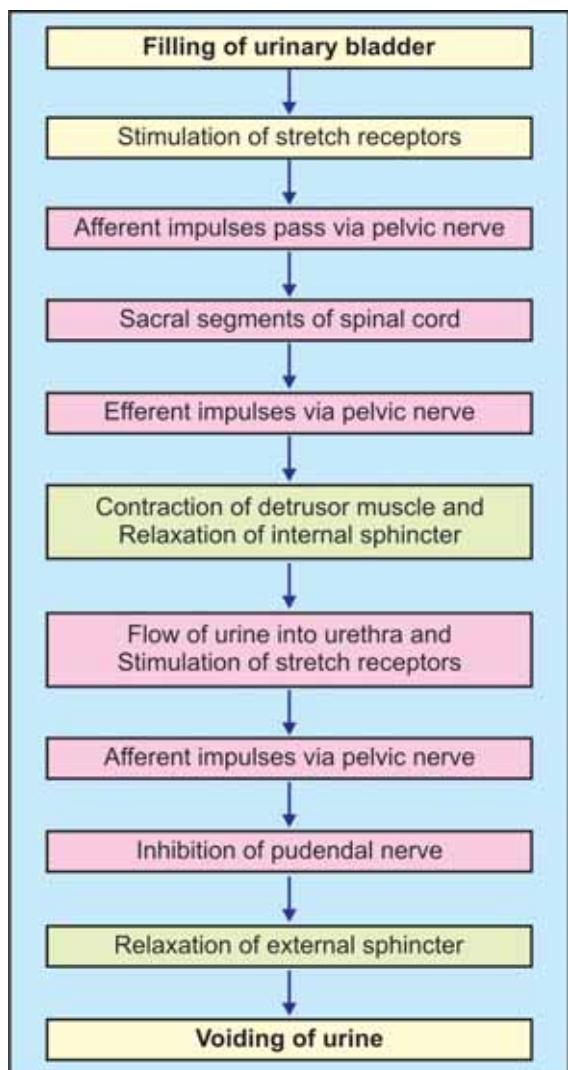


FIGURE 41-3: Micturition reflex

■ APPLIED PHYSIOLOGY

■ 1. ATONIC BLADDER – EFFECT OF DESTRUCTION OF SENSORY NERVE FIBERS

Atonic bladder is the urinary bladder with loss of tone in detrusor muscle. It is caused by

destruction of sensory (pelvic) nerve fibers of urinary bladder.

Due to the destruction of sensory nerve fibers, the bladder is filled up without any stretch signals to spinal cord. Detrusor muscle loses the tone and becomes flaccid. So, bladder is completely filled with urine. Later, overflow occurs in drops as and when urine enters the bladder. It is called overflow incontinence or overflow dribbling. It occurs in spinal injury and syphilis.

■ 2. AUTOMATIC BLADDER

Automatic bladder refers loss of voluntary control of micturition. So, even with small amount of urine collected in the urinary bladder, micturition reflex occurs resulting in emptying of urine. This occurs in transaction of spinal cord above the sacral segments.

■ 3. THE UNINHIBITED NEUROGENIC BLADDER

It is the urinary bladder with frequent and uncontrollable micturition caused by lesion in midbrain.

The lesion in midbrain causes continuous excitation of spinal micturition centers resulting in frequent and uncontrollable micturition. Even a small quantity of urine collected in bladder will elicit the micturition reflex.

■ 4. NOCTURNAL MICTURITION

Nocturnal micturition is the involuntary voiding of urine during night. It is otherwise known as enuresis or bed wetting. It occurs due to the absence of voluntary control of micturition. It is a common and normal process in infants and children below 3 years. It is because of incomplete myelination of motor nerve fibers of the bladder. When myelination is complete, voluntary control of micturition develops and bed wetting stops.

- **STRUCTURE OF SKIN**
 - INTRODUCTION
 - EPIDERMIS
 - DERMIS
 - APPENDAGES OF SKIN
 - COLOR OF THE SKIN
- **GLANDS OF SKIN**
 - SEBACEOUS GLANDS
 - SWEAT GLANDS
- **FUNCTIONS OF THE SKIN**

■ STRUCTURE OF SKIN

■ INTRODUCTION

Skin is the largest organ of the body. It is not uniformly thick. At some places, it is thick and in some places, it is thin. The average thickness of the skin is about 1 to 2 mm. In the sole of the foot, palm of the hand and in the interscapular region, it is considerably thick, measuring about 5 mm. In other areas of the body, the skin is thin. It is thinnest over eyelids and penis measuring about 0.5 mm only.

Skin is made up of two layers:

1. Outer epidermis
2. Inner dermis.

■ EPIDERMIS

The epidermis is the outer layer of skin. It is formed by stratified epithelium, which consists of 5 layers:

1. Stratum corneum

2. Stratum lucidum
3. Stratum granulosum
4. Stratum spinosum
5. Stratum germinativum

The important feature of epidermis is that, it does not have blood vessels (Fig. 42-1). The nutrition is provided to epidermis by the capillaries of dermis.

■ DERMIS

Dermis is the inner layer of the skin. It is a connective tissue layer made up of dense and stout collagen fibers, fibroblasts and histiocytes.

Dermis is made up of 2 layers:

1. Superficial papillary layer
2. Deeper reticular layer.

■ APPENDAGES OF SKIN

The hair follicles with hairs, nails, sweat glands, sebaceous glands and mammary glands are considered as appendages of the skin.

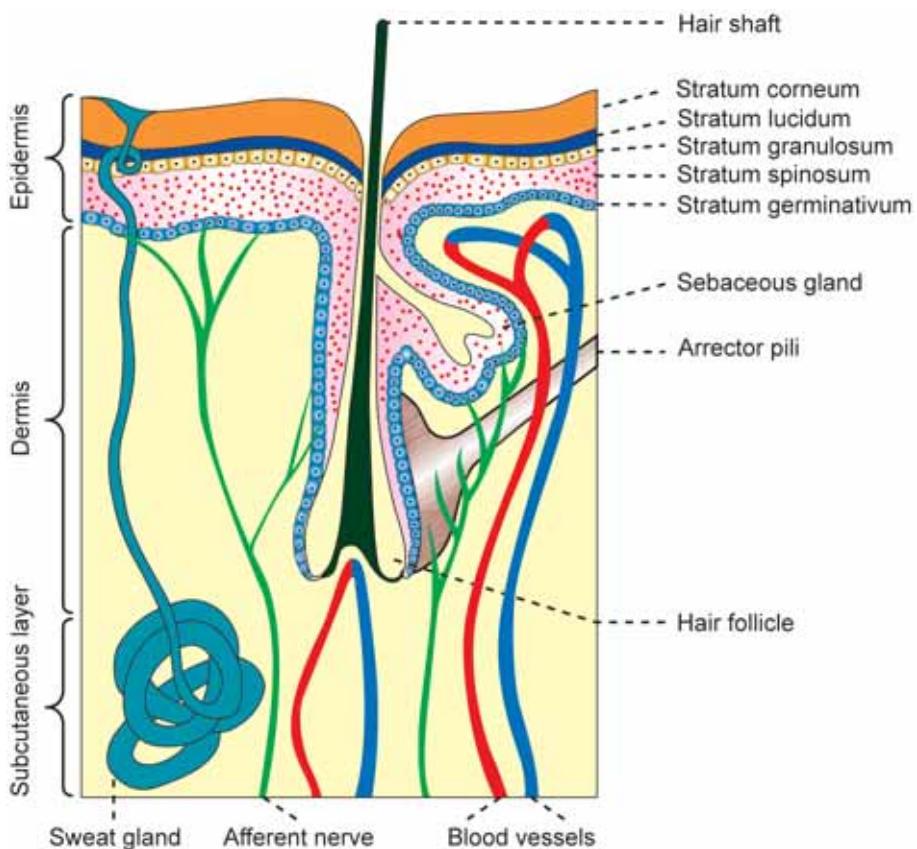


FIGURE 42-1: Structure of skin

■ COLOR OF THE SKIN

The color of the skin depends upon two important factors:

1. Pigmentation of skin
2. Hemoglobin in the blood.

1. Pigmentation of the Skin

Cells of the skin contain a brown pigment called melanin. Melanin is synthesized by melanocytes which are present mainly in the stratum germinativum and stratum spinosum of epidermis. After synthesis, this pigment spreads to the cells of the other layers.

Melanin

Melanin is the skin pigment and it forms the major color determinant of human skin. Skin becomes

dark when melanin content increases. It is protein in nature and it is synthesized from the amino acid tyrosine via dihydroxyphenylalanine (DOPA).

2. Hemoglobin in Blood

The amount and the nature of hemoglobin that circulates in the cutaneous blood vessels play an important role in the coloration of the skin.

Skin becomes:

- i. Pale when hemoglobin content decreases
- ii. Pink when blood rushes to skin due to cutaneous vasodilatation (blushing)
- iii. Bluish during cyanosis which is caused by excess amount of reduced hemoglobin.

■ GLANDS OF SKIN

The skin contains two types of glands, sebaceous glands and the sweat glands.

■ SEBACEOUS GLANDS

Sebaceous glands are simple or branched alveolar glands situated in the dermis of the skin. These glands are ovoid or spherical in shape and open into the neck of the hair follicle through a duct. In some areas like face, lips, nipple, glans penis and labia minora the sebaceous glands open directly into the exterior.

The sebaceous glands secrete an oily substance called sebum.

Composition of Sebum

Sebum contains:

1. Free fatty acids
2. Triglycerides
3. Squalene
4. Sterols
5. Waxes
6. Paraffin.

Functions of Sebum

1. The free fatty acid content of the sebum has antibacterial and antifungal actions. Thus, it prevents the infection of skin by bacteria or fungi
2. The lipid nature of sebum keeps the skin smooth and oily. It protects the skin from unnecessary desquamation and injury caused by dryness
3. The lipids of the sebum prevent heat loss from the body. It is particularly useful in cold climate.

Activation of Sebaceous Glands at Puberty

Sebaceous glands are inactive till puberty. At the time of puberty these glands are activated by sex hormones in both males and females.

At the time of puberty particularly in males, due to the increased secretion of sex hormones especially dehydroepiandrosterone, the sebaceous glands are stimulated suddenly. It leads to the development of acne on the face.

Acne

Acne is the localized inflammatory condition of the skin characterized by pimples on face, chest and back. It occurs because of over activity of

sebaceous glands. Acne vulgaris is the common type of acne that is developed during adolescence. Acne disappears within few years when the sebaceous glands become adapted to the sex hormones.

■ SWEAT GLANDS

Sweat glands are of two types:

- I. Eccrine glands
- II. Apocrine glands.

Eccrine Glands

The eccrine glands are tubular glands distributed throughout the body (Table 42-1). These glands open out through the sweat pore.

Secretory Activity of Eccrine Glands

Eccrine glands function throughout life since birth. These glands secrete a clear watery sweat. The secretion increases during increase in temperature and emotional conditions.

Eccrine glands play important role in regulating the body temperature by secreting sweat. Sweat contains water, sodium chloride, urea and lactic acid.

Control of Eccrine Glands

Eccrine glands are under nervous control and are supplied by sympathetic postganglionic cholinergic nerve fibers, which secrete acetylcholine. Stimulation of these nerves causes secretion of sweat.

Apocrine Glands

Apocrine glands are situated only in certain areas of the body like axilla, pubis, areola and umbilicus. These glands are also tubular in nature but open into the hair follicles.

Secretory Activity of Apocrine Glands

Apocrine sweat glands are nonfunctional till puberty and start functioning only at the time of puberty. In old age, the function of these glands gradually declines.

The secretion of the apocrine glands is thick and milky. At the time of secretion, it is odorless.

TABLE 42-1: Differences between eccrine and apocrine sweat glands

Features	Eccrine glands	Apocrine glands
1. Distribution	Throughout the body	Only in limited areas like axilla, pubis, areola and umbilicus
2. Opening	Exterior through sweat pore	Into hair follicle
3. Period of functioning	Function throughout life	Start functioning only at puberty
4. Secretion	Clear and watery	Thick and milky
5. Regulation of body temperature	Play important role in temperature regulation	Do not play any role in temperature regulation
6. Conditions when secretion increases	During increased temperature and emotional conditions	Only during emotional conditions
7. Control of secretory activity	Under nervous control	Under hormonal control
8. Nerve supply	Sympathetic cholinergic fibers	Sympathetic adrenergic fibers

When microorganisms grow in this secretion, a characteristic odor develops in the regions where apocrine glands are present. Secretion increases only in emotional conditions.

The apocrine glands do not play any role in temperature regulation like eccrine gland.

Control of Apocrine Glands

The apocrine glands are innervated by sympathetic adrenergic nerve fibers. But, the secretory activity is not under nervous control. However, adrenaline from adrenal medulla causes secretion by apocrine glands.

Glands of eyelids, glands of external auditory meatus and mammary glands are the modified apocrine glands.

■ FUNCTIONS OF THE SKIN

The primary function of skin is the protection of organs. However, it has many other important functions also.

■ 1. PROTECTIVE FUNCTION

Skin forms the covering of all the organs of the body and protects these organs from the following factors:

- i. Bacteria and toxic substances
- ii. Mechanical blow
- iii. Ultraviolet rays.

i. Protection from Bacteria and Toxic Substances

Skin covers the organs of the body and protects the organs from having direct contact with external environment. Thus, it prevents the bacterial infection.

The lysozyme secreted in skin destroys the bacteria. The stratum corneum of epidermis is responsible for the protective function of skin. This layer also offers resistance against toxic chemicals like acids and alkalis.

ii. Protection from Mechanical Blow

The skin is not tightly placed over the underlying organs or tissues. It is somewhat loose and moves over the underlying subcutaneous tissues. So, the mechanical impact of any blow to the skin is not transmitted to the underlying tissues.

iii. Protection from Ultraviolet Rays

Skin protects the body from ultraviolet rays of sunlight. Exposure to sunlight or to any other source of ultraviolet rays increases the production of melanin pigment in skin. Melanin absorbs ultraviolet rays. At the same time, the thickness of stratum corneum increases. This layer of epidermis also absorbs the ultraviolet rays.

■ 2. SENSORY FUNCTION

Skin is considered as the largest sense organ in the body. It has many nerve endings, which form the specialized cutaneous receptors (Chapter 85).

These receptors are stimulated by the sensations of touch, pain, pressure or temperature sensation and convey these sensations to the brain via afferent nerves. At the brain level, the perception of different sensations occurs.

■ 3. STORAGE FUNCTION

Skin stores fat, water, chloride and sugar. It can also store blood by the dilatation of the cutaneous blood vessels.

■ 4. SYNTHETIC FUNCTION

Vitamin D₃ is synthesized in skin by the action of ultraviolet rays from sunlight on cholesterol (Chapter 47).

■ 5. REGULATION OF BODY TEMPERATURE

Skin plays an important role in the regulation of body temperature. Excess heat is lost from the

body through skin by radiation, conduction, convection and evaporation. Sweat glands of the skin play active part in heat loss by secreting sweat. The lipid content of sebum prevents loss of heat from the body in cold environment. More details are given in next chapter.

■ 6. REGULATION OF WATER AND ELECTROLYTE BALANCE

Skin regulates water balance and electrolyte balance by excreting water and salts through sweat.

■ 7. EXCRETORY FUNCTION

Skin excretes small quantities of waste materials like urea, salts and fatty substance.

■ 8. ABSORPTIVE FUNCTION

Skin absorbs the fat soluble substances and some ointments.

■ 9. SECRETORY FUNCTION

Skin secretes sweat through sweat glands and sebum through sebaceous glands. By secreting sweat, skin regulates body temperature and water balance. Sebum keeps the skin smooth and moist.

Body Temperature

- INTRODUCTION
- BODY TEMPERATURE
 - NORMAL BODY TEMPERATURE
 - TEMPERATURE AT DIFFERENT PARTS OF THE BODY
 - VARIATIONS OF BODY TEMPERATURE
- HEAT BALANCE
 - HEAT GAIN OR HEAT PRODUCTION IN THE BODY
 - HEAT LOSS FROM THE BODY
- REGULATION OF BODY TEMPERATURE
 - HEAT LOSS CENTER
 - HEAT GAIN CENTER
 - MECHANISM OF TEMPERATURE REGULATION

■ INTRODUCTION

The living organisms are classified into two groups depending upon the maintenance (regulation) of body temperature:

1. Homeothermic animals
2. Poikilothermic animals.

■ HOMEOTHERMIC ANIMALS

Homeothermic animals are the animals in which the body temperature is maintained at a constant level irrespective of the environmental temperature. Birds and mammals including man belong to this category. They are also called warm blooded animals.

■ POIKILOTHERMIC ANIMALS

Poikilothermic animals are the animals in which the body temperature is not constant. It

varies according to environmental temperature. Amphibians and reptiles are the poikilothermic animals. These animals are also called cold blooded animals.

■ BODY TEMPERATURE

Body temperature can be measured by placing the clinical thermometer in different parts of the body such as:

1. Mouth (oral temperature)
2. Axilla (axillary temperature)
3. Rectum (rectal temperature)
4. Over the skin (surface temperature).

■ NORMAL BODY TEMPERATURE

The normal body temperature in human is 37°C (98.6°F) when measured by placing the clinical thermometer in the mouth (oral temperature). It

varies between 35.8°C and 37.3°C (96.4° and 99.1°F).

■ TEMPERATURE AT DIFFERENT PARTS OF THE BODY

Axillary temperature is 0.3 to 0.6°C (0.5 to 1°F) lower than the oral temperature. And, the rectal temperature is 0.3 to 0.6°C (0.5 to 1°F) higher than oral temperature. The superficial temperature (skin or surface temperature) varies between 29.5° and 33.9°C (85.1° and 93°F).

Core Temperature

Core temperature is the average temperature of structures present in deeper part of the body. The core temperature is always more than oral or rectal temperature. It is about 37.8°C (100°F).

■ VARIATIONS OF BODY TEMPERATURE

Physiological Variations

1. Age

In infants, the body temperature varies in accordance to environmental temperature for the first few days after birth. It is because the temperature regulating system does not function properly during infancy. In children the temperature is slightly (0.5°C) more than in adults because of more physical activities. In old age, since the heat production is less, the body temperature decreases slightly.

2. Sex

In females, the body temperature is less because of low basal metabolic rate when compared to that of males. During menstrual phase it decreases slightly.

3. Diurnal variation

In early morning, the temperature is 1°C less. In the afternoon, it reaches the maximum (about 1°C more than normal).

4. After meals

The body temperature rises slightly (0.5°C) after meals.

5. Exercise

During exercise, the temperature raises due to production of heat in muscles.

6. Sleep

During sleep, the body temperature decreases by 0.5°C.

7. Emotion

During emotional conditions, the body temperature increases.

8. Menstrual cycle

In females, immediately after ovulation, the temperature rises (0.5° to 1°C) sharply. It decreases (0.5°C) during menstrual phase.

Pathological Variations

Abnormal increase in body temperature is called hyperthermia or fever and decreased body temperature is called hypothermia.

■ HEAT BALANCE

Regulation of body temperature depends upon the balance between heat produced in the body and the heat lost from the body.

■ HEAT GAIN OR HEAT PRODUCTION IN THE BODY

The various mechanisms involved in the production of heat in the body are:

1. Metabolic Activities

The major portion of heat produced in the body is due to the metabolism of foodstuffs. Heat production is more during metabolism of fat. About 9 calories of heat is produced during metabolism of fats, when 1 liter of oxygen is utilized. For the same amount of oxygen, carbohydrate metabolism produces 4.7 calories of heat. Protein metabolism produces 4.5 calories/liter. Liver is the organ in which maximum heat is produced due to metabolic activity.

2. Muscular Activity

Heat is produced in the muscle both at rest and during activities. During rest, heat is produced by muscle tone. About 80% of heat of activity is produced by the activity of skeletal muscles.

3. Role of Hormones

Thyroxine and adrenaline increase the heat production by accelerating the metabolic activities.

4. Radiation of Heat from the Environment

Body gains heat by radiation. It occurs when the environmental temperature is higher than the body temperature.

5. Shivering

Shivering refers to shaking of the body caused by rapid involuntary contraction or twitching of the muscles during exposure to cold. It is a compensatory physiological mechanism in the body, during which enormous heat is produced.

■ HEAT LOSS FROM THE BODY

Maximum heat is lost from the body through skin and small amount of heat is lost through respiratory system, kidney and GI tract. When environmental temperature is less than body temperature, heat is lost from the body. Heat loss occurs by the following methods:

1. Conduction

Heat is lost from the surface of the body to other objects such as chair or bed by means of conduction.

2. Radiation

Sixty percent of heat is lost by means of radiation, i.e. transfer of heat by infrared electromagnetic radiation from body to other objects through the surrounding air.

3. Convection

Heat is conducted to the air surrounding the body and then carried away by air currents, i.e. convection.

4. Evaporation – Insensible Perspiration

Normally, a small quantity of water is continuously evaporated from skin and lungs. We are not aware of it. So it is called insensible perspiration or insensible water loss. It is about 50 mL/hour. When body temperature increases, more heat is lost by evaporation of more water.

5. Panting

Panting is the rapid shallow breathing associated with dribbling of more saliva. In some animals like dogs which do not have sweat glands, heat is lost by evaporation of water from lungs and saliva by means of panting.

■ REGULATION OF BODY TEMPERATURE

The body temperature is regulated by hypothalamus which sets the normal range of body temperature. The set point under normal physiological conditions is 37°C. Hypothalamus has two centers which regulate the body temperature (Fig. 43-1):

- A. Heat loss center
- B. Heat gain center.

■ HEAT LOSS CENTER

This center is situated in preoptic nucleus of anterior hypothalamus. Neurons in preoptic nucleus are heat sensitive nerve cells which are called thermoreceptors. Stimulation of preoptic nucleus results in cutaneous vasodilatation and sweating. Removal or lesion of this nucleus increases the body temperature.

■ HEAT GAIN CENTER

It is otherwise known as heat production center. It is situated in posterior hypothalamic nucleus.

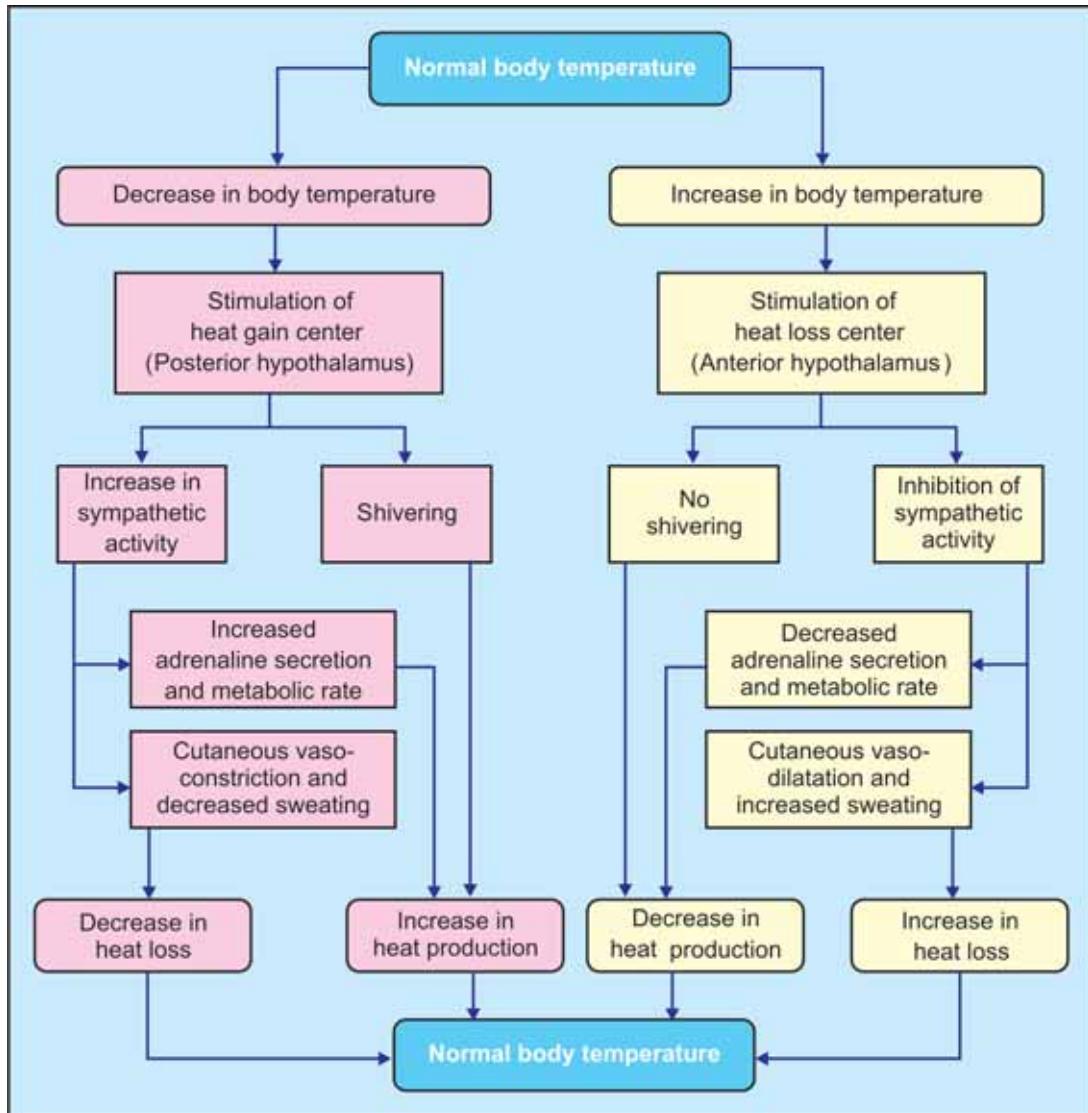


FIGURE 43-1: Regulation of body temperature

Stimulation of posterior hypothalamic nucleus causes shivering. The removal or lesion of this nucleus leads to fall in body temperature.

■ MECHANISM OF TEMPERATURE REGULATION

When Body Temperature Increases

When body temperature increases, blood temperature also increases. When blood with increased temperature passes through hypo-

thalamus, it stimulates the thermoreceptors present in the heat loss center in preoptic nucleus. Now, the heat loss center brings the temperature back to normal by two mechanisms:

1. Promotion of heat loss
2. Prevention of heat production

1. Promotion of heat loss

Heat loss center promotes heat loss from the body by:

- i. *Increasing the secretion of sweat:* When sweat secretion increases, more water is lost from skin along with heat
- ii. *Inhibiting the sympathetic centers in posterior hypothalamus:* This causes cutaneous vasodilatation. Now, blood flow through skin increases causing excess sweating. It increases the heat loss through sweat leading to decrease in body temperature.

2. Prevention of heat Production

Heat loss center prevents heat production in the body by inhibiting mechanisms involved in heat production such as shivering and chemical (metabolic) reactions.

When Body Temperature Decreases

When the body temperature decreases it is brought back to normal by two mechanisms:

1. Prevention of heat loss
2. Promotion of heat production.

1. Prevention of heat loss

When body temperature decreases, the preoptic thermoreceptors are not activated. So, the posterior hypothalamus is not inhibited. This causes cutaneous vasoconstriction. The blood

flow to skin decreases, and so the heat loss is prevented.

2. Promotion of heat production

The heat production is promoted by two ways:

- i. *Shivering:* The primary motor center for shivering is situated in posterior hypothalamus near the wall of the III ventricle. When body temperature is low, this center is activated by heat gain center and, shivering occurs. Enormous heat is produced during shivering due to severe muscular activities.
- ii. *Increased metabolic reactions:* The sympathetic centers, which are activated by heat gain center, stimulate secretion of adrenaline and noradrenaline. These hormones, particularly adrenaline increase heat production by accelerating cellular metabolic activities.

Simultaneously, hypothalamus secretes thyrotropic releasing hormone. It causes release of thyroid stimulating hormone from pituitary. It in turn increases release of thyroxine from thyroid. Thyroxine accelerates the metabolic activities in the body and increases heat production.

Chemical thermogenesis: It is the process in which heat is produced in the body by metabolic activities induced by hormones.

QUESTIONS IN RENAL PHYSIOLOGY AND SKIN

■ LONG QUESTIONS

1. Describe the process of urine formation.
2. What are the different stages of urine formation? Explain the glomerular filtration.
3. Give an account of role of renal tubule in the process of urine formation.
4. What is counter current mechanism? Describe the anatomical and physiological basis of counter current mechanism in kidney.
5. Describe the mechanism involved in the concentration of urine.
6. Give an account of micturition.
8. What is normal body temperature? Explain heat balance and regulation of body temperature. Add a note on fever.

■ SHORT QUESTIONS

1. Functions of kidney.
2. Structure of nephron.
3. Renal corpuscle.
4. Juxtaglomerular apparatus.
5. Renin–angiotensin system.
6. Peculiarities of renal circulation.
7. Autoregulation of renal circulation.

8. Glomerular filtration rate.
9. Effective filtration pressure in kidney.
10. Reabsorption of glucose in renal tubule.
11. Reabsorption of water in renal tubule.
12. Reabsorption of sodium in renal tubules.
13. Reabsorption of bicarbonate in renal tubules.
14. Secretion in renal tubule.
15. Renal medullary gradient.
16. Counter current multiplier.
17. Counter current exchanger.
18. Actions of hormones on renal tubules.
19. Acidification of urine.
20. Plasma clearance.
21. Nerve supply to urinary bladder and sphincters.
22. Cystometrogram.
23. Micturition reflex.
24. Structure of skin.
25. Functions of skin.
26. Sebaceous glands.
27. Sweat glands.
28. Differences between eccrine glands and apocrine glands.
29. Regulation of body temperature.
30. Heat balance.

SECTION 6

Endocrinology

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44

Introduction to Endocrinology

- INTRODUCTION
- ENDOCRINE GLANDS
- HORMONES
- HORMONAL ACTION

■ INTRODUCTION

All the physiological activities are regulated by two major systems in the body.

1. Nervous system
2. Endocrine system.

These two systems interact with one another and regulate the body functions. This section deals with endocrine system and Section 10 deals with nervous system. Endocrine system functions by secreting some chemical substances called hormones.

■ ENDOCRINE GLANDS

Endocrine glands are the glands which synthesize and release the classical hormones into the blood. The endocrine glands are also called ductless glands because the hormones secreted by them are released directly into blood without any duct.

Major endocrine glands are shown in Fig. 44-1.

The hormones secreted by the major endocrine glands are listed in Table 44-1.

The hormones secreted by the gonads are given in Table 44-2.

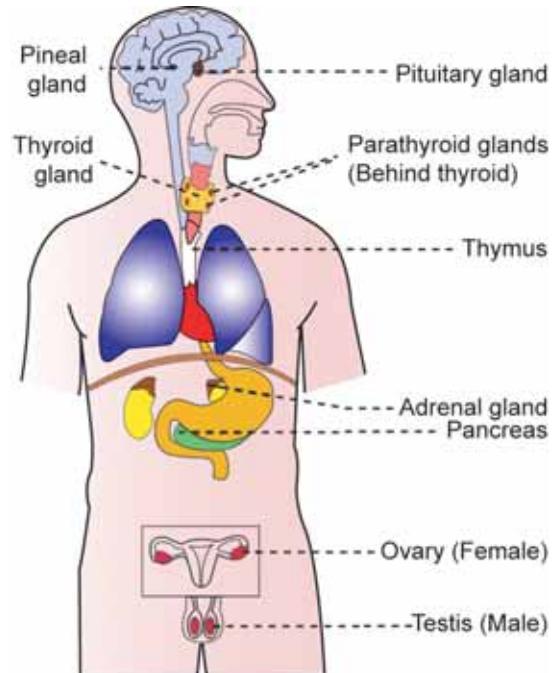


FIGURE 44-1: Major endocrine glands

The hormones secreted by other organs are given in Table 44-3.

The local hormones are listed in Table 44-4.

TABLE 44-1: Hormones secreted by major endocrine glands

Anterior pituitary	1. Growth hormone (GH) 2. Thyroid stimulating hormone (TSH) 3. Adrenocorticotropic hormone (ACTH) 4. Follicle stimulating hormone (FSH) 5. Luteinizing hormone (LH) 6. Prolactin
Posterior pituitary	1. Antidiuretic hormone (ADH) 2. Oxytocin
Thyroid gland	1. Thyroxine (T_4) 2. Tri-iodothyronine (T_3) 3. Calcitonin
Parathyroid gland	1. Parathormone
Pancreas — islets of Langerhans	1. Insulin 2. Glucagon 3. Somatostatin 4. Pancreatic polypeptide
Adrenal cortex	<i>Mineralocorticoids</i> 1. Aldosterone 2. 11 deoxycorticosterone <i>Glucocorticoids</i> 1. Cortisol 2. Corticosterone <i>Sex hormones</i> 1. Androgens 2. Estrogen 3. Progesterone
Adrenal medulla	<i>Catecholamines</i> 1. Adrenaline (Epinephrine) 2. Noradrenaline (Norepinephrine) 3. Dopamine

■ HORMONES

■ CLASSIFICATION OF HORMONES

Based on chemical nature the hormones are classified into three types:

TABLE 44-2: Hormones secreted by gonads

Testis	1. Testosterone 2. Dihydrotestosterone 3. Androstenedion
Ovary	1. Estrogen 2. Progesterone

TABLE 44-3: Hormones secreted by other organs

Pineal gland	Heart 1. Melatonin
Thymus	Placenta 1. Thymosin 2. Thymin
Kidney	Placenta 1. Human chorionic gonadotropin (hCG) 2. Human chorionic somatomammotropin 3. Estrogen 4. Progesterone

TABLE 44-4: Local hormones

1. Prostaglandins 2. Thromboxanes 3. Prostacyclin 4. Leukotrienes 5. Lipoxins 6. Acetylcholine 7. Serotonin 8. Histamine 9. Substance P 10. Heparin 11. Bradykinin 12. Gastrointestinal hormones

1. Steroid hormones

2. Protein hormones

3. Derivatives of the amino acid, called tyrosine.

Classification of hormones depending upon their chemical nature are given in Table 44-5.

TABLE 44-5: Classification of hormones depending upon chemical nature

Steroids	Proteins	Derivatives of tyrosine
Aldosterone	Growth hormone (GH)	Thyroxine (T_4)
11 deoxycorticosterone	Thyroid stimulating hormone (TSH)	Tri-iodothyronine (T_3)
Cortisol	Adrenocorticotrophic hormone (ACTH)	Adrenaline (Epinephrine)
Corticosterone	Follicle stimulating hormone (FSH)	Noradrenaline (Norepinephrine)
Testosterone	Luteinizing hormone (LH)	Dopamine
Dihydrotestosterone	Prolactin	
Dehydroepiandrosterone	Antidiuretic hormone (ADH)	
Androstenedione	Oxytocin	
Estrogen	Parathormone	
Progesterone	Calcitonin	
	Insulin	
	Glucagon	
	Somatostatin	
	Pancreatic polypeptide	
	Human chorionic gonadotropin (hCG)	
	Human chorionic somatomammotropin	

HORMONAL ACTION

Hormone does not act directly on the cellular structures. First it combines with receptors present on the target cells and forms a hormone-receptor complex. This hormone-receptor complex induces various changes or reactions in the target cells.

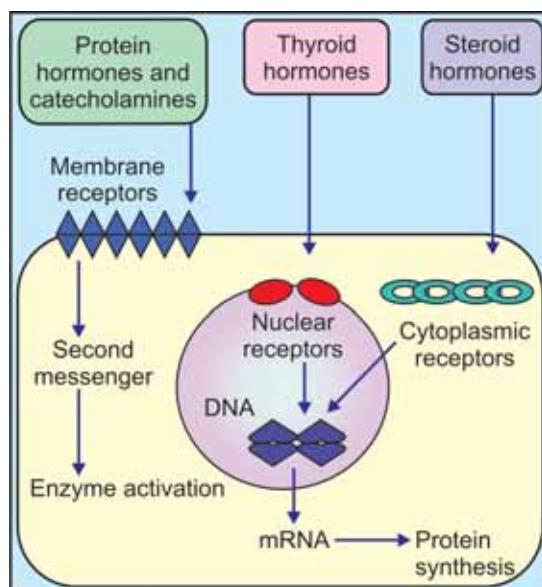
HORMONE RECEPTORS

The hormone receptors are the large proteins present in the target cells. Each receptor is specific for one single hormone, i.e. each receptor can combine with only one hormone.

Situation of the Hormone Receptors

The hormone receptors are situated either in cell membrane or cytoplasm or nucleus of the cells as follows:

1. *Cell membrane:* Receptors of protein hormones and adrenal medullary hormones (catecholamines) are situated in the cell membrane (Fig. 44-2)
2. *Cytoplasm:* Receptors of steroid hormones are situated in cytoplasm of target cells
3. *Nucleus:* Receptors of thyroid hormones are in the nucleus of the cell.

**FIGURE 44-2:** Situation of hormonal receptors

MECHANISM OF HORMONAL ACTION

On the target cell, the hormone-receptor complex acts by any one of the following mechanisms:

1. By altering the permeability of the cell membrane
2. By activating the intracellular enzyme
3. By activating the genes.

1. By Altering the Permeability of Cell Membrane

The neurotransmitter substances in a synapse or neuromuscular junction act by changing the permeability of postsynaptic membrane.

For example, in a neuromuscular junction, when an impulse (action potential) reaches the axon terminal of the motor nerve, acetylcholine is released from the vesicles. Acetylcholine increases permeability of postsynaptic membrane by opening the ligand gated sodium channels. So, sodium ions enter the neuromuscular junction from ECF through the channels. Sodium ions alter the resting membrane potential so that, endplate potential is developed.

2. By Activating the Intracellular Enzyme

The protein hormones and the catecholamines act by activating the intracellular enzymes.

The hormone, which acts on a target cell, is called first messenger or chemical mediator. This hormone, in combination with the receptor forms hormone-receptor complex. This in turn activates the enzymes of the cell and causes the formation of another substance called the second messenger.

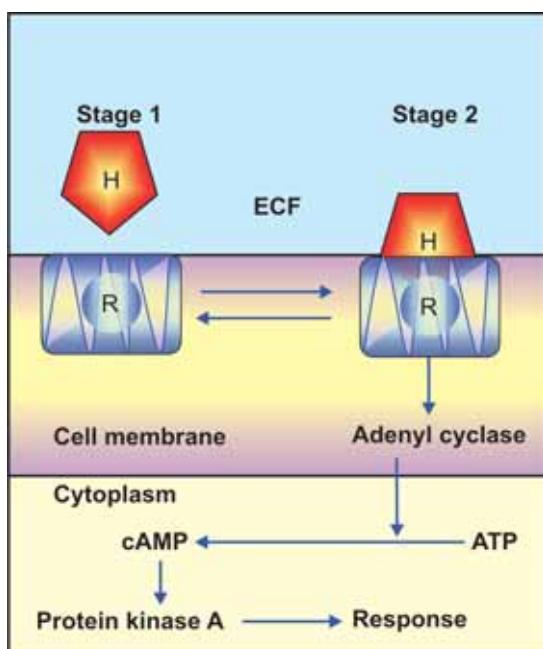


FIGURE 44-3: Mode of action of protein hormones and catecholamines. H = Hormone, R = Receptor

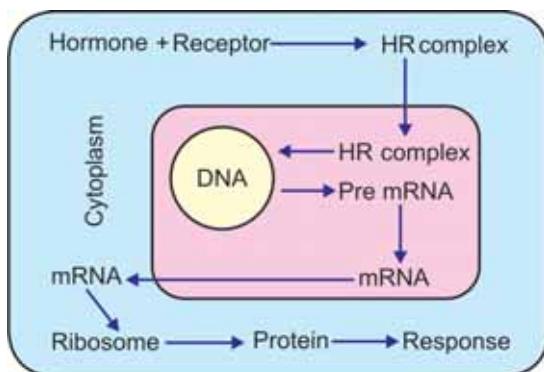


FIGURE 44-4: Mode of action of steroid hormones. Thyroid hormones also act in the similar way. But their receptors are in the nucleus. HR = Hormone-receptor complex

The second messenger produces the effects of the hormone inside the cells. The most common second messenger is adenosine monophosphate (cyclic AMP or cAMP).

Sequence of events in the activation of second messenger:

- The hormone binds with the receptor in the cell membrane and forms the hormone-receptor complex which activates the enzyme adenyl cyclase
- Adenyl cyclase converts the ATP of the cytoplasm into cAMP. Cyclic AMP executes the actions of hormone inside the cell, by stimulating the enzymes like protein kinase A (Fig. 44-3).

3. By Acting on Genes

Thyroid and steroid hormones act by activating the genes of the target cells.

Sequence of events during activation of genes:

- The hormone enters the interior of the cell and binds with receptor in cytoplasm (steroid hormone) or in nucleus (thyroid hormone) and forms hormone-receptor complex
- This complex binds to DNA and increases transcription of mRNA
- The mRNA moves out of nucleus and reaches ribosomes and activates them
- The activated ribosomes produce large quantities of proteins which produce the physiological responses in the target cells (Fig. 44-4).

45

Pituitary Gland

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- ANTERIOR PITUITARY
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 - HISTOLOGY
 - HORMONES
 - REGULATION
 - GROWTH HORMONE
 - OTHER HORMONES
- POSTERIOR PITUITARY
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 - HYPERACTIVITY OF ANTERIOR PITUITARY
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■ INTRODUCTION

The pituitary gland is also known as hypophysis. It is a small gland that lies at the base of the brain. It is connected with the hypothalamus by the pituitary stalk or hypophyseal stalk.

Pituitary gland is divided into two portions:

1. Anterior pituitary or adenohypophysis
2. Posterior pituitary or neurohypophysis.

Even though anterior pituitary and posterior pituitary are situated in close approximation, both are entirely different in their development, structure and function.

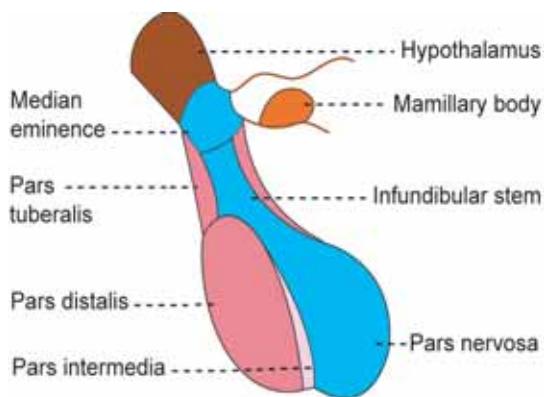


FIGURE 45-1: Parts of pituitary gland
■ Adenohypophysis ■ Neurohypophysis

■ ANTERIOR PITUITARY

■ PARTS

Anterior pituitary consists of three divisions (Fig. 45-1):

1. Pars distalis
2. Pars tuberalis
3. Pars intermedia.

■ HISTOLOGY

Depending upon the staining property, the cells of anterior pituitary are classified into two types:

1. Chromophobe cells which do not have granules and stain poorly. These cells are not secretory in nature
2. Chromophil cells which contain large granules and are stained darkly. According to the staining nature, the chromophil cells are of two types, acidophilic cells or alpha cells and basophilic cells or beta cells.

Based on the secretory nature the chromophil cells are classified into five types:

- i. Somatotropes which secrete growth hormone
- ii. Corticotropes which secrete adrenocorticotropic hormone
- iii. Thyrotropes which secrete thyroid stimulating hormone
- iv. Gonadotropes which secrete follicle stimulating hormone and luteinizing hormone
- v. Lactotropes which secrete prolactin.

Somatotropes and lactotropes are acidophilic cells, whereas others are basophilic cells.

■ HORMONES SECRETED BY ANTERIOR PITUITARY

Anterior pituitary is also known as the master gland because it regulates many other endocrine glands. Six hormones are secreted by the anterior pituitary:

1. Growth hormone (GH) or somatotropic hormone (STH)
2. Thyroid stimulating hormone (TSH) or thyrotropic hormone
3. Adrenocorticotrophic hormone (ACTH)
4. Follicle stimulating hormone (FSH)
5. Luteinizing hormone (LH in females) or interstitial cell stimulating hormone (ICSH in males)
6. Prolactin.

FSH and LH are together called gonadotropic hormones or gonadotropins because of their action on the gonads.

Recently, the hormone β -lipotropin is found to be secreted by anterior pituitary.

■ REGULATION OF SECRETION OF ANTERIOR PITUITARY HORMONES

Secretion of anterior pituitary hormones is regulated by hypothalamus. Hypothalamus secretes some releasing and inhibitory hormones (factors) which are transported from hypothalamus to anterior pituitary through hypothalamo-hypophyseal portal vessels.

Releasing and Inhibitory Hormones Secreted by Hypothalamus

1. Growth hormone releasing hormone (GHRH) — stimulates the release of GH
2. Growth hormone releasing polypeptide (GHRP) — stimulates the release of GHRH and GH
3. Growth hormone inhibitory hormone (GHIH) or somatostatin — inhibits GH release
4. Thyrotropic releasing hormone (TRH) — stimulates the release of TSH
5. Corticotropin releasing hormone (CRH) — stimulates the release of ACTH

6. Gonadotropin releasing hormone (GnRH) — the release of the gonadotropins — FSH and LH
7. Prolactin inhibitory hormone (PIH) — inhibits prolactin secretion.

■ GROWTH HORMONE

Growth hormone (GH) is secreted by the acidophils of the anterior pituitary, which are also known as somatotropes.

It is protein in nature having a single chain polypeptide with 191 amino acids. GH is transported in blood by GH binding proteins (GHBPs).

The basal level of GH concentration in blood of the normal adult is up to 300 g/dL and in children it is about 500 ng/dL. Its daily output in adults is 0.5 to 1.0 mg.

Actions of Growth Hormone

GH is responsible for the growth of almost all tissues of the body, which are capable of growing. It actually increases the size and number of cells by increasing the mitotic division. GH also causes specific differentiation of certain types of cells like bone cells and muscle cells.

GH also acts on the metabolism of all the three major types of foodstuffs in the body, viz. proteins, lipids and carbohydrates.

1. On Metabolism

GH increases the synthesis of proteins, mobilization of lipids and conservation of carbohydrates.

A. On protein metabolism

GH accelerates the synthesis of protein by:

- i. Increasing the amino acid transport through the cell membrane.
- ii. Increasing the RNA translation. Because of this, the ribosomes are activated and more proteins are synthesized.
- iii. Increasing the transcription of DNA to RNA. This, in turn accelerates the synthesis of proteins in the cells.
- iv. Decreasing the catabolism of protein.

- v. Promoting the anabolism of proteins indirectly by causing release of insulin which has anabolic effect on proteins.

B. On fat metabolism

GH mobilizes fats from adipose tissue. Because of this, the concentration of fatty acids increases in the body fluids. These fatty acids are used for the production of energy by the cells. So proteins are spared.

During the utilization of fatty acids for the production of energy, lot of acetoacetic acid is produced by the liver and released into the body fluids leading to ketosis. Sometimes excess mobilization of fat from the adipose tissue causes accumulation of fat in liver, resulting in fatty liver.

C. On carbohydrate metabolism

The main action of GH on carbohydrates is the conservation of glucose.

The effects of GH on the carbohydrate metabolism are:

- i. Decrease in the peripheral utilization of glucose for the production of energy.
- ii. Increase in the deposition of glycogen in the cells. Since, glucose is not utilized for energy production by the cells, it is converted into glycogen which is deposited in the cells.
- iii. Decrease in the uptake of glucose by the cells. As the deposition of glycogen increases, the cells become saturated with glycogen. Because of this, no more glucose can enter the cells. So the blood glucose level increases.
- iv. Diabetogenic effect of GH: Hypersecretion of GH increases blood glucose level enormously. It causes continuous stimulation of the β cells in the islets of Langerhans in pancreas and increases insulin secretion. In addition to this, the GH also stimulates the β cells of islets in pancreas directly and causes secretion of insulin. Because of the excess stimulation, the β cells are burnt out at one stage. This causes deficiency of insulin, which leads to true diabetes mellitus or full blown diabetes mellitus. This effect of GH is called the diabetogenic effect.

2. On Bones

In embryonic stage, GH is responsible for the differentiation and the development of bone cells. In later stages, GH increases the growth of the skeleton. It increases both the length as well as the thickness of the bones.

In the bones, GH increases:

- Protein synthesis by chondrocytes and osteogenic cells
- Multiplication of chondrocytes and osteogenic cells
- Formation of new bones by converting chondrocytes into osteogenic cells
- Increases the calcium absorption from intestine. By this GH enhances the availability of calcium for mineralization of bone matrix.

GH increases the length of the bones until epiphysis fuses with the shaft. Usually fusion occurs at puberty. After the epiphyseal fusion, length of the bones cannot be increased. However, it stimulates the osteoblasts strongly. So, the bone continues to grow in thickness throughout the life. Particularly, the membranous bones such as jaw bone and skull bones become thicker under the influence of GH.

Mode of Action of GH on Bones and Metabolism

GH acts on bones, growth and protein metabolism through a substance called somatomedin, which is secreted by liver. GH stimulates the liver to secrete somatomedin. Sometimes, in spite of normal secretion of GH, growth is arrested (dwarfism) due to the absence or deficiency of somatomedin.

Somatomedin

Somatomedin is a polypeptide. There are two types of somatomedins.

- Insulin like growth factor-I (IGF-I), which is also called somatomedin-C
- Insulin like growth factor-II.

Among the two somatomedins, the somatomedin-C (IGF-I) is responsible for the action of bones on bones and metabolism.

Regulation of GH Secretion

Secretion of GH is regulated by hypothalamus and feedback control.

Role of hypothalamus in the secretion of GH

Hypothalamus regulates GH secretion by releasing three hormones:

- GHRH that increases the secretion of GH by stimulating the somatotropes of anterior pituitary
- GHRP that promotes the release of GHRH from hypothalamus and GH from pituitary
- GHIH or somatostatin which inhibits the secretion of GH.

These three hormones are transported from hypothalamus to anterior pituitary by hypothalamo-hypophyseal portal blood vessels.

Hypothalamus is in turn influenced by many factors which cause increase or decrease in GH secretion.

Factors which increase the GH secretion:

- Hypoglycemia
- Fasting
- Starvation
- Exercise
- Stress and trauma
- Initial stages of sleep.

Factors which decrease the GH secretion:

- Hyperglycemia
- Increase in free fatty acids in blood
- Later stages of sleep.

Feedback control

GH secretion is under negative feedback control (Chapter 4). Hypothalamus releases GHRH and GHRP, which in turn promote the release of GH from anterior pituitary. GH acts on various tissues. It also activates the liver cells to secrete somatomedin-C (IGF-I).

Now, the somatomedin-C increases the release of GHIH from hypothalamus. GHIH in turn inhibits release of GH from pituitary. Somatomedin also inhibits the release of GHRP from hypothalamus. It acts on pituitary directly and inhibits the secretion of GH (Fig. 45-2).

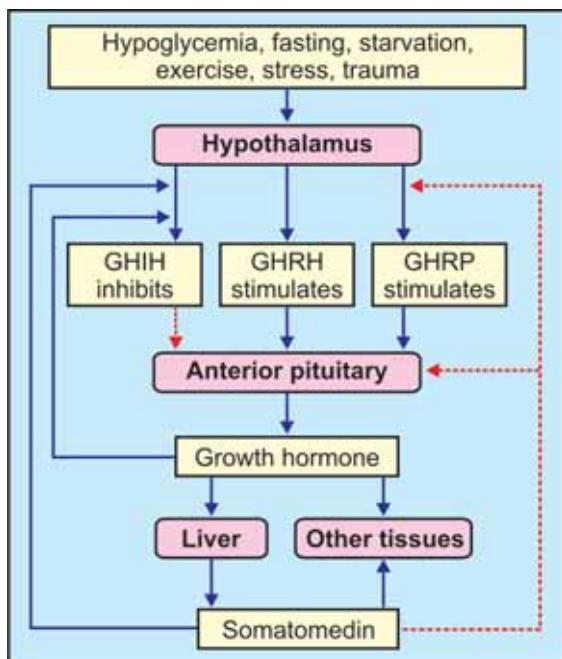


FIGURE 45-2: Regulation of GH secretion. GHIH = Growth hormone inhibitory hormone. GHRH = Growth hormone releasing hormone. GHRP = Growth hormone releasing polypeptide. Growth hormone and somatomedin stimulate hypothalamus to release GHIH. Somatomedin inhibits anterior pituitary directly. Solid blue line = stimulation/secretion. Dashed red line = inhibition

GH inhibits its own secretion by stimulating the release of GHIH from hypothalamus. This type of feedback is called short-loop feedback control. Similarly, GHRH inhibits its own release by short-loop feedback control.

Whenever, the blood level of GH decreases, the GHRH is secreted from the hypothalamus. It in turn causes secretion of GH from pituitary.

■ OTHER HORMONES OF ANTERIOR PITUITARY

Thyroid Stimulating Hormone (TSH)

TSH is necessary for the growth and the secretory activity of the thyroid gland.

Adrenocorticotropic Hormone (ACTH)

ACTH is necessary for the structural integrity and the secretory activity of adrenal cortex.

Follicle Stimulating Hormone (FSH)

Actions in males

In males, FSH acts along with testosterone and accelerates the process of spermatogenesis.

Actions in females

1. It is responsible for the development of graafian follicle from primordial follicle
2. It stimulates the theca cells of graafian follicle and causes secretion of estrogen (refer Chapter 54 for details)
3. Promotes aromatase activity in granulosa cells resulting in conversion of androgens into estrogen.

Luteinizing Hormone (LH)

Actions in males

In males, LH is known as interstitial cell stimulating hormone (ICSH) because it stimulates the interstitial cells of Leydig in testes. This hormone is essential for the secretion of testosterone from Leydig cells.

Actions in females

1. LH causes maturation of vesicular follicle into graafian follicle along with follicle stimulating hormone
2. It induces synthesis of androgens from theca cells of growing follicle
3. It is responsible for ovulation
4. It is necessary for the formation of corpus luteum
5. It activates the secretory functions of corpus luteum.

Prolactin

Prolactin is necessary for the final preparation of mammary glands for production and secretion of milk.

β Lipotropin

It mobilizes fat from adipose tissue and promotes lipolysis.

■ POSTERIOR PITUITARY

■ PARTS

Posterior pituitary consists of three divisions:

1. The pars nervosa or infundibular process
2. Neural stalk or infundibular stem
3. The median eminence.

The pars tuberalis of anterior pituitary and the neural stalk of posterior pituitary together form the hypophyseal stalk.

■ HISTOLOGY

Posterior pituitary is made up of nerve cells called pituicytes and unmyelinated nerve fibers. Pituicytes act as supporting cells and do not secrete any hormone. Neurohypophysis also has numerous blood vessels, hyaline bodies, neuroglial cells and mast cells.

■ HORMONES OF POSTERIOR PITUITARY

Posterior pituitary hormones are:

1. Antidiuretic hormone (ADH) or vasopressin
2. Oxytocin.

Actually, the posterior pituitary does not secrete any hormone. ADH and oxytocin are synthesized in the hypothalamus. Hence, these two hormones are called neurohormones.

■ ANTIDIURETIC HORMONE

ADH is secreted mainly by supraoptic nucleus of hypothalamus and in small quantity by paraventricular nucleus. From here, this hormone is transported to the posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract by means of axonic flow (Fig. 45-3).

Antidiuretic hormone is a polypeptide, containing 9 amino acids.

Actions

The major function of ADH is retention of water by acting on kidneys. It increases the facultative reabsorption of water from distal convoluted

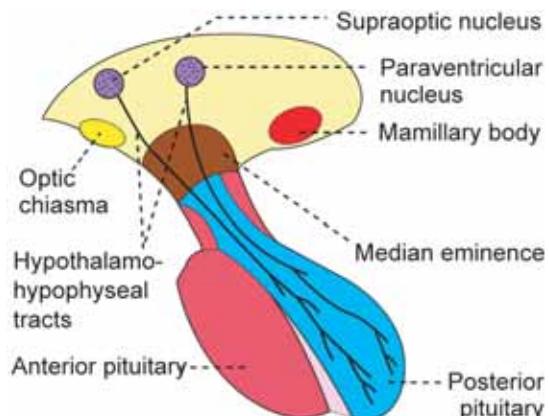


FIGURE 45-3: Hypothalamo-hypophyseal tracts

tubule and collecting duct in the kidneys (Chapter 37).

ADH increases water reabsorption in the tubular epithelial membrane by regulating the water channel proteins called aquaporins through V_2 receptors (Chapter 37).

Vasopressor Action

In large amount, the ADH shows vasoconstrictor action in all parts of the body. Due to the vasoconstriction, the blood pressure increases. ADH acts on blood vessels through V_{1A} receptors.

Regulation of Secretion

The secretion of ADH depends upon the volume of body fluid and the osmolarity of the body fluids.

The potent stimulants for ADH secretion are:

1. Decrease in the ECF volume
2. Increase in osmolar concentration in the ECF.

Role of osmoreceptors

The osmoreceptors are the receptors, which give response to change in the osmolar concentration of the blood. These receptors are situated in the hypothalamus near supraoptic and paraventricular nuclei. When osmolar concentration of blood increases, the osmoreceptors are activated. In turn, the osmoreceptors stimulate the supraoptic and paraventricular nuclei which send

motor impulses to posterior pituitary through the nerve fibers and cause release of ADH. ADH causes reabsorption of water from the renal tubules. This increases the volume of the ECF and restores the normal osmolarity.

■ OXYTOCIN

Oxytocin is secreted mainly by the paraventricular nucleus and a small quantity is secreted by the supraoptic nucleus in the hypothalamus. And it is transported from hypothalamus to posterior pituitary through the nerve fibers of hypothalamo-hypophyseal tract.

In the posterior pituitary, the oxytocin is stored in the nerve endings of hypothalamo-hypophyseal tract. When suitable stimuli reach the posterior pituitary from hypothalamus, oxytocin is released into the blood. Oxytocin is secreted in both males and females.

Oxytocin is a polypeptide, having 9 amino acids.

Actions in Females

In females, oxytocin acts on mammary glands and uterus.

Action of oxytocin on mammary glands

It causes ejection of milk from the mammary glands. The ducts of the mammary glands are lined by myoepithelial cells. Oxytocin causes contraction of the myoepithelial cells and squeezes the milk from alveoli of the mammary glands to the exterior through the duct system and nipple. The process by which the milk is ejected from the alveoli of mammary glands is called the milk ejection reflex or milk let down reflex. It is one of the neuroendocrine reflexes.

Milk ejection reflex

Plenty of touch receptors are present on the mammary glands, particularly around the nipple. When the infant suckles mother's nipple, the touch receptors are stimulated and impulses are discharged. Impulses from here are carried by

the somatic afferent nerve fibers and reach the paraventricular and supraoptic nuclei of hypothalamus.

Now, hypothalamus in turn, sends impulses to the posterior pituitary through hypothalamo-hypophyseal tract and cause release of oxytocin into the blood. When the hormone reaches the mammary gland, it causes contraction of myoepithelial cells resulting in ejection of milk from mammary glands (Fig. 45-4).

As this reflex is initiated by the nervous factors and completed by the hormonal action, it is called a neuroendocrine reflex. During this reflex, large amount of oxytocin is released by positive feedback mechanism.

Action on uterus

Oxytocin acts on pregnant uterus and nonpregnant uterus.

On pregnant uterus

Throughout the period of pregnancy, oxytocin secretion is inhibited by estrogen and progesterone. At the end of pregnancy, the secretion of these two hormones decreases suddenly and the secretion of oxytocin increases. Oxytocin causes contraction of uterus and helps in the expulsion of fetus.

During labor, large quantity of oxytocin is released by means of positive feedback mechanism, i.e. oxytocin induces contraction of uterus, which in turn causes release of more amount of oxytocin (Fig. 4-5).

The contraction of uterus during labor is also a neuroendocrine reflex. Oxytocin also stimulates the release of prostaglandins in the placenta. The prostaglandins intensify the uterine contraction induced by oxytocin.

On nonpregnant uterus

The action of oxytocin on nonpregnant uterus is to facilitate the transport of sperms through female genital tract up to fallopian tube by producing the uterine contraction during the sexual intercourse.

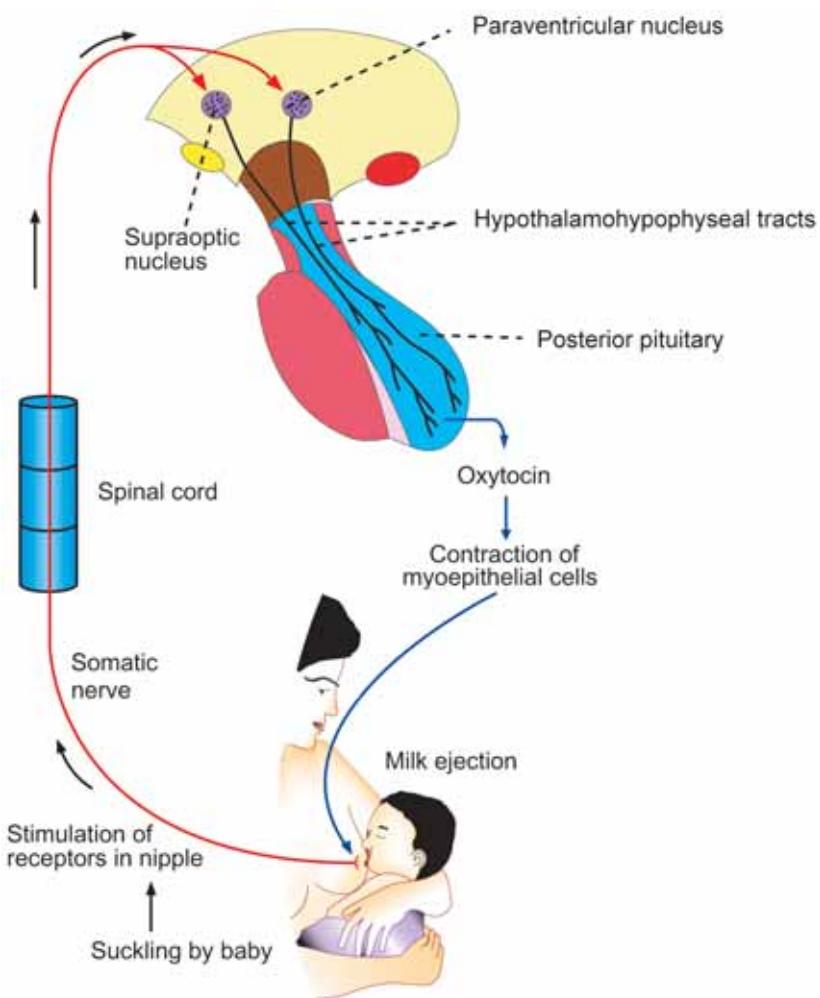


FIGURE 45-4: Milk ejection reflex

During the sexual intercourse, the receptors in the vagina are stimulated. The vaginal receptors generate the impulses, which are transmitted by somatic afferent nerves to the paraventricular and supraoptic nuclei of hypothalamus. When, these two nuclei are stimulated, oxytocin is released, and transported by blood. While reaching the female genital tract, the hormone causes antiperistaltic contractions of uterus towards the fallopian tube which accelerate the transport of sperms. It is also a neuroendocrine reflex.

The sensitivity of uterus to oxytocin is accelerated by estrogen and decreased by progesterone.

Action in Males

In males, the release of oxytocin increases during ejaculation. It facilitates release of sperm into urethra by causing contraction of smooth muscle fibers in reproductive tract particularly vas deferens.

Mode of Action of Oxytocin

Oxytocin acts on mammary glands and uterus by activating G protein-coupled oxytocin receptor.

■ APPLIED PHYSIOLOGY— DISORDERS OF PITUITARY GLAND

The disorders of pituitary gland are given in Table 45-1.

TABLE 45-1: Disorders of pituitary gland

Parts involved	Hyperactivity	Hypoactivity
Anterior pituitary	1. Gigantism 2. Acromegaly 3. Acromegalic gigantism 4. Cushing's disease	1. Dwarfism 2. Acromicria 3. Simmond's disease
Posterior pituitary	Syndrome of inappropriate hypersecretion of ADH (SIADH)	Diabetes insipidus
Anterior and posterior pituitary	- - -	Dystrophia adiposogenitalis

■ HYPERACTIVITY OF ANTERIOR PITUITARY

1. *Gigantism*

Gigantism is the pituitary disorder characterized by excess growth of the body. The subjects look like the giants with average height of about 7-8 feet.

Cause

Gigantism is due to hypersecretion of GH in childhood or in the pre-adult life before the fusion of epiphysis of bone with the shaft. It occurs due to pituitary tumors.

Signs and symptoms

- The general over growth of the person leads to the development of a huge stature with a height of more than 7 or 8 feet. The limbs are disproportionately long
- The giants are hyperglycemic and they develop glycosuria and pituitary diabetes. The hyperglycemia causes constant stimulation of β cells of islets of Langerhans in the pancreas and release of insulin. However, the over activity of β cells of Langerhans in pancreas leads to degeneration of these cells and deficiency of insulin. And, ultimately diabetes mellitus is developed
- The pituitary tumor itself causes constant headache
- Pituitary tumor also causes visual disturbances. It compresses the lateral fibers

of optic chiasma leading to bitemporal hemianopia (Chapter 106).

2. *Acromegaly*

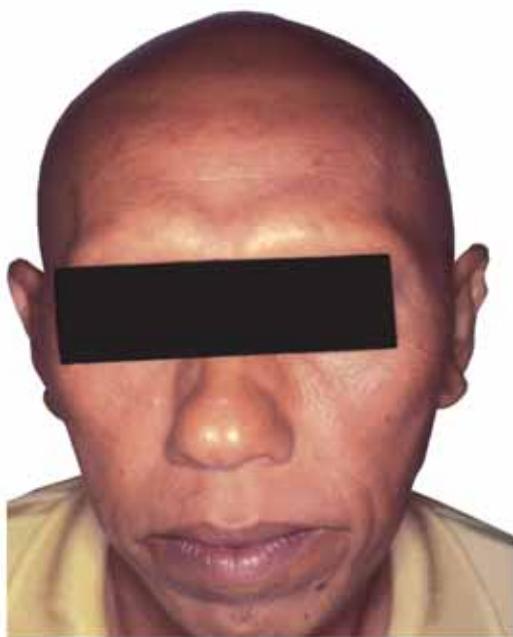
It is the disorder characterized by the enlargement, thickening and broadening of bones, particularly in the extremities of the body.

Cause

Acromegaly is due to hypersecretion of GH in adults after the fusion of epiphysis with shaft of the bone. Hypersecretion of GH is due to adenomatous tumor of anterior pituitary involving the acidophil cells.

Signs and symptoms

- The striking facial features are protrusion of supraorbital ridges, broadening of nose, thickening of lips, thickening and wrinkles formation on forehead, and protrusion of lower jaw (prognathism). The face with these features is called acromegalic or guerrilla face (Fig. 45-5)
- Enlargement of hands and feet (Fig. 45-6) with bowing of spine (kyphosis)
- The scalp is thickened and thrown into folds or wrinkles like bulldog scalp. There is general overgrowth of body hair
- The visceral organs such as lungs, heart, liver and spleen are enlarged
- Thyroid gland, parathyroid glands and the adrenal glands show hyperactivity
- Hyperglycemia and glucosuria occur resulting in diabetes mellitus



Guerrilla face: Protrusion of supraorbital ridges, broad nose, thickened lips and protrusion of lower jaw.



Wrinkled forehead, with other features of acromegalic face.

FIGURE 45-5: Acromegaly (Courtesy: Prof Mafauzy Mohamad)



FIGURE 45-6: A. Normal hand; B. Acromegalic hand (Courtesy: Prof Mafauzy Mohamad)

- vii. Hypertension
- viii. Headache
- xi. Visual disturbances—bitemporal hemianopia.

3. Acromegalic Gigantism

It is a rare disorder with symptoms of both gigantism and acromegaly. Hypersecretion of GH in children, before the fusion of epiphysis with

shaft of the bones causes gigantism. And, if hypersecretion of the GH is continued even after the fusion of epiphysis, the symptoms of acromegaly also appear.

4. Cushing's Disease

It is also a rare disease characterized by obesity. The details are given in Chapter 49.

■ HYPOACTIVITY OF ANTERIOR PITUITARY

1. Dwarfism

It is a pituitary disorder in children characterized by the stunted growth.

Causes

Reduction in the GH secretion in infancy or early childhood causes dwarfism. It occurs because of the following reasons:

- i. Deficiency of GHRH from hypothalamus
- ii. Deficiency of somatotropin-C

- iii. Atrophy or degeneration of acidophilic cells in the anterior pituitary
- iv. Tumor of chromophobes: It is a nonfunctioning tumor, which compresses and destroys the normal GH secreting cells
- v. Panhypopituitarism: In this condition, there is reduction in the secretion of all the hormones of anterior pituitary gland. This type of dwarfism is associated with other symptoms due to the deficiency of other anterior pituitary hormones.

Signs and symptoms

- i. The primary symptom of hypopituitarism in children is the stunted skeletal growth. The maximum height of anterior pituitary dwarf at the adult age is only about 3 feet
- ii. But the proportions of different parts of the body are almost normal. Only, the head becomes slightly larger in relation to the body
- iii. Pituitary dwarfs do not show any deformity and their mental activity is normal with no mental retardation
- iv. Reproductive function is not affected, if there is only GH deficiency. However, in panhypopituitarism (see below), the dwarfs do not obtain puberty due to deficiency of gonadotropin-releasing hormone.

Laron dwarfism

Laron dwarfism is a genetic disorder that occurs due to the presence of abnormal GH secretagogue receptors.

Psychogenic dwarfism

Dwarfism occurs if the child is exposed to extreme emotional deprivation or stress. The short stature is because of deficiency of GH. This type of dwarfism is called psychogenic dwarfism, psychosocial dwarfism or stress dwarfism.

Dwarfism in dystrophia adiposogenitalis

Dystrophia adiposogenitalis or Fröhlich's syndrome is a pituitary disorder (see below). Dwarfism occurs if it develops in children.

2. Acromicria

It is a rare disease in adults characterized by the atrophy of the extremities of the body.

Causes

Deficiency of GH in adults causes acromicria. The secretion of GH decreases in the following conditions:

- i. Deficiency of GH releasing hormone from hypothalamus
- ii. Atrophy or degeneration of acidophilic cells in the anterior pituitary
- iii. Tumor of chromophobes: It is a non-functioning tumor, which compresses and destroys the normal cells secreting the GH
- iv. Panhypopituitarism: In this condition, there is reduction in the secretion of all the hormones of anterior pituitary gland. Acromicria is associated with other symptoms due to the deficiency of other anterior pituitary hormones.

Signs and symptoms

- i. Atrophy and thinning of extremities of the body, (hands and feet) are the major symptoms in acromicria
- ii. Acromicria is mostly associated with hypothyroidism and hyposecretion of adrenocortical hormones
- iii. The person becomes lethargic and obese
- iv. There is loss of sexual functions.

3. Simmond's Disease

It is a rare pituitary disease. It is also called pituitary cachexia.

Causes

It occurs mostly in panhypopituitarism, i.e. hyposecretion of all the anterior pituitary hormones due to the atrophy or degeneration of anterior pituitary.

Symptoms

- i. A major feature of Simmond's disease is the rapidly developing senile decay. Thus, a 30

years old person looks like a 60 years old person

- ii. There is loss of hair over the body and loss of teeth
- iii. The skin on face becomes dry and wrinkled. So, there is shrunken appearance of facial features. It is the most common feature of this disease.

■ HYPERACTIVITY OF POSTERIOR PITUITARY

Syndrome of Inappropriate Hypersecretion of Antidiuretic Hormone (SIADH)

SIADH is the disease characterized by loss of sodium through urine due to hypersecretion of ADH.

Causes

It occurs due to cerebral tumors, lung tumors and lung cancers because the tumor cells and cancer cells secrete ADH.

In normal conditions ADH decreases the urine output by facultative reabsorption of water in distal convoluted tubule and the collecting duct. So, concentrated urine is formed with more sodium and other ions and less water. This decreases the osmolarity of plasma making it hypotonic. The hypotonic plasma inhibits ADH secretion resulting in restoration of plasma osmolarity.

However, in SIADH secretion of ADH from tumor or cancer cells is not inhibited by hypotonic plasma. So there is continuous loss of sodium resulting in persistent plasma hypotonicity.

Signs and symptoms

1. Loss of appetite
2. Weight loss
3. Nausea and vomiting
4. Headache
5. Muscle weakness, spasm and cramps
6. Fatigue
7. Restlessness and irritability.

In severe conditions, the patients die because of convulsions and coma.

■ HYPOACTIVITY OF POSTERIOR PITUITARY

Diabetes Insipidus

Diabetes insipidus is a posterior pituitary disorder characterized by excess excretion of water through urine.

Causes

This disorder develops due to the deficiency ADH which occurs in the following conditions:

- i. Lesion (injury) or degeneration of supraoptic and paraventricular nuclei of hypothalamus
- ii. Lesion in hypothalamo-hypophyseal tract
- iii. Atrophy of posterior pituitary
- iv. Inability of renal tubules to give response to ADH hormone. Such condition is called nephrogenic diabetic insipidus (see below).

Signs and symptoms

- i. *Polyuria*: Excretion of large quantity of dilute urine with increased frequency of voiding is called polyuria. Daily output of urine varies between 4 and 12 liters. In the absence of ADH, water is not reabsorbed from the renal tubule and collecting duct leading to loss of water through urine.
- ii. *Polydipsia*: Intake of excess water is called polydipsia. Loss of water due to polyuria stimulates the thirst center in hypothalamus resulting in intake of large quantity of water.
- iii. *Dehydration*: In some cases, the thirst center in the hypothalamus is also affected by the lesion. Water intake decreases in these patients and the loss of water through urine is not compensated. So, dehydration develops which may lead to death.

■ HYPOACTIVITY OF ANTERIOR AND POSTERIOR PITUITARY

Dystrophia Adiposogenitalis

Dystrophia adiposogenitalis is a disease characterized by obesity and hypogonadism affecting mainly the adolescent boys. It is also called Fröhlich's syndrome or hypothalamic eunuchism.

Causes

It is due to the hypoactivity of both anterior pituitary and posterior pituitary. The common cause of this disease is the tumor in pituitary gland and hypothalamic regions concerned with food intake and gonadal development.

Symptoms

Obesity is the common feature of this disorder. Due to the abnormal stimulation of feeding

center, the person overeats and becomes obese. Obesity is accompanied by sexual infantilism (failure to develop secondary sexual characters) or eunuchism. Dwarfism occurs if the disease starts in growing age. In children, it is called infantile or prepubertal type of Fröhlich's syndrome.

This disease develops in adults also. When it occurs in adults, it is called adult type of Fröhlich's syndrome. In adults, the major symptoms are obesity and atrophy of sex organs.

46

Thyroid Gland

- INTRODUCTION
- HISTOLOGY
- HORMONES
- SYNTHESIS OF THYROID HORMONES
- STORAGE OF THYROID HORMONES
- RELEASE OF THYROID HORMONES
- TRANSPORT OF THYROID HORMONES IN THE BLOOD
- FUNCTIONS OF THYROID HORMONES
- MODE OF ACTION OF THYROID HORMONES
- REGULATION OF SECRETION OF THYROID HORMONES
- APPLIED PHYSIOLOGY — DISORDERS OF THYROID GLAND
- THYROID FUNCTION TESTS

■ INTRODUCTION

Thyroid is an endocrine gland situated at the root of the neck on either side of the trachea. It has two lobes, which are connected in the middle by an isthmus (Fig. 46-1). It weighs about 20 to 40 gm in adults. Thyroid is larger in females than in males. The structure and the function of the thyroid gland change in different stages of the sexual cycle in females. Its function increases slightly during pregnancy and lactation and decreases during menopause.

■ HISTOLOGY OF THYROID GLAND

Thyroid gland is composed of large number of closed follicles. The follicles are lined with cuboidal epithelial cells, which are called the

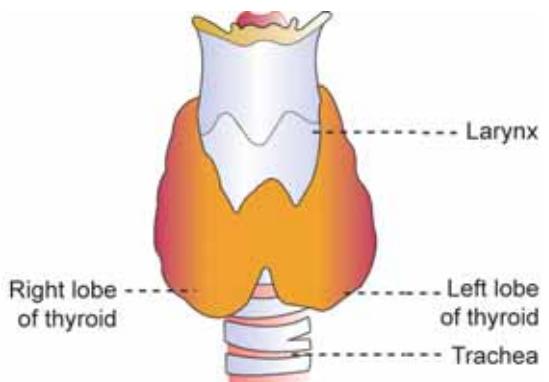


FIGURE 46-1: Thyroid gland

follicular cells. The follicular cavity is filled with a colloidal substance known as thyroglobulin which is secreted by the follicular cells. Follicular

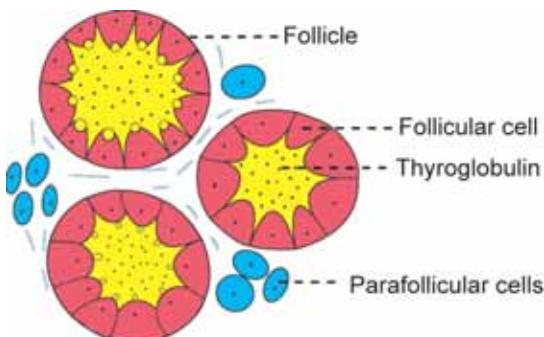


FIGURE 46-2: Histology of thyroid gland

cells secrete tetraiodothyronine (T_4 or thyroxine) and tri-iodothyronine (T_3). In between the follicles, the parafollicular cells are present (Fig. 46-2). These cells secrete calcitonin.

HORMONES OF THYROID GLAND

Thyroid gland secretes three hormones:

1. Tetraiodothyronine – T_4 (thyroxine)
2. Tri-iodothyronine – T_3
3. Calcitonin.

T_4 is otherwise known as thyroxine and it forms about 90% of the total secretion, whereas, T_3 is only 9 to 10%. But the potency of T_3 is four times more than that of T_4 .

SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones takes place in thyroglobulin present in follicular cavity. Iodine and tyrosine are essential for the formation of thyroid hormones. Iodine is consumed through diet. It is converted into iodide and absorbed from GI tract. Tyrosine is also consumed through diet and is absorbed from the GI.

For the synthesis of normal quantities of thyroid hormones, approximately 1 mg of iodine is required per week or about 50 mg per year. To prevent iodine deficiency, common table salt is iodized with one part of sodium iodide to every 100,000 parts of sodium chloride.

Various stages involved in the synthesis of thyroid hormones are:

1. Thyroglobulin synthesis

2. Iodide trapping or iodide pump
3. Oxidation of iodide
4. Iodination of tyrosine
5. Coupling reactions.

1. Thyroglobulin Synthesis

The endoplasmic reticulum and Golgi apparatus in the follicular cells of the thyroid gland synthesize and secrete a thyroglobulin continuously. Each thyroglobulin molecule contains 140 tyrosine molecules. After synthesis, the thyroglobulin is stored in the follicle.

2. Iodide Trapping or Iodide Pump

Iodide is transported actively from the blood into the follicular cell against the electrochemical gradient by a process called iodide trapping. Iodide is pumped with sodium into the follicular cell by sodium-iodide symport pump. From here, iodide is transported into the follicular cavity by an iodide-chloride pump.

3. Oxidation of the Iodide

Iodide must be oxidized to elementary iodine because only iodine is capable of combining with tyrosine to form thyroid hormones. The oxidation of iodide into iodine occurs inside the follicular cells in the presence of thyroid peroxidase.

4. Iodination of Tyrosine

The combination of iodine with tyrosine is known as iodination. It takes place in the follicle within thyroglobulin. First, iodine is released from follicular cells into the follicular cavity where it binds with thyroglobulin. This process is called organification of thyroglobulin. In the thyroglobulin, iodine combines with tyrosine which is already present there.

Binding of iodine (I) with tyrosine is accelerated by the enzyme iodinase which is secreted by the follicular cells (Fig. 46-3). Iodination of tyrosine occurs in several stages. Tyrosine is iodized first into monoiodotyrosine (MIT) and later into di-iodotyrosine (DIT). MIT and DIT are called the iodotyrosine residues.

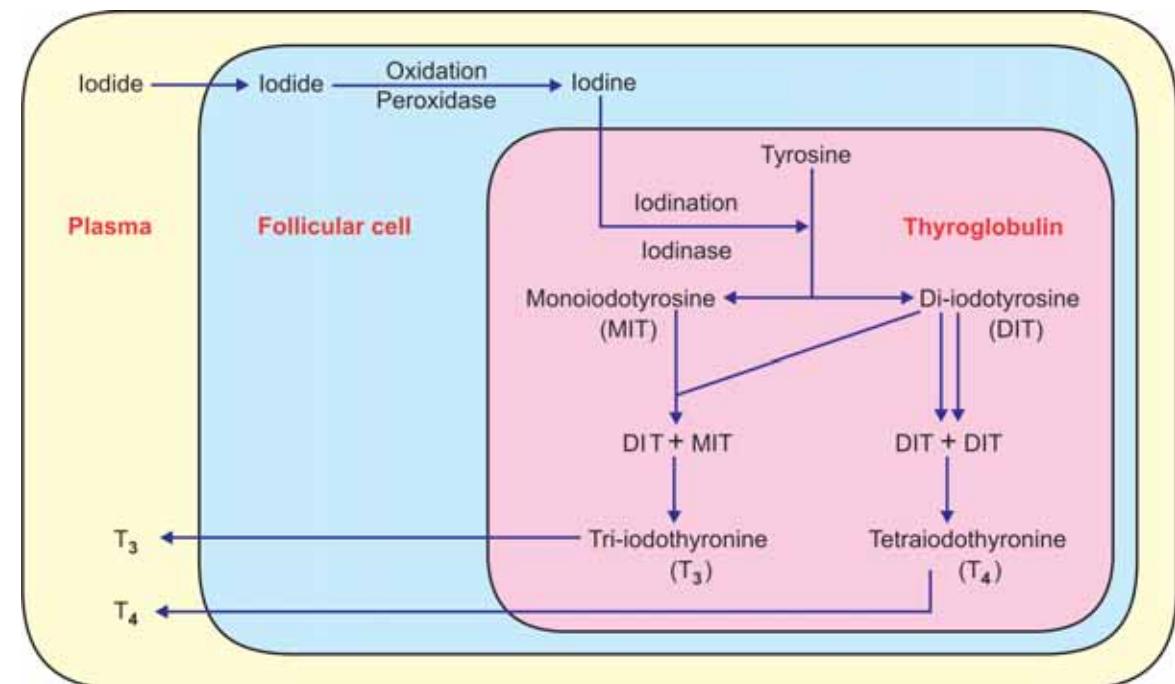


FIGURE 46-3: Synthesis of thyroid hormones

5. Coupling Reactions

The iodothyrosine residues get coupled with one another through coupling reactions. The coupling occurs in different configurations to give rise to different thyroid hormones:

- One molecule of DIT and one molecule of MIT combine to form tri-iodothyronine (T_3)
- Sometimes one molecule of MIT and one molecule of DIT combine to produce another form of T_3 called reverse T_3 or rT_3 . Reverse T_3 is only 1% of thyroid output
- Two molecules of DIT combine to form tetraiodothyronine (T_4) which is thyroxine.

Tyrosine + I = Monoiodotyrosine (MIT)

MIT + I = Di-iodotyrosine (DIT)

DIT + MIT = Tri-iodothyronine (T_3)

MIT + DIT = Reverse T_3

DIT + DIT = Tetraiodothyronine or Thyroxine (T_4)

combination with thyroglobulin, the thyroid hormones can be stored for several months. And, thyroid gland is unique in this, as it is the only endocrine gland that can store its hormones for a long period of about 4 months. So, when the synthesis of thyroid hormone stops, the signs and symptoms of deficiency do not appear for about 4 months.

■ RELEASE OF THYROID HORMONES FROM THE THYROID GLAND

Thyroglobulin itself is not released into the bloodstream. On the other hand, the hormones are first cleaved from the thyroglobulin.

Only T_3 and T_4 are released into the blood. In the peripheral tissues T_4 is converted into T_3 . A small amount of reverse T_3 is also formed. But reverse T_3 is biologically inactive.

The MIT and DIT are not released into blood. These iodothyrosine residues are deiodinated by an enzyme called iodothyrosine deiodinase resulting in release of iodine. The iodine is reutilized by the follicular cells for synthesis of

■ STORAGE OF THYROID HORMONES

After synthesis, the thyroid hormones remain in the form of vesicles within thyroglobulin. In

thyroid hormones. During congenital absence of iodotyrosine deiodinase, MIT and DIT are excreted in urine and the symptoms of iodine deficiency develop.

■ TRANSPORT OF THYROID HORMONES IN THE BLOOD

The normal plasma level of total T₃ is 0.12 mg/dL and that of total T₄ is 8 mg/dL. The thyroid hormones are transported in the blood in combination with three types of plasma proteins.

1. Thyroxine binding globulin (TBG)
2. Thyroxine binding prealbumin (TBPA)
3. Albumin.

■ FUNCTIONS OF THYROID HORMONES

Thyroid hormones have two major effects on the body:

- I. To increase the overall metabolic rate in the body
- II. To stimulate growth in children.

The actions of thyroid hormones are:

■ 1. ON BASAL METABOLIC RATE

Thyroxine increases the metabolic activities of almost all tissues of the body except brain, retina, spleen, testes and lungs. It increases the basal metabolic rate (BMR) by increasing the oxygen consumption of the tissues. The action that increases the BMR is called calorigenic action.

■ 2. ON PROTEIN METABOLISM

Thyroid hormones increase synthesis of proteins. Thyroxine accelerates protein synthesis by increasing:

- i. Translation of RNA in the cells
- ii. Transcription of DNA to RNA
- iii. Activity of mitochondria
- iv. Activity of cellular enzymes.

Though thyroxine increases protein synthesis, it also causes catabolism of proteins.

■ 3. ON CARBOHYDRATE METABOLISM

Thyroxine stimulates almost all processes involved in the metabolism of carbohydrate.

It increases:

- i. Absorption of glucose from GI tract
- ii. Glucose uptake by the cells, by accelerating transport of glucose through cell membrane
- iii. Breakdown of glycogen into glucose
- iv. Gluconeogenesis.

■ 4. ON FAT METABOLISM

Thyroxine decreases the fat storage by mobilizing it from adipose tissues and fat depots. The mobilized fat is converted into free fatty acid and transported by blood. Thus, thyroxine increases the free fatty acid level in blood.

■ 5. ON PLASMA AND LIVER FATS

Even though there is increase in the blood level of free fatty acids, thyroxine specifically decreases the cholesterol, phospholipids and triglyceride levels in the plasma. So, in hyposecretion of thyroxine, the cholesterol level in plasma increases resulting in atherosclerosis.

Thyroxine also increases deposition of fats in the liver leading to fatty liver. Thyroxine decreases plasma cholesterol level by increasing its excretion from liver cells into bile. Cholesterol enters the intestine through bile and then it is excreted through the feces.

■ 6. ON VITAMIN METABOLISM

Thyroxine increases the formation of many enzymes. Since, the vitamins form the essential parts of the enzymes, it is believed that the vitamins may be utilized during the formation of the enzymes. Hence, vitamin deficiency is possible during hypersecretion of thyroxine.

■ 7. ON BODY TEMPERATURE

Thyroid hormone increases the heat production in the body by accelerating various cellular metabolic processes and increasing BMR.

■ 8. ON GROWTH

Thyroid hormones have general and specific effects on growth. Lack of thyroxine arrests the growth and increase in thyroxine secretion accelerates the growth of the body especially in growing children. At the same time, the closure

of epiphysis occurs at an early age under the influence of thyroxine. So, the height of the individual may be slightly less.

Thyroxine is more important to promote growth and development of the brain during fetal life and the first few years of postnatal life. Lack of thyroid hormones at this period leads to mental retardation.

■ 9. EFFECT ON BODY WEIGHT

Thyroxine is essential for maintaining body weight. Increase in thyroxine secretion decreases the body weight and fat storage; and decrease in thyroxine secretion increases the body weight because of fat deposition.

■ 10. EFFECT ON BLOOD

Thyroxine increases the production of RBCs. It is one of the important general factors necessary for erythropoiesis. Thus, thyroxine increases erythropoietic activity and blood volume.

■ 11. ON CARDIOVASCULAR SYSTEM

Thyroxine increases overall activity of cardiovascular system:

i. On Heart

Thyroxine acts directly on heart and increases rate and force of contraction.

ii. On Blood Vessels

Thyroxine causes vasodilatation by increasing the metabolic activity. During metabolic activity, production of metabolites is increased. The metabolites cause vasodilatation and increase the blood flow.

iii. On Arterial Blood Pressure

Thyroxine increases systolic blood pressure by increasing rate and force of contraction of the heart, blood volume and cardiac output. At the same time it decreases diastolic pressure by its vasodilator effect. So only the pulse pressure increases and the mean pressure is not altered.

■ 12. EFFECT ON RESPIRATION

Thyroxine increases the rate and force of respiration indirectly. The increased metabolic rate (caused by thyroxine) increases the demand for oxygen and formation of excess carbon dioxide. These two factors stimulate the respiratory centers to increase the rate and force of respiration.

■ 13. ON GASTROINTESTINAL TRACT

Generally, thyroxine increases the appetite and food intake. It also increases the secretions and movements of GI tract.

■ 14. ON CENTRAL NERVOUS SYSTEM

Thyroxine is very essential for the development and maintenance of normal functioning of the central nervous system.

i. On Development of Central Nervous System

Thyroxine is very important to promote growth and development of the brain during fetal life and during the first few years of postnatal life. Thyroid deficiency in infants results in mental retardation.

ii. On the Normal Function of Central Nervous System

Thyroxine is a stimulating factor for the brain so normal functioning of the brain needs the presence of thyroxine. Thyroxine also increases the blood flow to brain.

Thus, during the hypersecretion of thyroxine there is excess stimulation of the central nervous system. So, the person is likely to have extreme nervousness and may develop psycho-neurotic problems such as anxiety complexes, excess worries. Hyposecretion of thyroxine leads to lethargy and somnolence (excess sleep).

■ 15. ON SKELETAL MUSCLE

Thyroxine is essential for the normal activity of the skeletal muscles. Slight increase in thyroxine level makes the muscles to work with

more vigor. But, hypersecretion of thyroxine causes weakness of the muscles due to the catabolism of proteins. Lack of thyroxine makes the muscles more sluggish.

■ 16. ON SLEEP

Normal thyroxine level is essential to maintain normal sleep. Hypersecretion of thyroxine causes excessive stimulation of the muscles and central nervous system. So, the person feels tired, exhausted, and feels like sleeping. But, the person cannot sleep because of the stimulatory effect of thyroxine on neurons. On the other hand, hyposecretion of thyroxine causes somnolence.

■ 17. ON SEXUAL FUNCTION

Normal thyroxine level is essential for normal sexual function. In men, hypothyroidism leads to complete loss of libido (sexual drive). And hyperthyroidism leads to impotence.

In women, hypothyroidism causes menorrhagia and polymenorrhea (Chapter 55). In some women, it causes irregular menstruation and occasionally amenorrhea. Hyperthyroidism in women leads to oligomenorrhea and sometimes amenorrhea (Chapter 55).

■ 18. ON OTHER ENDOCRINE GLANDS

Because of its metabolic effects, thyroxine increases the demand for secretion of other endocrine glands.

■ MODE OF ACTION OF THYROID HORMONES

Thyroid hormones act by activating the genes (Chapter 44).

■ REGULATION OF SECRETION OF THYROID HORMONES

The secretion of thyroid hormones is controlled by anterior pituitary and hypothalamus through feedback mechanism (Fig. 46-4).

■ ROLE OF PITUITARY GLAND

Thyroid Stimulating Hormone

Thyroid stimulating hormone (TSH) secreted by anterior pituitary is the major factor regulating the synthesis and release of thyroid hormones.

TSH is a peptide hormone with one α chain and one β chain. Normal plasma level of TSH is approximately 2 U/mL.

Actions of TSH

TSH increases:

1. The number of thyroid cells, which are cuboidal in nature and, then it converts them into columnar cells and causes the development of thyroid follicles
2. The size and secretory activity of the cells
3. The iodide pump and iodide trapping in the cells
4. The thyroglobulin secretion into the follicles
5. Iodination of tyrosine and coupling to form the hormones
6. Proteolysis of the thyroglobulin, by which, release of hormone is enhanced and the colloidal substance is decreased.

Mode of Action of TSH

TSH acts through cyclic AMP mechanism.

■ ROLE OF HYPOTHALAMUS

Hypothalamus regulates thyroid secretion by controlling TSH secretion through thyrotropic releasing hormone (TRH) from hypothalamus. From hypothalamus, TRH is transported through the hypothalamo-hypophyseal portal vessels to the anterior pituitary. After reaching the pituitary gland, the TRH causes the release of TSH.

■ FEEDBACK CONTROL

Thyroid hormones regulate their own secretion through negative feedback control by inhibiting the release of TRH from hypothalamus and TSH from anterior pituitary (Fig. 46-4).

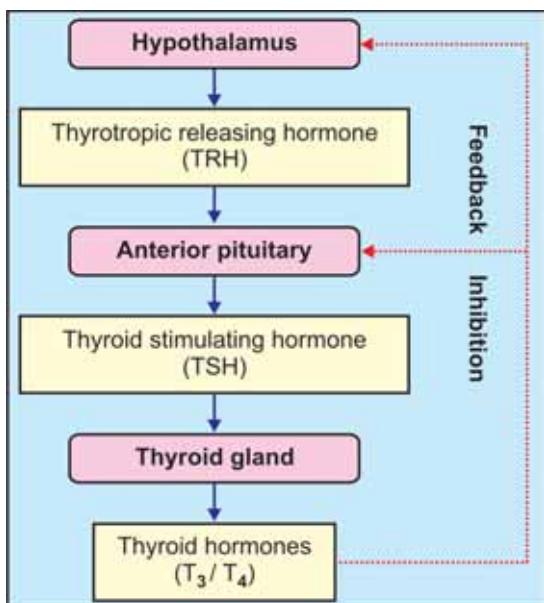


FIGURE 46-4: Regulation of secretion of thyroid hormones

■ ROLE OF IODIDE

Iodide is an important factor regulating the synthesis of thyroid hormones. When the dietary level of iodine is moderate, the blood level of thyroid hormones is normal. However, when iodine intake is high, the enzymes necessary for synthesis of thyroid hormones are inhibited by iodide itself resulting in suppression of hormone synthesis.

■ APPLIED PHYSIOLOGY— DISORDERS OF THYROID GLAND

■ 1. HYPERTHYROIDISM

Causes for Hyperthyroidism

i. Graves' disease

Graves' disease is an autoimmune disease. Normally, thyroid stimulating hormone (TSH) combines with surface receptors of thyroid cells and causes the synthesis of thyroid hormones. In Graves' disease the B lymphocytes (plasma cells) produce autoimmune antibodies called thyroid stimulating autoantibodies. These antibodies act like TSH by binding with membrane receptors of TSH and activating cAMP

system of the thyroid follicular cells. This results in hypersecretion of thyroid hormones.

ii. Thyroid adenoma

Sometimes, a localized tumor develops in the thyroid tissue. It is known as thyroid adenoma and it secretes large quantities of thyroid hormones.

Signs and Symptoms of Hyperthyroidism

- i. Intolerance to heat because production of more heat during increased basal metabolic rate caused by hyperthyroidism
- ii. Increased sweating due to vasodilatation
- iii. Decreased body weight due to fat mobilization
- iv. Diarrhea due to increased motility of GI tract
- v. Muscular weakness due to excess protein catabolism
- vi. Neuronal disturbances such as nervousness, extreme fatigue, inability to sleep, mild tremor in hands and psychoneurotic symptoms such as hyperexcitability, extreme anxiety or worry
- vii. Toxic goiter
- viii. Oligomenorrhea or amenorrhea
- ix. Exophthalmos
- x. Polycythemia
- xi. Tachycardia and atrial fibrillation
- xii. Systolic hypertension
- xiii. Cardiac failure.

Exophthalmos

Protrusion of eye balls is called exophthalmos. Most, but not all hyperthyroid patients develop some degree of protrusion of eyeballs.

Causes for exophthalmos

Exophthalmos in hyperthyroidism is due to the edematous swelling of the retro-orbital tissues and degenerative changes in the extraocular muscles. Severe exophthalmic conditions lead to blindness because of two reasons:

- i. Protrusion of the eyeball stretches and damages the optic nerve resulting in blindness or
- ii. Due to the protrusion of eyeballs, the eyelids cannot be closed completely while blinking

or during sleep. So, the constant exposure of eyeball to atmosphere causes dryness of the cornea leading to irritation and infection. It finally results in ulceration of the cornea leading to blindness.

■ 2. HYPOTHYROIDISM

Decreased secretion of thyroid hormones is called hypothyroidism. Hypothyroidism leads to myxedema in adults and cretinism in children.

Myxedema

It is the hypothyroidism in adults characterized by generalized edematous appearance.

Causes for myxedema

Myxedema occurs due to diseases of thyroid gland, genetic disorder or iodine deficiency. In addition, it is also caused by deficiency of thyroid stimulating hormone or thyrotropic releasing hormone.

Signs and symptoms of myxedema

Typical feature of this disorder is an edematous appearance throughout the body. It is associated with the following symptoms:

- i. Swelling of the face
- ii. Bagginess under the eyes
- iii. Nonpitting type of edema, i.e. when pressed, it does not make pits and the edema is hard
- iv. Atherosclerosis: It is the hardening of the walls of arteries because of accumulation of fat. In myxedema it occurs because of increased plasma level of cholesterol which leads to deposition of cholesterol on the walls of the arteries.

Atherosclerosis produces arteriosclerosis which refers to thickening and stiffening of arterial wall. Arteriosclerosis causes hypertension.

Other general features of hypothyroidism in adults are:

- i. Anemia
- ii. Fatigue and muscular sluggishness
- iii. Extreme somnolence with sleeping up to 14 to 16 hours per day
- iv. Menorrhagia and polymenorrhea

- v. Decreased cardiovascular functions such as reduction in rate and force of contraction of the heart, cardiac output and blood volume
- vi. Increase in body weight
- vii. Constipation
- viii. Mental sluggishness
- ix. Depressed hair growth
- x. Scaliness of the skin
- xi. Frog like husky voice
- xii. Cold intolerance.

Cretinism

Cretinism is the hypothyroidism in children characterized by stunted growth.

Causes for cretinism

Cretinism occurs due to congenital absence of thyroid gland, genetic disorder or lack of iodine in the diet.

Features of cretinism

- i. A newborn baby with thyroid deficiency may appear normal at the time of birth because thyroxine might have been supplied from mother. But a few weeks after birth, the baby starts developing the signs like sluggish movements and croaking sound while crying. Unless treated immediately, the baby will be mentally retarded permanently.
- ii. Skeletal growth is more affected than the soft tissues. So, there is stunted growth with bloated body. The tongue becomes so big, that it hangs down with dripping of saliva. The big tongue obstructs swallowing and breathing. The tongue produces characteristic guttural breathing that may sometimes choke the baby.

Cretin vs dwarf

A cretin is different from pituitary dwarf. In cretinism, there is mental retardation and the different parts of the body are disproportionate. Whereas, in dwarfism, the development of nervous system is normal and the parts of the body are proportionate (Fig. 46-5). The reproductive function is affected in cretinism but in dwarfism, it may be normal.



FIGURE 46-5: Cretinism (3 months old baby)
(Courtesy: Prof Mafauzy Mohamad)

■ 3. GOITER

Goiter means enlargement of the thyroid gland. It occurs both in hypothyroidism and hyperthyroidism.

Goiter in Hyperthyroidism — Toxic Goiter

Toxic goiter is the enlargement of thyroid gland with increased secretion of thyroid hormones caused by thyroid tumor.

Goiter in Hypothyroidism — Nontoxic Goiter

Nontoxic goiter is the enlargement of thyroid gland without increase in hormone secretion. It is also called hypothyroid goiter (Fig. 46-6). Based on the cause, the nontoxic hypothyroid goiter is classified into two types:

- Endemic colloid goiter
- Idiopathic nontoxic goiter.

i. Endemic colloid goiter

It is the nontoxic goiter caused by iodine deficiency. It is also called iodine deficiency goiter. Iodine deficiency occurs when intake is less than 50 µg /day. Because of lack of iodine, there is no formation of hormones. By feedback



FIGURE 46-6: Nontoxic goiter
(Courtesy: Prof Mafauzy Mohamad)

mechanism, hypothalamus and anterior pituitary are stimulated. It increases the secretion of TRH and TSH. The TSH then causes the thyroid cells to secrete tremendous amounts of thyroglobulin into the follicle. As there are no hormones to be cleaved, the thyroglobulin remains as it is and, gets accumulated in the follicles of the gland. This increases the size of gland.

ii. Idiopathic nontoxic goiter

It is the goiter due to unknown cause. Enlargement of thyroid gland occurs even without iodine deficiency. The exact cause is not known.

Some foodstuffs contain goitrogenic substances (goitrogens) such as goitrin. These substances contain antithyroid substances like propylthiouracil. Goitrogens suppress the synthesis of thyroid hormones. Therefore, TSH secretion increases resulting in enlargement of the gland. Such goitrogens are found in vegetables like turnips and cabbages. Soybean also contains some amount of goitrogens.

The goitrogens become active only during low iodine intake.

■ THYROID FUNCTION TESTS

The following tests are commonly done to assess the functional status of thyroid gland:

- Measurement of concentration of T_3 and T_4 in plasma
- Measurement of measurement of TRH and TSH in plasma
- Measurement of basal metabolic rate.

47

Parathyroid Glands and Physiology of Bone

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- PARATHORMONE
 - ACTIONS OF PARATHORMONE
 - REGULATION OF PARATHORMONE SECRETION
- APPLIED PHYSIOLOGY — DISORDERS OF PARATHYROID GLANDS
 - HYPOPARATHYROIDISM — HYPOCALCEMIA
 - HYPERPARATHYROIDISM — HYPERCALCEMIA
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- PHYSIOLOGY OF BONE
 - FUNCTIONS OF BONE
 - CELL TYPES OF BONE
 - BONE REMODELING
 - APPLIED PHYSIOLOGY — DISEASES OF BONE

■ INTRODUCTION

There are four parathyroid glands located immediately behind thyroid gland at the upper and lower poles (Fig. 47-1). The parathyroid glands are very small in size measuring about 6 mm long, 3 mm wide and 2 mm thick with dark brown color.

Histology: Each parathyroid gland is made up of chief cells and oxyphil cells. The chief cells secrete parathormone. The function of the oxyphil cell is not known. It is believed that oxyphil cells are the degenerated chief cells.

Parathormone is essential for the maintenance of blood calcium level within a very narrow critical level.

■ PARATHORMONE

Parathormone (PTH) is secreted by the chief cells of the parathyroid glands. It is protein in nature having 84 amino acids. The normal plasma level of PTH is about 1.5 to 5.5 ng/dL.

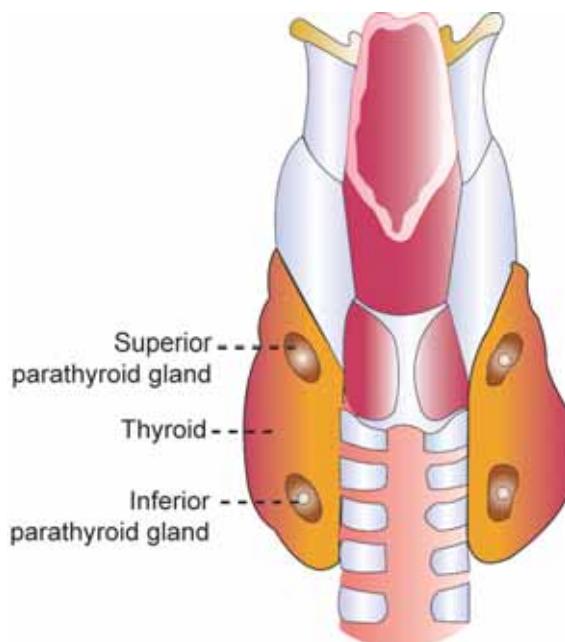


FIGURE 47-1: Parathyroid glands on the posterior surface of thyroid gland

■ ACTIONS OF PARATHORMONE

PTH maintains the blood calcium level and blood phosphate level.

On Blood Calcium Level

The primary action of PTH is to maintain the blood calcium level within the critical range of 9 to 11 mg/dL. The blood calcium level has to be maintained critically because, it is very important for many of the activities in the body. PTH maintains the blood calcium level by acting on:

1. Bones
2. Kidneys
3. GI tract.

1. On bone

PTH increases resorption of calcium from the bones by acting on osteoblasts, osteocytes and osteoclasts of the bone.

PTH increases the permeability of the membranes of osteoblasts and osteocytes for calcium ions. So calcium ions move from these bone cells into the blood.

PTH stimulates osteoclasts and causes release of proteolytic enzymes and some acids such as citric acid and lactic acid. All these substances digest or dissolve the organic matrix of the bone, releasing the calcium ions into the plasma.

2. On kidneys

PTH increases the reabsorption of calcium from distal convoluted tubule and proximal part of collecting duct into the plasma. It also increases the formation of 1,25-dihydroxycholecalciferol (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys which is necessary for absorption of calcium from GI tract.

3. On gastrointestinal tract

PTH increases the absorption of calcium from GI tract by increasing the formation of 1,25-dihydroxycholecalciferol in the kidneys.

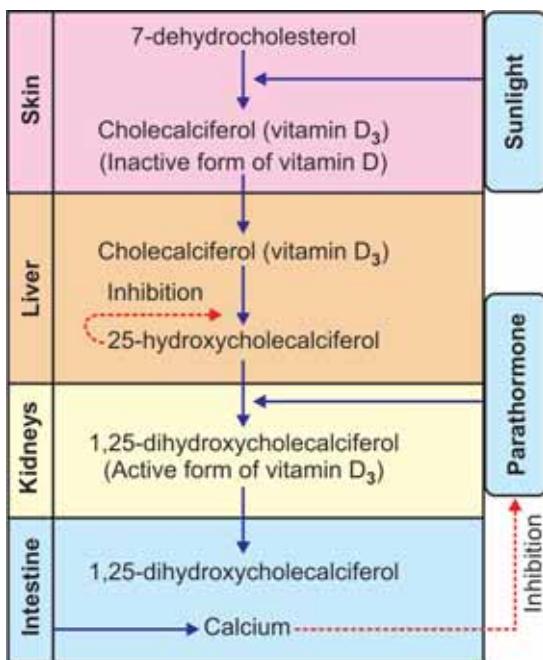


FIGURE 47-2: Schematic diagram showing activation of vitamin D

Activation of vitamin D: There are various forms of vitamin D but, the most important one is vitamin D₃. It is also known as cholecalciferol. Vitamin D₃ is synthesized in the skin from 7-dehydrocholesterol by the action of ultraviolet rays from the sunlight. It is also obtained from dietary sources. The activation of vitamin D₃ occurs in two steps (Fig. 47-2).

In the first step, cholecalciferol (vitamin D₃) is converted into 25-hydroxycholecalciferol in the liver. This process is limited and is inhibited by 25-hydroxycholecalciferol itself by feedback mechanism.

In the second step, 25-hydroxycholecalciferol is converted into 1,25-dihydroxycholecalciferol (calcitriol) in kidney. And, it is the active form of vitamin D₃. This step needs the presence of PTH.

The 1,25-dihydroxycholecalciferol increases the absorption of calcium and phosphate from intestine.

On Blood Phosphate Level

PTH decreases blood level of phosphate by acting on:

1. Bones
2. Kidneys
3. GI tract.

1. On bone

PTH increases the phosphate absorption from bones.

2. On kidneys

Phosphaturic action: Phosphaturic action is the effect of PTH by which phosphate is excreted in urine. PTH inhibits reabsorption of phosphate from renal tubules so that excretion of phosphate through urine increases.

3. On gastrointestinal tract

PTH increases the formation of 1,25-dihydroxycholecalciferol in the kidneys. This vitamin in turn increases the absorption of phosphate along with calcium.

Mode of Action of PTH

On the target cells, PTH executes its action through cAMP.

■ REGULATION OF PARATHORMONE SECRETION

Blood level of calcium is the main factor that regulates the secretion of PTH. Blood phosphate level also influences PTH secretion.

Blood Level of Calcium

PTH secretion is inversely proportional to blood calcium level. Increase in blood calcium level decreases PTH secretion.

Blood Level of Phosphate

PTH secretion is directly proportional to blood phosphate level. Whenever the blood level of phosphate increases, it combines with ionized

calcium to form calcium hydrogen phosphate. This decreases ionized calcium level in blood which stimulates PTH secretion.

■ APPLIED PHYSIOLOGY — DISORDERS OF PARATHYROID GLANDS

The disorders of parathyroid glands are of two types:

- I. Hypoparathyroidism
- II. Hyperparathyroidism.

■ HYPOPARTHYROIDISM — HYPOCALCEMIA

Hypoparathyroidism leads to hypocalcemia (decrease in blood calcium level).

Causes for Hypoparathyroidism

1. Surgical removal of parathyroid glands (parathyroidectomy)
2. Removal of parathyroid glands during surgical removal of thyroid gland (thyroidectomy)
3. Autoimmune disease
4. Deficiency of receptors for PTH in the target cells. In this, the PTH secretion is normal or increased but the hormone cannot act on the target cells. This condition is called pseudohypoparathyroidism.

Hypocalcemia and Tetany

Hypoparathyroidism causes hypocalcemia by decreasing the resorption of calcium from bones. It causes neuromuscular hyperexcitability resulting in hypocalcemic tetany. Normally, tetany occurs when blood calcium level falls below 6 mg/dL from its normal value of 9.4 mg/dL.

Hypocalcemic Tetany

Tetany is an abnormal condition characterized by painful muscular spasm (involuntary contraction of muscle or group of muscles) particularly in feet and hand. It is because of hyperexcitability of nerves and skeletal muscles due to calcium deficiency.

The signs and symptoms of hypocalcemic tetany:

1. Hyper-reflexia and convulsions

The increased neural excitability results in hyper-reflexia (overactive reflex actions) and convulsive muscular contractions.

2. Carpopedal spasm

Carpopedal spasm is the spasm (violent and painful muscular contraction) in hand and feet that occurs due to hypocalcemia. During the spasm, the hand shows a peculiar attitude with flexion at wrist joint and metacarpophalangeal joints, adduction of the thumb, and extension of interphalangeal joints (Fig. 47-3).

3. Laryngeal stridor

Stridor means noisy breathing. Laryngeal stridor means a loud crowing sound during inspiration which occurs mainly due to laryngospasm (involuntary contraction of laryngeal muscles). Laryngeal stridor is a common feature of hypocalcemic tetany.

4. Cardiovascular changes

- i. Dilatation of the heart
- ii. Prolonged duration of ST segment and QT interval in ECG
- iii. Arrhythmias (irregular heartbeat)
- iv. Hypotension
- v. Heart failure.

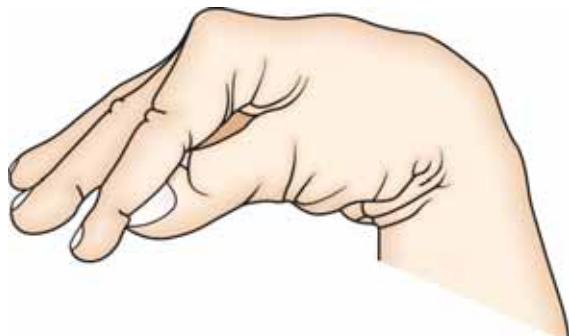


FIGURE 47-3: Carpopedal spasm

5. Other features

- i. Decreased permeability of the cell membrane
- ii. Dry skin with brittle nails
- iii. Hair loss
- iv. Seizures
- v. Signs of mental retardation in children or dementia in adults (Chapter 101).

When the calcium level falls below 4 mg/dL it becomes fatal. During such severe hypocalcemic conditions, tetany occurs so quickly that a person develops spasm of different groups of muscles in the body. Worst affected are the laryngeal and bronchial muscles which develop respiratory arrest resulting in death.

Latent Tetany

Latent or subclinical tetany is the neuromuscular hyperexcitability due to hypocalcemia that develops before the onset of tetany. It is characterized by general weakness and cramps in feet and hand. The hyperexcitability in these patients is detected by some signs, which do not appear in normal persons.

1. Trousseau's sign

It is the spasm of the hand that is developed after 3 minutes of arresting the blood flow to lower arm and hand. The blood flow to lower arm and hand is arrested by inflating the blood pressure cuff 20 mm Hg above the patient's systolic pressure.

2. Chvostek's sign

Chvostek's sign is the twitch of the facial muscles caused by a gentle tap over the facial nerve in front of the ear. It is due to the hyperirritability of facial nerve.

3. Erb sign

Hyperexcitability of the skeletal muscles even to a mild electrical stimulus is called Erb sign. It is also called Erb-Westphal sign.

■ HYPERPARATHYROIDISM—HYPERCALCEMIA

Hyperparathyroidism results in hypercalcemia (increase in blood calcium level).

Causes of Hyperparathyroidism

- 1. Tumor in parathyroid glands
- 2. Compensatory hypertrophy of parathyroid glands in response to hypocalcemia which occurs due to other pathological conditions such as chronic renal failure, vitamin D deficiency and rickets
- 3. Hyperplasia (abnormal increase in the number of cells) of all the parathyroid glands.

Hypercalcemia

Hypercalcemia is the increase in plasma calcium level. It occurs in hyperparathyroidism because of increased resorption of calcium from bones.

The common signs and symptoms of hypercalcemia:

- i. Depression of the nervous system
- ii. Sluggishness of reflex activities
- iii. Reduced ST segment and QT interval in ECG
- iv. Lack of appetite
- v. Constipation.

The depressive effects of hypercalcemia are noticed when the blood calcium level increases to 12 mg/dL. The condition becomes severe with 15 mg/dL and it becomes lethal when blood calcium level reaches 17 mg/dL.

The other effects of hypercalcemia:

- i. **Bone diseases:** Bone diseases like osteitis fibrosa cystica develop.
- ii. **Parathyroid poisoning:** It is the condition characterized by severe manifestations that occur when blood calcium level rises above 15 mg/dL along with increase in phosphate level leading to formation of calcium-phosphate crystals. The calcium-phosphate crystals may be deposited in the tubules of the kidneys, thyroid gland, alveoli of lungs, gastric mucosa and in the

wall of the arteries. Calcium deposition results in dysfunction of these organs. Renal stones are formed when it is deposited in kidney.

■ PARATHYROID FUNCTION TESTS

1. Measurement of blood calcium level
2. Chvostek's sign and Trousseau's sign for hypoparathyroidism.

■ CALCITONIN

Source of Secretion

Calcitonin is secreted by the parafollicular cells or clear cells (C cells) situated amongst the follicles in thyroid gland.

Chemistry and Plasma Level

It is a polypeptide chain with 32 amino acids. Its molecular weight is about 3,400. Plasma level of calcitonin is 1 to 2 ng/L.

■ ACTIONS OF CALCITONIN

1. On Blood Calcium Level

Calcitonin plays an important role in controlling the blood calcium level. It decreases the blood calcium level and thereby counteracts parathormone.

Calcitonin reduces the blood calcium level by acting on bones, kidneys and intestine.

i. On bones

Calcitonin stimulates osteoblastic activity and facilitates the deposition of calcium on bones. At the same time, it suppresses the activity of osteoclasts and inhibits the resorption of calcium from bones. It inhibits even the development of new osteoclasts in bones.

ii. On kidney

Calcitonin increases the excretion of calcium through urine, by inhibiting the reabsorption of calcium from the renal tubules.

iii. On intestine

It prevents the absorption of calcium from intestine into the blood.

2. On Blood Phosphate Level

With respect to calcium, calcitonin is an antagonist to PTH. But it has similar actions of PTH with respect to phosphate. It decreases the blood level of phosphate by acting on bones and kidneys.

i. On bones

Calcitonin inhibits the resorption of phosphate from bone and stimulates deposition of phosphate on bones.

ii. On kidney

Calcitonin increases the excretion of phosphate through urine, by inhibiting phosphate reabsorption from renal tubules.

■ REGULATION OF CALCITONIN SECRETION

High calcium content in plasma stimulates the calcitonin secretion through a calcium receptor in parafollicular cells. Gastrin also is known to stimulate release of calcitonin.

■ CALCIUM METABOLISM

■ IMPORTANCE OF CALCIUM

Calcium is very essential for many activities in the body such as:

1. Teeth and bone formation
2. Neuronal activity
3. Skeletal muscle activity
4. Cardiac activity
5. Smooth muscle activity
6. Secretory activity of the glands
7. Cell division and growth
8. Coagulation of blood.

■ NORMAL VALUE

In a normal young healthy adult, there is about 1100 g of calcium in the body. It forms about 1.5%

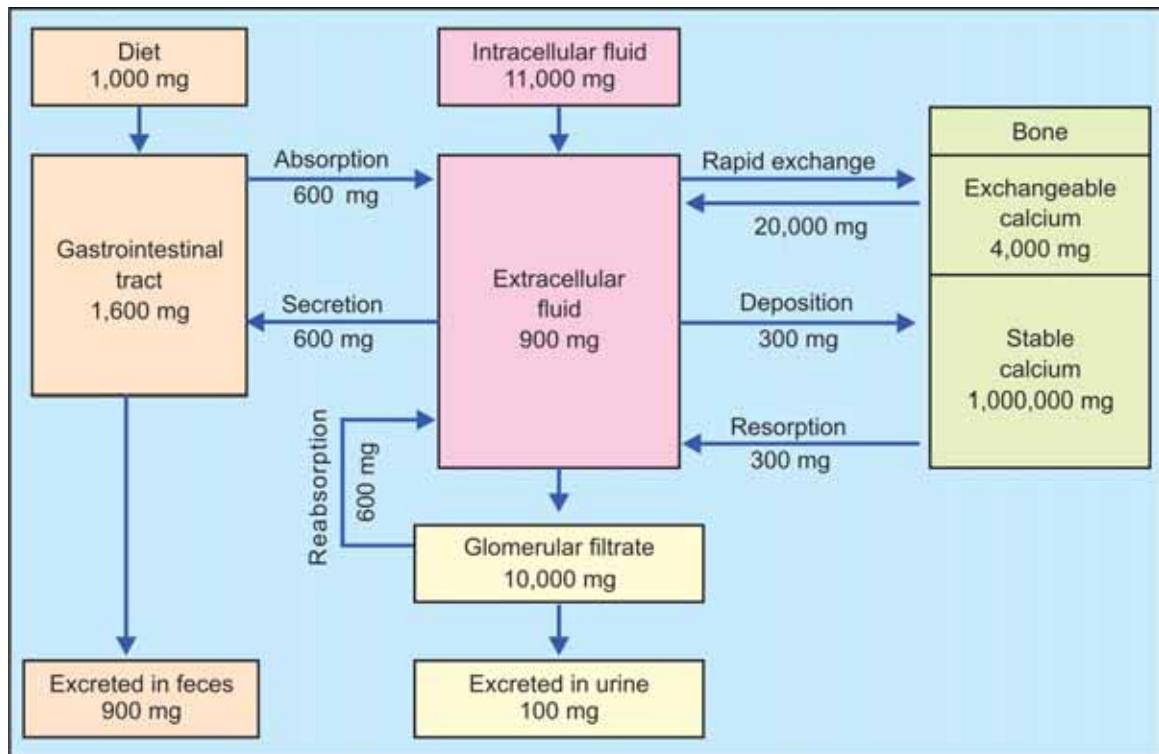


FIGURE 47-4: Schematic diagram showing calcium metabolism. The values belong to adults

of total body weight. Ninety nine percent of calcium is present in the bones and teeth and the rest is present in the plasma. The normal blood calcium level ranges between 9 and 11 mg/dL.

■ TYPES OF CALCIUM

Calcium in Plasma

Calcium is present in three forms in plasma:

- Ionized or diffusible calcium
- Nonionized or nondiffusible calcium
- Calcium bound to albumin.

Ionized calcium is found freely in the plasma and it forms about 50% of plasma calcium. It is essential for the vital functions like neuronal activity, muscle contraction, cardiac activity, secretions in the glands, blood coagulation, etc. About 8 to 10% of plasma calcium is present in nonionic form such as calcium bicarbonate.

About 40 to 42% of calcium is bound with plasma protein particularly, albumin.

Calcium in Bones

Calcium is constantly removed from bone and deposited in bone. The process of calcium metabolism is explained schematically in Fig. 47-4.

■ SOURCE OF CALCIUM

1. Dietary Source

Calcium is available in several foodstuffs such as milk, cheese, vegetables, meat, egg, grains, sugar, coffee, tea, chocolate, etc.

2. From Bones

Besides dietary calcium, blood also gets calcium from bones by resorption.

DAILY REQUIREMENTS OF CALCIUM

1 to 3 years	= 500 mg
4 to 8 years	= 800 mg
9 to 18 years	= 1300 mg
19 to 50 years	= 1000 mg
51 years and above	= 1200 mg
Pregnant ladies and lactating mothers	= 1300 mg

ABSORPTION AND EXCRETION OF CALCIUM

Calcium taken through dietary sources is absorbed from the GI tract into blood and distributed to various parts of the body. Depending upon the blood level, the calcium is either deposited in the bone or removed from the bone (resorption). Calcium is excreted from the body through urine and feces.

Absorption from GI Tract

Calcium is absorbed from duodenum by carrier mediated active transport and from the rest of the small intestine by facilitated diffusion. Vitamin D is essential for the absorption of calcium from GI tract.

Excretion

While passing through the kidney, a large quantity of calcium is filtered in the glomerulus. From the filtrate, 98 to 99% of calcium is reabsorbed from renal tubules into the blood and only a small quantity is excreted through urine.

Most of the filtered calcium is reabsorbed in the distal convoluted tubules and proximal part of collecting duct. In distal convoluted tubule parathormone increases the reabsorption. In collecting duct vitamin D increases the reabsorption and calcitonin decreases reabsorption.

About 1000 mg of calcium is excreted daily. Out of this 900 mg is excreted through feces and 100 mg through urine.

REGULATION OF BLOOD CALCIUM LEVEL

Blood calcium level is regulated mainly by three hormones (Figs 47-5 and 47-6):

1. Parathormone
2. 1,25-dihydroxycholecalciferol (calcitriol)
3. Calcitonin.

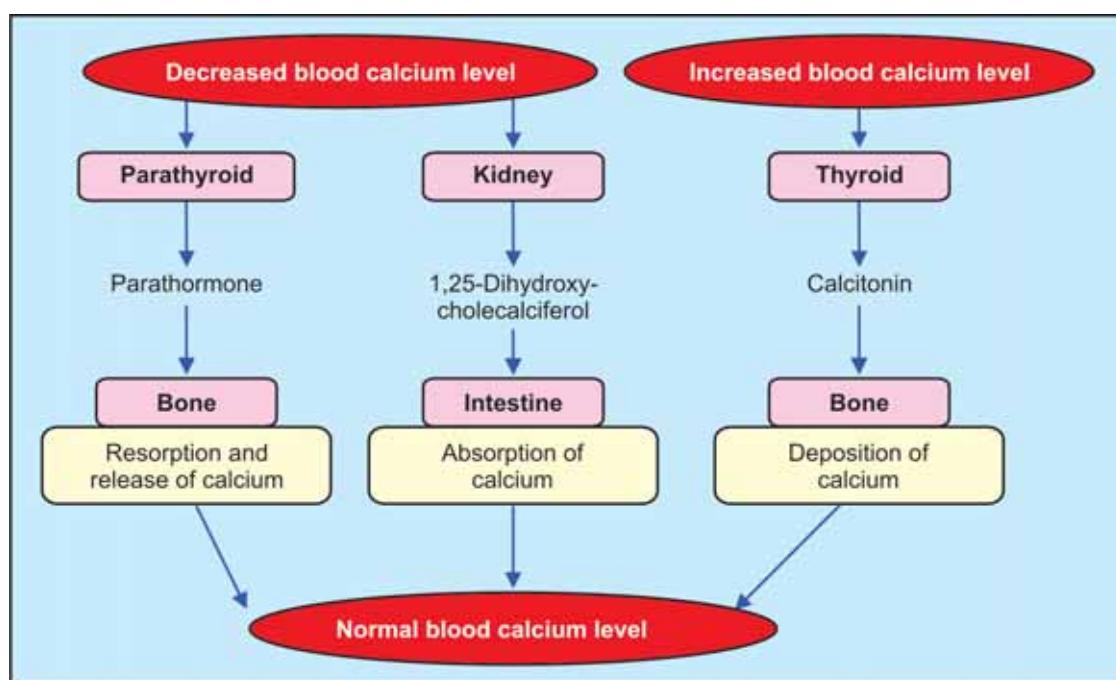


FIGURE 47-5: Schematic diagram showing regulation of blood calcium level

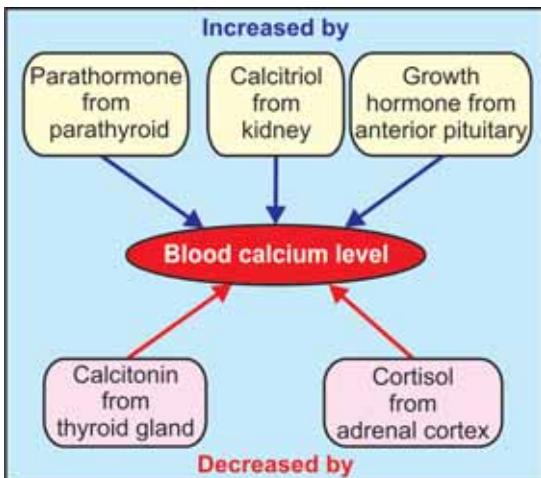


FIGURE 47-6: Effect of hormones on blood calcium level

1. Parathormone

It is a protein hormone secreted by parathyroid gland and its main function is to increase the blood calcium level by mobilizing calcium from bone (resorption) (see above for details).

2. 1,25-Dihydroxycholecalciferol — Calcitriol

It is a steroid hormone synthesized in kidney. It is the activated form of vitamin D. Its main action is to increase the blood calcium level by increasing the calcium absorption from the small intestine (see above for details).

3. Calcitonin

It is a protein hormone secreted by parafollicular cells of thyroid gland. It is a calcium lowering hormone. It reduces the blood calcium level mainly by decreasing bone resorption (see above for details).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also influence the calcium level.

1. Growth hormone

It increases the blood calcium level by increasing the intestinal calcium absorption.

2. Glucocorticoids

Glucocorticoids (cortisol) decrease blood calcium by inhibiting intestinal absorption and increasing the renal excretion of calcium.

■ PHOSPHATE METABOLISM

Phosphorus (P) is an essential mineral that is required by every cell in the body for normal function. Phosphorus is present in many food substances, such as peas, dried beans, nuts, milk, cheese and butter. Inorganic phosphorus (Pi) is in the form of the phosphate (PO_4). The majority of the phosphorus in the body is found as phosphate. Phosphorus is also the body's source of phosphate. In the body, phosphate is the most abundant intracellular anion.

■ IMPORTANCE OF PHOSPHATE

1. Phosphate is an important component of many organic substances such as, ATP, DNA, RNA and many intermediates of metabolic pathways
2. Along with calcium it forms an important constituent of bone and teeth
3. It forms a buffer in the maintenance of acid–base balance.

■ NORMAL VALUE

Total amount of phosphate in the body is 500 to 800 g. Though it is present in every cell of the body, 85 to 90% of body's phosphate is found in the bones and teeth. Normal plasma level of phosphate is 4 mg/dL.

■ REGULATION OF PHOSPHATE LEVEL

Phosphorus is taken through dietary sources. It is absorbed from the GI tract into blood and distributed to various parts of the body. While passing through the kidney, a large quantity of phosphate is excreted through urine. Phosphate homeostasis depends upon three processes:

1. Absorption from gastrointestinal tract
2. Resorption from bone
3. Excretion through urine.

These three processes are regulated by three hormones:

1. Parathormone
2. Calcitonin
3. 1,25-dihydroxycholecalciferol (calcitriol).

1. Parathormone

Parathormone stimulates resorption of phosphate from bone, and increases its urinary excretion. It also increases the absorption of phosphate from gastrointestinal tract through calcitriol. The overall action of parathormone decreases the plasma level of phosphate.

2. Calcitonin

Calcitonin also decreases the plasma level of phosphate by inhibiting bone resorption and stimulating urinary excretion.

3. 1,25-Dihydroxycholecalciferol — Calcitriol

This hormone increases absorption of phosphate from small intestine (Fig. 47-7).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone, and glucocorticoids also influence the phosphate level.

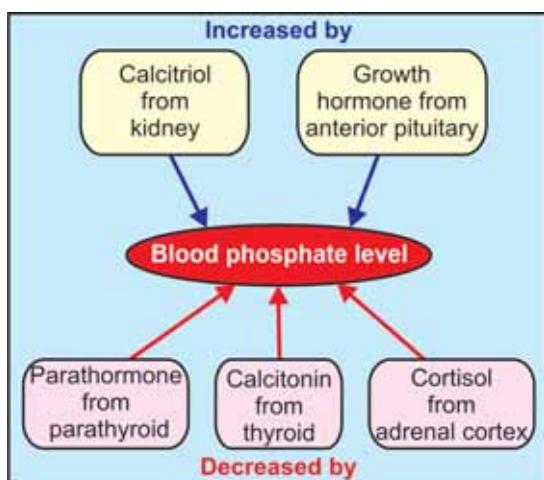


FIGURE 47-7: Effect of hormones on blood phosphate level

1. Growth hormone

It increases the blood phosphate level by increasing the intestinal phosphate absorption.

2. Glucocorticoids

Glucocorticoids (cortisol) decrease blood phosphate by inhibiting intestinal absorption and increasing the renal excretion of phosphate.

■ PHYSIOLOGY OF BONE

Bone or osseous tissue is a specialized rigid connective tissue that forms the skeleton. It consists of special type of cells and tough intercellular matrix of ground substance. The matrix is formed by organic substances like collagen and it is strengthened by the deposition of mineral salts like calcium phosphate and calcium carbonate. Throughout life, the bone is renewed by the process of bone formation and bone resorption.

■ FUNCTIONS OF BONE

1. Protective function – protects the soft tissues and vital organs of the body
2. Mechanical function – supports the body and brings out various movements of the body
3. Metabolic function – metabolism and homeostasis of calcium and phosphate in the body
4. Hemopoietic function – red bone marrow in the bones is the site of production of blood cells.

■ CELL TYPES OF BONE

Bone has three major types of cells:

1. Osteoblasts
2. Osteocytes
3. Osteoclasts.

1. Osteoblasts

Osteoblasts are the bone cells that are concerned with bone formation. These cells are situated in the outer surface of bone, the marrow cavity and epiphyseal plate. The osteoblasts arise from the giant multinucleated primitive cells called the osteoprogenitor cells.

Functions of osteoblasts

Osteoblasts

- i. Are responsible for the synthesis of bone matrix
- ii. Are rich in the enzymes alkaline phosphatase, which is necessary for deposition of calcium in the bone matrix (calcification)
- iii. Synthesize the proteins called matrix glaprotein and osteopontin, which are involved in the calcification.

Fate of osteoblasts

After taking part in bone formation, the osteoblasts differentiate into osteocytes, which are trapped inside the lacunae of calcified bone.

2. Osteocytes

Osteocytes are the cells concerned with maintenance of bone. Osteocytes are small flattened and rounded cells embedded in the bone lacunae. These bone cells are the main cells of developed bone and are derived from the matured osteoblasts.

Functions of osteocytes

- i. Help to maintain the bone as living tissue because of their metabolic activity
- ii. Maintain the exchange of calcium between the bone and ECF.

3. Osteoclasts

Osteoclasts are the bone cells that are concerned with bone resorption. Osteoclasts are the giant phagocytic multinucleated cells found in the lacunae of bone matrix. These bone cells are derived from hemopoietic stem cells via monocytes (CFU-M).

Functions of osteoclasts

- i. Responsible for bone resorption during bone remodeling
- ii. Synthesis and release of lysosomal enzymes necessary for bone resorption into the bone resorbing compartment.

■ BONE REMODELING

Bone remodeling is a dynamic lifelong process in which old bone is resorbed and new bone is formed. The process of remodeling extends for about 100 days in compact bone and about 200 days in spongy bone.

Bone remodeling includes two processes:

1. Bone resorption: Destruction of entire bone matrix and removal of calcium (osteoclastic activity). Osteoclasts are responsible for this
2. Bone formation: Development and mineralization of new matrix (osteoblastic activity). Osteoblasts are responsible for this.

Significance of Bone Remodeling

In children

1. Thickness of bone increases
2. Bone obtains strength in proportion to the growth
3. Shape of the bone is re-altered in relation to the growth of the body.

In adults

1. It is responsible for the maintenance of toughness of bone
2. Ensures the mechanical integrity of skeleton throughout life
3. Plays important role in calcium homeostasis.

■ APPLIED PHYSIOLOGY — DISEASES OF BONE

1. Osteoporosis

Osteoporosis is the bone disease characterized by the loss of bone matrix and minerals. The meaning of the word osteoporosis is 'porous bones'. It occurs due to excessive bone resorption and decreased bone formation.

The loss of bone matrix and minerals leads to loss of bone strength associated with architectural deterioration of bone tissue. Ultimately, the bones become fragile with high-risk of fracture. Commonly affected bones are vertebrae and hip. Osteoporosis is common in women after 60 years.

2. Rickets

Rickets is the bone disease in children characterized by inadequate mineralization of bone matrix. It occurs due to vitamin D deficiency. Vitamin D deficiency develops due to insufficiency in diet or due to inadequate exposure to sunlight.

The deficiency of vitamin D affects the reabsorption of calcium and phosphorus from renal tubules resulting in calcium deficiency. It causes inadequate mineralization of epiphyseal growth plate in growing bones. This defect produces various manifestations.

Manifestations of rickets

- i. Collapse of chest wall: Due to the flattening of sides of thorax with projecting sternum called pigeon chest, chicken chest or pectus carinatum
- ii. Rachitic rosary: A visible swelling where the ribs join their cartilages
- iii. Kyphosis: The excess curvature of upper back bone with convexity backward (forward bending or forward curvature)

- iv. Lordosis: The excess forward curvature of back bone in lumbar region
- v. Scoliosis: The lateral curvature of spine
- vi. Bowing of hands and legs
- vii. Enlargement of liver and spleen
- viii. Tetany in advanced stages. The patient may die because of tetany involving the respiratory muscles.

3. Osteomalacia

The rickets in adults is called osteomalacia or adult rickets. It occurs because of deficiency of vitamin D. It also occurs due to prolonged damage of kidney (renal rickets).

- The characteristic features of osteomalacia:
- i. Vague pain
 - ii. Tenderness in bones and muscles
 - iii. Myopathy leading to waddling gait (gait means the manner of walking). In waddling gait, the feet are wide apart and walk resembles that of a duck.
 - iv. Occasional hypoglycemic tetany.

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Endocrine Functions of Pancreas

- ISLETS OF LANGERHANS
- INSULIN
 - ACTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- GLUCAGON
 - ACTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- SOMATOSTATIN
 - ACTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- PANCREATIC POLYPEPTIDE
 - ACTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- REGULATION OF BLOOD SUGAR LEVEL
 - NORMAL BLOOD SUGAR LEVEL
 - ROLE OF LIVER IN THE MAINTENANCE OF BLOOD SUGAR LEVEL
 - ROLE OF INSULIN IN THE MAINTENANCE OF BLOOD SUGAR LEVEL
 - ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD SUGAR LEVEL
 - ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD SUGAR LEVEL
- APPLIED PHYSIOLOGY
 - HYPOACTIVITY — DIABETES MELLITUS
 - HYPERACTIVITY — HYPERINSULINISM

■ ISLETS OF LANGERHANS

The endocrine function of pancreas is performed by the islets of Langerhans. Human pancreas contains about 1 to 2 million islets.

Islets of Langerhans consist of four types of cells:

1. A cells or α cells which secrete glucagon
2. B cells or β cells which secrete insulin
3. D cells or δ cells which secrete somatostatin
4. F cells or PP cells which secrete pancreatic polypeptide.

■ INSULIN

Insulin is secreted by B cells or the β cells in the islets of Langerhans of pancreas. Insulin is a polypeptide with 51 amino acids. It has two amino acid chains called α and β chains which are linked by disulfide bridges. The α chain of insulin contains 21 amino acids, and β chain contains 30 amino acids.

Basal level of insulin in plasma is 10 μ U/mL.

■ ACTIONS

Insulin is the important hormone that is concerned with regulation of carbohydrate metabolism and blood sugar level. It is also concerned with metabolism of proteins and fats.

1. On Carbohydrate Metabolism

Insulin is the only antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that reduces blood sugar level. Insulin reduces the blood sugar level by its following actions on carbohydrate metabolism are:

i. Increases transport and uptake of glucose by the cells

Insulin facilitates the transport of glucose from the blood into the cells by increasing the permeability of cell membrane to glucose. Insulin stimulates the rapid uptake of glucose by all the tissues particularly liver, muscle and adipose tissues. However, insulin is not required for glucose uptake in some tissues like brain (except hypothalamus), renal tubules, mucous

membrane of intestine and RBCs. Insulin also increases the number of glucose transporters called GLUT 4 in the cell membrane.

ii. Promotes peripheral utilization of glucose

Insulin promotes the peripheral utilization of glucose. In the presence of insulin, the glucose which enters the cell is oxidized immediately. The rate of utilization depends upon intake of glucose.

iii. Promotes storage of glucose — glycogenesis

Insulin promotes the rapid conversion of glucose into glycogen (glycogenesis), which is stored in muscle and liver. Thus, glucose is stored in these two organs in the form of glycogen. Insulin activates the enzymes, which are necessary for glycogenesis. In liver, when glycogen content increases beyond its storing capacity, insulin causes conversion of glucose into fatty acids.

iv. Inhibits glycogenolysis

Insulin prevents the breakdown of glycogen into glucose in muscle and liver.

v. Inhibits gluconeogenesis

Insulin prevents gluconeogenesis, i.e. the formation of glucose from proteins.

Thus, insulin decreases the blood sugar level by:

- i. Facilitating transport and uptake of glucose by the cells
- ii. Increasing peripheral utilization of glucose
- iii. Increasing the storage of glucose by converting it into glycogen in liver and muscle
- iv. Inhibiting glycogenolysis
- v. Inhibiting gluconeogenesis.

2. On Protein Metabolism

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins by:

- i. Facilitating the transport of amino acids into the cell from blood. Insulin actually,

- increases the permeability of cell membrane for amino acids
- ii. Accelerating the synthesis of proteins by influencing the transcription of DNA and by increasing the translation of mRNA
- iii. Preventing the catabolism of proteins by decreasing the activity of cellular enzymes, which act on proteins
- iv. Preventing the conversion of proteins into glucose.

Thus, insulin is responsible for conservation and storage of proteins in the body.

3. On Fat Metabolism

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue. Actions of insulin on fat metabolism are:

i. Synthesis of fatty acids and triglycerides

Insulin promotes the transport of excess glucose into cells particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:
a. Glucose into fatty acids
b. Fatty acids into triglycerides.

ii. Transport of fatty acids into adipose tissue

Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. Storage of fat

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes, which degrade the triglycerides.

4. On Growth

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins. It enhances the transport of amino acids into the cells and synthesis of proteins in the cells. It also has the protein-sparing effect, i.e. it causes conservation of proteins by increasing the glucose utilization by the tissues.

■ MODE OF ACTION

On the target cells, insulin binds with the receptor protein and forms the insulin-receptor complex. This executes the action by activating the intracellular enzyme system.

■ REGULATION OF SECRETION

Insulin secretion is mainly regulated by blood glucose level. In addition, other factors like amino acids, lipid derivatives, gastrointestinal and endocrine hormones and autonomic nerve fibers also stimulate insulin secretion.

1. Role of Blood Glucose Level

When the blood glucose level is normal (80 to 100 mg/dL), the rate of insulin secretion is low (up to 10 µU/minute). When the blood glucose level increases between 100 to 120 mg/dL, the rate of insulin secretion rises rapidly to 100 µU /minute. When the blood glucose level rises above 200 mg/dL, the rate of insulin secretion also rises very rapidly up to 400 µU /minute.

2. Role of Proteins

The excess amino acids in blood also stimulate insulin secretion.

3. Role of Lipid Derivatives

The β ketoacids such as acetoacetate also increase insulin secretion.

4. Role of Gastrointestinal Hormones

Insulin secretion is increased by some of the gastrointestinal hormones such as gastrin, secretin, cholecystokinin, and GIP.

5. Role of Endocrine Hormones

The diabetogenic hormones like glucagon, growth hormone, and cortisol increase the blood sugar level which, in turn, stimulate insulin secretion indirectly. The prolonged hypersecretion of these hormones causes exhaustion of β cells resulting in diabetes mellitus.

6. Role of Autonomic Nerves

The stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion.

■ GLUCAGON

Glucagon is secreted from A cells or α cells in the islets of Langerhans of pancreas. It is also secreted from A cells of stomach and L cells of intestine. Glucagon is a polypeptide with 29 amino acids.

■ ACTIONS

Actions of glucagon are antagonistic to those of insulin. It increases the blood sugar level and peripheral utilization of lipids and facilitates the conversion of proteins into glucose.

1. On Carbohydrate Metabolism

Glucagon increases the blood glucose level by increasing glycogenolysis and gluconeogenesis in liver and releasing glucose into the blood.

2. On Protein Metabolism

Glucagon increases transport of amino acids into liver cells. The amino acids are utilized for gluconeogenesis.

3. On Fat Metabolism

Glucagon shows lipolytic and ketogenic actions. It increases lipolysis by increasing the release of free fatty acids from adipose tissue and making them available for peripheral utilization. The lipolytic activity of glucagon, in turn, promotes ketogenesis (formation of ketone bodies) in liver.

4. Other Actions

Glucagon:

- Inhibits the secretion of gastric juice
- Increases the secretion of bile from liver.

■ MODE OF ACTION

On the target cells (mostly liver cells) glucagon causes formation of cyclic AMP which brings out the actions of glucagon.

■ REGULATION OF SECRETION

The secretion of glucagon is controlled mainly by blood glucose and amino acid levels in the blood.

1. Role of Blood Glucose Level

The important factor that regulates the secretion of glucagon is the decrease in blood glucose level. When blood glucose level decreases below 80 mg/dL of blood, α cells of islets of Langerhans are stimulated and more glucagon is released. The glucagon in turn increases the blood glucose level. On the other hand, when the blood sugar level increases, α cells are inhibited and the secretion of glucagon decreases.

2. Role of Amino Acid Level in Blood

Increase in amino acid level in blood stimulates the secretion of glucagon. Glucagon, in turn, converts the amino acids into glucose.

3. Role of Other Factors

Factors which increase glucagon secretion:

- Exercise
- Stress
- Gastrin
- Cholecystokinin
- Cortisol.

Factors which inhibit glucagon secretion:

- Somatostatin
- Insulin
- Free fatty acids
- Ketones.

■ SOMATOSTATIN

Somatostatin is secreted from hypothalamus, D cells (δ cells) in islets of Langerhans of pancreas and D cells in stomach and upper part of small intestine. Somatostatin is a polypeptide.

■ ACTIONS

- Somatostatin acts within islets of Langerhans and, inhibits α and β cells, i.e. it inhibits the secretion of both glucagon and insulin

2. It decreases the motility of stomach, duodenum and gallbladder
3. It reduces the secretion of gastrointestinal hormones gastrin, CCK, GIP and VIP
4. Hypothalamic somatostatin inhibits secretion of GH and TSH from anterior pituitary. That is why, it is also called growth hormone inhibitory hormone (GHIH).

■ MODE OF ACTION

Somatostatin brings out its actions through cAMP.

■ REGULATION OF SECRETION

The secretion of pancreatic somatostatin is stimulated by glucose, amino acids and cholecystokinin. The tumor of D cells of islets of Langerhans causes hypersecretion of somatostatin. It leads to hyperglycemia and other symptoms of diabetes mellitus.

The secretion of somatostatin in GI tract increases by the presence of chyme containing glucose and proteins in stomach and small intestine.

■ PANCREATIC POLYPEPTIDE

Pancreatic polypeptide is secreted by F cells or PP cells in the islets of Langerhans of pancreas. It is also found in small intestine. It is a polypeptide with 36 amino acids.

■ ACTIONS

The exact physiological action of pancreatic polypeptide is not known. It is believed to increase the secretion of glucagon from α cells in islets of Langerhans.

■ MODE OF ACTION

Pancreatic polypeptide brings out its actions through cAMP.

■ REGULATION OF SECRETION

Secretion of pancreatic polypeptide is stimulated by the presence of chyme containing more proteins in the small intestine.

■ REGULATION OF BLOOD SUGAR LEVEL (BLOOD GLUCOSE LEVEL)

■ NORMAL BLOOD SUGAR LEVEL

In normal persons, blood sugar level is controlled within a narrow range. In the early morning after overnight fasting, the blood sugar level is low ranging between 70 and 110 mg/dL of blood. Between first and second hour after meals (postprandial), the blood sugar level rises to 100 to 140 mg/dL. The sugar level in the blood is brought back to normal at the end of second hour after the meals.

The blood sugar regulating mechanism is operated through liver and muscle by the influence of the pancreatic hormones insulin and glucagon. Many other hormones are also involved in the regulation of blood sugar level. Among all the hormones, insulin is the only hormone that reduces the blood sugar level and it is called the antidiabetogenic hormone. The hormones, which increase blood sugar level, are called diabetogenic hormones or anti-insulin hormones.

Necessity of Regulation of Blood Glucose Level

Regulation of blood sugar (glucose) level is very essential because, glucose is the only nutrient that is utilized for energy by many tissues such as brain tissues, retina and germinal epithelium of the gonads.

■ ROLE OF LIVER IN THE MAINTENANCE OF BLOOD SUGAR LEVEL

Liver serves as an important glucose buffer system. When blood sugar level increases after a meal, the excess glucose is converted into glycogen and stored in liver. Afterwards, when blood sugar level falls, the glycogen in liver is converted into glucose and released into the blood. The storage of glycogen and release of glucose from liver are mainly regulated by insulin and glucagon.

■ ROLE OF INSULIN IN THE MAINTENANCE OF BLOOD SUGAR LEVEL

Insulin decreases the blood sugar level and it is the only antidiabetic hormone available in the body (Refer the actions on insulin on carbohydrate metabolism in this chapter).

■ ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD SUGAR LEVEL

Glucagon increases the blood sugar level (Refer actions of glucagon on carbohydrate metabolism in this chapter).

■ ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD SUGAR LEVEL

The other hormones which increase the blood sugar level are:

1. Growth hormone (Chapter 45)
2. Thyroxine (Chapter 46)
3. Cortisol (Chapter 49)
4. Adrenaline (Chapter 50).

Thus, liver helps to maintain the blood sugar level by storing glycogen when blood glucose level is high after meals; and by releasing glucose, when blood sugar level is low after 2 to 3 hours of food intake. Insulin helps to control the blood sugar level, especially after meals. Glucagon and other hormones help to maintain the blood sugar level by raising it in between the meals.

■ APPLIED PHYSIOLOGY

■ HYPOACTIVITY — DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by high blood sugar (glucose) level associated with other manifestations. In most of the cases, the diabetes mellitus develops due to the deficiency of insulin.

Types of Diabetes Mellitus

Diabetes mellitus is of two types, Type I and Type II. The differences between the two types are given in Table 48-1.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to the deficiency of insulin. So it is also called insulin dependent diabetes mellitus (IDDM). Type I diabetes mellitus may occur at any age of life but, it usually occurs before 40 years of age. When it occurs at infancy (due to congenital disorder) or in childhood, it is called juvenile diabetes.

Causes of type I diabetes mellitus

1. Degeneration of β cells in the islets of Langerhans of pancreas
2. Destruction of β cells by viral infection
3. Congenital disorder of β cells
4. Destruction of β cells during autoimmune diseases.

Type II Diabetes Mellitus

It is due to the absence or deficiency of insulin receptors. It usually occurs after 40 years hence, it is called maturity onset diabetes mellitus. This type of diabetes mellitus is also called noninsulin dependent diabetes mellitus (NIDDM).

Causes for type II diabetes mellitus

In this type of diabetes the structure and function of β cells and the blood level of insulin are normal. But the insulin receptors are reduced in number or absent in the body. The major causes for type II diabetes are:

1. Hereditary disorders
2. Other endocrine disorders.

Diabetes mellitus associated with other endocrine disorders

Diabetes is very common in some of the endocrine disorders like gigantism, acromegaly, and Cushing's syndrome. The hyperglycemia in these conditions causes excess stimulation of β cells. The constant and excess stimulation, in turn causes burning out and degeneration of β cells. The β cell exhaustion leads to permanent diabetes mellitus. This type of diabetes mellitus is called secondary diabetes.

TABLE 48-1: Differences between type I and type II diabetes mellitus

Features	Type I (IDDM)	Type II (NIDDM)
Age of onset	Usually before 40 years	Usually after 40 years
Major cause	Lack of insulin	Lack of insulin receptor
Insulin deficiency	Yes	Partial deficiency
Immune destruction of β cells	Yes	No
Involvement of other endocrine disorders	No	Yes
Hereditary cause	Yes	May or may not be
Need for insulin	Always	Not in initial stage May require in later stage
Insulin resistance	No	Yes
Control by oral hypoglycemic agents	No	Yes
Symptoms appear	Rapidly	Slowly
Body weight	Usually thin	Usually overweight
Stress induced obesity	No	Yes
Ketosis	Yes	May or may not be

Signs and Symptoms of Diabetes Mellitus

Various manifestations of diabetes mellitus develop because of three major setbacks of insulin deficiency:

1. Increased blood sugar level (300 to 400 mg/dL) due to reduced utilization by tissue
2. Mobilization of fats from adipose tissue for energy purpose, leading to elevated fatty acid content in blood. This causes deposition of fat on the wall of arteries and development of atherosclerosis
3. Depletion of proteins from the tissues.

Following are the signs and symptoms of diabetes mellitus:

1. Glucosuria

Loss of glucose in urine is known as glucosuria. Normally, glucose does not appear in urine. When glucose level rises above 180 mg/dL in blood, glucose appears in urine. It is the renal threshold level for glucose.

2. Osmotic diuresis

Diuresis due to osmotic effects is called osmotic diuresis. The excess glucose in the renal tubules develops osmotic effect. The osmotic effect decreases the reabsorption of water from renal tubules resulting in diuresis. It leads to polyuria and polydipsia.

3. Polyuria

Excess urine formation with increase in frequency of voiding urine is called polyuria. It is due to the osmotic diuresis caused by increase in blood sugar level.

4. Polydipsia

The increase in water intake is called polydipsia. The excess loss of water decreases water content and increases salt content in the body. This stimulates the thirst center in hypothalamus. Thirst center in turn increases the intake of water.

5. Polyphagia

Polyphagia means the intake of excess food. It is very common in diabetes mellitus.

6. Asthenia

The loss of strength is called asthenia. The body becomes very weak. There is loss of energy. Asthenia is because of protein depletion which is caused by lack of insulin.

7. Acidosis

During insulin deficiency glucose cannot be utilized by the peripheral tissues for energy. So, a large amount of fat is broken down to release energy. It causes the formation of excess ketoacids leading to acidosis.

8. Acetone breathing

In cases of severe ketoacidosis, acetone is expired in the expiratory air, giving the characteristic acetone or fruity breath odor. It is a life-threatening condition of severe diabetes.

9. Kussmaul breathing

Kussmaul breathing is the increase in rate and depth of respiration caused by severe acidosis.

10. Circulatory shock

The osmotic diuresis leads to dehydration, which causes circulatory shock. It occurs only in severe diabetes.

11. Coma

Due to Kussmaul breathing, a large amount of carbon dioxide is lost during expiration. It leads to drastic reduction in the concentration of bicarbonate ions causing severe acidosis and coma. It occurs in severe cases of diabetes mellitus.

Increase in blood sugar level develops hyperosmolarity of plasma which also leads to coma. It is called hyperosmolar coma.

Complications of Diabetes Mellitus

Prolonged hyperglycemia in diabetes mellitus causes dysfunction and injury of many tissues resulting in some complications such as:

1. Cardiovascular complications like hypertension and myocardial infarction
2. Degenerative changes in retina called diabetic retinopathy
3. Degenerative changes in kidney known as diabetic nephropathy
4. Degeneration of autonomic and peripheral nerves called diabetic neuropathy.

Diagnostic Tests for Diabetes Mellitus

Diagnosis of diabetes mellitus includes the determination of:

1. Fasting blood sugar
2. Postprandial blood sugar
3. Glucose tolerance test (GTT)
4. Glycosylated (glycated) Hb.

■ HYPERACTIVITY — HYPERINSULINISM

Hyperinsulinism is the hypersecretion of insulin.

Cause of Hyperinsulinism

Hyperinsulinism occurs due to the tumor of β cells in the islets of Langerhans.

Signs and Symptoms of Hyperinsulinism

1. Hypoglycemia

The blood sugar level falls below 50 mg/dL.

2. Manifestations of central nervous system

Manifestations of central nervous system occur when the blood sugar level decreases. All the manifestations are together called neuroglycopenic symptoms.

Initially, the activity of neurons increases resulting in nervousness, tremor all over the body and sweating. If not treated immediately, it leads to clonic convulsions and unconsciousness. Slowly, the convulsions cease and coma occurs due to damage of neurons.

Adrenal Cortex

- FUNCTIONAL ANATOMY OF ADRENAL GLANDS
- HORMONES OF ADRENAL CORTEX
- MINERALOCORTICOIDS
 - FUNCTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- GLUCOCORTICOIDS
 - FUNCTIONS
 - MODE OF ACTION
 - REGULATION OF SECRETION
- ADRENAL SEX HORMONES
- APPLIED PHYSIOLOGY
 - HYPERACTIVITY OF ADRENAL CORTEX
 - HYPOACTIVITY OF ADRENAL CORTEX

■ FUNCTIONAL ANATOMY OF ADRENAL GLANDS

There are two adrenal glands. Each gland is situated on the upper pole of each kidney. Because of the situation, adrenal glands are otherwise called suprarenal glands. Each gland is made of two parts, the adrenal cortex and adrenal medulla. Adrenal cortex is the outer portion constituting 80% of the gland. Adrenal medulla is the central portion of gland constituting 20%.

Adrenal cortex is formed by three distinct layers of structures (Fig. 49-1).

1. Zona glomerulosa – outer layer
2. Zona fasciculata – middle layer
3. Zona reticularis – inner layer

■ HORMONES OF ADRENAL CORTEX

The hormones secreted by adrenal cortex are collectively known as adrenocortical hormones or corticosteroids. Based on their functions the corticosteroids are classified into three groups:

1. Mineralocorticoids
2. Glucocorticoids
3. Sex hormones.

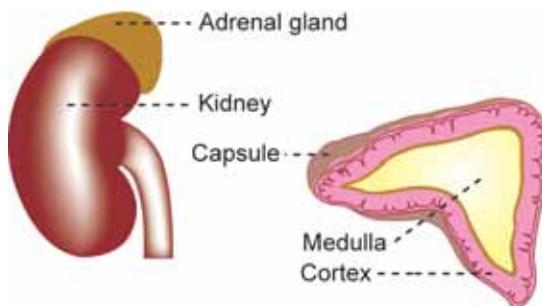


FIGURE 49-1: Adrenal gland

■ MINERALOCORTICOIDS

Mineralocorticoids are the corticosteroids that act on the minerals (electrolytes) particularly sodium and potassium. The mineralocorticoids are secreted by zona glomerulosa of adrenal cortex.

Mineralocorticoids are:

1. Aldosterone
2. 11-Deoxycorticosterone.

Mineralocorticoids are C₂₁ steroids having 21 carbon atoms. Plasma level of aldosterone and 11-Deoxycorticosterone is 0.006 µg/dL.

■ FUNCTIONS OF MINERALOCORTICOIDS

Ninety percent of mineralocorticoid activity is provided by aldosterone.

Life Saving Hormone

Aldosterone is very essential for life and it is usually called life saving hormone because, the total loss of this hormone causes death within 3 days to 2 weeks. It is mainly because of loss of mineralocorticoids which are essential to maintain the osmolarity and volume of ECF.

Actions of aldosterone are:

1. On Sodium Ions

Aldosterone increases reabsorption of sodium from distal convoluted tubule and the collecting duct in kidney.

2. On Extracellular Fluid Volume

When sodium ions are reabsorbed from the renal tubules, almost an equal amount of water is also reabsorbed. So the net result is the increase in ECF volume.

Even though aldosterone increases the sodium reabsorption from the renal tubules, the concentration of sodium in the body does not increase very much because of simultaneous reabsorption of water.

But still, there is possibility for mild increase in concentration of sodium in the blood (mild hypernatremia). It induces thirst leading to intake of water which again increases the ECF volume and blood volume.

3. On Blood Pressure

Increase in ECF volume and the blood volume finally leads to increase in blood pressure.

Aldosterone escape or escape phenomenon

Aldosterone escape refers to escape of the kidney from salt-retaining effects of excess secretion of aldosterone as in the case of primary hyperaldosteronism.

Mechanism of aldosterone escape

When aldosterone level increases, there is excess retention of sodium and water. This increases the ECF volume and blood pressure. Aldosterone induced high blood pressure decreases the ECF volume through two types of reactions:

- i. It stimulates secretion of atrial natriuretic peptide (ANP) from atrial muscles of the heart: ANP causes excretion of sodium in spite of increase in aldosterone secretion
- ii. It causes pressure diuresis (excretion of excess salt and water by high blood pressure) through urine. This decreases the salt and water content in ECF in spite of hypersecretion of aldosterone (Fig. 49-2).

Because of aldosterone escape, edema does not occur in primary hyperaldosteronism.

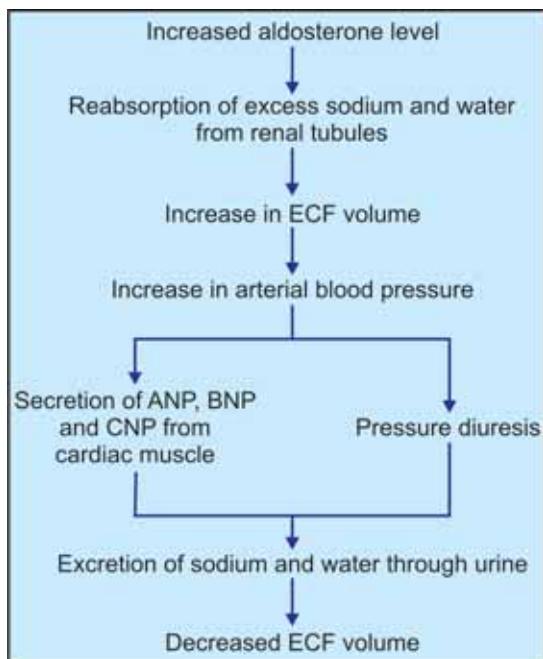


FIGURE 49-2: Aldosterone escape. ANP = atrial natriuretic peptide. BNP = brain natriuretic peptide. CNP = C-type natriuretic peptide.

4. On Potassium Ions

Aldosterone increases the potassium excretion through the renal tubules.

5. On Hydrogen Ion Concentration

While increasing the sodium reabsorption from the renal tubules, aldosterone causes tubular secretion of hydrogen ions which is essential to maintain acid–base balance in the body.

6. On Sweat Glands and Salivary Glands

Aldosterone has almost the similar effect on sweat glands and salivary glands as it shows on renal tubules. Sodium is reabsorbed from sweat glands under the influence of aldosterone, thus the loss of sodium from the body is prevented. Same effect is shown on saliva also. Thus, aldosterone helps conservation of sodium in the body.

7. On Intestine

Aldosterone increases sodium absorption from the intestine, especially from the colon and prevents loss of sodium through feces.

■ MODE OF ACTION

Mineralocorticoids act through the messenger RNA mechanism.

■ REGULATION OF SECRETION

Aldosterone secretion is regulated by four important factors (Fig. 49-3). The stimulatory agents for aldosterone secretion are given below in the order of their potency:

1. Increase in potassium ion concentration in ECF
2. Decrease in sodium ion concentration in ECF
3. Decrease in ECF volume
4. Adrenocorticotrophic hormone.

Increase in the concentration of potassium ions is the most effective stimulant for aldosterone secretion. It acts directly on zona glomerulosa and increases the secretion of aldosterone. Decrease in sodium ion concentration and ECF volume stimulates aldosterone secretion through renin-angiotensin mechanism. Renin secreted from juxtaglomerular apparatus of kidney acts on angiotensinogen in the plasma and converts it into angiotensin I, which is converted into angiotensin II by converting enzyme (ACE) secreted by lungs. Angiotensin II acts on the zona glomerulosa to secrete more aldosterone. Aldosterone, in turn, increases the retention of sodium and water and excretion of potassium leading to increase in the sodium ion concentration and ECF volume.

Now, the increased sodium ion concentration and the ECF volume inhibit the juxtaglomerular apparatus and stop the release of renin. So, angiotensin II is not formed and release of aldosterone from adrenal cortex is stopped.

Adrenocorticotrophic hormone mainly stimulates the secretion of glucocorticoids. It has only a mild stimulating effect on aldosterone secretion.

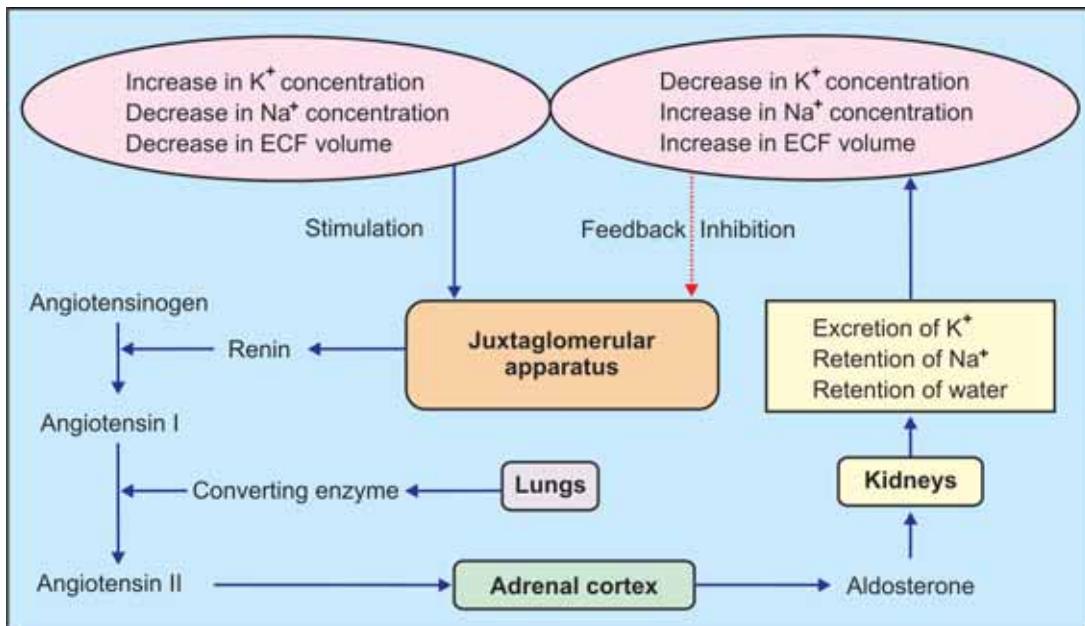


FIGURE 49-3: Regulation of aldosterone secretion

■ GLUCOCORTICOIDS

Glucocorticoids are the corticosteroids which act mainly on glucose metabolism. Glucocorticoids are secreted mainly by zona fasciculata of adrenal cortex. A small quantity of glucocorticoids is also secreted by zona reticularis.

Glucocorticoids are:

1. Cortisol
2. Corticosterone
3. Cortisone.

Glucocorticoids are C_{21} steroids having 21 carbon atoms. The plasma level of cortisol is $13.9 \mu\text{g/dL}$ and that of corticosterone is $0.4 \mu\text{g/dL}$.

■ FUNCTIONS OF GLUCOCORTICOIDS

Cortisol or hydrocortisone is more potent and it has 95% of glucocorticoid activity. Corticosterone is less potent showing only 4% of glucocorticoid activity. Cortisone with 1% activity is secreted in minute quantity.

Life Protecting Hormone

Like aldosterone, cortisol is also essential for life but in a different way. Aldosterone is a life saving hormone, whereas cortisol is a life protecting hormone because, it helps to withstand the stress and trauma in life.

Glucocorticoids have metabolic effects on carbohydrates, proteins, fats and water. These hormones also show mild mineralocorticoid effect.

1. On Carbohydrate Metabolism

Glucocorticoids increase the blood glucose level by two ways:

- i. By promoting gluconeogenesis in liver from amino acids
- ii. By inhibiting glucose uptake and utilization by peripheral cells

2. On Protein Metabolism

Glucocorticoids promote catabolism of proteins leading to decrease in cellular proteins and

increase in plasma amino acids and protein content in liver by the following methods:

- i. Glucocorticoids decrease the protein in the body cells except liver cells by accelerating protein catabolism and release of amino acids from the tissues
- ii. Glucocorticoids increase the transport of amino acids into hepatic cells. In hepatic cells, the amino acids are used for synthesis of proteins, plasma proteins and for gluconeogenesis.

Thus, glucocorticoids cause mobilization of proteins from tissues other than liver.

3. On Fat Metabolism

Glucocorticoids cause mobilization and redistribution of fats. The actions on fats are:

- i. Mobilization of fatty acids from adipose tissue
 - ii. Increasing the concentration of fatty acids in blood
 - iii. Increasing the utilization of fat for energy.
- By increasing the utilization of fats for energy release, glucocorticoids cause the formation of a large amount of ketone bodies. It is called ketogenic effect of glucocorticoids.

4. On Water Metabolism

Glucocorticoids accelerate the excretion of water and play an important role in the maintenance of water balance.

5. On Mineral Metabolism

Glucocorticoids enhance the retention of sodium and to a lesser extent increase the excretion of potassium. Glucocorticoids decrease blood calcium by inhibiting absorption of calcium from intestine and increasing the excretion of calcium through urine.

6. On Bone

Glucocorticoids stimulate the bone resorption (osteoclastic activity) and inhibit bone formation and mineralization (osteoblastic activity).

7. On Muscles

Glucocorticoids cause catabolism of proteins from muscle.

8. On Blood Cells

Glucocorticoids decrease the number of circulating eosinophils by increasing the destruction of eosinophils in reticuloendothelial cells. These hormones also decrease the number of basophils, and lymphocytes and, increase the number of circulating neutrophils, RBCs and platelets.

9. On Vascular Response

Presence of glucocorticoids is essential for the constrictor action of adrenaline and noradrenaline. In adrenal insufficiency, the blood vessels fail to respond to adrenaline and noradrenaline leading to vascular collapse.

10. On Central Nervous System

Glucocorticoids are essential for normal functioning of nervous system. Insufficiency of these hormones causes personality changes like irritability and lack of concentration.

11. Permissive Action of Glucocorticoids

Permissive action of glucocorticoids refers to execution of actions of some hormones only in the presence of glucocorticoids. Examples are:

- i. Calorigenic effects of glucagon
- ii. Lipolytic effects of catecholamines
- iii. Pressor effects of catecholamines
- iv. Bronchodilator effect of catecholamines.

12. On Resistance to Stress

The exposure to any type of stress, either physical or mental, increases the secretion of ACTH. ACTH in turn increases glucocorticoid secretion. The increase in glucocorticoid level is very essential for survival, as it offers high resistance to the body against stress.

It is assumed that the glucocorticoids enhance the resistance by the following ways:

- i. Immediate release and transport of amino acids from tissues to liver cells for synthesis of new proteins and other

- substances which are essential to withstand the stress
- ii. Release of fatty acids from cells for production of more energy during stress
 - iii. Enhancement of vascular reactivity to catecholamines and fatty acid mobilizing action of catecholamines, which are necessary to withstand the stress
 - iv. Prevention of severity of other changes in the body caused by stress.

13. Anti-inflammatory Effects

Inflammation is defined as a localized protective response induced by injury or destruction of tissues. When the tissue is injured by mechanical or chemical factors, some substances are released from the affected area, which produce series of changes in the affected area.

Glucocorticoids prevent the inflammatory changes in the injured or infected tissues by:

- i. Inhibiting the release of proteolytic enzymes responsible for inflammation
- ii. Preventing rush of blood to the injured area by enhancing vasoconstrictor action of catecholamines
- iii. Inhibiting migration of leukocytes into the affected area
- iv. Preventing loss of fluid from plasma into the affected tissue by decreasing the permeability of capillaries
- v. Reducing the reactions of tissues by suppressing T cells and other leukocytes

In addition to preventing inflammatory reactions, if inflammation has already started, the glucocorticoids cause an early resolution of inflammation and rapid healing.

14. Anti-allergic Actions

Corticosteroids prevent the various reactions in allergic conditions as in the case of inflammation.

15. Immunosuppressive Effects

Glucocorticoids suppress the immune system of the body by decreasing the number of circulating T lymphocytes. It is done by suppressing lymphoid tissues (lymph nodes and thymus) and

proliferation of T cells. Glucocorticoids also prevent release of interleukin-2 by T cells.

Thus, hypersecretion or excess use of glucocorticoids decreases the immune reactions against all foreign bodies entering the body. It leads to severe infection causing death.

The immunological reactions, which are common during organ transplantation, may cause rejection of the transplanted tissues. Glucocorticoids are used to suppress the immunological reactions, because of their immuno-suppressive action.

■ MODE OF ACTION

Glucocorticoids act through the messenger RNA mechanism.

■ REGULATION OF SECRETION

Anterior pituitary regulates glucocorticoid secretion by secreting ACTH. ACTH secretion is regulated by hypothalamus through corticotropin releasing factor (CRF).

Role of Anterior Pituitary — ACTH

Anterior pituitary controls the activities of adrenal cortex by secreting ACTH. ACTH is secreted by the basophilic chromophilic cells of anterior pituitary. It is a single chained polypeptide with 39 amino acids. Its concentration in plasma is 3 ng/dL.

ACTH is mainly concerned with the regulation of cortisol secretion. It plays only a minor role in the regulation of mineralocorticoid secretion.

Actions

ACTH is necessary for the structural integrity and the secretory activity of adrenal cortex. It has other functions also.

Actions of ACTH on adrenal cortex (adrenal actions)

1. Maintenance of structural integrity and vascularization of zona fasciculata and zona reticularis of adrenal cortex. In hypophysectomy, these two layers in the adrenal cortex are atrophied

2. Conversion of cholesterol into pregnenolone, which is the precursor of glucocorticoids. Thus, adrenocorticotrophic hormone is responsible for synthesis of glucocorticoids
3. Release of glucocorticoids
4. Prolongation of glucocorticoid action on various cells.

Other (nonadrenal) actions of ACTH

1. Mobilization of fats from tissues
2. Melanocyte stimulating effect. Because of structural similarity with melanocyte stimulating hormone, ACTH shows melanocyte stimulating effect. It causes darkening of skin by acting on melanophores which are the cutaneous pigment cells containing melanin.

Mode of action of ACTH

ACTH acts by the formation of cyclic AMP.

Role of Hypothalamus

Hypothalamus also plays an important role in the regulation of cortisol secretion by controlling the ACTH secretion through corticotropin releasing factor (CRF). It is also called corticotropin releasing hormone. CRF reaches the anterior pituitary through the hypothalamo-hypophyseal portal vessels.

CRF stimulates the corticotropes of anterior pituitary and causes synthesis and release of ACTH.

CRF secretion is induced by several factors such as emotion, stress, trauma and circadian rhythm. CRF in turn, causes release of ACTH, which induces glucocorticoid secretion.

Feedback Control

Cortisol regulates its own secretion through negative feedback control by inhibiting the release of CRF from hypothalamus and ACTH from anterior pituitary (Fig. 49-4).

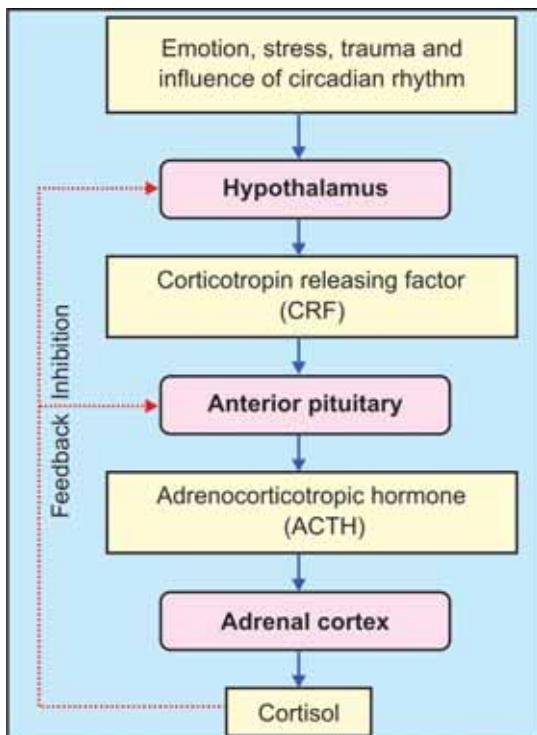


FIGURE 49-4: Regulation of cortisol secretion

■ ADRENAL SEX HORMONES

Adrenal sex hormones are secreted mainly by zona reticularis. Zona fasciculata secretes small quantities of sex hormones. Most of the hormones are male sex hormones (androgens). But small quantities of estrogen and progesterone are also secreted by adrenal cortex. The androgens secreted by adrenal cortex are:

1. Dehydroepiandrosterone
2. Androstenedione
3. Testosterone.

Dehydroepiandrosterone is the most active adrenal androgen.

The androgens, in general, are responsible for masculine features of the body (Chapter 53). But in normal conditions, the adrenal androgens have insignificant physiological effects, because of the low amount of secretion both in males and females.

In congenital hyperplasia of adrenal cortex or tumor of zona reticularis, an excess quantity of androgens is secreted. In males, it does not produce any special effect because, a large

quantity of androgens is produced by testes also. But in females, the androgens produce masculine features. Some of the androgens are converted into testosterone. Testosterone is responsible for the androgenic activity in adrenogenital syndrome or congenital adrenal hyperplasia.

■ APPLIED PHYSIOLOGY

■ HYPERACTIVITY OF ADRENAL CORTEX

1. Cushing's syndrome
2. Hyperaldosteronism
3. Adrenogenital syndrome.

1. Cushing's Syndrome

Cushing's syndrome is a disorder characterized by obesity.

Causes

Cushing's syndrome is due to the hypersecretion of glucocorticoids, particularly cortisol. It may be due to either pituitary origin or adrenal origin.

If it is due to pituitary origin it is known as Cushing's disease. If it is due to adrenal origin it is called Cushing's syndrome. Generally, these two terms are used interchangeably.

Pituitary origin

Increased secretion of ACTH causes hyperplasia of adrenal cortex leading to hypersecretion of cortisol.

Adrenal origin

Cortisol secretion is increased by:

- i. Tumor or carcinoma in zona fasciculata of adrenal cortex
- ii. Prolonged treatment with exogenous glucocorticoids
- iii. Prolonged treatment with high dose of ACTH

Signs and Symptoms

- i. Characteristic feature of this disease is the disproportionate distribution of body fat resulting in some abnormal features:

- a. Moon face: The edematous facial appearance due to fat accumulation and retention of water and salt
- b. Torso: Accumulation of fat in chest and abdomen. Arms and legs are very slim in proportion to torso (torso means trunk of the body)
- c. Buffalo hump: Due to fat deposit on the back of neck and shoulder
- d. Pot belly: Due to fat accumulation in upper abdomen (Fig. 49-5).
- ii. Purple striae: Reddish purple stripes on abdomen due to three reasons:
 - a. Stretching of abdominal wall by excess subcutaneous fat
 - b. Rupture of subdermal tissues due to stretching
 - c. Deficiency of collagen fibers due to protein catabolism.
- iii. Thinning of extremities
- iv. Thinning of skin and subcutaneous tissues due to protein catabolism
- v. Darkening of skin on neck (acanthosis)
- vi. Pigmentation of skin – hypersecretion of ACTH which has got melanocyte stimulating effect
- vii. Facial redness (facial plethora)
- viii. Facial hair growth (hirsutism)
- ix. Weakening of muscles because of protein depletion
- x. Bone resorption and osteoporosis due to protein depletion. Bone becomes susceptible to easy fracture
- xi. Hyperglycemia due to gluconeogenesis (from proteins) and inhibition of peripheral



Pot belly with purple striae



Fat deposition in upper abdomen, thorax and face (moon face) with thin hands

FIGURE 49-5: Cushing's syndrome
(Courtesy: Prof Mafauzy Mohamad)

- utilization of glucose. Hyperglycemia leads to glucosuria and adrenal diabetes
- xii. Hypertension by the mineralocorticoid effects of glucocorticoids – retention of sodium and water results in increase in ECF volume and blood volume leading to hypertension
- xiii. Immunosuppression resulting in susceptibility for infection
- xiv. Poor wound healing.

2. Hyperaldosteronism

Increased secretion of aldosterone is called hyperaldosteronism.

Causes

Depending upon the causes, hyperaldosteronism is classified into two types:

- i. Primary hyperaldosteronism which occurs due to tumor in zona glomerulosa of adrenal cortex. It is otherwise known as Conn's syndrome
- ii. Secondary hyperaldosteronism which occurs due to extra-adrenal causes such as congestive cardiac failure, nephrosis, toxemia of pregnancy and cirrhosis of liver.

Signs and Symptoms

- i. Increase in ECF volume and blood volume
- ii. Hypertension due to increase in ECF volume and blood volume
- iii. Severe depletion of potassium. Prolonged depletion of potassium causes renal damage. The kidneys fail to produce concentrated urine. It leads to polyuria and polydipsia
- iv. Muscular weakness due to potassium depletion
- v. Metabolic alkalosis due to secretion of large amount of hydrogen ions into renal tubules. Metabolic alkalosis reduces blood calcium level causing tetany.

3. Adrenogenital Syndrome

Under normal conditions, adrenal cortex secretes small quantities of androgens which do

not have any significant effect on sex organs or sexual function. However, secretion of abnormal quantities of adrenal androgens develops adrenogenital syndrome.

Causes

It is due to the tumor of zona reticularis in adrenal cortex.

Symptoms

Adrenogenital syndrome is characterized by the tendency for the development of secondary sexual character of opposite sex.

In females, increased secretion of androgens causes development of male secondary sexual characters. The condition is called adrenal virilism.

In males, the tumor of estrogen secreting cells produces more than normal quantity of estrogens resulting in symptoms such as feminization, gynecomastia (enlargement of breast) and atrophy of testis.

■ HYPOACTIVITY OF ADRENAL CORTEX

1. Addison's disease or chronic adrenal insufficiency
2. Congenital adrenal hyperplasia.

1. Addison's Disease or Chronic Adrenal Insufficiency

It is the failure of adrenal cortex to secrete corticosteroids. It is classified into three types:

- i. Primary Addison's disease that occurs due to adrenal cause
- ii. Secondary Addison's disease which is due to failure of anterior pituitary to secrete ACTH
- iii. Tertiary Addison's disease which is due to failure of hypothalamus to secrete CRF.

Causes for Primary Addison's Disease

- i. Atrophy or destruction of adrenal cortex
- ii. Malignancy of adrenal cortex

- iii. Congenital failure to secrete cortisol
- iv. Adrenalectomy and failure to take hormone therapy.

Signs and Symptoms

The signs and symptoms develop in Addison's disease because of deficiency of both cortisol and aldosterone. The common signs and symptom are:

- i. Pigmentation of skin and mucous membrane
- ii. Muscular weakness
- iii. Dehydration with loss of sodium
- iv. Hypotension
- v. Decrease in size of the heart
- vi. Hypoglycemia
- vii. Nausea, vomiting and diarrhea
- viii. Loss of body weight
- ix. Susceptibility to any type of infection
- x. Inability to withstand any stress resulting in Addisonian crisis (see below).

Addisonian Crisis or Adrenal Crisis or Acute Adrenal Insufficiency

It is a common symptom of Addison's disease characterized by sudden collapse associated with an increase in need for large quantities of glucocorticoids. The condition becomes fatal if not treated in time.

Causes

- i. Exposure to even mild stress
- ii. Hypoglycemia due to fasting
- iii. Trauma
- iv. Surgical operation
- v. Sudden withdrawal of glucocorticoid treatment.

2. Congenital Adrenal Hyperplasia

It is a congenital disorder characterized by increase in size of adrenal cortex. Size increases due to abnormal increase in the number of steroid secreting cortical cells.

Causes

Even though the size of the gland increases, cortisol secretion decreases. It is because of



FIGURE 49-6: Congenital adrenal hyperplasia (Macrogenitosomia praecox)
(Courtesy: Prof Mafauzy Mohamad)

the congenital deficiency of the enzymes necessary for the synthesis of cortisol, particularly, 21-hydroxylase.

Lack of this enzyme reduces the synthesis of cortisol. It, in turn, increases the secretion of ACTH from pituitary by feedback mechanism. ACTH stimulates the adrenal cortex causing hyperplasia with the accumulation of lipid droplets. Cortisol cannot be synthesized because of lack of 21-hydroxylase. Therefore, due to the constant stimulation of adrenal cortex by ACTH, the secretion of androgens increases. It results in sexual abnormalities such as virilism.

Symptoms

The characteristic features of adrenal hyperplasia are virilism and excess body growth.

In boys

Adrenal hyperplasia produces a condition known as macrogenitosomia praecox (Fig. 49-6). The features of this condition are:

- i. Precocious body growth, causing stocky appearance called Infant Hercules
- ii. Precocious sexual development with enlarged penis even at age of 4 years.

In girls

In girls, adrenal hyperplasia produces masculinization. It is otherwise called virilism. In some cases of genetic disorders, the female child is born with external genitalia of male type. This condition is called pseudohermaphroditism.

Adrenal Medulla

- INTRODUCTION
- HORMONES OF ADRENAL MEDULLA
- SYNTHESIS OF CATECHOLAMINES
- METABOLISM OF CATECHOLAMINES
- ACTIONS OF ADRENALINE AND NORADRENALINE
- REGULATION OF SECRETION OF ADRENALINE AND NORADRENALINE
- DOPAMINE
- APPLIED PHYSIOLOGY – PHEOCHROMOCYTOMA

■ INTRODUCTION

Medulla is the inner part of the adrenal gland and it forms 20% of mass of adrenal gland. It is made up of interlacing cords of cells known as chromaffin cells, pheochrom cells or chromophil cells. These cells contain fine granules which are stained brown by potassium dichromate. The chromaffin cells are of two types:

1. Adrenaline secreting cells (90%)
2. Noradrenaline secreting cells (10%).

■ HORMONES OF ADRENAL MEDULLA

Adrenal medullary hormones are the amines derived from catechol and so these hormones are called catecholamines. Three catecholamines are secreted by medulla:

1. Adrenaline or epinephrine
2. Noradrenaline or norepinephrine
3. Dopamine.

■ PLASMA LEVEL OF CATECHOLAMINES

1. Adrenaline : 3 µg/dL
2. Noradrenaline : 30 µg/dL
3. Dopamine : 3.5 µg/dL

■ SYNTHESIS OF CATECHOLAMINES

Catecholamines are synthesized from the amino acid tyrosine in the chromaffin cells of adrenal medulla (Fig. 50-1). These hormones are formed from phenylalanine also. But phenylalanine has to be converted into tyrosine.

Stages of synthesis of catecholamines:

1. Formation of tyrosine from phenylalanine in the presence of enzyme phenylalanine hydroxylase
2. Uptake of tyrosine from blood into the chromaffin cells of adrenal medulla by active transport

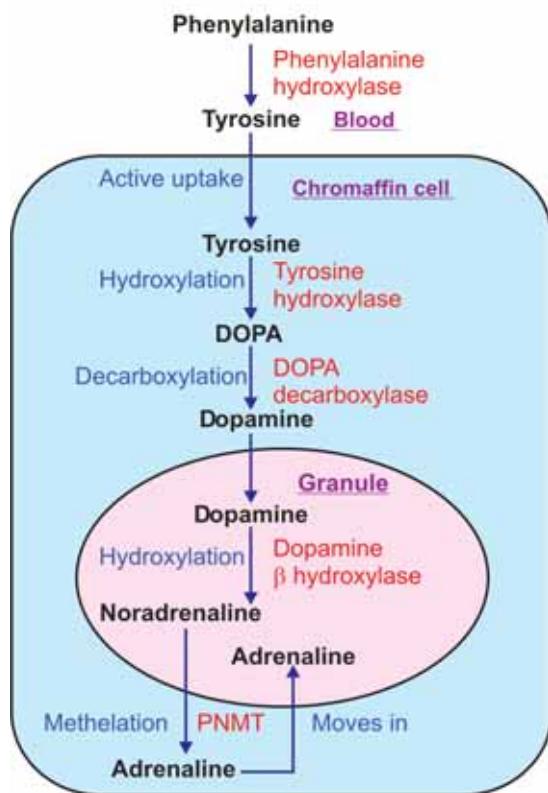


FIGURE 50-1: Synthesis of catecholamines.
PNMT = Phenyl-ethanolamine-N-methyltransferase
DOPA = Dihydroxyphenylalanine

3. Conversion of tyrosine into dihydroxyphenylalanine (DOPA) by hydroxylation in the presence of tyrosine hydroxylase
4. Decarboxylation of DOPA into dopamine by DOPA decarboxylase
5. Entry of dopamine into granules of chromaffin cells
6. Hydroxylation of dopamine into noradrenaline by the enzyme dopamine beta hydroxylase
7. Release of noradrenaline from granules into the cytoplasm
8. Methylation of noradrenaline into adrenaline by the most important enzyme called phenylethanolamine-N-methyltransferase (PNMT). PNMT is present in chromaffin cells.

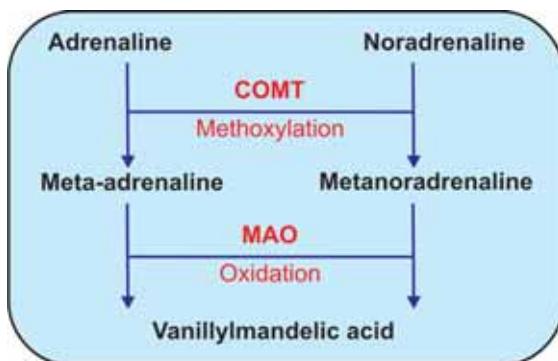


FIGURE 50-2: Metabolism of catecholamines
COMT = Catechol – O – methyltransferase
MAO = Monoamine oxidase

METABOLISM OF CATECHOLAMINES

Eighty five percent of noradrenaline is taken up by the sympathetic adrenergic neurons. The biological inactivation (degradation) and removal of remaining 15% of noradrenaline and adrenaline (Fig. 50-2) occurs in the following manner:

1. Adrenaline is methoxylated into meta-adrenaline. Noradrenaline is methoxylated into metanoradrenaline. The methoxylation occurs in the presence of 'Catechol-O-Methyltransferase' (COMT). Meta-adrenaline and metanoradrenaline are together called metanephries
2. Then, oxidation of metanephries into vanillyl-mandelic acid (VMA) occurs by monoamine oxidase (MAO)
3. Catecholamines are removed from body through urine in three forms:
 - i. 15% as free adrenaline and free noradrenaline
 - ii. 50% as free or conjugated meta-adrenaline and meta noradrenaline
 - iii. 35% as VMA.

ACTIONS OF ADRENALINE AND NORADRENALINE

Adrenaline and noradrenaline stimulate the nervous system. Adrenaline has significant effects

TABLE 50-1: Adrenergic receptors

Receptor	Mode of Action	Response
Alpha ₁ receptor	Activates IP ₃ through phospholipase C	Mediates more of noradrenaline actions than adrenaline actions
Alpha ₂ receptor	Inhibits adenyl cyclase and cAMP	
Beta ₁ receptor	Activates adenyl cyclase and cAMP	Mediates actions of adrenaline and noradrenaline equally
Beta ₂ receptor	Activates adenyl cyclase and cAMP	Mediates more of adrenaline actions than noradrenaline actions

on metabolic functions and both adrenaline and noradrenaline have significant effects on cardiovascular system.

■ MODE OF ACTION OF ADRENALINE AND NORADRENALINE – ADRENERGIC RECEPTORS

Adrenaline and noradrenaline execute their actions by binding with receptors called adrenergic receptors which are present in the target organs.

Adrenergic receptors are of two types:

1. Alpha adrenergic receptors
2. Beta adrenergic receptors.

Alpha receptors and, beta receptors are divided into beta₁ and beta₂ receptors. Refer Table 50-1 for their mode of action and response.

■ ACTIONS

The effects of adrenaline and noradrenaline on various target organs depend upon the type of receptors present in the cells of the organs. Adrenaline acts through both alpha and beta receptors equally. Noradrenaline acts mainly through alpha receptors and occasionally through beta receptors.

1. On Metabolism (via Alpha and Beta Receptors)

Adrenaline influences the metabolic functions more than noradrenaline.

- i. *General metabolism:* Adrenaline increases oxygen consumption and carbon dioxide removal. It increases basal meta-

bolic rate. So, it is said to be a calorogenic hormone

- ii. *Carbohydrate metabolism:* Adrenaline increases the blood glucose level. It is by increasing the glycogenolysis in liver and muscle. So, a large quantity of glucose enters the circulation
- iii. *Fat metabolism:* Adrenaline causes mobilization of free fatty acids from adipose tissues. Catecholamines need the presence of glucocorticoids for this action.

2. On Blood (via Beta Receptors)

Adrenaline decreases blood coagulation time. It increases RBC count in blood by contracting smooth muscles of splenic capsule and releasing RBCs from spleen into circulation.

3. On Heart (via Beta Receptors)

Adrenaline has stronger effects on heart than noradrenaline. It increases overall activity of the heart, i.e.

- i. Heart rate (chronotropic effect)
- ii. Force of contraction (inotropic effect)
- iii. Excitability of heart muscle (bathmotropic effect)
- iv. Conductivity in heart muscle (dromotropic effect).

4. On Blood Vessels (via Alpha and Beta₂ Receptors)

Noradrenaline has strong effects on blood vessels. It causes constriction of blood vessels

throughout the body via alpha receptors. So it is called 'General vasoconstrictor'. The vasoconstrictor effect of noradrenaline increases total peripheral resistance.

Adrenaline also causes constriction of blood vessels. However, it causes dilatation of blood vessels in skeletal muscle, liver and heart through beta₂ receptors. So, the total peripheral resistance is decreased by adrenaline.

5. On Blood Pressure (via Alpha and Beta Receptors)

Adrenaline increases systolic blood pressure by increasing the force of contraction of the heart and cardiac output. But, it decreases diastolic blood pressure by reducing the total peripheral resistance. Noradrenaline increases diastolic pressure due to general vasoconstrictor effect by increasing the total peripheral resistance. It also increases the systolic blood pressure to a slight extent by its actions on heart. The action of catecholamines on blood pressure needs the presence of glucocorticoids.

Thus, hypersecretion of catecholamines leads to hypertension.

6. On Respiration (via Beta₂ Receptors)

Adrenaline increases rate and force of respiration. Adrenaline injection produces apnea, which is known as adrenaline apnea. It also causes bronchodilation.

7. On Skin (via Alpha and Beta₂ Receptors)

Adrenaline causes contraction of arrector pili. It also increases the secretion of sweat.

8. On Skeletal Muscle (via Alpha and Beta₂ Receptors)

Adrenaline causes severe contraction and quick fatigue of skeletal muscle. It increases glycogenolysis and release of glucose from muscle into blood. It also causes vasodilatation in skeletal muscles.

9. On Smooth Muscle (via Alpha and Beta Receptors)

Catecholamines cause contraction of smooth muscles in the following organs:

- i. Splenic capsule
- ii. Sphincters of GI tract
- iii. Arrector pili of skin
- iv. Gallbladder
- v. Uterus
- vi. Dilator pupillae of iris
- vii. Nictitating membrane of cat.

Catecholamines cause relaxation of smooth muscles in some organs like:

- i. Nonsphincteric part of GI tract (esophagus, stomach and intestine)
- ii. Bronchioles
- iii. Urinary bladder.

10. On Central Nervous System (via Beta Receptors)

Adrenaline increases the activity of brain. Adrenaline secretion increases during 'fight or flight reactions' after exposure to stress. It enhances the cortical arousal and other facilitatory functions of central nervous system.

11. Other Effects of Catecholamines

- i. On salivary glands (via alpha and beta₂ receptors) – cause vasoconstriction in salivary gland leading to mild increase in salivary secretion
- ii. On sweat glands (via beta₂ receptors) – increase the secretion of apocrine sweat glands
- iii. On lacrimal glands (via alpha receptors) – increase the secretion of tears
- iv. On ACTH secretion (via alpha receptors) – adrenaline increases ACTH secretion
- v. On nerve fibers (via alpha receptors) – adrenaline decreases the latency of action potential in the nerve fibers, i.e. electrical activity is accelerated
- vi. On renin secretion (via beta receptors) – increase the secretion of renin from juxtaglomerular apparatus of the kidney.

■ REGULATION OF SECRETION OF ADRENALINE AND NORADRENALINE

Adrenaline and noradrenaline are secreted from adrenal medulla in small quantities even during rest. During stress conditions, due to sympathoadrenal discharge, a large quantity of catecholamines is secreted. These hormones prepare the body for fight or flight reactions.

Catecholamine secretion increases in exposure to cold and hypoglycemia also.

■ DOPAMINE

Dopamine is secreted by adrenal medulla. The type of cells secreting this hormone is not known. Dopamine is also secreted by dopaminergic neurons in some areas of brain particularly, basal ganglia. In brain, this hormone acts as a neurotransmitter.

The injected dopamine produces the following effects:

1. Vasoconstriction by releasing norepinephrine
2. Vasodilatation in mesentery
3. Increase in heart rate via beta receptors
4. Increase in systolic blood pressure. Dopamine does not affect diastolic blood pressure.

Deficiency of dopamine in basal ganglia produces nervous disorder called Parkinsonism (Chapter 94).

■ APPLIED PHYSIOLOGY – PHEOCHROMOCYTOMA

Pheochromocytoma is a condition characterized by hypersecretion of catecholamines.

Cause

Pheochromocytoma is caused by tumor of chromophil cells in adrenal medulla. It is also caused rarely by tumor of sympathetic ganglia (extra adrenal pheochromocytoma).

Signs and Symptoms

The characteristic feature of pheochromocytoma is hypertension. This type of hypertension is known as endocrine or secondary hypertension.

Other features are:

1. Anxiety
2. Chest pain
3. Fever
4. Headache
5. Hyperglycemia
6. Metabolic disorders
7. Nausea and vomiting
8. Palpitation
9. Polyuria and glucosuria
10. Sweating and flushing
11. Tachycardia
12. Weight loss.

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Endocrine Functions of Other Organs

- PINEAL GLAND
- THYMUS
- KIDNEYS
- HEART

■ PINEAL GLAND

■ SITUATION AND STRUCTURE

Pineal gland is otherwise called epiphysis. It is a small cone shaped structure. In human, it is about 10 mm long. Pineal gland is located in diencephalic area of brain above the hypothalamus. In human, pineal gland has two types of cells:

1. Parenchymal cells, which are large epithelial cells
2. Neuroglial cells.

In adults, the pineal gland is calcified. But, the epithelial cells exist and secrete the hormonal substance.

■ FUNCTIONS

Pineal gland has two functions:

1. It controls the sexual activities in animals by regulating the seasonal fertility. However, the pineal gland plays little role in regulating the sexual functions in human being.
2. The parenchymal cells of pineal gland secrete a hormonal substance called melatonin.

Melatonin

Melatonin is secreted by the parenchymal cells of pineal gland. It is an indole (N-acetyl-5 methoxytryptamine).

Actions

Melatonin acts mainly on gonads. Its action differs from species to species. In some animals, it stimulates the gonads while in other animals it inhibits the gonads.

In humans, it inhibits the onset of puberty by inhibiting the gonads.

Diurnal variation in melatonin secretion

Melatonin secretion is more in darkness than in daylight. In animals the secretion of melatonin varies according to activities in different periods of the day, i.e. circadian rhythm. Hypothalamus is responsible for the circadian fluctuations of melatonin secretion.

■ THYMUS

■ SITUATION

It is situated in front of trachea below the thyroid gland. Thymus is small in newborn infants and gradually enlarges till puberty, and then decreases in size.

■ FUNCTIONS

Thymus has lymphoid function and endocrine function. It plays an important role in development of immunity in the body. It has two functions:

1. Processing the T lymphocytes
2. Endocrine function.

1. Processing the T Lymphocytes

Thymus plays an essential role in the development of immunity by processing the T lymphocytes (Chapter 13). The lymphocytes, which are produced in bone marrow, are processed in thymus into T lymphocytes. It occurs during the period between three months before birth and three months after birth. So, the removal of thymus 3 months after birth will not affect the cell mediated immunity.

2. Endocrine Function of Thymus

Thymus secretes two hormones:

- i. Thymosin
- ii. Thymin.

Thymosin

Thymosin is a peptide. It accelerates lymphopoiesis and proliferation of T lymphocytes.

Thymin

It is also called thymopoietin. It suppresses the neuromuscular activity by inhibiting acetylcholine release. Hyperactivity of thymus causes myasthenia gravis.

■ KIDNEYS

Kidneys secrete five hormonal substances:

1. Erythropoietin
2. Thrombopoietin
3. Renin
4. 1,25-Dihydroxycholecalciferol (calcitriol)
5. Prostaglandins.

Recently, it is discovered that kidney secretes small quantity of C-type natriuretic peptide (see below).

■ 1. ERYTHROPOIETIN

Erythropoietin is secreted by endothelial cells of peritubular capillaries in the kidney. It is a glycoprotein with 165 amino acids.

Erythropoietin stimulates the bone marrow and causes erythropoiesis. More details are given in Chapter 8.

■ 2. THROMBOPOIETIN

Thrombopoietin is a glycoprotein. It is secreted by kidneys and liver. It stimulates production of platelets.

■ 3. RENIN

Renin is secreted by granular cells of juxtaglomerular apparatus of the kidney.

Actions of Renin

When renin is released into the blood, it acts on a specific plasma protein called α_2 globulin. It is also called angiotensinogen or renin substrate.

Renin converts angiotensinogen into angiotensin I which is converted into angiotensin II by a converting enzyme. The other details of renin and angiotensin II are given in Chapter 35.

■ 4. 1,25-DIHYDROXYCHOLECALCIFEROL – CALCITRIOL

Formation of 1,25-Dihydroxycholecalciferol

1,25-dihydroxycholecalciferol is otherwise known as calcitriol or activated vitamin D. It is formed from cholecalciferol which is present in skin and intestine. The cholecalciferol (vitamin D₃) from skin or intestine is converted into 25-hydroxy-cholecalciferol in liver. This in turn, is activated into 1,25-dihydroxycholecalciferol by parathor-mone in kidney (refer Chapter 47).

Action of 1,25-Dihydroxycholecalciferol

The activated vitamin D plays an important role in the maintenance of blood calcium level. It acts on the intestinal epithelium and enhances absorption of calcium from intestine into the blood. Details are given in Chapter 47.

■ 5. PROSTAGLANDINS

The prostaglandins secreted from kidney are PGA₂ and PGE₂. These hormones are secreted

by juxtapaglomerular cells and type I interstitial cells present in medulla of kidney. The prostaglandins decrease the blood pressure by systemic vasodilatation, diuresis and natriuresis. Details of prostaglandins are given in Chapter 52.

■ HEART

Heart secretes the hormones atrial natriuretic peptide and brain natriuretic peptide. Recently another peptide called C-type natriuretic peptide is found in heart.

■ ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is a polypeptide with 28 amino acids. It is secreted by atrial musculature of the heart. Recently, it is found in hypothalamus of brain also. However, its action in brain is not known.

ANP is secreted during overstretching of atrial muscles in conditions like increase in blood volume. ANP in turn increases excretion of sodium (followed by water excretion) through urine and helps in the maintenance of ECF volume and blood volume. It also lowers blood pressure.

Effect of ANP on Sodium Excretion

ANP increases excretion of sodium ions through urine by:

1. Increasing glomerular filtration rate
2. Inhibiting sodium reabsorption from distal convoluted tubules and collecting ducts
3. Increasing the secretion of sodium into the renal tubules.

Escape phenomenon

Thus, ANP is responsible for escape phenomenon, and prevention of edema in primary hyperaldosteronism in spite of increased ECF volume (Refer Chapter 52 for details).

Effect of ANP on Blood Pressure

ANP decreases the blood pressure by:

1. Vasodilatation
2. Inhibiting renin secretion from juxtapaglomerular apparatus
3. Inhibiting vasoconstrictor effect of angiotensin II
4. Inhibiting vasoconstrictor effects of catecholamines.

■ BRAIN NATRIURETIC PEPTIDE

Brain natriuretic peptide (BNP) is also called B-type natriuretic peptide. It is a polypeptide with 32 amino acids. It is secreted by the cardiac muscle. It is also secreted in some parts of brain. The stimulant for its secretion is not known.

BNP has same actions of ANP (see above). On brain, its actions are not known.

■ C-TYPE NATRIURETIC PEPTIDE

C-type natriuretic peptide (CNP) is the newly discovered peptide hormone. It is a 22 amino acid peptide. Initially, it was identified in brain. Now it is known to be secreted by several tissues which include myocardium, endothelium of blood vessels, gastrointestinal tract and kidneys. The functions of this hormone are not fully studied. It is believed that it has similar action of atrial natriuretic peptide.

Local Hormones

- INTRODUCTION
- LOCAL HORMONES SYNTHESIZED IN TISSUES
 - PROSTAGLANDINS AND ITS RELATED HORMONES
 - OTHER LOCAL HORMONES SYNTHESIZED IN TISSUES
- LOCAL HORMONES SYNTHESIZED IN TISSUES

■ INTRODUCTION

Local hormones are the substances which act on the same area of their secretion or in immediate neighborhood. The endocrine hormones are secreted in one place but execute their actions on some other remote place.

Local hormones are produced in tissues and blood. These hormones are usually released in an inactive form and are activated by some conditions or substances.

Local hormones are classified into two types:

- I. Hormones synthesized in tissues
- II. Hormones synthesized in blood.

■ LOCAL HORMONES SYNTHESIZED IN TISSUES

The local hormones synthesized in the tissues are:

- A. Prostaglandins and related substances
- B. Other local hormones synthesized in tissues.

■ PROSTAGLANDINS AND ITS RELATED HORMONES

Prostaglandins and other hormones which are derived from arachidonic acid are collectively called eicosanoids. The eicosanoids are:

1. Prostaglandins
2. Thromboxanes
3. Prostacyclin
4. Leukotrienes
5. Lipoxins.

1. *Prostaglandins*

Prostaglandins were first discovered and isolated from human semen. However, now it is believed that almost all the tissues of the body including renal tissues synthesize prostaglandins. Prostaglandins are unsaturated fatty acids with a cyclopentane ring and 20 carbon atoms.

Types

A variety of prostaglandins are identified. Active forms of prostaglandins are PGA₂, PGD₂, PGE₂, and PGF₂.

Actions

- i. *On blood:* Prostaglandins accelerate the capacity of RBCs to pass through minute blood vessels
- ii. *On blood vessels:* PGE₂ causes vaso-dilatation

- iii. *On GI tract:* The prostaglandins reduce gastric secretion. In experimental animals, prostaglandins inhibit the formation of peptic ulcer.
- iv. *On respiratory system:* PGE₂ causes bronchodilatation.
- v. *On lipids:* Some of the prostaglandins inhibit the release of free fatty acids from adipose tissue.
- vi. *On nervous system:* In brain, prostaglandins control or alter the actions of neurotransmitters.
- vii. *On reproduction:* Prostaglandins play an important role in regulating the reproductive cycle. These hormones also cause degeneration of corpus luteum (luteolysis). Prostaglandins increase the velocity of sperm transport in female genital tract.
- Prostaglandins (PGE₂) play an important role during parturition and facilitate labor by increasing the force of uterine contractions.
- When injected intra-amniotically during pregnancy, prostaglandins induce abortion. When injected during last stages of pregnancy, the prostaglandins induce labor.
- viii. *On kidney:* The prostaglandins stimulate juxtaglomerular apparatus and enhance the secretion of renin, diuresis and natriuresis.

2. Thromboxanes

Thromboxanes are derived from arachidonic acid. Thromboxanes are of two types:

- i. Thromboxane A₂ which is secreted in platelets
- ii. Thromboxane B₂ the metabolite of thromboxane A₂.

The thromboxane A₂ causes vasoconstriction. It plays an important role in hemostasis by accelerating aggregation of platelets. It also accelerates the clot formation.

3. Prostacyclin

Prostacyclin is also a derivative of arachidonic acid. It is produced in the endothelial cells and smooth muscle cells of blood vessels.

It causes vasodilatation and inhibits platelet aggregation.

4. Leukotrienes

Leukotrienes are derived from arachidonic acid via 5-hydroperoxy eicosatetraenoic acid (5-HETE). Leukotrienes are the mediators of allergic responses. These hormones also promote inflammatory reactions.

The release of leukotrienes increases when some allergic agents combine with antibodies like IgE.

The leukotrienes cause:

- i. Bronchiolar constriction
- ii. Arteriolar constriction
- iii. Vascular permeability
- iv. Attraction of neutrophils and eosinophils towards the site of inflammation.

5. Lipoxins

Lipoxins are also derived from arachidonic acid via 15-hydroperoxy eicosatetraenoic acid (15-HETE). Lipoxins are of two types namely, Lipoxin A and Lipoxin B.

Lipoxin A causes dilation of minute blood vessels. Both the types inhibit the cytotoxic effects of killer T cells.

■ OTHER LOCAL HORMONES SYNTHESIZED IN TISSUES

In addition to prostaglandins and related hormonal substances, tissues secrete some more hormones which are listed below.

1. Acetylcholine
2. Serotonin
3. Histamine
4. Substance P
5. Heparin
6. Leptin
7. GI hormones.

1. Acetylcholine

Acetylcholine is the cholinergic neurotransmitter. It is the transmitter substance at neuromuscular junction. It is also released by following nerve endings:

- i. Preganglionic parasympathetic nerve
- ii. Postganglionic parasympathetic nerve
- iii. Preganglionic sympathetic nerve
- iv. Postganglionic sympathetic cholinergic nerves such as:
 - a. Nerves supplying eccrine sweat glands
 - b. Sympathetic vasodilator nerves in skeletal muscle
- v. Nerves in amacrine cells of retina

Acetylcholine is also secreted by mast cell, gastric mucosa, lungs and brain.

Acetylcholine produces the excitatory function of synapse by opening the sodium channels. Acetylcholine is very quick in action. It is also destroyed immediately after executing the action by the enzyme acetylcholinesterase. This enzyme is present in basal lamina of the synaptic cleft.

Acetylcholine activates smooth muscles in GI tract, urinary tract and skeletal muscles. It inhibits cardiac function and causes vasodilatation.

2. Serotonin

It is otherwise known as 5-hydroxytryptamine. Serotonin is secreted in the following structures:

- i. Hypothalamus
- ii. Limbic system
- iii. Cerebellum
- iv. Spinal cord
- v. Retina
- vi. GI tract
- vii. Lungs
- viii. Platelets

Serotonin is an inhibitory substance. It inhibits impulses of pain sensation in posterior gray horn of spinal cord. It causes mood depression and sleep. It also causes vasoconstriction.

3. Histamine

It is secreted in nerve endings of hypothalamus, limbic cortex and other parts of cerebral cortex. It is an excitatory neurotransmitter substance secreted in spinal cord.

Histamine is also released from tissues during allergic condition, inflammation or damage. It causes vasodilatation and enhances the capillary permeability for fluid and plasma proteins from blood into the affected tissues. So, the accumulation of fluid with proteins develops local edema.

In GI tract, histamine increases the motility.

4. Substance P

Substance P is the neurotransmitter for pain. It is secreted by nerve endings (first order neurons of pain pathway) in spinal cord and retina.

It is also the neurotransmitter substance in GI tract. The presence of chyme in duodenum causes secretion of substance P. In GI tract, it increases the mixing and propulsive movements of small intestine.

5. Heparin

Heparin is produced in mast cells. Mast cells are the wandering cells present immediately outside the capillaries in large number of tissues or organs, which contain more connective tissue. These wandering cells are abundant in liver and lungs. Basophils also secrete heparin. Heparin is a naturally produced anticoagulant (Refer Chapter 15 for other details).

6. Leptin

Leptin (in Greek it means thin) is a protein hormone with 167 amino acids. It is secreted by adipocytes in adipose tissues.

Leptin plays an important role in controlling the adipose tissue and food intake. Leptin acts on hypothalamus and inhibits the feeding center resulting in stoppage of food intake (Chapter 92). At the same time it also stimulates the metabolic reactions involved in utilization of fat stored in adipose tissue for energy. Thus, the circulating leptin level informs the brain about the energy storage and the necessity to regulate food intake and metabolic reactions.

7. Gastrointestinal Hormones

- i. Gastrin (Chapter 28)
- ii. Secretin (Chapter 29)
- iii. Cholecystokinin (Chapter 29)
- iv. Gastric inhibitory peptide – GIP (Chapter 28)
- v. Vasoactive intestinal polypeptide – VIP (Chapter 28)
- vi. Pancreatic polypeptide (Chapter 29)
- vii. Somatostatin (Chapter 29)
- viii. Peptide YY (Chapter 29)

■ LOCAL HORMONES PRODUCED IN BLOOD

The local hormones produced in the blood are:

- A. Serotonin
- B. Angiotensinogen
- C. Kinins.

Serotonin is described above. Angiotensinogen is explained in Chapter 35.

■ KININS

Kinins are protein hormones circulating in blood.

There are two types of kinins:

- 1. Bradykinin
- 2. Kallidin.

Actions of bradykinin

Bradykinin:

- 1. Dilates blood vessels and decreases the blood pressure. It is considered as a potent vasodilator
- 2. Increases the blood flow throughout the body by its vasodilator action
- 3. Increases permeability of capillaries during inflammatory conditions resulting in edema in the affected area
- 4. Stimulates pain receptors
- 5. Causes contraction of smooth muscles of intestine.

Action of kallidin

Kallidin is also a vasodilator hormone.

QUESTIONS IN ENDOCRINOLOGY

■ LONG QUESTIONS

1. Enumerate the hormones secreted by pituitary gland. Describe the actions and regulation of secretion of growth hormone. Write in brief about effects of hypersecretion of anterior pituitary gland.
2. Describe the synthesis, storage, release, transport, functions and regulation of secretion of thyroid hormones.
3. Explain the functions and regulation of secretion of parathormone. Add a note on the disorders of parathormone secretion.
4. Explain the regulation of blood calcium level. Add a note on tetany.
5. Enlist the hormones secreted by pancreas. Explain the functions and regulation of secretion of insulin.
6. Describe in detail the regulation of blood sugar level.
7. Classify the hormones secreted by adrenal cortex. Explain the actions and regulation of secretion of cortisol.
8. Enumerate the corticosteroids. Describe the actions and regulation of secretion of aldosterone.
9. What are catecholamines? Explain the synthesis, metabolism, actions and regulation of secretion of catecholamines.

■ SHORT QUESTIONS

1. Growth hormone.
2. Thyroid stimulating hormone.
3. Adrenocorticotropic hormone.
4. Gonadotropins.
5. Somatomedin.
6. Oxytocin.
7. Antidiuretic hormone.
8. Milk ejection/neuroendocrine reflex.
9. Gigantism.
10. Acromegaly.

11. Dwarfism.
12. Acromicria.
13. Simmond's disease.
14. Fröhlich's syndrome.
15. Disorders of posterior pituitary gland.
16. Diabetes insipidus.
17. Synthesis of thyroid hormones.
18. Thyroglobulin.
19. Thyroxine.
20. Hyperthyroidism/Graves' disease.
21. Hypothyroidism.
22. Goiter.
23. Cretinism.
24. Myxedema.
25. Parathormone.
26. Tetany.
27. Hypercalcemia/hypocalcemia.
28. Insulin.
29. Glucagon.
30. Somatostatin.
31. Diabetes mellitus.
32. Hyperinsulinism.
33. Cortisol.
34. Nonmetabolic actions of cortisol.
35. Aldosterone.
36. Aldosterone escape.
37. Adrenal androgens.
38. Cushing's syndrome or disease.
39. Hyperaldosteronism.
40. Endocrine function of heart.
41. Adrenogenital syndrome.
42. Addison's disease.
43. Synthesis of catecholamines.
44. Actions of catecholamines.
45. Dopamine.
46. Pheochromocytoma.
47. Functions of pineal gland.
48. Functions of thymus.
49. Prostaglandins.
50. Acetylcholine.

SECTION 7

Reproductive System

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Male Reproductive System

- INTRODUCTION
- PRIMARY SEX ORGANS IN MALES – TESTES
- ACCESSORY SEX ORGANS IN MALES
- FUNCTIONS OF TESTIS
- GAMETOGENIC FUNCTIONS OF TESTIS – SPERMATOGENESIS
- ENDOCRINE FUNCTIONS OF TESTIS
- SEMEN
- MALE CLIMACTERIC
- APPLIED PHYSIOLOGY

■ INTRODUCTION TO MALE REPRODUCTIVE SYSTEM

Reproductive system ensures the continuation of the species. The organs of the reproductive system are of two groups namely internal reproductive organs and external genital organs. Gonads are the main organs which produce the gametes i.e., sperm and ovum. A pair of testes (singular – testis) produces sperms in males and a pair of ovaries produces ovum in females.

Male reproductive system includes the primary sex organs and accessory sex organs.

■ PRIMARY SEX ORGANS IN MALES – TESTES

Testis is the primary sex organ or gonad in males. There are two testes in almost all the species. The testes are ovoid or walnut shaped bodies located in the sac like structure called scrotum (Fig. 53-1)

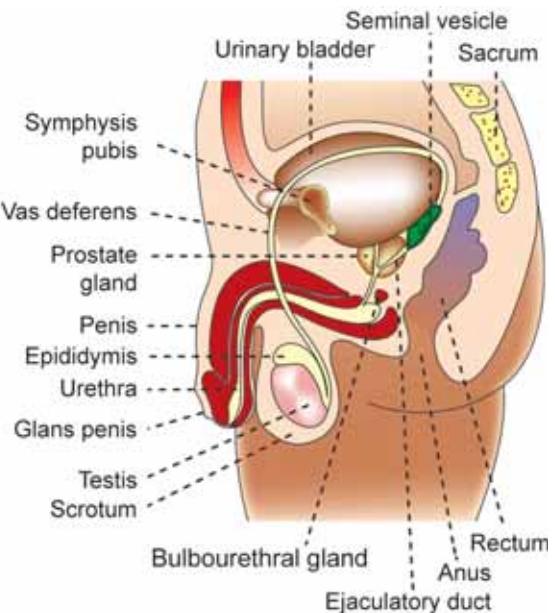


FIGURE 53-1: Male reproductive system and other organs of pelvis

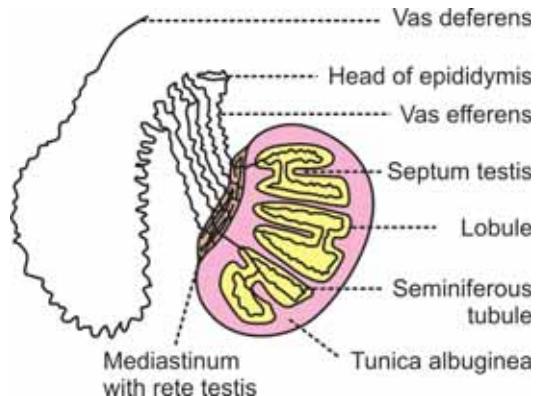


FIGURE 53-2: Structure of testis

■ COVERINGS OF TESTIS

Each testis is enclosed by three coverings.

1. Tunica vasculosa which is the innermost covering. It is made up of connective tissue and it is rich in blood vessels.
2. Tunica albuginea which is the middle covering. It is a dense fibrous capsule.
3. Tunica vaginalis which is the outermost covering. It is formed by visceral and parietal layers.

The tunica albuginea on the posterior surface of testis is thickened to form the mediastinum testis. From this, the connective tissue septa called septula testis radiate into testis and bind with tunica albuginea at various points. By this, the interior of testis is divided into a number of pyramidal lobules, with bases directed towards the periphery and the apices towards the mediastinum (Fig. 53-2).

The septula do not form complete partition. Because of this, the lobules of testis anastomose with one another at many places.

■ FUNCTIONAL ANATOMY OF TESTIS

Each testis has about 200 to 300 lobules. Each lobule contains 1 to 4 coiled tubules known as the seminiferous tubules. Seminiferous tubules continue as the vas efferens, which form the epididymis. It is continued as vas deferens. The terminal portion of vas deferens is called ampulla (Fig. 53-3).

Seminiferous Tubules

Seminiferous tubules are thread like convoluted tubular structures in which the spermatozoa or sperms are produced. There are about 400 to 600 seminiferous tubules in each testis. The length of each seminiferous tubule is between 30 and 70 cm. The diameter of the tubules is between 150 and 300 μ . The seminiferous tubules are surrounded and supported by interlobular connective tissue (Fig. 53-2).

The wall of the seminiferous tubule is formed by three layers:

1. The outer capsule or tunica propria
2. A thin homogeneous basement membrane
3. The stratified epithelium which consists of two types of cells:
 - i. Spermatogenic cells or germ cells
 - ii. Supporting cells called Sertoli cells.

Spermatogenic Cells

The spermatogenic cells or germ cells present in seminiferous tubules are the precursor cells of spermatozoa. These cells lie in between Sertoli cells and are arranged in an orderly manner in 4 to 8 layers. In children, the spermatogenic cells are in the primitive stage called spermatogonia. With onset of puberty, these cells develop into sperms through different stages.

Sertoli Cells

Sertoli cells are the large and tall irregular columnar cells present in seminiferous tubule. The spermatogenic cells are attached to Sertoli cells by means of cytoplasmic connection.

Functions of Sertoli cells

Sertoli cells:

1. Support and nourish the spermatogenic cells till the spermatozoa are released from them
2. Secrete the enzyme aromatase which converts androgens into estrogen
3. Secrete androgen binding protein (ABP) which is essential for testosterone activity particularly in spermatogenesis.
4. Secrete estrogen binding protein (EBP)

5. Secrete inhibin which inhibits the release of FSH from anterior pituitary
6. Secrete activin which increases FSH release
7. Secrete Müllerian regression factor (MRF) in fetal testes. MRF is also called Müllerian inhibiting substance (MIS). MRF is responsible for the regression of Müllerian duct during sex differentiation in fetus (see below).

Blood-Testis Barrier

Blood-testis barrier is a mechanical barrier that separates blood from seminiferous tubules of the testes. It is formed by tight junctions between the adjacent Sertoli cells near the basal membrane of seminiferous tubule.

Blood-testes barrier protects the seminiferous tubules and spermatogenic cells by preventing the entry of toxic substances from blood into testis. At the same time it permits nutritive and other essential substances necessary for spermatogenic cells.

Rete Testis

Each seminiferous lobules open into a network of thin walled channels called the rete testis.

Vas Efferens

From rete testis, 8 to 15 tubules called vas efferens arise. Vas efferens join together and form the head of epididymis and then converge to form duct of epididymis (Fig. 53-3).

Epididymis

The duct of epididymis is an enormously convoluted tubule with a length of about 4 meters. It begins at head, where it receives vas efferens.

Vas Deferens

At the caudal pole of testis, epididymis turns sharply upon itself and continues as vas deferens without any definite demarcation.

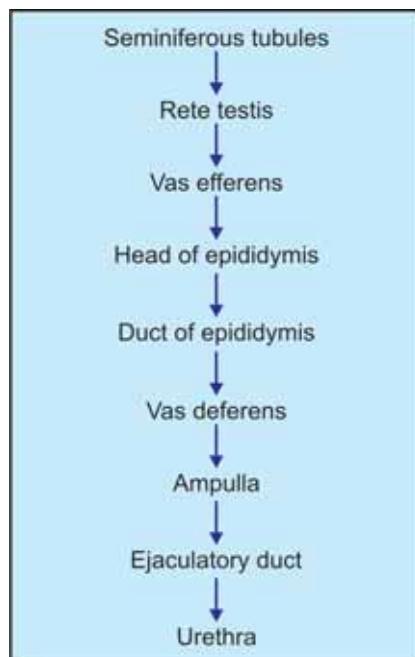


FIGURE 53-3: Pathway for passage of sperms

Interstitial Cells of Leydig

Interstitial cells of Leydig are the hormone secreting cells of the testes situated in between the seminiferous tubules.

■ ACCESSORY SEX ORGANS IN MALES

Accessory sex organs in males are:

1. Seminal vesicles
2. Prostate gland
3. Urethra
4. Penis.

■ SEMINAL VESICLES

Seminal vesicles are the paired glands situated in lower abdomen on either side of prostate gland behind urinary bladder. Each seminal vesicle is a hollow sac of irregular shape. It is lined by complexly folded mucous membrane which secretes seminal fluid.

Seminal fluid is added to semen in the ejaculatory duct through ampulla of vas deferens. The ejaculatory duct passes through prostate to form internal urethra.

Properties and Composition of Seminal Fluid

The seminal fluid is mucoid and viscous in nature. It is neutral or slightly alkaline in reaction. It adds to the bulk of semen as it forms 60% of total semen. The seminal vesicles secrete several important substances. Refer Fig. 53-7 for the products of seminal fluid.

Functions of Seminal Fluid

1. Nutrition to sperms

The fructose and other nutritive substances in seminal fluid are utilized by sperms after being ejaculated into female genital tract.

2. Clotting of semen

As soon as semen is ejaculated it is clotted because of conversion of fibrinogen of seminal fluid into fibrin. Clotting of semen is essential for holding the sperms in uterine cervix.

3. On fertilization

The prostaglandin of seminal fluid enhances fertilization of ovum by the following processes:

- i. Increasing the receptive capacity of cervical mucosa for sperms
- ii. Causing reverse peristaltic movement of uterus and fallopian tubes. This, in turn, increases the rate of transport of sperms in female genital tract during coitus.

■ PROSTATE GLAND

Human prostate gland weighs about 40 g. It is formed by 20 to 30 separate secretory glands, which open separately into the urethra. Prostate secretes prostatic fluid.

Properties and Composition of Prostatic Fluid

The prostate fluid is a thin, milky and alkaline fluid. It forms 30% of total semen. Refer Fig. 53-7 for the products secreted by prostate gland.

Functions of Prostatic Fluid

1. Maintenance of sperm motility

The prostatic fluid provides optimum pH for the motility of sperms. Generally, sperms are non-motile at a pH of less than 6.0. There are two factors which decrease the pH and motility of sperm:

- i. Metabolic end products from sperm which make the fluid in vas deferens acidic
- ii. Vaginal secretions in females are highly acidic with a pH of 3.5 to 4.0.

The prostatic secretion neutralizes the acidity and maintains a pH of 6.0 to 6.5. At this pH, the sperms become motile and the chances of fertilization are enhanced.

2. Clotting of semen

The clotting enzymes present in prostatic fluid convert fibrinogen (from seminal vesicles) into clot.

3. Lysis of clot

The clot is dissolved by fibrinolysin of the prostatic fluid so that, the sperms become motile.

■ URETHRA

Urethra has two parts namely, internal urethra and external urethra. Internal urethra is the continuation of ejaculatory duct. Internal urethra passes through penis as external urethra. Urethra contains mucus glands throughout its length, which are called glands of Littré. The bilateral bulbourethral glands also open into the urethra.

■ PENIS

Penis is the male genital organ. Urethra passes through penis and opens to the exterior. Penis

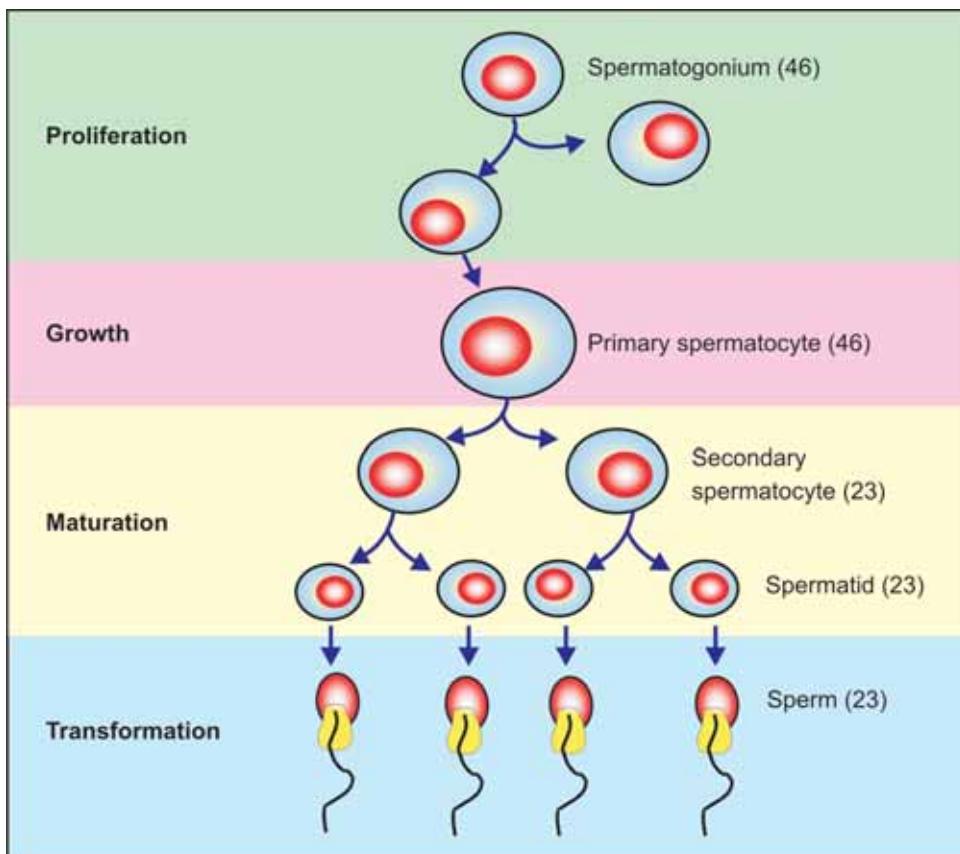


FIGURE 53-4: Spermatogenesis. Number in parenthesis indicate chromosomal number

is formed by three erectile tissue masses, i.e. a paired corpora cavernosa and an unpaired corpus spongiosum. The corpus spongiosum surrounds the urethra and terminates distally to form glans penis.

■ FUNCTIONS OF TESTIS

Testis performs two functions:

1. Gametogenic function by which gametes are produced in the gonads
2. Endocrine function by which male sex hormones are secreted.

■ GAMETOGENIC FUNCTIONS OF TESTIS – SPERMATOGENESIS

Spermatogenesis is the process by which the male gametes called spermatozoa (sperms) are

formed from the primitive spermatogenic cells (spermatogonia) in the testis (Fig. 53-4). It takes 74 days for the formation of sperm from a primitive germ cell.

■ STAGES OF SPERMATOGENESIS

Spermatogenesis occurs in four stages:

1. Stage of proliferation
2. Stage of growth
3. Stage of maturation
4. Stage of transformation.

1. Stage of Proliferation

Each spermatogonium contains diploid number (23 pairs) of chromosomes. One member of each pair is derived from mother and the other one from the father. The 23 pairs include 22 pairs of

autosomal chromosomes and one pair of sex chromosomes. The sex chromosomes are one X chromosome and one Y chromosome.

During the proliferative stage, spermatogonia divide by mitosis without any change in chromosomal number. In man, there are usually seven generations of spermatogonia. During this stage, the spermatogonia migrate along with Sertoli cells towards the lumen of seminiferous tubule.

The last generation of spermatogonia enters the stage of growth as primary spermatocyte.

2. Stage of Growth

In this stage, the primary spermatocyte grows into a large cell. Apart from growth, there is no other change in spermatocyte during this stage.

3. Stage of Maturation

After reaching the full size, each primary spermatocyte quickly undergoes meiotic or maturation division, which occurs in two phases:

First phase

In the first phase each primary spermatocyte divides into two secondary spermatocytes. The significance of the first meiotic division is that each secondary spermatocyte receives only the haploid or half the number of chromosomes. 23 chromosomes include 22 autosomes and an X or a Y chromosome.

Second phase

During this phase, each secondary spermatocyte undergoes second meiotic division resulting in two smaller cells called spermatids. Each spermatid has haploid number of chromosomes.

4. Stage of Transformation

There is no further division. The spermatids are transformed into matured spermatozoa (sperms). Transformation occurs in two stages.

i. Spermeogenesis

It is the process by which spermatids become matured spermatozoa. The changes taking place during this stage are:

- i. Condensation of nuclear material
- ii. Formation of acrosome, mitochondrial spiral filament and tail structures
- iii. Removal of unwanted quantity of cytoplasm.

ii. Spermination

Spermination is the process by which the matured sperms are released from Sertoli cells into the lumen of seminiferous tubules. Structure of sperm is explained later in this chapter.

■ ROLE OF SERTOLI CELLS IN SPERMATOGENESIS

Sertoli cells:

1. Support and nourish the germ cells
2. Provide hormonal substances necessary for spermatogenesis
3. Secrete androgen binding protein (ABP) which is essential for testosterone activity, particularly on spermatogenesis
4. Release sperms into lumen of seminiferous tubules (spermination).

■ ROLE OF HORMONES IN SPERMATOGENESIS

Spermatogenesis is influenced by many hormones which act either directly or indirectly: Table 53-1 gives the hormones essential for each stage of spermatogenesis. The hormones necessary for spermatogenesis are:

1. FSH
2. LH
3. GH
4. Testosterone
5. Estrogen
6. Inhibin
7. Activin.

TABLE 53-1: Hormones necessary for spermatogenesis

Stage of spermatogenesis	Hormones necessary
1. Stage of proliferation	FSH Growth hormone
2. Stage of growth	Testosterone Growth hormone
3. Stage of maturation	Testosterone Growth hormone
4. Stage of transformation	Testosterone Estrogen

1. FSH

FSH is responsible for the initiation of spermatogenesis. It binds with Sertoli cells and spermatogonia and induces the proliferation of spermatogonia. It also stimulates formation of estrogen and androgen binding protein from Sertoli cells (Fig. 53-5).

2. LH

In males this hormone is called interstitial cell stimulating hormone. It is essential for the secretion of testosterone from Leydig cells.

3. GH

Growth hormone is essential for the general metabolic processes in testis. It is also necessary for proliferation of spermatogonia. In pituitary dwarfs, the spermatogenesis is severely affected.

4. Testosterone

Testosterone is responsible for sequence of remaining stages in spermatogenesis. It is also responsible for maintenance of spermatogenesis. Testosterone activity is largely influenced by androgen binding protein.

5. Estrogen

It is formed from testosterone in Sertoli cells. It is necessary for spermatogenesis.

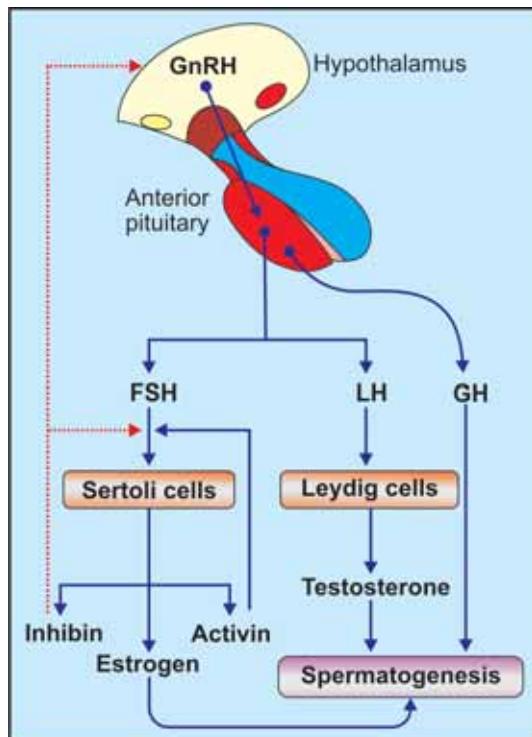


FIGURE 53-5: Role of hormones in spermatogenesis
Blue arrow = Stimulation. Red dotted arrow = Inhibition

6. Inhibin

Inhibin is a peptide hormone and serves as a transforming growth factor. It is secreted by Sertoli cells. In females, it is secreted by granulosa cells of ovarian follicles. Its secretion is stimulated by FSH.

Inhibin inhibits FSH secretion through feedback mechanism leading to decrease in the pace of spermatogenesis.

7. Activin

It is also a peptide hormone secreted in gonads along with inhibin. The exact location of its secretion in testis is not known. It is suggested that it is secreted by Sertoli cells and Leydig cells.

Activin has opposite actions of inhibin. It increases secretion of FSH and accelerates spermatogenesis.

■ OTHER FACTORS AFFECTING SPERMATOGENESIS

Spermatogenesis is also influenced by some other factors:

1. Increase in the body temperature prevents spermatogenesis. It occurs in cryptorchidism (see below). Normally, the temperature in the scrotum is about 2°C less than the body temperature. But in cryptorchidism the testes are in the abdomen where the temperature is always higher than that of scrotum. Increase in temperature stops spermatogenesis.
2. Infectious diseases such as mumps cause degeneration of seminiferous tubules and absence of spermatogenesis.

■ ENDOCRINE FUNCTIONS OF TESTIS

Testis secretes male sex hormones which are collectively called the androgens. Androgens secreted by testis are:

1. Testosterone
2. Dihydrotestosterone
3. Androstenedione.

The androgens are secreted in large quantities by interstitial cells of Leydig in testes and in small quantity by zona reticularis in adrenal cortex.

Androgens are steroid hormones synthesized from cholesterol or acetate. Testosterone is a C19 steroid. The plasma level of testosterone in an adult male varies between 300 and 700 ng/dL. In adult female the testosterone level is 30 to 60 mg/dL.

■ FUNCTIONS OF TESTOSTERONE

In general, testosterone is secreted in fetal life and adult life. But, in childhood, practically no testosterone is secreted approximately until 10 to 12 years of age. Afterwards, the testosterone secretion starts and, it increases rapidly at the onset of puberty and lasts through most of the remaining part of life. The secretion starts decreasing after 40 years and becomes almost zero by the age of 90 years.

Functions of Testosterone in Fetal Life

The fetal testes begin to secrete testosterone at about 2nd to 4th month of fetal life. Testosterone performs three functions in fetus:

1. Sex differentiation in fetus
2. Development of accessory sex organs
3. Descent of the testes.

1. Sex differentiation in fetus

Testosterone is responsible for the sex differentiation of fetus. Fetus has two genital ducts:

- i. Müllerian duct which gives rise to female accessory sex organs such as vagina, uterus and fallopian tube
- ii. Wolffian duct which gives rise to male accessory sex organs such as epididymis, vas deferens and seminal vesicles.

If testosterone is secreted from the genital ridge of the fetus at about 7th week of intrauterine life, the Müllerian duct system disappears and male sex organs develop from Wolffian duct.

In addition to testosterone, Müllerian regression factor (MRF) secreted by Sertoli cells is also responsible for regression of Müllerian duct.

In the absence of testosterone, Wolffian duct regresses and female sex organs develop from Müllerian duct.

2. Development of accessory sex organs and external genitalia

Testosterone is also essential for the growth of the external genitalia viz. penis and scrotum and other accessory sex organs namely genital ducts, seminal vesicles and prostate.

3. Descent of testes

Initially, testes are developed in the abdominal cavity and are later pushed down into the scrotum through inguinal canal just before birth. The process by which testes enter the scrotum is called the descent of testes. Testosterone is necessary for descent of testes.

Cryptorchidism

Cryptorchidism is a congenital disorder characterized by the failure of one or both the

testes to descent from abdomen into scrotum. In such case, the testes are called undescended testes. Administration of testosterone or gonadotropic hormones (which stimulate Leydig cells) causes descent of testes. Surgery is required if the inguinal canal is narrow. Males with untreated testes are prone for testicular cancer.

Functions of Testosterone in Adult Life

Testosterone has two important functions in adult:

1. Effect on sex organs
2. Effect on secondary sexual characters.

1. Effect on sex organs

Testosterone increases the size of penis, scrotum and the testes after puberty. All these organs are enlarged at least 8 folds between the onset of puberty and the age of 20 years, under the influence of testosterone. Testosterone is also necessary for spermatogenesis.

2. Effect on secondary sexual characters

Secondary sexual characters are the physical and behavioral characteristics that distinguish the male from female. These characters appear at the time of puberty. Testosterone is responsible for the development of secondary sexual characters in males.

The secondary sexual characters in males are:

i. Effect on muscular growth

Testosterone increases the muscle mass due to its anabolic effects on proteins. It accelerates transport of amino acids into the muscle cells, synthesis of proteins and storage of proteins in the muscles. It also decreases breakdown of proteins.

ii. Effect on bone growth

After puberty, testosterone increases the thickness of bones by increasing the matrix content and calcium deposition. The increase in matrix content in bones is because of its

anabolic effects on protein. The deposition of calcium is secondary to the increase in bone matrix.

In addition to increase in the size and strength of bones, testosterone also causes early fusion of epiphyses of long bones with shaft. So, if testes are removed before puberty, the fusion of epiphyses is delayed and the height of the person increases.

iii. Effect on shoulder and pelvic bones

Testosterone causes broadening of shoulders and it has a specific effect on pelvis which results in:

- a. Lengthening of pelvis
- b. Funnel like shape of pelvis
- c. Narrowing of pelvic outlet.

Thus, pelvis in males is different from that of females, which is broad and round or oval in shape.

iv. Effect on skin

Testosterone increases the thickness of skin and ruggedness of subcutaneous tissue by increasing the deposition of proteins in skin. It also increases the quantity of melanin pigment, which is responsible for the deepening of the skin color.

Testosterone enhances the secretory activity of sebaceous glands. So, at the time of puberty, when the body is exposed to sudden increase in testosterone secretion, the excess secretion of sebum leads to development of acne on the face. After few years, the skin gets adapted to testosterone secretion and, acne disappears.

v. Effect on hair distribution

The testosterone causes male type of hair distribution on the body, i.e. hair growth over the pubis, along linea alba up to umbilicus, on face, on chest and other parts of the body such as back and limbs. In males, the pubic hair has the base of the triangle downwards whereas in it is upwards. Testosterone decreases the hair growth on the head and may cause baldness if there is genetic background.

vi. Effect on voice

At the time of adolescence, the boys have a cracking voice. It is because of the testosterone effect which causes:

- Hypertrophy of laryngeal muscles
- Enlargement of larynx and lengthening
- Thickening of vocal cords.

Later, the cracking voice changes gradually into a typical adult male voice with a bossing sound.

vii. Effect on basal metabolic rate

At the time of puberty and earlier part of adult life, the testosterone increases the basal metabolic rate to about 5 to 10% by its anabolic effects on protein metabolism.

viii. Effect on electrolyte and water balance

Testosterone increases the sodium reabsorption from renal tubules along with water. It leads to increase in ECF volume.

ix. Effect on blood

Testosterone has got erythropoietic action. So, after puberty, testosterone causes mild increase in RBC count. It also increases the blood volume by increasing the water retention and ECF volume.

■ MODE OF ACTION OF TESTOSTERONE

Testosterone acts via genes.

■ REGULATION OF TESTOSTERONE SECRETION

In Fetus

During fetal life, the testosterone secretion from testis is stimulated by human chorionic gonadotropin, which has the properties similar to those of luteinizing hormone. Human chorionic gonadotropin stimulates the development of Leydig cells in the fetal testes and promotes testosterone secretion.

In Adults

LH or ICSH stimulates the Leydig cells and the quantity of testosterone secreted is directly proportional to the amount of LH available.

Secretion of LH from anterior pituitary gland is stimulated by LHRH from hypothalamus.

Feedback Control

Testosterone regulates its own secretion by negative feedback mechanism. It acts on hypothalamus and inhibits the secretion of LHRH. When LHRH secretion is inhibited, LH is not released from anterior pituitary resulting in stoppage of testosterone secretion from testes. On the other hand, when testosterone production is low, lack of inhibition of hypothalamus leads to secretion of testosterone through LHRH and LH (Fig. 53-6).

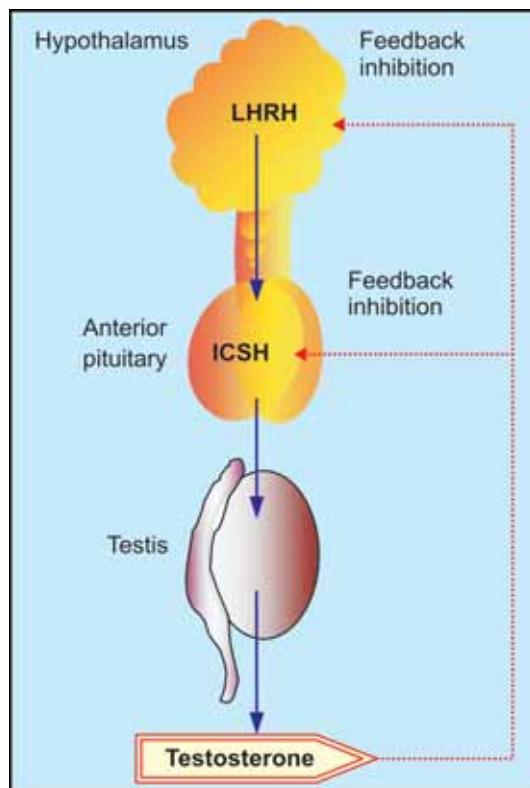


FIGURE 53-6: Regulation of testosterone secretion
LHRH = Luteinizing hormone releasing hormone
ICSH = Interstitial cell stimulating hormone

■ SEMEN

Semen is a white or grey fluid that contains spermatozoa (sperms). It is the collection of fluids from testes, seminal vesicles, prostate gland and bulbourethral glands. Semen is discharged during sexual act and the process of discharge of semen is called ejaculation.

Testes contribute sperms. The prostate secretion gives milky appearance to semen. And, the secretions from seminal vesicles and bulbourethral glands provide mucoid consistency to semen.

At the time of ejaculation, human semen is liquid in nature. Immediately, it coagulates and after some time it becomes liquid again.

The fibrinogen secreted from seminal vesicle is converted into a weak coagulum by the clotting enzymes secreted from prostate gland. The coagulum is liquefied after about 30 minutes, as it is lysed by fibrinolysin. Fibrinolysin is the activated form of profibrinolysin produced in prostate gland.

When semen is ejaculated, the sperms are nonmotile due to the viscosity of coagulum. When the coagulum dissolves, the sperms become motile.

■ PROPERTIES OF SEMEN

1. Specific gravity : 1.028
2. Volume : 2 to 6 mL per ejaculation
3. Reaction : It is alkaline with a pH of 7.5. The alkalinity is due to the secretions from prostate gland.

■ COMPOSITION OF SEMEN

Semen contains 10% sperms and 90% of fluid part which is called seminal plasma. The seminal plasma contains the products from seminal vesicle and prostate gland (Fig. 53-7). It also has small amount of secretions from the mucus glands, particularly the bulbourethral glands.

■ SPERM

Sperm or spermatozoon (pleural = spermatozoa) is the male reproductive cell, developed in the testis. The total count of sperm is about 100 to 150 million/mL of semen. Sterility occurs when the sperm count falls below 20 millions/mL.

Though the sperms can be stored in male genital tract for longer periods, after ejaculation

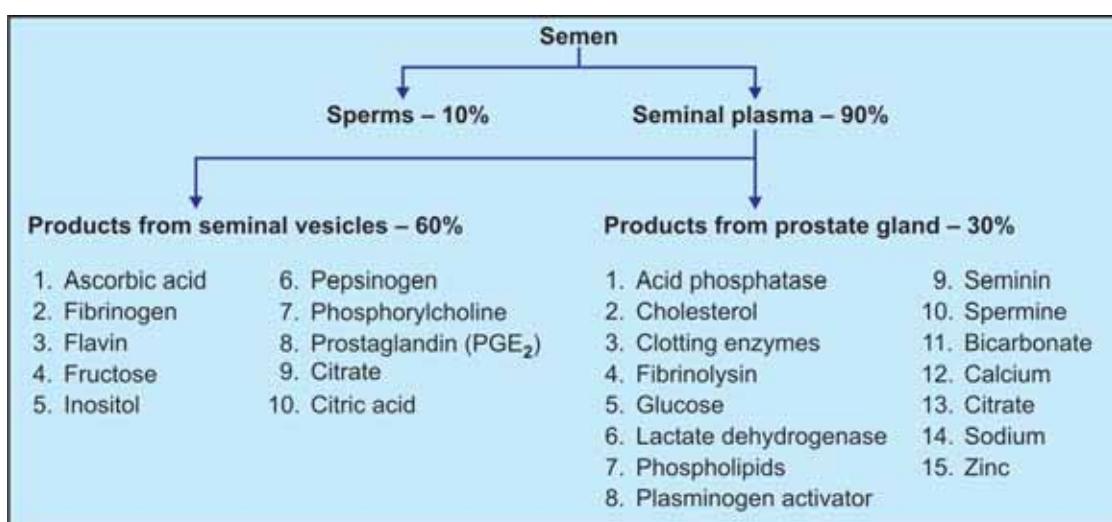


FIGURE 53-7: Composition of semen

the survival time is only about 24 to 48 hours at a temperature equivalent to body temperature.

The rate of motility of sperm in female genital tract is about 3 mm/minute. The sperms reach the fallopian tube in about 30 to 60 minutes after sexual intercourse. The uterine contractions during sexual act facilitate the movement of sperms.

Structure of Sperm

The matured sperm is $60\text{ }\mu$ long. Each sperm consists four parts:

1. Head
2. Neck
3. Body
4. Tail.

1. Head

Head of sperm is oval in shape (in front view), with a length of 3 to $5\text{ }\mu$ and width of up to $3\text{ }\mu$. The anterior portion of head is thin (Fig. 53-8).

The head is formed by thin cytoplasm with a condensed nucleus and it is covered by a thin cell membrane. The anterior two thirds of the head is like a thick cap and it is called acrosome. Acrosome develops from Golgi apparatus and it is made up of mucopolysaccharide and acid phosphatase. It also contains hyaluronidase and proteolytic enzymes which are essential for the sperm to fertilize the ovum.

2. Neck

The head is connected to the body by a short neck. Its anterior end is formed by thick disk shaped anterior end knob, which is also called proximal centriole. The posterior end is formed by another similar structure known as posterior end knob. It gives rise to the axial filament of body.

Often, the neck and body of sperm are together called midpiece.

3. Body

It is cylindrical with a length of 5 to $9\text{ }\mu$ and the thickness of $1\text{ }\mu$. The body of the sperm consists of a central core called axial filament covered by thin cytoplasmic capsule.

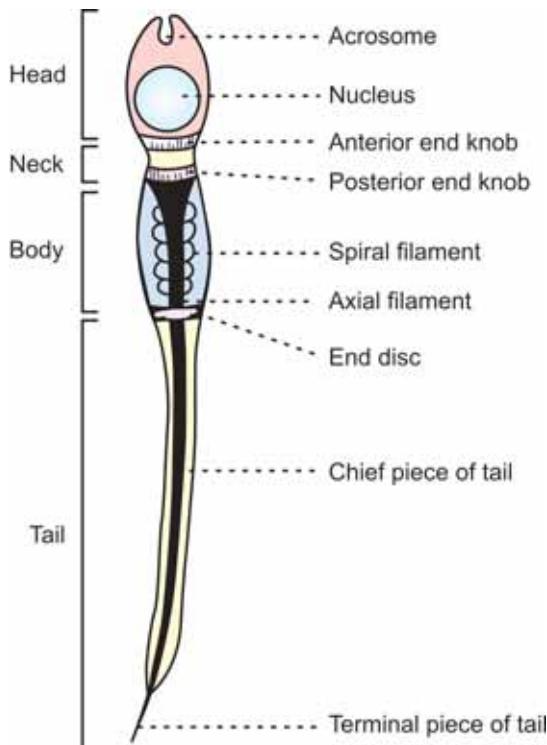


FIGURE 53-8: Human sperm

The axial filament starts from posterior end knob of the neck. It passes through the body and a perforated disc called end disc or end ring centriole. Finally, the axial filament reaches the tail as axial thread.

In the body, the axial filament is surrounded by a closely wound spiral filament consisting of mitochondria.

4. Tail

The tail of the sperm consists of two segments:

- i. The chief or main piece of tail which is enclosed by cytoplasmic capsule and has an axial thread. It is 40 to $50\text{ }\mu$ long
- ii. The terminal or end piece of tail that has only the axial filament.

■ MALE CLIMACTERIC

Male andropause or climacteric is the condition in men characterized by emotional and physical changes in the body due to low androgen level

with aging. It is also called viropause. After the age of 50, testosterone secretion starts declining because of decrease in number and secretory activity of Leydig cells.

■ APPLIED PHYSIOLOGY

■ EFFECTS OF EXTRIPATION OF TESTES

The removal of testes is called castration. The effects of castration depend upon the age when testes are removed.

1. Effects of Extripation of Testes before Puberty – Eunuchism

If a boy loses the testes before puberty, he continues to have infantile sexual characters throughout life. This condition is called eunuchism. The height of the person is slightly more but the bones are weak and thin. The muscles become weak and shoulder remains narrow.

The sex organs do not increase in size, and, the male secondary sexual characters do not develop. The voice remains like that of a child.

There is abnormal deposition of fat on buttocks, hip, pubis and breast, resembling the feminine distribution.

2. Effects of Extripation of Testes Immediately after Puberty

If testes are removed after puberty, some of the male secondary sexual characters revert to those of a child and other masculine characters are retained.

Sex organs are depressed. Seminal vesicles and prostate undergo atrophy. Penis remains smaller. Voice remains mostly masculine but other secondary sexual characters like masculine hair distribution, musculature and thickness of bones are lost. There may be loss of sexual desire and sexual activities.

3. Effect of Extripation of Testes in Adults

Removal of testis in adults does not cause loss of secondary sexual characters. But, accessory sex organs start degenerating. The sexual desire is not totally lost. Erection occurs but ejaculation

is rare because of degeneration of accessory sex organs and lack of sperms.

■ HYPERGONADISM IN MALES

Hypergonadism is the condition characterized by hypersecretion of sex hormones from gonads.

Cause

Hypergonadism in males is mainly due to the tumor of Leydig cells. It is common in prepubertal boys who develop precocious pseudo puberty.

Symptoms

There is rapid growth of musculature and bones. But, the height of the person is less because of early closure of epiphysis. There is excess development of sex organs and secondary sexual characters.

The tumors also secrete estrogenic hormones which cause gynecomastia (the enlargement of breasts).

■ HYPOGONADISM IN MALES

Hypogonadism is a condition characterized by reduction in the functional activity of gonads.

Causes

The hypogonadism in males is due to various abnormalities of testes:

1. The congenital non-functioning of testes
2. Under developed testes due to absence of human chorionic gonadotropins in fetal life
3. Cryptorchidism associated with partial or total degeneration of testes
4. Castration
5. Absence of androgen receptors in testes
6. Disorder of gonadotropes (cells secreting gonadotropins) in anterior pituitary
7. Hypothalamic disorder.

Signs and Symptoms

The clinical picture of male hypogonadism depends upon whether the testicular deficiency develops before or after puberty.

Before puberty

The features of hypogonadism are similar to those developed due to extirpation of testes before puberty, which are described above.

After puberty

The symptoms are similar to those developed due to the removal of testes after puberty (see above).

In adults

The same symptoms, which develop after extirpation of testis, occur in this condition.

Hypogonadism caused by testicular disorders increases the gonadotropin secretion and the condition is called hypergonadotropic hypogonadism. Hypogonadism that occurs due to deficiency of gonadotropins (pituitary or hypothalamic disorder) is called hypogonadotropic hypogonadism.

Dystrophia adiposogenitalis

It is the disorder characterized by obesity and hypogonadism in adolescent boys. It is also called Fröhlich's syndrome or hypothalamic eunuchism. Refer Chapter 45 for details.

Female Reproductive System

- FEMALE REPRODUCTIVE ORGANS
- SEXUAL LIFE IN FEMALES
- OVARIAN HORMONES
- CLIMACTERIC AND MENOPAUSE

■ FEMALE REPRODUCTIVE ORGANS

Female reproductive system comprises primary sex organs and accessory sex organs (Figs 54-1 and 54-2).

■ PRIMARY SEX ORGANS – OVARIES

The primary sex organs are a pair of ovaries, which produce eggs or ova and secrete female sex hormones, the estrogen and progesterone.

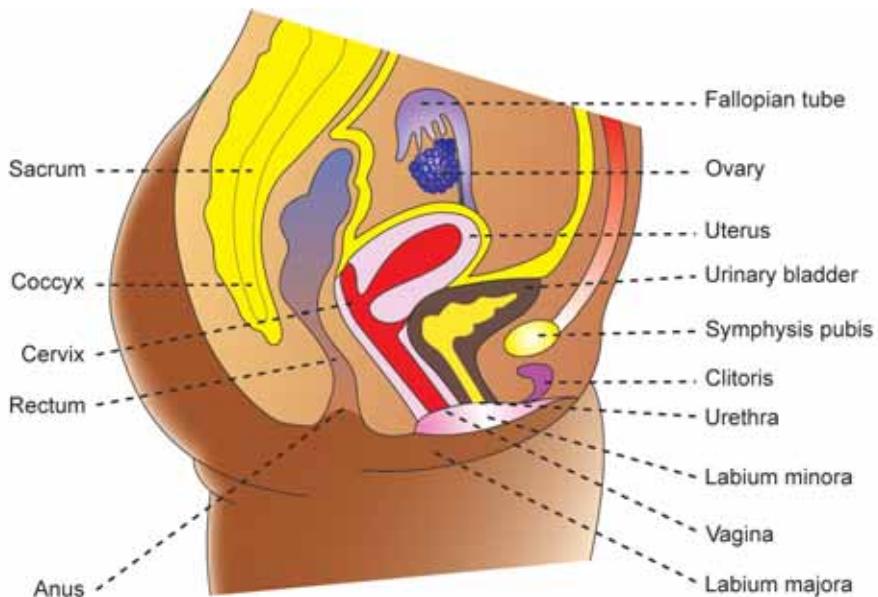


FIGURE 54-1: Female reproductive organs and other organs of pelvis

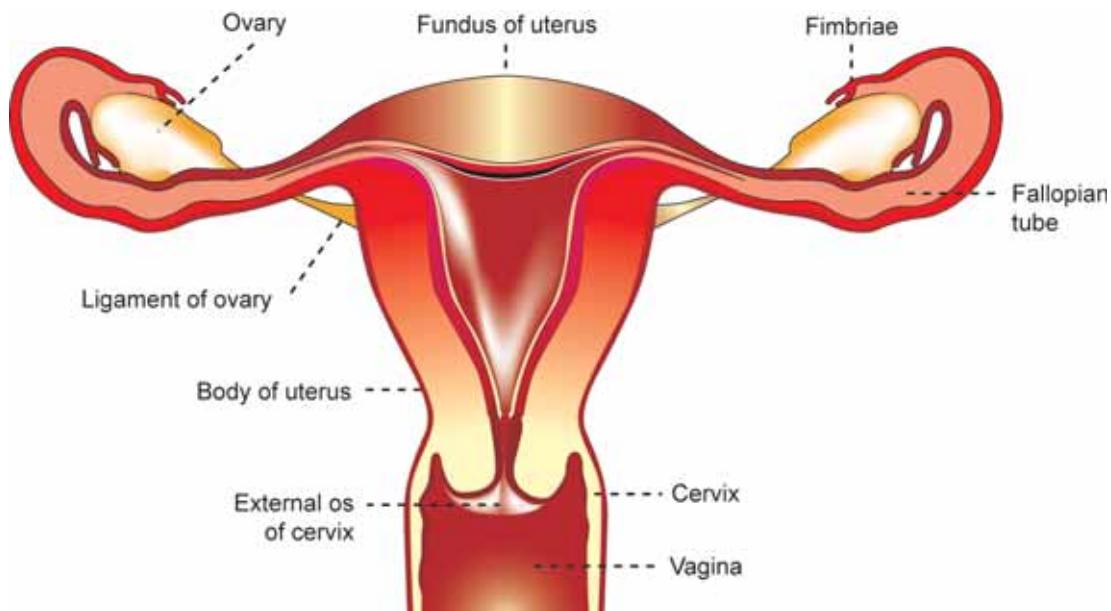


FIGURE 54-2: Female reproductive system

Ovaries are flattened ovoid bodies with dimensions of 4 cm in length, 2 cm in width and 1 cm in thickness. On cross section, each ovary shows two zones:

1. Medulla
2. Cortex.

Medulla

The medulla is otherwise known as zona vasculosa. It is the inner portion of the ovary. It has the stroma of loose connective tissues. It contains blood vessels, lymphatics, nerve fibers and bundles of smooth muscle fibers near the hilum.

Cortex

It is the outer broader portion and has compact cellular layers. Cortex is lined by the germinal epithelium underneath a fibrous layer known as tunica albuginea. The cortex consists of ovarian follicles at different stages, connective tissue and interstitial.

In the intrauterine life, the outer part of cortex contains germinal epithelium, which is derived from the germinal ridges. When the fetus develops, the germinal epithelium gives rise to a

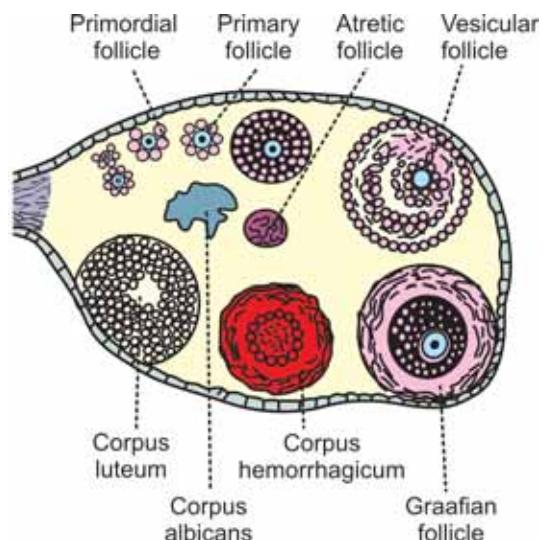


FIGURE 54-3: Ovarian follicles and corpus luteum

number of primordial ova. The primordial ova move towards the inner substance of cortex. A layer of granulose cells from the ovarian stroma surround the ova. The primordial ovum along with granulose cells is called the primordial follicle (Fig. 54-3).

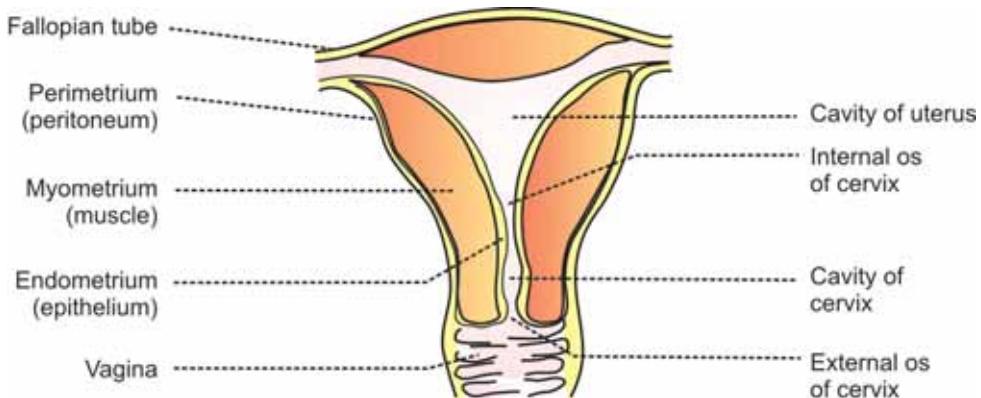


FIGURE 54-4: Section of uterus

At 7th or 8th month of intrauterine life, about 6 million primordial follicles are found in the ovary. But, at the time of birth, only 1 million primordial follicles are seen in both the ovaries and, the rest of the follicles degenerate. At the time of puberty, the number decreases further to about 3,00,000 to 4,00,000. After menarche, during every menstrual cycle, one of the follicles matures and releases its ovum. During every menstrual cycle, only one ovum is released from any one of the ovaries.

During every cycle, many of the follicles degenerate and become atretic follicles which disappear without leaving any scar.

Functions of Ovary

1. Secretion of female sex hormones
2. Oogenesis
3. Menstrual cycle.

■ ACCESSORY SEX ORGANS

The accessory sex organs in females are:

1. A system of genital ducts that includes fallopian tubes, uterus, cervix and vagina
2. External genitalia which are labia majora, labia minora and clitoris.

The mammary glands are not the female genital organs but are the important glands of female reproductive system.

Uterus

Uterus or womb is a hollow muscular organ with a thick wall. It lies in the pelvic cavity in between rectum and urinary bladder on its posterior side. The central cavity of uterus opens into vagina through cervix. On either side at its upper part, the fallopian tubes open. Uterus communicates with peritoneal cavity through fallopian tubes. The dome-shaped part of the body which lies above a plane passing through the points of entrance of the fallopian tubes is known as the fundus.

There is a constriction almost at the middle of uterus called isthmus. It divides the uterus into two portions:

1. The portion above the isthmus called the body of uterus
2. Portion below the isthmus called cervix.

Structure of uterus

Uterus is made up of 3 layers:

1. Outer serous layer derived from peritoneum (Fig. 54-4)
2. Middle muscular layer or myometrium made up of smooth muscle fibers
3. Inner mucus layer or endometrium made up of ciliated columnar epithelial cells, connective tissue and uterine glands.

Cervix

Cervix is the lower constricted part of uterus. It is divided into two portions:

1. Upper supravaginal portion which communicates with body of uterus through internal os (orifice) of cervix
2. Lower vaginal portion which communicates with vagina through external os.

Vagina

Vagina is a short tubular organ. It is lined by mucous membrane which is formed by stratified epithelial cells.

■ OVARIAN HORMONES

Ovary secretes the female sex hormones estrogen and progesterone. Ovary also secretes few more hormones namely, inhibin, relaxin and small quantities of androgens.

■ ESTROGEN

In a normal nonpregnant female, estrogen is secreted in large quantity by theca interna cells of ovarian follicles and in small quantity by corpus luteum of the ovaries. A small quantity of estrogen is also secreted by adrenal cortex. In pregnancy, a large amount of estrogen is secreted by the placenta.

Estrogen is a C₁₈ steroid and it is present in three forms in plasma:

1. β estradiol
2. Estrone
3. Estriol.

The quantity and potency of β estradiol are more than those of estrone and estriol.

The plasma level of estrogen in females at normal reproductive age varies during different phases of menstrual cycle. In follicular phase, it is 30 to 200 pg/mL (Fig. 55-4). In normal adult male estrogen level is 12 to 34 pg/mL.

Functions of Estrogen

The major function of the estrogen is to promote cellular proliferation and tissue growth in the sexual organs and in other tissues related to reproduction.

Effects of estrogen are:

1. Effect on ovarian follicles

Estrogen promotes the growth of ovarian follicles by increasing the proliferation of the follicular cells. It also increases the secretory activity of theca cells (Refer chapter 55 for details).

2. Effect on uterus

Estrogen produces the following changes in uterus:

- i. Enlargement of uterus to about double of its childhood size by the proliferation of endometrial cells
- ii. Increase in the blood supply to endometrium
- iii. Deposition of glycogen and fats in endometrium
- iv. Proliferation and dilatation of blood vessels of endometrium
- v. Proliferation and dilatation of the endometrial glands, which become more tortuous with increased blood flow
- vi. Increase in the spontaneous activity of the uterine muscles and their sensitivity to oxytocin
- vii. Increase in the contractility of the uterine muscles due to increase in actomyosin concentration.

All these changes prepare uterus for pregnancy.

3. Effect on fallopian tubes

Estrogen:

- i. Acts on the mucosal lining of the fallopian tubes and increases the number and size of the epithelial cells, especially the ciliated epithelial cells lining the fallopian tubes
- ii. Increases the activity of the cilia, so that the movement of the ovum in the fallopian tube is facilitated
- iii. Enhances the proliferation of glandular tissues in fallopian tubes.

All these changes are necessary for fertilization of ovum.

4. Effect on vagina

Estrogen:

- Changes the vaginal epithelium from cuboidal into stratified type. The stratified epithelium is more resistant to trauma and infection
- Increases the layers of the vaginal epithelium by proliferation
- Reduces the pH of vagina making it more acidic.

All these changes are necessary for prevention of certain common vaginal infections such as gonorrhreal vaginitis. Such infections can be cured by administration of estrogen.

5. Effect on secondary sexual characters

Estrogen is responsible for the development of secondary sexual characters in females.

The secondary sexual characters in female are:

- Hair distribution:** Hair develops in the pubic region and axilla. In females, pubic hair has the base of the triangle upwards. Body hair growth is less. Scalp hair grows profusely.
- Skin:** Estrogen renders softness and smoothness to the skin. It also increases the vascularity of the skin
- Body shape:** The shoulders become narrow, hip broadens, the thighs converge, and the arms diverge. The fat deposition increases in the breasts and buttocks
- Pelvis:** Estrogen has a specific effect on pelvis which results in:
 - Broadening of pelvis with increased transverse diameter
 - The round or oval-shape of pelvis
 - Round or oval-shaped pelvic outlet.
 Thus, pelvis in females is different from that of males, which is funnel-shaped.
- Voice:** The larynx remains in prepubertal stage, which produces high pitch voice.

6. Effect on breast

Estrogen causes:

- Development of stromal tissues of breasts

- Growth of an extensive ductile system
- Deposition of fat in the ductile system

All these effects prepare the breasts for lactation.

7. Effect on bones

Estrogen increases osteoblastic activity. So, at the time of puberty, the growth rate increases enormously. But, at the same time, estrogen causes early fusion of the epiphysis with the shaft. This effect is much stronger in the females than the similar effect of testosterone in males. As a result, the growth of the females usually ceases few years earlier than in the males.

In old age, the estrogen is not secreted or it becomes scanty. It leads to osteoporosis in which the bones become extremely weak and fragile. And, because of this, the bones are highly susceptible for fractures (Chapter 47).

8. Effect on metabolism

- On protein metabolism:** Estrogen induces anabolism of proteins by which it increases the total body protein.
- On fat metabolism:** Estrogen causes deposition of fat in the subcutaneous tissues, breasts, buttocks and thighs. The overall specific gravity of the female body is considerably lesser than that of males because of the fat deposition.

9. Effect on electrolyte balance

Estrogen causes sodium and water retention from the renal tubules. This effect is normally insignificant but in pregnancy, it becomes more significant.

Mode of Action of Estrogen

The estrogen acts through genes.

Regulation of Estrogen Secretion

The secretion of estrogen is regulated by FSH released from anterior pituitary. The release of FSH is stimulated by gonadotropin-releasing hormone (GnRH) secreted from hypothalamus.

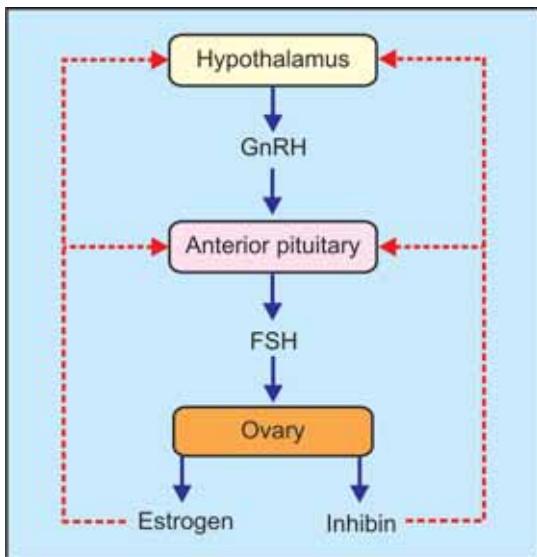


FIGURE 54-5: Regulation of estrogen secretion.
Red dashed lines indicate inhibition

FSH stimulates the secretory activities of theca and granulosa cells. Estrogen inhibits secretion of FSH and GnRH by negative feedback. Inhibin secreted by granulosa cells (Chapter 55) also decreases estrogen secretion by inhibiting secretion of FSH and GnRH (Fig. 54-5).

■ PROGESTERONE

A small quantity of progesterone is secreted by theca interna cells of ovaries during the first half of menstrual cycle, i.e. during follicular stage. But, a large quantity of progesterone is secreted during the latter half of each menstrual cycle, i.e. during secretory phase by the corpus luteum. Small amount of progesterone is secreted from adrenal cortex also.

During pregnancy, large amount of progesterone is secreted by the corpus luteum in the first trimester. In the second trimester corpus luteum degenerates. Placenta secretes large quantity of progesterone in second and third trimesters.

Progesterone is a C₂₁ steroid. The plasma level of progesterone in females at normal reproductive age varies during different phases of menstrual cycle. In follicular phase, it is about 0.9 ng/mL (Fig. 55-4). In normal adult male progesterone level is 0.3 ng/mL.

Functions of Progesterone

Progesterone is concerned mainly with the final preparation of the uterus for pregnancy and the breasts for lactation. The effects of progesterone are:

1. Effect on fallopian tubes

Progesterone promotes secretory activities of mucosal lining of the fallopian tubes. The secretions of fallopian tubes are necessary for nutrition of the fertilized ovum while it is in fallopian tube before implantation.

2. Effect on uterus

Progesterone promotes secretory activities of uterine endometrium during the secretory phase of the menstrual cycle. Thus, uterus is prepared for implantation of the fertilized ovum.

Progesterone:

- Increases the thickness of the endometrium by increasing the number and size of the cells
- Increases the size of uterine glands and these glands become more tortuous
- Increases secretory activities of epithelial cells of uterine glands
- Increases the deposition of lipid and glycogen in the stromal cells of endometrium
- Increases the blood supply to endometrium
- Decreases the frequency of uterine contractions during pregnancy. Because of this, the expulsion of the implanted ovum is prevented.

3. Effect on cervix

Progesterone increases thickness of cervical mucosa and thereby inhibits transport of sperm into uterus. This effect is utilized in the contraceptive actions of mini pills.

4. Effect on mammary glands

Progesterone promotes the development of the lobules and alveoli of the mammary glands by proliferating and enlarging the alveolar cells. It also makes the breasts secretory in nature. It

makes the breasts to swell by increasing the secretory activity and fluid accumulation in the subcutaneous tissue.

5. Effect on hypothalamus

Progesterone inhibits the release of LH from hypothalamus through feedback effect. This effect is utilized for its contraceptive action.

6. Thermogenic effect

Progesterone increases the body temperature after ovulation. The mechanism of thermogenic action is not known. It is suggested that progesterone increases the body temperature by acting on hypothalamic centers for temperature regulation.

7. Effect on respiration

During luteal phase of menstrual cycle and during pregnancy, progesterone increases the ventilation via respiratory center. This results in decreased PCO_2 in the alveoli.

8. Effect on electrolyte balance

Progesterone increases reabsorption of sodium and water from the renal tubules. However, in large doses, it is believed to cause excretion of sodium and water. This may be due to an indirect effect, i.e. progesterone combines with the same receptors, which bind with aldosterone. So, the action of aldosterone is blocked leading to excretion of sodium and water.

Mode of Action of Progesterone

Like estrogen, progesterone also acts through genes.

Regulation of Secretion of Progesterone

LH from anterior pituitary activates the corpus luteum to secrete progesterone. Secretion of LH is influenced by the gonadotropin-releasing hormone secreted in hypothalamus. Progesterone inhibits release of LH from anterior pituitary by negative feedback.

■ CLIMACTERIC AND MENOPAUSE

Climacteric is the period in old age when reproductive system undergoes changes due to the decreased secretion of sex hormones estrogen and progesterone. It occurs at the age of 45 to 55. In females, climacteric is accompanied by meno-pause.

Menopause is defined as the period characterized by the permanent cessation of menstruation. Normally, it occurs at the age of 45 to 55 years.

In some women, the menstruation stops suddenly. In others, the menstrual flow decreases gradually during every cycle and finally it stops. Sometimes irregular menstruation occurs with lengthening or shortening of the period with less or more flow.

Early menopause may occur because of surgical removal of ovaries (oophorectomy) or uterus (hysterectomy) as a part of treatment for abnormal menstruation. Usually, females with short menstrual cycle attain menopause earlier than the females with longer cycle. Cigarette smoking causes earlier onset of menopause.

■ CHANGES DURING MENOPAUSE – POSTMENOPAUSAL SYNDROME

Postmenopausal syndrome is the group of symptoms that appear in women immediately after menopause. It is characterized by certain physical, physiological and psychological changes. The symptoms start appearing soon after the ovaries stop functioning.

The cause for the symptoms is the lack of estrogen and progesterone. The symptoms may persist till the body gets acclimatized to the absence of estrogen and progesterone.

The symptoms do not appear in all women. Some women develop mild symptoms and some women develop severe symptoms. The symptoms last for few months to few years.

Most of the women manage it very well. But, about 15% of the women need treatment. In many cases, psychotherapy works very well. If it fails, hormone replacement therapy is given.

Menstrual Cycle

- INTRODUCTION
- OVARIAN CHANGES DURING MENSTRUAL CYCLE
- UTERINE CHANGES DURING MENSTRUAL CYCLE
- CHANGES IN CERVIX DURING MENSTRUAL CYCLE
- CHANGES IN VAGINA DURING MENSTRUAL CYCLE
- REGULATION OF MENSTRUAL CYCLE
- APPLIED PHYSIOLOGY – ABNORMAL MENSTRUATION

■ INTRODUCTION

■ DEFINITION

The cyclic events that take place in a rhythmic fashion during the reproductive period of a woman's life is called menstrual cycle. The menstrual cycle starts at the age of 12 to 15 years, which marks the onset of puberty. The commencement of menstrual cycle is called menarche. The menstrual cycle ceases at the age of 45 to 50 years. The permanent cessation of menstrual cycle in old age is called meno-pause.

■ DURATION OF MENSTRUAL CYCLE

The duration of menstrual cycle is usually 28 days. But, under physiological conditions, it may vary between 20 and 40 days.

■ CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, series of changes occur in ovary and accessory sex organs. All these changes which take place simultaneously are divided into 4 groups:

- I. Ovarian changes
- II. Uterine changes
- III. Vaginal changes
- IV. Changes in cervix.

■ OVARIAN CHANGES DURING MENSTRUAL CYCLE

The changes in the ovary during each menstrual cycle occur in two phases.

- A. Follicular phase
- B. Luteal phase.

■ FOLLICULAR PHASE

Follicular phase extends from the 5th day of the cycle until the time of ovulation, which takes place on 14th day. During this phase development of ovarian follicles and maturation of ovum take place.

Ovarian Follicles

Ovarian follicles are present the stroma of cortex. Each follicle consists of the ovum surrounded by epithelial cells namely granulosa cells. The

follicles gradually grow into a matured follicle through various stages:

1. Primordial Follicle

At the time of puberty, both the ovaries contain about 4,00,000 primordial follicles. The diameter of the primordial follicle is about 15 to 20 μ and that of ovum is about 10 μ . Each primordial follicle has an ovum which is incompletely surrounded by the granulosa cells (Fig. 54-3). These cells are believed to provide nutrition to the ovum during childhood.

Granulosa cells also secrete the oocyte maturation inhibiting factor which keeps the ovum in the immature stage. All the ova present in the ovaries are formed before birth. No new ovum is developed after birth.

At the onset of puberty, under the influence of FSH and LH the primordial follicles start growing through various stages.

2. Primary Follicle

The primordial follicle becomes the primary follicle, when the ovum is completely surrounded by the granulosa cells. During this stage the follicle and the ovum inside the follicle increase in size. The diameter of the follicle increases to 30 to 40 μ and that of ovum increases to about 20 μ . The follicle is not covered by a definite connective tissue capsule.

The characteristic changes taking place during the development of primary follicles are:

- i. Proliferation of granulosa cells and increase in size of the follicle
- ii. Increase in size of ovum
- iii. Onset of formation of connective tissue capsule around the follicle.

The primary follicle develops into vesicular follicle.

3. Vesicular Follicle

Under the influence of FSH, about 6-12 primary follicles start growing and develop into the vesicular follicles. The changes, which take place during development of vesicular follicles are:

- a. Changes in granulosa cells

- b. Changes in ovum
- c. Formation of capsule.

a. Changes in granulosa cells

- i. First, the proliferation of granulosa cells occurs
- ii. A cavity called follicular cavity or antrum is formed in between the granulosa cells
- iii. Antrum is filled with a serous fluid called the liquor folliculi
- iv. Ovum is pushed to one side and it is surrounded by granulosa cells which forms the germ hill or cumulus oophorus
- v. Granulosa cells which line the antrum form membrana granulosa
- vi. Cells of germ hill become columnar and form corona radiata.

b. Changes in ovum

- i. First, the ovum increases in size and its diameter increases to 100 to 150 μ
- ii. Nucleus becomes larger and vesicular
- iii. Cytoplasm becomes granular
- iv. Thick membrane is formed around the ovum which is called zona pellucida
- v. A narrow cleft called perivitelline space appears between ovum and zona pellucida.

c. Formation of capsule

The spindle cells from the stroma of ovarian cortex are modified and form a covering sheath around the follicle. The covering sheath is known as follicular sheath or theca folliculi.

The theca folliculi divides into two layers:

- i. *Theca interna*: It is the inner vascular layer with loose connective tissue and epithelial cells with lipid granules. The epithelial cells become secretory in nature and start secreting the female sex hormones, especially estrogen which is released into the fluid of antrum.
- ii. *Theca externa*: It is the outer layer of the follicular capsule and consists of thickly packed fibers and spindle shaped cells.

After about 7th day of menstrual cycle, one of the vesicular follicles outgrows the others

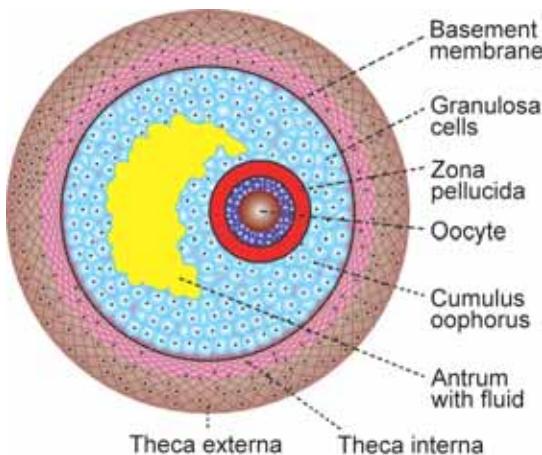


FIGURE 55-1: Graafian follicle

and becomes the dominant follicle. It develops further to form graafian follicle. The other vesicular follicles degenerate by means of apoptosis.

4. Graafian Follicle

Graafian follicle is the matured ovarian follicle with maturing ovum. It is named after the Dutch physician and anatomist Regnier De Graff (Fig. 55-1). Many changes take place during the development of graafian follicle:

- i. The size of the follicle increases to about 10 to 12 mm
- ii. At one point, the follicle encroaches upon tunica albuginea and protrudes upon the surface of the ovary. This protrusion is called stigma. At the stigma, the tunica albuginea becomes thin
- iii. Follicular cavity becomes larger and distended with fluid
- iv. Ovum attains maximum size
- v. Zona pellucida becomes thick
- vi. The corona radiata becomes prominent
- vii. Small spaces filled with fluid appear between the cells of germ hill outside the corona radiata. These spaces weaken the attachment of the ovum to the follicular wall
- viii. Theca interna becomes prominent. Its thickness becomes double with formation of rich capillary network

- ix. On 14th day of menstrual cycle, the graafian follicle is ready for the process of ovulation.

■ OVULATION

Ovulation is the process in which there is rupture of graafian follicle with consequent discharge of ovum into abdominal cavity. This occurs after the maturity of follicle. It is influenced by LH. The ovulation occurs usually on 14th day of menstrual cycle in a normal cycle of 28 days. The ovum enters the fallopian tube.

Process of Ovulation

Ovulation is a gradual process that occurs in different stages:

1. Rupture of graafian follicles takes place at the stigma
2. Follicular fluid oozes out
3. Germ hillock is freed from wall
4. Ovum is expelled out into the abdominal cavity along with some amount of fluid and granulosa cells
5. From abdominal cavity, the ovum enters the fallopian tube through the fimbriated end.

The ovum becomes haploid before or during ovulation by the formation of polar bodies. After ovulation, the ovum is viable only for 48 hours. So fertilization should take place during this period.

After fertilization, the ovum is called zygote. From the fallopian tube, the zygote reaches the uterus on 3rd day after ovulation. And, the implantation of the zygote in the uterine wall occurs on 6th or 7th day.

If fertilization does not occur, the ovum degenerates. Generally, only one ovum is released from one of the ovaries.

Determination of Ovulation Time

Different methods are available to determine the ovulation time:

1. *Determination of basal body temperature:* There is a slight fall in the basal temperature just prior to ovulation. And, the temperature increases after ovulation. The alteration in the temperature is very mild and it is about ± 0.3 to 0.5°C .

2. *Determination of hormonal excretion in urine:* At the time of ovulation, there is an increase in the urinary excretion of metabolic end products of estrogen and progesterone.
3. *Determination of hormonal level in plasma:* Plasma level of FSH, LH, estrogen and progesterone is altered at the time of ovulation and after ovulation.
4. *Ultrasound scanning:* Process of ovulation is observed by ultrasound scanning.
5. *Cervical mucus pattern:* When the cervical mucus spread on a slide is examined under microscope, it shows a fern pattern. This pattern disappears after ovulation.

Significance of Determining Ovulation Time

Family planning by rhythm method may be well adopted by determination of ovulation time (Chapter 57).

LUTEAL PHASE

This phase extends between 15th and 28th day of menstrual cycle. During this phase corpus luteum is developed and hence this phase is called luteal phase (Fig. 55-2).

Corpus Luteum

Corpus luteum is a glandular yellow body developed from the ruptured graafian follicle after the release of ovum. It is also called yellow body.

Development of Corpus Luteum

Soon after the rupture of graafian follicle and release of ovum, the follicle is filled with blood. Now the follicle is called corpus hemorrhagicum. The blood clots slowly. The corpus hemorrhagicum is transformed into a corpus luteum.

In the corpus luteum, the granulosa cells and theca interna cells are transformed into lutein cells namely granulosa lutein cells and theca lutein cells by accumulation of fine lipid granules and the yellowish pigment granules. The yellowish pigment granules give the characteristic yellow color to corpus luteum.

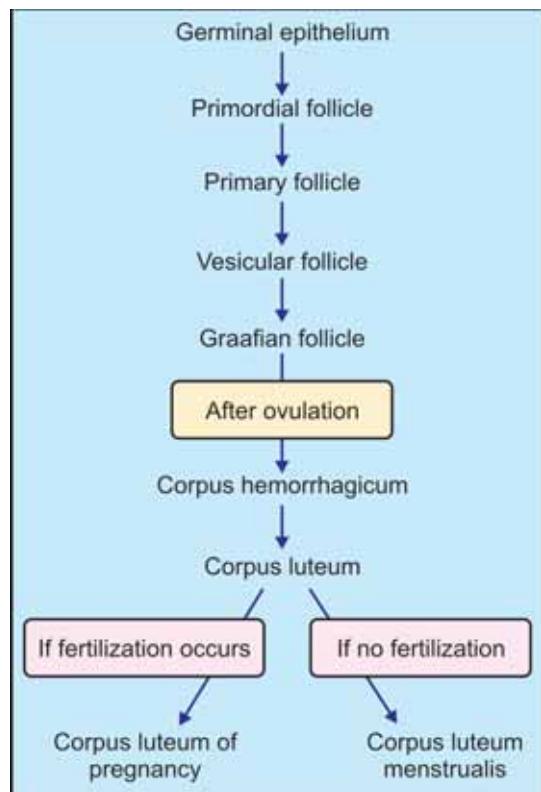


FIGURE 55-2: Ovarian follicles

Functions of Corpus Luteum

1. Secretion of hormones

The corpus luteum acts as a temporary endocrine gland. It secretes large quantity of progesterone and small amount of estrogen. LH influences the secretion of these two hormones.

2. Maintenance of pregnancy

If pregnancy occurs, corpus luteum maintains the pregnancy for about three months of pregnancy till placenta starts secreting estrogen and progesterone. Abortion occurs if corpus luteum becomes inactive or removed before third month of pregnancy, i.e. before placenta starts secreting the hormones.

Fate of Corpus Luteum

Fate of corpus luteum depends upon whether the ovum is fertilized or not.

1. If the ovum is not fertilized

If fertilization does not take place, the corpus luteum reaches the maximum size about one week after ovulation. During this period, it secretes large quantity of progesterone with small quantity of estrogen. Then, it degenerates into the corpus luteum menstrualis. The cells decrease in size and the corpus luteum becomes smaller and involuted. Afterwards, the corpus luteum menstrualis is transformed into a whitish scar called corpus albicans. The process by which corpus luteum undergoes regression is called luteolysis.

2. If ovum is fertilized

If ovum is fertilized and pregnancy occurs, the corpus luteum persists and increases in size. It attains a diameter of 20 to 30 mm and it is transformed into corpus luteum graviditatis (verum) or corpus luteum of pregnancy. It remains in the ovary for 3 to 4 months. During this period, it secretes large amount of progesterone with small quantity of estrogen, which are essential for the maintenance of pregnancy. After 3 to 4 months, placenta starts secreting these hormones and corpus luteum degenerates.

■ UTERINE CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, along with ovarian changes, uterine changes also occur simul-

taneously. The changes in uterus take place in three phases:

- Menstrual phase
- Proliferative phase
- Secretory phase.

■ MENSTRUAL PHASE

After ovulation, if pregnancy does not occur, the thickened endometrium is shed or desquamated. This desquamated endometrium is expelled out through vagina along with some blood and tissue fluid. The process of shedding and exit of uterine lining along with blood and fluid is called menstruation or menstrual bleeding. It lasts for about 4 to 5 days (Fig. 55-3). This period is called menstrual phase or menstrual period.

The day when bleeding starts is considered as the first day of the menstrual cycle. Two days before onset of bleeding, that is on 26th or 27th day of the previous cycle, there is sudden reduction in the release of estrogen and progesterone from ovary. Decreased level of these two hormones is responsible for menstruation.

Changes in Endometrium during Menstrual Phase

1. Lack of estrogen and progesterone causes sudden involution of endometrium and reduction in the thickness of endometrium up to 65% of original thickness

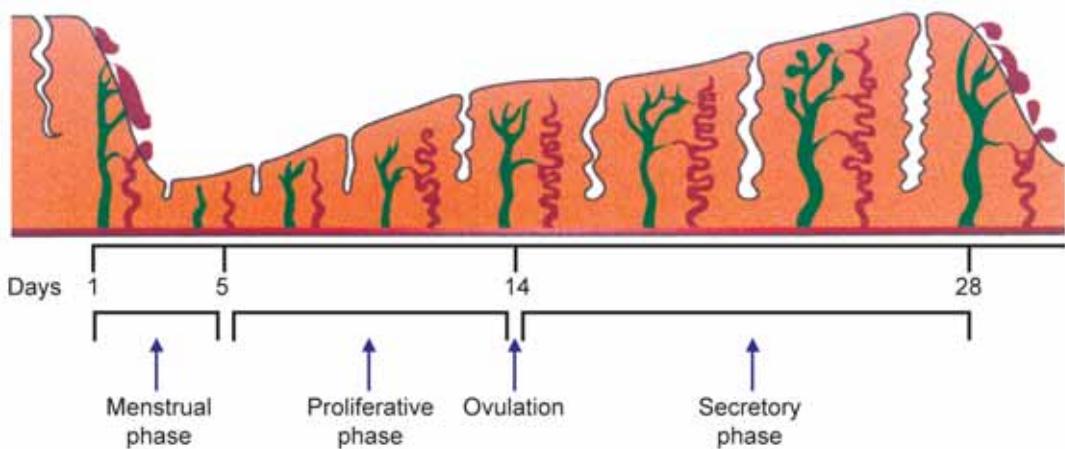


FIGURE 55-3: Uterine changes during menstrual cycle

2. During the next 24 hours, the tortuous blood vessels in the endometrium undergo severe constriction.
3. The vasoconstriction leads to hypoxia which results in necrosis of the endometrium, rupture of blood vessels and oozing of blood
5. The outer layer of the necrotic endometrium is separated and passes out along with blood
7. This process is continued for about 24 to 36 hours
8. Within 48 hours after the reduction in the secretion of estrogen and progesterone, the superficial layers of endometrium are completely desquamated
9. The desquamated tissues and the blood in the endometrial cavity initiate the contraction of uterus
10. Uterine contractions expel the blood along with desquamated uterine tissues to the exterior through vagina.

During normal menstruation, about 35 mL of blood along with 35 mL of serous fluid is expelled. The blood clots as soon as it oozes into the uterine cavity. The fibrinolysis causes lysis of clot in uterine cavity itself so that, the expelled menstrual fluid does not clot. However, in the pathological conditions involving uterus, the lysis of blood clot does not occur. So the menstrual fluid comes out with blood clot.

Menstruation stops between 3rd and 7th day of menstrual cycle. At the end of menstrual phase, the thickness of endometrium is only about 1 mm. This is followed by proliferative phase.

■ PROLIFERATIVE PHASE

Proliferative phase extends usually from 5 to 14th day of menstruation, i.e. between the day when menstruation stops and the day of ovulation. It corresponds to the follicular phase of ovarian cycle.

At the end of menstrual phase, only a thin layer (1 mm) of endometrium remains as, most of the endometrial stroma is desquamated.

Changes in Endometrium during Proliferative Phase

1. The endometrial cells proliferate rapidly
2. The epithelium reappears on the surface of endometrium within the first 4 to 7 days
3. The uterine glands start developing within the endometrial stroma
4. Blood vessels also appear in the stroma
5. The proliferation of endometrial cells occurs continuously so that the endometrium reaches the thickness of 3 to 4 mm at the end of proliferative phase.

All these uterine changes during proliferative phase occur because of the influence of estrogen released from ovary. On 14th day, ovulation occurs under the influence of LH. This is followed by secretory phase.

■ SECRETORY PHASE

Secretory phase extends between 15th and 28th day of the menstrual cycle, i.e. between the day of ovulation and the day when menstruation of next cycle commences.

After ovulation, corpus luteum is developed in the ovary. It secretes a large quantity of progesterone along with a small amount of estrogen. Estrogen causes further proliferation of cells in uterus, so that, the endometrium becomes more thick. Progesterone causes further enlargement of endometrial stroma and further growth of glands.

Under the influence of progesterone, the endometrial glands commence their secretory function. Many changes occur in the endometrium before commencing the secretory function.

Changes in Endometrium during Secretory Phase

1. The glands of the endometrium become more tortuous.
2. The cytoplasm of stromal cells increases because of the deposition of glycogen and lipids
3. Many new blood vessels appear within endometrial stroma and blood supply to endometrium increases.

Actually, secretory phase is the preparatory period during which, the uterus is prepared for implantation of ovum. At the end of secretory phase, the thickness of endometrium is 5 to 6 mm. All these uterine changes during secretory phase occur due to the influence of estrogen and progesterone. Estrogen is responsible for repair of damaged endometrium and growth of the glands. Progesterone is responsible for further growth of these structures and secretory activities in the endometrium.

If a fertilized ovum is implanted during this phase and, if the implanted ovum starts developing into a fetus, further changes occur in the uterus for the survival of the developing fetus. If the implanted ovum is unfertilized or if pregnancy does not occur, menstruation occurs after this phase and a new cycle begins.

■ CHANGES IN CERVIX DURING MENSTRUAL CYCLE

The mucous membrane of cervix also shows cyclic changes during different phases of menstrual cycle.

Proliferative Phase

Under the influence of estrogen, during proliferative phase, the mucous membrane of cervix becomes thinner and more alkaline. It helps in the survival and motility of spermatozoa.

Secretory Phase

Because of actions of progesterone during secretory phase, the mucus membrane of cervix becomes more thick and adhesive.

■ CHANGES IN VAGINA DURING MENSTRUAL CYCLE

Proliferative Phase

The epithelial cells of vagina are cornified. Estrogen released from ovary is responsible for the cornification of vaginal epithelial cells.

Secretory Phase

Vaginal epithelium proliferates due to the actions of progesterone. The vaginal epithelium is

infiltrated with leukocytes. These two changes increase the resistance for infection.

■ REGULATION OF MENSTRUAL CYCLE

Menstrual cycle is regulated by hormones of hypothalamo-pituitary-ovarian axis.

■ HORMONES INVOLVED IN REGULATION

Hormones involved in regulation of menstrual cycle are:

1. Hypothalamic hormone – GnRH
2. Anterior pituitary hormones – FSH and LH
3. Ovarian hormones – Estrogen and progesterone.

Hypothalamic Hormone

GnRH from hypothalamus triggers the cyclic changes during menstrual cycle by stimulating secretion of FSH and LH from anterior pituitary.

Anterior Pituitary Hormones

FSH and LH secreted from anterior pituitary modulate the ovarian and uterine changes by acting directly and/or indirectly via ovarian hormones. FSH stimulates the recruitment and growth of immature ovarian follicles. LH triggers ovulation and sustains corpus luteum.

Secretion of FSH and LH is under the influence of GnRH.

Ovarian Hormones

Estrogen and progesterone which are secreted by follicle and corpus luteum show many activities during menstrual cycle. Ovarian follicle secretes large quantity of estrogen and corpus luteum secretes large quantity of progesterone.

Estrogen secretion reaches the peak twice in each cycle; once during follicular phase just before ovulation and another one during luteal phase (Fig. 55-4). On the other hand progesterone is virtually absent during follicular phase till prior to ovulation. But it plays a critical role during luteal phase.

Estrogen is responsible for the growth of follicles. Both the steroids act together to produce the changes in uterus, cervix and vagina.

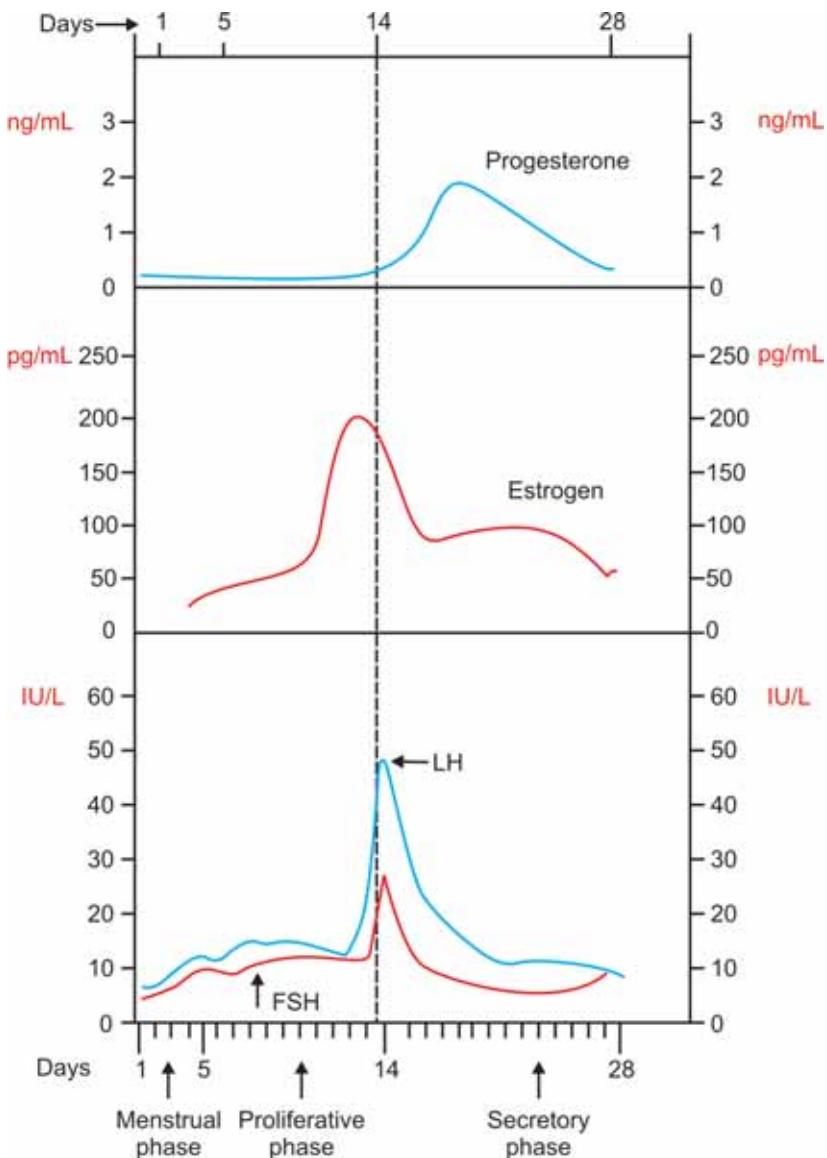


FIGURE 55-4: Hormonal level during menstrual cycle

Both the ovarian hormones are under the influence of GnRH which acts via FSH and LH. In addition, the secretion of GnRH, FSH and LH is regulated by ovarian hormones.

■ APPLIED PHYSIOLOGY – ABNORMAL MENSTRUATION

1. *Amenorrhea*: Absence of menstruation

2. *Hypomenorrhea*: Decreased menstrual bleeding
3. *Menorrhagia*: Excess menstrual bleeding
4. *Oligomenorrhea*: Decreased frequency of menstrual bleeding
5. *Polymenorrhea*: Increased frequency of menstruation
6. *Dysmenorrhea*: Menstruation with pain
7. *Metrorrhagia*: Uterine bleeding in between menstruations.

Pregnancy, Mammary Glands and Lactation

- INTRODUCTION
- FERTILIZATION OF THE OVUM
- SEX CHROMOSOMES AND SEX DETERMINATION
- IMPLANTATION AND DEVELOPMENT OF EMBRYO
- PLACENTA
- GESTATION PERIOD
- PARTURITION
- PREGNANCY TESTS
- DEVELOPMENT OF MAMMARY GLANDS
- LACTATION

■ INTRODUCTION

Ovum is released from graafian follicle of ovary into the abdominal cavity at the time of ovulation. From abdominal cavity the ovum enters one of the fallopian tubes via fimbriated end.

■ FERTILIZATION OF THE OVUM

Fertilization refers to fusion (union) of male and female gamates (sperm and ovum) to form a new offspring.

Ovum is released into abdominal cavity during ovulation. If sexual intercourse occurs at this time and semen is ejaculated in the vagina, the sperms travel through the vagina and uterus to reach the fallopian tube. Among 200 to 300 millions of sperms entering female genital tract, only one succeeds in fertilizing the ovum.

During fertilization, the sperm enters the ovum by penetrating granulosa cells present around

the ovum. It is facilitated by hyaluronidase and proteolytic enzymes present in the acrosome of sperm.

■ SEX CHROMOSOMES AND SEX DETERMINATION

■ SEX CHROMOSOMES

All the dividing cells in the body have 23 pairs of chromosomes. Among the 23 pairs, 22 pairs are called somatic chromosomes or autosomes. The remaining one pair of chromosomes is called sex chromosomes. Sex chromosomes are X and Y chromosomes.

■ SEX DETERMINATION

Sex chromosomes are responsible for sex determination. During fertilization of ovum, 23 chromosomes from ovum and 23 chromosomes from

the sperm unite together to form the 23 pairs (46) of chromosomes in the fertilized ovum. Now, sex determination occurs. Ovum contains the X chromosome. Sperm has either X chromosome or Y chromosome. When the ovum is fertilized by a sperm with X chromosome, the child will be female with XX chromosome. And, if the ovum is fertilized by a sperm with Y chromosome, the sex of the child will be male with XY chromosome. So, the sex of the child depends upon the male partner.

Role of testosterone in sex differentiation is explained in Chapter 53.

■ IMPLANTATION AND DEVELOPMENT OF EMBRYO

Implantation is the process by which the fertilized ovum implants (fixes itself or gets attached) in the endometrial lining of uterus. After the fertilization, the ovum is known as zygote. The zygote takes three to five days to reach the uterine cavity from fallopian tube. While travelling through the fallopian tube, the zygote receives its nutrition from the secretions of fallopian tube.

After reaching the uterus, the developing zygote remains freely in the uterine cavity for two to four days before it is implanted. Just before implantation, the zygote develops into morula.

Already uterus is prepared by progesterone secreted from the corpus luteum during secretory phase of menstrual cycle. After implantation, morula develops into embryo. Placenta develops between morula and endometrium.

■ PLACENTA

Placenta is a temporary membranous vascular organ that develops in females during pregnancy. It is expelled after child birth. Placenta forms a link between the fetus and mother. It is considered as an anchor for the growing fetus. It is not only the physical attachment between the fetus and mother, but also forms the physiological connection between the two.

Placenta is implanted in the wall of the uterus. It is formed from both embryonic and maternal

tissues. So, it consists of two parts namely the fetal part and the mother's part. It is connected to the fetus by umbilical cord which contains blood vessels and connective tissue.

The delivery of fetus is followed by the expulsion of placenta. After expulsion of the placenta, the umbilical cord is cut. The site of the attachment of placenta in the center of the anterior abdomen of fetus is called navel or umbilicus.

■ FUNCTIONS OF PLACENTA

1. Nutritive Function

The various nutritive substances, electrolytes and hormones necessary for the development of fetus diffuse from the mother's blood into the fetal blood through placenta.

2. Excretory Function

The metabolic end products and other waste products from the fetal body are excreted into the mother's blood through placenta.

3. Respiratory Function

Fetal lungs are nonfunctioning and placenta forms the respiratory organ for fetus. Oxygen necessary for fetus is received by diffusion from the maternal blood and, carbon dioxide from the fetal blood diffuses into the mother's blood through placenta.

4. Endocrine Function

Hormones secreted by placenta are:

1. Human chorionic gonadotropin
2. Estrogen
3. Progesterone
4. Human chorionic somatomammotropin
5. Relaxin.

1. Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a glycoprotein.

Actions of hCG:

- i. *On corpus luteum:* hCG is responsible for the preservation and the secretory activity

of corpus luteum. Progesterone and estrogen secreted by corpus luteum are essential for the maintenance of pregnancy. Deficiency or absence of hCG during the first two months of pregnancy leads to termination of pregnancy (abortion), because of involution of corpus luteum.

- ii. *On fetal testes:* Action of hCG on fetal testes is similar to that of LH in adults. It stimulates the interstitial cells of Leydig and causes secretion of testosterone which is necessary for the development of sex organs in male fetus.

2. Estrogen

Placental estrogen is similar to ovarian estrogen in structure and function.

Actions of placental estrogen

- i. *On uterus:* Causes enlargement of the uterus so that, the growing fetus can be accommodated
- ii. *On breasts:* Responsible for the enlargement of the breasts and growth of the duct system in the breasts
- iii. *On external genitalia:* Causes enlargement of the female external genitalia
- iv. *On pelvis:* Relaxes pelvic ligaments. It facilitates the passage of the fetus through the birth canal at the time of labor.

3. Progesterone

Placental progesterone is similar to ovarian progesterone in structure and function.

Actions of placental progesterone

- i. *On endometrium of uterus:* Accelerates the proliferation and development of decidual cells in the endometrium of uterus. The decidual cells are responsible for the supply of nutrition to the embryo in the early stage
- ii. *On the movements of uterus:* Inhibits the contraction of muscles in the pregnant uterus. It is an important function of

progesterone as it prevents expulsion of fetus during pregnancy

- iii. *On breasts:* Causes enlargement of breasts and growth of duct system of the breasts. Progesterone is responsible for further development and preparation of mammary glands for lactation.

4. Human Chorionic Somatomammotropin

Human chorionic somatomammotropin (hCS) is a protein hormone secreted from placenta. It is often called placental lactogen. It acts like prolactin and growth hormone secreted from pituitary. So, it is believed to act on mammary glands and to enhance the growth of fetus by influencing the metabolic activities. It increases the amount of glucose and lipids in the maternal blood which are transferred to fetus.

Actions of hCS

- i. *On breasts:* In experimental animals, administration of hCS causes enlargement of mammary glands and induces lactation. That is why, it is named as somatomammotropin. However, the action of this hormone on the breasts of pregnant women is not known
- ii. *On protein metabolism:* hCS acts like GH on protein metabolism. It causes anabolism of proteins and accumulation of proteins in the fetal tissues. Thus, the growth of fetus is enhanced
- iii. *On carbohydrate metabolism:* It reduces the peripheral utilization of glucose in the mother leading to availability of large quantity of glucose to the growing fetus
- iv. *On lipid metabolism:* It mobilizes fat from the adipose tissue of the mother. A large amount of free fatty acid is made available as the source of energy in the mother's body. It compensates the loss of glucose from the mother's blood to fetus.

5. Relaxin

Relaxin is a polypeptide which is secreted by corpus luteum. It is also secreted in large quantity

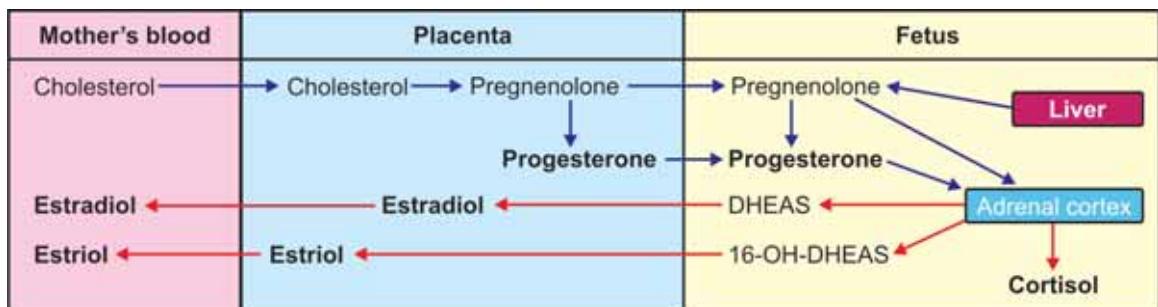


FIGURE 56-1: Fetoplacental unit

by placenta and mammary glands at the time of labor.

Fetoplacental Unit

Fetoplacental unit refers to the interaction between fetus and placenta in the formation of steroid hormones. The interaction between fetus and placenta occurs because, some of the enzymes involved in steroid synthesis present in fetus are absent in placenta and, those enzymes which are absent in fetus are present in placenta.

Due to this interaction during synthesis of steroid hormones, fetus and placenta are together called fetoplacental unit (Fig. 56-1).

GESTATION PERIOD

Gestation period refers to the pregnancy period. The average gestation period is about 280 days or 40 weeks from the date of last menstrual period (LMP). Traditionally it is calculated as 10 lunar months. However, in terms of modern calendar it is calculated as 9 months and 7 days. If the menstrual cycle is normal 28 day cycle, the fertilization of ovum by the sperm occurs on 14th day after last menstrual period. Thus, the actual duration of human pregnancy is $280 - 14 = 266$ days. If the pregnancy ends before 28th week, it is referred as miscarriage.

PARTURITION

Parturition is the expulsion or delivery of the fetus from the mother's body. It occurs at the end of pregnancy. The process by which the delivery

of fetus occurs is called labor. It involves various actions, like contraction of uterus, dilatation of cervix and opening of vaginal canal.

■ STAGES OF PARTURITION

Parturition occurs in three stages:

First Stage

First, the strong uterine contractions called labor contractions commence. The labor contractions arise from the fundus of uterus and move downwards so that the head of fetus is pushed against the cervix. It results in dilatation of cervix and opening of vaginal canal. This stage extends for a variable period of time.

Second Stage

In this stage, the fetus is delivered out from uterus through cervix and vaginal canal. This stage lasts for about one hour.

Third Stage

During this stage, the placenta is detached from the decidua and is expelled out from uterus. It occurs within 10 to 15 minutes after the delivery of the child.

■ PREGNANCY TESTS

Pregnancy test is the test used to detect or confirm pregnancy. The basis of pregnancy tests is to determine the presence of the human chorionic gonadotropin (hCG) in the urine of woman suspected for pregnancy. Both biological

and immunological tests are available to determine the presence of hCG in the urine of the pregnant woman. However, biological tests for pregnancy are replaced by immunological tests because of several disadvantages.

■ IMMUNOLOGICAL TESTS

Immunological tests are more accurate and the result is obtained quickly within few minutes. These tests are based on double antigen antibody reactions. The most commonly performed immunological test is known as Gravindex test.

Principle

Principle is to determine the agglutination of sheep RBCs coated with hCG. Latex particles could also be used instead of sheep RBCs.

Requisites

1. *Antiserum from rabbit*

Urine from a pregnant woman is collected and hCG is isolated. This hCG is injected into a rabbit.

The rabbit develops antibodies against hCG. The antibodies are called hCG antibody or anti hCG. The rabbit's blood is obtained and serum is separated. The serum containing hCG antibody is called rabbit antiserum or hCG antiserum. It is readily available in the market.

2. *Red blood cells from sheep*

The RBCs are obtained from sheep's blood and are coated with pure hCG obtained from urine of the pregnant women. Nowadays, instead of sheep's RBCs, the rubberized synthetic particles called the latex particles are used.

3. *Urine*

Fresh urine sample of the woman, who needs to confirm pregnancy, is collected.

Procedure

1. One drop of hCG antiserum is taken on a glass slide. One drop of urine from the woman who wants to confirm pregnancy is added to this and both are mixed well. If urine contains

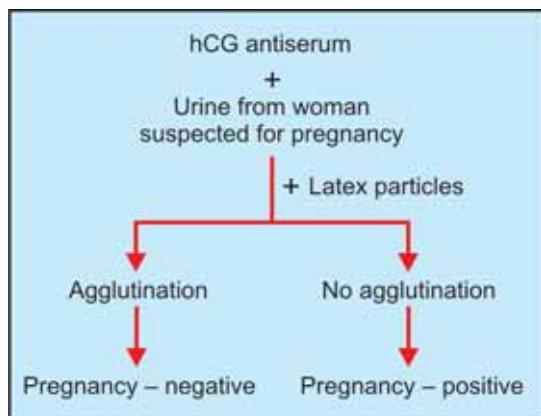


FIGURE 56-2: Immunological test for pregnancy

hCG, all the antibodies of antiserum are used up for agglutination of hCG molecules. The agglutination of hCG molecules by the antiserum is not visible because it is colorless

2. Now, one drop of latex particles is added to this and mixed.

Observation and Result

If the urine contains hCG, it is agglutinated by the antibodies of the antiserum and, all the antibodies are fully used up. No free antibody is available. Later when latex particles are added, these particles are not agglutinated because the free antibody is not available. Thus, the absence of agglutination of latex particles confirms pregnancy.

If the urine without hCG is mixed with antiserum, the antibodies are freely available. When the latex particles are added, the antibodies cause agglutination of these latex particles. The agglutination of latex particles can be seen clearly even with naked eye. Thus, the presence of agglutination of latex particles indicates that, the woman is not pregnant (Fig. 56-2).

■ DEVELOPMENT OF MAMMARY GLANDS

■ AT BIRTH

At the time of birth, the mammary gland is rudimentary and consists of only a tiny nipple and few radiating ducts from it.

■ AT CHILDHOOD

Till puberty, there is no difference in the structure of mammary gland between male and female.

■ AT PUBERTY

At the time of puberty and afterwards there is a vast change in the structure of female mammary gland due to hormonal influence. The beginning of changes in the mammary gland is called thelarche. It occurs at the time of puberty, just before menarche (Chapter 55). At puberty, there is growth of duct system and formation of glandular tissue. Progressive enlargement occurs, which is also due to the deposition of fat.

■ DURING PREGNANCY

During pregnancy, the mammary glands enlarge to a great extent accompanied by marked changes in structure. During first half of pregnancy, the duct system develops further with appearance of many new alveoli. No milk is secreted by the gland now.

During the second half, there is enormous growth of glandular tissues and the development is completed for the production of milk just before the end of gestation period.

■ ROLE OF HORMONES IN GROWTH OF MAMMARY GLANDS

Various hormones are involved in the development and growth of breasts at different stages.

1. Estrogen causes growth and branching of duct system and accumulation of fat in breasts
2. Progesterone stimulates the development of glandular tissues and stroma of mammary glands
3. Prolactin is necessary for milk secretion. It also accelerates growth of mammary glands during pregnancy by causing proliferation of epithelial cells of alveoli
4. Placental hormones namely estrogen and progesterone cause further development of

mammary glands during pregnancy by stimulating the proliferation of ducts and glandular cells.

5. Other hormones such as growth hormone, thyroxine, cortisol and relaxin enhance the overall growth and development of mammary glands in all stages.

■ LACTATION

Lactation means synthesis, secretion and ejection of milk. It involves two processes:

- A. Milk secretion
- B. Milk ejection.

■ MILK SECRETION

Synthesis of milk by alveolar epithelium and its passage through the duct system is called milk secretion. This process occurs in two phases:

1. Initiation of milk secretion or lactogenesis
2. Maintenance of milk secretion or galactopoiesis.

1. Initiation of Milk Secretion or Lactogenesis

Although small amount of milk secretion occurs at later months of pregnancy, a free flow of milk occurs only after the delivery of the child. The milk which is secreted initially before parturition is called colostrum.

Colostrum is lemon yellow in color and it is rich in protein (particularly globulins) and salts. But its sugar content is low. It contains almost all the components of milk except fat.

Role of hormones in lactogenesis

During pregnancy, particularly in later months, large quantity of prolactin is secreted. But the activity of this hormone is suppressed by estrogen and progesterone secreted by placenta. Because of this, lactation is prevented during pregnancy.

Immediately after the delivery of the baby and expulsion of placenta, there is sudden loss of estrogen and progesterone. Now, the prolactin

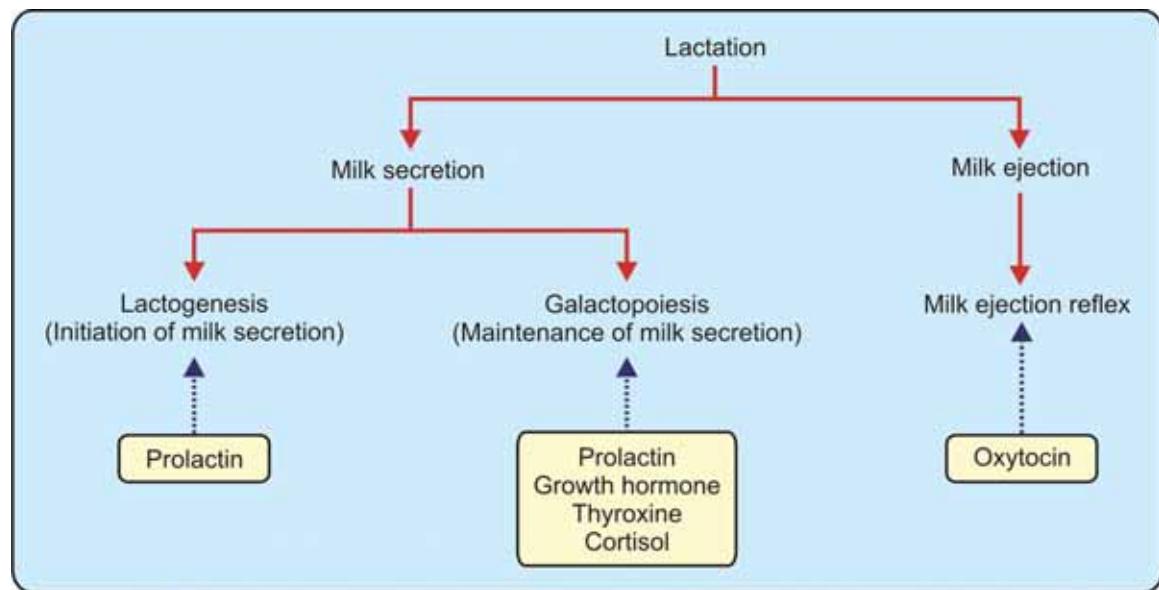


FIGURE 56-3: Process of lactation and role of hormones

is free to exert its action on breasts and to promote lactogenesis.

2. Maintenance of Milk Secretion or Galactopoiesis

The galactopoiesis occurs up to 7 to 9 months after delivery of child provided feeding the baby with mother's milk is continued till then. In fact, the milk production is continued only if feeding the baby is continued.

Role of hormones in galactopoiesis

Galactopoiesis depends upon prolactin secretion. Other hormones like growth hormone, thyroxine and cortisol are essential for continuous supply

of glucose, amino acids, fatty acids, calcium and other substances necessary for the milk production (Fig. 56-3).

■ MILK EJECTION

Milk ejection is the discharge of milk from mammary gland. It depends upon suckling exerted by the baby and on contractile mechanism in breast, which expels milk from alveoli into the ducts.

Milk ejection is a reflex phenomenon. It is called milk ejection reflex or milk let down reflex. It is a neuroendocrine reflex.

Milk Ejection Reflex

It is explained in Chapter 45.

Fertility Control

- INTRODUCTION
- RHYTHM METHOD (SAFE PERIOD)
- MECHANICAL BARRIERS – PREVENTION OF ENTRY OF SPERM INTO UTERUS
- CHEMICAL METHODS
- ORAL CONTRACEPTIVES (PILL METHOD)
- INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD)
- MEDICAL TERMINATION OF PREGNANCY (MTP) – ABORTION
- SURGICAL METHOD (STERILIZATION) – PERMANENT METHOD

■ INTRODUCTION

Fertility control is the use of any method or device to prevent pregnancy. It is also called birth control, family planning, or contraception. The fertility control techniques may be temporary or permanent. Several methods are available for fertility control.

■ RHYTHM METHOD (SAFE PERIOD)

Rhythm method of fertility control is based on the time of ovulation. After ovulation, i.e. on the 14th day of menstrual cycle, the ovum is fertilized during its passage through fallopian tubes. Its viability is only for 2 days after ovulation, and should be fertilized within this period.

The sperms survive only for about 24 to 48 hours after ejaculation in the female genital tract. If sexual intercourse occurs during this period, i.e. few days before and few days after ovulation, there is chance of pregnancy. This

period is called the dangerous period. Pregnancy can be avoided if there is no sexual intercourse during this period. The prevention of pregnancy by avoiding sexual mating during this period is called rhythm method.

The periods, when pregnancy does not occur are 4 to 5 days after menstrual bleeding and 5 to 6 days before the onset of next cycle. These periods are together called safe period.

Advantages and Disadvantages

It is one of the most successful methods of fertility control provided the woman knows the exact day of ovulation. However, it is not a successful method because of various reasons. Basic knowledge about the menstrual cycle is necessary to determine the day of ovulation. Self restrain is essential to avoid sexual intercourse. Because of the practical difficulties, this method is not popular.

■ MECHANICAL BARRIERS – PREVENTION OF ENTRY OF SPERM INTO UTERUS

Mechanical barriers are used to prevent the entry of sperm into uterine cavity. These barriers are called condoms. The male condom is a leak proof sheath, made of latex. It covers the penis and does not allow entrance of semen into the female genital tract during coitus.

In females, the commonly used condom is cervical cap or diaphragm. It covers the cervix and prevents entry of sperm into uterus.

■ CHEMICAL METHODS

Chemical substances, which destroy the sperms, are applied in female genital tract before coitus. Destruction of sperms is called spermicidal action. The spermicidal substances are available in the form of foam tablet, jelly, cream and paste.

■ ORAL CONTRACEPTIVES (PILL METHOD)

The oral contraceptives are the drugs taken by mouth (pills) to prevent pregnancy. These pills prevent pregnancy by inhibiting maturation of follicles and ovulation. This leads to alteration of normal menstrual cycle. The menstrual cycle becomes the anovulatory cycle.

This method of fertility control is called pill method and pills are called contraceptive pills or birth control pills. These pills contain synthetic estrogen and progesterone.

Contraceptive pills are of three types:

1. Classical or combined pills
2. Sequential pills
3. Minipills or micropills.

■ 1. CLASSICAL OR COMBINED PILLS

The classical or combined pills contain a moderate dose of synthetic estrogen like ethinyl estradiol or mestranol and a mild dose of synthetic progesterone like norethindrone or norgestrel.

The pills are taken daily from 5 to 25th day of menstrual cycle. The withdrawal of the pills

after 25th day causes menstrual bleeding. The intake of pills is resumed again after 5th day of the next cycle.

Mechanism of Action

During the continuous intake of the pills, there is relatively large amount of estrogen and progesterone in the blood. It suppresses the release of gonadotropins, FSH and LH from pituitary by means of feedback mechanism. The lack of FSH and LH prevents the maturation of follicle, and ovulation. In addition, progesterone increases the thickness of mucosa in cervix, which is not favorable for transport of sperm. When the pills are withdrawn after 21 days the menstrual flow starts.

■ 2. SEQUENTIAL PILLS

Sequential pills contain a high dose of estrogen along with moderate dose of progesterone. These pills are taken in two courses.

- i. Daily for 15 days from 5 to 20th day of the menstrual cycle and then
 - ii. During the last 5 days, i.e. 23 to 28th day.
- Sequential pills also prevent ovulation.

■ 3. MINIPIILLS OR MICROPILLS

The minipills contain a low dose of only progesterone and are taken throughout the menstrual cycle. It prevents pregnancy without affecting ovulation. The progesterone increases the thickness of cervical mucosa, so that the transport of sperms is inhibited. It also prevents implantation of ovum.

■ DISADVANTAGES AND ADVERSE EFFECTS OF ORAL CONTRACEPTIVES

About 40% of women who use contraceptive pills may have minor transient side effects. However, long-term use of oral contraceptives causes some serious side effects.

■ LONG-TERM CONTRACEPTIVES

To avoid taking pills daily, the long-term contraceptives are used. These contraceptives are in

the form of implants containing mainly progesterone. The implants which are inserted beneath the skin release the drug slowly and prevent fertility for 4 to 5 years. Though it seems to be effective, it may produce amenorrhea.

■ INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD) – PREVENTION OF FERTILIZATION AND IMPLANTATION OF OVUM

The fertilization and the implantation of ovum are prevented by inserting some object made from metal or plastic into uterine cavity. Such object is called intrauterine contraceptive device (IUCD).

■ MECHANISM OF ACTION OF IUCD

IUCD prevents fertilization and implantation of the ovum. The IUCD with copper content has spermicidal action also. The IUCD which is loaded with synthetic progesterone slowly releases progesterone. Progesterone causes thickening of cervical mucus and prevents entry of sperm into uterus.

The common intrauterine contraceptive device is Lippe's loop, which is 'S' shaped and made of plastic and copper T which is made up of copper. It is inserted into the uterine cavity by using some special applicator.

■ DISADVANTAGES OF IUCD

IUCD has some disadvantages. It has the tendency to:

1. Cause heavy bleeding in some women
2. Promote infection
3. Come out of uterus accidentally.

■ MEDICAL TERMINATION OF PREGNANCY (MTP) – ABORTION

The abortion is done during first few months of pregnancy. This method is called medical termination of pregnancy (MTP). There are three ways of doing MTP.

■ 1. DILATATION AND CURETTAGE (D AND C)

In this method, the cervix is dilated and the implanted ovum or zygote is removed.

■ 2. VACUUM ASPIRATION

The implanted ovum is removed by vacuum aspiration method. This is done up to 12 weeks of pregnancy.

■ 3. ADMINISTRATION OF PROSTAGLANDIN

Administration of prostaglandin like PGE₂ and PGF₂ intravaginally increases uterine contractions resulting in abortion.

■ SURGICAL METHOD (STERILIZATION) – PERMANENT METHOD

Permanent sterility is obtained by surgical methods. It is also called sterilization.

■ TUBECTOMY

In tubectomy, the fallopian tubes are cut and both the cut ends are ligated. It prevents entry of ovum into uterus. The operation is done through vaginal orifice in the postpartum period. During other periods, it is done by abdominal incision. Tubectomy is done quickly (in few minutes) by using a laparoscope.

Though tubectomy causes permanent sterility, if necessary recanalization of fallopian tube can be done using plastic tube by another surgical procedure.

■ VASECTOMY

In vasectomy, the vas deferens is cut and the cut ends are ligated. So the sperms cannot enter the ejaculatory duct and the semen is devoid of sperms. It is done by surgical procedure with local anesthesia. If necessary, the recanalization of vas deferens can be done with plastic tube.

QUESTIONS IN REPRODUCTIVE SYSTEM

■ LONG QUESTIONS

1. Describe the functions of testis and regulation of testicular functions.
2. Describe the actions and regulation of secretion of testosterone.
3. What are the female sex hormones? Explain their actions.
4. What is menstrual cycle? Explain the ovarian changes taking place during menstrual cycle.
5. Describe the uterine changes during menstrual cycle.

■ SHORT QUESTIONS

1. Spermatogenesis.
2. Sertoli cells.
3. Testosterone.
4. Cryptorchidism.
5. Secondary sexual characters in males.
6. Semen.
7. Effects of removal of testes.

8. Estrogen.
9. Progesterone.
10. Follicle stimulating hormone.
11. Luteinizing hormone.
12. Gonadotropins.
13. Secondary sexual characters in females.
14. Ovarian follicles.
15. Ovulation.
16. Corpus luteum.
17. Functions of placenta.
18. Pregnancy tests.
19. Role of hormones in lactation.
20. Prolactin.
21. Milk ejection reflex.
22. Safe period/Rhythm method.
23. Oral contraceptives.
24. MTP.
25. Tubectomy.
26. Contraceptive methods in males.
27. Condoms.
28. IUCD.
29. Vasectomy.
30. Contraceptive methods in females.

SECTION 8

Cardiovascular System

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Introduction to Cardiovascular System

- CARDIOVASCULAR SYSTEM
- HEART
- ACTIONS OF THE HEART
- BLOOD VESSELS
- DIVISIONS OF CIRCULATION

■ CARDIOVASCULAR SYSTEM

Cardiovascular system is made up of heart and blood vessels. Heart pumps the blood into the blood vessels. Blood vessels circulate the blood throughout the body and transport nutrients and oxygen to the tissues and remove carbon dioxide and waste products from the tissues.

■ HEART

Heart is a muscular organ that pumps blood throughout the circulatory system. It is situated in between the two lungs in the mediastinum. It is made up of four chambers – two atria and two ventricles. The musculature is more and thick in the ventricles than in the atria. The force of contraction of the heart depends upon the muscles.

■ RIGHT SIDE OF THE HEART

Right side of the heart has two chambers, the upper right atrium and lower right ventricle. Right atrium is a thin walled and low pressure chamber. It has got the pacemaker known as sinoatrial node that produces cardiac impulses and atrio-

ventricular node that conducts the impulses to the ventricles. It receives venous (deoxygenated) blood via two large veins:

1. Superior vena cava that returns the venous blood from the head, neck and upper limbs
2. Inferior vena cava that returns the venous blood from lower parts of the body (Fig. 58-1). Right atrium communicates with the right ventricle through the tricuspid valve. Venous blood from the right atrium enters the right ventricle through this valve.

From the right ventricle, pulmonary artery arises. It carries the venous blood from right ventricle to the lungs. In the lungs, the deoxygenated blood is oxygenated.

■ LEFT SIDE OF THE HEART

Left side of the heart has two chambers, the upper left atrium and lower left ventricle. Left atrium is a thin walled and low pressure chamber. It receives oxygenated blood from the lungs through pulmonary veins. This is the only exception in the body where an artery carries venous blood and vein carries the arterial blood.

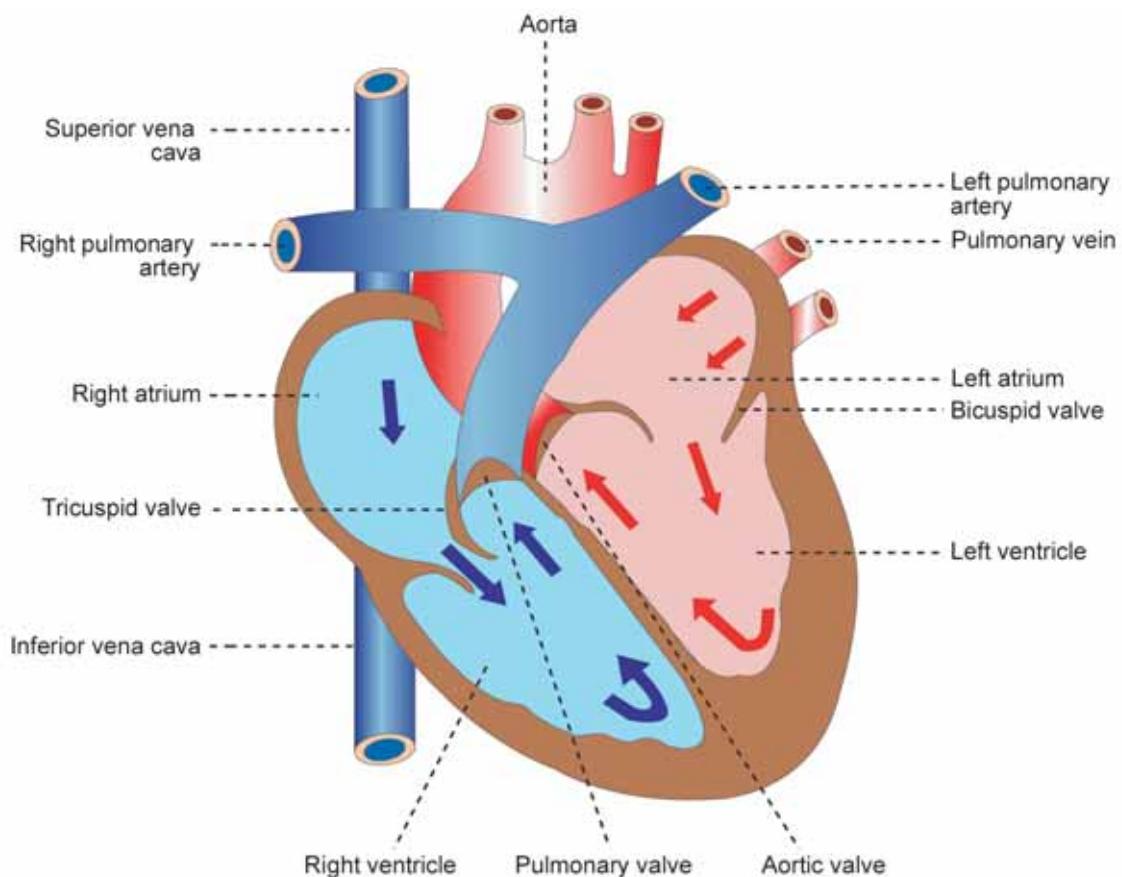


FIGURE 58-1: Section of the heart

Blood from left atrium enters the left ventricle through the mitral valve (bicuspid valve). Wall of the left ventricle is very thick. Left ventricle pumps the arterial blood to different parts of the body through systemic aorta.

■ SEPTA OF THE HEART

Right and left atria of the heart are separated from one another by interatrial septum. The ventricles are separated from one another by interventricular septum.

■ LAYERS OF WALL OF THE HEART

Heart is made up of three layers of tissues:

1. Outer pericardium
2. Middle myocardium
3. Inner endocardium.

■ PERICARDIUM

Pericardium is the outer covering of the heart. It is made up of two layers

- i. Outer parietal pericardium which forms a strong protective sac around the heart
- ii. Inner visceral pericardium or epicardium that covers myocardium.

These two layers are separated by a space called pericardial cavity which contains a thin film of fluid.

■ MYOCARDIUM

Myocardium is the middle layer of the wall of the heart and it is formed by cardiac muscle fibers. It forms the bulk of the heart and it is responsible for the pumping action of the heart. Refer Chapter 20 for features of cardiac muscles.

Myocardium is formed by three types of cardiac muscle fibers:

- i. Muscle fibers which form the contractile unit of the heart
- ii. Muscle fibers which form pacemaker
- iii. Muscle fibers which form the conductive system.

i. Muscle Fibers which Form the Contractile Unit of the Heart

These cardiac muscle fibers are striated fibers and are similar to the skeletal muscles in structure. But, unlike the skeletal muscle fibers, the cardiac muscle fibers are involuntary in nature.

The cardiac muscle fiber is covered by sarcolemma. It has a centrally placed nucleus. The myofibrils are embedded in the sarcoplasm. The sarcomere of the cardiac muscle has muscle proteins namely, actin, myosin, troponin and tropomyosin. The cardiac muscles also have sarcotubular system like that of skeletal muscle.

The important difference between skeletal muscle and cardiac muscle is that the cardiac muscle fiber is branched and the skeletal muscle is not branched.

Intercalated disk

Intercalated disk is a tough double membranous structure situated at the junction between the branches of neighboring cardiac muscle fibers. It is formed by the fusion of the membrane of the cardiac muscle branches (Fig. 58-2).

The intercalated disks form adherens junctions which play an important role in contraction of the muscle as a single unit (Chapter 2).

Syncytium

The structure of cardiac muscle is considered as a syncytium. The word syncytium refers to the tissue in which there is cytoplasmic continuity between the adjacent cells. However, in cardiac muscle there is no continuity of the cytoplasm and the muscle fibers are separated from each other by cell membrane. But at the sides, membranes of the adjacent muscle fibers fuse

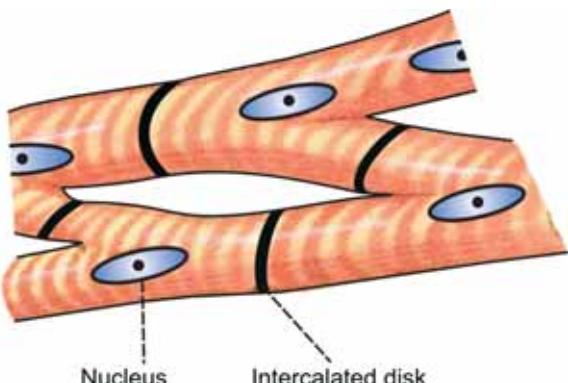


FIGURE 58-2: Cardiac muscle fibers

together to form gap junctions which facilitates the rapid conduction of electrical activity from one fiber to another. This makes the cardiac muscle fibers act like a single unit referred as physiological syncytium.

The syncytium in human heart has two portions, atrial syncytium and ventricular syncytium which are connected by atrioventricular ring.

ii. Muscle Fibers which Form the Pacemaker

Some of the muscle fibers of the heart are modified into a specialized structure known as pacemaker. The muscle fibers forming the pacemaker have less striation.

Pacemaker

Pacemaker is structure in the heart that generates the impulses for heart beat. It is formed by the pacemaker cells called P cells. Sinoatrial (SA) node forms the pacemaker in human heart. Details of pacemaker are given in next chapter.

iii. Muscle Fibers which Form the Conductive System

The conductive system of the heart is formed by the modified cardiac muscle fibers. The impulses from SA node are transmitted to the atria directly. However, the impulses are transmitted to the ventricles, through various components of conducting system which are given in the next chapter.

■ ENDOCARDIUM

Endocardium is the inner most layer of the heart wall. It is a thin, smooth and glistening membrane. It is formed by a single layer of endothelial cells lining the inner surface of the heart. Endocardium continues as endothelium of the blood vessels.

■ VALVES OF THE HEART

There are four valves in human heart. Two of the valves are in between the atria and the ventricles called atrioventricular valves. The other two are the semilunar valves, placed at the opening of the blood vessels arising from the ventricles, i.e. systemic aorta and pulmonary artery. The valves of the heart permit the flow of blood through the heart in only one direction.

Atrioventricular Valves

Left atrioventricular valve is otherwise known as mitral valve or bicuspid valve. It is formed by two valvular cusps or flaps (Fig. 58-3). Right atrioventricular valve is known as tricuspid valve and it is formed by three cusps.

The brim of the atrioventricular valves is attached to the atrioventricular ring, which is the fibrous connection between the atria and ventricles. The cusps of the valves are attached to the papillary muscles by means of chordae tendinae. The papillary muscles arise from the inner surface of the ventricles. The papillary muscles play an important role in closure of the cusps and in preventing the back flow of blood from ventricle to atria during ventricular contraction.

Atrioventricular valves open only towards ventricles and prevent the backflow of blood into atria.

Semilunar Valves

The semilunar valves are present at the openings of systemic aorta and pulmonary artery and are known as aortic valve and pulmonary valve respectively. Because of the half moon shape, these two valves are called semilunar valves. The semilunar valves are made up of three flaps.

The semilunar valves open only towards the aorta and pulmonary artery and prevent the backflow of blood into the ventricles.

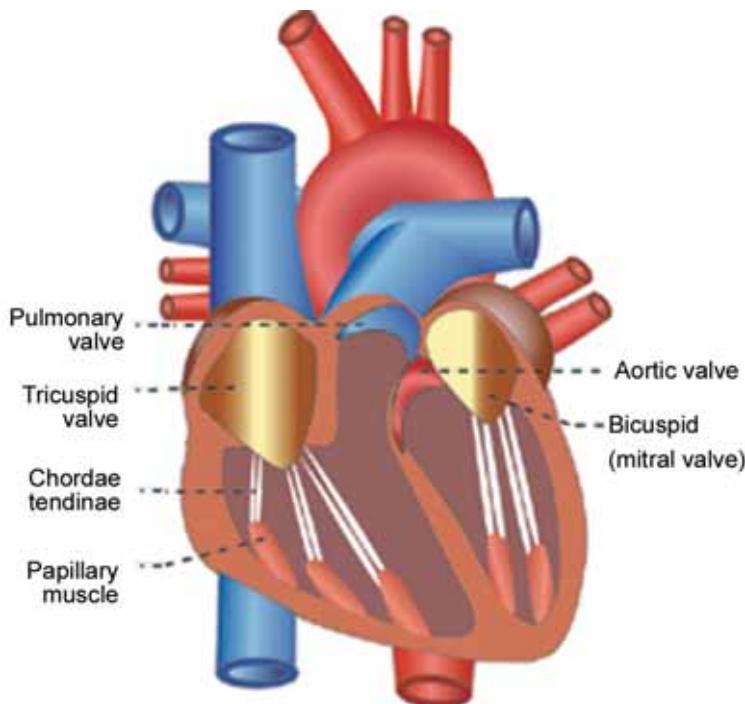


FIGURE 58-3: Valves of the heart

■ ACTIONS OF THE HEART

The actions of the heart are classified into four types:

1. Chronotropic action
2. Inotropic action
3. Dromotropic action
4. Bathmotropic action.

■ CHRONOTROPIC ACTION

Chronotropic action is the frequency of heartbeat or heart rate. It is of two types:

- i. Tachycardia or increase in heart rate
- ii. Bradycardia or decrease in the heart rate.

■ INOTROPIC ACTION

Force of contraction of heart is called inotropic action. It is of two types:

- i. Positive inotropic action or increase in the force of contraction
- ii. Negative inotropic action or decrease in the force of contraction.

■ DROMOTROPIC ACTION

Dromotropic action is the conduction of impulse through heart. It is of two types:

- i. Positive dromotropic action or increase in the velocity of conduction
- ii. Negative dromotropic action or decrease in the velocity of conduction

■ BATHMOTROPIC ACTION

Bathmotropic action is the excitability of cardiac muscle. It is also of two types:

- i. Positive bathmotropic action or increase in the excitability of cardiac muscle
- ii. Negative bathmotropic action or the decrease in the excitability of cardiac muscle.

Regulation of Actions of the Heart

All the actions of the heart are continuously regulated. It is essential for the heart to cope up with the needs of the body. All the actions are altered by the stimulation of nerves supplying the heart or some hormones or hormonal substances secreted in the body.

■ BLOOD VESSELS

The vessels of circulatory system are divided into arterial system and venous system.

■ ARTERIAL SYSTEM

The arterial system comprises the aorta, arteries and arterioles. The walls of the aorta and arteries are formed by three layers.

1. Outer tunica adventitia, which is made up of connective tissue layer. It is the continuation of fibrous layer of parietal pericardium
2. Middle tunica media, which is formed by smooth muscles
3. Inner tunica intima, which is made up of endothelium. It is the continuation of endocardium.

The arterial branches become narrower and their walls become thinner while reaching the periphery. The aorta has got the maximum diameter of about 25 mm. The diameter of the arteries is gradually decreased and at the end arteries it is about 4 mm. It further decreases to 30 μ in the arterioles and ends up with 10 μ in the terminal arterioles. The resistance (peripheral resistance) is offered to the blood flow in the arterioles and so these vessels are called resistant vessels.

The arterioles are continued as capillaries which are small, thin walled vessels having a diameter of about 5 to 8 μ . The capillaries are functionally very important because, the exchange of materials between the blood and the tissues occurs through these vessels.

■ VENOUS SYSTEM

From the capillaries venous system starts and it includes the venules, veins and vena cavae. The capillaries end in the venules. The venules are smaller vessels with thin muscular wall than the arterioles. The diameter of the venules is about 20 μ . At a given time, large quantity of blood is held in venules and so the venules are called capacitance vessels. The venules are continued as veins, which have the diameter of 5 mm. The veins form superior and inferior vena cavae which have a diameter of about 30 mm (Table 58-1).

TABLE 58-1: Structural and dimensional differences between different blood vessel walls

Blood vessel	Diameter	Thickness of the wall	Elastic tissue	Smooth muscle fibers	Fibrous tissue
Aorta	25 mm	2 mm	More	Less	More
Artery	4 mm	1 mm	More	More	Moderate
Arteriole	30 μ	6 μ	Moderate	More	Moderate
Terminal arteriole	10 μ	2 μ	Less	More	Moderate
Capillary	8 μ	0.5 μ	Absent	Absent	Moderate
Venule	20 μ	1 μ	Absent	Absent	Less
Vein	5 mm	0.5 mm	Less	More	Moderate
Vena cava	30 mm	1.5 mm	Less	More	More

The walls of the veins and vena cavae are made up of inner endothelium, elastic tissues, smooth muscles and outer connective tissue layer. In the veins and vena cavae, the elastic tissue is less but the smooth muscle fibers are more.

■ DIVISIONS OF CIRCULATION

Blood flows through two divisions of circulating system:

1. Systemic circulation
2. Pulmonary circulation.

■ SYSTEMIC CIRCULATION

It is otherwise known as greater circulation (Fig. 58-4). The blood pumped from left ventricle passes through a series of blood vessels of arterial system and reaches the tissues. Exchange of various substances between blood and the tissues takes place in the capillaries. After the exchange of substances in the capillaries, the blood enters the venous system and returns to right atrium and then the right ventricles.

■ PULMONARY CIRCULATION

It is otherwise called lesser circulation. Blood is pumped from right ventricle to lungs through pulmonary artery. The exchange of gases occurs between blood and alveoli of the lungs through

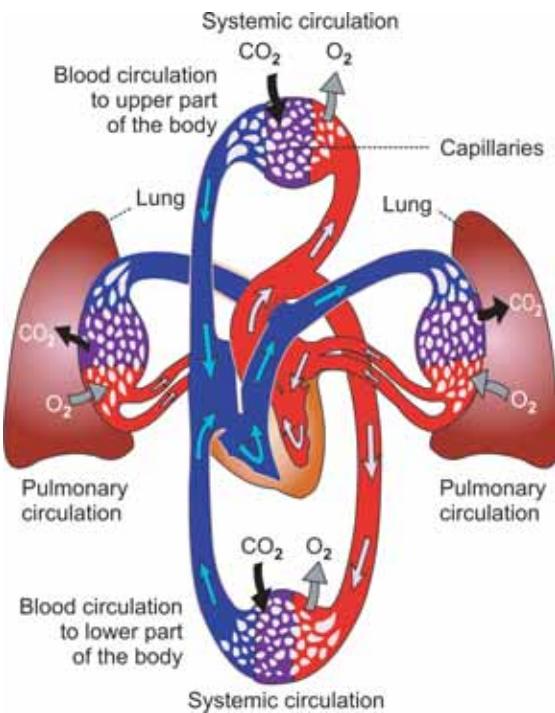


FIGURE 58-4: Systemic and pulmonary circulation

pulmonary capillary membrane. The oxygenated blood returns to left atrium through the pulmonary veins.

Thus, the left side of the heart contains oxygenated or arterial blood and the right side of the heart contains the venous blood.

Properties of Cardiac Muscle

■ EXCITABILITY

- DEFINITION
- ELECTRICAL POTENTIALS IN CARDIAC MUSCLE
- IONIC BASIS OF ACTION POTENTIAL
- SPREAD OF ACTION POTENTIAL THROUGH CARDIAC MUSCLE

■ RHYTHMICITY

- DEFINITION
- PACEMAKER
- ELECTRICAL POTENTIAL IN SA NODE

■ CONDUCTIVITY

- CONDUCTIVE SYSTEM IN HUMAN HEART
- VELOCITY OF IMPULSES AT DIFFERENT PARTS OF THE CONDUCTIVE SYSTEM

■ CONTRACTILITY

- ALL OR NONE LAW
- STAIRCASE PHENOMENON
- SUMMATION OF SUBLIMINAL STIMULI
- REFRACTORY PERIOD

■ EXCITABILITY

■ DEFINITION

Excitability is defined as the ability of a living tissue to give response to a stimulus. In all the tissues, the initial response to a stimulus is the electrical activity in the form of action potential. It is followed by mechanical activity in the form of contraction, secretion, etc.

■ ELECTRICAL POTENTIALS IN CARDIAC MUSCLE

Refer Chapter 23 for basics of electrical potentials in the muscle.

Resting Membrane Potential

The resting membrane potential in:

Single cardiac muscle fiber	: - 85 to - 95 mV
SA node	: - 55 to - 60 mV
Purkinje fibers	: - 90 to -100 mV.

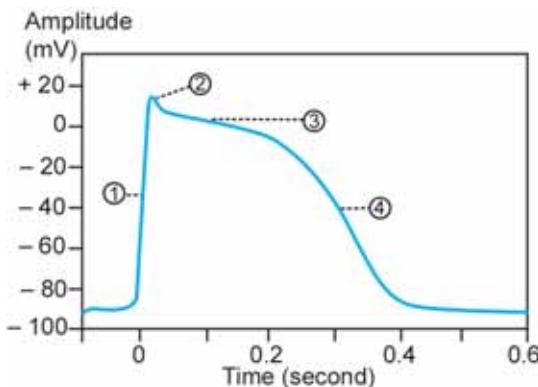


FIGURE 59-1: Action potential in ventricular muscle.
1 = Depolarization, 2 = Initial rapid repolarization,
3 = Plateau, 4 = Final repolarization

Action Potential

Action potential in a single cardiac muscle fiber occurs in 4 phases:

1. Initial depolarization
2. Initial repolarization
3. A plateau – final depolarization
4. Final repolarization.

Approximate duration of action potential in cardiac muscle is 250 to 350 msec (0.25 to 0.35 sec).

1. Initial Depolarization

Initial depolarization is very rapid and it lasts for about 2 msec. The amplitude of the depolarization is about + 20 mV (Fig. 59-1).

2. Initial Repolarization

Immediately after depolarization, there is an initial rapid repolarization for a short period of about 2 msec. The end of rapid repolarization is represented by a notch.

3. Plateau – Final Depolarization

Afterwards, the muscle fiber remains in the depolarized state for sometime before further repolarization. It forms the plateau (stable period) in the action potential curve. The plateau lasts for about 200 msec (0.2 sec) in atrial muscle fibers and for about 300 msec (0.3 sec) in

ventricular muscle fibers. Due to the long plateau in action potential, the contraction time is longer in cardiac muscle by about 5 to 15 times than in skeletal muscle.

4. Final Repolarization

Final repolarization occurs after the plateau. It is a slow process and it lasts for about 50 to 80 msec (0.05 to 0.08 sec) before the re-establishment of resting membrane potential.

■ IONIC BASIS OF ACTION POTENTIAL

1. Initial depolarization is due to opening of fast sodium channels and the rapid influx of sodium ions as in the case of skeletal muscle fiber
2. Initial repolarization is due to the transient (short duration) opening of potassium channels and efflux of a small quantity of potassium ions from the muscle fiber. Simultaneously, the fast sodium channels close suddenly and slow sodium channels open resulting in slow influx of a low quantity of sodium ions.
3. Plateau (final depolarization) is because of the opening of calcium channels. These channels are kept opened for a longer period and cause influx of large number of calcium ions. Already the slow sodium channels are opened through which slow influx of sodium ions continues. The entry of both calcium and sodium ions is responsible for prolonged depolarization, i.e. plateau.
4. Final repolarization is due to increase in efflux of potassium ions increases.

Restoration of resting membrane potential

At the end of final repolarization, all the sodium ions, which entered the cell throughout the process of action potential move out of the cell and potassium ions move inside by sodium-potassium pump. Simultaneously, the excess of calcium ions, which entered the muscle fiber also move out through sodium-calcium pump. Thus, the resting membrane potential is restored.

■ SPREAD OF ACTION POTENTIAL THROUGH CARDIAC MUSCLE

The action potential spreads through the cardiac muscle very rapidly. It is because of the presence of gap junctions between the cardiac muscle fibers. The gap junctions are permeable junctions and allow free movement of ions. Due to this, the action potential spreads rapidly from one muscle fiber to another fiber.

The action potential is transmitted from atria to ventricles through the fibers of specialized conductive system, which is explained later in this chapter.

■ RHYTHMICITY

■ DEFINITION

Rhythmicity is the ability of a tissue to produce its own impulses regularly. It is more appropriately named as autorhythmicity. It is also called self excitation. The property of rhythmicity is present in all the tissues of the heart. However, heart has a specialized excitatory structure from which the discharge of impulses is rapid. This specialized structure is called pacemaker. From this, the impulses spread to other parts through the specialized conductive system.

■ PACEMAKER

Pacemaker is defined as the part of the heart from which the impulses for heartbeat are produced normally. It is formed by the pacemaker cells called P cells. In mammalian heart, the pacemaker is sinoatrial node (SA node).

SA Node

SA node is a small strip of modified cardiac muscle situated in the superior part of lateral wall of right atrium, just below the opening of superior vena cava. The fibers of this node do not have contractile elements. These fibers are continuous with fibers of atrial muscle, so that the impulses from the SA node spread rapidly through atria.

Other parts of heart like AV node, atria and ventricle also can produce the impulses and function as pacemaker. Still SA node is called the pacemaker because the rate of production of impulse (rhythmicity) is more in SA node than in other parts. It is about 70 to 80/minute.

Spread of Impulses from SA Node

The mammalian heart has got a specialized conductive system by which, the impulses from SA node spreads to other parts of the heart (see below).

Rhythmicity of Other Parts of the Heart

Though the SA node is the pacemaker in mammalian heart, other parts of the heart also have the property of rhythmicity. The rhythmicity of different parts:

1. AV node : 40 to 60/minute
2. Atrial muscle : 40 to 60/minute
3. Purkinje fibers : 35 to 40/minute
4. Ventricular muscle : 20 to 40/minute

■ ELECTRICAL POTENTIAL IN SA NODE

Resting Membrane Potential — Pacemaker Potential

Pacemaker potential is the unstable resting membrane potential in SA node. It is also called prepotential.

The electrical potential in SA node is different from that of other cardiac muscle fibers. In the SA node each impulse triggers the next impulse. It is mainly due to the unstable resting membrane potential.

The resting membrane potential in SA node has a negativity of -55 to -60 mV. It is different from the negativity of -85 to -95 mV in other cardiac muscle fibers.

Action Potential

The depolarization starts very slowly and the threshold level of -40 mV is reached very slowly. After the threshold level, rapid depolarization occurs up to $+5$ mV. It is followed by rapid repolarization. Once again, the resting

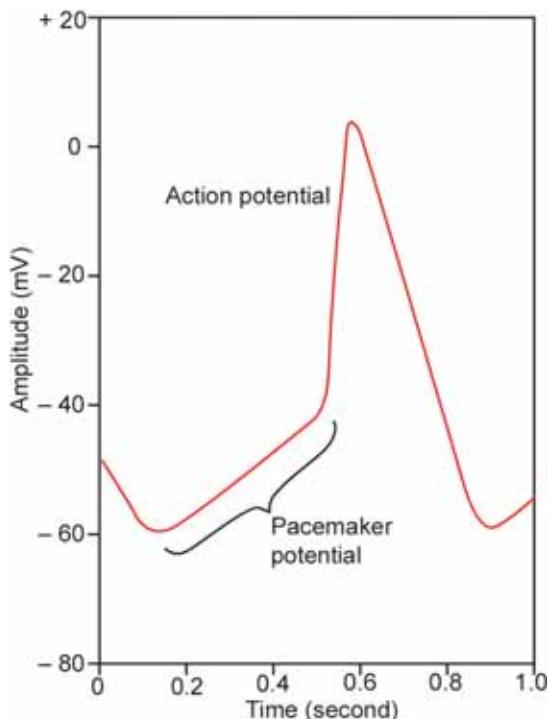


FIGURE 59-2: Pacemaker potential

membrane potential becomes unstable and reaches the threshold level slowly (Fig. 59-2).

■ CONDUCTIVITY

Human heart has a specialized conductive system through which the impulses from SA node

are transmitted to all other parts of the heart (Fig. 59-3).

■ CONDUCTIVE SYSTEM IN HUMAN HEART

The conductive system of the heart is formed by the modified cardiac muscle fibers. The conductive tissues of the heart are also called the junctional tissues. The conductive system in human heart comprises:

1. AV node
2. Bundle of His
3. Right and left bundle branches
4. Purkinje fibers.

SA node is situated in right atrium just below the opening of superior vena cava. AV node is situated in right posterior portion of intra-atrial septum. The impulses from SA node are conducted throughout right and left atria. The impulses also reach the AV node via some specialized fibers called intermodal fibers. There are three types of intermodal fibers:

1. Anterior internodal fibers of Bachman
2. Middle internodal fibers of Wenckebach
3. Posterior internodal fibers of Thorel.

All these fibers from SA node converge on AV node and interdigitate with fibers of AV node. From AV node, the bundle of His arises. It divides into right and left bundle branches which run on either side of the interventricular septum. From each branch of Bundle of His,

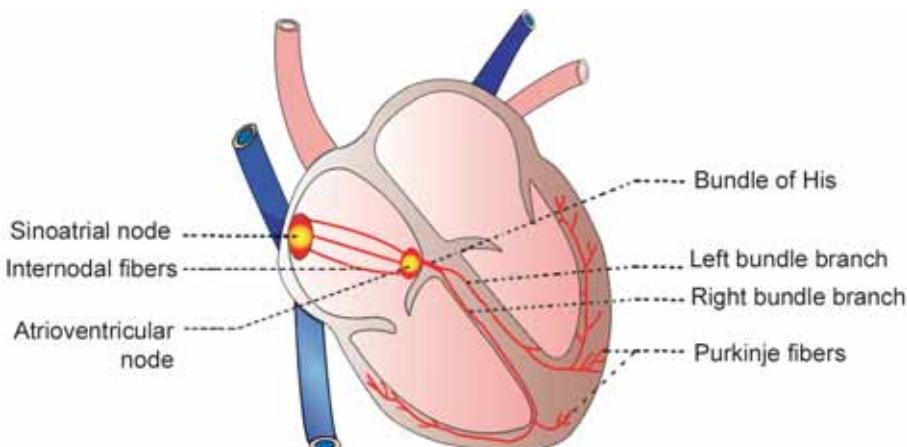


FIGURE 59-3: Sinoatrial node and conductive system of the heart

many Purkinje fibers arise and spread all over the ventricular myocardium.

■ VELOCITY OF IMPULSES AT DIFFERENT PARTS OF THE CONDUCTIVE SYSTEM

1. Atrial muscle fibers : 0.3 meter/second
2. Internodal fibers : 1.0 meter/second
3. AV node : 0.05 meter/second
4. Bundle of His : 0.12 meter/second
5. Purkinje fibers : 4.0 meter/second
6. Ventricular muscle fibers : 0.5 meter/second

Thus, the velocity of impulses is maximum in Purkinje fibers and minimum at AV node.

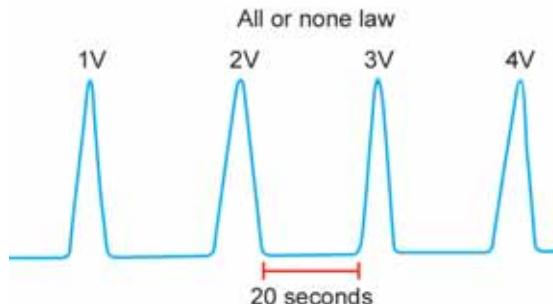
■ CONTRACTILITY

Contractility is ability of the tissue to shorten in length (contraction) after receiving a stimulus. Various factors affect the contractile properties of the cardiac muscle.

The contractile properties are:

■ ALL OR NONE LAW

According to all or none law, when a stimulus is applied, whatever may be the strength, the whole cardiac muscle gives maximum response or it does not give any response at all. Below the threshold level, i.e. if the strength of stimulus is not adequate, the muscle does not give response.



Cause for All or None Law

All or none law is applicable to whole cardiac muscle. It is because of syncytial arrangement of cardiac muscle. In the case of skeletal muscle, all or none law is applicable only to a single muscle fiber.

■ STAIRCASE PHENOMENON

When the ventricle is stimulated successively (at a short interval of two seconds) without changing the strength, the force of contraction increases gradually for the first few contractions, and then it remains same. Gradual increase in the force of contraction is called staircase phenomenon.

Cause for Staircase Phenomenon

The staircase phenomenon occurs because of the beneficial effect which facilitates the force of successive contraction. So, there is a gradual increase in force of contraction (Fig. 59-4).

■ SUMMATION OF SUBLIMINAL STIMULI

When a stimulus with a subliminal strength is applied, the heart does not show any response. When few stimuli with same subliminal strength are applied in succession, the heart shows response by contraction. It is due to the summation of the stimuli.

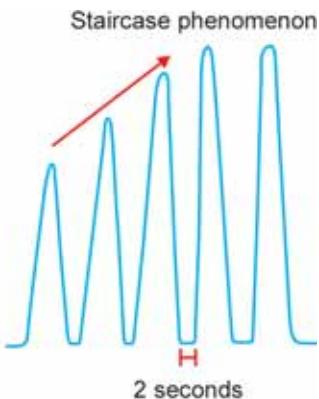


FIGURE 59-4: All or none law and staircase phenomenon in cardiac muscle

■ REFRACtORY PERIOD

Refractory period is the period in which the muscle does not show any response to a stimulus. It is of two types:

1. Absolute refractory period
2. Relative refractory period.

Absolute Refractory Period

Absolute refractory period is the period during which the muscle does not show any response at all, whatever may be the strength of the stimulus. It is because, the depolarization occurs during this period. So a second depolarization is not possible.

Relative Refractory Period

The relative refractory period is the period during which the muscle shows response if the strength of stimulus is increased to maximum.

It is the stage at which the muscle is in repolarizing state.

Refractory Period in Cardiac Muscle

Cardiac muscle has a long refractory period compared to that of skeletal muscle. The absolute refractory period extends throughout contraction period of cardiac muscle. It is for 0.27 sec and relative refractory period extends during first half of relaxation period which is about 0.26 sec. So, the total refractory period is 0.53 sec.

Significance of Long Refractory Period in Cardiac Muscle

Long refractory period in cardiac muscle has three advantages:

1. Summation of contractions does not occur
2. Fatigue does not occur
3. Tetanus does not occur.

Cardiac Cycle

- DEFINITION
- EVENTS OF CARDIAC CYCLE
- SUBDIVISIONS AND DURATION OF EVENTS OF CARDIAC CYCLE
- DESCRIPTION OF ATRIAL EVENTS
- DESCRIPTION OF VENTRICULAR EVENTS

■ DEFINITION

Cardiac cycle is defined as the sequence of coordinated events in the heart which are repeated during every heartbeat in a cyclic manner. Each heartbeat consists of two major periods called systole and diastole. Systole is the contraction of the cardiac muscle and diastole is the relaxation of cardiac muscle.

■ EVENTS OF CARDIAC CYCLE

The events of cardiac cycle are classified into two divisions:

1. Atrial events which constitute atrial systole and atrial diastole
2. Ventricular events which constitute ventricular systole and ventricular diastole.

However, in clinical practice, the term 'systole' refers to ventricular systole and 'diastole' refers to ventricular diastole.

■ SUBDIVISIONS AND DURATION OF EVENTS OF CARDIAC CYCLE

When the heart beats at the normal rate of 72 minute, the duration of each cardiac cycle is about 0.8 second.

■ ATRIAL EVENTS

1. Atrial systole = 0.11 (0.1) sec
2. Atrial diastole = 0.69 (0.7) sec

■ VENTRICULAR EVENTS

The duration of ventricular systole is 0.27 second and that of diastole is 0.53 second. Generally, ventricular systole is divided into two subdivisions and ventricular diastole is divided into five subdivisions. The subdivisions and the duration of ventricular events are:

Ventricular Systole

	Time (sec)
1. Isometric contraction	= 0.05
2. Ejection period	= 0.22
	<hr/>
	0.27

Ventricular Diastole

1. Protodiastole	= 0.04
2. Isometric relaxation	= 0.08
3. Rapid filling	= 0.11
4. Slow filling	= 0.19
5. Last rapid filling or atrial systole	= 0.11
	<hr/>
	0.53

The total duration of ventricular events is $0.27 + 0.53 = 0.8$ second.

Among the atrial events, atrial systole occurs during the last phase of ventricular diastole. Atrial diastole is not considered as a separate phase, since it coincides with whole of ventricular systole and earlier part of ventricular diastole.

■ DESCRIPTION OF ATRIAL EVENTS

For the sake of better understanding, the description of events of cardiac cycle is commenced with atrial systole.

■ ATRIAL SYSTOLE

Atrial systole is also known as second or last rapid filling phase or presystole. It is considered as the last phase of ventricular diastole. Its duration is 0.11 second.

During this period, only a small amount, i.e. 10% of blood is forced from atria into ventricles. Atrial systole is not essential for the maintenance of circulation. Many persons with atrial fibrillation survive for years, without suffering from circulatory insufficiency. However, such persons feel difficult to cope up with physical stress like exercise.

During atrial systole, the intra-atrial pressure increases. Intraventricular pressure and ventricular volume also increase but slightly.

Fourth heart sound

Contraction of atrial musculature causes production of fourth heart sound.

■ ATRIAL DIASTOLE

After atrial systole, the atrial diastole starts. Atrial diastole lasts for about 0.7 sec (accurate duration is 0.69 sec). This long atrial diastole is necessary because, this is the period during which atrial filling takes place. Right atrium receives deoxygenated blood from all over the body through superior and inferior vena cavae. Left atrium receives oxygenated blood from lungs through pulmonary veins.

Atrial Events vs Ventricular Events

Out of 0.7 sec of atrial diastole, first 0.3 sec (0.27 sec accurately) coincides with ventricular systole. So, the heart relaxes as a whole for 0.4 sec. Figure 60-1 shows the correlation between atrial and ventricular events of cardiac cycle.

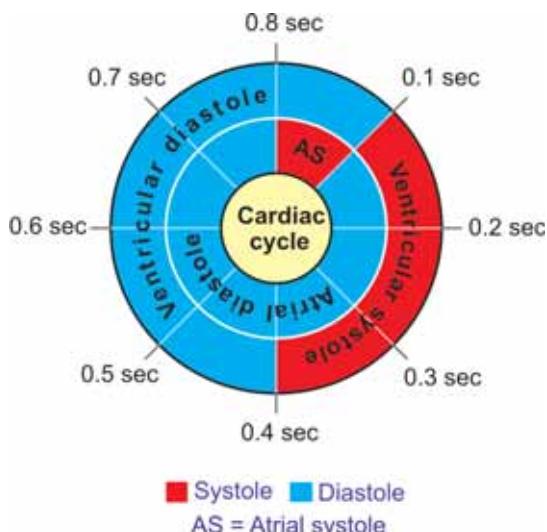


FIGURE 60-1: Atrial and ventricular events of cardiac cycle

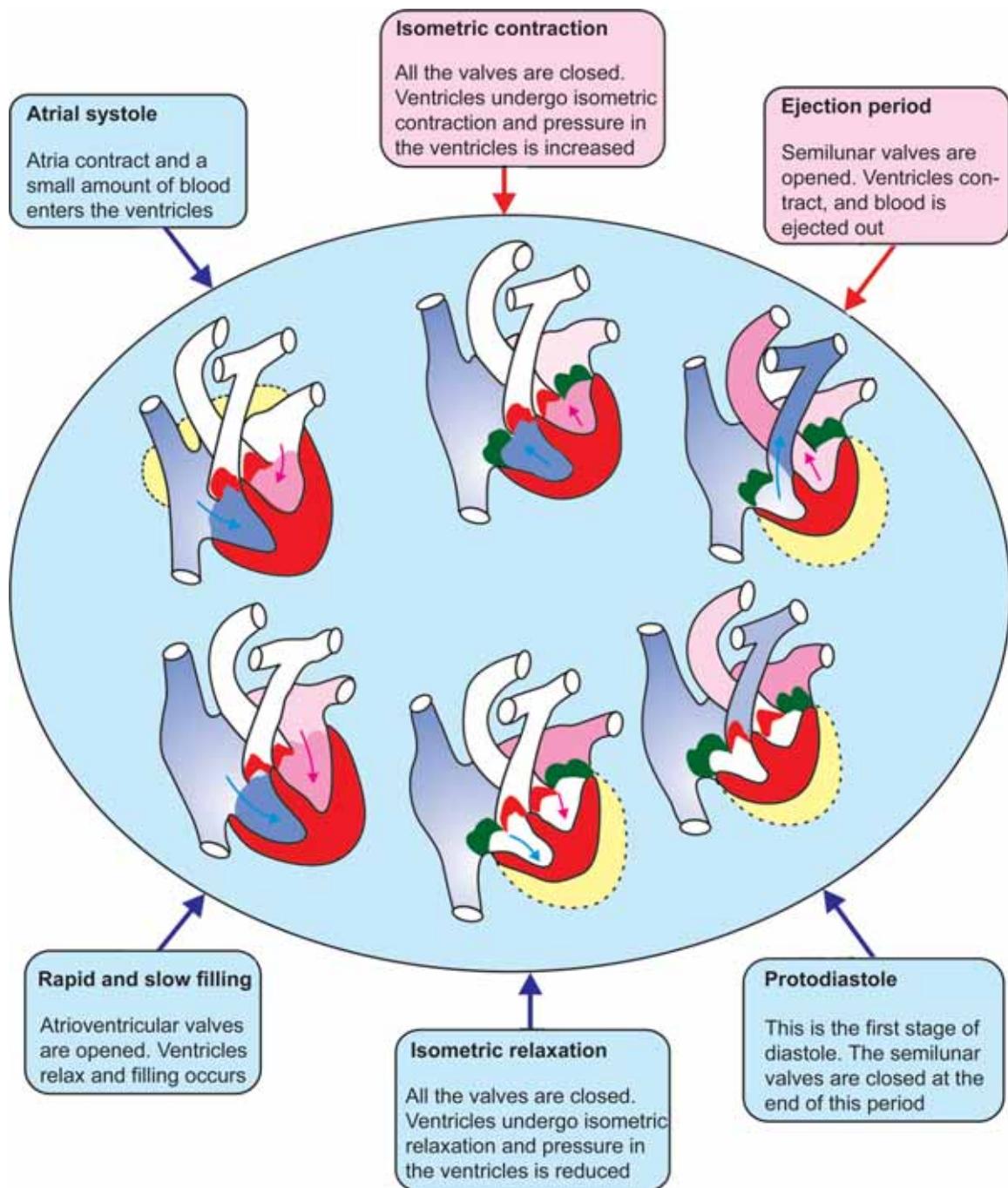
■ DESCRIPTION OF VENTRICULAR EVENTS

■ VENTRICULAR SYSTOLE

1. Isometric Contraction

Isometric contraction is the type of muscular contraction characterized by increase in tension without any change in the length of muscle fibers. Isometric contraction of ventricular muscle is also called isovolumetric contraction.

Isometric contraction period in cardiac cycle is the first phase of ventricular systole. It lasts for 0.05 second. Immediately after atrial systole, the atrioventricular valves are closed due to increase in ventricular pressure. The semilunar valves are already closed. Now, the ventricles contract as closed cavities in such a way that, there is no change in the volume of ventricular chambers or in the length of muscle fibers. Only,

**FIGURE 60-2: Events of cardiac cycle**

the tension increases in ventricular musculature leading to a sharp increase in intraventricular pressure (Fig. 60-2).

First heart sound

Closure of atrioventricular valves at the beginning of this phase produces first heart sound.

TABLE 60-1: Pressure changes during cardiac cycle

Area	Maximum pressure	Minimum pressure
Left atrium	7 to 8 mm Hg	0 to 2 mm Hg
Right atrium	5 to 6 mm Hg	0 to 2 mm Hg
Left ventricle	120 mm Hg	5 mm Hg
Right ventricle	25 mm Hg	2 to 3 mm Hg
Systemic aorta	120 mm Hg	80 mm Hg
Pulmonary artery	25 mm Hg	7 to 8 mm Hg

Significance of isometric contraction

During isometric contraction period, the ventricular pressure increases greatly (Table 60-1). When this pressure increases above the pressure in the aorta and pulmonary artery, the semilunar valves open. Thus, the pressure rise in the ventricle caused by isometric contraction is responsible for opening of semilunar valves leading to ejection of blood from the ventricles into aorta and pulmonary artery.

2. Ejection Period

Due to the opening of semilunar valves and the contraction of ventricles, the blood is ejected out of both the ventricles. Hence, this period is called ejection period. The duration of this period is 0.22 second.

Ejection period is of two stages:

1. First stage is called the rapid ejection period. Immediately after the opening of semilunar valves, a large amount of blood is rapidly ejected from both the ventricles. It lasts for 0.13 second.
2. Second stage is called the slow ejection period. During this stage, the blood is ejected slowly with much less force. The duration of this period is 0.09 second.

■ VENTRICULAR DIASTOLE

1. Protodiastole

It is the first stage of ventricular diastole hence the name protodiastole. Duration of this period is 0.04 second. During this period the pressure

in ventricles drops due to ejection of blood. At the end of this period intraventricular pressure becomes less than the pressure in aorta and pulmonary artery. This causes closure of semilunar valves. The atrioventricular valves are already closed (see above). No other change occurs in the heart during this period. Thus, protodiastole indicates only the end of systole and beginning of diastole.

Second heart sound

Closure of semilunar valves during this phase produces second heart sound.

2. Isometric Relaxation

Isometric relaxation is the type of muscular relaxation characterized by decrease in tension without any change in the length of muscle fibers. Isometric relaxation of ventricular muscle is also called isovolumetric relaxation.

During isometric relaxation period, once again all the valves of the heart are closed (Fig. 60-2). Now, both the ventricles relax as closed cavities without any change in volume or length of the muscle fiber. The intraventricular pressure decreases during this period. Duration of isometric relaxation period is 0.08 second.

Significance of isometric relaxation

During isometric relaxation period, the ventricular pressure decreases greatly. When the ventricular pressure becomes less than the pressure in the atria, the atrioventricular valves open. This leads to ventricular filling.

3. Rapid Filling

When AV valves are opened, there is a sudden rush of blood from atria into ventricles. So this period is called the first rapid filling period. Filling during this period occurs without atrial systole. About 70% of filling takes place during this phase which lasts for 0.11 second.

Third heart sound

Rushing of blood into ventricles during this phase causes production of third heart sound (Fig. 60-3).

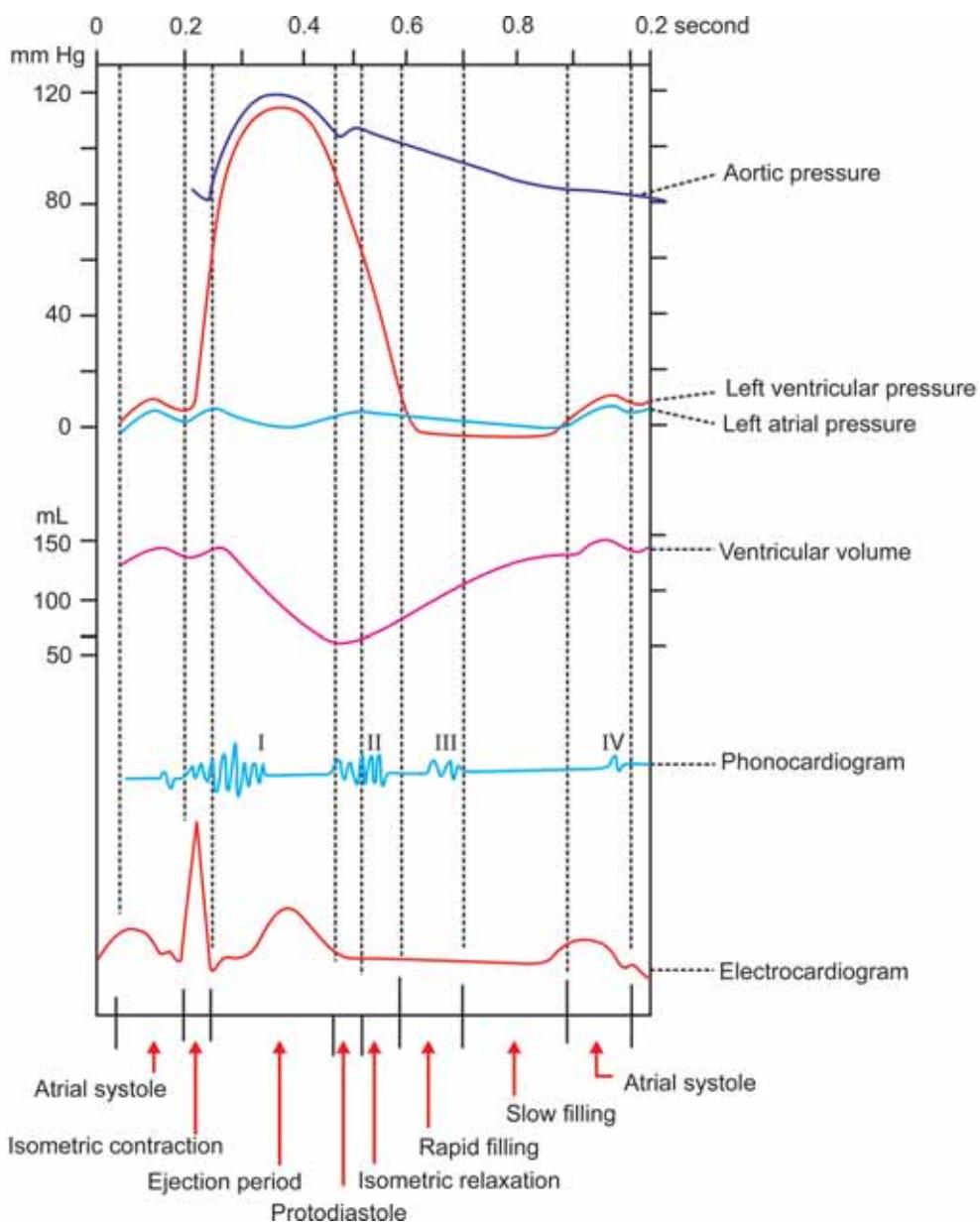


FIGURE 60-3: Comprehensive diagram showing ECG, phonocardiogram, pressure changes and volume changes during cardiac cycle

4. Slow Filling

After the sudden rush of blood, the ventricular filling becomes slow. Now, it is called the slow filling. It is also called diastasis. Filling during this phase also occurs without atrial systole. About 20% of filling occurs in this phase. Duration of slow filling phase is 0.19 second.

5. Last Rapid Filling or Atrial Systole

After slow filling period, the atria contract and push a small amount of blood into the ventricles. About 10% of ventricular filling takes place during this period.

Heart Sounds

- INTRODUCTION
- DESCRIPTION OF DIFFERENT HEART SOUNDS
 - FIRST HEART SOUND
 - SECOND HEART SOUND
 - THIRD HEART SOUND
 - FOURTH HEART SOUND
- METHODS OF STUDY OF HEART SOUNDS
- CARDIAC MURMUR

■ INTRODUCTION

Heart sounds are the sounds produced by the mechanical activities of the heart during each cardiac cycle. Generally, heart sounds are produced by:

1. Flow of blood through the chambers of the heart
2. Contraction of cardiac muscle
3. Closure of valves of the heart.

The heart sounds are heard by placing the ear over the chest or by using a stethoscope or microphone. These sounds are also recorded graphically.

Four heart sounds are produced during each cardiac cycle. The first and second heart sounds are called classical heart sounds. These sounds are more prominent and resemble the spoken words 'LUB' (or LUBB) and 'DUB' (or DUP) respectively. These two heart sounds are heard by using the stethoscope.

■ IMPORTANCE OF HEART SOUNDS

The study of heart sounds has important diagnostic value in clinical practice because the alteration in the heart sounds indicates the cardiac diseases involving the valves of the heart.

■ DESCRIPTION OF DIFFERENT HEART SOUNDS

■ FIRST HEART SOUND

First heart sound is heard during isometric contraction period and earlier part of ejection period (Table 61-1).

Causes

The major cause for first heart sound is the sudden and synchronous (simultaneous) closure of atrioventricular valves. In addition to this, the ejection of blood from ventricles into aorta and

TABLE 61-1: Heart sounds

Features	First heart sound	Second heart sound	Third heart sound	Fourth heart sound
Occurs during	Isometric contraction period and part of ejection period	Protodiastole and part of isometric relaxation	Rapid filling phase	Atrial systole
Cause	Closure of atrioventricular valves	Closure of semilunar valves	Rushing of blood into ventricle	Contraction of atrial musculature
Characteristics	Long, soft and low pitched. Resembles the word 'LUB'	Short, sharp and high pitched. Resembles the word 'DUB'	Low pitched	Inaudible sound
Duration (sec)	0.10 to 0.17	0.10 to 0.14	0.07 to 0.10	0.02 to 0.04
Frequency (cycles per sec)	25 to 45	50	1 to 6	1 to 4
Relation with ECG	Coincides with peak of R' wave	Precedes or appears 0.09 second after peak of 'T' wave	Between 'T' wave and 'P' wave	Between 'P' wave and 'Q' wave
No. of vibrations in phonocardiogram	9 to 13	4 to 6	1 to 4	1 to 2

pulmonary artery and contraction of cardiac muscles also contribute in the production of the first heart sound.

Characteristics

The first heart sound is a long, soft and low pitched sound. It resembles the spoken word 'LUBB'. The duration of this sound is 0.10 to 0.17 second. Its frequency is 25 to 45 cycles/second.

First Heart Sound and ECG

First heart sound coincides with peak of 'R' wave in ECG.

■ SECOND HEART SOUND

The second heart sound is produced at the end of protodiastolic period.

Cause

The second heart sound is produced due to the sudden and synchronous closure of the semilunar valves.

Characteristics

The second heart sound is a short, sharp and high pitched sound. It resembles the spoken word 'DUBB' (or DUP). The duration of the second heart sound is 0.10 to 0.14 seconds. Its frequency is 50 cycles/second.

Second Heart Sound and ECG

The second heart sound coincides with the 'T' wave in ECG. Sometimes, it may precede the 'T' wave or it may commence after the peak of 'T' wave.

■ THIRD HEART SOUND

The third heart sound is a low pitched sound that is produced during rapid filling period of the cardiac cycle. Usually, the third heart sound is inaudible by stethoscope and it can be heard only by using microphone.

Cause

Third heart sound is produced by the rushing of blood into ventricles during rapid filling phase.

Characteristics

Third heart sound is a short and low pitched sound. The duration of this sound is 0.07 to 0.10 second. Its frequency is 1 to 6 cycles/second.

Conditions when Third Heart Sound becomes Audible by Stethoscope

Third heart sound can be heard by stethoscope in children and athletes. Pathological conditions when third heart sound becomes loud and audible by stethoscope are aortic regurgitation, cardiac failure and cardiomyopathy with dilated ventricles.

When third heart sound is heard by stethoscope the condition is called triple heart sound. Third heart sound is usually heard best with the bell of stethoscope placed at the apex beat area when the patient is in left lateral decubitus (lying on left side) position.

Third Heart Sound and ECG

It appears between 'T' and 'P' waves of ECG.

■ FOURTH HEART SOUND

Normally the fourth heart sound is an inaudible sound. It becomes audible only in pathological conditions. It is studied only by graphical recording that is by phonocardiography. This sound is produced during atrial systole (late diastole) and it is considered as the physiologic atrial sound.

Cause

Fourth heart sound is produced by contraction of atrial musculature during atrial systole.

Characteristics

Fourth heart sound is a short and low pitched sound. The duration of this sound is 0.02 to 0.04 second. And its frequency is 1 to 4 cycles/second.

Conditions when Fourth Heart Sound becomes Audible

Fourth heart sound becomes audible by stethoscope when the ventricles become stiff. Ventricular stiffness occurs in conditions like ventricular hypertrophy, long standing hypertension and aortic stenosis. To overcome the ventricular stiffness, the atria contract forcefully producing audible fourth heart sound.

When fourth heart sound is heard by stethoscope the condition is called triple heart sound. It is usually heard best with the bell of stethoscope placed at the apex beat area when the patient is in supine or left semilateral position.

Fourth Heart Sound and ECG

Fourth heart sound coincides with the interval between the end of 'P' wave and the onset of 'Q' wave.

■ METHODS OF STUDY OF HEART SOUNDS

Heart sounds are studied by three methods:

1. By using stethoscope
2. By using microphone
3. By phonocardiogram.

■ BY USING STETHOSCOPE — AUSCULTATION AREAS

The first and second heart sounds are heard on the auscultation areas by using the stethoscope. The chest piece of the stethoscope is placed over 4 areas on the chest, which are called auscultation areas. The four auscultation areas are:

i. Mitral Area (Bicuspid Area)

It is in the left 5th intercostal space about 10 cm away from the midline (midclavicular line).

The sound produced by the closure of mitral valve (first heart sound) is heard well on this area. This area is also called apex beat area because apex beat is felt in this area. Apex beat is the thrust of the apex of the ventricles against the chest wall during systole.

ii. Tricuspid Area

This area is on the xiphoid process. The sound produced by the closure of tricuspid valve (first heart sound) is transmitted well into this area.

iii. Pulmonary Area

The pulmonary area is on the left 2nd intercostal space close to sternum. Sound produced by the closure of pulmonary valve (second heart sound) is heard well on this area.

iv. Aortic Area

This area is over the right 2nd intercostal space close to the sternum. On this area, the sound produced by the closure of aortic valve (second heart sound) is heard well.

The first heart sound is best heard in mitral and tricuspid areas. However, it is heard in other areas also but the intensity is less. Similarly, the second heart sound is best heard in pulmonary and aortic areas. It is also heard in other areas with less intensity.

■ BY MICROPHONE

A highly sensitive microphone is placed over the chest. The heart sounds are amplified by means of an amplifier and heard by using a loudspeaker. First, second and third heart sounds are heard by this method.

■ BY PHONOCARDIOGRAM

Phonocardiography is the technique used to record the heart sounds. Phonocardiogram is the graphical record of the heart sounds. It is done by placing an electronic sound transducer over the chest. This transducer is connected to a recording device like polygraph. All the four heart

sounds can be recorded in phonocardiogram. It helps to analyze the frequency of the sound waves (Fig. 60-3).

■ CARDIAC MURMUR

Cardiac murmur is the abnormal or unusual heart sound heard by stethoscope along with normal heart sounds. Cardiac murmur is also called abnormal heart sound or cardiac bruit. The abnormal sound is produced because of the change in the pattern of blood flow. Normally, blood flows in stream line through the heart and the blood vessels. However, during the abnormal conditions like valvular diseases, the blood flow becomes turbulent. It produces the cardiac murmur.

The cardiac murmur is heard by placing the chest piece of the stethoscope over the auscultatory areas. The murmur due to disease of a particular valve is heard well over the auscultatory area of that valve. Sometimes, the murmur is felt by palpation as "thrills". In some patients, the murmur is heard without any aid even at a distance of few feet away from the patient.

Valvular diseases are of two types:

1. Stenosis or narrowing of the heart valve: The blood flows rapidly with turbulence through the narrow orifice of the valve resulting in murmur.
2. Incompetence or weakening of the heart valve: When the valve becomes weak, it cannot close properly. It causes back flow of blood resulting in turbulence. This disease is also called regurgitation or valvular insufficiency.

■ CLASSIFICATION OF MURMUR

Cardiac murmur is classified into three types:

1. Systolic murmur produced during systole of the heart
2. Diastolic murmur produced during diastole of the heart
3. Continuous murmur produced continuously.

Electrocardiogram

- DEFINITIONS
- USES OF ECG
- ELECTROCARDIOGRAPHIC GRID
- ECG LEADS
- WAVES OF NORMAL ECG
- INTERVALS AND SEGMENTS OF ECG

■ DEFINITIONS

Electrocardiography

Electrocardiography is the technique by which the electrical activities of the heart are studied.

Electrocardiograph

Electrocardiograph is the instrument (ECG machine) by which the electrical activities of the heart are recorded.

Electrocardiogram

Electrocardiogram (ECG) is the record or graphical registration of electrical activities of the heart, which occur prior to the onset of mechanical activities. It is the summed electrical activity of all the cardiac muscle fibers recorded from the surface of the body.

■ USES OF ECG

ECG is useful in determining and diagnosing the following:

1. Heart rate
2. Heart rhythm

3. Abnormal electrical conduction
4. Poor blood flow to heart muscle (ischemia)
5. Heart attack
6. Coronary artery disease
7. Hypertrophy of heart chambers.

■ ELECTROCARDIOGRAPHIC GRID

The paper that is used for recording ECG is called ECG paper. The electrocardiograph or ECG machine amplifies the electrical signals produced from the heart and records these signals on a moving ECG paper. ECG grid refers to the markings (lines) on ECG paper. The ECG paper has horizontal and vertical lines at regular intervals of 1 mm. Every 5th line (5 mm) is thickened.

■ DURATION

The duration of different ECG waves is denoted by the vertical lines.

- Interval between two thick lines (5 mm)
= 0.2 second.
Interval between two thin lines (1 mm)
= 0.04 second.

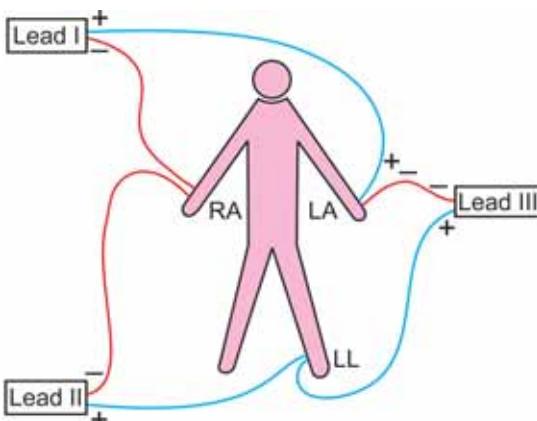


FIGURE 62-1: Position of electrodes for standard limb leads. RA = Right arm. LA = Left arm. LL = Left leg

■ AMPLITUDE

The amplitude of ECG waves is denoted by horizontal lines.

Interval between two thick lines (5 mm)

= 0.5 mV.

Interval between two thin lines (1 mm)

= 0.1 mV.

■ SPEED OF THE PAPER

The movement of paper can be adjusted in two speeds, 25 mm/second and 50 mm/second. Usually, the speed of the paper during recording is fixed at 25 mm/second. If the heart rate is very high, the speed of the paper is changed to 50 mm/second.

■ ECG LEADS

ECG is recorded by placing series of electrodes on the surface of the body. These electrodes are called ECG leads and are connected to the ECG machine.

The electrodes are fixed on the limbs. Usually right arm, left arm and left leg are chosen. The heart is said to be in the center of an imaginary equilateral triangle drawn by connecting the roots of these three limbs. This triangle is called Einthoven's triangle. The electrical potential generated from the heart appears simultaneously on the roots of these three limbs.

ECG is recorded in 12 leads which are generally classified into two categories.

- Bipolar leads
- Unipolar leads

■ BIPOLAR LIMB LEADS

Bipolar limb leads are otherwise known as standard limb leads. Two limbs are connected to obtain these leads and both the electrodes are active recording electrodes, i.e. one electrode is positive and the other one is negative (Fig. 62-1).

There are three standard limb leads:

- Limb lead I
- Limb lead II
- Limb lead III

Lead I

Lead I is obtained by connecting right arm and left arm. The right arm is connected to the negative terminal of the instrument and the left arm is connected to the positive terminal.

Lead II

Lead II is obtained by connecting right arm and left leg. The right arm is connected to the negative terminal of the instrument and the left leg is connected to the positive terminal.

Lead III

Lead III is obtained by connecting left arm and left leg. The left arm is connected to the negative terminal of the instrument and the left leg is connected to the positive terminal.

■ UNIPOLAR LEADS

Here, one electrode is active electrode and the other one is an indifferent electrode. The active electrode is positive and the indifferent electrode is serving as a composite negative electrode.

The unipolar leads are of two types:

- Unipolar limb leads
- Unipolar chest leads.

1. Unipolar Limb Leads

These leads are also called augmented limb leads. The active electrode is connected to one of the limbs. The indifferent electrode is obtained by connecting the other two limbs through a resistance.

Unipolar limb leads are of three types:

- i. aVR lead in which the active electrode is from right arm
- ii. aVL lead in which the active electrode is from left arm
- iii. aVF lead in which the active electrode is from left leg (foot).

2. Unipolar Chest Leads

Chest leads are also called precordial leads. The indifferent electrode is obtained by connecting the three limbs – left arm, left leg and right arm through a resistance of 5000 ohms. The active electrode is placed on six points over the chest (Fig. 62-2). This electrode is known as the chest electrode and the six points over the chest are called V₁, V₂, V₃, V₄, V₅, and V₆. V indicates vector, which shows the direction of flow of current.

Position of chest leads:

- V₁ : Over 4th intercostal space near right sternal margin
 V₂ : Over 4th intercostal space near left sternal margin

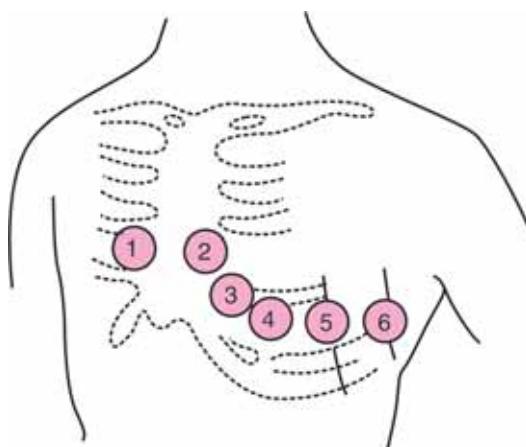


FIGURE 62-2: Position of electrodes for chest leads (V₁ to V₆)

V₃ : In between V₂ and V₄

V₄ : Over left 5th intercostal space on the mid clavicular line

V₅ : Over left 5th intercostal space on the anterior axillary line

V₆ : Over left 5th intercostal space on the mid axillary line.

■ WAVES OF NORMAL ELECTROCARDIOGRAM

A normal ECG consists of waves, complexes, intervals and segments. The waves of ECG recorded by Limb Lead II are considered as the typical waves. Normal electrocardiogram has the following waves namely P, Q, R, S and T (Table 62-1 and Figs 62-3 and 62-4)). Einthoven had named the waves of ECG starting from the middle of the English alphabets (P) instead of starting from the beginning (A).

The major complexes in ECG are:

1. 'P' wave, the atrial complex
2. 'QRS' complex, the initial ventricular complex
3. 'T' wave, the final ventricular complex.
4. 'QRST', the ventricular complex.

■ 'P' WAVE

It is a positive wave and the first wave in ECG. It is also called atrial complex.

Cause

'P' wave is a positive wave produced due to the depolarization of atrial musculature. Atrial repolarization is not recorded as a separate wave in ECG because it merges with QRS complex.

Duration

0.1 second.

Amplitude

0.1 to 0.12 mV.

■ 'QRS' Complex

It is also called the initial ventricular complex. 'Q' wave is a small negative wave. It is continued as the tall 'R' wave, which is a positive wave. 'R'

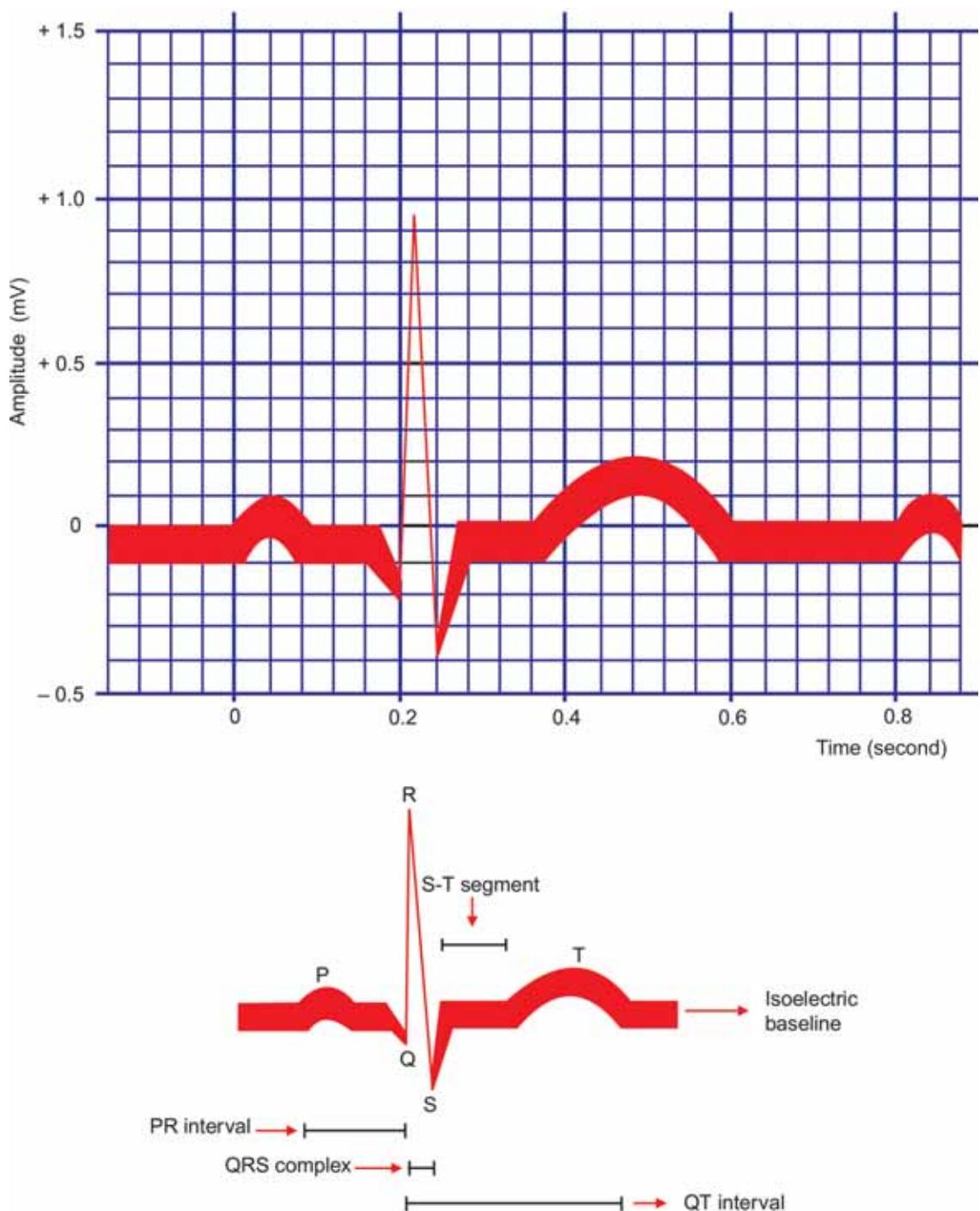


FIGURE 62-3: Waves of normal ECG

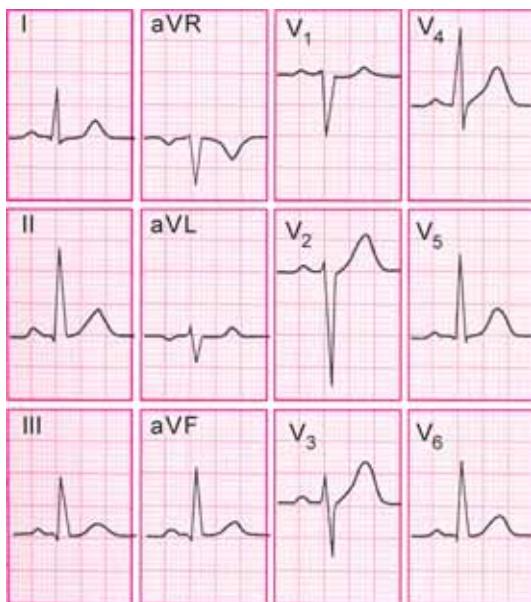


FIGURE 62-4: 12 – lead ECG
(Courtesy: Dr Atul Luthra)

wave is followed by a small negative wave, the 'S' wave.

Cause

'QRS' complex is due to depolarization of ventricular musculature. 'Q' wave is due to the depolarization of basal portion of interventricular septum. 'R' wave is due to the depolarization of apical portion of interventricular septum and apical portion of ventricular muscle. And, 'S' wave is due to the depolarization of basal portion of ventricular muscle near the atrioventricular ring.

Duration

0.08 to 0.10 second.

Amplitude

'Q' wave: 0.1 to 0.2 mV.

'R' wave: 1 mV.

'S' wave: 0.4 mV.

■ 'T' WAVE

It is the final ventricular complex and is a positive wave.

Cause

'T' wave is due to the repolarization of ventricular musculature.

Duration

0.2 second.

Amplitude

0.3 mV.

■ 'U' WAVE

'U' wave is not always seen. It is also an insignificant wave in ECG. It is supposed to be due to repolarization of papillary muscle.

■ INTERVALS AND SEGMENTS OF ECG

■ 'P-R' INTERVAL

It is the interval between the onset of 'P' wave and the onset of 'Q' wave.

'P-R' interval signifies the atrial depolarization and conduction of impulses through AV node. It shows the duration of conduction of the impulses from the SA node to ventricles through atrial muscle and AV node.

It is represented by the short isoelectric (zero voltage) period after the end of 'P' wave and onset of 'Q' wave. It denotes the time taken for the passage of depolarization within AV node.

Duration

The normal duration is 0.18 second and varies between 0.12 and 0.2 second. If it is more than 0.2 second, that signifies the delay in the conduction of impulse from SA node to the ventricles. Usually, the delay occurs in the AV node. So it is called the AV nodal delay.

■ 'Q-T' INTERVAL

It is the interval between the onset of 'Q' wave and the end of 'T' wave.

'Q-T' interval indicates the ventricular depolarization and ventricular repolarization, i.e. it signifies the electrical activity in ventricles.

TABLE 62-1: Waves of normal ECG

Wave/Segment	From - To	Cause	Duration (second)	Amplitude (mV)
P wave	— — —	Atrial depolarization	0.1	0.1 to 0.12
QRS complex	Onset of Q wave to the end of S wave	Ventricular depolarization	0.08 to 0.10	Q = 0.1 to 0.2 R = I S = 0.4
T wave	— — —	Ventricular repolarization	0.2	0.3
P-R interval	Onset of P wave to onset of Q wave	Atrial depolarization and conduction through AV node	0.18 (0.12 to 0.2)	— — —
Q-T interval	Onset of Q wave and end of T wave	Electrical activity in ventricles	0.4 to 0.42	— — —
S-T segment	End of S wave and onset of T wave	Isoelectric	0.08	— — —

Duration

Between 0.4 and 0.42 second.

■ ‘S-T’ SEGMENT

The time interval between the end of ‘S’ wave and the onset of ‘T’ wave is called ‘S-T’ segment. It is an isoelectric period.

J Point

The point where ‘S-T’ segment starts is called ‘J’ point. It is the junction between the QRS complex and ‘S-T’ segment.

Duration of ‘S-T’ Segment

0.08 second.

■ ‘R-R’ INTERVAL

‘R-R’ interval is the time interval between two consecutive ‘R’ waves. ‘R-R’ interval signifies the duration of one cardiac cycle.

Duration

The normal duration of ‘R-R’ interval is 0.8 second.

Cardiac Output

- INTRODUCTION
- DEFINITIONS AND NORMAL VALUES
 - STROKE VOLUME
 - MINUTE VOLUME
 - CARDIAC INDEX
- VARIATIONS IN CARDIAC OUTPUT
 - PHYSIOLOGICAL VARIATIONS
 - PATHOLOGICAL VARIATIONS
- DISTRIBUTION OF CARDIAC OUTPUT
- FACTORS MAINTAINING CARDIAC OUTPUT
 - VENOUS RETURN
 - FORCE OF CONTRACTION
 - HEART RATE
 - PERIPHERAL RESISTANCE
- MEASUREMENT OF CARDIAC OUTPUT

■ INTRODUCTION

Cardiac output is the amount of blood pumped from each ventricle. Usually, it refers to the left ventricular output through aorta. Cardiac output is the most important factor in cardiovascular system, because, the rate of blood flow through different parts of the body depends upon the cardiac output.

■ DEFINITIONS AND NORMAL VALUES

Usually, cardiac output is expressed in three ways:

1. Stroke volume

2. Minute volume

3. Cardiac index.

However, in routine clinical practice cardiac output refers to minute volume.

■ 1. STROKE VOLUME

It is the amount of blood pumped out by each ventricle during each beat.

Normal value: 70 mL (60 to 80 mL) when the heart rate is normal (72/minute).

■ 2. MINUTE VOLUME

Minute volume is the amount of blood pumped out by each ventricle in one minute. It is the product of stroke volume and heart rate:

Minute volume = Stroke volume × Heart rate
Normal value: 5 liters/ ventricle/ minute.

■ 3. CARDIAC INDEX

Cardiac index is the minute volume expressed in relation to square meter of body surface area. It is defined as the amount of blood pumped out per ventricle/minute/ square meter of the body surface area.

Normal value: Cardiac index = 2.8 ± 0.3 liters/ square meter of body surface area/ minute.
(In an adult, the average body surface area is 1.734 square meter and normal minute volume is 5 liters/minute).

■ VARIATIONS IN CARDIAC OUTPUT

■ PHYSIOLOGICAL VARIATIONS

1. Age: In children, cardiac output is less because of less blood volume. The cardiac index is more than in adults because of less body surface area
2. Sex: In females, cardiac output is less. Cardiac index is more than in males, because of less body surface area
3. Body build: Greater the body build, more is the cardiac output
4. Diurnal variation: Cardiac output is low in early morning and increases in day time
5. Environmental temperature: Moderate change in temperature does not affect cardiac output. Increase in temperature above 30°C raises cardiac output
6. Emotional conditions: Anxiety, apprehension and excitement increase cardiac output about 50 to 100%
7. After meals: During the first one hour after taking meals, cardiac output increases
8. Exercise: Cardiac output increases during exercise
9. High altitude: In high altitude, the cardiac output increases
10. Posture: While changing from recumbent to upright position, the cardiac output decreases
11. Pregnancy: During the later months of pregnancy, cardiac output increases by 40%

12. Sleep: Cardiac output is slightly decreased or unaltered during sleep.

■ PATHOLOGICAL VARIATIONS

Conditions when Cardiac Output Increases

1. Fever
2. Anemia
3. Hyperthyroidism.

Conditions when Cardiac Output Decreases

1. Hypothyroidism
2. Atrial fibrillation
3. Heart block
4. Congestive cardiac failure
5. Shock
6. Hemorrhage.

■ DISTRIBUTION OF CARDIAC OUTPUT

The whole amount of blood pumped out by right ventricle goes to lungs. But, the blood pumped by left ventricle is distributed to different parts of the body. The fraction of cardiac output distributed to a particular region or organ depends upon the metabolic activities of that region or organ. The distribution of blood pumped out of left ventricle is:

Liver	:	1500 mL	=	30%
Kidneys	:	1300 mL	=	26%
Skeletal muscles	:	900 mL	=	18%
Brain	:	800 mL	=	16%
Skin, bone and GI tract	:	300 mL	=	6%
Heart	:	200 mL	=	4%
Total	:	5000 mL	=	100%

The heart, which pumps the blood to all the other organs, receives the least amount of blood.

■ FACTORS MAINTAINING CARDIAC OUTPUT

Cardiac output is maintained (determined) by four factors:

1. Venous return
2. Force of contraction

3. Heart rate
4. Peripheral resistance.

■ 1. VENOUS RETURN

Venous return is the amount of blood, which is returned to the heart from different parts of the body. When it increases, the ventricular filling and cardiac output are increased. Thus, cardiac output is directly proportional to venous return provided the other factors (force of contraction, heart rate and peripheral resistance) remain constant.

Venous return in turn depends upon respiratory pump and muscle pump.

i. Respiratory Pump

Respiratory pump is the respiratory activity that helps return of the blood back to heart during inspiration. It is also called abdominothoracic pump. During inspiration, thoracic cavity expands and makes the intrathoracic pressure more negative. It increases the diameter of inferior vena cava resulting in increased venous return. At the same time, descent of diaphragm increases the intra-abdominal pressure which compresses abdominal veins and pushes the blood upward towards the heart and thereby the venous return is increased.

Respiratory pump is much stronger in forced respiration and in severe muscular exercise.

ii. Muscle Pump

Muscle pump is the muscular activity that helps return of the blood back to heart. When muscular activity increases the venous return is more.

When the skeletal muscles contract the vein located in between the muscles is compressed. The valve of the vein proximal to the contracting muscles (Fig. 63-1A) is opened and the blood is propelled towards the heart. The valve of the vein distal to the muscles is closed by the back flow of blood.

During the relaxation of the muscles (Fig. 63-1B), the valve proximal to the muscles closes and prevents the back flow of the blood. And the valve distal to the muscles opens and allows the blood to flow upwards.

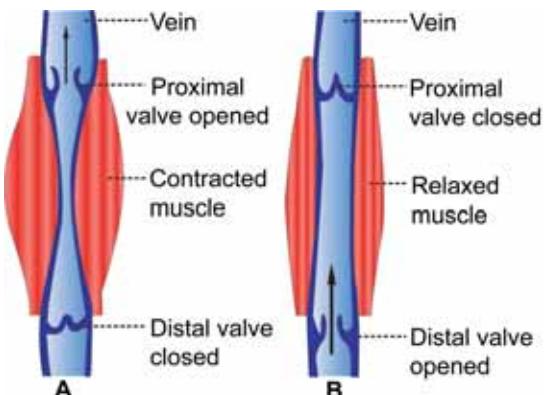


FIGURE 63-1: Mechanism of muscle pump

■ 2. FORCE OF CONTRACTION

The cardiac output is directly proportional to the force of contraction provided the other three factors remain constant. Force of contraction depends upon diastolic period and ventricular filling. Frank-Starling law of heart is applicable to this.

According to Frank-Starling law, the force of contraction of heart is directly proportional to the initial length of muscle fibers before the onset of contraction.

The force of contraction also depends upon preload and after load.

Preload

Preload is the stretching of the cardiac muscle fibers at the end of diastole just before contraction. Preload depends upon venous return and ventricular filling. During diastolic period due to the ventricular filling, the ventricular pressure increases. This causes stretching of muscle fibers resulting in increase in their length. The length of the muscle fibers determines the force of contraction and cardiac output.

The force of contraction of heart and cardiac output are directly proportional to preload.

Afterload

Afterload is the force against which the ventricles must contract and eject the blood. The force is determined by the arterial pressure. At the end of isometric contraction period, the semilunar

valves are opened and blood is ejected into the aorta and pulmonary artery. So the pressure increases in these two vessels. Now, the ventricles have to work against this pressure for further ejection. Thus, the afterload for left ventricle is determined by aortic pressure and afterload for right ventricular pressure is determined by pressure in pulmonary artery.

The force of contraction of heart and cardiac output are inversely proportional to afterload.

A. During contraction of the muscle. B. During relaxation of the muscle.

■ 3. HEART RATE

Cardiac output is directly proportional to heart rate provided the other three factors remain constant. Moderate change in heart rate does not alter the cardiac output. If there is a marked increase in heart rate, cardiac output is increased.

If there is marked decrease in heart rate, cardiac output is decreased.

■ 4. PERIPHERAL RESISTANCE

Peripheral resistance is the resistance offered to blood flow at the peripheral blood vessels. Peripheral resistance is the resistance or load against which the heart has to pump the blood. So, the cardiac output is inversely proportional to peripheral resistance.

The resistance is offered at arterioles. So, the arterioles are called resistant vessels. In the body, the maximum peripheral resistance is offered at the splanchnic region.

■ MEASUREMENT OF CARDIAC OUTPUT

The methods used to measure cardiac output are:

1. By using Fick's principle
2. Indicator (dye) dilution technique
3. Thermodilution technique
4. Ultrasonic Doppler transducer technique
5. Doppler echocardiography
6. Ballistocardiography.

1. By Using Fick's Principle

According to this principle, the amount of a substance taken up by an organ (or by the whole body) or given out in a unit of time is the product of amount of blood flowing through the organ and the arteriovenous difference of the substance across the organ.

$$\text{Amount of substance} = \frac{\text{Amount of blood taken or given}}{\text{Arteriovenous difference}} \times \text{flow}/\text{minute}$$

The Fick's principle is modified to measure the cardiac output or a part of cardiac output (amount of blood to an organ). Thus, cardiac output or the amount of blood flowing through an organ in a given unit of time is determined by the formula given below.

By using Fick's principle, cardiac output is measured in two ways:

- i. By using oxygen consumption
- ii. By using carbon dioxide given out.

Measurement of Cardiac Output by Using Oxygen Consumption

Fick's principle is used to measure cardiac output by determining the amount of oxygen consumed in the body in a given period of time and dividing this value by the arteriovenous difference across the lungs.

Oxygen consumption: To measure the amount of oxygen consumed, a respirometer is used.

Oxygen content in arterial blood: For determining the oxygen content in arterial blood, blood is collected from any artery. Oxygen content is determined by blood gas analysis.

Oxygen content in venous blood: For determining the oxygen content of venous blood, only mixed venous blood is used, since oxygen content is different in different veins. The mixed venous blood is collected from right atrium or pulmonary artery. It is done by introducing a catheter through basilar vein of forearm. Oxygen is determined from this blood by blood gas analysis.

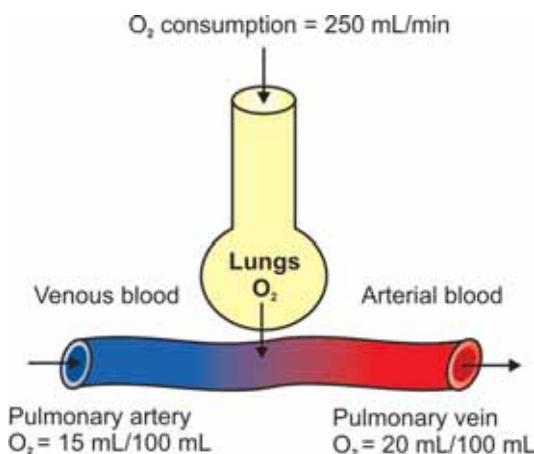


FIGURE 63-2: Oxygen consumption

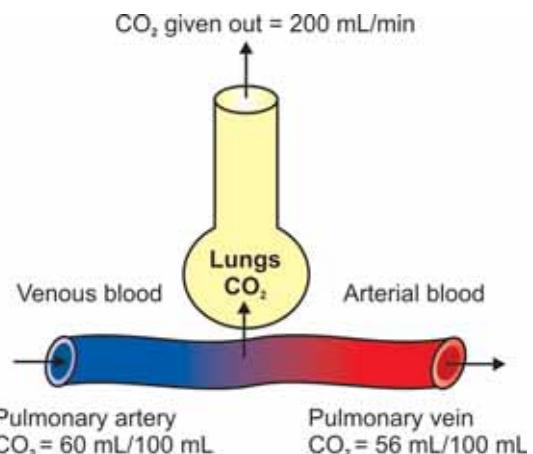


FIGURE 63-3: Carbon dioxide given out

Calculation

For example, in a subject the following data are obtained (Fig. 63-2):

$$\begin{aligned} O_2 \text{ consumed (by lungs)} &= 250 \text{ mL/minute} \\ O_2 \text{ content in arterial blood} &= 20 \text{ mL/100 mL} \\ O_2 \text{ content in venous blood} &= 15 \text{ mL/100 mL} \end{aligned}$$

$$\begin{aligned} \text{Cardiac output} &= \frac{O_2 \text{ consumed (in mL/minute)}}{\text{Arteriovenous } O_2 \text{ difference}} \\ &= \frac{250}{5/100} = \frac{250 \times 100}{5} = 5000 \text{ mL/minute} \end{aligned}$$

5 mL of oxygen is taken by 100 mL of blood while passing through the lungs. Thus, 250 mL of oxygen is taken by 5000 mL of blood. Since, cardiac output is equivalent to the amount of blood passing through pulmonary circulation, the cardiac output = 5 liters/minute.

Measurement of Cardiac Output by Using Carbon Dioxide

The cardiac output is also measured by knowing the arteriovenous difference of carbon dioxide and amount of carbon dioxide given out from lungs (Fig. 63-3).

Calculation

For example, in a subject

$$CO_2 \text{ removed by lungs} = 200 \text{ mL/minute}$$

$$\begin{aligned} CO_2 \text{ content in arterial blood} &= 56 \text{ mL/100 mL} \\ CO_2 \text{ content in venous blood} &= 60 \text{ mL/100 mL} \end{aligned}$$

$$\text{Cardiac output} = \frac{CO_2 \text{ given out (in mL/minute)}}{\text{Arteriovenous } CO_2 \text{ difference}}$$

$$\begin{aligned} \text{Cardiac output} &= \frac{200}{60-56 \text{ mL}/100 \text{ mL}} \\ &= \frac{200 \times 400}{4} \\ &= 5000 \text{ mL} = 5 \text{ liters/minute} \end{aligned}$$

Since, cardiac output is equal to amount of blood passing through lungs (pulmonary circulation), the cardiac output = 5 liters/minute.

2. Indicator (Dye) Dilution Method

The indicator dilution technique is described in detail in Chapter 5. Marker substance used to measure cardiac output is lithium chloride.

3. Thermodilution Technique

Cardiac output can also be measured by thermodilution technique or thermal indicator method. This method is the modified indicator dilution method. It is the popular method to measure cardiac output.

In this method, a known volume of cold sterile solution is injected into the right atrium by using a catheter. Cardiac output is measured by determining the resultant change in the blood temperature in pulmonary artery. For this purpose, two thermistors (temperature transducers) are used. One of them is placed in the inferior vena cava and the second one is placed in pulmonary artery.

4. Esophageal Doppler Transducer Technique

This technique involves insertion of a flexible probe into mid thoracic part of esophagus. A pulse wave ultrasonic Doppler transducer is fixed at the tip of the probe. This transducer calculates the velocity of blood flow in descending aorta (refer ultrasonic Doppler flow meter for details). The diameter of aorta is determined by echocardiography (see below). Cardiac output is calculated by using the values of velocity of blood flow and diameter of aorta.

5. Doppler Echocardiography

Doppler echocardiography is a method for detecting the direction and velocity of moving blood within the heart. This is also a popular method to measure cardiac output.

6. Ballistocardiographic Method

Ballistocardiography is the technique to record the movements of the body caused by ballistic recoil associated with contraction of heart and ejection of blood. It is based on Newton's third law of motion (for every action there is an equal and opposite reaction). When heart pumps blood into aorta and pulmonary artery, a recoiling force is exerted against heart and the body. It is similar to that of ballistic recoil when a bullet is fired from a rifle.

Pulsations due to this ballistic recoil can be recorded graphically by making the subject to lie on a suspended bed movable in the long axis of the body. The cardiac output is determined by analyzing the graph obtained.

Heart Rate

- HEART RATE
 - NORMAL HEART RATE
 - TACHYCARDIA
 - BRADYCARDIA
- REGULATION OF HEART RATE
- VASOMOTOR CENTER
 - VASOCONSTRICTOR AREA
 - VASODILATOR AREA
 - SENSORY AREA
- MOTOR (EFFERENT) NERVE FIBERS TO HEART
 - PARASYMPATHETIC NERVE FIBERS
 - SYMPATHETIC NERVE FIBERS
- SENSORY (AFFERENT) NERVE FIBERS FROM HEART
- FACTORS AFFECTING VASOMOTOR CENTER – REGULATION OF VAGAL TONE
 - IMPULSES FROM HIGHER CENTERS
 - IMPULSES FROM RESPIRATORY CENTERS
 - IMPULSES FROM BARORECEPTORS
 - IMPULSES FROM CHEMORECEPTORS
 - IMPULSES FROM RIGHT ATRIUM
 - IMPULSES FROM OTHER AFFERENT NERVES

■ HEART RATE

■ NORMAL HEART RATE

Normal heart rate is 72/minute. It ranges between 60 and 80 per minute.

■ TACHYCARDIA

Tachycardia is the increase in the heart rate above 100/minute.

Physiological conditions when tachycardia occurs are:

1. Childhood

2. Exercise
3. Pregnancy
4. Emotional conditions such as anxiety.

Pathological conditions when tachycardia occurs are:

1. Fever
2. Anemia
3. Hypoxia
4. Hyperthyroidism
5. Hypersecretion of catecholamines
6. Cardiomyopathy
7. Valvular heart diseases.

■ BRADYCARDIA

Bradycardia is the decrease in the heart rate below 60/minute.

Physiological conditions when bradycardia occurs are:

1. Sleep
2. Athletic heart.

Pathological conditions when bradycardia occurs are:

1. Hypothermia
2. Hypothyroidism
3. Heart attack
4. Congenital heart disease
5. Degenerative process of aging
6. Obstructive jaundice
7. Increased intracranial pressure.

■ REGULATION OF HEART RATE

Heart rate is maintained within normal range constantly. It is subjected for variation during normal physiological conditions such as exercise, emotion, etc. However, under physiological conditions, the altered heart rate is quickly brought back to normal. Heart rate is regulated by the nervous mechanism which consists of three components:

- I. Vasomotor center
- II. Motor (efferent) nerve fibers to the heart
- III. Sensory (afferent) nerve fibers from the heart.

■ VASOMOTOR CENTER – CARDIAC CENTER

Vasomotor center is the nervous center that regulates the heart rate. It also regulates the blood pressure. Earlier it was called the cardiac center.

Vasomotor center is bilaterally situated in the reticular formation of medulla oblongata and the lower part of the pons.

Vasomotor center has three areas:

1. Vasoconstrictor area
2. Vasodilator area
3. Sensory area.

■ VASOCONSTRICCTOR AREA – CARDIOACCELERATOR CENTER

Situation

It is situated in the reticular formation of medulla in the floor of the IV ventricle and it forms the lateral portion of vasomotor center. It is otherwise known as pressor area or cardioaccelerator center.

Function

This area increases the heart rate by sending accelerator impulses to heart through sympathetic nerves. It also causes constriction of blood vessels.

■ VASODILATOR AREA – CARDIOINHIBITORY CENTER

Situation

It is also situated in the reticular formation of medulla oblongata in the floor of IV ventricle. It forms the medial portion of vasomotor center. It is also called depressor area or cardioinhibitory center.

Function

This area decreases the heart rate by sending inhibitory impulses to the heart through vagus nerve. It also causes dilatation of blood vessels.

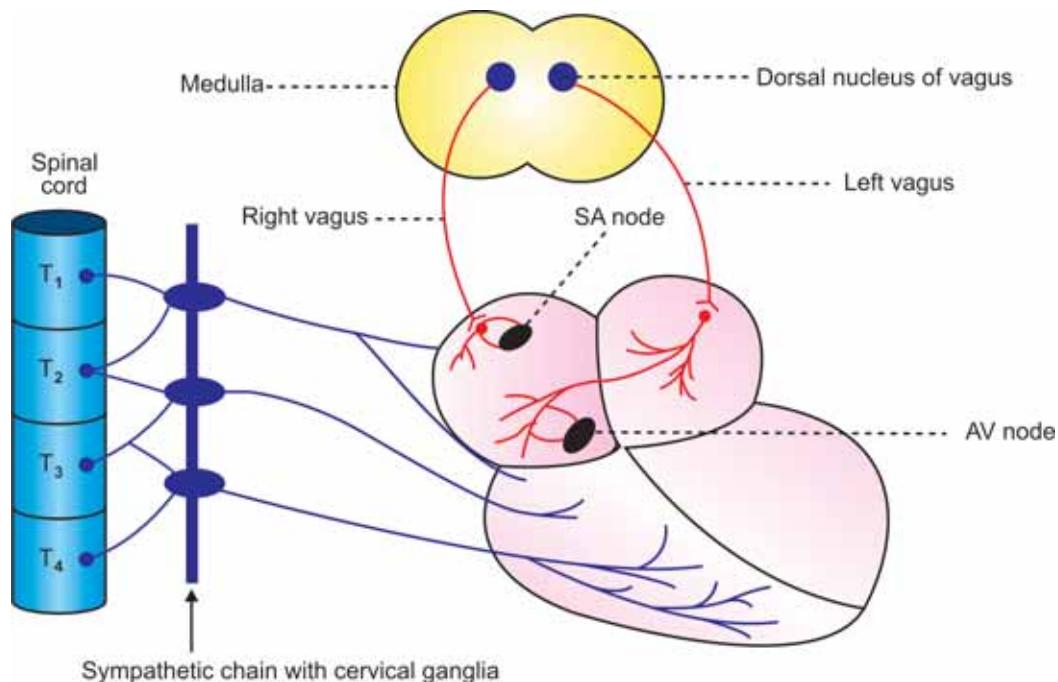


FIGURE 64-1: Nerve supply to heart

■ SENSORY AREA

It is in the posterior part of vasomotor center, which lies in nucleus of tractus solitarius in medulla and pons. This area receives sensory impulse via glossopharyngeal nerve and vagus nerve from periphery, particularly, from the baroreceptors. In turn, this area controls the vasoconstrictor and vasodilator areas.

■ MOTOR (EFFECTER) NERVE FIBERS TO HEART

Heart receives efferent nerves from both the divisions of autonomic nervous system. Parasympathetic fibers arise from the medulla oblongata and pass through vagus nerve. The sympathetic fibers arise from upper thoracic (T_1 to T_4) segments of spinal cord (Fig. 64-1).

■ PARASYMPATHETIC NERVE FIBERS

Origin

The parasympathetic nerve fibers supplying heart arise from the dorsal nucleus of vagus

situated in the floor of the fourth ventricle in medulla oblongata.

Distribution

The preganglionic parasympathetic nerve fibers from dorsal nucleus of vagus reach the heart and terminate on postganglionic neurons. The postganglionic fibers from these neurons innervate heart muscle. Most of the fibers from right vagus terminate in SA node. Remaining fibers supply the atrial muscles and AV node. Most of the fibers from left vagus supply AV node and some fibers supply the atrial muscle and SA node. Ventricles do not receive the vagus nerve supply.

Function

The vagus nerve is cardioinhibitory in function and carries inhibitory impulses from vasodilator area to the heart.

Vagal Tone

Vagal tone is the continuous stream of inhibitory impulses arising from vasodilator area. Heart

rate is kept under control because of vagal tone. The impulses from vasodilator area pass through vagus nerve, reach the heart and exert inhibitory effect on heart. The heart rate is inversely proportional to vagal tone.

■ SYMPATHETIC NERVE FIBERS

Origin

The preganglionic fibers of the sympathetic nerves to heart arise from lateral grey horns of the first 4 thoracic (T_1 to T_4) segments of the spinal cord.

Course and Distribution

The preganglionic fibers reach the superior, middle and inferior cervical sympathetic ganglia situated in the sympathetic chain. The inferior cervical sympathetic ganglion fuses with first thoracic sympathetic ganglion forming stellate ganglion.

From these ganglia, the postganglionic fibers arise. The postganglionic fibers form superior, middle and inferior cervical sympathetic nerves. The superior sympathetic nerve innervates larger arteries and base of the heart. The middle one supplies the rest of the heart. The inferior nerve serves as sensory (afferent) nerve from the heart.

Function

The sympathetic nerves are cardioaccelerator in function and carry cardioaccelerator impulses from vasoconstrictor area to the heart.

Sympathetic Tone

Sympathetic tone or cardioaccelerator tone is the continuous stream of impulses produced by the vasoconstrictor area. The impulses pass through sympathetic nerves and accelerate the heart rate.

Under normal conditions, the vagal tone is dominant over sympathetic tone. Whenever vagal tone is reduced or abolished, the sympathetic tone becomes powerful.

■ SENSORY (AFFERENT) NERVE FIBERS FROM HEART

The afferent (sensory) nerve fibers from the heart pass through the inferior cervical sympathetic nerve. These nerve fibers carry sensations of stretch and pain from the heart to the brain via spinal cord.

■ FACTORS AFFECTING VASOMOTOR CENTER – REGULATION OF VAGAL TONE

The vasomotor center regulates the cardiac activity by receiving impulses from different sources in the body. After receiving the impulses from different sources, the vasodilator area alters the vagal tone and modulates the activities of the heart. The various sources from which the impulses reach the vasomotor center are:

■ 1. IMPULSES FROM HIGHER CENTERS

The vasomotor center is mainly controlled by the impulses from the higher centers in the brain. The higher centers are the following:

Cerebral Cortex

Area 13 in cerebral cortex is concerned with emotional reactions of the body. During emotional conditions, this area sends inhibitory impulses to the vasodilator area. This causes reduction in vagal tone leading to cardioacceleration.

Hypothalamus

Hypothalamus influences the heart rate via vasomotor center. Stimulation of posterior and lateral hypothalamic nuclei causes tachycardia. Stimulation of preoptic and anterior nuclei causes bradycardia.

■ 2. IMPULSES FROM RESPIRATORY CENTERS

In forced breathing, heart rate increases during inspiration and decreases during expiration. This

variation is called respiratory sinus arrhythmia. This is common in some children and in some adults even during quiet breathing.

■ 3. IMPULSES FROM BARORECEPTORS – MAREY'S REFLEX

Baroreceptors

The baroreceptors or pressoreceptors are the receptors, which give response to change in blood pressure.

Situation

Baroreceptors are of two types, carotid baroreceptors and aortic baroreceptors. Carotid baroreceptors are situated in the carotid sinus, which is present in the wall of the internal carotid artery near the bifurcation of common carotid artery. The aortic baroreceptors are situated in the wall of the arch of aorta.

Nerve Supply

Carotid baroreceptors are supplied by Hering's nerve, which is the branch of glossopharyngeal (IX cranial) nerve. The aortic baroreceptors are supplied by aortic nerve, which is a branch of vagus (X cranial) nerve (Fig. 64-2). The nerve fibers from the baroreceptors reach the nucleus of tractus solitarius situated adjacent to vaso-motor center.

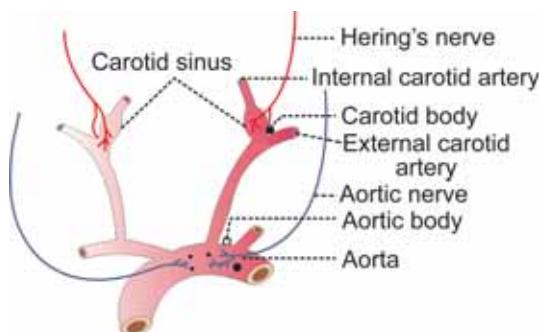


FIGURE 64-2: Nerve supply to baroreceptors and chemoreceptors

Function – Marey's Reflex

The baroreceptors regulate the heart rate through a reflex called Marey's reflex. The stimulus for this reflex is increase in blood pressure.

Marey's reflex is a cardioinhibitory reflex that decreases heart rate when blood pressure increases. Whenever, the blood pressure increases, the aortic and carotid baroreceptors are stimulated and stimulatory impulses are sent to nucleus of tractus solitarius via Hering's nerve and aortic nerve (afferent nerves). Now, the nucleus of tractus solitarius stimulates the vasodilator area, which in turn increases the vagal tone leading to decrease in heart rate (Fig. 64-3).

When pressure is less, the baroreceptors are not stimulated. So, no impulses go to the nucleus of tractus solitarius and heart rate is not decreased.

Thus, the heart rate is inversely proportional to blood pressure.

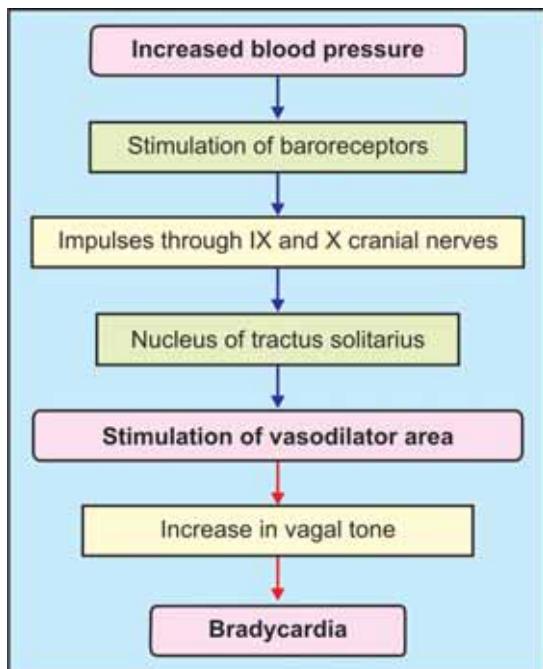


FIGURE 64-3: Marey's (cardioinhibitory) reflex

Marey's law

According to Marey's law, the pulse rate (which represents heart rate) is inversely proportional to blood pressure.

The baroreceptors produce the Marey's reflex only during resting conditions. So, in many conditions such as exercise, there is an increase in both blood pressure and heart rate.

■ 4. IMPULSES FROM CHEMORECEPTORS

Chemoreceptors

Chemoreceptors are receptors giving response to change in chemical constituents of blood, particularly oxygen, carbon dioxide and hydrogen ion concentration.

Situation

Peripheral chemoreceptors are situated in the carotid body and aortic body adjacent to baroreceptors.

Nerve Supply

The chemoreceptors in the carotid body are supplied by Hering's nerve, which is the branch of glossopharyngeal nerve and those in aortic body are supplied by the aortic branch of vagus nerve (Fig. 64-2).

Function

Whenever there is hypoxia, hypercapnia, and increased hydrogen ions concentration in the blood, the chemoreceptors are stimulated and inhibitory impulses are sent to vasodilator area. Vagal tone decreases and heart rate increases. The chemoreceptors play a major role in maintaining respiration than the heart rate.

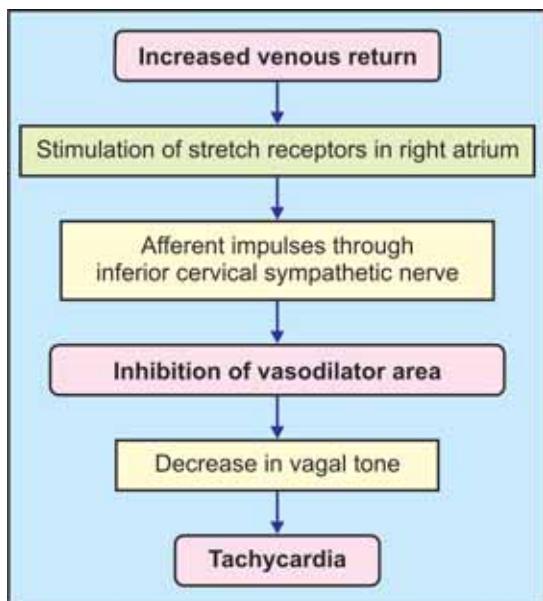


FIGURE 64-4: Bainbridge (cardioaccelerator) reflex

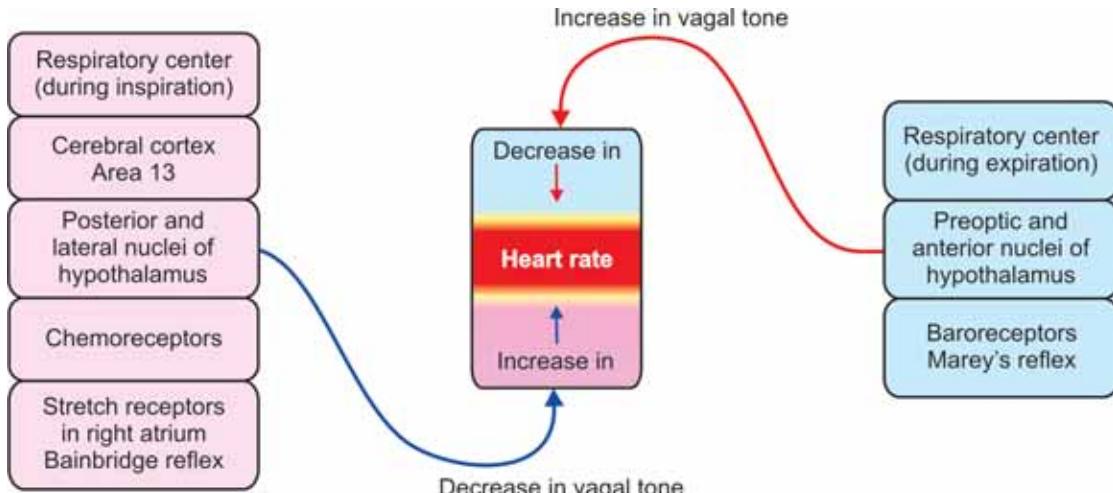


FIGURE 64-5: Factors regulating vagal tone and heart rate

Sinoaortic Mechanism and Buffer Nerves

Sinoaortic mechanism is the mechanism of baroreceptors and chemoreceptors in carotid and aortic regions that regulates heart rate, blood pressure and respiration. The nerves from these receptors are called buffer nerves.

■ 5. IMPULSES FROM RIGHT ATRIUM – BAINBRIDGE REFLEX

Bainbridge reflex is a cardioaccelerator reflex that increases the heart rate when venous return is increased. Since, this reflex arises from right atrium, it is also called right atrial reflex.

There are some stretch receptors in the wall of right atrium. When venous return increases, the right atrium is distended. The right atrial distention stimulates the stretch receptors. The stretch receptors, in turn, send inhibitory

impulses through inferior cervical sympathetic nerve to vasodilator area of vasomotor center. The vasodilator area is inhibited resulting in decrease in vagal tone and increase in heart rate (Fig. 64-4).

■ 6. IMPULSES FROM OTHER AFFERENT NERVES

Stimulation of sensory nerves produces varying effects.

Examples:

- i. Stimulation of receptors in nasal mucous membrane causes bradycardia. The impulses from nasal mucous membrane pass via the branches of V cranial nerve and decrease the heart rate.
- ii. Most of the painful stimuli cause tachycardia and some cause bradycardia. The impulses are transmitted via pain nerve fibers (Fig. 64-5).

Arterial Blood Pressure

- DEFINITIONS AND NORMAL VALUES
- VARIATIONS
- DETERMINANTS OF ARTERIAL BLOOD PRESSURE
- REGULATION OF ARTERIAL BLOOD PRESSURE
- NERVOUS MECHANISM
- RENAL MECHANISM
- HORMONAL MECHANISM
- LOCAL MECHANISM
- APPLIED PHYSIOLOGY

■ DEFINITIONS AND NORMAL VALUES

Arterial blood pressure is defined as the lateral pressure exerted by the column of blood on the wall of arteries. Arterial blood pressure is expressed in four different terms:

1. Systolic blood pressure
2. Diastolic blood pressure
3. Pulse pressure
4. Mean arterial blood pressure.

■ 1. SYSTOLIC BLOOD PRESSURE

Systolic blood pressure (systolic pressure) is defined as the maximum pressure exerted in the arteries during systole of the heart. The normal systolic pressure is 120 mm Hg. It ranges between 110 and 140 mm Hg.

■ 2. DIASTOLIC BLOOD PRESSURE

Diastolic blood pressure (diastolic pressure) is defined as the minimum pressure in the arteries

during diastole of the heart. The normal diastolic pressure is 80 mm Hg. It varies between 60 and 80 mm Hg.

■ 3. PULSE PRESSURE

Pulse pressure is the difference between the systolic pressure and diastolic pressure. Normally, it is 40 mm Hg (120 to 80).

■ 4. MEAN ARTERIAL BLOOD PRESSURE

It is the average pressure existing in the arteries. It is not the arithmetic mean of systolic and diastolic pressures. It is the diastolic pressure plus one-third of pulse pressure. To determine the mean pressure, the diastolic pressure is considered than the systolic pressure because the diastolic period of cardiac cycle is longer (0.53 second) than the systolic period (0.27 second). Normal mean arterial pressure is 93 mm Hg ($80 + 13 = 93$).

VARIATIONS

PHYSIOLOGICAL VARIATIONS

1. Age

Arterial blood pressure increases as age advances.

The systolic pressure in different age:

In newborn	:	40 mm Hg
After 15 days	:	70 mm Hg
After 1 month	:	90 mm Hg
At puberty	:	20 mm Hg
At 50 years	:	140 mm Hg
At 70 years	:	160 mm Hg
At 80 years	:	180 mm Hg

The diastolic pressure in different age:

At puberty	:	80 mm Hg
At 50 years	:	85 mm Hg
At 70 years	:	90 mm Hg
At 80 years	:	95 mm Hg

2. Sex

In females, up to the period of menopause, the arterial pressure is about 5 mm Hg less than in males of same age. After menopause, the pressure in females becomes equal to that in males of same age.

3. Body Built

The pressure is more in obese persons than in lean persons.

4. Diurnal Variation

In early morning, the pressure is slightly low. It gradually increases and reaches the maximum at noon. It becomes low in evening.

5. After Meals

The arterial blood pressure is increased for few hours after meals due to increase in cardiac output.

6. During Sleep

Usually, the pressure is reduced up to 15 to 20 mm Hg during deep sleep. However, it

increases slightly during sleep associated with dreams.

7. Emotional Conditions

During excitement or anxiety, the blood pressure is increased due to release of adrenaline.

8. After Exercise

After moderate exercise, systolic pressure increases by 20 to 30 mm Hg above the basal level due to increase in force of contraction and stroke volume. Normally, diastolic pressure is not affected by moderate exercise. It is because the diastolic pressure depends upon peripheral resistance, which is not altered by moderate exercise.

After severe muscular exercise, the systolic pressure rises by 40 to 50 mm Hg above the basal level. But, the diastolic pressure reduces because the peripheral resistance decreases in severe muscular exercise. More details are given in Chapter 71.

PATHOLOGICAL VARIATIONS

Pathological variations of arterial blood pressure are hypertension and hypotension. Refer applied physiology of this chapter for details.

DETERMINANTS OF ARTERIAL BLOOD PRESSURE – FACTORS MAINTAINING ARTERIAL BLOOD PRESSURE

Some factors are necessary for the maintenance of normal blood pressure, which are called local factors, mechanical factors or determinants of blood pressure. These factors are divided into two types:

- Central factors which are pertaining to the heart:
 1. Cardiac output
 2. Heart rate
- Peripheral factors which are pertaining to blood and blood vessels:
 1. Peripheral resistance
 2. Blood volume
 3. Venous return

4. Elasticity of blood vessels
5. Velocity of blood flow
6. Diameter of blood vessels
7. Viscosity of blood.

■ CENTRAL FACTORS

1. Cardiac Output

Systolic pressure is directly proportional to cardiac output. Whenever the cardiac output increases, the systolic pressure is increased and, when cardiac output is less, the systolic pressure is reduced. The cardiac output increases in muscular exercise, emotional conditions, etc. So in these conditions the systolic pressure is increased. In conditions like myocardial infarction, the cardiac output decreases resulting in fall in systolic pressure.

2. Heart Rate

Moderate changes in heart rate do not affect arterial blood pressure much. However, marked alteration in the heart rate affects the blood pressure by altering cardiac output (Chapter 63).

■ PERIPHERAL FACTORS

1. Peripheral Resistance

It is the resistance offered to the blood flow at the periphery. The resistance is offered at arterioles, which are called the resistant vessels. This is the important factor, which maintains diastolic pressure. The diastolic pressure is directly proportional to peripheral resistance. When peripheral resistance increases, diastolic pressure is increased and when peripheral resistance decreases, the diastolic pressure is decreased.

2. Blood Volume

Blood pressure is directly proportional to blood volume. Blood volume maintains the blood pressure through the venous return and cardiac output. If the blood volume increases, there is increase in venous return and cardiac output resulting in elevation of blood pressure.

3. Venous Return

Blood pressure is directly proportional to venous return. When venous return increases, there is increase in ventricular filling and cardiac output resulting in elevation of arterial blood pressure.

4. Elasticity of Blood Vessels

Blood pressure is inversely proportional to the elasticity of blood vessels. Due to the elastic property, the blood vessels are distensible and are able to maintain the pressure. When the elastic property is lost, the blood vessels become rigid (arteriosclerosis) and pressure increases as in old age. The deposition of cholesterol, fatty acids and calcium ions cause rigidity of blood vessels (atherosclerosis) leading to increased blood pressure.

5. Velocity of Blood Flow

The pressure in a blood vessel is directly proportional to the velocity of blood flow. If the velocity of the blood flow increases, the resistance is increased. So, the pressure is increased.

6. Diameter of Blood Vessels

The arterial blood pressure is inversely proportional to diameter of the blood vessel. If the diameter decreases, the peripheral resistance increases leading to increase in the pressure.

7. Viscosity of Blood

Arterial blood pressure is directly proportional to the viscosity of blood. When viscosity of blood increases, the frictional resistance is increased and this increases the pressure.

■ REGULATION OF ARTERIAL BLOOD PRESSURE

Arterial blood pressure varies even under physiological conditions. However, immediately it is brought back to normal level because of the presence of well organized regulatory mechanisms in the body. Body has four such regulatory

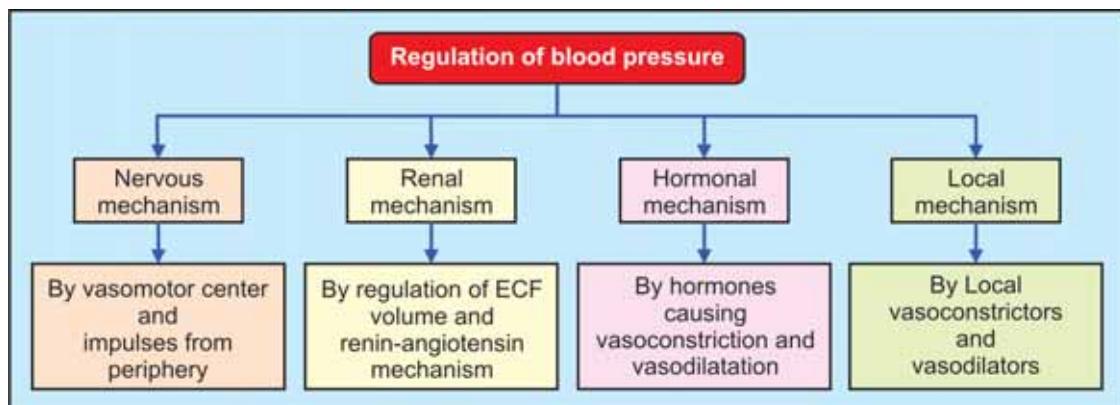


FIGURE 65-1: Regulation of blood pressure

mechanisms to maintain the blood pressure within normal limits (Fig. 65-1):

- I. Nervous mechanism or short-term regulatory mechanism
- II. Renal mechanism or long-term regulatory mechanism
- III. Hormonal mechanism
- IV. Local mechanism.

■ NERVOUS MECHANISM FOR REGULATION OF BLOOD PRESSURE – SHORT-TERM REGULATION

The nervous regulation is rapid among all the mechanisms involved in the regulation of arterial blood pressure. When the blood pressure alters, the nervous system brings the pressure back to normal within few minutes. Although nervous mechanism is quick in action, it operates only for a short period and then it adapts to the new pressure. Hence, it is called short-term regulation. The nervous mechanism regulating the arterial blood pressure operates through the vasomotor system.

■ VASOMOTOR SYSTEM

The vasomotor system includes three components:

1. Vasomotor center
2. Vasoconstrictor fibers
3. Vasodilator fibers.

1. Vasomotor Center

Vasomotor center is bilaterally situated in the reticular formation of medulla oblongata and the lower part of the pons.

Vasomotor center consists of three areas:

- i. Vasoconstrictor area
- ii. Vasodilator area
- iii. Sensory area.

i. Vasoconstrictor area

It is also called the pressor area. It forms the lateral portion of vasomotor center. Vasoconstrictor area sends impulses to blood vessels through sympathetic vasoconstrictor fibers. So, the stimulation of this area causes vasoconstriction and rise in arterial blood pressure. This area is also concerned with acceleration of heart rate (Chapter 64).

ii. Vasodilator area

It is otherwise called depressor area. It forms the medial portion of vasomotor center. This area suppresses the vasoconstrictor area and causes vasodilatation. It is also concerned with cardioinhibition (Chapter 64).

iii. Sensory area

It is in the nucleus of tractus solitarius, which is situated in the posterolateral part of medulla and pons. This area receives sensory impulses via

glossopharyngeal and vagal nerves from the periphery, particularly, from the baroreceptors. Sensory area in turn, controls the vasoconstrictor and vasodilator areas.

2. Vasoconstrictor Fibers

The vasoconstrictor fibers belong to the sympathetic division of autonomic nervous system. These fibers cause vasoconstriction by the release of the neurotransmitter substance, noradrenaline.

Vasomotor tone

Vasomotor tone is the continuous discharge of impulses from vasoconstrictor center through the vasoconstrictor fibers. The vasomotor tone plays an important role in regulating the pressure by producing a constant partial state of constriction of the blood vessels. Thus, the arterial blood pressure is directly proportional to the vasomotor tone. The vasomotor tone is also called sympathetic vasoconstrictor tone or sympathetic tone.

3. Vasodilator Fibers

Vasodilator fibers are of three types:

- i. Parasympathetic vasodilator fibers
- ii. Sympathetic vasodilator fibers
- iii. Antidromic vasodilator fibers.

i. Parasympathetic vasodilator fibers

These vasodilator fibers cause dilatation of blood vessels by releasing the chemical mediator, acetylcholine.

ii. Sympathetic vasodilator fibers

Some of the sympathetic fibers cause vasodilation in certain areas by secreting acetylcholine. Such fibers are called sympathetic vasodilator or sympathetic cholinergic fibers. The sympathetic cholinergic fibers, which supply the blood vessels of skeletal muscles are important in increasing the blood flow to muscles by vasodilatation during conditions like exercise.

iii. Antidromic vasodilator fibers

Normally, the impulses produced by a cutaneous receptor (like pain receptor) pass through sensory nerve fibers. But, some of these impulses pass through the other branches of the axon in the opposite direction and reach the blood vessels supplied by these branches. These impulses now dilate the blood vessels. It is called the antidromic or axon reflex. And, the nerve fibers are called antidromic vasodilator fibers.

■ MECHANISM OF ACTION OF VASOMOTOR CENTER IN THE REGULATION OF BLOOD PRESSURE

The vasomotor center regulates the arterial blood pressure by causing vasoconstriction or vasodilatation. However, its actions depend upon the impulses it receives from other structures such as baroreceptors, chemoreceptors, higher centers and respiratory centers. Among these structures, baroreceptors and chemoreceptors play a major role in the short-term regulation of blood pressure.

1. Baroreceptor Mechanism

The baroreceptors are the receptors, which give response to change in blood pressure.

Refer Chapter 64 for details of baroreceptors.

Functions

When blood pressure increases: When arterial blood pressure rises rapidly, the baroreceptors are activated and send stimulatory impulses to nucleus of tractus solitarius through glossopharyngeal and vagus nerves. Now, the nucleus of tractus solitarius acts on both vasoconstrictor area and vasodilator areas of vasomotor center. It inhibits the vasoconstrictor area and excites the vasodilator area.

The inhibition of vasoconstrictor area reduces vasomotor tone. Reduction in vasomotor tone causes vasodilatation resulting in decreased peripheral resistance. The simultaneous

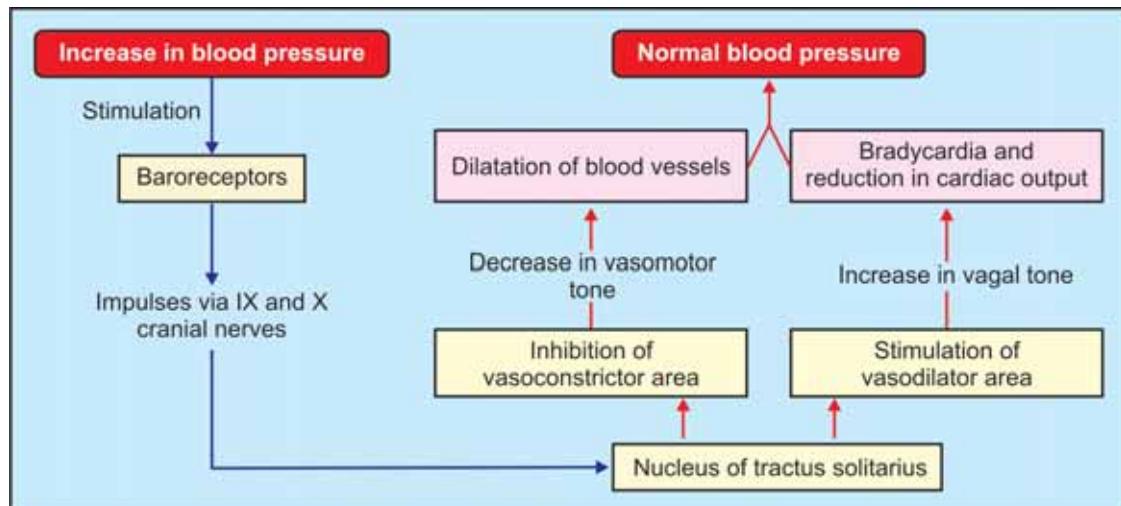


FIGURE 65-2: Regulation of blood pressure by baroreceptor mechanism

excitation of vasodilator center increases vagal tone (Chapter 64). This decreases the rate and force of contraction of heart leading to reduction in cardiac output. These two factors, i.e. decreased peripheral resistance and reduced cardiac output bring the arterial blood pressure back to normal level (Fig. 65-2).

When blood pressure decreases: The fall in arterial blood pressure or the occlusion of common carotid arteries decreases the pressure in carotid sinus. This causes inactivation of baroreceptors. Now, there is no inhibition of vasoconstrictor center or excitation of vasodilator center. Therefore, the blood pressure rises.

2. Chemoreceptor Mechanism

Chemoreceptors are the receptors giving response to change in chemical constituents of blood. Peripheral chemoreceptors influence the vasomotor center. Refer Chapter 64 for details of peripheral chemoreceptors are situated in the carotid body and aortic body (Chapter 64).

Function

Peripheral chemoreceptors are sensitive to lack of oxygen, excess of carbon dioxide and hydrogen ion concentration in blood. Whenever blood pressure decreases, the blood flow

decreases resulting in decreased oxygen content and excess of carbon dioxide and hydrogen ion. These factors stimulate the chemoreceptors, which send impulses to stimulate the vasoconstrictor center. The blood pressure rises and blood flow increases. Chemoreceptors play a major role in maintaining respiration rather than blood pressure (Chapter 77).

Sinoaortic mechanism

Mechanism of action of baroreceptors and chemoreceptors in carotid and aortic region constitute sinoaortic mechanism. The nerves from the baroreceptors and chemoreceptors are called buffer nerves because these nerves regulate the heart rate (Chapter 64), blood pressure and respiration (Chapter 77).

3. Higher Centers

The vasomotor center is also controlled by the impulses from the two higher centers in the brain.

i. Cerebral cortex

Area 13 in cerebral cortex is concerned with emotional reactions. During emotional conditions, this area sends impulses to vasomotor center. The vasomotor center is activated, the vasomotor tone is increased and the pressure rises.

ii. Hypothalamus

Stimulation of posterior and lateral nuclei of hypothalamus causes vasoconstriction and increase in blood pressure. Stimulation of preoptic area causes vasodilatation and decrease in blood pressure. The impulses from hypothalamus are mediated via vasomotor center.

4. Respiratory Centers

During the beginning of expiration, arterial blood pressure increases slightly, i.e. by 4 to 6 mm Hg. And it decreases during later part of expiration and during inspiration. It is because of two factors:

- i. Radiation of impulses from respiratory centers towards vasomotor center at different phases of respiratory cycle
- ii. Pressure changes in thoracic cavity leading to alteration of venous return and cardiac output.

■ RENAL MECHANISM FOR REGULATION OF BLOOD PRESSURE – LONG-TERM REGULATION

The kidneys play an important role in the long-term regulation of arterial blood pressure.

Kidneys regulate arterial blood pressure by two ways:

1. By regulation of ECF volume
2. Through renin-angiotensin mechanism.

■ BY REGULATION OF EXTRACELLULAR FLUID VOLUME

When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium by means of pressure diuresis and pressure natriuresis. Pressure diuresis is the excretion of large quantity of water in urine because of increased blood pressure. Even a slight increase in blood pressure doubles the water excretion. Pressure natriuresis is the excretion of large quantity of sodium in urine.

Because of diuresis and natriuresis, there is decrease in the ECF volume and blood volume,

which in turn brings the arterial blood pressure back to normal level.

When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output resulting in restoration of blood pressure.

■ THROUGH RENIN-ANGIOTENSIN MECHANISM

The details about source of renin secretion, formation of angiotensin and conditions when renin is secreted are described in Chapter 35.

Actions of Angiotensin II

When blood pressure and ECF volume decrease, renin secretion from kidneys is increased. It converts angiotensinogen into angiotensin I. This is converted into angiotensin II by ACE (angiotensin converting enzyme).

Angiotensin II acts in two ways to restore the blood pressure:

- i. It causes constriction of arterioles in the body so that the peripheral resistance is increased, and blood pressure rises. In addition, angiotensin II causes constriction of afferent arterioles in kidneys so that the glomerular filtration reduces. This results in retention of water and salts. This increases ECF volume to normal level. This in turn increases the blood pressure to normal level.
- ii. Simultaneously, angiotensin II stimulates the adrenal cortex to secrete aldosterone. This hormone increases reabsorption of sodium from renal tubules. Sodium reabsorption is followed by water reabsorption resulting in increased ECF volume and blood volume. It increases the blood pressure to normal level (Fig. 65-3).

Actions of Angiotensin III and Angiotensin IV

Like angiotensin II, the angiotensins III and IV also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone (Chapter 35).

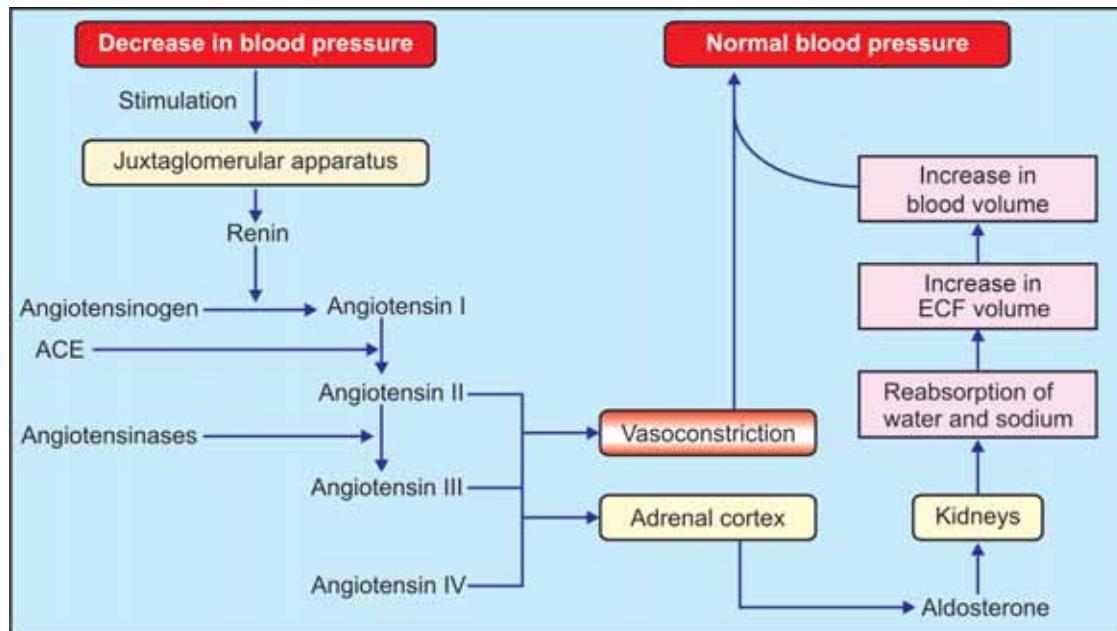


FIGURE 65-3: Regulation of blood pressure by renin-angiotensin mechanism.
ACE = Angiotensin converting enzyme

■ HORMONAL MECHANISM FOR REGULATION OF BLOOD PRESSURE

Many hormones are involved in the regulation of blood pressure.

Hormones which Increase the Blood Pressure

1. Adrenaline
2. Noradrenaline
3. Thyroxine
4. Aldosterone
5. Vasopressin
6. Angiotensin
7. Serotonin.

Hormones which Decrease the Blood Pressure

1. Vasoactive intestinal polypeptide (VIP)
2. Bradykinin
3. Prostaglandin
4. Histamine
5. Acetylcholine

6. Atrial natriuretic peptide
7. Brain natriuretic peptide
8. C-type natriuretic peptide.

■ LOCAL MECHANISM FOR REGULATION OF BLOOD PRESSURE

In addition to nervous, renal and hormonal mechanisms, some local substances also regulate the blood pressure. The local substances regulate the blood pressure by vasoconstriction or vasodilatation.

■ LOCAL VASOCONSTRICATORS

The local vasoconstrictor substances are of vascular endothelial origin and are known as endothelins (ET). Endothelins are peptides with 21 amino acids. Endothelins are produced by stretching of blood vessels. These peptides act by activating phospholipase, which in turn activates the prostacyclin and thromboxane A₂. These two substances cause constriction of blood vessels and increase in blood pressure.

■ LOCAL VASODILATORS

The local vasodilators are of two types:

1. Vasodilators of metabolic origin such as carbon dioxide, lactate, hydrogen ions and adenosine
2. Vasodilators of endothelial origin such as nitric oxide (NO).

■ APPLIED PHYSIOLOGY

The pathological variations of arterial blood pressure are:

- I. Hypertension
- II. Hypotension.

■ HYPERTENSION

Definition

Hypertension is defined as the persistent high blood pressure. Clinically, when the systolic pressure remains elevated above 150 mm Hg and diastolic pressure remains elevated above 90 mm Hg, it is considered as hypertension. If there is increase only in systolic pressure, it is called systolic hypertension.

Types of Hypertension

Hypertension is divided into two types:

1. Primary hypertension
2. Secondary hypertension.

1. Primary hypertension or essential hypertension

Primary hypertension is the elevated blood pressure in the absence of any underlying disease. It is also called essential hypertension. The arterial blood pressure is increased because of increased peripheral resistance, which occurs due to some unknown cause.

2. Secondary hypertension

Secondary hypertension is the high blood pressure due to some underlying disorders. The different forms of secondary hypertension are:

- i. Cardiovascular hypertension that is produced due to the cardiovascular disorders such as atherosclerosis

(hardening of blood vessels by fat deposition) and coarctation (narrowing) of aorta

- ii. Endocrine hypertension which is due to hyperactivity of some endocrine glands such as pheochromocytoma, hyperaldosteronism and Cushing's syndrome
- iii. Renal hypertension that is caused by renal diseases like glomerulonephritis and stenosis of renal arteries
- iv. Neurogenic hypertension which is developed by nervous disorders such as increased intracranial pressure and lesion in tractus solitarius
- v. Hypertension during pregnancy which is due to toxemia of pregnancy.

■ HYPOTENSION

Definition

Hypotension is the low blood pressure. When the systolic pressure is less than 90 mm Hg, it is considered as hypotension.

Types

1. Primary hypotension
2. Secondary hypotension.

1. Primary hypotension

Primary hypotension is the low blood pressure that develops in the absence of any underlying disease and develops due to some unknown cause. It is also called essential hypotension. Frequent fatigue and weakness are the common symptoms of this condition. However, the persons with primary hypotension are not easily susceptible to heart or renal disorders.

2. Secondary hypotension

It is the hypotension that occurs due to some underlying diseases. The diseases which cause hypotension are:

- i. Myocardial infarction
- ii. Hypoactivity of pituitary gland
- iii. Hypoactivity of adrenal glands
- iv. Tuberculosis
- v. Nervous disorders.

Venous Pressure and Capillary Pressure

- **VENOUS PRESSURE**
 - DEFINITION AND NORMAL VALUES
 - EFFECT OF RESPIRATION ON VENOUS PRESSURE
- **CAPILLARY PRESSURE**
 - DEFINITION AND NORMAL VALUES
 - REGIONAL VARIATIONS

■ VENOUS PRESSURE

■ DEFINITION AND NORMAL VALUES

Venous pressure is the pressure exerted by the contained blood in the veins. The pressure in vena cava and right atrium is called central venous pressure. And the pressure in peripheral veins is called peripheral venous pressure.

Pressure is not the same in all the veins. It varies in different veins in the extremities of the body and also varies from central veins to peripheral veins.

Venous Pressure in the Extremities of the Body

Venous pressure is less in the parts of the body above the level of the heart and it is more in parts below the level of the heart.

Pressure in jugular vein: 5.1 mm Hg (6.9 cm H₂O).

Pressure in dorsal venous arch of foot: 13.2 mm Hg (17.9 cm H₂O).

(1 mm Hg pressure = 1.359 cm H₂O pressure).

Venous Pressure in Central and Peripheral Veins

Pressure is greater in peripheral veins than in central veins.

Pressure in antecubital vein: 7.1 mm Hg (9.6 cm H₂O).

Pressure in superior vena cava: 4.6 mm Hg (6.2 cm H₂O).

■ EFFECT OF RESPIRATION ON VENOUS PRESSURE

The effect of respiration on venous pressure is demonstrated by some procedures which exaggerate these effects on venous pressure. Such procedures are Valsalva maneuver and Müller's maneuver.

Valsalva Maneuver or Valsalva Experiment

Valsalva maneuver is the forced expiratory effort with closed glottis. It is performed by attempting to exhale forcibly while keeping the mouth and nose closed.

During this maneuver, the intrathoracic pressure increases greatly and causes the following effects:

1. Compression of central vein in thorax
2. Accumulation of blood in peripheral veins like veins of neck, face and limbs leading to increase in peripheral venous pressure to about 30 cm H₂O
3. Decrease in the venous return to right atrium
4. Decrease in central venous pressure.

Valsalva maneuver is used as a diagnostic tool to evaluate the cardiovascular disorders.

Müller's Maneuver or Müller's Experiment

Müller's maneuver or experiment is the forced inspiratory effort with closed glottis. It is performed by attempting to inhale forcibly while keeping the mouth and nose closed. It is also called reverse Valsalva maneuver.

During this maneuver, the intrathoracic pressure decreases greatly (becomes more negative) and causes the following effects:

1. Dilatation of right atrium and central vein because of increase in negative intrathoracic pressure
2. Rapid emptying of blood from peripheral veins into the central veins
3. Increase in central venous pressure and decrease in the peripheral venous pressure. The peripheral venous pressure falls below 3 to 4 cm H₂O.

Müller's maneuver is used to evaluate upper respiratory tract problems and sleep apnea syndrome.

CAPILLARY PRESSURE

DEFINITION AND NORMAL VALUES

Capillary pressure is the pressure exerted by the blood contained in capillary. It is also called capillary hydrostatic pressure.

Capillary pressure is responsible for the exchange of various substances between blood and interstitial fluid through capillary wall.

Capillary pressure varies depending upon the function of the organ or the region of the body. Generally, the pressure in the arterial end of capillary is about 30 to 32 mm Hg and in venous end it is 15 mm Hg.

REGIONAL VARIATIONS

The capillary pressure varies in different organs particularly in kidneys and lungs. The regional variation in capillary pressure is in relation to the physiological activities of the particular region. So, it has some functional significance.

Capillary Pressure in Kidney

In kidney, the glomerular capillary pressure is high. It is about 60 mm Hg. This high capillary pressure is responsible for glomerular filtration.

Capillary Pressure in Lungs

In lungs, the pulmonary capillary pressure is low. It is about 7 mm Hg. It favors exchange of gases between blood and alveoli.

Arterial Pulse and Venous Pulse

■ ARTERIAL PULSE

- INTRODUCTION
- ARTERIAL PULSE TRACING
- PULSE POINTS
- EXAMINATION OF RADIAL PULSE

■ VENOUS PULSE

- INTRODUCTION
- EXAMINATION OF VENOUS PULSE
- JUGULAR VENOUS PULSE TRACING

■ ARTERIAL PULSE

■ INTRODUCTION

The arterial pulse is defined as the pressure changes transmitted in the form of waves through the arterial wall and blood column from heart to the periphery.

When heart contracts the blood is ejected into aorta with great force. It causes distension of this blood vessel and a rise in pressure. A pressure wave is produced on the elastic wall of the aorta. It travels rapidly from the heart and can be felt after a brief interval, at any superficial peripheral artery like radial artery at wrist.

Pulse rate is the accurate measure of heart rate except in conditions like pulses deficit.

Velocity of Transmission of Pulse

The average velocity at which the pulse wave is transmitted varies between 7 and 9 meters/

second. Pulse wave travels faster than blood flow. The maximum velocity of blood flow in the body (in larger arteries) is only 50 cm/second.

■ ARTERIAL PULSE TRACING

The arterial pulse is recorded by using polygraph. The pulse recorded in radial artery or femoral artery is the typical peripheral pulse (Fig. 67-1). The peripheral pulse tracing has three main features.

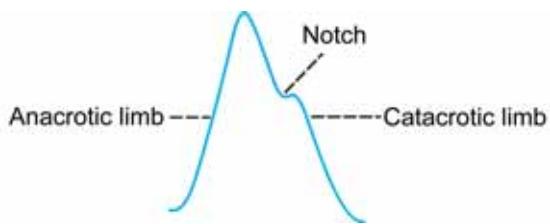


FIGURE 67-1: Radial pulse tracing

1. Anacrotic Limb

It is ascending limb or upstroke. It is also called primary wave. It is due to the rise in pressure during systole.

2. Catacrotic Limb

It is descending limb or downstroke. It is due to the fall in pressure during diastole.

3. Catacrotic Notch

In the upper part of the catacrotic limb of pulse tracing, a small notch appears. It is known as catacrotic notch or incisura. This notch is produced by the backflow of blood during the closure of semilunar valves at the beginning of diastolic period, which produces slight increase in the pressure.

4. Pre and Postcatacrotic Waves

The wave appearing before the notch is called precatacrotic wave. The wave appearing after the notch is called postcatacrotic wave.

■ PULSE POINTS

Usually, the pulse is palpated on the radial artery because it is easily approachable and placed superficially. However, arterial pulse can be felt in different areas on the body. These areas are called pulse points.

1. Temporal pulse – over the temple in front of the ear on superficial temporal artery
2. Facial pulse – on facial artery at the angle of jaw
3. Carotid pulse – in the neck along the anterior border of sternocleidomastoid muscle on common carotid artery
4. Axillary pulse – in axilla on axillary artery
5. Brachial pulse – in cubital fossa along medial border of biceps muscle on brachial artery
6. Radial pulse – over the thumbside of wrist between tendons of brachioradialis and flexor carpi radialis muscles on radial artery

7. Ulnar pulse – over the little fingerside of wrist on ulnar artery
8. Femoral pulse – in the groin on femoral artery
9. Popliteal pulse – behind knee in the popliteal fossa on popliteal artery
10. Dorsalis pedis pulse – over the dorsum of the foot on dorsalis pedis artery
11. Tibialis pulse – over the back of the ankle behind medial malleolus on posterior tibial artery.

■ EXAMINATION OF RADIAL PULSE

Examination of pulse is a valuable clinical procedure. Pulse represents the heartbeat. By examining pulse, important information regarding cardiac function such as rate of contraction, rhythmicity, etc. can be obtained. In addition, an experienced physician can determine the mean arterial pressure by hardness of pulse and its amplitude.

Pulse is examined by placing the tips of three fingers, index finger, middle finger and ring finger on the artery. While examining the pulse, the following features are observed:

1. Rate
2. Rhythm
3. Character
4. Volume
5. Condition of blood vessel wall
6. Delayed pulse.

1. Rate

The number of pulse per minute is pulse rate. It has to be counted at least for 30 seconds. Pulse rate in adults is 72/minute.

2. Rhythm

The regularity of pulse is known as rhythm. Under normal conditions, the pulse appears at regular intervals. The rhythm of the pulse becomes irregular in conditions like atrial fibrillation. The irregular rhythm of pulse is of two types, regularly irregular and irregularly irregular.

3. Character

The character of the pulse is observed while examining the pulse. It denotes the tension on the vessel wall produced by the waves of pulse.

4. Volume

It is the determination of the movement of the vessel wall produced by the transmission of pulse wave. It is also a measure of pulse pressure. It depends upon the condition of the blood vessel.

5. Condition of Wall of the Blood Vessel

It is assessed by feeling and rolling the radial artery against the underlying bones. Normally, the wall of the vessel is not palpable in children and young adults. However, in old age the wall of the vessel becomes rigid and palpable. In abnormal conditions like arteriosclerosis, it is felt as a hard rope.

6. Delayed Pulse

Sometimes the arrival of pulse in certain peripheral arteries is delayed. It is an important feature to be noted because it is useful in diagnosis of certain diseases. For example, while palpating radial pulse and femoral pulse simultaneously, there is a short delay in the arrival of femoral pulse wave. It is called femoral delay, radial femoral delay or radiofemoral delay.

■ VENOUS PULSE

■ INTRODUCTION

Venous pulse is defined as the pressure changes transmitted in the form of waves from right atrium to the veins near the heart. Venous pulse is observed only in larger veins near the heart such as jugular vein.

Evaluation of the venous pulse is an integral part of the physical examination because it reflects right atrial pressure and hemodynamic events in right atrium. Venous pulse recording is used to determine the rate of atrial contraction,

just as the record of arterial pulse is used to determine the rate of ventricular contraction.

In addition, many phases of cardiac cycle can be recognized by means of venous pulse tracing. It is the simple and accurate method to measure duration of different phases in diastole. It also represents the atrial pressure changes taking place during cardiac cycle.

■ EXAMINATION OF VENOUS PULSE

Inspection of jugular vein pulsations is routinely done by bedside examination of neck veins. It provides valuable information about the cardiac function.

To observe the pulsation of the internal jugular vein, the head of the subject is tilted upwards at 45°. However, in patients with increased venous pressure, the head should be tilted as much as 90°. The pulsations of jugular vein can be noticed when light is passed across the skin overlying internal jugular vein with relaxed neck muscles. Simultaneous palpation of the left carotid artery helps the examiner confirm the venous pulsations.

■ JUGULAR VENOUS PULSE TRACING

The recording of jugular venous pulse is also called phlebogram. It is similar to intra-atrial pressure curve (Fig. 67-2).

Phlebogram also has three positive waves — a, c, v and three negative waves — x, x₁, y.

'a' Wave

It is the first wave and is a positive wave. It is due to rise in atrial pressure during atrial systole.

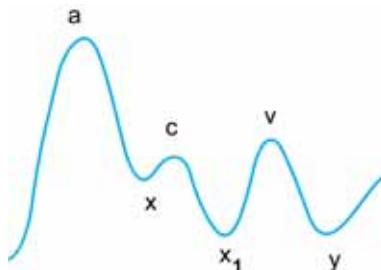


FIGURE 67-2: Phlebogram

'x' Wave

This negative wave is due to fall of pressure in atrium and coincides with atrial diastole and beginning of ventricular systole.

'c' Wave

This positive wave occurs due to rise in atrial pressure during isometric contraction period. During this period the atrioventricular valves bulge into the atria and increase the pressure in the atria slightly.

'x₁' Wave

It is a negative wave and it is due to fall in pressure during ejection period. During ejection

period, the atrioventricular ring is pulled towards ventricles causing fall in atrial pressure.

'v' Wave

This positive wave is due to rise in atrial pressure. The pressure increases because of atrial filling (venous return). It is obtained during isometric relaxation period or during atrial diastole.

'y' Wave

This negative wave denotes fall in pressure in atria. It is due to the opening of atrioventricular valve and emptying of blood into the ventricle. It appears during rapid and slow filling periods. 'y' wave is followed by 'a' wave and the cycle is repeated.

Regional Circulation

- CORONARY CIRCULATION
- CEREBRAL CIRCULATION
- SPLANCHNIC CIRCULATION
- CAPILLARY CIRCULATION
- SKELETAL MUSCLE CIRCULATION
- CUTANEOUS CIRCULATION

■ CORONARY CIRCULATION

■ DISTRIBUTION OF CORONARY BLOOD VESSELS

Coronary Arteries

Heart muscle is supplied by two coronary arteries, the right and left coronary arteries, which are the first branches of aorta. The arteries encircle the heart in the manner of a crown hence the name coronary arteries (Latin word corona = crown).

Branches of coronary arteries

The coronary arteries divide and subdivide into smaller branches, which run all along the surface of the heart. The smaller branches are called epicardiac arteries and give rise to further smaller branches known as final arteries or intramural vessels. The final arteries run at right angles through the heart muscle near the inner aspect of wall of the heart.

Venous Drainage

The venous drainage from the heart muscle is by three types of vessels:

1. *Coronary sinus*: It is the larger vein draining 75% of total coronary flow. It drains blood from left side of the heart and opens into right atrium near tricuspid valve
2. *Anterior coronary veins*: The anterior coronary veins drain blood from right side of the heart and open directly into right atrium
3. *Thebesian veins*: Thebesian veins drain deoxygenated blood from myocardium directly into the concerned chamber of the heart.

Physiological Shunt

Physiological shunt is the diverted route (diversion) through which the venous blood is mixed with arterial blood. The deoxygenated blood flowing from thebesian veins into cardiac chambers makes up part of normal physiological shunt. The other component of physiological

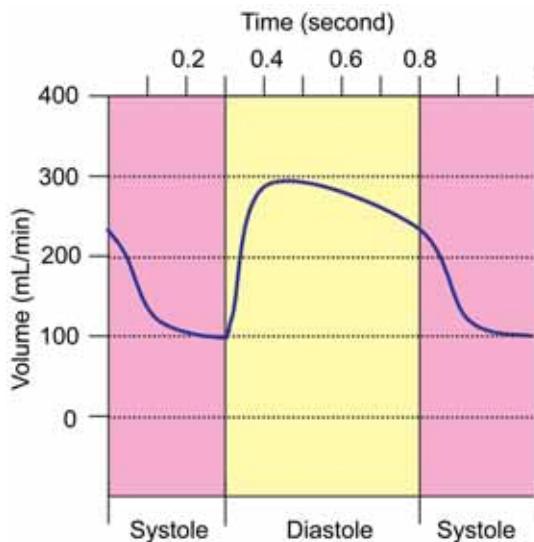


FIGURE 68-1: Phasic changes in coronary blood flow

shunt is the drainage of deoxygenated blood from bronchial circulation into pulmonary vein without being oxygenated (Chapter 72).

■ NORMAL CORONARY BLOOD FLOW

Normal blood flow through coronary circulation is about 200 mL/minute. It forms 4% of cardiac output. It is about 65 to 70 mL/minute/100 g of cardiac muscle.

■ PHASIC CHANGES CORONARY BLOOD FLOW

The blood flow through coronary arteries is not constant. It decreases during systole and increases during diastole (Fig. 68-1).

During contraction, the coronary blood vessels are compressed and blood flow is reduced. During diastole, the compression is released and the blood vessels are distended. So, the blood flow is increased.

■ APPLIED PHYSIOLOGY – CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is the heart disease that is caused by inadequate blood

supply to cardiac muscle due to occlusion of coronary artery. It is also called coronary heart disease.

Coronary Occlusion

Coronary occlusion means the partial or complete obstruction of the coronary artery. The occlusion occurs because of atherosclerosis, a condition associated with deposition of cholesterol on the walls of the artery. In due course, this part of the arterial wall becomes fibrotic and it is called atherosclerotic plaque. The plaque is made up of cholesterol, calcium and other substances from blood. Because of the atherosclerotic plaque the lumen of the coronary artery becomes narrow. In severe conditions, the artery is completely occluded.

Smaller blood vessels are occluded by the thrombus or part of atherosclerotic plaque detached from coronary artery. This thrombus or part of the plaque is called embolus.

Myocardial Ischemia

Myocardial ischemia is the reaction of a part of myocardium in response to hypoxia. Hypoxia develops when blood flow to a part of myocardium decreases severely due to occlusion of a coronary artery.

When the ischemia is mild due to obstruction of smaller blood vessel, the blood flow can be restored by rapid development of coronary collateral arteries.

Necrosis

Necrosis refers to death of cells or tissues by injury or disease in a localized area. When coronary occlusion is severe involving larger blood vessels, the severe ischemia leads to necrosis of myocardium. Necrosis is irreversible.

Myocardial Infarction – Heart Attack

Myocardial infarction is the necrosis of myocardium caused by insufficient blood flow due to embolus, thrombus or vascular spasm. It is also called heart attack. In myocardial

infarction, death occurs rapidly due to ventricular fibrillation.

Common symptoms of myocardial infarction are:

1. Cardiac pain
2. Nausea
3. Vomiting
4. Palpitations
5. Difficulty in breathing
6. Extreme weakness
7. Sweating
8. Anxiety.

Cardiac Pain – Angina Pectoris

Cardiac pain is the chest pain that is caused by myocardial ischemia. It is also called angina pectoris. It is the common manifestation of coronary artery disease. The pain starts beneath the sternum and radiates to the surface of left arm and left shoulder. The cardiac pain is called referred pain since it is felt over the body away from the heart. It is because, heart and left arm develop from the same dermatomal segment in embryo.

CEREBRAL CIRCULATION

IMPORTANCE

Brain tissues need adequate blood supply continuously. Stoppage of blood flow for 5 seconds leads to unconsciousness, and for 5 minutes leads to irreparable damage to the brain cells.

CEREBRAL BLOOD VESSELS

Brain receives blood from the basilar artery and internal carotid artery. The branches from these arteries form circle of Willis. The venous drainage is by sinuses, which open into internal jugular vein.

NORMAL CEREBRAL BLOOD FLOW

Normally, brain receives 750 to 800 mL of blood per minute. It is about 15 to 16% of total cardiac

output and about 50 to 55 mL/100 grams of brain tissue per minute.

APPLIED PHYSIOLOGY – STROKE

Definition

Stroke is the sudden death of neurons in localized area of brain due to inadequate blood supply. It is characterized by reversible or irreversible paralysis with other symptoms. Stroke is also called cardiovascular accident (CVA) or brain attack.

Causes

1. Heart disease
2. Hypertension
3. High cholesterol in blood
4. High blood sugar – diabetes mellitus
5. Heavy smoking
6. Heavy alcohol consumption.

Symptoms

Symptoms of stroke depend upon the area of brain that is damaged. Generally, stroke causes dizziness, loss of consciousness, coma or death.

Other features of stroke are:

1. Weakness
2. Numbness or paralysis particularly on one side of the body
3. Impairment of speech
4. Emotional disturbances
5. Loss of coordination
6. Loss of memory.

SPLANCHNIC CIRCULATION

INTRODUCTION

The splanchnic or visceral circulation constitutes three portions:

1. Mesenteric circulation supplying blood to GI tract
2. Splenic circulation supplying blood to spleen
3. Hepatic circulation supplying blood to liver.

The unique feature of splanchnic circulation is that, the blood from mesenteric bed and

spleen forms a major amount of blood flowing to liver. Blood flows to liver from GI tract and spleen through portal system.

■ MESENTERIC CIRCULATION

Distribution of Blood Flow

Stomach — 35 mL/100 gm/minute
Intestine — 50 mL/100 gm/minute
Pancreas — 80 mL/100 gm/minute

■ SPLENIC CIRCULATION

Importance of Splenic Circulation

Spleen is the main reservoir for blood. Due to the dilatation of blood vessels, a large amount of blood is stored in spleen. And the constriction of blood vessels by sympathetic stimulation releases blood into circulation.

Storage of Blood

In spleen, two structures are involved in storage of blood namely, splenic venous sinuses and splenic pulp.

The small arteries and arterioles open directly into the venous sinuses. When spleen expands, the sinuses swell and large quantity of blood is stored. The capillaries of splenic pulp are highly permeable. So, most of the blood cells pass through capillary membrane and are stored in the pulp. The venous sinuses and the pulp are lined with reticuloendothelial cells.

■ HEPATIC CIRCULATION

Hepatic Blood Vessels

Liver receives blood from two sources:

1. Hepatic artery from aorta
2. Portal vein from mesenteric and splenic vascular bed.

More details are given in Chapter 30.

Normal Blood Flow

Liver receives maximum amount of blood as compared to any other organ in the body since,

most of the metabolic activities are carried out in the liver. The blood flow to liver is 1,500 mL/minute, which forms 30% of cardiac output. It is about 100 mL/100 g of tissue/minute.

Normally, about 1100 mL of blood flows through portal vein and remaining 400 mL of blood flows through hepatic artery. However, portal vein carries only about 25% of oxygen to liver. It is because it carries the blood, which has already passed through the blood vessels of GI tract where oxygen might have been used. Hepatic artery transports 75% of oxygen to the liver.

■ CAPILLARY CIRCULATION

■ MICROCIRCULATION

Microcirculation refers to the flow of blood through the minute blood vessels such as arterioles, capillaries and venules. Capillary circulation forms the major part of microcirculation. The capillaries are formed by single layer of endothelial cells which are wrapped around by pericytes.

■ FEATURES OF CAPILLARIES

Capillaries arise from arterioles and form the area for the actual function of circulatory system, i.e. exchange of materials between blood and tissues. Structurally, capillaries are very narrow and short. However, quantitatively, these vessels outnumber the other blood vessels. About ten billion capillaries are present in the body.

Each capillary lies in a very close proximity to the cells of the tissues at a distance of about 20 to 30 mm. This enables easy and rapid exchange of substances between blood and the tissues through interstitial fluid.

■ PATTERN OF CAPILLARY SYSTEM

Capillaries are disposed between arterioles and venules. From the arterioles, the meta-arterioles take origin (Fig. 68-2). From meta-arterioles, two types of capillaries arise:

1. Preferential channels
2. True capillaries.

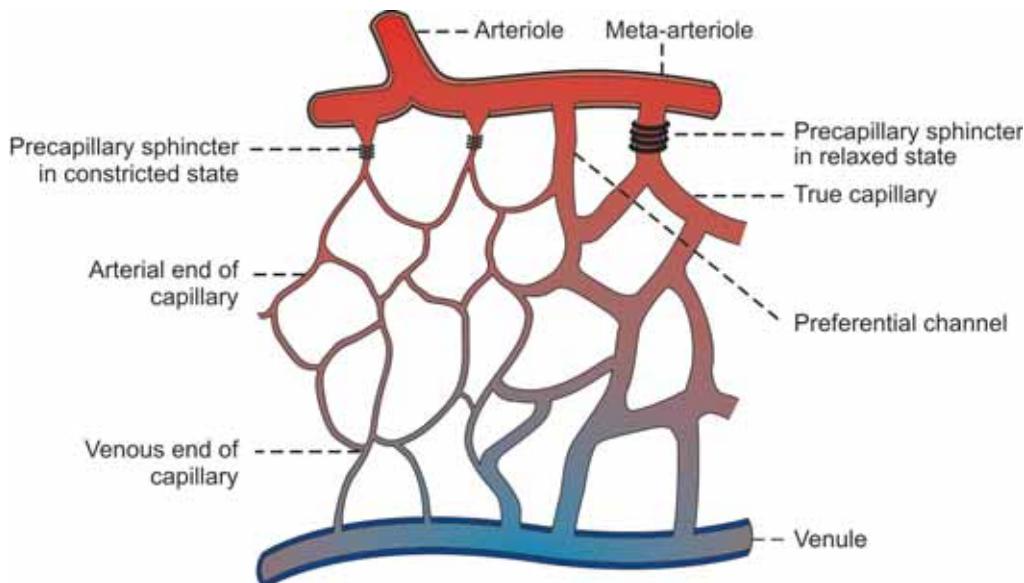


FIGURE 68-2: Capillary bed

1. Preferential Channels

The preferential channels or continuous capillaries have same diameter as meta-arterioles. After arising from the meta-arterioles, the preferential channels form a network and finally join the venules.

2. True Capillaries

The diameter of the true capillaries is less than that of the meta-arterioles. Arising from meta-arterioles, the true capillaries also form a network and join the venules.

At the beginning of true capillaries, there is an encircling of smooth muscle fibers. It functions as a sphincter; so it is known as precapillary sphincter. It controls the blood flow through true capillaries.

■ ANATOMICAL AND PHYSIOLOGICAL SHUNTS

Anatomical Shunt

Anatomical shunt is the direct link between arterioles and venules. It is also called arteriovenous shunt. Flow of blood through the

capillaries where exchange of nutrients, gases and other substances takes place is called nutritional flow. The flow of blood through anatomical shunt is called non-nutritional flow. Non-nutritional blood flow occurs in many tissues of the body particularly during resting conditions when metabolic activities are low.

Physiological Shunt

Physiological shunt is the link between arterial and venous side of circulation provided by meta-arteriole. Many tissues of the body such as muscles do not have anatomical shunts. However, the meta-arteriole in these tissues acts as the physiological shunt between arterial and venous sides of the circulation. The non-nutritional blood flow occurs through physiological shunt under resting conditions.

Shunt in Capillaries vs Shunt in Heart

Physiological shunt in capillaries is different from physiological shunt in heart. In capillaries the oxygenated blood flows towards deoxygenated blood. But in heart, the deoxygenated blood flows towards the oxygenated blood (see above).

■ PECULIARITIES OF CAPILLARY BLOOD FLOW

1. The blood does not pass through capillary system continuously. It is because of the alternate constriction and dilatation of meta-arterioles and alternate opening and closure of precapillary sphincters
2. The direction of blood flow through capillaries is not fixed as in the case of other blood vessels. The blood may flow in opposite direction in two adjacent capillaries
3. In capillaries, blood flows as a single pile or single row of blood cells. In other blood vessels, the blood flows in either axial stream containing mainly blood cells or peripheral stream containing plasma
4. Under resting conditions, most of the capillaries lie in collapsed state. Only during activity, all the capillaries open up and increase the vascularity
5. The amount of blood flowing through capillary system throughout the body is very low. It is only about 150 mL/minute
6. The velocity of blood flow is least in capillaries. It is only about 0.5 to 1 mm/second. It facilitates exchange of substances between capillaries and tissues.

■ FUNCTIONS OF CAPILLARIES

The most important function of capillaries is the exchange of substances between blood and tissues. Oxygen, nutrients and other essential substances enter the tissues from capillary blood; carbon dioxide, metabolites and other unwanted substances are removed from the tissues by capillary blood. Exchange of materials across the capillary endothelium occurs primarily by diffusion. It also occurs by means of filtration and pinocytosis.

■ SKELETAL MUSCLE CIRCULATION

■ BLOOD FLOW TO SKELETAL MUSCLES

During resting condition, blood flow to skeletal muscle is 4 to 7 mL/100 gram/minute. During exercise, it increases to about 100 mL/100 gram/minute.

■ MUSCULAR CONTRACTION AND BLOOD FLOW

During contraction of the muscle, the blood vessels are compressed and the blood flow decreases. And during the relaxation of the muscle, the compression of the blood vessels is relieved and the blood flow increases.

In severe muscular exercise, the blood flow increases in between the muscular contractions.

■ CUTANEOUS CIRCULATION

■ ARCHITECTURE OF CUTANEOUS BLOOD VESSELS

1. The arterioles arising from the smaller arteries reach the dermis
2. After taking origin, the arterioles turn horizontally and give rise to meta-arterioles
3. From meta-arterioles, hairpin shaped capillary loops arise. The arterial limb of the loop ascends vertically and turns to form a venous limb, which descends down
4. After reaching the base of dermis, few venous limbs of neighboring papillae unite to form the collecting venule
5. The collecting venules anastomose with one another to form the subpapillary venous plexus
6. The subpapillary plexus runs horizontally and drain into deeper veins.

■ FUNCTIONS OF CUTANEOUS CIRCULATION

Cutaneous blood flow performs two functions:

1. The supply of nutrition to skin
2. The loss of heat from the body and regulation of body temperature.

■ BLOOD FLOW TO SKIN

Under normal conditions, the blood flow to skin is about 250 mL/square meter/minute. When the body temperature increases, cutaneous blood flow increases up to 2800 mL/sq. meter/minute because of cutaneous vasodilatation.

Fetal Circulation and Respiration

- INTRODUCTION
- BLOOD VESSELS IN FETUS
- FETAL LUNGS
- CHANGES IN CIRCULATION AND RESPIRATION AFTER BIRTH – NEONATAL CIRCULATION AND RESPIRATION

■ INTRODUCTION

Fetal circulation is different from that of adults because of the presence of placenta. Since fetal lungs are nonfunctioning, placenta is responsible for exchange of gases between fetal blood and mother's blood. So the blood from right ventricle is diverted to placenta.

The development of heart is completed at fourth week of intrauterine life and, it starts beating at the rate of 65 per minute. Along with heart, the blood vessels also develop. The heart rate gradually increases and reaches the maximum rate of about 140 beats per minute just before birth.

Fetus is connected with the mother through the placenta. Fetal blood passes to placenta through umbilical vessels and the maternal blood runs through uterine vessels. These two sets of blood vessels lie in close proximity in the placenta through which the exchange of substances takes place between mother's blood and fetal blood. However, there is no direct admixture of maternal and fetal blood (Fig. 69-1).

■ BLOOD VESSELS IN FETUS

As the fetal lungs are nonfunctioning, there is no necessity of large amount of blood to be pumped into lungs. Instead, the fetal heart pumps large quantity of blood into the placenta for exchange of substances. From placenta, the umbilical veins collect the blood, which has more oxygen and nutrients. The umbilical vein passes through liver. Some amount of blood is supplied to liver from umbilical vein. However, a large quantity of blood is diverted from umbilical vein into the inferior vena cava through ductus venosus. Liver receives blood from portal vein also.

In liver, the oxygenated blood mixes slightly with deoxygenated blood and enters the right atrium via inferior vena cava. From right atrium, major portion of blood is diverted into left atrium via foramen ovale. Foramen ovale is an opening in intra-atrial septum.

Blood from the upper part of the body enters the right atrium through superior vena cava. From right atrium, blood enters right ventricle.

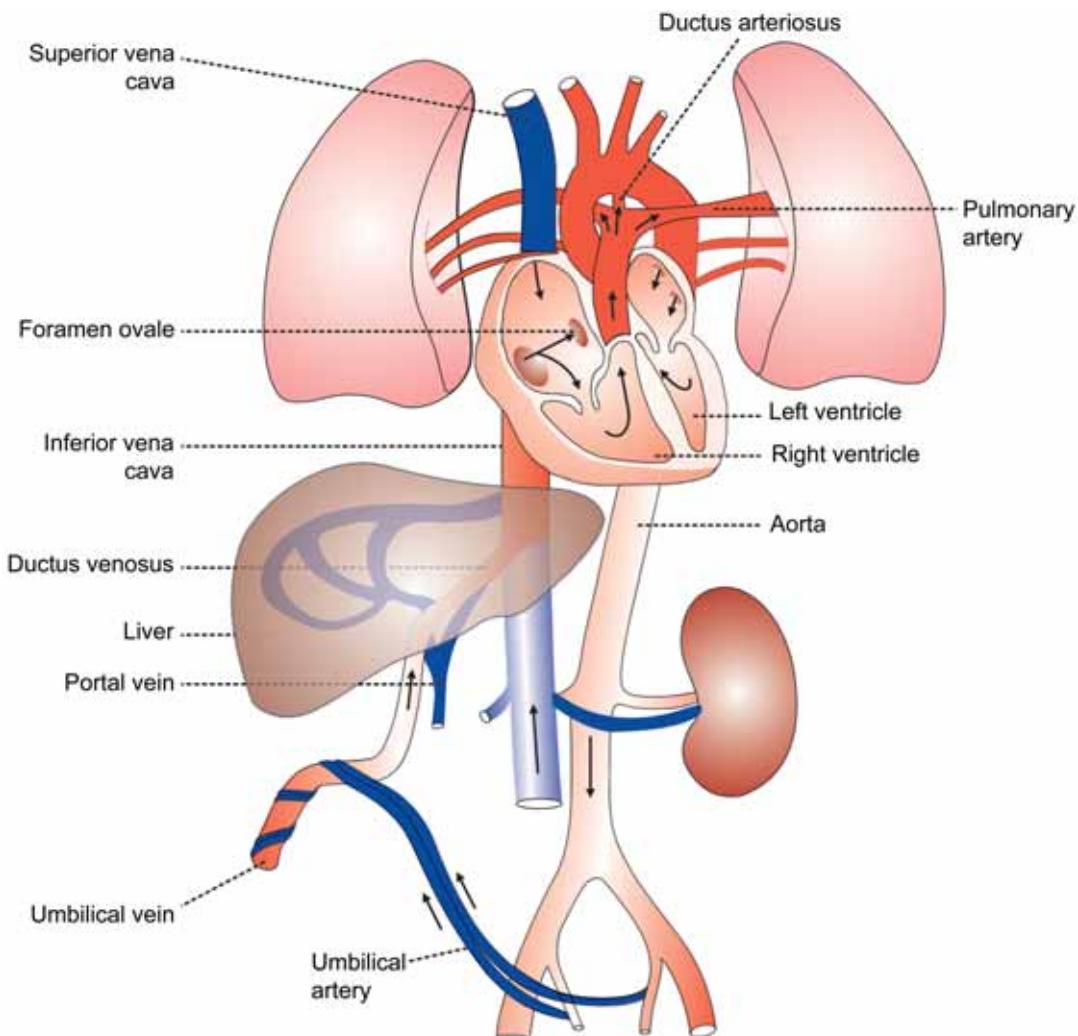


FIGURE 69-1: Fetal circulation

From here, blood is pumped into pulmonary artery. From pulmonary artery, blood enters the systemic aorta through ductus arteriosus. Only a small quantity of blood is supplied to fetal lungs. Blood from left ventricle is pumped into aorta. Fifty percent of blood from aorta reaches the placenta through umbilical arteries.

■ FETAL LUNGS

Pulmonary vascular resistance is very high in fetus because of non functioning of lungs. It is the resistance offered to blood flow through pulmonary vascular bed. The high resistance

increases the pressure in the blood vessels of lungs. Because of the high pressure, the blood is diverted from pulmonary artery into aorta via ductus arteriosus.

■ CHANGES IN CIRCULATION AND RESPIRATION AFTER BIRTH – NEONATAL CIRCULATION AND RESPIRATION

■ 1. FIRST BREATH OF THE CHILD

When fetus is delivered and umbilical cord is cut and tied, the lungs start functioning. When

placental blood flow is cut off, there is sudden hypoxia and hypercapnia. Now, the respiratory center is strongly stimulated by these two factors and, the respiration starts. Initially, there is gasping, which is followed by normal respiration.

■ 2. FLOW OF BLOOD TO LUNGS

Lungs expand during the first breath of the infant. The expansion of lungs causes immediate reduction in the pulmonary vascular resistance and a sudden fall in pressure in the blood vessels of lungs. Therefore, the blood flow from pulmonary artery to lungs increases.

■ 3. CLOSURE OF FORAMEN OVALE

When blood starts flowing through the pulmonary circulation, the oxygenated blood from the lungs

returns to left atrium. It causes increase in the left atrial pressure. Simultaneously, due to stoppage of blood from placenta, pressure in inferior vena cava is decreased. It leads to fall in right atrial pressure. Thus, the pressure in right atrium is less and the pressure in left atrium is already high. This causes the closure of foramen ovale. Within few days after birth, the foramen ovale closes completely and fuses with the atrial wall.

■ 4. REVERSAL OF BLOOD FLOW IN DUCTUS ARTERIOSUS

In fetus, since pulmonary arterial pressure is very high, the blood passes from pulmonary artery into aorta via ductus arteriosus. However, in neonatal life, since the systemic arterial pressure

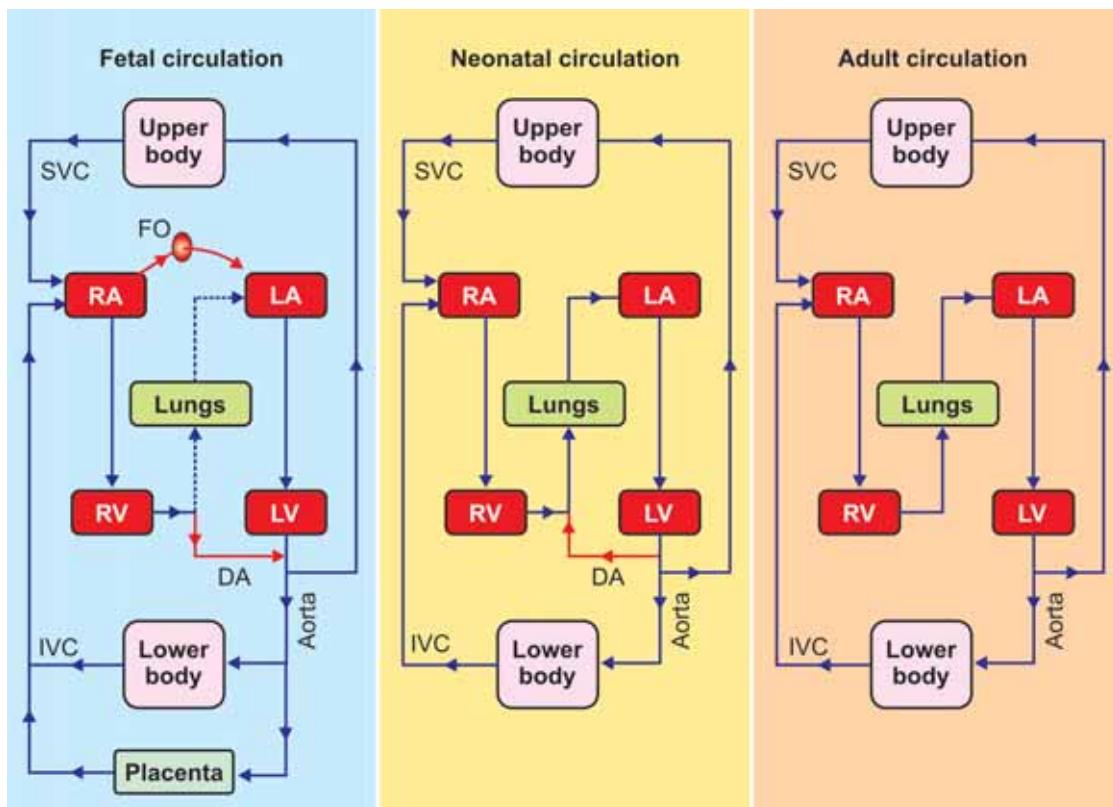


FIGURE 69-2: Fetal, neonatal and adult circulation. RA = Right atrium. LA = Left atrium. RV = Right ventricle. LV = Left ventricle. FO = Foramen ovale. DA = Ductus arteriosus. SVC = Superior vena cava. IVC = Inferior vena cava. Dashed blue line (Fetal circulation) indicates flow of very less quantity of blood

is more than pulmonary arterial pressure, the blood passes in opposite direction in ductus arteriosus, i.e. from systemic aorta into pulmonary aorta (Fig. 69-2). The reversed flow in ductus arteriosus is heard as continuous murmur in infants.

■ 5. CLOSURE OF DUCTUS VENOSUS

Due to the contraction of smooth muscle near junction between umbilical vein and ductus venosus, the constriction and closure of ductus

venosus occurs. Later, the ductus venosus becomes fibrous band.

■ 6. CLOSURE OF DUCTUS ARTERIOSUS

The ductus arteriosus starts closing due to narrowing. It closes completely after two days and the adult type of circulation starts. In some rare cases, the ductus arteriosus does not close. It remains intact producing a continuous murmur. The condition with intact ductus arteriosus is known as patent ductus arteriosus.

Hemorrhage, Circulatory Shock and Heart Failure

- **HEMORRHAGE**
 - DEFINITION
 - TYPES AND CAUSES
 - EFFECTS OF HEMORRHAGE
- **CIRCULATORY SHOCK**
 - DEFINITION
 - MANIFESTATIONS OF SHOCK
- **HEART FAILURE**
 - DEFINITION
 - CAUSES
 - SIGNS AND SYMPTOMS

■ HEMORRHAGE

■ DEFINITION

Hemorrhage is the excess loss of blood due to the rupture of blood vessels.

■ TYPES AND CAUSES OF HEMORRHAGE

Hemorrhage occurs due to various reasons. Based on the cause, hemorrhage is classified into five categories:

1. Accidental hemorrhage
2. Capillary hemorrhage
3. Internal hemorrhage
4. Postpartum hemorrhage
5. Hemorrhage due to premature detachment of placenta.

1. *Accidental Hemorrhage*

It occurs in road accidents and industrial accidents, which are very common in the developed and developing countries.

2. *Capillary Hemorrhage*

Capillary hemorrhage is the bleeding due to the rupture of blood vessels, particularly capillaries. It is very common in brain (cerebral hemorrhage) and heart during cardiovascular diseases.

3. *Internal Hemorrhage*

Internal hemorrhage is the bleeding in viscera. It is caused by rupture of blood vessels in the viscera.

4. Postpartum Hemorrhage

Excess bleeding that occurs immediately after labor (delivery of the baby) is called postpartum hemorrhage.

5. Hemorrhage Due to Premature Detachment of Placenta

In some cases, the placenta is detached from the uterus of mother before the due date of delivery causing severe hemorrhage.

■ EFFECTS OF HEMORRHAGE

Many effects are observed during and after hemorrhage. The effects are different in acute hemorrhage and chronic hemorrhage.

Acute Hemorrhage

Acute hemorrhage is the sudden loss of large quantity of blood. It occurs in conditions like accidents. Decreased blood volume in acute hemorrhage causes hypovolemic shock.

Chronic Hemorrhage

Chronic hemorrhage is the loss of blood either by internal or by external bleeding over a long period of time. Internal bleeding occurs in conditions like ulcer. External bleeding occurs in conditions like hemophilia and excess vaginal bleeding (menorrhagia). Chronic hemorrhage produces different types of effects such as anemia.

Compensatory Effects

After hemorrhage, series of compensatory reactions develop in the body to cope up with the blood loss. Some of the compensatory reactions take place immediately after hemorrhage and others at a later period.

■ CIRCULATORY SHOCK

■ DEFINITION

Shock is a general term that refers to the depression or suppression of body functions

produced by any disorder. Circulatory shock refers to the shock developed by inadequate blood flow throughout the body. It is a life-threatening condition and if the affected person is not treated immediately it may result in death.

■ MANIFESTATIONS OF SHOCK

The characteristic feature of all types of circulatory shock is the insufficient blood flow to the tissues particularly the brain. The blood flow decreases due to the reduction in cardiac output. Following are the manifestations of circulatory shock:

1. When cardiac output reduces, the arterial blood pressure drops down
2. Low blood pressure produces reflex tachycardia and reflex vasoconstriction
3. The pulse also becomes feeble
4. The velocity of the blood flow decreases resulting in stagnant hypoxia
5. Skin becomes pale and cold
6. Cyanosis in many parts of the body, particularly ear lobes and fingertips
7. Decrease in renal blood flow, GFR and urinary output
8. Acceleration of metabolic activities of myocardium resulting in accumulation of excess lactic acid and acidosis
9. Acidosis decreases the efficiency of myocardium leading to further reduction in cardiac output
10. So, the blood flow to vital organs is severely affected
11. The lack of blood flow to the brain tissues produces ischemia resulting in fainting and irreparable damage to the brain.
12. Finally the damage of brain tissues and cardiac arrest kill the victim.

■ HEART FAILURE

■ DEFINITION

Heart failure or cardiac failure is the condition in which the heart loses the ability to pump sufficient amount of blood to all parts of the body. Heart failure may involve left ventricle or right ventricle or both. It may be acute or chronic.

Acute Heart Failure

Acute heart failure refers to sudden and rapid onset of signs and symptoms of abnormal heart functions. Its symptoms are severe initially. However, the symptoms last for a very short-time and the condition improves rapidly.

Chronic Heart Failure

Chronic heart failure is the heart failure that is characterized by the symptoms that appear slowly over a period of time and become worst gradually.

Congestive Heart Failure

It is a general term used to describe heart failure resulting in accumulation of fluid in lungs and other tissues. When heart is not able to pump blood through aorta, the blood remains in heart. It results in dilatation of the chambers and accumulation of blood in veins (vascular congestion). This condition is also manifested by fluid retention and pulmonary edema.

■ CAUSES OF HEART FAILURE

The common causes of heart failure are:

1. Coronary artery disease
2. Defective heart valves
3. Arrhythmia (abnormal heartbeat)
4. Cardiac muscle disease such as cardiomyopathy
5. Hypertension
6. Congenital heart disease

7. Diabetes
8. Hyperthyroidism
9. Anemia
10. Lung disorders
11. Inflammation of cardiac muscle (myocarditis) due to viral infection, drugs, alcohol, etc.

■ SIGNS AND SYMPTOMS OF HEART FAILURE

Signs and Symptoms of Chronic Heart Failure

1. Fatigue and weakness
2. Rapid and irregular heartbeat
3. Shortness of breathing
4. Fluid retention and weight gain
5. Loss of appetite, nausea and vomiting
6. Cough
8. Chest pain, if developed by myocardial infarction.

Signs and Symptoms of Acute Heart Failure

The signs and symptoms of acute heart failure may be same as chronic heart failure. But the signs and symptoms appear suddenly and severely. When heart starts to fail suddenly, the fluid accumulates in lungs causing pulmonary edema. It results in sudden and severe shortness of breath, cough with pink, foamy mucus and heart palpitations. It may lead to sudden death, if not attended immediately.

Cardiovascular Adjustments during Exercise

- INTRODUCTION
- TYPES OF EXERCISE
- AEROBIC AND ANAEROBIC EXERCISES
- SEVERITY OF EXERCISE
- EFFECTS OF EXERCISE

■ INTRODUCTION

During exercise, there is an increase in metabolic needs of body tissues, particularly the muscles. Various adjustments, which take place in the body, are aimed at

1. Supply of nutrients and oxygen to muscles and other tissues involved in exercise
2. Prevention of increase in body temperature.

■ TYPES OF EXERCISE

Exercise is generally classified into two types depending upon the type of muscular contraction.

1. Dynamic exercise
2. Static exercise.

■ DYNAMIC EXERCISE

The dynamic exercise involves isotonic muscular contraction and keeps the joints and muscles moving. Examples are swimming, bicycling, walking, etc. External work is involved in this type of exercise. The shortening of muscle fibers against load is called external work.

In this type of exercise, the heart rate, force of contraction, cardiac output and systolic blood

pressure increase. However, the diastolic blood pressure is unaltered or decreased. It is because, during dynamic exercise, the peripheral resistance is unaltered or decreased.

■ STATIC EXERCISE

Static exercise involves isometric muscular contraction without movement of joints. Example is pushing heavy object. This is a type of exercise without the performance of external work. During this exercise, apart from increase in heart rate, force of contraction, cardiac output and systolic blood pressure, the diastolic blood pressure also increases. It is because of increase in peripheral resistance during static exercise.

■ AEROBIC AND ANAEROBIC EXERCISES

Based on the type of metabolism (energy producing process) involved, the exercise is classified into two types:

1. Aerobic exercise
2. Anaerobic exercise.

■ AEROBIC EXERCISE

Aerobic means 'with air' or 'with oxygen'. The energy is obtained by utilizing nutrients in the presence of oxygen. Aerobic exercise involves activities with lower intensity, which is performed for longer period. At the beginning, the body obtains energy by burning glycogen stored in liver. After about 20 minutes, when stored glycogen is exhausted, the body starts burning fat. Body fat is converted into glucose, which is utilized for energy.

Examples of aerobic exercise:

1. Fast walking
2. Jogging
3. Running
4. Bicycling
5. Skiing
6. Skating
7. Hockey
8. Soccer
9. Tennis
10. Badminton
11. Swimming
12. Rowing.

■ ANAEROBIC EXERCISE

Anaerobic means 'without air' or 'without oxygen'. Body obtains energy by burning glycogen stored in the muscles without oxygen. Anaerobic exercise involves exertion for short periods followed by periods of rest. It uses the muscles at high intensity and a high rate of work for a short period.

Burning glycogen without oxygen liberates lactic acid. Accumulation of lactic acid leads to fatigue. Therefore, this type of exercise cannot be performed for longer period. And a recovery period is essential before going for another burst of anaerobic exercise. Anaerobic exercise helps to increase the muscle strength.

Examples of anaerobic exercise:

1. Pull ups
2. Push ups
3. Weightlifting
4. Sprinting
5. Any other rapid burst of strenuous exercise.

■ SEVERITY OF EXERCISE

The cardiovascular and other changes in the body depend upon the severity of exercise also. Based on severity, the exercise is classified into three types:

1. Mild exercise
2. Moderate exercise
3. Severe exercise.

■ 1. MILD EXERCISE

It is the very simple form of exercise like slow walking. Little or no change occurs in cardiovascular system during mild exercise.

■ 2. MODERATE EXERCISE

Moderate exercise does not involve strenuous muscular activity and it can be performed for a longer period. Exhaustion does not occur at the end of moderate exercise. The examples of this type of exercise are fast walking and slow running.

■ 3. SEVERE EXERCISE

Severe exercise involves strenuous muscular activity and it can be performed only for short duration. Fast running for a distance of 100 or 400 meters is the best example of this type of exercise. Complete exhaustion occurs at the end of severe exercise.

■ EFFECTS OF EXERCISE ON CARDIOVASCULAR SYSTEM

■ 1. ON BLOOD

Red blood cell count increases because of release of erythropoietin from juxtaglomerular apparatus due to hypoxia. The pH of blood decreases due to increased carbon dioxide content.

■ 2. ON BODY FLUIDS

More heat is produced during exercise and the thermoregulatory system is activated. This in turn,

causes secretion of large amount of sweat leading to:

- i. Fluid loss
- ii. Reduced blood volume
- iii. Hemoconcentration
- iv. Sometimes, severe exercise leads to dehydration.

■ 3. ON HEART RATE

Heart rate increases during exercise. Even the thought of exercise or preparation for exercise increases the heart rate. It is because of impulses from cerebral cortex to medullary centers, which reduces vagal tone.

In moderate exercise, the heart rate increases to 180 beats/minute. In severe muscular exercise it reaches 240 to 260 beats/minute. The increased heart rate during exercise is mainly vagal withdrawal and increase in sympathetic tone.

■ 4. ON CARDIAC OUTPUT

Cardiac output increases up to 20 liters/minute in moderate exercise and up to 35 liters/minute during severe exercise. The increase in cardiac output is directly proportional to the increase in the amount of oxygen consumed during exercise.

■ 5. ON VENOUS RETURN

Venous return increases during exercise because of muscle pump, respiratory pump and splanchnic vasoconstriction.

■ 6. ON BLOOD FLOW TO SKELETAL MUSCLES

There is increase in the amount of blood flowing to skeletal muscles during exercise. In resting

condition, the blood supply to the skeletal muscles is 3 to 4 mL/100 gram of the muscle/minute. It increases up to 60 to 80 mL in moderate exercise and up to 90 to 120 mL in severe exercise.

During the muscular activity, stoppage of blood flow occurs when the muscles contract. It is because of compression of blood vessels during contraction. And in between the contractions, the blood flow increases.

■ 7. ON BLOOD PRESSURE

During moderate isotonic exercise, the systolic pressure is increased. It is due to increase in heart rate and stroke volume. Diastolic pressure is not altered because peripheral resistance is not affected during moderate isotonic exercise.

In severe exercise involving isotonic muscular contraction, the systolic pressure enormously increases but the diastolic pressure decreases. The decrease in diastolic pressure is because of the decrease in peripheral resistance. Decrease in peripheral resistance is due to vasodilatation caused by metabolites.

During exercise involving isometric contraction, the peripheral resistance increases. So, the diastolic pressure also increases along with systolic pressure.

Blood Pressure after Exercise

After exercise, the blood pressure falls below the resting level. It is because of vasodilatation caused by metabolic end products accumulated in muscles during exercise. However, the pressure returns to resting level quickly as soon as the metabolic end products are removed from muscles.

QUESTIONS IN CARDIOVASCULAR SYSTEM

■ LONG QUESTIONS

1. Define cardiac cycle. Describe various events of cardiac.
2. Define electrocardiogram. Describe the waves, segments and intervals of normal ECG. Add a note on ECG leads.
3. Give the definitions, normal values and variations of cardiac output. Explain the factors regulating cardiac output.
4. What is cardiac output? Enumerate the various methods to measure cardiac output and, explain the measurement of cardiac output by applying Fick's principle.
5. Describe the innervation of heart and the regulation of heart rate.
6. Define arterial blood pressure. Describe the nervous regulation (short-term) of arterial blood pressure.
7. Describe renal mechanism of (long-term) regulation of arterial blood pressure.

■ SHORT QUESTIONS

1. Action potential in cardiac muscle.
2. Pacemaker.

3. Conductive system in heart.
4. Isometric contraction period.
5. Heart sounds.
6. Waves of normal ECG.
7. ECG leads.
8. Peripheral resistance.
9. Fick's principle.
10. Cardiac centers.
11. Nerve supply to heart.
12. Vagal tone.
13. Baroreceptors.
14. Chemoreceptors.
15. Bainbridge reflex.
16. Determinants of arterial blood pressure.
17. Vasomotor center.
18. Vasomotor tone.
19. Renal regulation of blood pressure.
20. Renin-angiotensin mechanism.
21. Hypertension.
22. Venous pressure.
23. Capillary pressure.
24. Arterial pulse.
25. Phlebogram/venous pulse.
26. Capillary circulation (microcirculation).
27. Effect of exercise on blood pressure.

SECTION 9

Respiratory System and Environmental Physiology

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Respiratory Tract and Pulmonary Circulation

- INTRODUCTION
- FUNCTIONAL ANATOMY OF RESPIRATORY TRACT
- RESPIRATORY UNIT
- NONRESPIRATORY FUNCTIONS OF RESPIRATORY TRACT
- RESPIRATORY PROTECTIVE REFLEXES
- PULMONARY CIRCULATION

■ INTRODUCTION

Respiration is the process by which oxygen is taken in and carbon dioxide is given out. The normal respiratory rate in adults is 12 to 16/minute.

■ TYPES OF RESPIRATION

Respiration is often classified into two types:

1. External respiration that involves exchange of respiratory gases, i.e. oxygen and carbon dioxide between lungs and blood.
2. Internal respiration which involves exchange of gases between blood and tissues.

■ PHASES OF RESPIRATION

Respiration occurs in two stages:

1. Inspiration during which the air enters the lungs from atmosphere
2. Expiration during which the air leaves the lungs.

■ FUNCTIONAL ANATOMY OF RESPIRATORY TRACT

Respiratory tract is the anatomical structure through which air moves in and out. It consists of nose, pharynx, larynx, trachea, bronchi and lungs (Fig. 72-1).

Pleura

Each lung is enclosed by a bilayered serous membrane called pleura or pleural sac. The two layers of pleura are the visceral and parietal layers. Visceral (inner) layer lines the surface of the lungs. At hilum, it is continuous with parietal (outer) layer, which is attached to the wall of the thoracic cavity.

The narrow space in between the two layers of pleura is called intrapleural space or pleural cavity. Its space contains a thin film of pleural fluid which is involved in the creating the negative pressure called intrapleural pressure within intrapleural space.

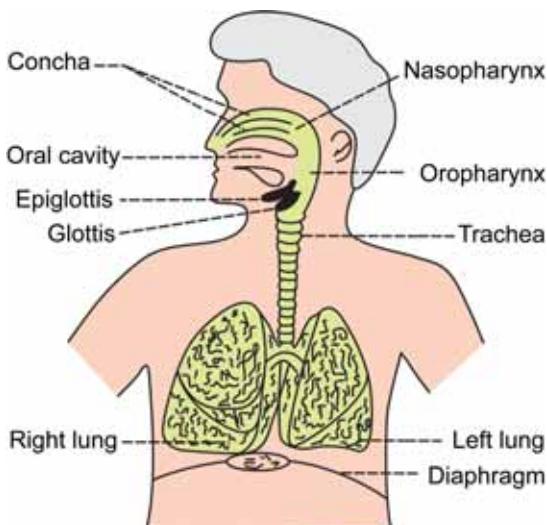


FIGURE 72-1: Respiratory tract

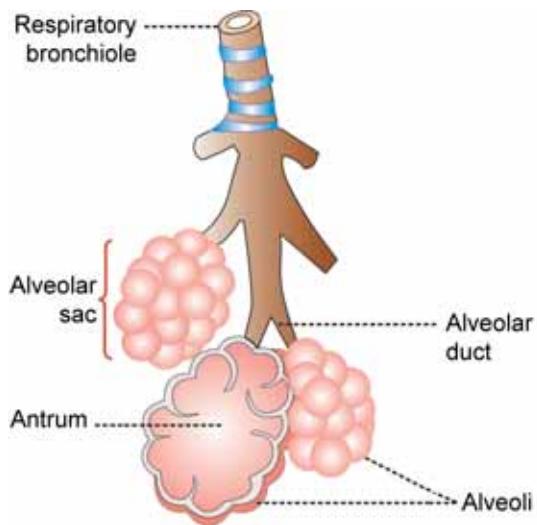


FIGURE 72-2: Respiratory unit

Tracheobronchial Tree

The trachea and bronchi are together called tracheobronchial tree. It forms a part of air passage.

The trachea bifurcates into two main or primary bronchi called right and left bronchi. Each primary bronchus enters the lungs and divides into secondary bronchi. The secondary bronchi divide into tertiary bronchi. In right lung, there are ten tertiary bronchi and, in left lung, there are eight tertiary bronchi.

The tertiary bronchi divide several times with reduction in length and diameter into many generations of bronchioles. When the diameter of bronchioles becomes 1 mm or less, it is called terminal bronchiole. Terminal bronchiole continues or divides into respiratory bronchiole, which has a diameter of 0.5 mm.

Generally, the respiratory tract is divided into two parts:

1. Upper respiratory tract which includes all the structures from nose up to vocal cords
2. Lower respiratory tract that includes trachea, bronchi and lungs.

■ RESPIRATORY UNIT

Lung parenchyma is formed by respiratory unit that forms the terminal portion of respiratory tract.

Respiratory unit is defined as the structural and functional unit of lung. The exchange of gases occurs only in this part of the respiratory tract.

■ STRUCTURE OF RESPIRATORY UNIT

The respiratory unit starts from the respiratory bronchioles (Fig. 72-2). Each respiratory bronchiole divides into alveolar ducts. Each alveolar duct enters an enlarged structure called the alveolar sac. The space inside the alveolar sac is called antrum. Alveolar sac consists of a cluster of alveoli. Few alveoli are present in the wall of alveolar duct also.

Thus, respiratory unit includes:

1. Respiratory bronchioles
2. Alveolar ducts
3. Alveolar sacs
4. Antrum
5. Alveoli.

Each alveolus is like a pouch with the diameter of about 0.2 to 0.5 mm. It is lined by epithelial cells called alveolar cells or pneumocytes. Alveolar cells are of two types:

- i. Type I alveolar cells which form the site of gaseous exchange between alveolus and blood
- ii. Type II alveolar cells which secrete the alveolar fluid and surfactant.

■ RESPIRATORY MEMBRANE

Respiratory membrane is the structure through which the exchange of gases occurs. It separates air in the alveoli from the blood in capillary. It is formed by the alveolar membrane and capillary membrane. Respiratory membrane has a surface area of 70 sq. meters and thickness of 0.5 microns. The structure of respiratory membrane is explained in Chapter 76 (Fig. 76-1).

■ NONRESPIRATORY FUNCTIONS OF RESPIRATORY TRACT

Besides the primary function of gaseous ex-change, the respiratory tract is involved in several nonrespiratory functions of the body.

■ 1. OLFACTION

Olfactory receptors present in the mucous membrane of nostril are responsible for olfactory sensation.

■ 2. VOCALIZATION

Along with other structures, larynx forms the speech apparatus.

■ 3. PREVENTION OF DUST PARTICLES

The dust particles, which enter the nostrils from air, are prevented from reaching the lungs by filtration action of the hairs in nasal mucous membrane. The small particles, which escape the hairs, are held by the mucus secreted by the nasal mucous membrane. Those dust particles, which escape the nasal hairs and nasal mucous membrane, are removed by the phagocytic action of the macrophages in the alveoli. The particles which escape the protective mechanisms in nose and alveoli are thrown out by cough reflex and sneezing reflex.

■ 4. DEFENSE MECHANISM

The defense functions of the lungs are performed by their own defenses and by the presence of various types of cells in the mucous membrane lining the alveoli of lungs. These cells are leuko-

cytes, macrophages, mast cells, natural killer cells and dendritic cells.

i. Lung's Own Defenses

The epithelial cells lining the air passage secrete some innate immune factors called defensins and cathelicidins. These substances are the antimicrobial peptides which play an important role in lung's natural defenses.

ii. Defense through Leukocytes

The leukocytes, particularly the neutrophils and lymphocytes present in the alveoli of lungs provide defense mechanism against bacteria and virus. The neutrophils kill the bacteria by phagocytosis. Lymphocytes develop immunity against bacteria.

iii. Defense through Macrophages

Macrophages engulf the dust particles and the pathogens, which enter the alveoli and thereby act as scavengers in lungs. Macrophages are also involved in the development of immunity by functioning as antigen presenting cells.

iv. Defense through Mast Cell

Mast cell produces the allergic reaction.

v. Defense through Natural Killer Cell

Natural killer (NK) cell destroys the micro-organisms like viruses and the viral infected or damaged cells, which may form the tumors. It also destroys the malignant cells and prevents development of cancerous tumors.

vi. Defense through Dendritic Cells

Dendritic cells in the lungs function as antigen presenting cells.

■ 5. MAINTENANCE OF WATER BALANCE

Respiratory tract plays a role in water loss mechanism. During expiration, water evaporates through the expired air and some amount of body water is lost by this process.

■ 6. REGULATION OF BODY TEMPERATURE

During expiration, along with water, heat is also lost from the body. Thus, respiratory tract plays a role in heat loss mechanism.

■ 7. REGULATION OF ACID-BASE BALANCE

Lungs play a role in maintenance of acid-base balance of the body by regulating the carbon dioxide content in blood. Carbon dioxide is produced during various metabolic reactions in the tissues of the body. When it enters the blood, carbon dioxide combines with water to form carbonic acid. Since carbonic acid is unstable, it splits into hydrogen and bicarbonate ions.



The entire reaction is reversed in lungs when carbon dioxide is removed from blood into the alveoli of lungs.



As carbon dioxide is a volatile gas, it is practically blown out by ventilation.

■ 8. ANTICOAGULANT FUNCTION

Mast cells in lungs secrete heparin. Heparin is an anticoagulant and it prevents the intravascular clotting.

■ 9. SECRETION OF ANGIOTENSIN CONVERTING ENZYME

Endothelial cells of the pulmonary capillaries secrete the angiotensin converting enzyme (ACE). It converts the angiotensin I into active angiotensin II which plays an important role in the regulation of ECF volume and blood pressure (Chapter 35).

■ 10. SYNTHESIS OF HORMONAL SUBSTANCES

Lung tissues are also known to synthesize the hormonal substances, prostaglandins, acetyl-

choline and serotonin which have many physiological actions in the body including regulation of blood pressure (Chapter 52).

■ RESPIRATORY PROTECTIVE REFLEXES

Respiratory protective reflexes are the reflexes that protect the lungs and air passage from foreign particles. The respiratory protective reflexes are:

■ COUGH REFLEX

Cough is a modified respiratory process characterized by forced expiration. It is the protective reflex that occurs because of irritation of respiratory tract and some other areas such as external auditory canal. Cough is produced mainly by irritant agents.

Mechanism

Cough begins with deep inspiration followed by forced expiration with closed glottis. This increases the intrapleural pressure above 100 mm Hg. Then, glottis opens suddenly with explosive outflow of air at a high velocity. The velocity of the airflow may reach 960 km/hour. It causes expulsion of irritants out of the respiratory tract.

■ SNEEZING REFLEX

Sneezing is also a modified respiratory process characterized by forced expiration. It is the protective reflex caused by irritation of nasal mucous membrane. Irritation of the nasal mucous membrane occurs because of dust particles, debris, mechanical obstruction of the airway, and excess fluid accumulation in the nasal passages.

Mechanism

Sneezing starts with deep inspiration, followed by forceful expiratory effort with opened glottis resulting in expulsion of irritant agents out of respiratory tract.

■ SWALLOWING (DEGLUTITION) REFLEX

Swallowing is a respiratory protective reflex that prevents entrance of food particles into the air passage during swallowing.

While swallowing of the food, the respiration is arrested for a while. The temporary arrest of respiration is called apnea. The arrest of breathing during swallowing is called swallowing apnea or deglutition apnea. It takes place during pharyngeal stage, i.e. II stage of deglutition and prevents entry of food particles into the respiratory tract. Refer Chapter 33 for details.

■ PULMONARY CIRCULATION

■ PULMONARY BLOOD VESSELS

Pulmonary blood vessels include pulmonary artery which carries deoxygenated blood to alveoli of lungs and bronchial artery which supply oxygenated blood to other structures of lungs (see below).

Pulmonary Artery

Pulmonary artery supplies deoxygenated blood pumped from right ventricle to alveoli of lungs (pulmonary circulation). After leaving the right ventricle, it divides into right and left branches. Each branch enters the corresponding lung along with primary bronchus. After entering the lung, the branch of the pulmonary artery divides into small vessels and finally forms the capillary plexus that is in intimate relationship to alveoli. Capillary plexus is solely concerned with alveolar gas exchange. Oxygenated blood from the alveoli is carried to left atrium by one pulmonary vein from each side.

Bronchial Artery

Bronchial artery arises from descending thoracic aorta. It supplies arterial blood to bronchi, connective tissue and other structures of lung stroma, visceral pleura and pulmonary lymph nodes. Venous blood from these structures is

drained by two bronchial veins from each side. However, the blood from distal portion of bronchial circulation is drained directly into the tributaries of pulmonary veins.

Physiological Shunt

Physiological shunt is a diversion through which the venous blood is mixed with arterial blood. The deoxygenated blood flowing from bronchial circulation into pulmonary veins without being oxygenated makes up part of normal physiological shunt. The other component of physiological shunt is the drainage of deoxygenated blood from thebesian veins into cardiac chambers directly (Chapter 68).

■ CHARACTERISTIC FEATURES OF PULMONARY BLOOD VESSELS

1. The pulmonary artery has a thin wall and it has only about 1/3 of thickness of the systemic aortic wall. The wall of other pulmonary blood vessels is also thin
2. The pulmonary blood vessels are highly elastic and more distensible
3. The smooth muscle coat is not well developed in the pulmonary blood vessels
4. True arterioles have less smooth muscle fibers
5. Pulmonary capillaries are larger than systemic capillaries.
6. Vascular resistance in pulmonary circulation is very less; it is only one tenth of systemic circulation
7. Pulmonary vascular system is a low pressure system (see below)
8. Pulmonary artery carries deoxygenated blood from heart to lungs and pulmonary veins carry oxygenated blood from lungs to heart
9. Physiological shunt is present.

■ PULMONARY BLOOD FLOW

The lungs receive the whole amount of blood that is pumped out from right ventricle. The output

of blood per minute is same in both the right and left ventricle. It is about 5 liters.

■ PULMONARY BLOOD PRESSURE

The pulmonary blood pressure is less than systemic blood pressure because the pulmonary blood vessels are more distensible than systemic blood vessels. Thus, the entire pulmonary vascular system is a low pressure bed.

Pulmonary Arterial Pressure

Systolic pressure : 25 mm Hg
Diastolic pressure : 10 mm Hg
Mean arterial pressure : 15 mm Hg

Pulmonary Capillary Pressure

The pulmonary capillary pressure is about 7 mm Hg.

73

Mechanics of Respiration

- RESPIRATORY MOVEMENTS
- RESPIRATORY PRESSURES
- COMPLIANCE
- WORK OF BREATHING

■ RESPIRATORY MOVEMENTS

■ INTRODUCTION

During normal quiet breathing, inspiration is the active process and expiration is the passive process. During inspiration, thoracic cage enlarges and lungs expand so that air enters the lungs easily. During expiration, the thoracic cage and lungs decrease in size and attain the preinspiratory position so that air leaves the lungs easily.

■ MUSCLES OF RESPIRATION

Muscles involved in inspiratory movements are known as inspiratory muscles and the muscles involved in expiratory movements are called expiratory muscles. However, the respiratory muscles are generally classified into two types:

1. Primary or major respiratory muscles which are responsible for change in size of thoracic cage during normal quiet breathing
2. Accessory respiratory muscles that help primary respiratory muscles during forced respiration.

Inspiratory Muscles

Primary inspiratory muscles are diaphragm and external intercostal muscles. Accessory inspiratory muscles are sternocleidomastoid, scaleni, anterior serrati, elevators of scapulae and pectorals.

Expiratory Muscles

Primary expiratory muscles are the internal intercostal muscles. Accessory expiratory muscles are the abdominal muscles.

■ MOVEMENTS OF THORACIC CAGE

Inspiration causes enlargement of thoracic cage. Thoracic cage enlarges because of increase in all diameters, viz. anteroposterior, transverse and vertical diameters. Increase in anteroposterior and transverse diameters occurs due to the elevation of ribs. The vertical diameter of thoracic cage is increased by the descent of diaphragm.

In general, the change in the size of thoracic cavity occurs because of the movements of four units of structures.

1. Thoracic lid
2. Upper costal series
3. Lower costal series
4. Diaphragm.

1. Thoracic Lid

The thoracic lid is formed by manubrium sterni and the first pair of ribs. Movement of thoracic lid increases the anteroposterior diameter of thoracic cage.

2. Upper Costal Series

The upper costal series is constituted by second to sixth pair of ribs. Upper costal series increases the anteroposterior and transverse diameter of the thoracic cage by pump handle movement and bucket handle movement.

Pump handle movement

During inspiration, there is elevation of upper costal series of ribs and upward and forward movement of sternum. This movement is called pump handle movement. It increases anteroposterior diameter of the thoracic cage.

Bucket handle movement

Simultaneously, the central portions of these ribs (arches of ribs) move upwards and outwards to a more horizontal position. This movement is called bucket handle movement and it increases the transverse diameter of thoracic cage.

3. Lower Costal Series

It is formed by the seventh to tenth pair of ribs. Movement of lower costal series increases the transverse diameter of the thoracic cage. These ribs also show bucket handle movement by swinging outward and upward.

The eleventh and twelfth pairs of ribs are the floating ribs, which are not involved in changing the size of thoracic cage.

4. Diaphragm

Movement of diaphragm increases the vertical diameter of thoracic cage. Normally, before inspiration the diaphragm is dome-shaped with

convexity facing upwards. During inspiration, due to the contraction of muscle fibers the central tendinous portion is drawn downwards so the diaphragm is flattened and increases the vertical diameter of the thoracic cage.

■ MOVEMENTS OF LUNGS

During inspiration, due to the enlargement of thoracic cage, the negative pressure is increased in the thoracic cavity. It causes expansion of the lungs. During expiration, the thoracic cavity decreases in size to the preinspiratory position. The pressure in the thoracic cage also comes back to the preinspiratory level. It compresses the lung tissues so that, the air is expelled out of lungs.

Collapsing Tendency of Lungs

The lungs are under constant threat to collapse even under resting conditions because of certain factors.

Factors causing collapsing tendency of lungs

Two factors are responsible for the collapsing tendency of lungs

1. Elastic property of lung tissues which show constant recoiling tendency and try to collapse the lungs
2. Surface tension exerted on the surface of the alveolar membrane by the fluid secreted from alveolar epithelium.

Fortunately, there are some factors which save the lungs from collapsing.

Factors preventing collapsing tendency of lungs

In spite of the elastic property of the lungs and the surface tension in the alveoli of lungs, the collapsing tendency of lungs is prevented by two factors:

1. Intrapleural pressure which is always negative (see below). Because of negativity, it keeps the lungs expanded and prevents the collapsing tendency of lungs produced by the elastic tissues
2. Surfactant secreted in alveolar epithelium. It reduces surface tension and prevents the collapsing tendency produced by surface tension.

Surfactant

Pulmonary surfactant is a surface acting material that decreases the surface tension on the alveolar membrane. It is secreted by two types of cells:

1. Type II alveolar epithelial cells in the lungs
2. Clara cells, which are situated in the bronchioles.

Chemistry

Surfactant is a lipoprotein complex formed by lipids especially phospholipids, proteins and ions. The phospholipid dipalmitoylphosphatidylcholine (DPPC) is the major component of surfactant.

Functions

1. The surfactant reduces the surface tension in the alveoli of lungs and prevents the collapsing tendency of lungs. The phospholipid molecule in the surfactant is responsible for this
2. The surfactant is responsible for stabilization of the alveoli, which is necessary to withstand the collapsing tendency.
3. It plays an important role in the inflation of lungs after birth. In fetus, lungs are solid and not expanded. First breath starts soon after birth. Although the respiratory movements are attempted by the infant, the lungs tend to collapse repeatedly. And, the presence of surfactant in the alveoli prevents the lungs from collapsing.
4. The hydrophilic proteins in surfactant play a role in defense in the lungs by destroying the bacteria and viruses.

Effect of deficiency of surfactant – respiratory distress syndrome

Deficiency or absence of surfactant in infants causes collapse of lungs. This condition is called respiratory distress syndrome or hyaline membrane disease. The deficiency of surfactant occurs in adults also and it is called adult respiratory distress syndrome (ARDS).

■ RESPIRATORY PRESSURES

Two types of pressures are exerted in the thoracic cavity and the lungs during the process of respiration:

1. Intrapleural pressure or intrathoracic pressure
2. Intra-alveolar pressure or intrapulmonary pressure.

■ INTRAPLEURAL PRESSURE

Definition

The intrapleural pressure is the pressure existing in pleural cavity, that is, in between the visceral and parietal layers of pleura. It is exerted by the suction of the fluid that lines the pleural cavity (Fig. 73-1). It is also called intrathoracic pressure since it is exerted in the whole of thoracic cavity.

Normal Values

Respiratory pressures are expressed in relation to atmospheric pressure which is 760 mm Hg. Intrapleural pressure is always negative.

The normal values are:

1. At the end of normal inspiration: -6 mm Hg ($760 - 6 = 754$ mm Hg)
2. At the end of normal expiration: -2 mm Hg ($760 - 2 = 758$ mm Hg)
3. At the end of forced inspiration: -30 mm Hg.

Cause for Negativity of Intrapleural Pressure

The pleural cavity is always lined by a thin layer of fluid that is secreted by the visceral layer of pleura. This fluid is constantly pumped from the pleural cavity into the lymphatic vessels. The pumping of fluid creates the negative pressure in the pleural cavity.

Significance of Intrapleural Pressure

Throughout the respiratory cycle intrapleural pressure remains lower than intra-alveolar pressure. This keeps the lungs always inflated.

The intrapleural pressure has two important functions:

- i. It prevents the collapsing tendency of lungs

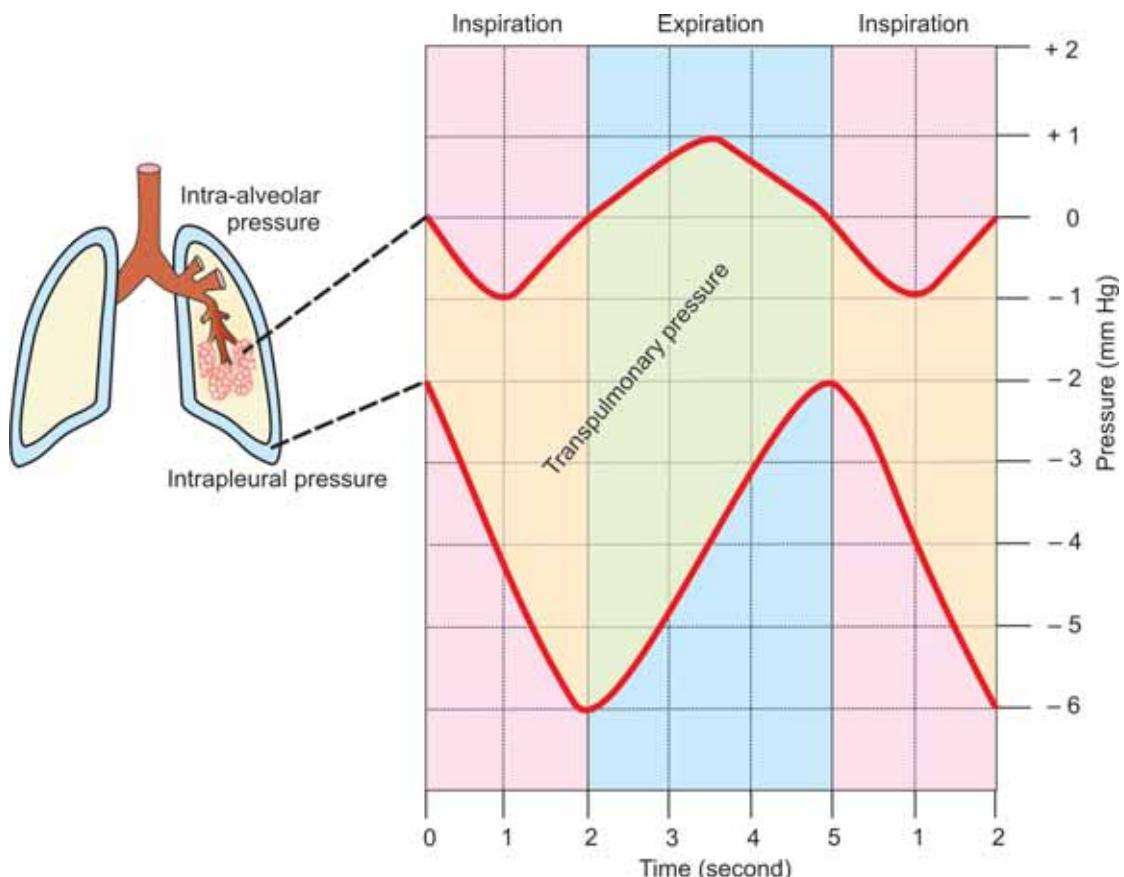


FIGURE 73-1: Changes in respiratory pressures during inspiration and expiration
'0' indicates the normal atmospheric pressure (760 mm Hg)

- ii. It causes dilatation of vena cava and larger veins in thorax. Also, the negative pressure acts like suction pump and pulls the venous blood from lower part of body towards the heart against gravity. Thus, the intrapleural pressure is responsible for the venous return. So, it is called the respiratory pump for venous return (Chapter 63).

■ INTRA-ALVEOLAR PRESSURE

Definition

Intra-alveolar pressure is the pressure existing in the alveoli of the lungs. It is also known as intrapulmonary pressure.

Normal Values

Normally, intra-alveolar pressure becomes negative during inspiration and positive during expiration.

The normal values are:

1. During normal inspiration: -1 mm Hg
 $(760 - 1 = 759 \text{ mm Hg})$
2. During normal expiration: $+1 \text{ mm Hg}$
 $(760 + 1 = 761 \text{ mm Hg})$
3. At the end of inspiration and expiration: Equal to atmospheric pressure (760 mm Hg)

Significance of Intra-alveolar Pressure

- i. It causes flow of air in and out of alveoli. During inspiration, the intra-alveolar

pressure becomes negative, so the atmospheric air enters the alveoli. And, during expiration, the air is expelled out of alveoli

- ii. It also helps in the exchange of gases between the alveolar air and the blood.

Transpulmonary Pressure

Transpulmonary pressure is the difference between intra-alveolar pressure and intrapleural pressure.

■ COMPLIANCE

■ DEFINITION

Compliance is the ability of the lungs and thorax to expand or it is the expansibility of lungs and thorax. It is defined as the change in volume per unit change in the pressure. Determination of compliance is useful as it is the measure of stiffness of lungs. Stiffer the lungs, less is the compliance.

■ NORMAL VALUES

The compliance is expressed in relation to respiratory pressures.

Compliance in Relation to Intra-alveolar Pressure

Compliance is the volume increase in lungs per unit increase in the intra-alveolar pressure.

1. Compliance of lungs and thorax together: 130 mL/1 cm H₂O pressure
2. Compliance of lungs alone: 220 mL/1 cm H₂O pressure.

Compliance in Relation to Intrapleural Pressure

Compliance is the volume increase in lungs per unit decrease in the intrapleural pressure.

1. Compliance of lungs and thorax together = 100 mL/1 cm H₂O pressure
2. Compliance of lungs alone = 200 mL/1 cm H₂O pressure.

Thus, if lungs are removed from thorax, the expansibility (compliance) of lungs alone is doub-

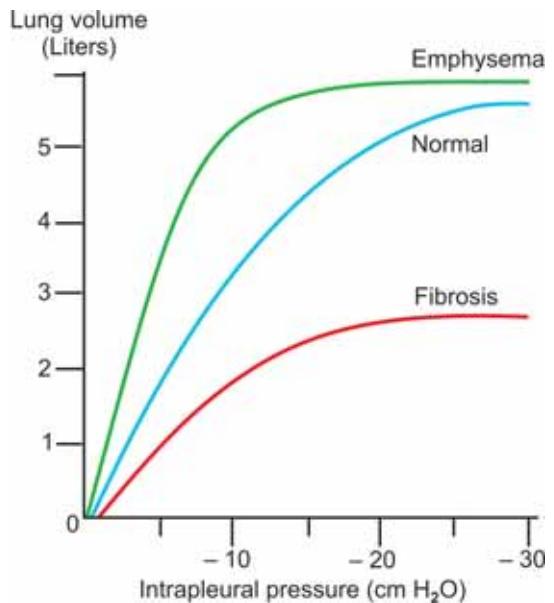


FIGURE 73-2: Variations in lung compliance

led. It is because of the absence of the inertia and the restriction exerted by the structures of thoracic cage, which interfere with expansion of lungs.

Variation in Compliance

Compliance increases in physiological and pathological conditions.

1. In old age, lung compliance increases due to loss of elastic property of lung tissues
2. In emphysema, lung compliance increases because of damage of alveolar membrane (Fig. 73-2).

Compliance decreases in pathological conditions such as:

1. Deformities of thorax like kyphosis and scoliosis
2. Paralysis of respiratory muscles
3. Pleural effusion
4. Fibrosis
5. Abnormal thorax.

■ WORK OF BREATHING

The work done by the respiratory muscles during breathing to overcome the resistance in the

thorax and respiratory tract is known as work of breathing.

■ WORK DONE BY RESPIRATORY MUSCLES

During the respiratory processes, inspiration is active process and the expiration is a passive process. So, during quiet breathing, the respiratory muscles perform the work only during inspiration and not during expiration.

The energy obtained during the work of breathing is utilized to overcome three types of resistance:

1. Airway resistance
2. Elastic resistance of lungs and thorax
3. Nonelastic viscous resistance.

1. Airway Resistance

Airway resistance is the resistance offered to the passage of air through respiratory tract. The work done to overcome this is called airway resistance work.

2. Elastic Resistance of Lungs and Thorax

The work done to overcome this elastic resistance is called compliance work.

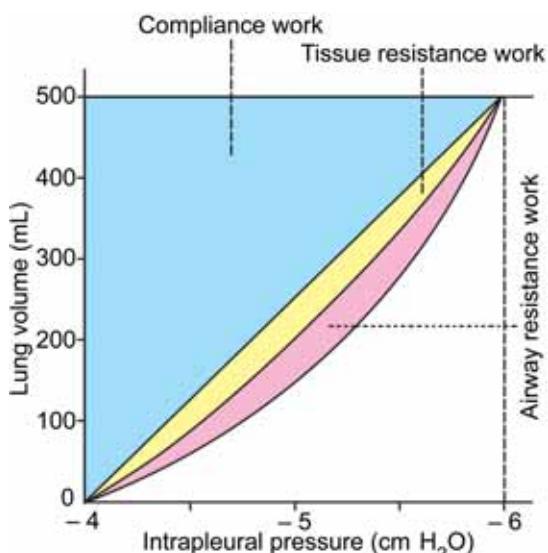


FIGURE 73-3: Work of breathing

3. Nonelastic Viscous Resistance

The work done to overcome this viscous resistance is called the tissue resistance work. The above factors are explained by the curve that shows the relation between lung volume and pleural pressure (Fig. 73-3).

Pulmonary Function Tests

- INTRODUCTION
- LUNG VOLUMES
 - TIDAL VOLUME
 - INSPIRATORY RESERVE VOLUME
 - EXPIRATORY RESERVE VOLUME
 - RESIDUAL VOLUME
- LUNG CAPACITIES
 - INSPIRATORY CAPACITY
 - VITAL CAPACITY
 - FUNCTIONAL RESIDUAL CAPACITY
 - TOTAL LUNG CAPACITY
- VITAL CAPACITY
- FORCED EXPIRATORY VOLUME OR TIMED VITAL CAPACITY
- RESPIRATORY MINUTE VOLUME
- MAXIMUM BREATHING CAPACITY OR MAXIMUM VENTILATION VOLUME
- PEAK EXPIRATORY FLOW RATE
- RESTRICTIVE AND OBSTRUCTIVE RESPIRATORY DISEASES

■ INTRODUCTION

Pulmonary function tests or lung function tests are useful in assessing the functional status of the respiratory system. These tests involve measurement of lung volumes and capacities.

The air in lung is classified into two divisions:

- I. Lung volumes
- II. Lung capacities.

Pulmonary function tests are carried out mostly by using spirometer (Fig. 74-1). The graphical recording of lung volumes and capacities is called spirogram (Fig. 74-2).

■ LUNG VOLUMES

Lung volumes are the static volumes of air breathed by an individual. The lung volumes are of four types.

■ 1. TIDAL VOLUME (TV)

Tidal volume is the volume of air breathed in and out of lungs in a single normal quiet respiration. Tidal volume signifies the normal depth of breathing.

Normal value = 500 mL (0.5 L)

■ 2. INSPIRATORY RESERVE VOLUME (IRV)

Inspiratory reserve volume is an additional volume of air that can be inspired forcefully after the end of normal inspiration.

Normal value = 3300 mL (3.3 L).

■ 3. EXPIRATORY RESERVE VOLUME (ERV)

Expiratory reserve volume is the additional volume of air that can be expired out forcefully, after normal expiration.

Normal value = 1000 mL (1 L).

■ 4. RESIDUAL VOLUME (RV)

Residual volume is the volume of air remaining in the lungs even after forced expiration. Normally, lungs cannot be emptied completely

even by forceful expiration. Some quantity of air always remains in the lungs even after the forced expiration. Residual volume helps to aerate the blood in between breathing and during expiration.

Normal value = 1200 mL (1.2 L)

■ LUNG CAPACITIES

Lung capacities are the combination of two or more lung volumes. Lung capacities are of four types.

■ 1. INSPIRATORY CAPACITY (IC)

Inspiratory capacity is the maximum volume of air that is inspired after normal expiration (end expiratory position). It includes tidal volume and inspiratory reserve volume (Figs. 74-2).

$$\text{IC} = \text{TV} + \text{IRV} \\ = 500 + 3300 = 3800 \text{ mL}$$

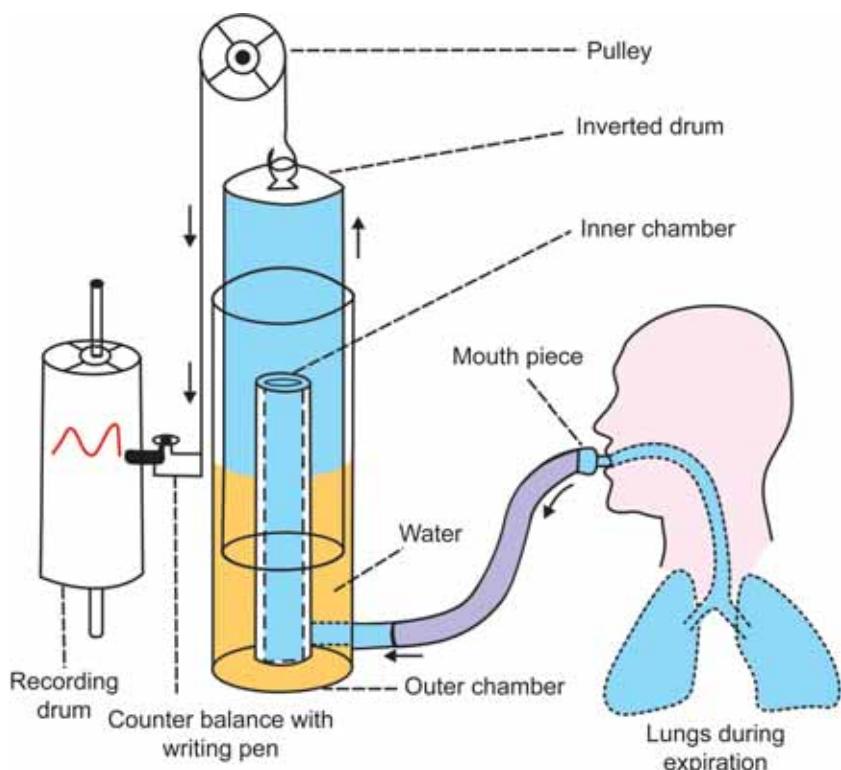


FIGURE 74-1: Spirometer. During expiration, the air enters the spirometer from lungs. The inverted drum moves up and the pen draws a downward curve on the recording drum

■ 2. VITAL CAPACITY (VC)

It is the maximum volume of air that can be expelled out forcefully after a deep (maximal) inspiration. Vital capacity includes inspiratory reserve volume, tidal volume and expiratory reserve volume.

$$\begin{aligned} \text{VC} &= \text{IRV} + \text{TV} + \text{ERV} \\ &= 3300 + 500 + 1000 = 4800 \text{ mL} \end{aligned}$$

■ 3. FUNCTIONAL RESIDUAL CAPACITY (FRC)

It is the volume of air remaining in the lungs after normal expiration (after normal tidal expiration). Functional residual capacity includes expiratory reserve volume and residual volume.

$$\begin{aligned} \text{FRC} &= \text{ERV} + \text{RV} \\ &= 1000 + 1200 = 2200 \text{ mL} \end{aligned}$$

■ 4. TOTAL LUNG CAPACITY (TLC)

Total lung capacity is the volume of air present in the lungs after a deep (maximal) inspiration. It includes all the volumes.

$$\begin{aligned} \text{TLC} &= \text{IRV} + \text{TV} + \text{ERV} + \text{RV} \\ &= 3300 + 500 + 1000 + 1200 = 6000 \text{ mL} \end{aligned}$$

■ VITAL CAPACITY

■ DEFINITION AND NORMAL VALUE

Definition and normal value of vital capacity are already given.

■ VARIATIONS OF VITAL CAPACITY

Physiological Variations

- Sex:* In females, vital capacity is less than in males
- Body built:* Vital capacity is slightly more in heavily built persons
- Posture:* Vital capacity is more in standing position and less in lying position
- Athletes:* Vital capacity is more in athletes
- Occupation:* Vital capacity is decreased in people with sedentary jobs. It is increased in persons who play musical wind instruments such as bugle and flute.

Pathological Variations

Vital capacity is reduced in the following respiratory diseases:

- Asthma
- Emphysema

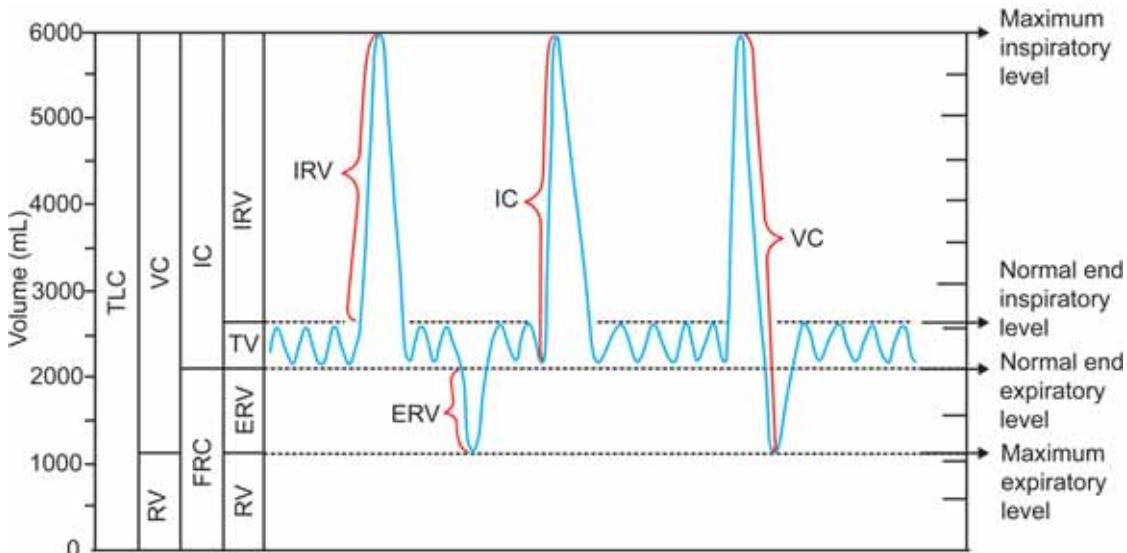


FIGURE 74-2: Spirogram. TV = Tidal volume. IRV = Inspiratory reserve volume. ERV = Expiratory reserve volume. RV = Residual volume. IC = Inspiratory capacity. FRC = Functional residual capacity. VC = Vital capacity. TLC = Total lung capacity

- iii. Weakness or paralysis of respiratory muscle
- iv. Pulmonary congestion
- v. Pneumonia
- vi. Pulmonary edema
- vii. Pulmonary tuberculosis.

■ FORCED EXPIRATORY VOLUME (FEV) OR TIMED VITAL CAPACITY

■ DEFINITION

Forced expiratory volume (FEV) is the volume of air, which can be expired forcefully in a given unit of time (after a deep inspiration). It is also called timed vital capacity.

FEV_1 : Volume of air expired forcefully in 1 second

FEV_2 : Volume of air expired forcefully in 2 seconds

FEV_3 : Volume of air expired forcefully in 3 seconds.

■ NORMAL VALUES

FEV in persons with normal respiratory functions is as follows:

FEV_1 = 83% of total vital capacity

FEV_2 = 94% of total vital capacity

FEV_3 = 97% of total vital capacity

After 3rd second = 100% of total vital capacity.

■ SIGNIFICANCE OF DETERMINING FEV

The vital capacity may be almost normal in some of the respiratory diseases. However, the FEV has great diagnostic value, as it is decreased significantly in some respiratory diseases. For example, it is very much decreased in the obstructive diseases like asthma and emphysema. It is slightly reduced in some of the restrictive respiratory diseases like fibrosis (Fig. 74-3).

■ RESPIRATORY MINUTE VOLUME (RMV)

Respiratory minute volume is the volume of air breathed in and out of lungs every minute. It is

the product of tidal volume (TV) and respiratory rate (RR).

$$RMV = TV \times RR$$

$$= 500 \times 12 = 6000 \text{ mL}$$

Normal respiratory minute volume is 6 L. It increases in physiological conditions such as voluntary hyperventilation, exercise and emotional conditions. It is reduced in respiratory diseases.

■ MAXIMUM BREATHING CAPACITY (MBC) OR MAXIMUM VENTILATION VOLUME (MVV)

Maximum breathing capacity (MBC) is the maximum volume of air which can be breathed in and out of lungs by forceful respiration (hyperventilation = increase in rate and force of respiration) per minute. It is also called maximum ventilation volume (MVV).

Normal value in adult male, it is 150 to 170 L/minute and, in females, it is 80 to 100 L/min. MBC is reduced in respiratory diseases.

■ PEAK EXPIRATORY FLOW RATE (PEFR)

Peak expiratory flow rate (PEFR) is the maximum rate at which the air can be expired after a deep inspiration. It is measured by Wright's peak flow meter or a mini peak flow meter.

Normal value is 400 L/minute.

■ SIGNIFICANCE OF DETERMINING PEFR

Determination of peak expiratory flow rate is useful for assessing the respiratory diseases especially to differentiate the obstructive and restrictive diseases. Generally, PEFR is reduced in all type of respiratory disease. However, the reduction is more significant in the obstructive diseases than in the restrictive diseases.

Thus, in restrictive diseases, the PEFR is 200 L/minute and in obstructive diseases, it is only 100 L/minute.

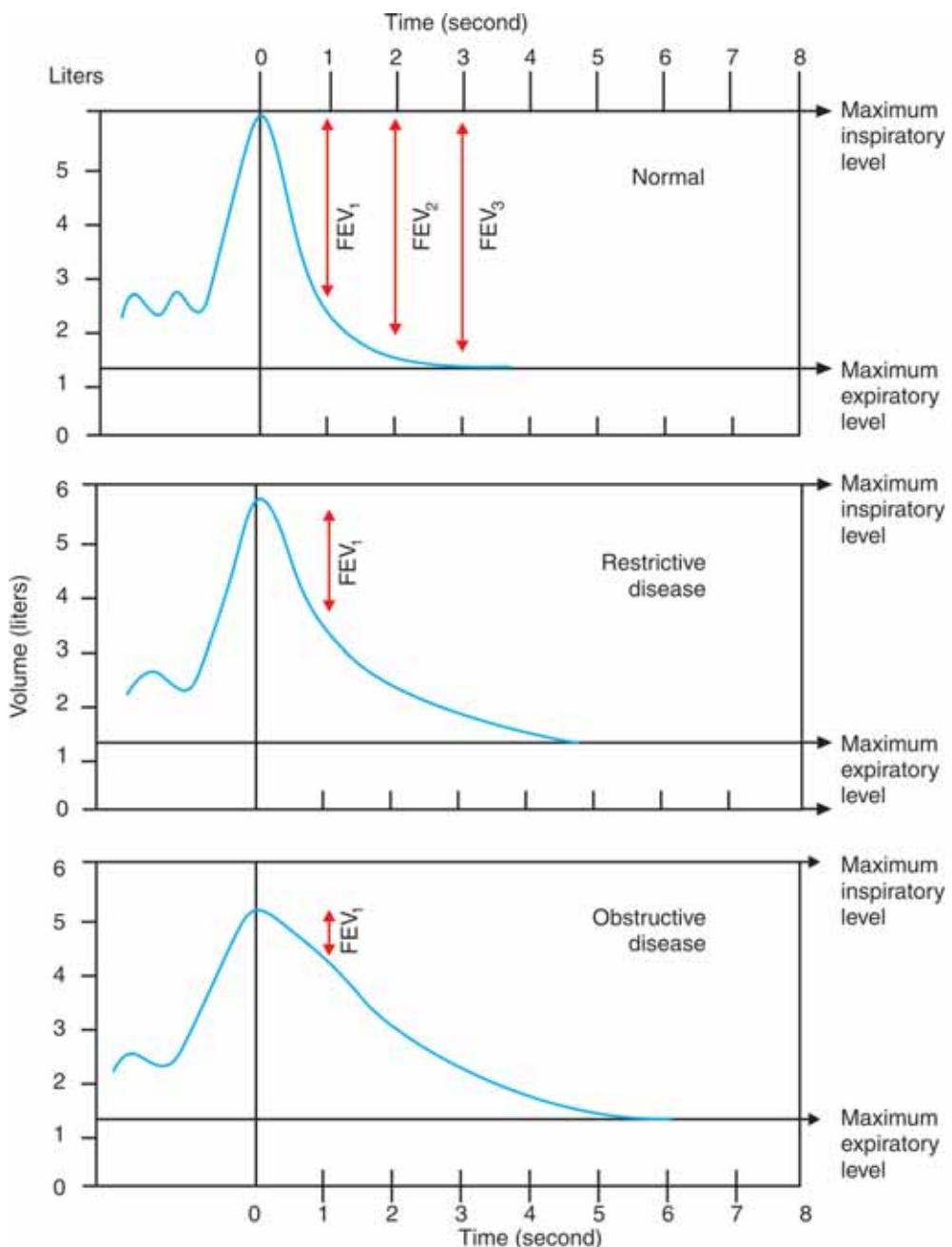


FIGURE 74-3: Forced expiratory volume

■ RESTRICTIVE AND OBSTRUCTIVE RESPIRATORY DISEASES

The diseases of respiratory tract are classified into two types:

1. Restrictive respiratory disease
2. Obstructive respiratory disease.

These two types of respiratory diseases are determined by lung functions tests, particularly FEV.

TABLE 74-1: Restrictive and obstructive respiratory diseases

Type	Disease	Structures involved
Restrictive respiratory diseases	Poliomyelitis	CNS
	Myasthenia gravis	CNS and thoracic cavity
	Flail chest (broken ribs)	Thoracic cavity
	Paralysis of diaphragm	CNS
	Spinal cord diseases	CNS
	Pleural effusion	Thoracic cavity
Obstructive respiratory diseases	Asthma	Lower respiratory tract
	Chronic bronchitis	
	Emphysema	
	Cystic fibrosis	
	Laryngotracheobronchitis	Upper respiratory tract
	Epiglottis	
	Tumors	
	Severe cough and cold with phlegm	

■ RESTRICTIVE RESPIRATORY DISEASE

Restrictive respiratory disease is the abnormal respiratory condition characterized by difficulty in inspiration. The expiration is not affected. Restrictive respiratory disease may be because of abnormality of lungs, thoracic cavity or/and nervous system.

■ OBSTRUCTIVE RESPIRATORY DISEASE

Obstructive respiratory disease is the abnormal respiratory condition characterized by difficulty in expiration. The obstructive and respiratory diseases are listed in Table 74-1.

Ventilation

- PULMONARY VENTILATION
 - DEFINITION
 - NORMAL VALUE AND CALCULATION
- ALVEOLAR VENTILATION
 - DEFINITION
 - NORMAL VALUE AND CALCULATION
- DEAD SPACE
 - DEFINITION
 - TYPES
 - NORMAL VALUE AND MEASUREMENT
- VENTILATION-PERFUSION RATIO
 - DEFINITION
 - NORMAL VALUE AND CALCULATION
 - SIGNIFICANCE
 - VARIATIONS
- INSPIRED AIR
- ALVEOLAR AIR
- EXPIRED AIR

■ PULMONARY VENTILATION

■ DEFINITION

Pulmonary ventilation is the volume of air moving in and out of lungs per minute in quiet breathing. It is also called respiratory minute volume (RMV).

■ NORMAL VALUE AND CALCULATION

Normal value of pulmonary ventilation is 6 L/minute. It is the product of tidal volume (TV) and the rate of respiration (RR). It is calculated by the formula:

Pulmonary ventilation

$$\begin{aligned}&= \text{Tidal volume} \times \text{Respiratory rate} \\&= 500 \text{ mL} \times 12/\text{minute} \\&= 6,000 \text{ mL} = 6 \text{ L/minute}\end{aligned}$$

■ ALVEOLAR VENTILATION

■ DEFINITION

Alveolar ventilation is the amount of air utilized for gaseous exchange every minute. Alveolar ventilation is different from pulmonary ventilation. In pulmonary ventilation, 6 L of air moves in and

out of lungs in every minute. But the whole volume of air is not utilized for exchange of gases. The volume of air subjected for exchange of gases is the alveolar ventilation. The air trapped in the respiratory passage (dead space) does not take part in gaseous exchange.

■ NORMAL VALUE AND CALCULATION

Normal value of alveolar ventilation is 4,200 mL (4.2 L)/ minute.

It is calculated by the formula given below.

$$\begin{array}{cccc} \text{Alveolar} & \text{Tidal} & \text{Dead} & \text{Respiratory} \\ \text{ventilation} & \text{volume} & \text{space} & \text{rate} \\ \hline & = (500 - 150) \times 12 \\ & = 4,200 \text{ mL} = 4.2 \text{ L/minute} \end{array}$$

■ DEAD SPACE

■ DEFINITION

Dead space is defined as the part of the respiratory tract, where gaseous exchange does not take place. The air present in the dead space is called dead space air.

■ TYPES OF DEAD SPACE

Dead space is of two types:

- I. Anatomical dead space
- II. Physiological dead space.

Anatomical Dead Space

It includes nose, pharynx, trachea, bronchi and branches of bronchi up to terminal bronchioles.

Physiological Dead Space

Physiological dead space includes the anatomical dead space plus two additional volumes.

1. The air in the alveoli, which are nonfunctioning. In some of the respiratory diseases, alveoli do not function because of dysfunction or destruction of alveolar membrane
2. The air in the alveoli, which do not receive adequate blood flow. Gaseous exchange does not take place during inadequate blood supply.

■ NORMAL VALUE AND MEASUREMENT OF DEAD SPACE

Under normal conditions, the physiological dead space is equal to anatomical dead space. It is because, all the alveoli are functioning and all alveoli receive adequate blood flow in normal conditions. The volume of normal dead space is 150 mL.

In respiratory disorders, which affect the pulmonary blood flow or the alveoli, the dead space increases. It is associated with reduction in alveolar ventilation.

The dead space is measured by single breath nitrogen washout method.

■ VENTILATION-PERFUSION RATIO

■ DEFINITION

The ventilation-perfusion ratio is the ratio of alveolar ventilation and the amount of blood that perfuse the alveoli.

It is expressed as V_A/Q

Where,

V_A is alveolar ventilation

Q is the blood flow (perfusion)

■ NORMAL VALUE AND CALCULATION

Normal Value

Normal value of ventilation-perfusion ratio is about 0.84.

Calculation

Alveolar ventilation is calculated by the formula:

$$\begin{array}{cccc} \text{Alveolar} & \text{Tidal} & \text{Dead} & \text{Respiratory} \\ \text{ventilation} & \text{volume} & \text{space} & \text{rate} \\ \hline & = (500 - 150) \times 12 \\ & = 4,200 \text{ mL/minute} \end{array}$$

Blood flow through alveoli

(Pulmonary blood flow) = 5,000 mL/minute

Therefore,

$$\text{Ventilation-perfusion ratio} = \frac{4,200}{5,000} = 0.84$$

■ SIGNIFICANCE OF VENTILATION-PERFUSION RATIO

The ventilation-perfusion ratio signifies the gaseous exchange. It is affected if there is any change in alveolar ventilation or in blood flow.

■ VARIATIONS IN VENTILATION-PERFUSION RATIO

Physiological Variation

1. Ratio increases, if ventilation increases without any change in blood flow
2. Ratio decreases if blood flow increases without any change in ventilation

Pathological Variation

In chronic obstructive pulmonary diseases (COPD), the ventilation is affected because of destruction of alveolar membrane. So, the ventilation-perfusion ratio reduces greatly.

■ INSPIRED AIR

Inspired air is the atmospheric air, which is inhaled during inspiration. The composition of inspired air is given in Table 75-1.

■ ALVEOLAR AIR

Alveolar air is the air present in the alveoli of lungs and it is collected by Haldane-Priestly tube. Alveolar air is different from the inspired air.

Differences between alveolar air and inspired air are:

1. The alveolar air is partially replaced by the atmospheric air during each breath
2. Oxygen diffuses from the alveolar air into pulmonary capillaries constantly
3. Carbon dioxide diffuses from pulmonary blood into alveolar air constantly
4. The dry atmospheric air is humidified, while passing through respiratory passage just before entering the alveoli (Table 75-1).

■ RENEWAL

The alveolar air is constantly renewed. The rate of renewal is slow during normal breathing. During each breath, out of 500 mL of tidal volume only 350 mL of air enters the alveoli and the remaining quantity of 150 mL (30%) becomes dead space air. Hence, the amount of alveolar air replaced by new atmospheric air with each breath is only about 70% of the total alveolar air. Thus,

$$\text{Alveolar air} = \frac{350}{500} \times 100 = 70\%$$

■ EXPIRED AIR

Expired air is the amount of air that is exhaled during expiration. It is a combination of dead space air and alveolar air. Expired air is collected by using Douglas bag.

The concentration of gases in expired air is somewhere between inspired air and alveolar air. The composition of expired air is given in Table 75-1.

TABLE 75-1: Composition of alveolar air, inspired air and expired air

Air	Inspired (atmospheric) air		Alveolar air		Expired air	
Gas	Content (mL %)	Partial pressure (mm Hg)	Content (mL %)	Partial pressure (mm Hg)	Content (mL %)	Partial pressure (mm Hg)
Oxygen	20.84	159.00	13.60	104.00	15.70	120.00
Carbon dioxide	0.04	0.30	5.30	40.00	3.60	27.00
Nitrogen	78.62	596.90	74.90	569.00	74.50	566.00
Water vapor etc.	0.50	3.80	6.20	47.00	6.20	47.00
Total	100.00	760.00	100.00	760.00	100.00	760.00

Exchange and Transport of Respiratory Gases

- EXCHANGE OF RESPIRATORY GASES IN LUNGS
- EXCHANGE OF RESPIRATORY GASES AT TISSUE LEVEL
- TRANSPORT OF OXYGEN
- TRANSPORT OF CARBON DIOXIDE

■ EXCHANGE OF RESPIRATORY GASES IN LUNGS

In the lungs, exchange of respiratory gases takes place between the alveoli and the blood. The exchange of gases occurs through bulk flow diffusion (Chapter 3).

Respiratory unit is the structure through which the exchange of gases between blood and alveoli takes place. Refer Chapter 72 for details.

■ RESPIRATORY MEMBRANE

Exchange of respiratory gases takes place through respiratory membrane. It is formed by the epithelium of the respiratory unit and endothelium of pulmonary capillary. The epithelium of the respiratory unit is a very thin layer (Chapter 72). Since the capillaries are in close contact with this membrane, the alveolar air is in close proximity to capillary blood. This facilitates the gaseous exchange between air and blood (Fig. 76-1).

The respiratory membrane is formed by different layers of structures belonging to the alveoli and capillaries. The different layers of respiratory membrane are as follows from within outside:

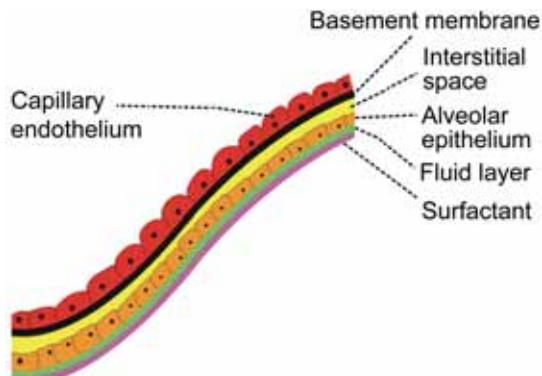


FIGURE 76-1: Structure of respiratory membrane

From Alveolar Portion

1. Monomolecular layer of surfactant, which spreads over the surface of the fluid lining of alveoli
2. A thin layer of fluid that lines the alveoli
3. The alveolar epithelial layer, which is composed of thin epithelial cells resting on a basement membrane

In between Alveolar Portion and Capillary Portion

4. An interstitial space

From Capillary Portion

5. Basement membrane of capillary
6. Capillary endothelial cells.

The average diameter of pulmonary capillary is only $8\text{ }\mu$, which means that the red blood cells with a diameter of $7.4\text{ }\mu$ actually squeeze through the capillaries. Therefore, the membrane of red blood cells is in close contact with capillary wall. This facilitates the quick exchange of oxygen and carbon dioxide between the blood and alveoli.

■ DIFFUSING CAPACITY

The diffusing capacity is defined as the volume of gas that diffuses through the respiratory membrane each minute for a pressure gradient of 1 mm Hg.

Diffusing Capacity for Oxygen and Carbon Dioxide

Diffusing capacity for oxygen is 21 mL/minute/1 mm Hg. Diffusing capacity for carbon dioxide is 400 mL/minute/1 mm Hg. Thus, the diffusing capacity for carbon dioxide is about 20 times more than that of oxygen.

Factors Affecting Diffusing Capacity

1. Pressure gradient

Diffusing capacity is directly proportional to the pressure gradient. Pressure gradient is the difference between the partial pressure of a gas in the alveoli and pulmonary capillary blood (see below). It is the major factor which affects the diffusing capacity.

2. Solubility of gas in fluid medium

Diffusing capacity is directly proportional to solubility of the gas. If the solubility of a gas is more in the fluid medium, a large number of molecules dissolve in it and diffuse easily.

3. Total surface area of respiratory membrane

Diffusing capacity is directly proportional to surface area of respiratory membrane. The surface area of respiratory membrane in each

lung is about 70 sq. m. If the total surface area of respiratory membrane decreases, the diffusing capacity for the gases is decreased.

4. Molecular weight of the gas

Diffusing capacity is inversely proportional to molecular weight of the gas. If the molecular weight is more, the density is more and the rate of diffusion is less.

5. Thickness of respiratory membrane

Diffusion is inversely proportional to the thickness of respiratory membrane. More the thickness of respiratory membrane less is the diffusion. It is because the distance through which the diffusion takes place is long.

■ DIFFUSION OF OXYGEN

Entrance of Oxygen from Atmospheric Air into the Alveoli

The partial pressure of oxygen in the atmospheric air is 159 mm Hg and in the alveoli, it is 104 mm Hg. Because of the pressure gradient of 55 mm Hg, oxygen easily enters from atmospheric air into the alveoli (Table 76.1).

Diffusion of Oxygen from Alveoli into the Blood

When the blood is flowing through the pulmonary capillary, RBC is exposed to oxygen only for 0.75 sec at rest and only for 0.25 sec during severe exercise. So the diffusion of oxygen must be quicker and effective. Fortunately, this is possible because of pressure gradient.

The partial pressure of oxygen in the pulmonary capillary is 40 mm Hg and in the alveoli, it is 104 mm Hg. The pressure gradient is 64 mm Hg. It facilitates the diffusion of oxygen from alveoli into the blood (Fig. 76-2).

■ DIFFUSION OF CARBON DIOXIDE

Diffusion of Carbon Dioxide from Blood into Alveoli

The partial pressure of carbon dioxide in alveoli is 40 mm Hg whereas in the blood it is 46 mm Hg.

TABLE 76-1: Partial pressure and content of oxygen and carbon dioxide in alveoli, capillaries and tissue

Gas	Arterial end of pulmonary capillary	Alveoli	Venous end of pulmonary capillary	Arterial end of systemic capillary	Tissue	Venous end of systemic capillary
PO ₂ (mm Hg)	40	104	104	95	40	40
Oxygen content (mL %)	14	—	19	19	—	14
PCO ₂ (mm Hg)	46	40	40	40	46	46
Carbon dioxide content (mL %)	52	—	48	48	—	52

The pressure gradient of 6 mm Hg is responsible for the diffusion of carbon dioxide from blood into the alveoli (Fig. 76-3).

Diffusion of Carbon Dioxide from the Alveoli into the Atmospheric Air

In the atmospheric air, the partial pressure of carbon dioxide is very insignificant and is only about 0.3 mm Hg whereas, in the alveoli, it is

40 mm Hg. So, carbon dioxide enters passes to atmosphere from alveoli easily.

■ EXCHANGE OF RESPIRATORY GASES AT TISSUE LEVEL

■ DIFFUSION OF OXYGEN FROM BLOOD INTO THE TISSUES

The partial pressure of oxygen in the venous end of pulmonary capillary is 104 mm Hg. However,

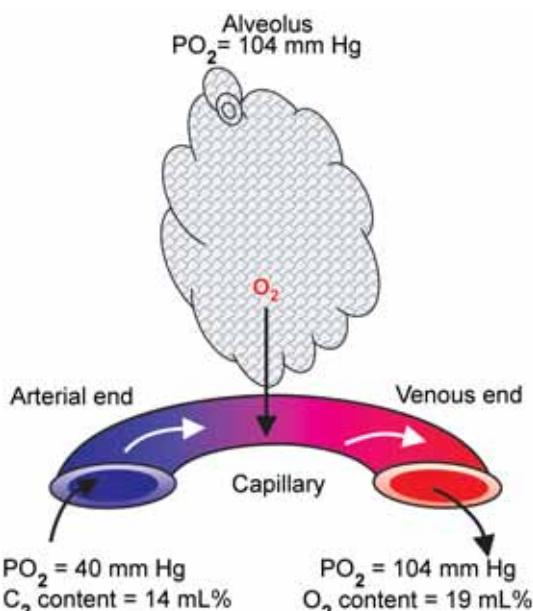


FIGURE 76-2: Diffusion of oxygen from alveolus to pulmonary capillary

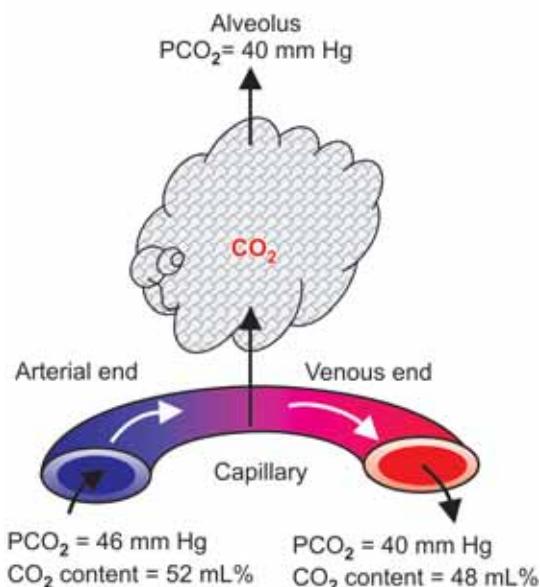


FIGURE 76-3: Diffusion of carbon dioxide from pulmonary capillary to alveolus

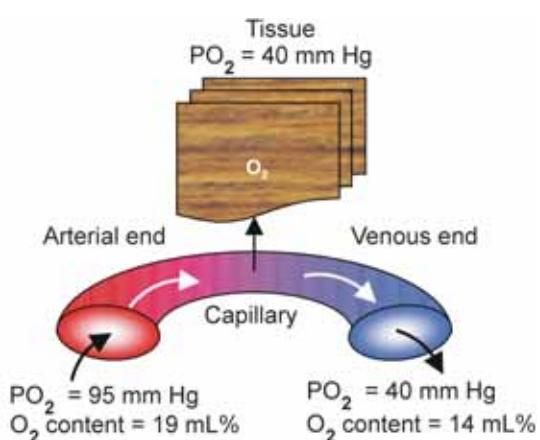


FIGURE 76-4: Diffusion of oxygen from capillary to tissue

the partial pressure of oxygen in the arterial end of systemic capillary is only 95 mm Hg. It may be because of the physiological shunt in lungs (Chapter 72). About 2% of blood reaches the heart without being oxygenated.

The average oxygen tension in the tissues is 40 mm Hg. It is because of continuous metabolic activity and constant utilization of oxygen. Thus, a pressure gradient of about 55 mm Hg exists between capillary blood and the tissues so that oxygen can easily diffuse into the tissues (Fig. 76-4).

The oxygen content in arterial blood is 19 mL% and, in the venous blood, it is 14 mL%. Thus, the diffusion of oxygen from blood to the tissues is 5 mL/100 mL of blood.

■ DIFFUSION OF CARBON DIOXIDE FROM TISSUES INTO THE BLOOD

Due to the continuous metabolic activity, carbon dioxide is produced constantly in the cells of the tissues. So, the partial pressure of carbon dioxide is high in the cells and is about 46 mm Hg. The partial pressure of carbon dioxide in arterial blood is 40 mm Hg. The pressure gradient of 6 mm Hg is responsible for the diffusion of carbon dioxide from tissues to the blood (Fig 76-5).

The carbon dioxide content in arterial blood is 48 mL%. And, in the venous blood, it is 52 mL%. So, the diffusion of carbon dioxide

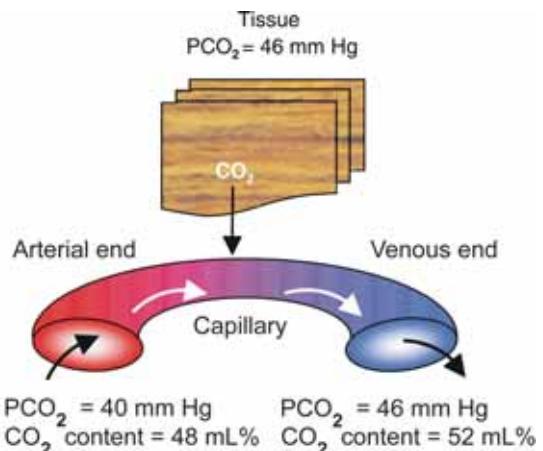


FIGURE 76-5: Diffusion of carbon dioxide from tissue to capillary

from tissues to the blood is 4 mL/100 mL of blood.

■ TRANSPORT OF OXYGEN

Oxygen is transported from alveoli to the tissue by the blood in two forms:

1. As simple physical solution
2. In combination with hemoglobin.

■ TRANSPORT OF OXYGEN AS SIMPLE SOLUTION

Oxygen dissolves in water of plasma and is transported in this physical form. The amount of oxygen transported in this way is very negligible. It is only 0.3 mL/100 mL of plasma. It is about 3% of total oxygen in blood.

■ IN COMBINATION WITH HEMOGLOBIN

Oxygen combines with hemoglobin in blood and is transported as oxyhemoglobin. The transport of oxygen in this form is important because, maximum amount (97%) of oxygen is transported by this method.

Oxygen combines with hemoglobin only as a physical combination. It is only oxygenation and not oxidation. This type of combination of oxygen with hemoglobin has got some advantages. Oxygen can be readily released from hemoglobin when it is needed.

TABLE 76-2: Gases in arterial and venous blood

Gas		Arterial blood	Venous blood
Oxygen	Partial pressure (mm Hg)	95	40
	Content (mL %)	19	14
Carbon dioxide	Partial pressure (mm Hg)	40	46
	Content (mL %)	48	52

Oxygen combines with the iron in heme part of hemoglobin.

Oxygen Carrying Capacity of Blood

The oxygen carrying capacity of blood is amount of oxygen transported by blood. One gram of hemoglobin carries 1.34 mL of oxygen. It is called oxygen carrying capacity of hemoglobin. The normal hemoglobin content in blood is 15 g%. So, the blood with 15 g% of hemoglobin should carry 20.1 mL% of oxygen, i.e. 20.1 mL of oxygen in 100 mL of blood. But, the blood with 15 g% of hemoglobin carries only 19 mL% of oxygen, i.e. 19 mL of oxygen is carried by 100 mL of blood (Table 76-2). The oxygen carrying capacity of blood is only 19 mL% because the hemoglobin is not fully saturated with oxygen. It is saturated only for about 95%.

OXYGEN HEMOGLOBIN DISSOCIATION CURVE

Oxygen hemoglobin dissociation curve is the curve that demonstrates the relationship between partial pressure of oxygen and the percentage saturation of hemoglobin with oxygen. It explains the affinity of hemoglobin for oxygen.

Normally in the blood, hemoglobin is saturated with oxygen only up to 95%. The saturation of hemoglobin with oxygen depends upon the partial pressure of oxygen. When the partial pressure of oxygen is more, hemoglobin accepts oxygen and when the partial pressure of oxygen is less, hemoglobin releases oxygen.

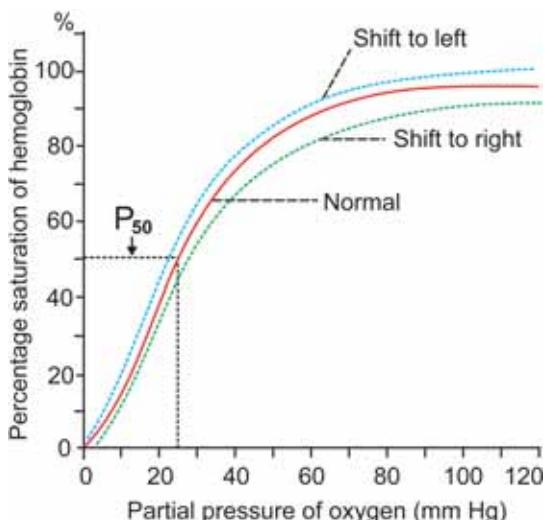


FIGURE 76-6: Oxygen hemoglobin dissociation curve

Normal Oxygen Hemoglobin Dissociation Curve

Under normal conditions, the oxygen hemoglobin dissociation curve is 'S' shaped or sigmoid shaped (Fig. 76-6). The lower part of the curve indicates dissociation of oxygen from hemoglobin. The upper part of the curve indicates the acceptance of oxygen by hemoglobin depending upon the partial pressure of oxygen.

P_{50}

P_{50} is the partial pressure of oxygen at which hemoglobin saturation with oxygen is 50%. When the partial pressure of oxygen is 25 to 27 mm Hg, the hemoglobin is saturated to about 50%. That is, the blood contains 50% of oxygen. At 40 mm Hg of partial pressure of oxygen, the saturation is 75%. It becomes 95% when the partial pressure of oxygen is 100 mm Hg.

Factors Affecting Oxygen Hemoglobin Dissociation Curve

The oxygen hemoglobin dissociation curve is shifted to left or right by various factors:

- I. Shift to left indicates acceptance (association) of oxygen by hemoglobin
- II. Shift to right indicates dissociation of oxygen from hemoglobin.

I. Shift to right

The oxygen hemoglobin dissociation curve is shifted to right in the following conditions:

1. Decrease in partial pressure of oxygen
2. Increase in partial pressure of carbon dioxide (Bohr's effect)
3. Increase in hydrogen ion concentration and decrease in pH (acidity)
4. Increased body temperature
5. Excess of 2,3-diphosphoglycerate (DPG) which is a byproduct of carbohydrate metabolism present in red blood corpuscles.

II. Shift to left

Shift of the oxygen hemoglobin dissociation curve to left occurs in the following conditions:

1. In fetal blood because, fetal hemoglobin has got more affinity for oxygen than the adult hemoglobin.
2. Decrease in hydrogen ion concentration and increase in pH (alkalinity).

Bohr's Effect

Bohr's effect is the effect by which the presence of carbon dioxide decreases the affinity of hemoglobin for oxygen. In the tissues, due to continuous metabolic activities, the partial pressure of carbon dioxide is very high and it enters the blood. The presence of carbon dioxide in blood decreases the affinity of hemoglobin for oxygen so that oxygen is released from the blood to the tissues. The oxygen dissociation curve is shifted to right.

■ TRANSPORT OF CARBON DIOXIDE

Carbon dioxide is transported by the blood from tissues to the alveoli. The partial pressure and content of carbon dioxide in arterial blood and venous blood are given in Table 76-2. Carbon dioxide is transported in the blood in four ways.

1. As dissolved form – 7%
2. As carbonic acid – negligible
3. As bicarbonates – 63%
4. As carbamino compounds – 30%.

■ TRANSPORT OF CARBON DIOXIDE AS DISSOLVED FORM

Carbon dioxide diffuses into blood and dissolves in the fluid of plasma forming a simple solution. Only about 3 mL/100 mL of plasma of carbon dioxide is transported as dissolved state. It is about 7% of total carbon dioxide in the blood.

■ TRANSPORT OF CARBON DIOXIDE AS CARBONIC ACID

Part of dissolved carbon dioxide in plasma combines with the water to form carbonic acid. This reaction is very slow and the transport of carbon dioxide in this form is negligible.

■ TRANSPORT OF CARBON DIOXIDE AS BICARBONATE

About 63% of carbon dioxide is transported as bicarbonate. From plasma, the carbon dioxide enters the RBCs. In the RBCs, carbon dioxide combines with water to form carbonic acid. The reaction inside RBCs is very rapid. The rapid formation of carbonic acid inside the RBCs is due to the presence of an enzyme called carbonic anhydrase. This enzyme accelerates the reaction. Carbonic anhydrase is present only inside the RBCs and not in the plasma. That is why the carbonic acid formation is at least 200 to 300 times more in the RBCs than in plasma.

The carbonic acid is very unstable. Almost all carbonic acid (99.9%) formed in RBCs, dissociates into bicarbonate and hydrogen ions. The concentration of bicarbonate ions in RBC increases more and more. Due to concentration gradient, bicarbonate ions diffuse through the cell membrane into the plasma.

Chloride Shift or Hamburger Phenomenon

Chloride shift or Hamburger phenomenon is the exchange of a chloride ion for a bicarbonate ion across the erythrocyte membrane.

Chloride shift occurs when carbon dioxide enters the blood from tissues. In plasma, plenty of sodium chloride is present. It dissociates into

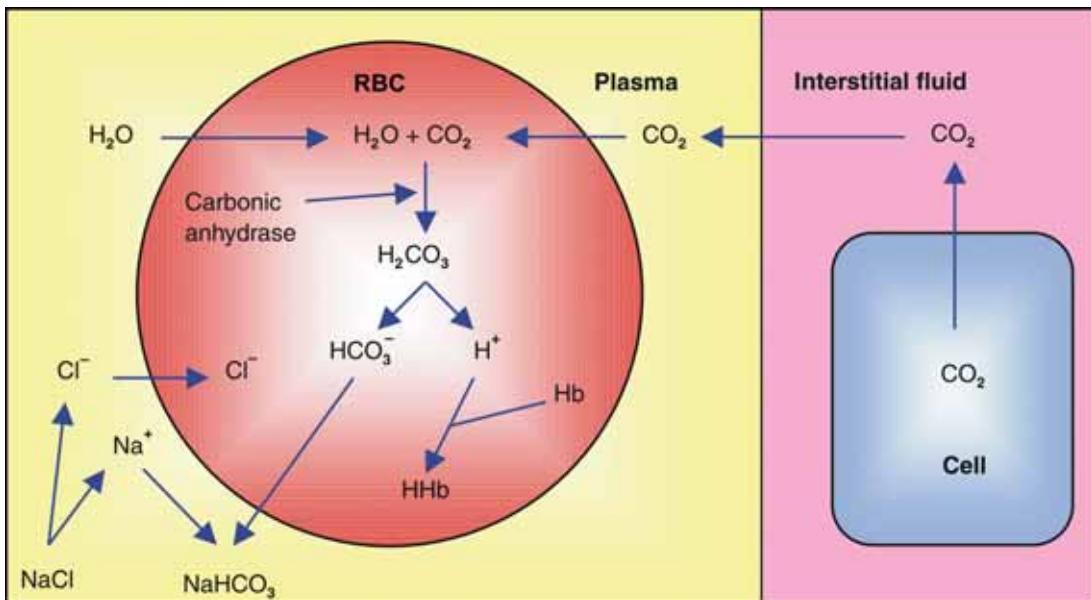


FIGURE 76-7: Transport of carbon dioxide in blood in the form of bicarbonate and chloride shift

sodium and chloride ions (Fig. 76-7). When the negatively charged bicarbonate ions move out of RBC into the plasma, the negatively charged chloride ions move into the RBC in order to maintain the electrolyte equilibrium (ionic balance).

Reverse Chloride Shift

Reverse chloride shift is the process by which the chloride ions are moved back into plasma from RBC. This occurs in lungs.

When the blood reaches the alveoli, sodium bicarbonate in the plasma dissociates into sodium and bicarbonate ions. Bicarbonate ion moves into the RBC. It makes chloride ion to move out of the RBC into the plasma, where it combines with sodium and forms sodium chloride.

■ TRANSPORT OF CARBON DIOXIDE AS CARBAMINO COMPOUNDS

About 30% of carbon dioxide is transported as carbamino compounds. Carbon dioxide is transported in blood in combination with

hemoglobin and plasma proteins. Carbon dioxide combines with hemoglobin to form carbamino hemoglobin or carbhemoglobin. And, it combines with plasma proteins to form carbamino proteins. The carbamino hemoglobin and carbamino proteins are together called carbamino compounds.

The carbon dioxide combines with proteins or hemoglobin with a loose bond so that, carbon dioxide is easily released into alveoli, where the partial pressure of carbon dioxide is low. Thus, the combination of carbon dioxide with proteins and hemoglobin is a reversible one. The amount of carbon dioxide is transported in combination with plasma proteins is very less compared to the amount transported in combination with hemoglobin. It is because, the quantity of proteins in plasma is only half of the quantity of hemoglobin.

■ CARBON DIOXIDE DISSOCIATION CURVE

Carbon dioxide is transported in blood as physical solution and in combination with water, plasma proteins and hemoglobin. The amount of carbon

dioxide combining with blood depends upon the partial pressure of carbon dioxide.

Carbon dioxide dissociation curve is the curve that demonstrates the relationship between the partial pressure of carbon dioxide and the quantity of carbon dioxide that combines with blood.

Normal Carbon Dioxide Dissociation Curve

The normal carbon dioxide dissociation curve shows that the carbon dioxide content in the blood is 48 mL% when the partial pressure of carbon dioxide is 40 mm Hg and, it is 52 mL% when the partial pressure of carbon dioxide is 48 mm Hg. The carbon dioxide content becomes 70 mL% when the partial pressure is about 100 mm Hg (Fig. 76-8).

Haldane Effect

Haldane effect is the effect by which combination of oxygen with hemoglobin displaces carbon dioxide from hemoglobin. The excess of oxygen

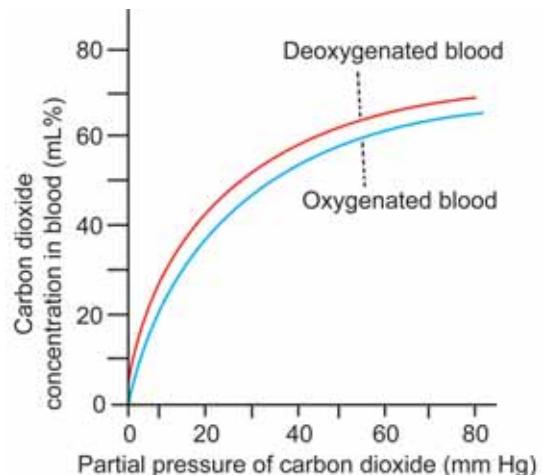


FIGURE 76-8: Carbon dioxide dissociation curve

content in blood causes shift of the carbon dioxide dissociation curve to the right.

Significance of Haldane effect

Haldane's effect is essential for release of carbon dioxide from blood into the alveoli of lungs and uptake of oxygen by the blood.

77

Regulation of Respiration

- INTRODUCTION
- NERVOUS MECHANISM
 - RESPIRATORY CENTERS
 - CONNECTIONS OF RESPIRATORY CENTERS
 - INTEGRATION OF RESPIRATORY CENTERS
 - FACTORS AFFECTING RESPIRATORY CENTERS
- CHEMICAL MECHANISM
 - CENTRAL CHEMORECEPTORS
 - PERIPHERAL CHEMORECEPTORS

■ INTRODUCTION

Respiration is a reflex process. But it can be controlled voluntarily also. Voluntary arrest of respiration (voluntary apnea) is possible only for a short period of about 40 seconds. However, by practice, breathing can be withheld for a long period. At the end of that period, the person is forced to breathe.

However, normally, the quiet regular breathing takes place because of regulatory mechanisms.

Respiration is regulated by two mechanisms:
A. Nervous or neural mechanism
B. Chemical mechanism.

■ NERVOUS MECHANISM

Nervous mechanism that regulates respiration includes respiratory centers, afferent nerves and efferent nerves.

■ RESPIRATORY CENTERS

Respiratory centers are group of neurons, which control the rate, rhythm and force of respiration. These centers are bilaterally situated in reticular formation of the brainstem (Fig. 77-1). Depending upon the situation in the brainstem, the respiratory centers are classified into two groups:

- I. Medullary centers which are made up of:
 1. Dorsal respiratory group of neurons
 2. Ventral respiratory group of neurons
- II. Pontine centers which are:
 1. Pneumotaxic center
 2. Apneustic center.

■ MEDULLARY CENTERS

1. *Dorsal Respiratory Group of Neurons*

Dorsal respiratory group of neurons are responsible for basic rhythm of respiration (see

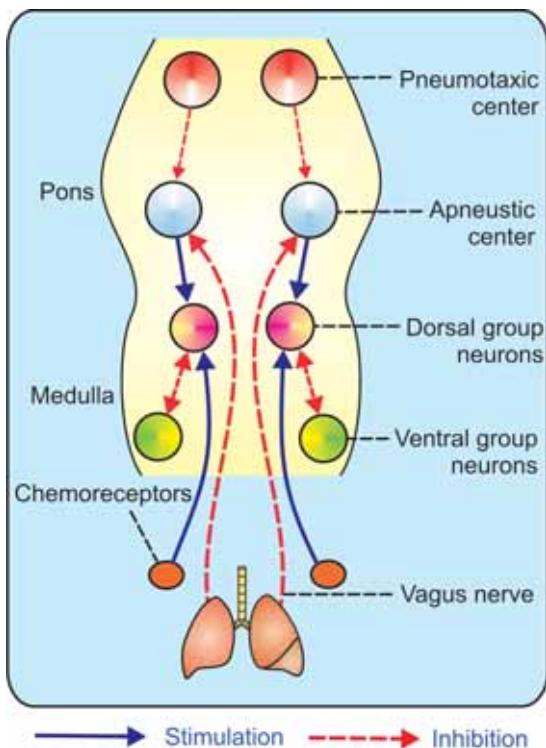


FIGURE 77-1: Nervous regulation of respiration

below for details). Electrical stimulation of these neurons in animals causes contraction of inspiratory muscles and prolonged inspiration.

2. Ventral Respiratory Group of Neurons

Ventral respiratory group of neurons are inactive during quiet breathing and become active during forced breathing. During forced breathing, these neurons stimulate both inspiratory muscles and expiratory muscles.

Electrical stimulation of the inspiratory neurons in ventral group causes contraction of inspiratory muscles and prolonged inspiration. Stimulation of expiratory neurons causes contraction of expiratory muscles and prolonged expiration.

■ PONTINE CENTERS

1. Pneumotaxic Center

The pneumotaxic center controls the medullary respiratory centers, particularly the dorsal group neurons. It acts through apneustic center. The

pneumotaxic center inhibits the apneustic center so that the dorsal group of neurons is inhibited. Because of this inspiration stops and expiration starts. Thus, the pneumotaxic center influences the switching between inspiration and expiration.

The pneumotaxic center increases the respiratory rate by reducing the duration of inspiration.

Stimulation of pneumotaxic center causes prolongation of expiration by inhibiting the dorsal respiratory group of neurons through apneustic center.

2. Apneustic Center

The apneustic center increases the depth of inspiration by acting directly on the dorsal group neurons.

The stimulation of apneustic center causes apneusis. Apneusis is an abnormal pattern of respiration or breathing irregularity characterized by prolonged inspiration followed by short, inefficient expiration.

■ CONNECTIONS OF RESPIRATORY CENTERS

Efferent Pathway

The nerve fibers from the respiratory centers leave brainstem and descend in spinal cord and terminate on the motor neurons in the anterior horn cells of cervical and thoracic segments of spinal cord. From the motor neurons of spinal cord two sets of nerve fibers arise:

1. Phrenic nerve fibers ($C_3 - C_5$) which supply the diaphragm
2. The intercostal nerve fibers ($T_1 - T_{11}$) which supply the external intercostal muscles.

Afferent Pathway

Impulses from peripheral chemoreceptors and baroreceptors are carried to the respiratory centers by the branches of glossopharyngeal and vagus nerves. Vagal nerve fibers also carry impulses from the stretch receptors of lungs to the respiratory centers.

Thus, the respiratory centers receive afferent impulses from different parts of the body and, modulate the movements of thoracic cage and lungs accordingly through efferent nerve fibers.

■ INTEGRATION OF RESPIRATORY CENTERS

Role of Medullary Centers

Rhythmic discharge of inspiratory impulses

Dorsal respiratory group neurons maintain the normal rhythm of respiration by rhythmic discharge of impulses (action potentials). These impulses are transmitted to the respiratory muscles by phrenic and intercostal nerves.

Inspiratory Ramp

Inspiratory ramp is the pattern of discharge from dorsal respiratory group neurons characterized by steady increase in amplitude of the action potential. To start with, the amplitude of the action potential is low due to the activation of only few neurons. Later, more and more neurons are activated leading to gradual increase in the amplitude of the action potential in a ramp fashion. The impulses of this type of firing from dorsal group neurons are called inspiratory ramp signals.

The impulses from dorsal group of neurons are produced only for a period of 2 seconds during which inspiration occurs. After 2 seconds, the ramp signals stop abruptly and do not appear for another 3 seconds. The switching off ramp signals causes expiration. At the end of 3 seconds, the inspiratory ramp signals reappear in the same pattern, and the cycle is repeated.

Significance of inspiratory ramp signals

The significance of inspiratory ramp signals is that there is a slow and steady inspiration so that, the filling of lungs with air is also steady.

Role of Pontine Centers

Pontine respiratory centers regulate the medullary centers. The apneustic center accelerates the activity of dorsal group of neurons and the stimulation of this center, causes prolonged inspiration.

The pneumotaxic center inhibits the apneustic center and restricts the duration of inspiration.

■ FACTORS AFFECTING RESPIRATORY CENTERS

The respiratory centers regulate the respiratory movements, by receiving impulses from various sources in the body.

1. Impulses from Higher Centers

Higher centers alter the respiration by sending impulses directly to the dorsal group neurons. The impulses from various parts of cerebral cortex such as anterior cingulate gyrus, olfactory tubercle and posterior orbital gyrus inhibit the respiration. The impulses from motor area and Sylvian area of cerebral cortex cause forced breathing.

2. Impulses from Stretch Receptors of Lungs: Hering-Breuer Reflex

Hering-Breuer reflex is a protective reflex that restricts the inspiration and prevents over stretching of lung tissues. It is initiated by the stimulation of stretch receptors of air passage.

Stretch receptors give response to stretch of the tissues. During inspiration, there is stretching of lungs due to entrance of air resulting in stimulation of stretch receptors. The impulses from stretch receptors pass through vagal afferent fibers to respiratory centers and inhibit the dorsal group neurons. So inspiration stops and expiration starts (Fig. 77-2). Thus, the overstretching of lung tissues is prevented.

However, Hering-Breuer reflex does not operate during quiet breathing. It operates, only when the tidal volume increases beyond 1000 mL.

This reflex is also called Hering-Breuer inflation reflex since it occurs due to inflation of lungs during inspiration. The reverse of this reflex is called Hering-Breuer deflation reflex and it takes place during expiration. During expiration as the stretching of lungs is abolished, the deflation of lungs occurs.

3. Impulses from 'J' Receptors of Lungs

'J' receptors are juxtagapillary receptors which are present on the wall of the alveoli and having close contact with the pulmonary capillaries.

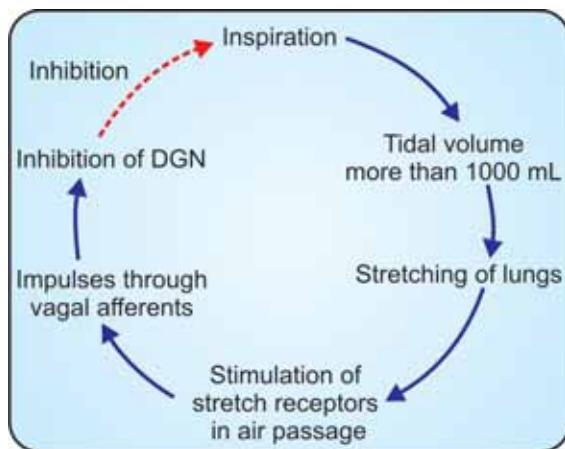


FIGURE 77-2: Hering-Breuer inflation reflex. DGN = Dorsal respiratory group of neurons. Dashed red arrow indicates inhibition

The stimulation of the 'J' receptors produces a reflex response, which is characterized by apnea. Apnea is followed by hyperventilation. The role of 'J' receptors in physiological conditions is not clear. However, these receptors are responsible for hyperventilation in the patients affected by pulmonary congestion and left heart failure.

4. Impulses from Irritant Receptors of Lungs

Besides stretch receptors, there is another type of receptors in the bronchi and bronchioles, called irritant receptors. The irritant receptors are stimulated by irritant chemical agents such as ammonia and sulfur dioxide.

Stimulation of irritant receptors produces reflex hyperventilation along with bronchospasm. Hyperventilation along with bronchospasm prevents further entry of harmful agents into the alveoli.

5. Impulses from Baroreceptors

The baroreceptors are the receptors which give response to change in blood pressure. Refer Chapter 64 for details of baroreceptors.

Function

Whenever arterial blood pressure increases, baroreceptors are activated and send inhibitory impulses to vasomotor center in medulla oblongata. This causes decrease in blood pressure and inhibition of respiration. However, in physiological conditions, the role of baroreceptors in regulation of respiration is insignificant.

6. Impulses from Chemoreceptors

Chemoreceptors play an important role in the chemical regulation of respiration. The details of the chemoreceptors and chemical regulation of respiration are explained later in this chapter.

7. Impulses from Proprioceptors

Proprioceptors are the receptors, which give response to the change in the position of the body. These receptors are situated in joints, tendons and muscles. The proprioceptors are stimulated during the muscular exercise and, send impulses to brain particularly, the cerebral cortex through somatic afferent nerves. Cerebral cortex in turn causes hyperventilation by sending impulses to the medullary respiratory centers.

8. Impulses from Thermoreceptors

Thermoreceptors are the cutaneous receptors, which give response to change in the environmental temperature. There are two types of temperature receptors, namely, the receptors for cold and the receptors for warmth. When the body is exposed to cold or when cold water is applied over the body, the cold receptors are stimulated and, send impulses to cerebral cortex via somatic afferent nerves. Cerebral cortex in turn stimulates the respiratory centers and causes hyperventilation.

9. Impulses from Pain Receptors

The pain receptors are those which give response to pain stimulus. Whenever pain

receptors are stimulated, the impulses are sent to the cerebral cortex via somatic afferent nerves. Cerebral cortex in turn stimulates the respiratory centers and causes hyperventilation.

■ CHEMICAL MECHANISM

The chemical mechanism of regulation of respiration is operated through the chemoreceptors which give response to chemical changes in blood such as:

1. Hypoxia (decreased PO_2)
2. Hypercapnia (increased PCO_2)
3. Increased hydrogen ion concentration.

Types of Chemoreceptors

Chemoreceptors are classified into two groups:

1. Central chemoreceptors
2. Peripheral chemoreceptors.

■ CENTRAL CHEMORECEPTORS

The chemoreceptors present in the brain are called the central chemoreceptors. These chemoreceptors are situated in medulla oblongata, close to dorsal respiratory group of neurons.

Mechanism of Action

The main stimulant for the central chemoreceptors is the increased hydrogen ion concentration.

However, if hydrogen ion concentration increases in the blood, it cannot stimulate the central chemoreceptors because, the hydrogen ions from blood cannot cross the bloodbrain barrier and blood cerebrospinal fluid barrier.

On the other hand, if carbon dioxide increases in the blood, it can easily cross the blood-brain barrier and blood cerebrospinal fluid barrier and enter the interstitial fluid of brain

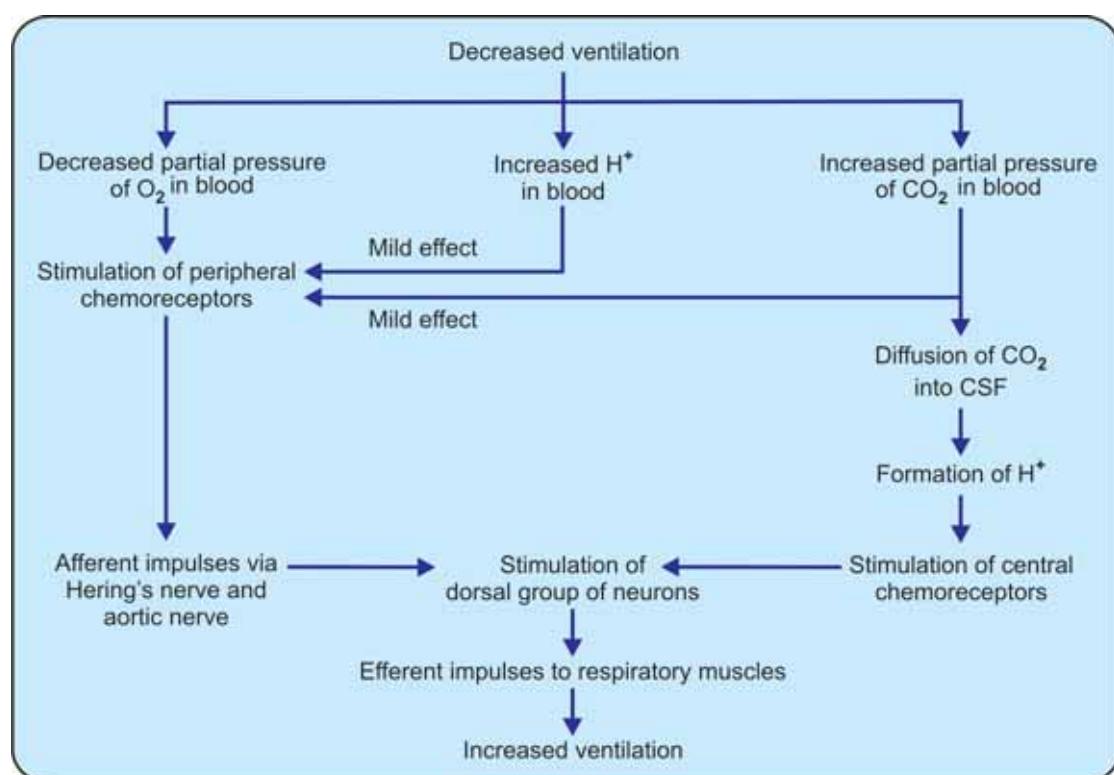


FIGURE 77-3: Chemical regulation of respiration

or the cerebrospinal fluid. There, the carbon dioxide combines with water to form carbonic acid. Since carbonic acid is unstable, it immediately dissociates into hydrogen ion and bicarbonate ion (Fig. 77-3).



The hydrogen ions stimulate the central chemoreceptors. Chemoreceptors in turn send stimulatory impulses to dorsal respiratory group of neurons causing increased ventilation (increased rate and force of breathing). Because of this, the excess carbon dioxide is washed out and the respiration is brought back to normal.

■ PERIPHERAL CHEMORECEPTORS

Chemoreceptors present in the carotid and aortic region are called peripheral chemoreceptors. Refer Chapter 64 for details.

Mechanism of Action

Reduction in partial pressure of oxygen is the most potent stimulant for the peripheral chemoreceptors. Whenever, the partial pressure of oxygen decreases, the chemoreceptors are stimulated and send impulses through aortic and Hering's nerves. These impulses reach the respiratory centers, particularly the dorsal group of neurons and stimulate them. Dorsal group of neurons send stimulatory impulses to respiratory muscles resulting in increased ventilation. This provides enough oxygen and rectifies the lack of oxygen.

The peripheral chemoreceptors are mildly sensitive to the increased partial pressure of carbon dioxide and increased hydrogen ion concentration.

Disturbances of Respiration

- APNEA
- HYPERVENTILATION
- HYPOVENTILATION
- HYPOXIA
- OXYGEN TOXICITY (POISONING)
- HYPERCAPNEA
- HYPOCAPNEA
- ASPHYXIA
- DYSPNEA
- PERIODIC BREATHING
- CYANOSIS
- CARBON MONOXIDE POISONING

■ APNEA

Apnea is defined as temporary arrest of breathing. Apnea can also be produced voluntarily which is called breath holding or voluntary apnea. The breath holding time is known as apnea time. It is about 40 to 60 seconds in a normal person, after a deep inspiration.

Apnea occurs in the following conditions:

1. Voluntary effort (voluntary apnea or breath holding)
2. After hyperventilation
3. During deglutition (deglutition apnea - Chapter 33)
4. During stimulation of vagus nerve in animals (vagal apnea)

5. After injection of adrenaline (adrenaline apnea)
6. Sleep apnea (apnea during sleep).

■ HYPERVENTILATION

Hyperventilation means increased pulmonary ventilation due to forced breathing. Both rate and force of breathing are increased.

Hyperventilation occurs in conditions like exercise. Voluntarily hyperventilation also can be produced.

■ HYPOVENTILATION

Hypoventilation is the decrease in pulmonary ventilation caused by decrease in rate or force of breathing.

Hypoventilation occurs when respiratory centers are suppressed, or by administration of some drugs. It occurs during partial paralysis of respiratory muscles also.

■ HYPOXIA

Hypoxia is the reduced availability of oxygen to the tissues.

■ CLASSIFICATION AND CAUSES OF HYPOXIA

Four important factors which lead to hypoxia are:

1. Oxygen tension in arterial blood
2. Oxygen carrying capacity of blood
3. Velocity of blood flow
4. Utilization of oxygen by the cells.

On the basis of these factors, hypoxia is classified into four types (Table 78-1):

- I. Hypoxic hypoxia
- II. Anemic hypoxia
- III. Stagnant hypoxia
- IV. Histotoxic hypoxia.

Each type of hypoxia may be acute or chronic. Simultaneously, two or more types of hypoxia may be present.

I. Hypoxic Hypoxia

Hypoxic hypoxia means the decreased oxygen content in the blood. It is also called arterial hypoxia.

Causes for hypoxic hypoxia

- i. Low oxygen tension in inspired (atmospheric) air
- ii. Respiratory disorders
- iii. Cardiac disorders.

Characteristic features of hypoxic hypoxia

It is characterized by reduced oxygen tension in arterial blood. All other features remain normal (Table 78-1).

II. Anemic Hypoxia

Anemic hypoxia is the condition characterized by the inability of blood to carry enough amount of oxygen. The oxygen availability is normal. But the blood is not able to take up sufficient amount of oxygen due to anemic condition.

Causes of anemic hypoxia

Any condition that causes anemia can cause anemic hypoxia. It occurs because of the following conditions:

- i. Decreased number of RBCs
- ii. Decreased hemoglobin content in the blood
- iii. Formation of altered hemoglobin
- iv. Combination of hemoglobin with gases other than oxygen and carbon dioxide.

Characteristic features of anemic hypoxia

Anemic hypoxia is characterized by the inability of blood to carry sufficient oxygen. All other features remain normal (Table 78-1).

III. Stagnant Hypoxia

It is the hypoxia caused by decreased velocity of blood flow. It is otherwise called hypokinetic hypoxia.

Causes of stagnant hypoxia

Stagnant hypoxia occurs mainly due to reduction in velocity of blood flow. The velocity of blood flow decreases in the following conditions:

- i. Congestive cardiac failure
- ii. Hemorrhage
- iii. Surgical shock
- iv. Vasospasm
- v. Thrombosis
- vi. Embolism.

Characteristic features of stagnant hypoxia

The characteristic feature of stagnant hypoxia is the decreased velocity of blood flow. All other features remain normal (Table 78-1).

TABLE 78-1: Characteristic features of different types of hypoxia

Features	Hypoxic hypoxia	Anemic hypoxia	Stagnant hypoxia	Histotoxic hypoxia
1. PO ₂ in arterial blood	Reduced	Normal	Normal	Normal
2. O ₂ carrying capacity of blood	Normal	Reduced	Normal	Normal
3. Velocity of blood flow	Normal	Normal	Reduced	Normal
4. Utilization of O ₂ by tissues	Normal	Normal	Normal	Reduced
5. Efficacy of O ₂ therapy	100%	75%	< 50%	Not useful

IV. Histotoxic Hypoxia

It is the type of hypoxia produced by the inability of tissues to utilize oxygen.

Causes for histotoxic hypoxia

Histotoxic hypoxia occurs due to cyanide or sulfide poisoning. These substances destroy the cellular oxidative enzymes. So, even if oxygen is supplied, the tissues are not in a position to utilize it.

Characteristic features of histotoxic hypoxia

Here, the tissues are not able to use the oxygen even if it is delivered. All other features remain normal (Table 78-1).

EFFECTS OF HYPOXIA

Acute and severe hypoxia leads to unconsciousness. If not treated immediately, brain death occurs. Chronic hypoxia produces various symptoms in the body.

1. Effects on Blood

Hypoxia stimulates the secretion of erythropoietin from kidney. Erythropoietin increases production of RBCs. Thus, the oxygen carrying capacity of blood is improved by increase in RBC count and hemoglobin content.

2. Effects on Cardiovascular System

Initially, due to the reflex stimulation of cardiac and vasomotor centers, there is increase in rate and force of contraction of heart, cardiac

output and blood pressure. Later, there is reduction in the rate and force of contraction of heart. Cardiac output and blood pressure are also decreased.

3. Effects on Respiration

Initially, the respiratory rate is increased due to chemoreceptor reflex. Because of this large amount of carbon dioxide is washed out leading to alkalemia. Later, the respiration tends to be shallow and periodic. Finally, the rate and force of breathing are reduced to a great extent due to the failure of respiratory centers.

4. Effects on Digestive System

Hypoxia is associated with loss of appetite, nausea and vomiting. Mouth becomes dry and there is a feeling of thirst.

5. Effects on Kidney

Juxtaglomerular apparatus of kidney secretes erythropoietin. Alkaline urine is excreted.

6. Effects on Central Nervous System

In mild hypoxia, the symptoms are similar to those of alcoholic intoxication.

The individual is depressed, apathetic with general loss of self control. The person becomes talkative, quarrelsome, ill tempered and rude. The subject starts shouting, singing or crying.

There is disorientation, and loss of discriminative ability and loss of power of judgment. Memory is impaired. Weakness, lack

of coordination and fatigue of muscles are common in hypoxia.

If hypoxia is acute and severe, there is sudden loss of consciousness. If not treated immediately, coma occurs which leads to death.

■ TREATMENT FOR HYPOXIA — OXYGEN THERAPY

The best treatment for hypoxia is oxygen therapy, i.e. treating the affected person with oxygen. Pure oxygen or oxygen combined with another gas is administered.

Efficacy of Oxygen Therapy in Different Types of Hypoxia

Oxygen therapy is not effective equally in all types of hypoxia. The value of oxygen therapy depends upon the type of hypoxia. In hypoxic hypoxia, the oxygen therapy is 100% useful. In anemic hypoxia, oxygen therapy is moderately effective to about 70%. In stagnant hypoxia, the effectiveness of oxygen therapy is less than 50%. In histotoxic hypoxia, the oxygen therapy is not useful at all. It is because, even if oxygen is delivered, the cells cannot utilize oxygen.

■ OXYGEN TOXICITY (POISONING)

Oxygen toxicity is the increased oxygen content in tissues beyond certain critical level. It is also called oxygen poisoning. It occurs because of breathing pure oxygen with high pressure of 2-3 atmospheres (hyperbaric oxygen).

■ EFFECTS OF OXYGEN TOXICITY

1. Lung tissues are affected first with tracheobronchial irritation and pulmonary edema
2. The metabolic rate increases in all the body tissues and the tissues are burnt out by excess heat. The heat also destroys cytochrome system leading to damage of tissues

3. When brain is affected, first hyperirritability occurs. Later, it is followed by increased muscular twitching, ringing in ears and dizziness
4. Finally, the toxicity results in convulsions, coma and death.

■ HYPERCAPNEA

Hypercapnea is the increased carbon dioxide content of blood. It occurs in conditions, which leads to blockage of respiratory pathway as in case of asphyxia. It also occurs while breathing air containing excess carbon dioxide content.

■ EFFECTS OF HYPERCAPNEA

1. Excess stimulation of respiratory centers leading to dyspnea
2. Reduction in pH of blood
3. Increase in heart rate and blood pressure
4. Headache, depression and laziness
5. Muscular rigidity, tremors and convulsions
6. Giddiness and loss of consciousness.

■ HYPOCAPNEA

Hypocapnea is the decreased carbon dioxide content in blood. It occurs in conditions associated with hypoventilation.

■ EFFECTS OF HYPOCAPNEA

1. Rate and force of respiration decrease
2. The pH of blood increases leading to respiratory alkalosis
3. Calcium concentration decreases resulting in tetany
4. Dizziness, mental confusion, muscular twitching and loss of consciousness

■ ASPHYXIA

Asphyxia is the condition characterized by combination of hypoxia and hypercapnea due to obstruction of air passage. It develops due to acute obstruction of air passage in conditions like strangulation, hanging and drowning.

■ EFFECTS OF ASPHYXIA

The effects of asphyxia develop in three stages:

1. Stage of hyperpnea
2. Stage of convulsions
3. Stage of collapse.

1. Stage of Hyperpnea

Hyperpnea is the first stage of asphyxia. It extends for about 1 minute. In this stage, breathing becomes deep and rapid. It is due to the powerful stimulation of respiratory centers by accumulation of carbon dioxide. Hyperpnea is followed by dyspnea and cyanosis. The eyes become more prominent.

2. Stage of Convulsions

This stage is characterized mainly by convulsions (uncontrolled involuntary muscular contractions). Duration of this stage is less than one minute. The following effects develop in this stage due to the effect of hypercapnia on brain and spinal cord:

- i. Expiratory efforts become more violent
- ii. Generalized convulsions appear
- iii. Heart rate increases
- iv. Arterial blood pressure greatly increases
- v. Consciousness is lost.

3. Stage of Collapse

This stage lasts for about three minutes. The effects of this stage are:

- i. Depression of brain centers due to lack of oxygen. So, the convulsions disappear
- ii. Respiratory gasping occurs with stretching of the body and opening of mouth as if gasping for breath
- iii. Dilatation of pupils
- iv. Reduction in heart rate
- v. Loss of all reflexes
- vi. Increase in the duration between the gasps
- vii. Finally, the death.

All together, asphyxia extends only for 5 minutes. The person can be saved by timely help such as relieving the respiratory obstruction, good aeration, etc. Otherwise, death occurs.

■ DYSPNEA

Dyspnea means difficulty in breathing. It is otherwise called the air hunger. Normally, the breathing goes on without consciousness. When the breathing enters the consciousness and produces discomfort, it is called dyspnea. Dyspnea is also defined as "a consciousness of necessity for increased respiratory effort".

Physiologically, dyspnea occurs during severe muscular exercise. The pathological conditions when dyspnea occurs are respiratory, cardiac and metabolic disorders.

■ PERIODIC BREATHING

Periodic breathing is the abnormal or uneven respiratory rhythm. It is of two types:

1. Cheyne-Stokes breathing
2. Biot's breathing.

■ CHEYNE-STOKES BREATHING

Cheyne-Stokes breathing is the periodic breathing characterized by rhythmic hyperpnea and apnea. It is the most common type of periodic breathing. It is marked by two alternate patterns of respiration:

- i. Hyperpneic period
- ii. Apneic period

Hyperpneic Period — Waxing and Waning of Breathing

To begin with, the breathing is shallow. The force of respiration increases gradually and reaches the maximum (hyperpnea). Then, it decreases gradually and reaches minimum and is followed by apnea. The gradual increase followed by gradual decrease in force of respiration is called waxing and waning of breathing (Fig. 78-1).

Apneic Period

When, the force of breathing is reduced to minimum, cessation of breathing occurs for a short period. It is again followed by hyperpneic period and the cycle is repeated.

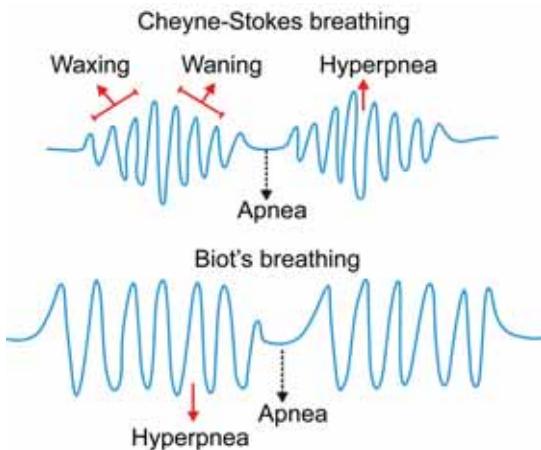


FIGURE 78-1: Periodic breathing

Causes for waxing and waning

Initially, during forced breathing, large quantity of carbon dioxide is washed out from blood leading to inactivation of respiratory centers. It causes apnea. During apnea, there is accumulation of carbon dioxide with reduction in oxygen tension resulting in activation of respiratory centers. This causes gradual increase in the force of breathing to the maximum. And the cycle is repeated.

Conditions when Cheyne-Stokes Breathing Occurs

Cheyne-Stokes breathing occurs in both physiological and pathological conditions.

Physiological conditions when Cheyne-Stokes breathing occurs

- During deep sleep
- In high altitude
- After prolonged voluntary hyperventilation
- In newborn babies
- After severe muscular exercise.

Pathological conditions when Cheyne-Stokes breathing occurs

- During increased intracranial pressure

- During cardiac failure
- During renal diseases
- Poisoning by narcotics
- In premature infants.

■ BIOT'S BREATHING

It is another form of periodic breathing characterized by period of apnea and hyperpnea. There is no waxing and waning of breathing (Fig. 78-1). After apneic period, hyperpnea occurs abruptly.

Causes of Abrupt Apnea and Hyperpnea

Due to apnea, carbon dioxide accumulates and it stimulates the respiratory centers leading to hyperventilation. During hyperventilation, lot of carbon dioxide is washed out. So, the respiratory centers are not stimulated and apnea occurs.

Conditions when Biot's Breathing Occurs

Biot's breathing occurs only in pathological conditions such as nervous disorders.

■ CYANOSIS

Cyanosis is defined as diffused bluish coloration of skin and mucous membrane. It is due to the presence of large amount of reduced hemoglobin in the blood.

Cyanosis is distributed all over the body. But, it is more marked in certain regions such as lips, cheeks, ear lobes, nose and fingertips above the base of the nail.

■ CONDITIONS WHEN CYANOSIS OCCURS

- Any condition which leads to arterial hypoxia and stagnant hypoxia.
- Conditions when altered hemoglobin like methemoglobin or sulfhemoglobin is formed.
- Conditions like polycythemia when blood flow is slow.

■ CARBON MONOXIDE POISONING

Carbon monoxide is a dangerous gas. The common sources for carbon monoxide are exhaust of gasoline engines, coal mines, gases from guns, deep wells and underground drainage system.

■ EFFECTS OF CARBON MONOXIDE

Carbon monoxide is a dangerous because it displaces oxygen from hemoglobin by binding with same site in hemoglobin for oxygen. So, oxygen transport and oxygen carrying capacity of the blood are decreased.

■ SYMPTOMS OF CARBON MONOXIDE POISONING

The symptoms of carbon monoxide poisoning depend upon the concentration of this gas in air:

1. While breathing air with 1% of carbon monoxide, mild symptoms like headache and nausea appear
2. While breathing air containing carbon monoxide more than 1% causes convulsions, cardiorespiratory arrest, loss of consciousness and coma.
3. High carbon monoxide content in air causes death.

High Altitude and Deep Sea Physiology

■ HIGH ALTITUDE

■ BAROMETRIC PRESSURE AND PARTIAL PRESSURE OF OXYGEN AT DIFFERENT ALTITUDES

■ CHANGES IN THE BODY AT HIGH ALTITUDE

■ MOUNTAIN SICKNESS

■ ACCLIMATIZATION

■ DEEP SEA PHYSIOLOGY

■ BAROMETRIC PRESSURE AT DIFFERENT DEPTHS

■ EFFECT OF HIGH BAROMETRIC PRESSURE — NITROGEN NARCOSIS

■ DECOMPRESSION SICKNESS

■ HIGH ALTITUDE

Any altitude above 8000 ft from mean sea level is called high altitude. People can ascend up to this level without any adverse effect. The different altitudes are given in Table 79-1.

At high altitudes, the barometric pressure is low. However, the amount of oxygen available in the atmosphere is same as it is at the sea level. Due to low barometric pressure, the partial pressure of gases, particularly oxygen decreases leading to hypoxia.

The carbon dioxide in high altitude is very much negligible and it does not create any problem.

■ BAROMETRIC PRESSURE AND PARTIAL PRESSURE OF OXYGEN AT DIFFERENT ALTITUDES

The barometric pressure decreases at different altitudes and, accordingly the partial pressure of oxygen also decreases leading to various

effects on the body. Barometric pressure and partial pressure of oxygen at different altitudes and their common effects on the body are given in Table 79-2.

■ CHANGES IN THE BODY AT HIGH ALTITUDE

When a person is exposed to high altitude particularly by rapid ascent, the various systems in the body cannot cope with the lowered oxygen tension and, the effects of hypoxia start. Besides, hypoxia, other factors such as expansion of gases, fall in atmospheric temperature and light rays are also responsible for the changes in the functions of the body at high altitude.

■ MOUNTAIN SICKNESS

Definition

Mountain sickness is the condition characterized by adverse effects of hypoxia at high

altitude. It is commonly developed in persons going to high altitude for the first time. It occurs within a day in these persons before they get acclimatized to the altitude.

Symptoms

In mountain sickness, the symptoms occur mostly in digestive system, cardiovascular system, respiratory system and nervous system. The symptoms of mountain sickness are:

1. Digestive system

Loss of appetite, nausea and vomiting occur because of expansion of gases in the gastrointestinal tract.

2. Cardiovascular system

Heart rate increases.

3. Respiratory system

Pulmonary blood pressure increases due to increased blood flow. Blood flow increases because of vasodilatation induced by hypoxia. Increased pulmonary blood pressure results in pulmonary edema which causes breathlessness.

4. Nervous system

The symptoms of nervous system are headache, depression, disorientation, irritability, lack of sleep, weakness and fatigue.

TABLE 79-1: Barometric pressure, partial pressure of oxygen and common effects at different altitudes

Altitude (feet)	Barometric pressure (mm Hg)	Partial pressure of oxygen (mm Hg)	Common effects
Sea Level	760	159	————
5,000	600	132	No hypoxia
10,000	523	110	Mild symptoms of hypoxia start appearing
15,000	400	90	Moderate hypoxia develops with following symptoms: — Reduction in visual acuity — Effects on mental functions: — Improper judgment and — Feeling of over confidence
20,000	349	73	Severe hypoxia appears with cardiorespiratory symptoms such as: — Increase in heart rate and cardiac output — Increase in respiratory rate and respiratory minute volume This is the highest level for permanent inhabitants
25,000	250	62	This is the critical altitude for survival — Hypoxia becomes severe — Breathing oxygen becomes essential
29,628	235	49	This is the height of Mount Everest
30,000	226	47	Symptoms become severe even with oxygen
50,000	87	18	Hypoxia becomes more severe even with pure oxygen

Treatment

Mountain sickness is treated by oxygen therapy.

■ ACCLIMATIZATION

Definition

Acclimatization refers to the adaptations or the adjustments by the body in high altitude. While staying at high altitudes for several days to several weeks, a person slowly gets adapted or adjusted to the low oxygen tension so that, hypoxic effects are reduced. It enables the person to ascent further.

Changes during Acclimatization

The various changes during acclimatization help the body to cope with the adverse effects of hypoxia at high altitude. Following changes occur in the body during acclimatization:

1. Changes in blood

During acclimatization, the RBC count increases and packed cell volume rises from the normal value of 45% to about 59%. The hemoglobin content in the blood rises from 15 g% to 20 g%. So, the oxygen carrying capacity of the blood is increased. Thus, more oxygen can be carried to tissues in spite of hypoxia.

Increase in RBC count, packed cell volume and hemoglobin content is due to erythropoietin that is released from juxtaglomerular apparatus of kidney

2. Changes in cardiovascular system

Overall activity of cardiovascular system is increased in high altitude. There is increase in rate and force of contraction of heart, cardiac output and blood pressure. Hypoxia induced vasodilatation increases the vascularity in the body. So, blood flow to the vital organs such as heart, brain, muscles, etc. increases.

3. Respiratory system

- i. Pulmonary ventilation increases up to 65% due to the stimulation of chemoreceptors. This helps the person to ascend several thousand feet

- ii. Pulmonary hypertension develops due to increased cardiac output, and pulmonary blood flow
- iii. Diffusing capacity of gases increases in the alveoli due to the increase in pulmonary blood flow and pulmonary ventilation. It enables more diffusion of oxygen in blood.

4. Changes in tissues

Both in human beings and animals residing at high altitudes permanently, the cellular oxidative enzymes involved in metabolic reactions are more than in the inhabitants at sea level.

Even, when a sea level inhabitant stays at high altitude for certain period, the amount of oxidative enzymes is not increased. So, the elevation in the amount of oxidative enzymes occurs only in fully acclimatized persons. An increase in the number of mitochondria is observed in these persons.

■ DEEP SEA PHYSIOLOGY

In high altitude, the problem is with low atmospheric (barometric) pressure. In deep sea or mines, the problem is with high barometric pressure. The increased pressure decreases the volume of gases and produces compression effect on the body and internal organs.

■ BAROMETRIC PRESSURE AT DIFFERENT DEPTHS

At sea level, the barometric pressure is 760 mm Hg, which is referred as 1 atmosphere. At the depth of every 33 feet (about 10 m), the pressure increases by one atmosphere. Thus, at the depth of 33 feet, the pressure is two atmospheres. It is due to the air above water and the weight of water itself. The pressure at different depths is given in Table 79-2.

■ EFFECT OF HIGH BAROMETRIC PRESSURE — NITROGEN NARCOSIS

Narcosis refers to unconsciousness or stupor (lethargy with suppression of sensations and feelings) produced by drugs. Nitrogen narcosis means narcotic effect produced by nitrogen at high pressure.

Nitrogen narcosis is common in deep sea divers who breathe compressed air (air under high pressure). Breathing compressed air (air under high pressure) is essential for a deep sea diver or an underwater tunnel worker. It is to equalize the surrounding high pressure acting on thoracic wall and abdomen.

Symptoms

The first symptom starts appearing at a depth of 120 feet. The person becomes very jovial and careless without understanding the seriousness of the conditions. Other symptoms are given in Table 79-2.

Mechanism

Nitrogen is soluble in fat. During compression by high barometric pressure in deep sea, nitrogen escapes from blood vessels and gets dissolved in the fat present in various parts of the body, especially the neuronal membranes.

TABLE 79-2: Barometric pressure and the effects at different depth

Depth (feet)	Atmospheric Pressure	Effects on the subject
Sea Level	1	—
33	2	—
66	3	—
100	4	Symptoms of nitrogen narcosis appear
133	5	Lack of concentration Becomes jovial and careless
166	6	Starts feeling drowsy
200	7	Feels fatigued, weak and careless
233	8	Looses power of judgment. Unable to do skilled work
266	9	Becomes unconscious
Barometric pressure: 1 atmosphere = 760 mm Hg		

The dissolved nitrogen acts like an anesthetic agent suppressing the neuronal excitability. Nitrogen remains in dissolved form in the fat till the person remains in the deep sea. When he ascends up, decompression sickness develops.

■ DECOMPRESSION SICKNESS

Definition

Decompression sickness is the disorder that occurs when a person returns rapidly to normal surroundings (atmospheric pressure) from the area of high atmospheric pressure like deep sea. It is also known as dysbarism, compressed air sickness, caisson disease, bends or diver's palsy.

Cause

The high barometric pressure at deep sea leads to compression of gases in the body. Compression reduces the volume of gases.

Among the respiratory gases, oxygen is utilized by tissues. Carbon dioxide can be expired out. But, nitrogen being an inert gas is neither utilized nor expired. When it is compressed, it escapes from blood vessels and enters the organs. As it is fat soluble, it gets dissolved in the fat of the tissues and tissue fluids.

As long as the person remains in deep sea, nitrogen remains in solution and does not cause any problem. But, if the person ascends rapidly and returns to atmospheric pressure, nitrogen is decompressed and escapes from the tissues and forms bubbles. The bubbles obstruct the blood vessels and produce decompression sickness.

Symptoms

The symptoms of decompression sickness are mainly due to the escape of nitrogen from the tissues in the form of bubbles. The symptoms of decompression sickness are:

1. Pain in joints, numbness, tingling itching and muscle cramps due to the presence of bubbles in myelin sheath of sensory nerve fibers
2. Coronary ischemia due to occlusion of coronary arteries by bubbles

3. Damage of brain or spinal cord because of obstruction of blood vessels by the bubbles
4. Dizziness, paralysis of muscle, shortness of breath and choking
5. Finally, fatigue and severe pain leading to unconsciousness and death.

Prevention

Decompression sickness is prevented by taking proper precautionary measures. While returning to mean sea level, the ascent should be very slow with short stay at regular intervals. The

stepwise ascent allows nitrogen to come back to the blood without forming bubbles. It prevents the decompression sickness.

Treatment

If a person is affected by decompression sickness, first recompression should be done. It is done by keeping the person in a recompression chamber. Then, he is brought back to atmospheric pressure by reducing the pressure slowly. Oxygen therapy may be useful.

Effects of Exposure to Cold and Heat

■ EFFECTS OF EXPOSURE TO COLD

- HEAT PRODUCTION
 - PREVENTION OF HEAT LOSS
 - EFFECTS OF EXPOSURE TO SEVERE COLD
- ## ■ EFFECTS OF EXPOSURE TO HEAT
- HEAT EXHAUSTION
 - DEHYDRATION EXHAUSTION
 - HEAT CRAMPS
 - HEATSTROKE

■ EFFECTS OF EXPOSURE TO COLD

During exposure to cold, the body temperature is maintained by two mechanisms (Chapter 43).

- A. Heat production
- B. Prevention of heat loss.

■ HEAT PRODUCTION

When the body is exposed to cold, the heat is produced by the following activities:

1. *By Increased Metabolic Activities*

The heat gain center in hypothalamus is stimulated during exposure to cold. It causes secretion of adrenaline and noradrenaline by activating sympathetic centers. These hormones, especially adrenaline increase heat production by accelerating cellular metabolic activities.

2. *By Shivering*

Shivering is the increased involuntary muscular activity with slight vibration of the body in

response to fear, onset of fever or exposure to cold. Shivering occurs when the body temperature falls to about 25°C (77°F). During exposure to cold, the heat gain center activates the motor center for shivering situated in posterior hypothalamus and, shivering occurs. Enormous heat is produced during shivering due to severe muscular activities.

■ PREVENTION OF HEAT LOSS

When the body is exposed to cold, the heat gain center in the posterior nucleus of hypothalamus is stimulated. It activates the sympathetic centers in posterior hypothalamus resulting in cutaneous vasoconstriction and decrease in blood flow. Due to decrease in cutaneous blood flow, sweat secretion is decreased and heat loss is prevented.

■ EFFECTS OF EXPOSURE TO SEVERE COLD

Exposure of body to severe cold leads to death if quick remedy is not provided. The survival time

depends upon the temperature of the environment.

If a person is exposed to ice cold water, i.e. 0°C for 20 to 30 minutes, the body temperature falls below 25°C (77°F) and the person can survive if he is placed immediately in hot water tub with a temperature of 43°C (110°F). The survival time at 9°C (28°F) is about 1 hour and the survival time at 15.5°C (60°F) is about 5 hours.

The effects of exposure of body to extreme cold are:

1. Loss of temperature regulating capacity
2. Frostbite.

Loss of Temperature Regulating Capacity

The temperature regulating capacity of hypothalamus is affected when the body temperature reduces to about 34.4°C (94°F). The hypothalamus totally loses the power of temperature regulation when body temperature falls below 25°C (77°F). Shivering does not occur.

In addition to loss of hypothalamic function, the metabolic activities are also suppressed. Sleep or coma develops due to depression of the central nervous system.

Frostbite

Frostbite is the freezing of the surface of the body when it is exposed to cold. It occurs due to sluggishness of blood flow. Most commonly the exposed areas such as ear lobes and digits of hands and feet are affected. Frostbite is common in mountaineers. Prolonged exposure will lead to permanent damage of the cells followed by thawing and gangrene (death and decay of tissues) formation.

EFFECTS OF EXPOSURE TO HEAT

HEAT EXHAUSTION

Heat exhaustion is the body's response to excess loss of water and salt through sweat caused by exposure to hot environmental conditions. In fact it is the warning that body is

getting too hot. Heat exhaustion results in loss of consciousness and collapse.

DEHYDRATION EXHAUSTION

Prolonged exposure to heat results in dehydration. It is due to excessive sweating. Dehydration leads to fall in cardiac output, and blood pressure. Collapse occurs if treatment is not given immediately.

HEAT CRAMPS

Severe painful cramps occur due to reduction in the quantity of salts and water as a result of increased sweating during the continuous exposure to heat.

HEATSTROKE

Heatstroke

Heatstroke is an abnormal increase in body temperature that occurs during exposure to extreme heat. It is characterized by increase in body temperature above 41°C (106°F) accompanied by some physical and neurological symptoms. Compared to other effects of exposure to heat such as heat exhaustion and heat cramps, heatstroke is very severe and often becomes fatal if not treated immediately. The hypothalamus loses the power of regulating body temperature.

Sunstroke is the heatstroke that is caused by prolonged exposure to sun during summer in desert or tropical areas.

Features

The common features of heatstroke are nausea, vomiting, dizziness, headache, abdominal pain, difficulty in breathing, vertigo, confusion, muscle cramps, convulsions, paralysis and unconsciousness. If immediate and vigorous treatment is not given, the damage of brain tissues occurs, resulting in coma and death.

Treatment

The person affected by heatstroke must be treated before the damage of organs. Immediate cooling of the body is the usual treatment.

Artificial Respiration

- CONDITIONS WHEN ARTIFICIAL RESPIRATION IS REQUIRED
- METHODS OF ARTIFICIAL RESPIRATION
 - MANUAL METHODS
 - MECHANICAL METHODS

■ CONDITIONS WHEN ARTIFICIAL RESPIRATION IS REQUIRED

Artificial respiration is required whenever there is arrest of breathing without cardiac failure. The arrest of breathing occurs in the following conditions:

1. Accidents
2. Drowning
3. Gas poisoning
4. Electric shock
5. Anesthesia.

The tissues of brain, particularly the tissues of cerebral cortex are affected by irreversible changes if oxygen supply is stopped for 5 minutes. So, the artificial respiration (resuscitation) must be started quickly without any delay, before the development of cardiac failure.

The purpose of artificial respiration is to ventilate the alveoli and to stimulate the respiratory centers.

■ METHODS OF ARTIFICIAL RESPIRATION

The methods of artificial respiration are of two types:

1. Manual methods
2. Mechanical methods.

■ MANUAL METHODS

Manual methods of artificial respiration can be applied quickly without waiting for the availability of any mechanical aids.

The person affected must be provided with clear air. The clothes around neck and chest regions must be loosened. Mouth, face and throat should be cleared of mucus, saliva, foreign particles, etc. The tongue must be drawn forward and, it must be prevented from falling posteriorly which may cause airway obstruction. There are two manual methods:

- i. Mouth to mouth method
- ii. Holger Nielson method.

Mouth to Mouth Method

The subject is kept in supine position. The resuscitator (the person who gives artificial respiration) kneels at the side of the subject. By keeping the thumb on subject's mouth, the lower jaw is pulled downwards. The nostrils of the subject are closed with the thumb and index finger of the other hand.

The resuscitator then takes a deep breath and exhales into the subject's mouth forcefully. The volume of air exhaled must be twice the normal tidal volume. This expands the subject's lungs.

Then, the resuscitator removes his mouth from that of the subject. Now, a passive expiration occurs in the subject due to the elastic recoil of the lungs. The procedure is repeated at a rate of 12 to 14 times a minute, till normal respiration is restored.

Mouth to mouth method is the most effective manual method because, the carbon dioxide in expired air from the resuscitator can directly stimulate the respiratory centers and facilitates the onset of respiration. The only disadvantage is that, the close contact between the mouths of resuscitator and the subject may not be acceptable for various reasons.

Holger Nielsen Method or Back Pressure Arm Lift Method

The subject is placed in the prone position with head turned to one side. The hands are placed under the cheeks with flexion at elbow joint and abduction of arms at the shoulders. The resuscitator kneels beside the head of the subject. By placing the palm of the hands over the back of the subject, the resuscitator bends forward with straight arms (without flexion at elbow) and applies pressure on the back of the subject.

The weight of the resuscitator and the pressure on the back of the subject compresses his chest and expels air from the lungs. Later, the resuscitator leans back. At the same time, he draws the subject's arm forward by holding it just above elbow.

This procedure causes expansion of thoracic cage and flow of air into the lungs. The movements are repeated at the rate of 12 per minute, till the normal respiration is restored.

■ MECHANICAL METHODS

Mechanical methods of artificial respiration become necessary when the subject needs artificial respiration for long periods. It is essential during the respiratory failure due to paralysis of respiratory muscles or any other cause. The mechanical methods are of two types:

- i. Drinker's method
- ii. Ventilation method.

Drinker's Method

The machine used in this method is called iron lung chamber or tank respirator. The equipment has an airtight chamber made of iron or steel. The subject is placed inside this chamber with the head outside the chamber.

By means of some pumps, the pressure inside the chamber is made positive and negative alternately. During the negative pressure in the chamber, the subject's thoracic cage expands and inspiration occurs. And, during positive pressure, the expiration occurs.

By using the tank respirator, the patient can survive for a longer time, even up to the period of one year till the natural respiratory functions are restored.

Ventilation Method

A rubber tube is introduced into the trachea of the patient through the mouth. By using a pump, air or oxygen is pumped into the lungs with pressure intermittently. When air is pumped, inflation of lungs occurs. When it is stopped, expiration occurs and the cycle is repeated.

The apparatus used for ventilation is called ventilator.

Effects of Exercise on Respiration

■ INTRODUCTION

■ EFFECTS OF EXERCISE ON RESPIRATION

- PULMONARY VENTILATION
- DIFFUSING CAPACITY FOR OXYGEN
- CONSUMPTION OF OXYGEN
- OXYGEN DEBT
- VO₂ MAX

■ INTRODUCTION

Muscular exercise brings about a lot of changes on various systems of the body. The degree of changes depends upon the severity of exercise. Refer Chapter 71 for types and severity of exercise.

■ EFFECTS OF EXERCISE ON RESPIRATION

■ EFFECT ON PULMONARY VENTILATION

Normal pulmonary ventilation is 6 L/minute. In moderate exercise, it increases to about 60 L/minute. In severe muscular exercise, it rises still further up to 100 liters/minute.

■ EFFECT ON DIFFUSING CAPACITY FOR OXYGEN

The diffusing capacity for oxygen is about 21 mL/minute at resting condition. It rises to

45 to 50 mL/minute during moderate exercise due to increase in blood flow through the pulmonary capillaries.

■ EFFECT ON CONSUMPTION OF OXYGEN

The oxygen consumed by the tissues, particularly the skeletal muscles is increased during exercise because of increased metabolic activities.

■ OXYGEN DEBT

Oxygen debt is the extra amount oxygen required by the muscles during recovery from severe muscular exercise. After a period of severe muscular exercise, the amount of oxygen consumed is greatly increased. The oxygen required is more than the quantity available to the muscle.

So, an extra amount of oxygen must be made available in the body after the severe muscular exercise. The oxygen debt is about six times

more than the amount of oxygen consumed under resting conditions.

■ **VO₂ MAX**

VO₂ Max is the amount of oxygen consumed under maximal aerobic metabolism. It is the

product of maximal cardiac output and maximal amount of oxygen consumed by the muscle.

In a normal active and healthy male, the VO₂ Max is 35 to 40 mL/kg body weight/minute. In females, it is 30 to 35 mL/kg/minute. There is an increase of VO₂ Max by 50% during exercise.

QUESTIONS IN RESPIRATORY SYSTEM AND ENVIRONMENTAL PHYSIOLOGY

■ LONG QUESTIONS

1. Explain the transport of oxygen in blood.
2. Explain the transport of carbon dioxide in blood.
3. Describe the nervous regulation of respiration.
4. Describe the chemical regulation of respiration.
5. What is hypoxia? Describe the types, causes and effects of hypoxia. Add a note on oxygen therapy.

■ SHORT QUESTIONS

1. Respiratory unit.
2. Respiratory membrane.
3. Nonrespiratory functions of respiratory tract/lungs.
4. Characteristic features of pulmonary circulation.
5. Surfactant.
6. Respiratory pressures.
7. Compliance.
8. Work of breathing.
9. Lung volumes/capacities/spirogram
10. Vital capacity.
11. Forced expiratory volume.
12. Alveolar ventilation.

13. Dead space.
14. Oxygen hemoglobin dissociation curve.
15. Carbon dioxide dissociation curve.
16. Bohr's effect.
17. Haldane effect.
18. Chloride shift.
19. Diffusing capacity.
20. Exchange of gases between alveoli and blood.
21. Exchange of gases between blood and tissues.
22. Respiratory centers.
23. Inspiratory ramp.
24. Hering-Breuer reflex.
25. Chemoreceptors.
26. Apnea.
27. Hypoxia.
28. Asphyxia.
29. Dyspnea.
30. Periodic breathing.
31. Cyanosis.
32. Mountain sickness.
33. Acclimatization.
34. Decompression sickness.
35. Effects of sudden exposure to cold.
36. Effects of sudden exposure to heat.
37. Artificial respiration.
38. Respiratory changes during exercise.

SECTION 10

Nervous System

CHAPTERS

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Introduction to Nervous System

- DIVISIONS OF NERVOUS SYSTEM
 - CENTRAL NERVOUS SYSTEM
 - PERIPHERAL NERVOUS SYSTEM

■ DIVISIONS OF NERVOUS SYSTEM

Nervous system controls all the activities of the body. It is quicker than the other control system in the body namely, the endocrine system. Primarily, the nervous system is divided into two parts.

1. Central nervous system
2. Peripheral nervous system.

■ CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) includes brain and spinal cord. It is formed by neurons and the supporting cells called neuroglia. The structures of brain and spinal cord are arranged in two layers, namely, the gray matter and white matter. The gray matter is formed by nerve cell bodies and the proximal parts of nerve fibers arising from the nerve cell body. The white matter is formed by nerve fibers.

In brain the white matter is centrally placed and gray matter is in the outer part. In spinal cord white matter is in the outer part and gray matter is in the inner part.

Brain is situated in the skull. It is continued as spinal cord in the vertebral canal through the foramen magnum of the skull bone. Brain and spinal cord are surrounded by three layers of meninges called the outer dura mater, middle

arachnoid mater and inner pia mater. The space between the arachnoid mater and pia mater is known as subarachnoid space. This space is filled with a fluid called cerebrospinal fluid (CSF). The brain and spinal cord are actually suspended in CSF. The important parts of brain and segments of spinal cord are shown in Figure 83-1.

Parts of Brain

Brain consists of three major divisions:

1. Prosencephalon
2. Mesencephalon
3. Rhombencephalon

1. Prosencephalon

It is otherwise known as forebrain. It is further divided into two parts:

- i. Telencephalon which includes cerebral hemispheres, basal ganglia, hippocampus and amygdaloid nucleus.
- ii. Diencephalon which consists of thalamus, hypothalamus, metathalamus and subthalamus.

2. Mesencephalon

It is also known as midbrain.

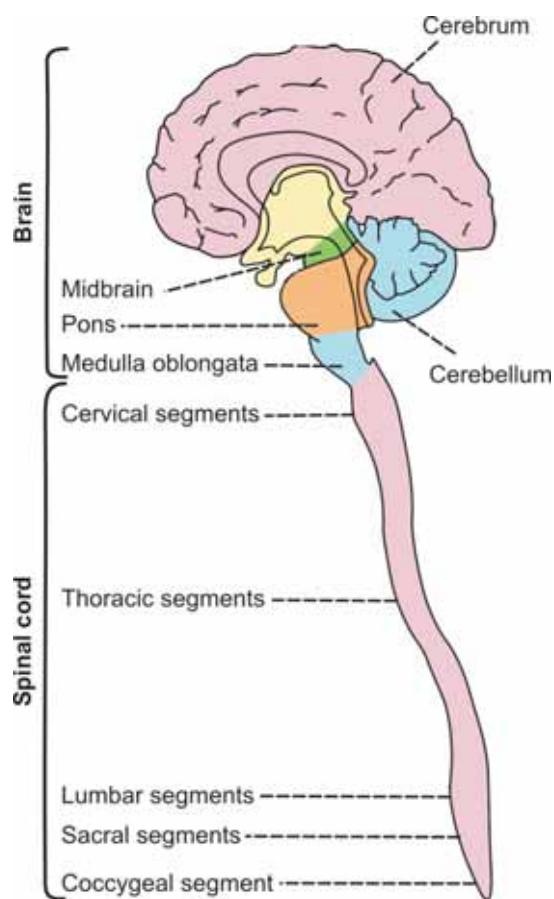


FIGURE 83-1: The parts of central nervous system

3. Rhombencephalon

Rhombencephalon or hindbrain is subdivided into two portions:

- Metencephalon formed by pons and cerebellum
- Myelencephalon or medulla oblongata (Fig. 83-2).

Midbrain, pons and medulla oblongata are together called the brainstem.

■ PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) is formed by the neurons and their processes present in all regions of the body. It consists of cranial nerves arising from brain and spinal nerves arising from the spinal cord. It is again divided into two subdivisions:

- Somatic nervous system
- Autonomic nervous system.

1. Somatic Nervous System

The somatic nervous system is concerned with somatic functions. It includes the nerves supplying the skeletal muscles. Somatic nervous system controls the movements of the body by acting on the skeletal muscles (Fig. 83-3).

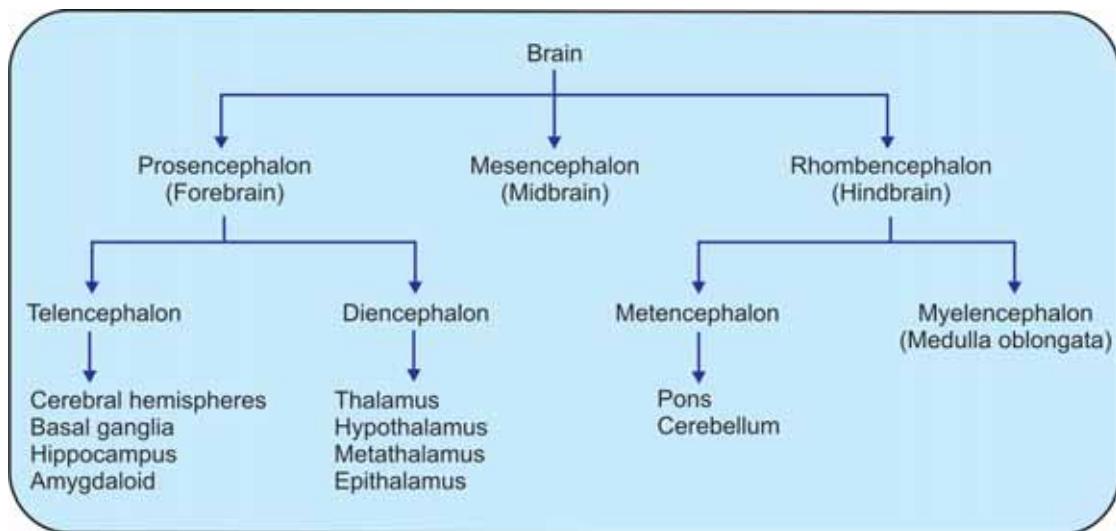


FIGURE 83-2: The parts of brain

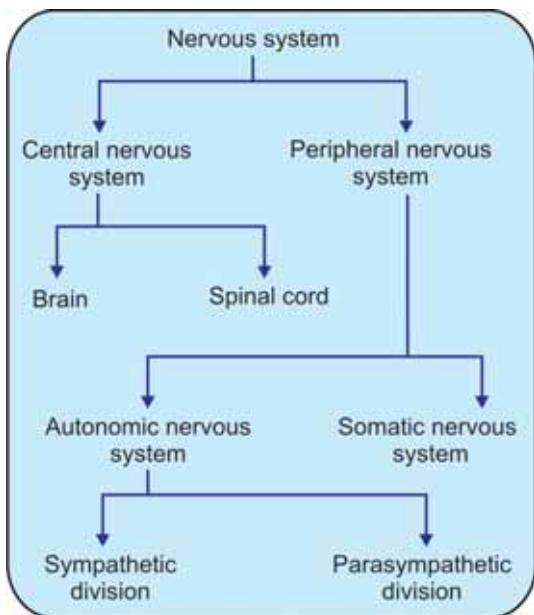


FIGURE 83-3: Organization of nervous system

2. Autonomic Nervous System

The autonomic nervous system is concerned with regulation of visceral or vegetative functions. So, it is otherwise called vegetative or involuntary nervous system. The autonomic nervous system consists of two divisions, sympathetic division and parasympathetic division.

Neuron and Neuroglia

■ NEURON

- CLASSIFICATION OF NEURON
 - STRUCTURE OF NEURON
 - NEUROTROPHINS
 - CLASSIFICATION OF NERVE FIBERS
 - PROPERTIES OF NERVE FIBERS
 - DEGENERATION OF NERVE FIBERS
 - REGENERATION OF NERVE FIBERS
- ## ■ NEUROGLIA
- DEFINITION
 - CLASSIFICATION

■ NEURON

Neuron is defined as the structural and functional unit of the nervous system. It is otherwise called nerve cell. Neuron is like any other cell in the body having nucleus and all the organelles in the cytoplasm. However, it is different from other cells by two ways:

1. Neuron has branches or processes called axon and dendrites
2. Neuron does not have centrosome; so it cannot undergo division.

■ CLASSIFICATION OF NEURON

The neurons are classified by three different methods.

- I. Depending upon number of poles
- II. Depending upon function
- III. Depending upon length of the axon.

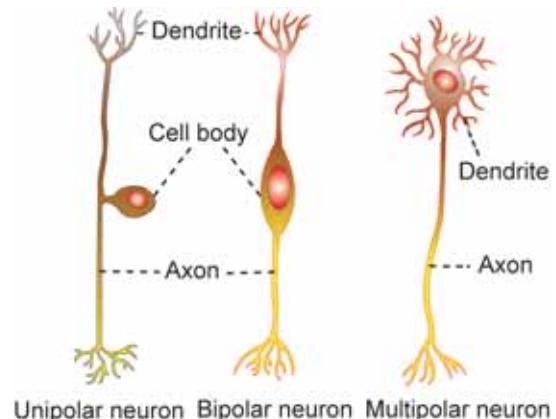


FIGURE 84-1: Types of neuron

Depending upon Number of Poles

Based on the number of poles from which the nerve fibers arise, neurons are divided into three types:

1. Unipolar neurons that have only one pole from which, both the axon and dendrite arise (Fig. 84-1)
2. Bipolar neurons which have two poles. Axon arises from one pole and dendrites arise from the other pole.
3. Multipolar neurons which have many poles. One of the poles gives rise to the axon and, all the other poles give rise to dendrites.

Depending upon Function

On the basis of function, the nerve cells are classified into two types:

1. Motor neurons or efferent neurons which carry the motor impulses from central nervous system to the peripheral effector organs like muscles, glands, blood vessels, etc.
2. Sensory neurons or afferent neurons which carry the sensory impulses from periphery to the central nervous system.

Depending upon Length of Axon

Depending upon the length of axon, neurons are divided into two types:

1. Golgi type I neurons that have long axons. The cell body of these neurons is in central nervous system and their axons reach the remote peripheral organs
2. Golgi type II neurons that have short axons. These neurons are present in cerebral cortex and spinal cord.

■ STRUCTURE OF NEURON

Each neuron is made up of three parts:

1. Nerve cell body
2. Dendrite
3. Axon.

The dendrite and axon together form the processes of neuron (Fig. 84-2). In general, the dendrites are short processes and the axons are long processes. The dendrites and axons are usually called nerve fibers.

Nerve Cell Body

The nerve cell body is also known as soma or perikaryon. It is irregular in shape and, it is constituted by a mass of cytoplasm called

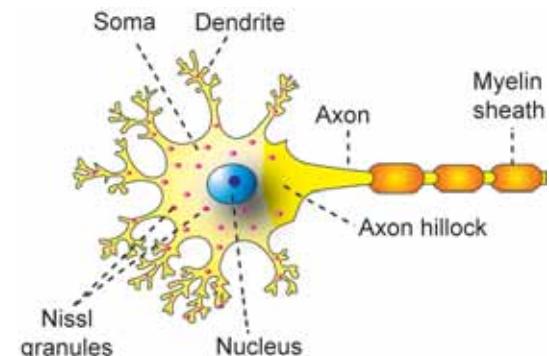


FIGURE 84-2: Structure of a neuron

neuroplasm which is covered by a cell membrane. The cytoplasm contains a large nucleus, Nissl bodies, neurofibrils, mitochondria and Golgi apparatus. Nissl bodies and neurofibrils are found only in nerve cell and not in other cells.

Nucleus

Each neuron has one nucleus which is centrally placed in the nerve cell body. The nucleus has one or two prominent nucleoli. The nucleus does not contain centrosome. So, the nerve cell cannot multiply like the other cells.

Nissl bodies

Nissl bodies or Nissl granules are small basophilic granules found in cytoplasm of neurons and are named after the discoverer. These bodies are present in the soma except in axon hillock. Nissl bodies are called tigroid substances since these bodies are responsible for the tigroid or spotted appearance of soma after suitable staining. The Nissl granules flow into the dendrites from soma, but not into axon. So, the dendrites are distinguished from axons by the presence of Nissl granules under microscope.

The Nissl bodies are membranous organelles containing ribosomes. So, these bodies are concerned with synthesis of proteins in the neurons. The proteins formed in soma are transported to the axon by axonal flow.

Neurofibrils

Neurofibrils are thread like structures present in the form of network in the soma and the nerve

processes. Presence of neurofibrils is another characteristic feature of the neurons.

Mitochondria

The mitochondria are present in the soma and in axon. As other cells, the mitochondria form the powerhouse of the nerve cell, where ATP is produced (Chapter 1).

Golgi apparatus

Golgi apparatus of the nerve cell body is similar to that of other cells. It is concerned with processing and packaging of proteins into granules (Chapter 1).

Dendrite

The dendrite is the branched process of the neuron and it is branched repeatedly. The dendrite may be present or absent. If present, it may be one or many in number. The dendrite has Nissl granules and neurofibrils.

Dendrite is conductive in nature. It transmits impulses towards the nerve cell body.

Axon

The axon is longer than dendrite. Each neuron has only one axon. The axon arises from axon hillock of the nerve cell body. The axon extends for a long distance away from the nerve cell body. The length of the longest axon is about one meter.

Organization of nerve

Many axons together form a bundle called fasciculus. Many fasciculi together form a nerve. The whole nerve is covered by tubular sheath, which is formed by areolar membrane. This sheath is called epineurium. Each fasciculus is covered by perineurium and each nerve fiber (axon) is covered by endoneurium (Fig. 84-3).

Internal structure of axon — Axis cylinder

The axon has a long central core of cytoplasm called axoplasm. The axoplasm is covered by the tubular sheath like membrane called

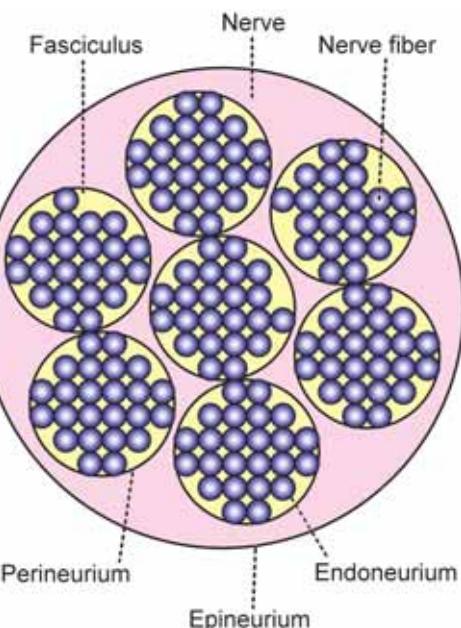


FIGURE 84-3: Cross section of a nerve

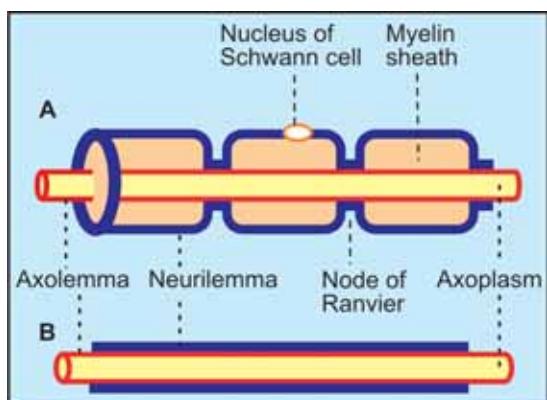


FIGURE 84-4: A. Myelinated nerve fiber
B. Non-myelinated nerve fiber

axolemma which is the continuation of the cell membrane of nerve cell body. The axoplasm along with the axolemma is called the axis cylinder of the nerve fiber (Fig. 84-4).

Axoplasm contains mitochondria, neurofibrils and axoplasmic vesicles. But, Nissl bodies are absent in the axon. The axis cylinder of the nerve fiber is covered by a membrane called neurilemma (see below).

Nonmyelinated nerve fiber

The nerve fiber described above is the non-myelinated nerve fiber which is not covered by myelin sheath.

Myelinated nerve fiber

The nerve fibers which are insulated by myelin sheath are called myelinated nerve fibers.

Myelin Sheath

Myelin sheath is a thick lipoprotein sheath that insulates the myelinated nerve fiber. Myelin sheath is not a continuous sheath. It is absent at regular intervals. The area where the myelin sheath is absent is called node of Ranvier. The segment of the nerve fiber between two nodes is called internode. Myelin sheath is responsible for the white color of the nerve fibers.

Chemistry of myelin sheath

Myelin sheath is formed by concentric layers of proteins alternating with lipids. The lipids are cholesterol, lecithin and cerebroside (sphingomyelin).

Formation of myelin sheath — Myelinogenesis

The formation of myelin sheath around the axon is called the myelinogenesis. It is formed by Schwann cells in neurilemma.

Functions of myelin sheath

1. *Faster conduction:* Myelin sheath is responsible for faster conduction of impulse through the nerve fibers. In the myelinated nerve fibers, the impulses jump from one node to another node by saltatory conduction.
2. *Insulating capacity:* Myelin sheath has a high insulating capacity. Because of this quality, the myelin sheath restricts the nerve impulse within the single nerve fiber, and prevents the stimulation of neighboring nerve fibers.

Neurilemma

Neurilemma is a thin membrane which surrounds the axis cylinder. It is also called neurilemmal

sheath or sheath of Schwann. It contains Schwann cells, which have flattened and elongated nuclei. The cytoplasm is thin and modified to form the thin sheath of neurilemma.

One nucleus is present in each internode of the axon. The nucleus is situated between myelin sheath and neurilemma.

In nonmyelinated nerve fiber, the neurilemma continuously surrounds axolemma. In myelinated nerve fiber, it covers the myelin sheath. At the node of Ranvier (where myelin sheath is absent), the neurilemma invaginates and runs up to axolemma in the form of a finger like process.

Functions of neurilemma

In nonmyelinated nerve fiber, the neurilemma serves as a covering membrane. In myelinated nerve fiber, it is necessary for the formation of myelin sheath (myelinogenesis).

■ NEUROTROPHINS — NEUROTROPHIC FACTORS

Neurotrophins or neurotrophic factors are the protein substances, which play important role in growth and functioning of nervous tissue. Neurotrophins are secreted by many tissues in the body particularly muscles, neuroglial cells and neurons.

Nerve Growth Factor

Nerve growth factor (NGF) is an important neurotrophin found in many peripheral tissues. It promotes early growth and development of neurons.

The commercial preparation of NGF extracted from snake venom and submaxillary glands of male mouse is used to treat many nervous disorders such as Alzheimer's disease, neuron degeneration in aging and neuron regeneration in spinal cord injury.

■ CLASSIFICATION OF NERVE FIBERS

The nerve fibers are classified by different methods. The basis of classification differs in each method. Nerve fibers are classified by six methods:

1. Depending upon structure
2. Depending upon distribution
3. Depending upon origin
4. Depending upon function
5. Depending upon secretion of neurotransmitter
6. Depending upon diameter and conduction of impulse (Erlanger-Gasser classification).

1. Depending upon Structure

Based on the structure, the nerve fibers are classified into two types:

- i. Myelinated nerve fibers that are covered by myelin sheath
- ii. Nonmyelinated nerve fibers which are not covered by myelin sheath.

2. Depending upon Distribution

Nerve fibers are classified into two types on the basis of the distribution:

- i. Somatic nerve fibers which supply the skeletal muscles of the body
- ii. Visceral or autonomic nerve fibers which supply internal organs of the body.

3. Depending upon Origin

On the basis of origin, the nerve fibers are divided into two types:

- i. Cranial nerves arising from brain
- ii. Spinal nerves arising from spinal cord.

4. Depending upon Function

Functionally, the nerve fibers are of two types:

- i. Sensory or afferent nerve fibers which carry sensory impulses from different parts of the body to the central nervous system
- ii. Motor or efferent nerve fibers which carry motor impulses from central nervous system to different parts of the body.

5. Depending upon Secretion of Neurotransmitter

Depending upon the neurotransmitter substance secreted, the nerve fibers are divided into two types:

- i. Adrenergic nerve fibers that secrete noradrenaline
- ii. Cholinergic nerve fibers that secrete acetylcholine.

6. Depending upon Diameter and Conduction of Impulses

Erlanger and Gasser classified the nerve fibers into three major types on the basis of diameter of the fibers and the rate of conduction of impulses:

1. Type A nerve fibers
2. Type B nerve fibers
3. Type C nerve fibers.

Among these fibers, type A nerve fibers are the thickest fibers and type C nerve fibers are the thinnest fibers. Type A nerve fibers are divided into four subtypes. Except 'C' type of fibers, all the nerve fibers are myelinated.

The velocity of impulse through a nerve fiber is directly proportional to the thickness of the fibers. The different types of nerve fibers along with diameter and velocity of conduction are given in the Table 84-1.

■ PROPERTIES OF NERVE FIBERS

Excitability

Excitability is defined as the physiochemical change that occurs in a tissue when a stimulus is applied.

The stimulus is defined as an external agent, which produces excitability in the tissues. When

TABLE 84-1: Types of nerve fibers

Type	Diameter (μ)	Velocity of conduction (meters/second)
A alpha	12 to 24	70 to 120
A Beta	6 to 12	30 to 70
A gamma	5 to 6	15 to 30
A delta	2 to 5	12 to 15
B	1 to 2	3 to 10
C	< 1.5	0.5 to 2

TABLE 84-2: Differences between electrical potential in nerve fiber and muscle fiber

Event	Nerve fiber	Skeletal muscle fiber
Resting membrane potential	-70 mV	-90 mV
Firing level	-55 mV	-75 mV
End of depolarization	+35 mV	+55 mV

the nerve fiber is stimulated action potential develops.

Action potential or nerve impulse

The action potential in a nerve fiber is similar to that in a muscle, except for some minor differences (Table 84-2). The action potential in a skeletal muscle fiber is described in Chapter 23.

The resting membrane potential in the nerve fiber is -70 mV. The firing level is at -55 mV. Depolarization ends at +35 mV (Fig. 84-5). Usually, the action potential starts in the initial segment of nerve fiber.

Conductivity

Conductivity is the ability of nerve fibers to transmit the impulse from the area of stimulation to the other areas. The action potential is transmitted through the nerve fiber as nerve impulse. Normally in the body, the action potential is transmitted through the nerve fiber in only one direction.

Mechanism of conduction of action potential

The depolarization occurs first at the site of stimulation in the nerve fiber. It causes depolarization of the neighboring areas. Like this, depolarization travels throughout the nerve fiber. Depolarization is followed by repolarization.

Conduction through myelinated nerve fiber — Saltatory conduction

Saltatory conduction is the form of conduction of nerve impulse in which, the impulse jumps from one node to another. Conduction of impulse through a myelinated nerve fiber is about 50

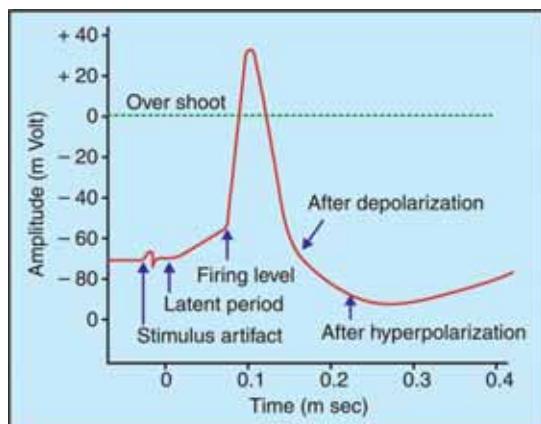


FIGURE 84-5: Action potential in nerve fiber

times faster than through a nonmyelinated fiber. It is because the action potential jumps from one node to another node of Ranvier instead of travelling through the entire nerve fiber (Fig. 84-6).

Mechanism of saltatory conduction

The myelin sheath is not permeable to ions. So, the entry of sodium from extracellular fluid into nerve fiber occurs only in the node of Ranvier, where the myelin sheath is absent. It causes depolarization in the node, and not in the inter-node. Thus, the depolarization occurs at successive nodes. So, the action potential jumps from one node to another. Hence, it is called saltatory conduction (saltare = jumping).

Refractory Period

Refractory period is the period at which the nerve does not give any response to a stimulus. Refractory period is of two types:

1. Absolute refractory period

Absolute refractory period is the period during which the nerve does not show any response at all, whatever may be the strength of stimulus.

2. Relative refractory period

It is the period, during which the nerve fiber shows response, if the strength of stimulus is increased to maximum.

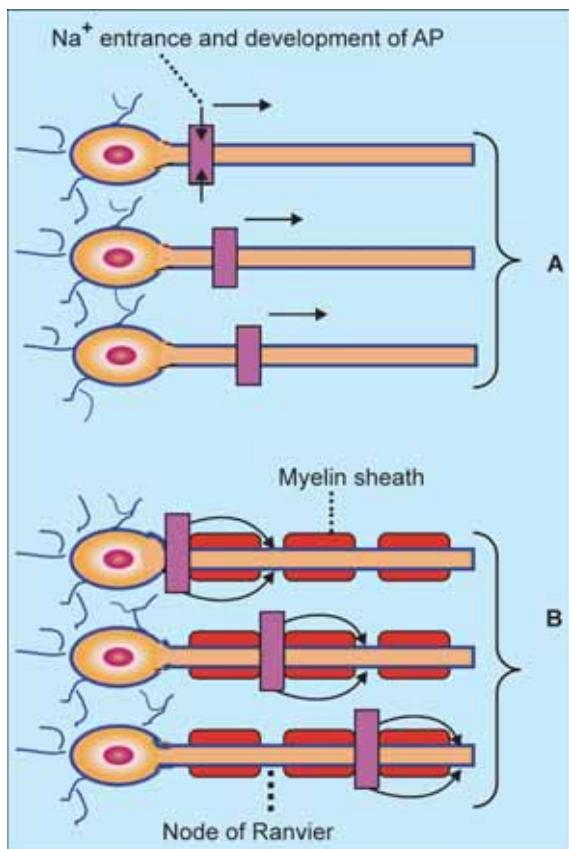


FIGURE 84-6: Mode of conduction through nerve fibers

A. Nonmyelinated nerve fiber — Continuous conduction
B. Myelinated nerve fiber — Saltatory conduction:
Impulse jumps from node to node. AP = Action potential

Absolute refractory period corresponds to the period from the time when firing level is reached till the time when $\frac{1}{3}$ of repolarization is completed. The relative refractory period extends through rest of the repolarization period.

Summation

When one subliminal stimulus is applied, it does not produce any response in the nerve fiber because, the subliminal stimulus is very weak. However, if two or more subliminal stimuli are applied within a short interval of about 0.5 m sec, the response is produced. It is because the subliminal stimuli are summed up together to

become strong enough to produce the response. This phenomenon is known as summation.

Adaptation

While stimulating a nerve fiber continuously, the excitability of the nerve fiber is greater in the beginning. Later the response decreases slowly and finally the nerve fiber does not show any response at all. This phenomenon is known as adaptation or accommodation.

The causes for adaptation are:

1. When a nerve fiber is stimulated continuously, depolarization occurs continuously
2. The continuous depolarization inactivates the sodium pump and increases the efflux of potassium ions.

Infatigability

A nerve fiber cannot be fatigued, even if it is stimulated continuously for a long time. The reason for this is the nerve fiber can conduct only one action potential at a time. At that time, it is completely refractory and does not conduct another action potential.

All or None Law

All or none law states that when a nerve is stimulated by a stimulus it gives maximum response or does not give response at all. Refer Chapter 59 for more details on all or none law.

■ DEGENERATION OF NERVE FIBERS

When a nerve fiber is injured, various changes occur in the nerve fiber and nerve cell body. All these changes are together called the degenerative changes. The injury occurs due to the obstruction of blood flow, local injection of toxic substances, crushing of nerve fiber or the transection of the fiber.

Degenerative Changes in the Neuron

Degeneration refers to deterioration or impairment or pathological changes of an injured tissue. When a peripheral nerve fiber is injured, the degenerative changes occur in the nerve cell

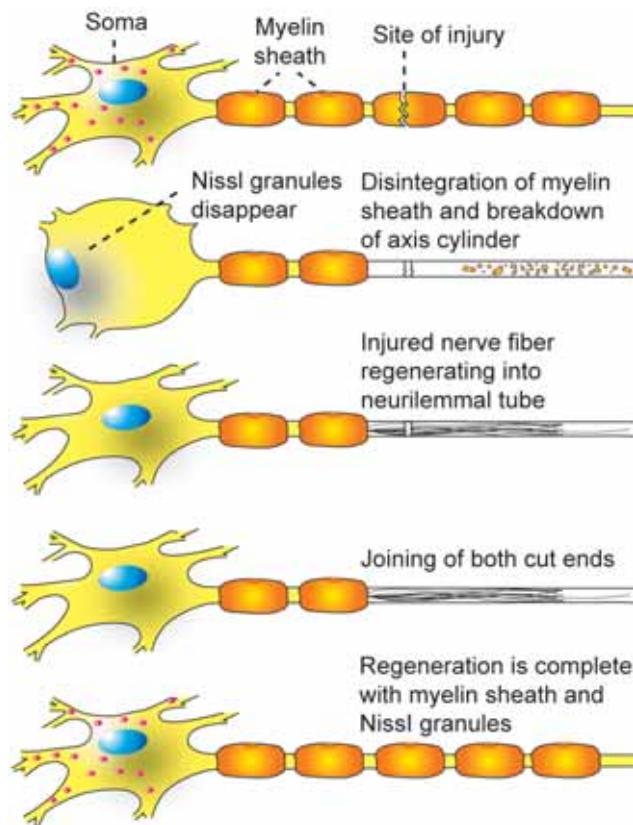


FIGURE 84-7: Degeneration and regeneration of nerve fiber

body and the nerve fiber same neuron and the adjoining neuron. Accordingly, the degenerative changes are classified into three types:

1. Wallerian degeneration
2. Retrograde degeneration
3. Transneuronal degeneration.

Wallerian or Orthograde Degeneration

Wallerian or orthograde degeneration is the pathological change that occurs in the distal cut end of nerve fiber (axon). It is named after the discoverer, Waller. Wallerian degeneration starts within 24 hours of injury. The change occurs throughout the length of distal part of nerve fiber simultaneously.

1. Axis cylinder swells and breaks up into small pieces. After few days, the broken pieces appear as debris in the space occupied by axis cylinder (Fig. 84-7).

2. The myelin sheath is slowly disintegrated into fat droplets. The changes in myelin sheath occur from 8th to 35th day.
3. The neurilemmal sheath is unaffected, but the Schwann cells multiply rapidly. The macrophages invade from outside. The macrophages remove the debris of axis cylinder and the fat droplets of disintegrated myelin sheath. So, the neurilemmal tube becomes empty. Later it is filled by the cytoplasm of Schwann cell. All these changes take place for about 2 months from the day of injury.

Retrograde Degeneration

Retrograde degeneration is the pathological changes which occur in the nerve cell body and axon proximal to the cut end.

Transneuronal Degeneration

If an afferent nerve fiber is cut, the degenerative changes occur in the neuron with which the afferent nerve fiber synapses. It is called transneuronal degeneration.

■ REGENERATION OF NERVE FIBER

The term regeneration refers to regrowth of lost or destroyed part of a tissue. The injured and degenerated nerve fiber can regenerate. It starts as early as 4th day after injury, but, becomes more effective only after 30 days and is completed in about 80 days.

Criteria for Regeneration

Regeneration is possible only if certain criteria are fulfilled by the degenerated nerve fiber:

1. The gap between the cut ends of the nerve should not exceed 3 mm
2. The neurilemma should be present
3. The nucleus must be intact
4. The two cut ends should remain in the same line.

Stages of Regeneration

1. First, some pseudopodia like extensions called fibrils grow from the proximal cut end of the nerve and move towards the distal cut end of the nerve fiber
2. Some of the fibrils enter the neurilemmal tube of distal end and form axis cylinder
3. Schwann cells line up in the neurilemmal tube and guide the fibrils into the tube
4. The axis cylinder is formed inside the neurilemmal tube in about 3 months after injury
5. The myelin sheath is formed by Schwann cells slowly and it is completed in one year
6. In the nerve cell body, first the Nissl granules appear followed by Golgi apparatus
7. The cell loses the excess fluid. The nucleus occupies the central portion

Though the anatomical regeneration occurs in the nerve, the functional recovery occurs after a long period.

■ NEUROGLIA

■ DEFINITION

Neuroglia or the glia (glia = glue) is the supporting cell of the nervous system. The neuroglial cells are non-excitatory and do not transmit nerve impulse (action potential). So, these cells are also called non-neuronal cells or glial cells.

■ CLASSIFICATION OF NEUROGLIAL CELLS

The neuroglial cells are distributed in central nervous system (CNS) as well as peripheral nervous system (PNS).

Central Neuroglial Cells

The neuroglial cells in CNS are of three types:

1. Astrocytes
2. Microglia
3. Oligodendrocytes.

1. Astrocytes

Astrocytes are star shaped neuroglial cells present in all the parts of the brain (Fig. 84-8). Astrocytes are of two types, fibrous astrocytes and protoplasmic astrocytes.

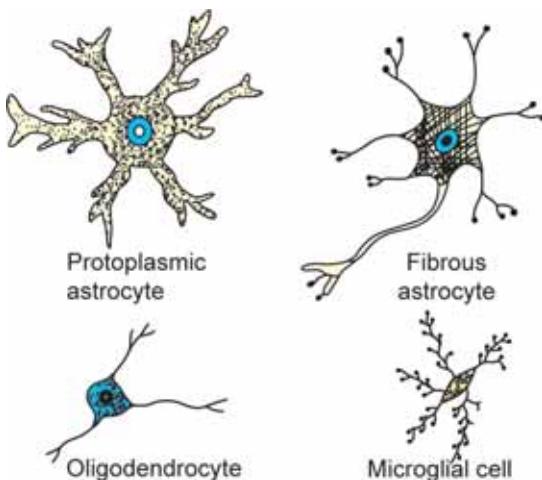


FIGURE 84-8: Neuroglial cells in CNS

Astrocytes:

- i. Twist around the nerve cells and form the supporting network in brain and spinal cord
 - ii. Form the blood-brain barrier and thereby regulate the entry of substances from blood into brain tissues (Chapter 102)
 - iii. Maintain the chemical environment of ECF around CNS neurons
 - iv. Provide calcium and potassium and regulate neurotransmitter level in synapses
2. *Microglia*

Microglia are the smallest neuroglial cells. These cells are derived from monocytes and enter the tissues of nervous system from blood. These phagocytic cells migrate to the site of infection or injury and are often called the macrophages of CNS.

Microglia engulf and destroy the microorganisms and cellular debris by means of Phagocytosis.

3. *Oligodendrocytes*

Oligodendrocytes are neuroglial cells which produce myelin sheath around nerve fibers in CNS.

Oligodendrocytes provide myelination around the nerve fibers in CNS where Schwann cells are absent

Peripheral Neuroglial Cells

The neuroglial cells in PNS are of two types:

1. Schwann cells
2. Satellite cells

1. *Schwann Cells*

Schwann cells are the major glial cells in PNS.

Schwann cells provide myelination (insulation) around the nerve fibers in PNS. These cells remove cellular debris during regeneration by their phagocytic activity.

2. *Satellite Cells*

Satellite cells are the glial cells present on the exterior surface of PNS neurons.

Satellite cells provide physical support to the PNS neurons.

Receptors

- DEFINITION
- CLASSIFICATION
 - EXTEROCEPTORS
 - INTEROCEPTORS
- PROPERTIES
 - SPECIFICITY OF RESPONSE
 - ADAPTATION — SENSORY ADAPTATION
 - RESPONSE TO INCREASE IN THE STRENGTH OF STIMULUS
 - SENSORY TRANSDUCTION
 - RECEPTOR POTENTIAL

■ DEFINITION

Receptors are the sensory (afferent) nerve endings that terminate in the periphery as bare unmyelinated nerve endings or in the form of specialized capsulated structures. When stimulated, receptors produce a series of impulses which are transmitted through the afferent nerves.

Actually receptors function like a transducer. Transducer is a device, which converts one form of energy into another.

So, the receptors are often defined as the biological transducers which convert various forms of energy (stimuli) in the environment into action potentials in nerve fiber.

■ CLASSIFICATION OF RECEPTORS

Generally, the receptors are classified into two types:

I. Exteroceptors

II. Interoceptors.

■ EXTEROCEPTORS

Exteroceptors are the receptors which give response to stimuli arising from outside the body.

The exteroceptors are divided into three groups.

1. *Cutaneous Receptors*

The receptors situated in the skin are called the cutaneous receptors. Cutaneous receptors are also called mechanoreceptors because of their response to mechanical stimuli such as touch, pressure and pain (Fig. 85-1). Touch and pressure receptors give response to vibration also. The different types of cutaneous receptors are given in Figure 85-2.

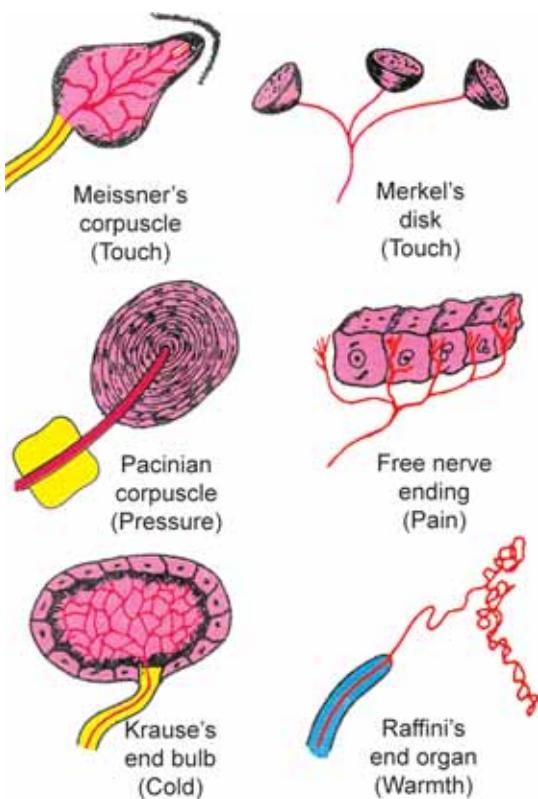


FIGURE 85-1: Cutaneous receptors

2. Chemoreceptors

The receptors, which give response to chemical stimuli, are called the chemoreceptors. Examples are given in Figure 85-2.

3. Telereceptors

Telereceptors are the receptors that give response to stimuli arising away from the body. These receptors are also called the distance receptors. Examples are given in Figure 85-2.

■ INTEROCEPTORS

Interoceptors are the receptors which give response to stimuli arising from within the body. Interoceptors are of two types:

1. Visceroceptors

Receptors situated in the viscera are called visceroreceptors. Visceroreceptors are listed in Figure 85-3.

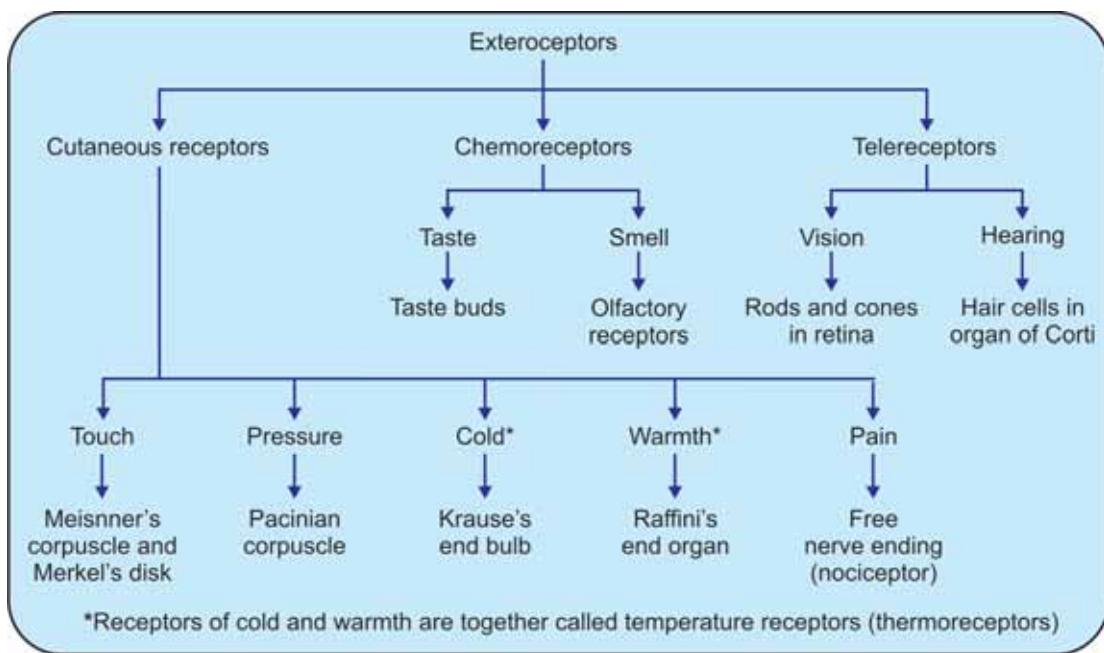


FIGURE 85-2: Exteroceptors

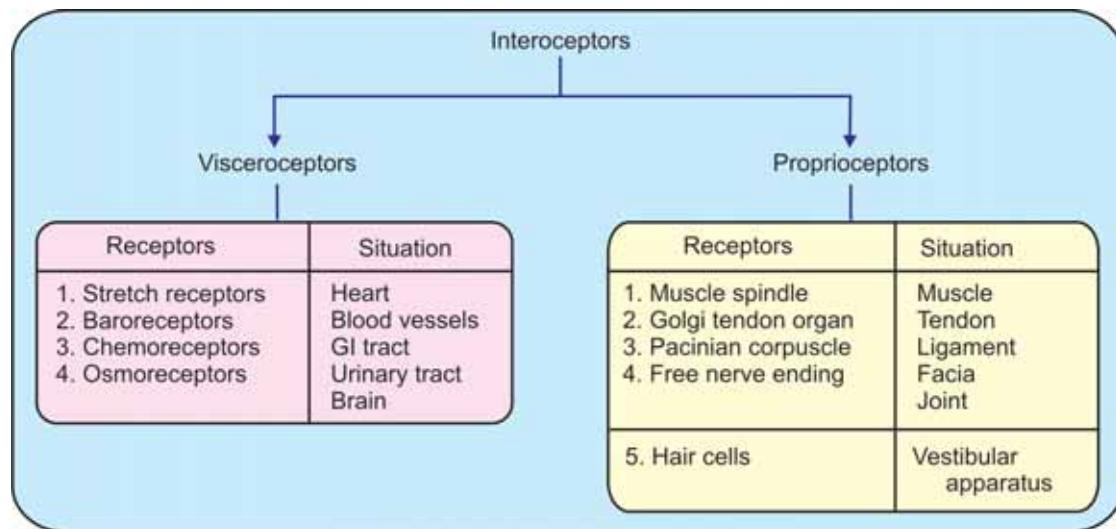


FIGURE 85-3: Interoceptors

2. Proprioceptors

Proprioceptors are the receptors which give response to change in the position of different parts of the body (Chapter 97). Proprioceptors are listed in Figure 85-3.

■ PROPERTIES OF RECEPTORS

■ 1. SPECIFICITY OF RESPONSE — MÜLLER'S LAW

Specificity of response or Müller's law refers to the response given by a particular type of receptor to a specific sensation. For example, pain receptors give response only to pain sensation. Similarly, temperature receptors give response only to temperature sensation. Specificity of response is also called doctrine of specific nerve energies.

■ 2. ADAPTATION — SENSORY ADAPTATION

Adaptation is the decrease in discharge of sensory impulses when a receptor is stimulated continuously with constant strength. It is also called sensory adaptation or desensitization. Depending upon adaptation time, the receptors are divided into two types:

- i. Phasic receptors, which get adapted rapidly. Touch and pressure receptors are the phasic receptors
- ii. Tonic receptors, which adapt slowly. Muscle spindle, pain receptors and cold receptors are the tonic receptors.

■ 3. RESPONSE TO INCREASE IN THE STRENGTH OF STIMULUS

During the stimulation of a receptor, if the response given by the receptor is to be doubled, the strength of stimulus must be increased 100 times. This phenomenon is called Weber-Fechner law, which states that the change in response of a receptor is directly proportional to the logarithmic increase in the intensity of stimulus.

■ 4. SENSORY TRANSDUCTION

Sensory transduction in a receptor is a process by which the energy (stimulus) in the environment is converted into electrical impulses (action potentials) in nerve fiber (transduction = conversion of one form of energy into another).

When a receptor is stimulated, it gives response by sending information about the stimulus to CNS. Series of events occur to carry out this function such as the development of

receptor potential in the receptor cell and development of action potential in the sensory nerve.

The sensory transduction varies depending upon the type of receptor. For example, the chemoreceptor converts chemical energy into action potential in the sensory nerve fiber. The touch receptor converts mechanical energy into action potential in the sensory nerve fiber.

■ 5. RECEPTOR POTENTIAL

Receptor potential is a nonpropagated transmembrane potential difference that develops when a receptor is stimulated. It is also called generator potential. The receptor potential is short lived and hence, it is called transient receptor potential.

Receptor potential is not action potential. It is a graded potential (Chapter 23). It is similar to excitatory postsynaptic potential (EPSP) in synapse, endplate potential in neuromuscular junction and electrotonic potential in the nerve fiber.

Properties of Receptor Potential

Receptor potential has two important properties:

- i. Receptor potential is nonpropagated. It is confined within the receptor itself
- ii. It does not obey all or none law.

Significance of Receptor Potential

When the receptor potential is sufficiently strong (when the magnitude is about 10 mV), it causes development of action potential in the sensory nerve.

Mechanism of Development of Receptor Potential

The pacinian corpuscles are generally used to study the receptor potential because of their large size and anatomical configuration. Pacinian corpuscles give response to pressure stimulus. When pressure stimulus is applied, the Pacinian corpuscle is compressed. This compression causes elongation or change in shape of the corpuscle. The change in shape of the corpuscle leads to the deformation of central fiber of the

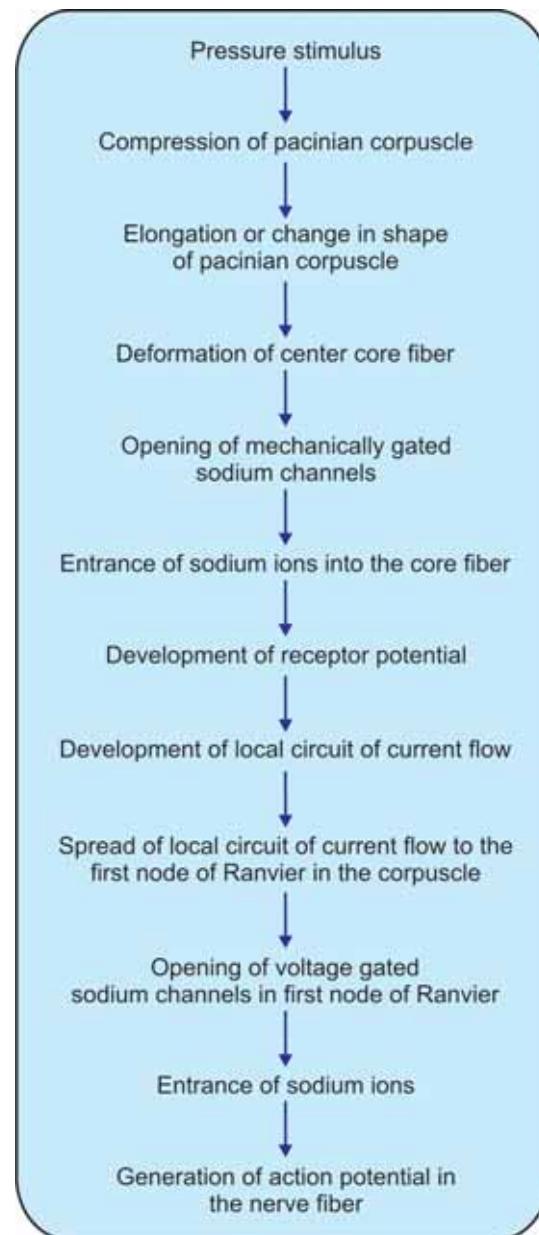


FIGURE 85-4:Schematic diagram showing development of receptor potential and generation of action potential in the nerve fiber

corpuscle. This results in the opening of mechanically gated sodium channels (Chapter 3). So, the positively charged sodium ions enter the interior of fiber. This produces a mild depolarization, i.e. receptor potential.

Generation of Action Potential in the Nerve Fiber

The receptor potential causes development of a local circuit of current flow which spreads along the unmyelinated part of the nerve fiber within the corpuscle.

When this local circuit of current reaches the first node of Ranvier within the corpuscle, it causes opening of voltage gated sodium channels and entrance of sodium ions into the nerve fiber. This leads to the development of action potential in the nerve fiber (Fig. 85-4).

Synapse and Neurotransmitters

- DEFINITION
- CLASSIFICATION
 - ANATOMICAL CLASSIFICATION
 - FUNCTIONAL CLASSIFICATION
- FUNCTIONAL ANATOMY
- FUNCTIONS
 - EXCITATORY SYNAPSE
 - INHIBITORY SYNAPSE
- PROPERTIES
 - ONE WAY CONDUCTION – BELL-MAGENDIE LAW
 - THE SYNAPTIC DELAY
 - FATIGUE
 - SUMMATION
 - ELECTRICAL PROPERTY
- NEUROTRANSMITTERS
 - DEFINITION
 - CLASSIFICATION

■ DEFINITION

Synapse is the junction between the two neurons. It is not the anatomical continuation. But, it is only a physiological continuity between two nerve cells.

■ CLASSIFICATION OF SYNAPSE

Synapse is classified by two methods, anatomical classification and functional classification.

■ ANATOMICAL CLASSIFICATION

Synapse is formed by axon of one neuron ending on the cell body, dendrite or axon of the next neuron. Depending upon the ending of axon, the synapse is classified into three types (Fig. 86-1):

1. Axoaxonic synapse in which axon of one neuron terminates on axon of another neuron
2. Axodendritic synapse in which axon of one neuron terminates on dendrite of another neuron

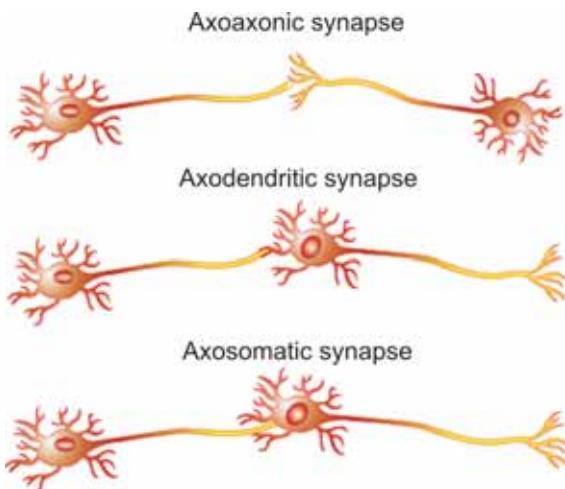


FIGURE 86-1: Anatomical synapses

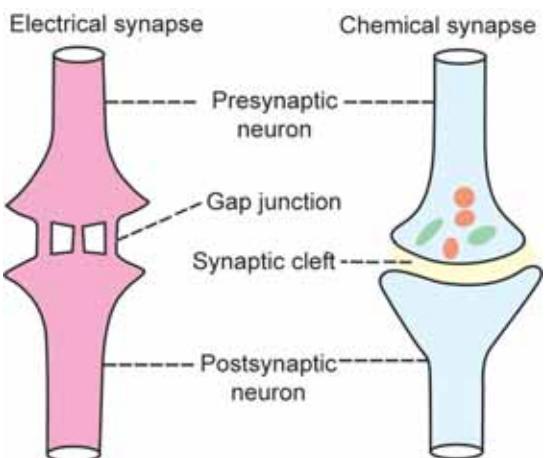


FIGURE 86-2: Electrical and chemical synapse

3. Axosomatic synapse in which axon of one neuron ends on soma (cell body) of another neuron.

■ FUNCTIONAL CLASSIFICATION

Function classification depends upon mode of impulse transmission. On this basis, synapse is classified into two types:

1. Electrical Synapse

Electrical synapse is the synapse in which the physiological continuity between the presynaptic and the postsynaptic neurons is provided by the gap junction between these two neurons (Fig. 86-2). There is direct exchange of ions between the two neurons through the gap junction. So, the action potential reaching the terminal portion of presynaptic neuron directly enters the postsynaptic neuron.

2. Chemical Synapse

Chemical synapse is the junction between a nerve fiber and a muscle fiber or between two nerve fibers, through which the signals are transmitted by the release of chemical transmitter. In the chemical synapse, there is no continuity between the presynaptic and postsynaptic neurons. These two neurons are

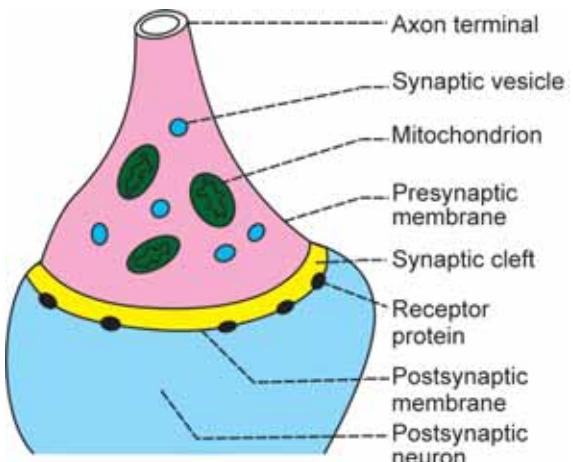


FIGURE 86-3: Structure of chemical synapse

separated by a space called synaptic cleft between the two neurons.

■ FUNCTIONAL ANATOMY OF CHEMICAL SYNAPSE

The functional anatomy of a chemical synapse is shown in Figure 86-3. The neuron from which the axon arises is called the presynaptic neuron and the neuron on which the axon ends is called postsynaptic neuron. The axon of the presynaptic neuron divides into many small branches before forming the synapse. The branches are known as presynaptic axon terminals.

Axon terminal has membrane known as presynaptic membrane. The presynaptic terminal has two important structures:

- Mitochondria, which help in the synthesis of neurotransmitter substances
- Synaptic vesicles, which store neurotransmitter substance.

The membrane of the postsynaptic neuron is called postsynaptic membrane. It contains some receptor proteins. The small space in between the presynaptic membrane and the postsynaptic membrane is called synaptic cleft. The basal lamina of this cleft contains cholinesterase, which destroys acetylcholine.

FUNCTIONS OF SYNAPSE

The function of the synapse is to transmit the impulses from one neuron to another. However, some synapses inhibit the impulses.

Accordingly, synapse is divided into two types:

- Excitatory synapses, which transmit the impulses — excitatory function
- Inhibitory synapses, which inhibit the transmission of impulses — inhibitory function.

EXCITATORY SYNAPSE

Excitatory synapse transmits the impulses from presynaptic neuron to postsynaptic neuron by the development of excitatory postsynaptic potential.

Excitatory Postsynaptic Potential

Excitatory postsynaptic potential (EPSP) is the nonpropagated electrical potential that develops during the process of synaptic transmission. When the action potential reaches the presynaptic axon terminal, the voltage gated calcium channels at the presynaptic membrane are opened. Now, the calcium ions enter the axon terminal from ECF (Fig. 86-4).

The calcium ions cause the release of neurotransmitter substance from the vesicles by means of exocytosis. The common neurotransmitter in synapse is acetylcholine.

The neurotransmitter passes through presynaptic membrane and synaptic cleft and

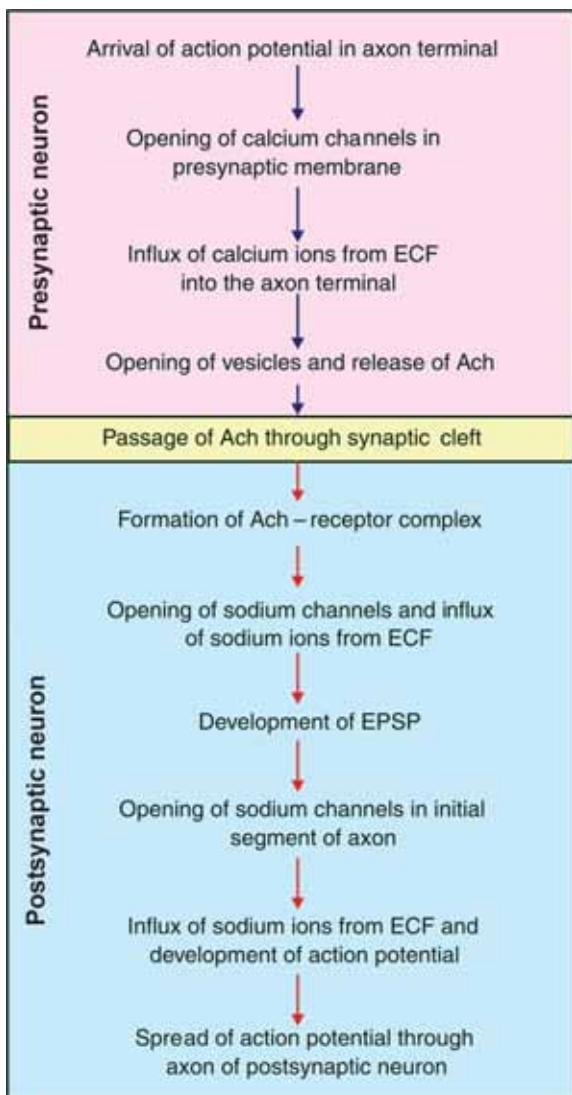


FIGURE 86-4: Sequence of events during synaptic transmission. Ach = Acetylcholine. ECF = Extracellular fluid. EPSP = Excitatory postsynaptic potential

reaches the postsynaptic membrane. Now, it binds with the receptor protein present in the postsynaptic membrane to form the neurotransmitter-receptor complex.

The neurotransmitter-receptor complex causes opening of ligand gated sodium channels. Now, the sodium ions from ECF enter the cell body of postsynaptic neuron. As the

sodium ions are positively charged, the resting membrane potential inside the cell body becomes slightly positive and a mild depolarization develops. This type of mild depolarization is called EPSP.

EPSP is confined only to the synapse. It is a graded potential (Chapter 23). It is similar to receptor potential and endplate potential.

Properties of EPSP

EPSP has two properties.

1. It is nonpropagated
2. It does not obey all or none law.

Significance of EPSP

The EPSP is not transmitted into the axon of postsynaptic neuron. However, it causes development of action potential in the axon.

When the EPSP is strong enough, it causes the opening of voltage gated sodium channels in the initial segment of axon. Now, due to the entrance of sodium ions, the depolarization occurs in the initial segment of axon and thus, the action potential develops. From here, the action potential spreads to other segment of the axon.

■ INHIBITORY SYNAPSE

Inhibitory synapse does not transmit the impulses from presynaptic neuron to postsynaptic neuron. Inhibition of synaptic transmission is classified into three types:

1. Postsynaptic inhibition
2. Presynaptic inhibition
3. Renshaw cell inhibition.

1. Postsynaptic Inhibition

Postsynaptic inhibition is the type of synaptic inhibition that occurs due to the release of an inhibitory neurotransmitter from presynaptic terminal instead of an excitatory neurotransmitter substance. It is also called direct inhibition. The inhibitory neurotransmitter develops inhibitory post synaptic potential (IPSP) instead of EPSP.

The inhibitory neurotransmitters are gamma amino butyric acid (GABA), dopamine and glycine.

Action of GABA — Development of IPSP

IPSP is the electrical potential in the form of hyperpolarization that develops during postsynaptic inhibition. The inhibitory neurotransmitter substance acts on postsynaptic membrane by binding with receptor. The transmitter – receptor complex opens the ligand gated potassium channels instead of sodium channels. Now, the potassium ions which are available in plenty in the cell body of postsynaptic neuron move to ECF. Simultaneously, chloride channels also open and chloride ions (which are more in ECF) move inside the cell body of postsynaptic neuron. The exit of potassium ions and influx of chloride ions cause more negativity inside, leading to hyperpolarization. The hyperpolarized state of the synapse inhibits synaptic transmission.

2. Presynaptic Inhibition

It is the synaptic inhibition which occurs because of the failure of presynaptic axon terminal to release the excitatory neurotransmitter substance. It is also called indirect inhibition.

3. Renshaw Cell Inhibition

It is the type of synaptic inhibition which is caused by Renshaw cells in spinal cord. Renshaw cells are small motor neurons scattered among the large a motor neurons in anterior gray horn of spinal cord (Chapter 88). The motor nerve fibers to effector organs arise from a motor neurons. Some of these fibers send collateral fibers to Renshaw cells.

When the motor neurons send motor impulses to effector organs, some of the impulses reach the Renshaw cell by passing through collaterals. Now, the Renshaw cell is stimulated. In turn, it sends inhibitory impulses to a motor neurons so that, the discharge from a motor neurons is reduced (Fig. 86-5).

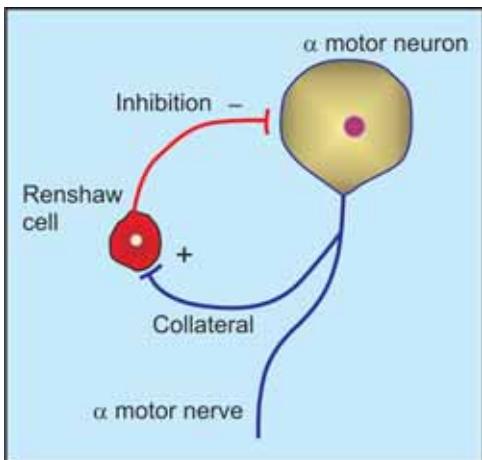


FIGURE 86-5: Renshaw cell inhibition

Significance of synaptic inhibition

The synaptic inhibition in CNS limits the number of impulses going to muscles and enables the muscles to act properly and appropriately.

■ PROPERTIES OF SYNAPSE

■ 1. ONE WAY CONDUCTION – BELL-MAGENDIE LAW

According to Bell-Magendie law, the impulses are transmitted only in one direction in synapse, i.e. from presynaptic neuron to postsynaptic neuron.

■ 2. THE SYNAPTIC DELAY

Synaptic delay is a short delay that occurs during the transmission of impulses through the synapse. It is due to the time taken for:

- i. Release of neurotransmitter
- ii. Passage of neurotransmitter from axon terminal to postsynaptic membrane
- iii. Action of the neurotransmitter to open the ionic channels in postsynaptic membrane.

The normal duration of synaptic delay is 0.3 to 0.5 msec. The synaptic delay is one of the causes for reaction time of the reflex activity.

Significance of determining synaptic delay

Determination of synaptic delay helps to find out whether the pathway for a reflex is monosynaptic or polysynaptic.

■ 3. FATIGUE

During continuous muscular activity, the synapse forms the seat of fatigue along with the Betz cells present in the motor area of the frontal lobe of the cerebral cortex (Refer Chapter 22 for details of fatigue). The fatigue at the synapse is due to the depletion of neurotransmitter substance, acetylcholine.

Depletion of acetylcholine occurs by two factors:

- i. Soon after the action, acetylcholine is destroyed by acetylcholinesterase
- ii. Due to continuous action, new acetylcholine is not synthesized.

These two factors lead to depletion of acetylcholine resulting in fatigue.

■ 4. SUMMATION

It is the fusion of effects or progressive increase in the excitatory postsynaptic potential (EPSP) in postsynaptic neuron when many presynaptic excitatory terminals are stimulated simultaneously or when single presynaptic terminal is stimulated repeatedly. The increased EPSP triggers the action potential in the initial segment of the axon of postsynaptic neuron (Fig. 86-6).

Summation is of two types:

- i. Spatial Summation which occurs when many presynaptic terminals are stimulated simultaneously
- ii. Temporal summation which occurs when one presynaptic terminal is stimulated repeatedly (Fig. 86-6).

■ 5. ELECTRICAL PROPERTY

The electrical properties of the synapse are the EPSP and IPSP, which are already described in this chapter.

TABLE 86-1: Neurotransmitters

Group	Name	Site of secretion	Action
Aminoacids	GABA	Cerebral cortex, cerebellum, basal ganglia, retina and spinal cord	Inhibitory
	Glycine	Forebrain, brainstem, spinal cord and retina	Inhibitory
	Glutamate	Cerebral cortex, brainstem, and cerebellum	Excitatory
	Aspartate	Cerebellum, spinal cord and retina	Excitatory
Amines	Noradrenaline	Postganglionic adrenergic sympathetic nerve endings, cerebral cortex, hypothalamus, basal ganglia, brainstem, locus ceruleus and spinal cord	Excitatory and Inhibitory
	Adrenaline	Hypothalamus, thalamus and spinal cord	Excitatory and Inhibitory
	Dopamine	Basal ganglia, hypothalamus, limbic system, neocortex, retina and sympathetic ganglia	Inhibitory
	Serotonin	Hypothalamus, limbic system, cerebellum, spinal cord, retina, GI tract, lungs and platelets	Inhibitory
	Histamine	Hypothalamus, cerebral cortex, GI tract and mast cells	Excitatory
Others	Nitric oxide	Many parts of CNS, neuromuscular junction and GI tract	Excitatory
	Acetylcholine	Preganglionic parasympathetic nerve endings Postganglionic parasympathetic nerve endings Preganglionic sympathetic nerve endings Postganglionic sympathetic cholinergic nerve endings Neuromuscular junction, cerebral cortex, hypothalamus, basal ganglia, thalamus, hippocampus and amacrine cells of retina	Excitatory

TABLE 86-2: Excitatory and inhibitory neurotransmitters

Excitatory neurotransmitters	Inhibitory neurotransmitters	Neurotransmitters with excitatory and inhibitory actions
<ol style="list-style-type: none"> 1. Acetylcholine 2. Nitric oxide 3. Histamine 4. Glutamate 5. Aspartate 	<ol style="list-style-type: none"> 1. GABA 2. Glycine 3. Dopamine 4. Serotonin 	<ol style="list-style-type: none"> 1. Noradrenaline 2. Adrenaline

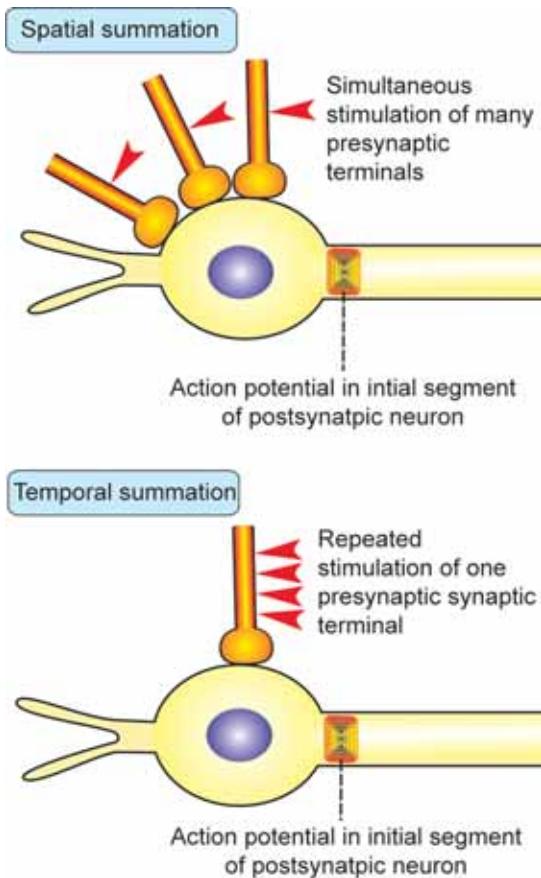


FIGURE 86-6: Spatial and temporal summation

■ NEUROTRANSMITTERS

■ DEFINITION

Neurotransmitter is a chemical substance that acts as the mediator for the transmission of nerve impulse from one neuron to another neuron through a synapse.

■ CLASSIFICATION OF NEUROTRANSMITTERS

Depending Upon Chemical Nature

Depending upon chemical nature, neurotransmitters are classified into three groups (Table 86-1):

1. Amino acids
2. Amines
3. Others

Depending Upon Function

Depending upon function, neurotransmitters are classified into two types:

1. Excitatory neurotransmitters which are responsible for the conduction of impulse
2. Inhibitory neurotransmitters which inhibit the conduction of impulse

Details of neurotransmitters are given in the Tables 86-1 and 86-2.

Reflex Activity

- DEFINITION AND SIGNIFICANCE OF REFLEXES
- REFLEX ARC
- CLASSIFICATION OF REFLEXES
- PROPERTIES OF REFLEXES
- REFLEXES IN MOTOR NEURON LESION

■ DEFINITION AND SIGNIFICANCE OF REFLEXES

Reflex activity is the response to a peripheral nervous stimulation that occurs without our consciousness. It is a type of protective mechanism and it protects the body from irreparable damages.

For example, when the hand is placed on a hot object, it is withdrawn immediately. When a very bright light is thrown into the eyes, eyelids are closed and pupil is constricted to prevent the damage of retina by the entrance of excessive light into the eyes.

■ REFLEX ARC

Reflex arc is the anatomical nervous pathway for a reflex action. A simple reflex arc includes five components (Fig. 87-1).

1. Receptor

It is the end organ, which receives the stimulus. When the receptor is stimulated, impulses are generated in afferent nerve.

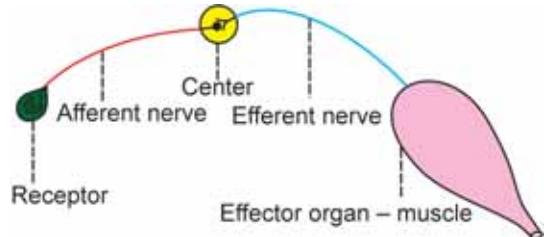


FIGURE 87-1: Simple reflex arc

2. Afferent Nerve

Afferent or sensory nerve transmits sensory impulses from the receptor to the center.

3. Center

The center is located in the brain or spinal cord. The center receives the sensory impulses via afferent nerve fibers and in turn, it generates appropriate motor impulses.

4. Efferent Nerve

Efferent or motor nerve transmits motor impulses from the center to the effector organ.

5. Effector Organ

The effector organ is the structure such as the muscle or gland where the activity occurs in response to the stimulus.

Afferent and efferent nerve fibers may be connected directly to the center. In some places, one or more neurons are interposed between these nerve fibers and the center. Such neurons are called connector neurons or internuncial neurons or interneurons.

■ CLASSIFICATION OF REFLEXES

Reflexes are classified by five different methods.

■ I. DEPENDING UPON WHETHER INBORN OR ACQUIRED

1. *Unconditioned Reflexes or Inborn Reflexes*

Unconditioned reflexes are the natural reflexes which are present since the time of birth hence the name inborn reflexes. Such reflexes do not require previous learning, training, or conditioning. The best example is the secretion of saliva when a drop of honey is kept in the mouth of a newborn baby for the first time. The baby does not know the taste of the honey but still saliva is secreted.

2. *Conditioned Reflexes or Acquired Reflexes*

Conditioned or acquired reflexes are the reflexes that are developed after conditioning or training. These reflexes are not inborn but acquired after birth. Such reflexes need previous learning, training, or conditioning. The example is the secretion of saliva by the sight, smell, thought or hearing of a known edible substance.

■ II. DEPENDING UPON THE SITUATION OF THE CENTER

1. *Cerebellar Reflexes*

Cerebellar reflexes are the reflexes which have the center in cerebellum.

2. Cortical Reflexes

Cortical reflexes are the reflexes that have the center in cerebral cortex.

3. Midbrain Reflexes

Midbrain reflexes are the reflexes which have the center in midbrain.

4. Bulbar or Medullary Reflexes

Bulbar or medullary reflexes are the reflexes which have the center in medulla oblongata.

5. Spinal Reflexes

Reflexes having their center in the spinal cord are called spinal reflexes.

■ III. DEPENDING UPON THE PURPOSE — FUNCTIONAL SIGNIFICANCE

1. *Protective Reflexes or Flexor Reflexes*

The protective reflexes are the reflexes which protect the body from nociceptive (harmful) stimuli. These reflexes are also called withdrawal reflexes or flexor reflexes. Protective reflexes involve flexion at different joints hence the name flexor reflexes.

2. *Antigravity Reflexes or Extensor Reflexes*

Antigravity reflexes are the reflexes that protect the body against the gravitational force. These reflexes are also called the extensor reflexes because, the extensor muscles contract during these reflexes resulting in extension at joints.

■ IV. DEPENDING UPON THE NUMBER OF SYNAPSE

1. *Monosynaptic Reflexes*

Reflexes having only one synapse in the reflex arc are called monosynaptic reflexes. Stretch reflex is the best example for monosynaptic reflex and it is elicited due to the stimulation of muscle spindle.

2. Polysynaptic Reflexes

Reflexes having more than one synapse in the reflex arc are called polysynaptic reflexes. Flexor reflexes (withdrawal reflexes) are the polysynaptic reflexes.

■ V. DEPENDING UPON CLINICAL BASIS

Depending upon clinical basis reflexes are classified into four types:

1. Superficial Reflexes

Superficial reflexes are the reflexes, which are elicited from the surface of the body. The superficial reflexes are of two types, mucous membrane reflexes (Table 87-1) and skin reflexes (Table 87-2).

2. Deep Reflexes

The deep reflexes are elicited from the deeper structures beneath the skin like tendon. These reflexes are otherwise known as tendon reflexes. The details of these are given in Table 87-3.

3. Visceral Reflexes

Visceral reflexes are the reflexes arising from the pupil and the visceral organs.

Visceral reflexes are:

- i. Pupillary reflexes in which, the size of pupil is altered (Chapter 107)
- ii. Oculocardiac reflex in which heart rate decreases due to the pressure applied over eyeball
- iii. Carotid sinus reflex in which the pressure over carotid sinus in neck due to tight collar decreases heart rate and blood pressure.

4. Pathological Reflexes

Pathological reflexes are the reflexes that are elicited only in pathological conditions. Three pathological reflexes are well known.

i. Babinski's sign

The abnormal plantar reflex is called Babinski's sign. It is also called Babinski's reflex or phenomenon. In the normal plantar reflex, a gentle scratch over the outer edge of the sole of the foot causes plantar flexion and adduction of all

TABLE 87-1: Superficial mucous membrane reflexes

Reflex	Stimulus	Response	Afferent Nerve	Center	Efferent Nerve
1. Corneal reflex	Irritation of cornea	Blinking of eye (closure of eyelids)	V cranial nerve	Pons	VII cranial nerve
2. Conjunctival reflex	Irritation of conjunctiva	Blinking of eye	V cranial nerve	Pons	VII cranial nerve
3. Nasal reflex (sneezing reflex)	Irritation of nasal mucous membrane	Sneezing	V cranial nerve	Motor nucleus of V cranial nerve	X cranial nerve and upper cervical nerves
				nerve	
4. Pharyngeal reflex	Irritation of pharyngeal mucous membrane	Retching or gagging (opening of mouth)	IX cranial nerve	Nuclei of X cranial nerve	X cranial nerve
5. Uvular reflex	Irritation of uvula	Raising of uvula	IX cranial nerve	Nuclei of X cranial nerve	X cranial nerve

TABLE 87-2: Superficial cutaneous reflexes

Reflex	Stimulus	Response	Center – spinal segments involved
1. Scapular reflex	Irritation of skin at the interscapular space	Contraction of scapular muscles and drawing in of scapula	C5 to T1
2. Upper abdominal reflex	Stroking the abdominal wall below the costal margin	Ipsilateral contraction of abdominal muscle and movement of umbilicus towards the site of stroke	T6 to T9
3. Lower abdominal reflex	Stroking the abdominal wall at umbilical and iliac level	Ipsilateral contraction of abdominal muscle and movement of umbilicus towards the site of stroke	T10 to T12
4. Cremasteric reflex	Stroking the skin at upper and inner aspect of thigh	Elevation of testicles	L1, L2
5. Gluteal reflex	Stroking the skin over glutei	Contraction of glutei	L4 to S1,2
6. Plantar reflex	Stroking the sole	Plantar flexion and adduction of toes	L5 to S2
7. Bulbocavernous reflex	Stroking the dorsum of glans penis	Contraction of bulbocavernous	S3, S4
8. Anal reflex	Stroking the perianal region	Contraction of anal sphincter	S4, S5

TABLE 87-3: Deep reflexes

Reflex	Stimulus	Response segments involved	Center – Spinal
1. Jaw jerk	Tapping middle of the chin with slightly opened mouth	Closure of mouth	Pons - V Cranial nerve
2. Biceps jerk	Percussion of biceps tendon	Flexion of forearm	C5, C6
3. Triceps jerk	Percussion of triceps tendon	Extension of forearm	C6, to C8
4. Supinator jerk or radial periosteal reflex	Percussion of tendon over distal end (styloid process) of radius	Supination and flexion of forearm	C7, C8
5. Wrist tendon or finger flexion reflex	Percussion of wrist tendons	Flexion of corresponding finger	C8, T1
6. Knee jerk or patellar tendon reflex	Percussion of patellar ligament	Extension of leg	L 2, To L4
7. Ankle jerk or Achilles tendon reflex	Percussion of Achilles tendon	Plantar flexion of foot	L 5 to S2

toes. But in Babinski's sign, there is dorsiflexion of great toe and fanning of other toes.

Babinski's sign is present in upper motor neuron lesion. Physiological conditions when Babinski's sign is present are infancy and deep sleep. It is present in infants because of non-myelination of pyramidal tracts.

ii. Clonus

Clonus is a series of rapid and repeated involuntary jerky movements, which occur while eliciting a deep reflex. It occurs in upper motor neuron lesion. When a deep reflex is elicited in a normal person, the contractions of a muscle or group of muscles are smooth and continuous. But in upper motor neuron lesion clonus occurs. It is because of hypertonicity of muscles and exaggeration of deep reflexes. Clonus is well seen in calf muscles producing ankle clonus and quadriceps producing patella clonus.

iii. Pendular movements

Pendular movements are the slow oscillatory movements (instead of brisk movements) that are developed while eliciting a tendon jerk. The pendular movements are very common while eliciting the knee jerk in patients affected by cerebellar lesion.

■ PROPERTIES OF REFLEXES

■ 1. ONE WAY CONDUCTION (BELL-MAGENDIE LAW)

During any reflex activity, the impulses are transmitted in only one direction through the reflex arc as per Bell-Magendie law. The impulses pass from receptors to the center and then from center to effector organ.

■ 2. REACTION TIME

Reaction time is the time interval between application of stimulus and the onset of reflex. It depends upon the length of afferent and efferent nerve fibers, velocity of impulse through these fibers and central delay. Central delay is

the delay at the synapse. It is also called synaptic delay.

■ 3. SUMMATION

Refer Chapter 86 for details of summation. The summation in reflex action is of two types.

i. *Spatial Summation*

When two afferent nerve fibers supplying a muscle are stimulated separately with subliminal stimulus, there is no response. But the muscle contracts when both the nerve fibers are stimulated together with same strength of stimulus. It is called spatial summation.

ii. *Temporal Summation*

When one nerve fiber is stimulated repeatedly with subliminal stimuli, these stimuli are summed up to give response in the muscle. It is called temporal summation.

Thus, both spatial summation and temporal summation play an important role in the facilitation of responses during the reflex activity.

■ 4. RECRUITMENT

Recruitment is defined as the successive activation of additional motor units with progressive increase in force of muscular contraction.

When an excitatory nerve is stimulated for a long time, there is a gradual increase in the response of reflex activities. It is due to the activation of more and more motor neurons. Recruitment is similar to the effect of temporal summation.

■ 5. AFTER DISCHARGE

After discharge is the persistence or continuation of response for some time even after cessation of stimulus. When a reflex action is elicited continuously for some time, and then the stimulation is stopped, the reflex activity (contraction) will be continued for some time even after the stoppage of the stimulus. It is because of the discharge of impulses from the center even after

stoppage of stimulus. The internuncial neurons are responsible for after discharge.

■ 6. REBOUND PHENOMENON

The reflex activities can be forcefully for some time. But, when the inhibition is suddenly removed, the reflex activity becomes more powerful than before inhibition. It is called rebound phenomenon. The reason for this state of over excitation is not known.

■ 7. FATIGUE

When a reflex activity is continuously elicited for a long time, the response is reduced slowly and at one stage, the response does not occur. This type of failure to give response to the

stimulus is called fatigue. The center or the synapse of the reflex arc is the first seat of fatigue.

■ REFLEXES IN MOTOR NEURON LESION

■ UPPER MOTOR NEURON LESION

During upper motor neuron lesion, all the superficial reflexes are lost. The deep reflexes are exaggerated and the Babinski's sign is present (Chapter 89).

■ LOWER MOTOR NEURON LESION

During lower motor lesion, all the superficial and deep reflexes are lost (Chapter 89).

Spinal Cord

- INTRODUCTION
- GRAY MATTER
- WHITE MATTER
- TRACTS IN SPINAL CORD
 - ASCENDING TRACTS
 - DESCENDING TRACTS

■ INTRODUCTION

The spinal cord lies loosely in the vertebral canal. It extends from foramen magnum where it is continuous with medulla oblongata, above and up to the lower border of first lumbar vertebra below.

Segments of Spinal Cord

Spinal cord is made up of 31 segments:

Cervical segments	=	8
Thoracic segments	=	12
Lumbar segments	=	5
Sacral segments	=	5
Coccygeal segment	=	1

In fact, the spinal cord is a continuous structure. The appearance of the segment is given by the nerves arising from the spinal cord which are called spinal nerve.

Spinal Nerves

The segments of spinal cord correspond to the 31 pairs of spinal nerves in a symmetrical manner: The spinal nerves are:

Cervical spinal nerves	=	8
Thoracic spinal nerves	=	12

Lumbar spinal nerves	=	5
Sacral spinal nerves	=	5
Coccygeal nerve	=	1

Nerve Roots

Each spinal nerve is formed by an anterior (ventral) root and a posterior (dorsal) root. Both the roots on either side leave the spinal cord through the corresponding intervertebral foramina.

■ INTERNAL STRUCTURE OF SPINAL CORD

The neural substance of spinal cord is divided into inner gray matter and outer white matter (Fig. 88-1).

■ GRAY MATTER OF SPINAL CORD

Gray matter of the spinal cord is the collection of nerve cell bodies, dendrites and parts of axons. It is placed centrally in the form of wings of the butterfly and it resembles the letter H. Exactly in the center of gray matter, there is a canal called the spinal canal.

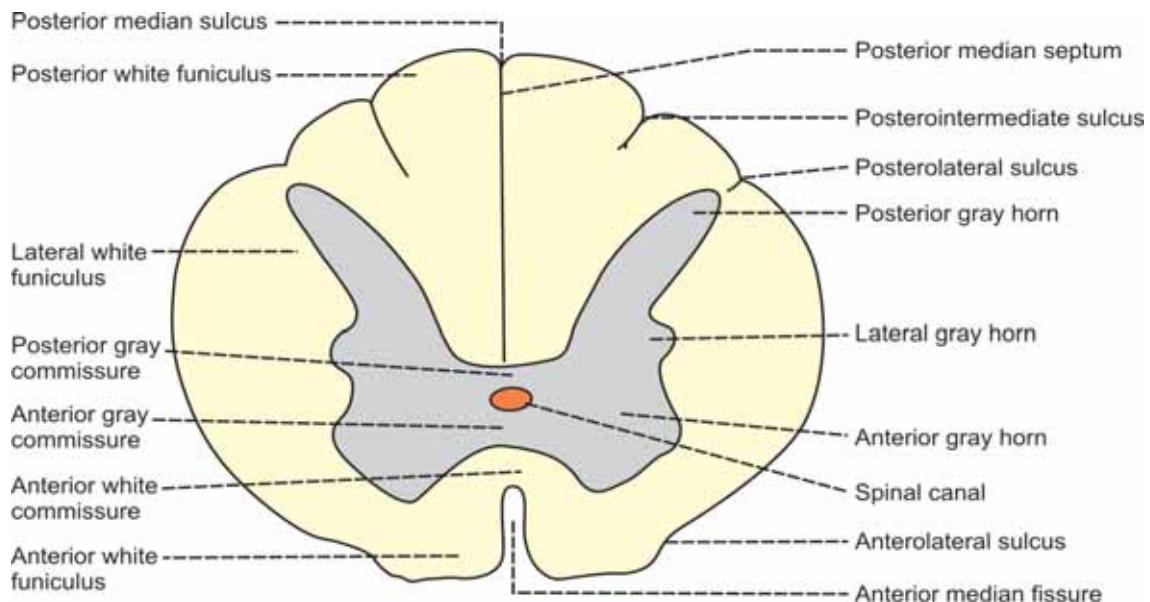


FIGURE 88-1: Section of spinal cord – thoracic segment

The ventral and the dorsal portions of each lateral half of gray matter are called ventral (anterior) and dorsal (posterior) gray horns respectively. In addition, the gray matter forms a small projection in between the anterior and posterior horns in all thoracic and first two lumbar segments. It is called the lateral gray horn. The part of the gray matter anterior to central canal is called the anterior gray commissure and the part of gray matter posterior to the central canal is called the posterior gray commissure.

Neurons in Gray Horn

Clusters of neurons are present in gray matter in the form of nuclei.

Nuclei in posterior gray horn

The posterior gray horn contains the nuclei of sensory neurons which receive impulses from various receptors of the body through posterior nerve root fibers. Sensory neurons are of four types (Fig. 88-2).

1. Marginal nucleus
2. Substantia gelatinosa of Rolando

3. Chief sensory nucleus
4. Clarke's nucleus.

Nuclei in lateral gray horn

Lateral gray horn has intermediolateral nucleus. The neurons of this nucleus give rise to sympathetic preganglionic fibers, which leave the spinal cord through the anterior nerve root. Intermediolateral nucleus extends between T1 and L2 segments of spinal cord.

Nuclei in anterior gray horn

Anterior gray horn contains the nuclei of lower motor neurons which are involved in motor function. Lower motor neurons are of three types.

1. Alpha motor neurons
2. Gamma motor neurons
3. Renshaw cells

WHITE MATTER OF SPINAL CORD

White matter of spinal cord surrounds the gray matter. It is formed by the bundles of nerve fibers. The anterior median fissure and the posterior

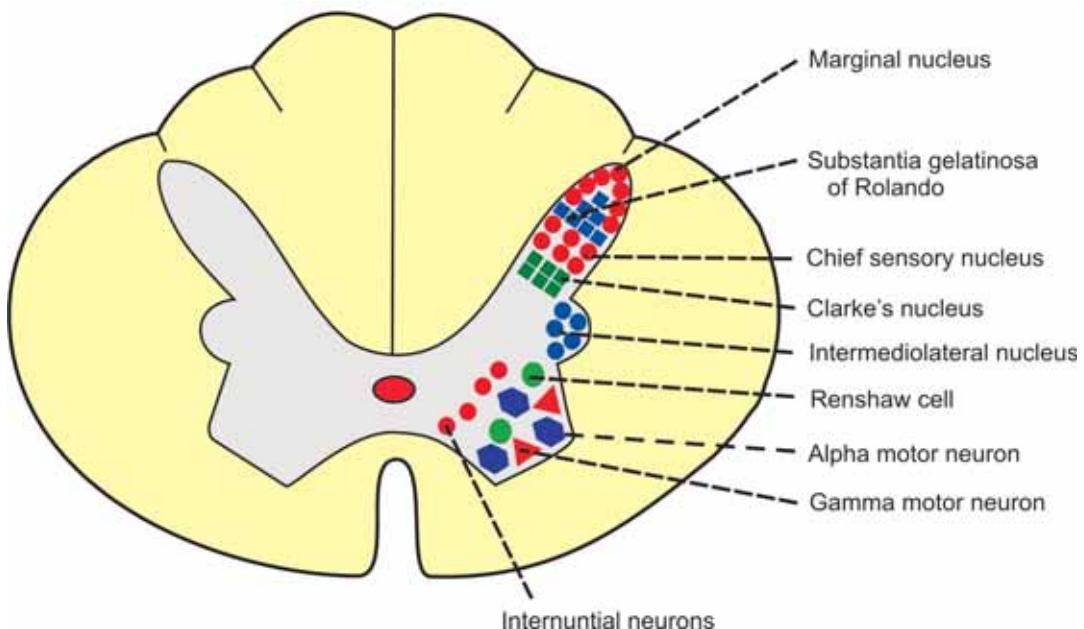


FIGURE 88-2: Nuclei in gray horn of spinal cord – thoracic segment

median septum divide the entire mass of white matter into two lateral halves. The band of white matter lying in front of anterior gray commissure is called the anterior white commissure.

Each half of the white matter is divided by the fibers of anterior and posterior nerve roots into three white columns or funiculi:

1. Anterior or ventral white column or funiculus
2. Lateral white column or funiculus
3. Posterior or dorsal white column or funiculus

■ TRACTS IN SPINAL CORD

Tracts of the spinal cord are collections of nerve fibers passing through the spinal cord. Spinal tracts are divided into two main groups:

- I. Short tracts which connect different parts of spinal cord itself.
- II. Long tracts which connect the spinal cord with other parts of central nervous system.

Long tracts are of two types:

1. Ascending tracts which carry sensory impulses from the spinal cord to brain
2. Descending tracts, which carry motor impulses from brain to the spinal cord.

■ ASCENDING TRACTS OF SPINAL CORD

The ascending tracts of spinal cord carry the impulses of various sensations to the brain.

The pathway for each sensation is formed by two or three groups of neurons:

1. First order neurons
2. Second order neurons
3. Third order neurons

First Order Neurons

First order neurons receive sensory impulses from the receptors and send them to sensory neurons present in the posterior gray horn of spinal cord through their fibers. The nerve cell bodies of these neurons are located in the posterior nerve root ganglion that lies outside the spinal cord.

Second Order Neurons

The second order neurons are the sensory neurons present in the posterior gray horn. The fibers from these neurons form the ascending tracts of spinal cord. These fibers carry sensory

impulses from spinal cord to different brain areas below cerebral cortex (subcortical areas) such as thalamus, cerebellum etc.

All the ascending tracts are formed by fibers of second order neurons of the sensory pathways except the ascending tracts in the posterior white column which are formed by the fibers of first order neurons.

TABLE 88-1: List of ascending tracts of spinal cord

White column	Tract
Anterior white column	1. Anterior spinothalamic tract
Lateral white column	2. Lateral spinothalamic tract 3. Ventral spinocerebellar tract 4. Dorsal spinocerebellar tract 5. Spinotectal tract 6. Spinoreticular tract 7. Spinoolivary tract 8. Spinovestibular tract
Posterior white column	9. Fasciculus gracilis 10. Fasciculus cuneatus 11. Comma tract of Schultze

Third Order Neurons

Third order neurons are in the subcortical areas. The fibers of these neurons carry the sensory impulses from subcortical areas to cerebral cortex.

The ascending tracts situated in different white columns are listed in Table 88-1. The features of the ascending tracts are given in Table 88-2.

■ 1. ANTERIOR SPINOthalamic TRACT

Anterior spinothalamic tract is formed by the fibers of second order neurons of the pathway for crude touch sensation (Figs 88-3 and 88-4). This tract is situated in anterior white column.

Origin

The fibers of anterior spinothalamic tract arise from cells of chief sensory nucleus of posterior gray horn which form the second order neurons. The first order neurons are situated in the posterior nerve root ganglia. These neurons receive the impulses from the pressure

Descending tracts

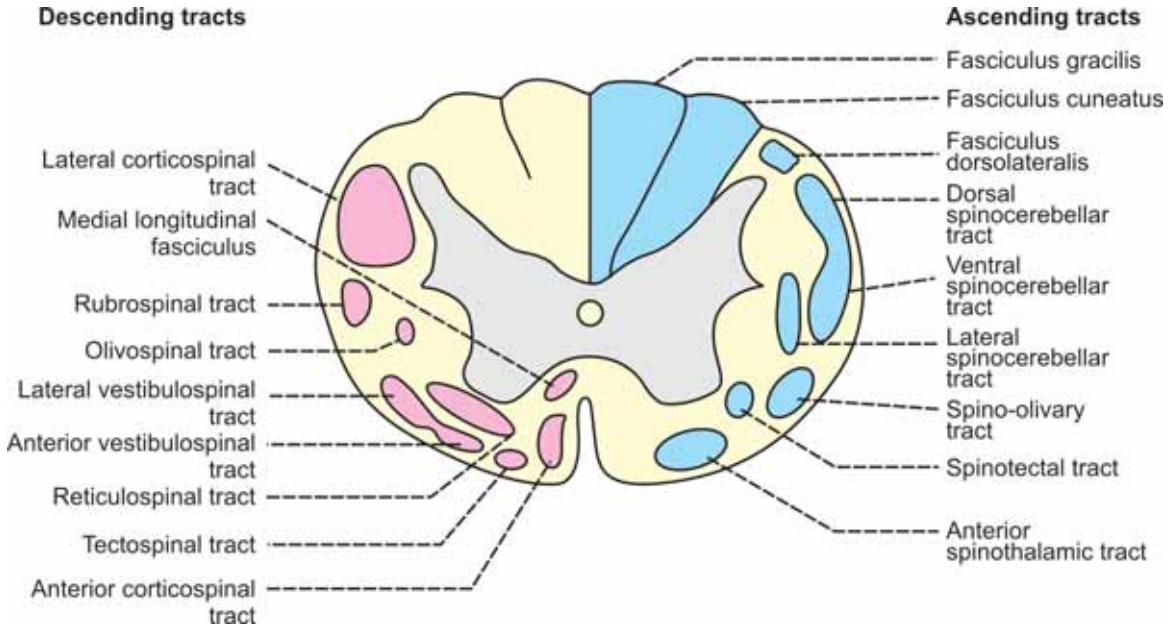


FIGURE 88-3: Tracts of spinal cord

TABLE 88-2: Ascending tracts of spinal cord

Situation	Tract	Origin	Course	Termination	Function
Anterior white column	1. Anterior spinothalamic tract	Chief sensory nucleus	Crossing in spinal cord forms spinal lemniscus	Ventral posterolateral nucleus of thalamus	Crude touch sensation
Lateral white column	2. Lateral spinothalamic tract	Substantia gelatinosa	Crossing in spinal cord forms spinal lemniscus	Ventral posterolateral nucleus of thalamus	Pain and temperature sensations
	3. Ventral spinocerebellar tract	Marginal nucleus	Crossing in spinal cord	Anterior lobe of cerebellum	Subconscious kinesthetic sensations
	4. Dorsal spinocerebellar tract	Clarke's nucleus	Uncrossed fibers	Anterior lobe of cerebellum	Subconscious kinesthetic sensations
	5. Spinotectal tract	Chief sensory nucleus	Crossing in spinal cord	Superior colliculus	Spinovisual reflex
	6. Fasiculus dorsolateralis	Posterior nerve root ganglion	Component of lateral spinothalamic tract	Substantia gelatinosa	Pain and temperature sensations
	7. Spinoreticular tract	Intermediolateral nucleus	Crossed and uncrossed fibers	Reticular formation of brainstem	Consciousness and awareness
	8. Spinoolivary tract	Nonspecific	Uncrossed fibers	Olivary nucleus	Proprioception
	9. Spinovestibular tract	Nonspecific	Crossed and uncrossed fibers	Lateral vestibular nucleus	Proprioception
Posterior white column	10. Fasciculus gracilis	Posterior nerve root ganglia	Uncrossed fibers No synapse in spinal cord	Nucleus gracilis in medulla	Tactile sensation Tactile localization Tactile discrimination
	11. Fasciculus cuneatus	Posterior nerve root ganglia	Uncrossed fibers No synapse in spinal cord	Nucleus cuneatus in medulla	Vibratory sensation Conscious kinesthetic sensation Stereognosis

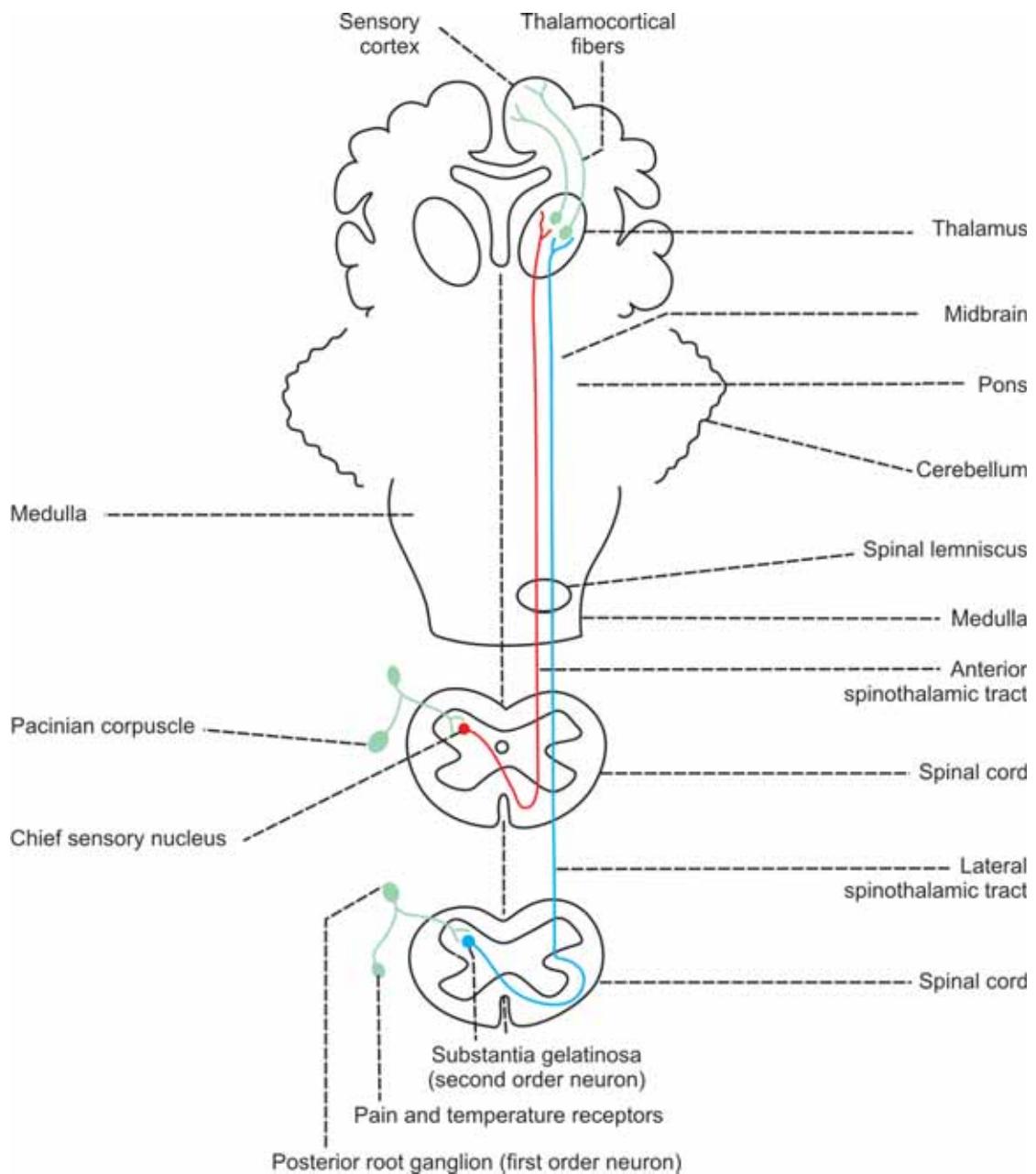


FIGURE 88-4: Spinothalamic tracts and pathways for crude touch, pain and temperature sensations. Anterior spinothalamic tract (red) carries crude touch sensation. Lateral spinothalamic tract (blue) carries pain and temperature sensations

receptors. The axons of the first order neurons reach the chief sensory nucleus through the posterior nerve root.

Course

This tract contains crossed fibers. After taking origin, these fibers cross obliquely in the anterior

white commissure and enter the anterior white column of opposite side. Here, the fibers ascend through other segments of spinal cord and brainstem (medulla, pons and midbrain) and reach thalamus.

Termination

The fibers of anterior spinothalamic tract terminate in the ventral posterolateral nucleus of thalamus. The fibers from thalamic nucleus carry the impulses to somesthetic area (sensory cortex) of cerebral cortex.

Function

This tract carries impulses of crude touch (proprioceptive) sensation. The bilateral lesion of this tract leads to loss of crude touch sensation. The unilateral lesion of this tract causes loss of crude touch sensation in the opposite side below the level of lesion (because fibers of this tract cross to the opposite side in spinal cord).

■ 2. LATERAL SPINOthalAMIC TRACT

Lateral spinothalamic tract is formed by the fibers from the second order neurons (Fig. 88-4). This tract is situated in the lateral white column.

Origin

The fibers of lateral spinothalamic tract take origin from marginal nucleus and substantia gelatinosa of Rolando.

Course

This tract has crossed fibers. After origin the fibers of this tract cross the mid line, reach the lateral column of opposite side and ascend. All the fibers pass through medulla, pons and midbrain reach thalamus.

Termination

The fibers of lateral spinothalamic tract terminate in the ventral posterolateral nucleus of

thalamus. From here, third order neuron fibers relay to the somesthetic area (sensory cortex) of cerebral cortex.

Function

The fibers of this tract carry impulses of pain and thermal sensations. The bilateral section of this tract leads to total loss of pain and temperature sensations on both the sides below the level of lesion. The unilateral lesion or sectioning of the lateral spinothalamic tract causes loss of pain and temperature sensations below the level of lesion in the opposite side.

■ 3. VENTRAL SPINOCEREBELLAR TRACT

Ventral spinocerebellar tract is also known as Gower's tract, indirect spinocerebellar tract or anterior spinocerebellar tract. It is constituted by the fibers of second order (Fig. 88-5). This tract is situated in lateral white column.

Origin

The fibers of this tract arise from the marginal nucleus in posterior gray horn. Neurons of marginal nucleus form the second order neurons.

The first order neurons in the posterior root ganglia receive the impulses of proprioception from the proprioceptors in muscle, tendon and joints. The fibers from the neurons of posterior root ganglia reach the marginal nucleus through posterior nerve root.

Course

This tract contains both crossed and uncrossed fibers. Majority of the fibers from the marginal nucleus cross the midline and ascend in lateral white column of opposite side. Some fibers ascend in the lateral white column of the same side. All the fibers reach the cerebellum by ascending through other spinal segments, medulla, pons, midbrain and superior cerebellar peduncle.

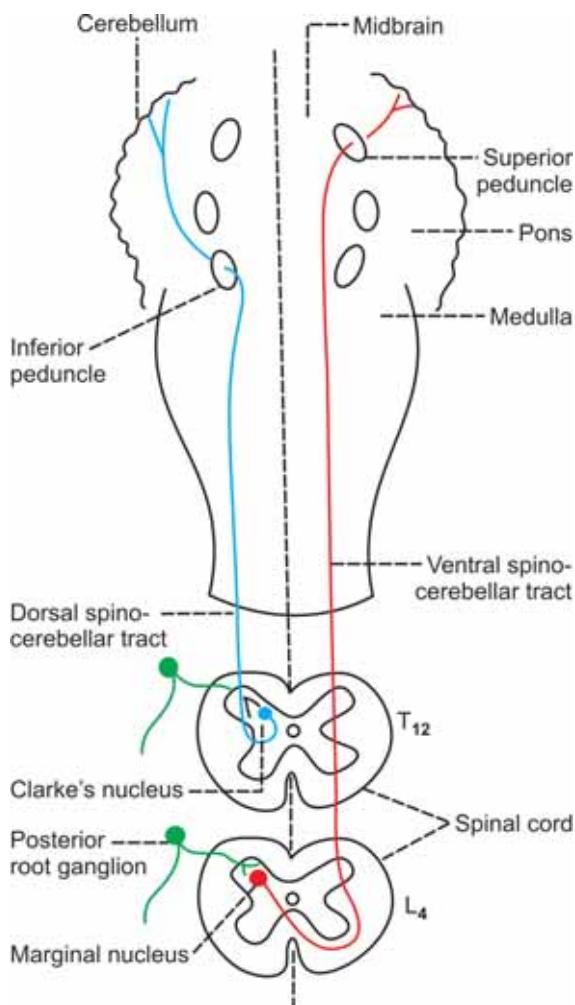


FIGURE 88-5: Spinocerebellar tracts and pathway for subconscious kinesthetic sensation

Termination

These fibers terminate in the anterior lobe of cerebellum.

Function

This tract carries the impulses of subconscious kinesthetic sensation (proprioceptive impulses from muscles, tendons and joints). The impulses of subconscious kinesthetic sensation are also called nonsensory impulses. The lesion of this tract leads to loss of subconscious kinesthetic sensation in the opposite side.

■ 4. DORSAL SPINOCEREBELLAR TRACT

It is otherwise called Flechsig's tract, direct spinocerebellar tract or posterior spinocerebellar tract. It is formed by the second order neuron fibers. The first order neurons are in the posterior nerve root ganglia (Fig. 88-5). It is situated in the lateral white column.

Origin

Fibers of this tract arise from the Clarke's nucleus in posterior gray matter. First appearance of the fibers is in the upper lumbar segments. From lower lumbar and sacral segments, the impulses are carried upwards by the dorsal nerve roots to the upper lumbar segments.

Course

This tract is formed by uncrossed fibers. The axons from neurons of Clarke's nucleus run to lateral column of same side ascend through other spinal segments and reach medulla oblongata. From here, the fibers reach the cerebellum through inferior cerebellar peduncle.

Termination

The fibers of this tract end in the cortex of anterior lobe of cerebellum along with ventral spinocerebellar tract fibers.

Function

Along with ventral spinocerebellar tract, the dorsal spinocerebellar tract carries the impulses of subconscious kinesthetic sensation, which are known as nonsensory impulses. Unilateral loss of the subconscious kinesthetic sensation occurs in lesion of this tract on the same side, as this tract has uncrossed fibers.

■ 5. SPINOTECTAL TRACT

The spinotectal tract is considered as a component of anterior spinothalamic tract. It is constituted by the fibers of second order neurons. It is situated in the lateral white column.

Origin

Fibers of this tract originate from the chief sensory nucleus. First appearance of the fibers is in upper lumbar segments.

Course

This tract contains crossed fibers. After taking origin, the fibers cross to opposite lateral column. Then, the fibers ascend to the midbrain along with anterior spinothalamic tract.

Termination

The fibers of spinotectal tract end in the superior colliculus in midbrain.

Function

This tract is concerned with spinovisual reflex.

■ 6. FASCICULUS DORSOLATERALIS

It is otherwise called tract of Lissauer. It is considered as a component of lateral spinothalamic tract. And, it is constituted by the fibers of first order neurons. This tract is situated in the lateral white column.

Origin

It is formed by the fibers arising from the cells of posterior root ganglia and enters the spinal cord through the lateral division of posterior nerve root.

Course

This tract contains uncrossed fibers. After entering the spinal cord, the fibers pass upwards or downwards for few segments on the same side and synapse with cells of substantia gelatinosa of Rolando. Axons from these cells (second order neurons) join the lateral spinothalamic tract.

Function

The fibers of the dorsolateral fasciculus carry impulses of pain and thermal sensations.

■ 7. SPINORETICULAR TRACT

Spinoreticular tract is formed by the fibers of second order neurons. It is situated in anterolateral white column.

Origin

The fibers of this tract arise from intermediolateral nucleus.

Course

This tract consists of crossed and uncrossed fibers. After taking origin, some of the fibers cross the midline and then ascend upwards. Remaining fibers ascend up in the same side without crossing.

Termination

All the fibers terminate in the reticular formation of brainstem.

Function

The fibers of the spinoreticular tract are the components of ascending reticular activating system and are concerned with consciousness and awareness.

■ 8. SPINO-OLIVARY TRACT

This tract is situated in anterolateral part of white column. Origin of the fibers of this tract is not specific. However, the fibers terminate in the olfactory nucleus of medulla oblongata. From here, the neurons project into cerebellum. This tract is concerned with proprioception.

■ 9. SPINOVESTIBULAR TRACT

The spinovestibular tract is situated in the lateral white column of the spinal cord. The fibers of this tract arise from all the segments of spinal cord and terminate on the lateral vestibular nucleus. This tract is also concerned with proprioception.

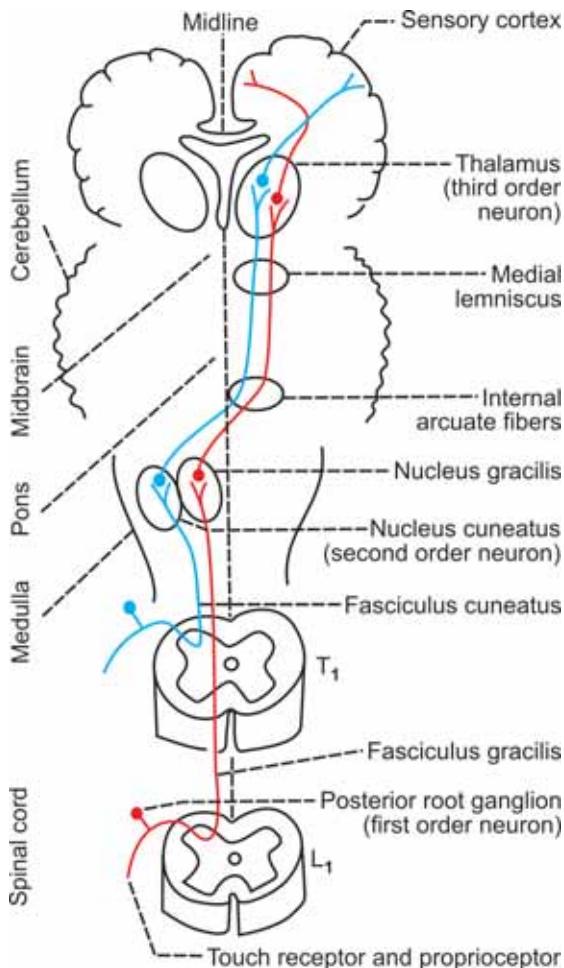


FIGURE 88-6: Ascending tracts in posterior white column of spinal cord and pathway for – (i) Fine touch sensation, (ii) Tactile localization, (iii) Tactile discrimination, (iv) Vibratory sensation, (v) Conscious kinesthetic sensation and (vi) Stereognosis

■ 10. FASCICULUS GRACILIS (TRACT OF GOLL) AND FASCICULUS CUNEATUS (TRACT OF BURDACH)

These two tracts are together called ascending posterior column tracts. These tracts are formed by the fibers from posterior root ganglia. Thus, both the tracts are constituted by the fibers of first order neurons of the sensory pathway (Fig. 88-6).

These two tracts are situated in posterior white column of spinal cord hence the name posterior column tracts. In the cervical and upper

thoracic segments of spinal cord, the posterior white column is divided into medial fasciculus gracilis and lateral fasciculus cuneatus.

Origin

Fibers of these two tracts are the axons of first order neurons. The cell body of these neurons is in the posterior root ganglia and, the fibers form the medial division (bundle) of the posterior nerve root.

Course

After entering the spinal cord, the fibers ascend through the posterior white column. These fibers do not synapse in the spinal cord.

The fasciculus gracilis contains the fibers from the lower extremities and lower parts of the body, i.e. from sacral, lumbar and lower thoracic ganglia of posterior nerve root. Fasciculus cuneatus contains fibers from upper part of the body, i.e. from upper thoracic and cervical ganglia of posterior nerve root.

Termination

These two tracts terminate in the medulla oblongata. The fibers of fasciculus gracilis terminate in the nucleus gracilis and the fibers of fasciculus cuneatus terminate in the nucleus cuneatus. The cells of these medullary nuclei form the second order neurons.

The axons of the second order neurons form the internal arcuate fibers. The internal arcuate fibers from both the sides cross the midline forming sensory decussation and then ascend through pons and midbrain as medial lemniscus. The fibers of medial lemniscus terminate in ventral posterolateral nucleus of thalamus. From here, fibers of the third order neurons relay to sensory area of cerebral cortex.

Functions

The tracts of the posterior white column convey impulses of following sensations:

- i. Fine (epicritic) tactile (touch) sensation
- ii. Tactile localization: It is the ability to locate the area of skin where the tactile stimulus is applied with closed eyes

- iii. Tactile discrimination (two point discrimination): It is the ability to recognize the two stimuli applied over the skin simultaneously with closed eyes
- iv. Sensation of vibration: It is the ability to perceive the vibrations (from a vibrating tuning fork placed over bony prominence) conducted to deep tissues through skin
- v. Conscious kinesthetic sensation: It is the sensation or awareness of various muscular activities in different parts of the body
- vi. Stereognosis: It is the ability to recognize the known objects by touch with closed eyes.

Effect of Lesion

The lesion in the fibers of these tracts or lesion in the posterior white column leads to the following symptoms on the same side below the lesion:

- i. Loss of fine tactile sensation. However, crude touch sensation is normal
- ii. Loss of tactile localization
- iii. Loss of two point discrimination
- iv. Loss of sensation of vibration
- v. Astereognosis: It is the inability to recognize known objects by touch while closing the eyes
- vi. Lack of ability to differentiate the weight of different objects
- vii. Loss of proprioception: It is inability to appreciate the position and movement of different parts of the body
- viii. Sensory ataxia or posterior column ataxia: It is the condition characterized by uncoordinated, slow and clumsy voluntary movements because of the loss of proprioception.

■ DESCENDING TRACTS OF SPINAL CORD

The descending tracts of the spinal cord are formed by motor nerve fibers arising from brain and descend into the spinal cord. These tracts carry motor impulses from brain to spinal cord.

TABLE 88-3: List of descending tracts of spinal cord

Type	Tract
Pyramidal tracts	1. Anterior corticospinal tract 2. Lateral corticospinal tract
Extrapyramidal tracts	1. Medial longitudinal fasciculus 2. Anterior vestibulospinal tract 3. Lateral vestibulospinal tract 4. Reticulospinal tract 5. Tectospinal tract 6. Rubrospinal tract 7. Olivospinal tract

The descending tracts of the spinal cord are of two types:

- I. Pyramidal tracts
- II. Extrapyramidal tracts.

The descending tracts are listed in Table 88-3. The features of the descending are given in Table 88-4.

■ PYRAMIDAL TRACTS

The pyramidal tracts were the first tracts to be found in man. These tracts of the spinal cord are concerned with voluntary motor activities of the body. These tracts are otherwise known as corticospinal tracts. There are two corticospinal tracts, the anterior corticospinal tract and lateral corticospinal tract.

While running from cerebral cortex towards spinal cord, the fibers of these two tracts give the appearance of a pyramid on the upper part of anterior surface of medulla oblongata (Fig. 88-7) and hence the name pyramidal tracts.

Origin

Fibers of pyramidal tracts arise from the following nerve cells in the cerebral cortex:

- i. Giant cells or Betz cells or pyramidal cells situated in area 4 (primary motor area) of frontal lobe
- ii. Premotor area (area 6) and supplementary motor areas
- iii. Other parts of frontal lobe
- iv. Somatosensory areas of parietal lobe.

TABLE 88-4: Descending tracts of spinal cord

Tract	Situation	Origin	Course	Function
Pyramidal tracts	1. Anterior corticospinal tract	Anterior white column	Motor and somatosensory areas of cerebral cortex	Uncrossed fibers i. Control of voluntary movements ii. Form upper motor neurons
	2. Lateral corticospinal tract	Lateral white column	Motor and somatosensory areas of cerebral cortex	Crossed fibers
Extrapyramidal tracts	1. Medial longitudinal fasciculus	Anterior white column	Vestibular nucleus Reticular formation Superior colliculus and cells of Cajal	Uncrossed fibers Extend up to upper cervical segments i. Coordination of reflex ocular movements ii. Integration of movements of eyes and neck
	2. Anterior vestibulospinal tract	Anterior white column	Medial vestibular nucleus	Uncrossed fibers Extend up to upper thoracic segments i. Maintenance of muscle tone and posture ii. Maintenance of position of head and body during acceleration
	3. Lateral vestibulospinal tract	Lateral white column	Lateral vestibular nucleus	Mostly uncrossed Extend to all segments i. Coordination of voluntary and reflex movements ii. Control of muscle tone iii. Control of respiration and diameter of blood vessels
	4. Reticulospinal tract	Anterior white fasciculus	Reticular formation of pons and medulla	Mostly uncrossed Extend up to thoracic segments Control of movement of head in response to visual and auditory impulses
5. Tectospinal tract	Anterior white column	Superior colliculus	Crossed fibers Extend up to lower cervical segments	Facilitatory influence on flexor muscle tone
6. Rubrospinal tract	Lateral white column	Red nucleus	Crossed fibers Extend up to thoracic segments	Control of movements due to proprioception
7. Olivospinal tract	Lateral white column	Inferior olive nucleus	Mostly crossed Extent – not clear	Termination – Fibers of all the tracts terminate in motor neurons situated in the anterior gray horn of spinal cord.

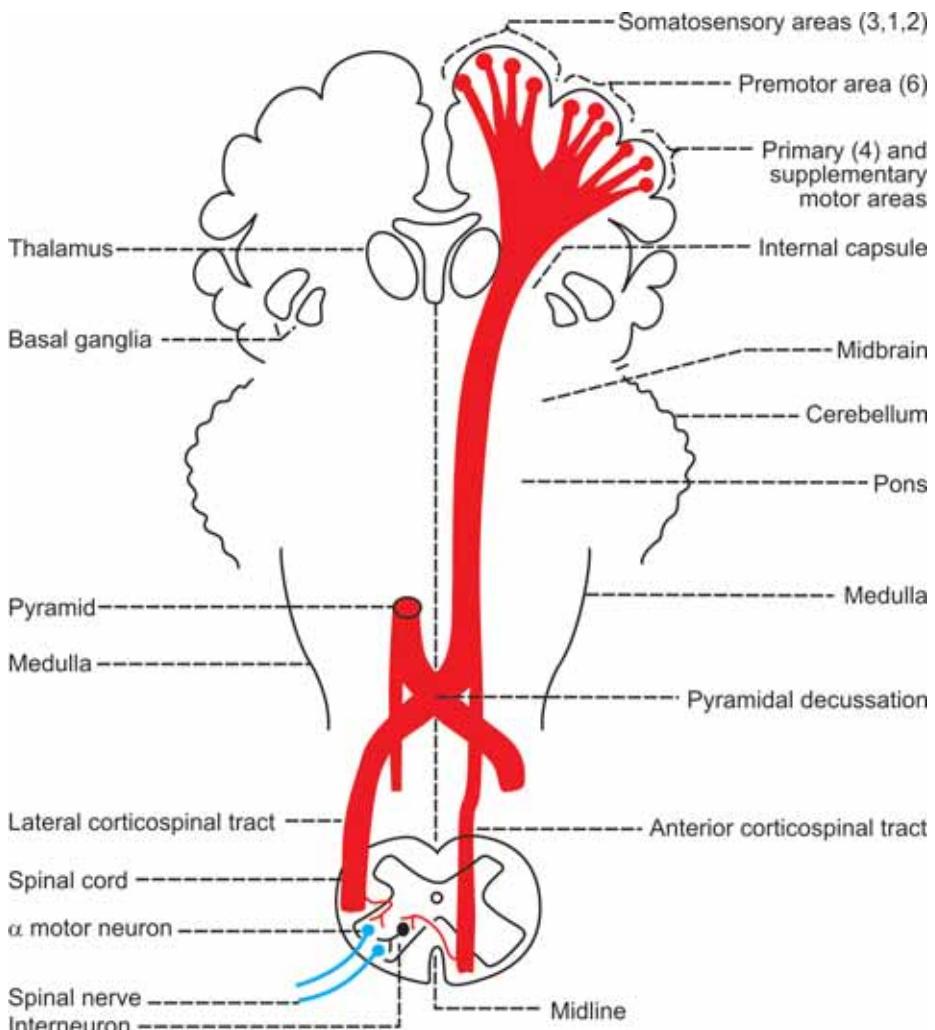


FIGURE 88-7: Pyramidal tracts

Course

After taking origin, the nerve fibers run downwards through cerebral hemisphere and converge in the form of a fan like structure called corona radiata.

Then the fibers descend down through internal capsule, midbrain and pons. In the upper part of medulla these fibers give the appearance of a pyramid. In the lower part of medulla, 80% of fibers from each side cross to the opposite side. While crossing the midline, the fibers of both sides form the pyramidal decussation.

After crossing and forming pyramidal decussation, these fibers descend through the

posterior part of lateral white column of the spinal cord as crossed pyramidal tract or lateral corticospinal tract or indirect corticospinal tract.

The remaining 20% of fibers do not cross to the opposite side but descend down through the anterior white column of the spinal cord as uncrossed pyramidal tract or anterior corticospinal tract or direct corticospinal tract.

Termination

All the fibers of pyramidal tracts terminate in the motor neurons of anterior gray horn. The axons of the motor neurons leave the spinal cord as

spinal nerves through anterior nerve roots and supply the skeletal muscles.

The neurons giving origin to the fibers of pyramidal tract are called the upper motor neurons. The motor neurons in the spinal cord are called the lower motor neurons.

Function

The pyramidal tracts are concerned with voluntary movements of the body. Fibers of the pyramidal tracts transmit motor impulses from motor area of cerebral cortex to the anterior motor neurons of the spinal cord. These two tracts are responsible for fine, skilled movements.

The lesion in the neurons of motor cortex and the fibers of pyramidal tracts is called the upper motor neuron lesion. Effects of upper motor lesion are given in the next Chapter.

■ EXTRAPYRAMIDAL TRACTS

The descending tracts of spinal cord other than pyramidal tracts are called extrapyramidal tracts. Extrapyramidal tracts are listed in Table 88-3.

■ 1. MEDIAL LONGITUDINAL FASCICULUS

Origin

The fibers of this tract take origin from brainstem. It is situated in anterior white column of the spinal cord.

Course

After entering the spinal cord from the brainstem, the fibers descend through anterior white column of the same side. In the spinal cord, this tract runs along with anterior vestibulospinal tract.

Termination

The fibers of this tract terminate in anterior motor neurons of the spinal cord along with fibers of anterior vestibulospinal tract.

Function

This tract helps in the coordination of reflex ocular movements and the integration of ocular and

neck movements. Reflex ocular movements and reflex neck movements are affected in the lesion of this tract.

■ 2. ANTERIOR VESTIBULOSPINAL TRACT

Origin

The fibers of this tract arise from the medial vestibular nucleus in medulla oblongata. It is situated in the anterior white column.

Course

The fibers of this tract run down from medulla into the anterior column of spinal cord. All the fibers are uncrossed.

Termination

Along with fibers of lateral vestibulospinal tract, the fibers of this tract terminate in anterior motor neurons directly or through internuncial neurons.

Function

The function of this tract is explained along with the function of lateral vestibulospinal tract.

■ 3. LATERAL VESTIBULOSPINAL TRACT

Origin

The fibers of this tract take origin from the lateral vestibular nucleus in medulla. This tract occupies the lateral white column of spinal cord.

Course

From medulla, most of the fibers descend directly through lateral column.

Termination

The fibers of this tract terminate in the anterior motor neurons.

Functions

The vestibulospinal tracts are concerned with adjustment of position of head and body during

angular and linear acceleration. During the lesion of these tracts the adjustment of head and body becomes difficult while walking.

■ 4. RETICULOSPINAL TRACT

Origin

Fibers of this tract arise from the reticular formation of pons and medulla. These fibers descend in anterior column and to some extent in the anterior part of lateral column. The reticulospinal tract is situated in the anterior white column.

Termination

The fibers of reticulospinal tract terminate in the gamma motor neurons of anterior gray horn.

Functions

The reticulospinal tract is concerned with control of movements and maintenance of muscle tone, respiration and diameter of blood vessels. Lesion of this tract causes disturbances in respiration, blood pressure, movements of body and muscle tone.

■ 5. TECTOSPINAL TRACT

Origin

The nerve fibers of this tract arise from superior colliculus of midbrain. This tract is situated in the anterior white column of the spinal cord.

Course

After taking origin from the superior colliculus, the fibers cross the midline in the dorsal tegmental decussation and descend in anterior column.

Termination

The fibers of this tract terminate in the anterior motor neurons of the spinal cord.

Function

This tract is responsible for the movement of head in response to visual and auditory stimuli.

■ 6. RUBROSPINAL TRACT

Origin

The fibers of this tract arise from red nucleus in midbrain. The rubrospinal tract is situated in the lateral white column.

Course

After arising from the red nucleus, the fibers cross the midline and descend into spinal cord through the reticular formation of pons and medulla.

Termination

The fibers of rubrospinal tract end in the anterior motor neurons of the spinal cord.

Function

This tract exhibits facilitatory influence upon the flexor muscle tone.

■ 7. OLIVOSPINAL TRACT

Origin

The nerve fibers of this tract take origin from the inferior olive nucleus present in the medulla oblongata. The olivospinal tract is present in the lateral white column.

Termination

The fibers of this tract terminate in the anterior motor neurons of the spinal cord.

Function

This tract is involved in reflex movements arising from the proprioceptors.

Somatosensory System and Somatomotor System

- SOMATOSENSORY SYSTEM
 - DEFINITION AND TYPES OF SENSATIONS
 - TYPES OF SOMATIC SENSATIONS
 - SENSORY PATHWAYS
 - SENSORY FIBERS OF TRIGEMINAL NERVE
 - APPLIED PHYSIOLOGY
- SOMATOMOTOR SYSTEM
 - MOTOR ACTIVITIES OF THE BODY
 - SOMATOMOTOR SYSTEM
 - CLASSIFICATION OF MOTOR PATHWAYS
 - UPPER MOTOR NEURON AND LOWER MOTOR NEURON
 - APPLIED PHYSIOLOGY

■ SOMATOSENSORY SYSTEM

■ DEFINITION AND TYPES OF SENSATIONS

Somatosensory system is defined as sensory system associated with different parts of the body. It is also defined as the faculty of bodily perception of various sensations.

Sensations are of two types:

1. Somatic sensations
2. Special sensations.

1. *Somatic Sensations*

Somatic sensations are the sensations arising from skin, muscles, tendons and joints. These

sensations have specific receptors, which respond to a particular type of stimulus.

2. *Special Sensations*

Special sensations are the complex sensations for which the body has some specialized sense organs. The special sensations are usually called special senses. Sensations of vision, hearing, taste and smell are the special sensations.

This chapter deals with somatic sensations.

■ TYPES OF SOMATIC SENSATIONS

Generally, somatic sensations are classified into three types:

- A. Epicretic sensations

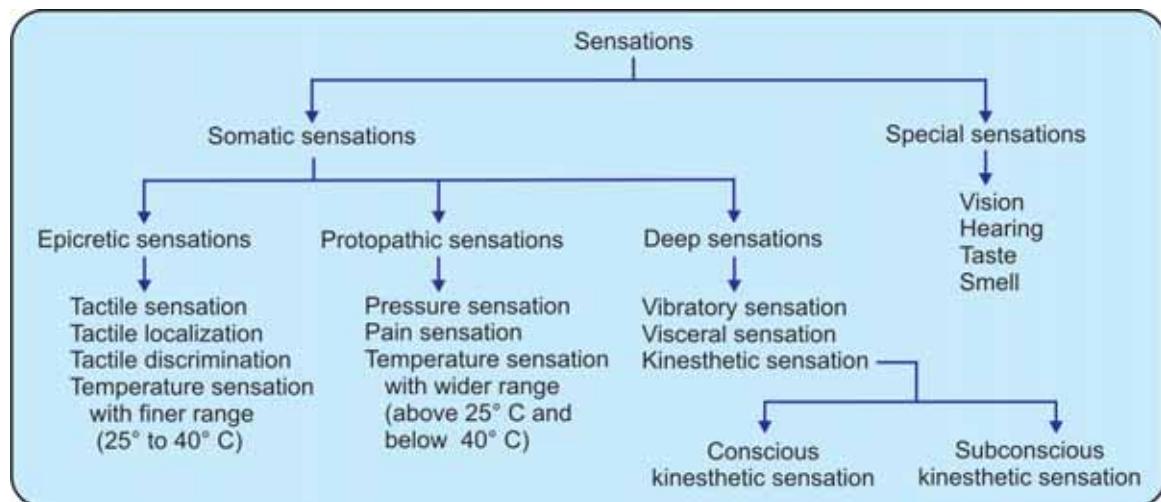


FIGURE 89-1: Classification of sensations

- B. Protopathic sensations
- C. Deep sensations (Fig. 89-1).

A. *Epicretic Sensations*

Epicretic sensations are the mild or light sensations. Such sensations are perceived more accurately. Epicretic sensations are:

1. Fine touch or tactile sensation
2. Tactile localization
3. Tactile discrimination
4. Temperature sensation with finer range between 25 and 40°C.

B. *Protopathic Sensations*

Protopathic sensations are the crude sensations. Protopathic sensations are:

1. Pressure sensation
2. Pain sensation
3. Temperature sensation with a wider range, i.e. above 40°C and below 25°C.

C. *Deep Sensations*

Deep sensations are the sensations arising from the deeper structures beneath the skin and the visceral organs. The deep sensations are classified into three types:

1. Sensation of vibration or pallesthesia
2. Kinesthetic sensation or kinesthesia: Sensation of position and movements of

different parts of the body. This sensation arises from the proprioceptors present in muscles, tendons, joints and ligaments.

The kinesthetic sensation is of two types.

- i. Conscious kinesthetic sensation
- ii. Subconscious kinesthetic sensation. The impulses of this sensation are called non-sensory impulses.

3. Visceral sensations arising from viscera.

■ SENSORY PATHWAYS

The nervous pathways of the sensations are called the sensory pathways. These pathways carry the impulses from the receptors in different parts of the body to the centers in brain.

The sensory pathways are of two types:

1. Pathways of somatosensory system
2. Pathways of viscerosensory system.

The pathways of somatosensory system convey the information from the sensory receptors in skin, skeletal muscles and joints. The pathways of this system are constituted by somatic nerve fibers called somatic afferent nerve fibers.

The pathways of viscerosensory system convey the information from the receptors of the viscera. The pathways of this system are constituted by visceral or autonomic fibers.

This chapter deals mainly with the somatosensory system.

TABLE 89-1: Sensory pathways

Sensation	Receptor	First order neuron in	Second order neuron in	Third order neuron in	Center
Fine touch Tactile localization Tactile discrimination Vibratory sensation Stereognosis	Meissner's corpuscles and Merkel's disk	Posterior nerve root ganglion – fibers form Fasciculus gracilis and Fasciculus cuneatus	Nucleus gracilis and Nucleus cuneatus – Fibers form internal arcuate fibers	Ventral posterolateral nucleus of thalamus	Sensory cortex
Pressure Crude touch	Pacinian corpuscle	Posterior nerve root ganglion	Chief sensory nucleus – fibers form anterior spinothalamic tract	Ventral posterolateral nucleus of thalamus	Sensory cortex
Temperature	Warmth-Raffini's end bulb Cold – Krause's end bulb	Posterior nerve root ganglion	Substantia gelatinosa – fibers form lateral spinothalamic tract	Ventral posterolateral nucleus of thalamus	Sensory cortex
Conscious kinesthetic sensation	Proprioceptors – Muscle spindle Golgi tendon apparatus	Posterior nerve root ganglion – fibers form Fasciculus gracilis and Fasciculus cuneatus	Nucleus gracilis and Nucleus cuneatus – Fibers form internal arcuate fibers	Ventral posterolateral nucleus of thalamus	Sensory cortex
Subconscious kinesthetic sensation	Proprioceptors – Muscle spindle Golgi tendon apparatus	Posterior nerve root ganglion	Nucleus of Clarke and Marginal nucleus – fibers form dorsal and ventral spinocerebellar tracts	—	Anterior lobe of cerebellum
Pain	Free nerve endings	Posterior nerve root ganglion Fast pain – A δ fibers Slow pain – C fibers	Fast pain – marginal nucleus in spinal cord Slow pain – substantia gelatinosa of Rolando Fibers form lateral spinothalamic tract	Ventral posterolateral nucleus of thalamus reticular formation and midbrain	Sensory cortex

Somatosensory Pathways

Each sensory pathway is constituted by two or three groups of neurons:

1. First order neurons
2. Second order neurons
3. Third order neurons.

The details of these neurons are given in Chapter 88. The pathways of some of the sensations like kinesthetic sensation have only first and second order neurons.

The details of the pathways are given in Table 89-1. The diagrams of the pathways are given in the previous chapter along with ascending tracts of spinal cord.

■ SENSORY FIBERS OF TRIGEMINAL NERVE

Trigeminal nerve is a mixed cranial nerve. It is the chief sensory nerve for face and the motor nerve for muscles of mastication. Trigeminal nerve carries somatosensory information from face, teeth, periodontal tissues (tissues around teeth), oral cavity, nasal cavity, cranial dura mater and major part of scalp to sensory cortex. It also conveys proprioceptive impulses from the extrinsic muscles of the eyeball. The functions of three divisions of trigeminal nerve are listed in Table 89-2.

TABLE 89-2: Functions of three divisions of trigeminal nerve

Division	Areas supplied	Function
Ophthalmic	Forehead Eye Front portion of nose	Sensory
Maxillary	Upper teeth, gums and lip Lower eyelid Sides of nose	
Mandibular	Lower teeth, gums and lip Jaw	Sensory Motor

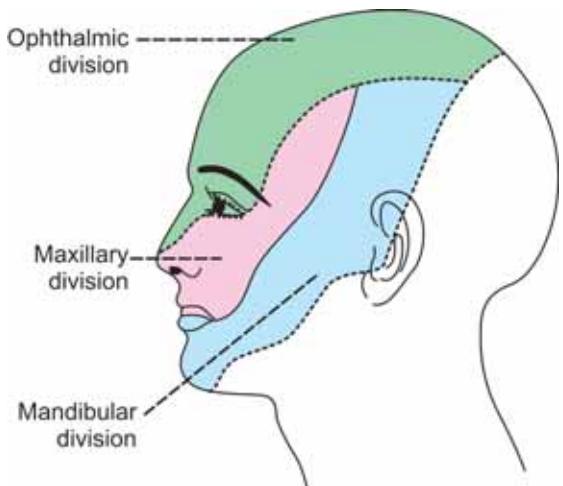


FIGURE 89-2: Cutaneous distribution (sensory) of the three divisions of trigeminal nerve

Origin

The sensory fibers of trigeminal nerve arise from the trigeminal ganglion situated near temporal bone. The peripheral processes of neurons in this ganglion form three divisions of trigeminal nerve namely, ophthalmic, mandibular and maxillary divisions. The cutaneous distribution of the three divisions of trigeminal nerve is shown in Figure 89-2.

The central processes from the neurons of trigeminal ganglion enter the pons in the form of sensory root.

Termination

After reaching the pons, the fibers of sensory root divide into two groups namely, descending fibers and ascending fibers. The descending fibers terminate on primary sensory nucleus and spinal nucleus of trigeminal nerve.

The ascending fibers of the sensory root terminate in the mesencephalic nucleus of trigeminal nerve situated in the brainstem above the level of primary sensory nucleus (Fig. 89-3).

Central Connections

Majority of fibers from the primary sensory nucleus and spinal nucleus of trigeminal nerve

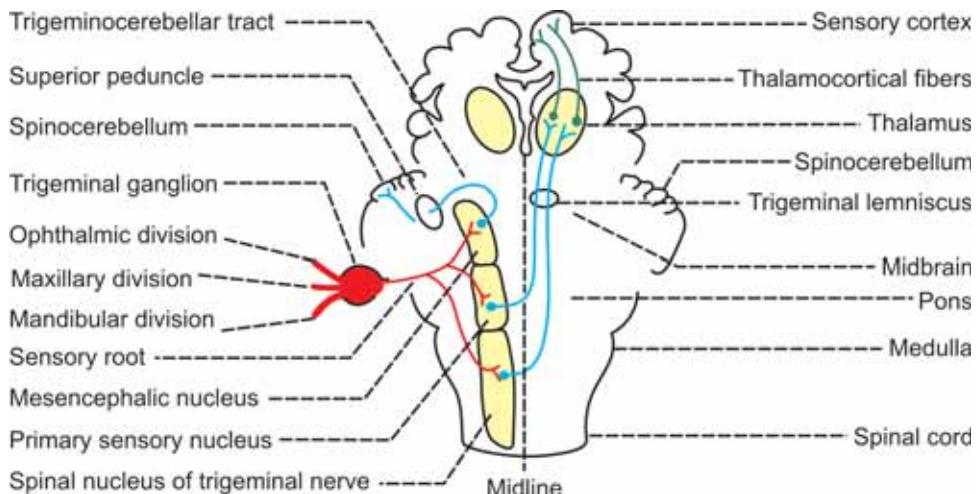


FIGURE 89-3: Diagrammatic representation of trigeminal pathway. Trigeminal lemniscus carries impulses of touch, pressure, pain and temperature sensations to somatosensory cortex. The trigeminocerebellar tract carries proprioceptive impulses to spinocerebellum

ascend in the form of trigeminal lemniscus and terminate in the ventral posteromedial nucleus of thalamus in the opposite side. Remaining fibers from these two nuclei terminate on the thalamic nucleus of the same side. From thalamus, the fibers reach the somatosensory areas of cerebral cortex.

The primary sensory nucleus and the spinal nucleus of trigeminal nerve relay the sensations of touch, pressure, pain and temperature from the regions mentioned above.

The fibers from mesencephalic nucleus form the trigeminocerebellar tract that enters spinocerebellum via the superior cerebellar peduncle of the same side. This nucleus conveys the proprioceptive impulses from the facial muscles, muscles of mastication and ocular muscles.

■ APPLIED PHYSIOLOGY

Lesions in sensory pathway affect the sensory functions of the body:

1. Anesthesia: Loss of all sensations
2. Hyperesthesia: Increased sensitivity to sensory stimuli
3. Hypoesthesia: Reduction in the sensitivity to sensory stimuli
4. Hemesthesia: Loss of all sensations in one side of the body
5. Paresthesia: Abnormal sensations such as tingling, burning, prickling and numbness
6. Hemiparesthesia: Abnormal sensations in one side of the body
7. Dissociated anesthesia: Loss of some sensations while other sensations are intact
8. General anesthesia: Loss of all sensations with loss of consciousness produced by anesthetic agents
9. Local anesthesia: Loss of sensations in a restricted area of the body
10. Spinal anesthesia: Loss of sensations, due to lesion in spinal cord or induced by anesthetic agents injected beneath the coverings of spinal cord
11. Tactile anesthesia: Loss of tactile sensations
12. Tactile hyperesthesia: Increased sensitivity to tactile stimuli
13. Analgesia: Loss of pain sensation
14. Hyperalgesia: Increased sensitivity to pain stimulus
15. Paralgesia: Abnormal pain sensation

16. Thermoanesthesia or thermanesthesia or thermalgesia: Loss of thermal sensation
17. Pallanesthesia: Loss of sensation of vibration
18. Astereognosis: Loss of ability to recognize any known object with closed eyes due to loss of cutaneous sensations
19. Illusion: Mental depression due to misinterpretation of a sensory stimulus
20. Hallucination: Feeling of a sensation without any stimulus.

■ SOMATOMOTOR SYSTEM

■ MOTOR ACTIVITIES OF THE BODY

The motor activities of the body are divided into two types:

1. The activities of skeletal muscles which are involved in the posture and movement
2. The activities of smooth muscles, cardiac muscles and other tissues, which are involved in the functions of various visceral organs.

The activities of the skeletal muscles (voluntary functions) are controlled by the somatomotor system, which is constituted by the somatic motor nerve fibers. The activities of tissues or the visceral organs (involuntary functions) are controlled by the visceral or autonomic nervous system, which is constituted by the sympathetic and parasympathetic systems. Autonomic nervous system is described in Chapter 103.

This chapter deals with somatomotor system.

■ TYPES OF MOVEMENTS

The movements of the body depend upon the different groups of skeletal muscles. Various types of movements or the motor activities brought about by these muscles are:

1. Execution of smooth, precise and accurate voluntary movements
2. Coordination of movements responsible for skilled activities
3. Coordination of movements responsible for maintenance of posture and equilibrium.

All these motor activities are controlled by different parts of the nervous system, which are together called the motor system.

The motor system includes spinal cord and its nerves, cranial nerves, brainstem, cerebral cortex, cerebellum and basal ganglia. The neuronal circuits between these parts of the nervous system which are responsible for the motor activities are called the motor pathways.

■ CLASSIFICATION OF MOTOR PATHWAYS

Motor pathways are divided into pyramidal and extrapyramidal tracts.

Pyramidal Tracts

The pyramidal tracts are those fibers, which form the pyramids in the upper part of medulla. Pyramidal tracts are the anterior and lateral corticospinal tracts. These tracts control the voluntary movements of the body (Chapter 88).

Extrapyramidal Tracts

Motor pathways other than pyramidal tracts are known as extrapyramidal tracts. Details of these tracts are given in Chapter 88. The extrapyramidal tracts are concerned with regulation of tone, posture and equilibrium.

■ UPPER MOTOR NEURON AND LOWER MOTOR NEURON

The neurons of the motor system are divided into upper motor neurons and lower motor neurons depending upon their location and termination.

Upper Motor Neuron

Upper motor neurons are the neurons in the higher centers of brain, which control the lower motor neurons. There are three types of upper motor neurons:

1. Motor neurons in the cerebral cortex. The fibers of these neurons form corticospinal (pyramidal) and corticobulbar tracts

TABLE 89-3: Effects of upper motor neuron lesion and lower motor neuron lesion

Effects		Upper motor neuron lesion	Lower motor neuron lesion
Clinical observation	1. Muscle tone	Hypertonia	Hypotonia
	2. Paralysis	Spastic type of paralysis	Flaccid type of paralysis
	3. Wastage of muscle	No wastage of muscle	Wastage of muscle occurs
	4. Superficial reflexes	Lost	Lost
	5. Plantar reflex	Abnormal plantar reflex – Babinski's sign	Plantar reflex – absent
	6. Deep reflexes	Exaggerated	Lost
	7. Clonus	Present	Not present
Clinical confirmation	8. Electrical activity	Normal	Absent
	9. Muscles affected	Groups of muscles are affected	Individual muscles are affected
	10. Fascicular twitch in EMG	Absent	Present

2. Neurons in the basal ganglia and brainstem nuclei
 3. Neurons in the cerebellum.

The motor neurons in the cerebral cortex, which give origin to pyramidal tracts, belong to the pyramidal system and the remaining motor neurons belong to extrapyramidal system.

Lower Motor Neuron

Lower motor neurons are the anterior gray horn cells in the spinal cord and the motor neurons of the cranial nerve nuclei situated in brainstem, which innervate the muscles directly.

The lower motor neurons constitute the "Final common pathway" of motor system. The lower motor neurons are under the influence of the upper motor neurons.

■ APPLIED PHYSIOLOGY

Effects of Lesion of Motor Neurons

The effects of lesions of upper motor neurons and lower motor neurons are given in Table 89-3.

The effects of lower motor neuron lesion are the loss of muscle tone and flaccid paralysis. The effects of upper motor neuron lesion depend upon the site:

1. The lesion in pyramidal system causes hypertonia and spastic paralysis
2. Lesion in basal ganglia produces hypertonia and rigidity involving both flexor and extensor muscles
3. Lesion in cerebellum causes hypotonia, muscular weakness and incoordination of movements.

Paralysis

Paralysis is defined as the complete loss of strength and functions of muscle group or a limb.

Causes for paralysis

Common causes for paralysis are trauma, tumor, stroke, cerebral palsy (condition caused by brain injury immediately after birth) and neurodegenerative diseases.

TABLE 89-4: Types of paralysis

Paralysis	Definition	Causes
Monoplegia	Paralysis of one limb	Isolated damage of central nervous system or peripheral nervous system
Diplegia	Paralysis of both the upper limbs or both the lower limbs	Isolated damage of brain
Hemiplegia	Paralysis of upper limb and lower limb on one side of the body	Lesion in motor cortex and corticospinal tracts in posterior limb of internal capsule on the side opposite the paralysis
Paraplegia	Paralysis of both the lower limbs	Injury to lower part of spinal cord
Quadriplegia or Tetraplegia	Paralysis of all the four limbs	Injury to upper part of spinal cord (shoulder level or above at which the motor nerves of upper limbs leave the spinal cord)

Types of paralysis

The paralysis of the muscles in the body depends upon the type and location of motor neurons affected by lesion. Different types of paralysis are given in Table 89-4.

Physiology of Pain

- INTRODUCTION AND DEFINITION
- BENEFITS OF PAIN SENSATION
- COMPONENTS OF PAIN SENSATION
- PATHWAYS OF PAIN SENSATION
- VISCERAL PAIN
- REFERRED PAIN
- ANALGESIA SYSTEM
- APPLIED PHYSIOLOGY

■ INTRODUCTION AND DEFINITION

Pain is defined as an unpleasant and emotional experience associated with or without actual tissue damage. The pain sensation is described in many ways like sharp, pricking, electric, dull ache, shooting, cutting, stabbing, etc. Often it induces crying and fainting.

It is produced by real or potential injury to the body. Often it is expressed in terms of injury. For example, pain produced by fire is expressed as burning sensation; pain produced by severe sustained contraction of skeletal muscles is expressed as cramps.

■ BENEFITS OF PAIN SENSATION

Pain is an important sensory symptom. Though it is an unpleasant sensation, it has protective or survival benefits such as:

1. It gives warning signal about the existence of a problem or threat. It also creates the awareness of injury

2. It prevents further damage by causing reflex withdrawal of the body from the source of injury
3. It forces the person to rest or to minimize the activities thus enabling the rapid healing of the injured part
4. It urges the person to take required treatment to prevent major damage.

■ COMPONENTS OF PAIN SENSATION

A pain stimulus produces two pain sensations

1. Fast pain
2. Slow pain.

Fast pain is the first sensation whenever a pain stimulus is applied. It is experienced as a bright, sharp and localized pain sensation. The fast pain is followed by the slow pain which is experienced as a dull, diffused and unpleasant pain.

The receptors for both the components of pain are the same, i.e. the free nerve endings. But, the afferent nerve fibers are different. The

fast pain sensation is carried by A_δ fibers and the slow pain sensation is carried by C type of nerve fibers.

■ PATHWAYS OF PAIN SENSATION

Pain sensation from various parts of body is carried to brain by different pathways which are:

1. Pathway from skin and deeper structures
2. Pathway from face
3. Pathway from viscera
4. Pathway from pelvic region.

■ PATHWAY OF PAIN SENSATION FROM SKIN AND DEEPER STRUCTURES

Receptors

The receptors of pain sensation are the free nerve endings which are distributed throughout the body.

First Order Neurons

First order neurons are the cells in the posterior nerve root ganglia which receive the impulses of pain sensation from the pain receptors through their dendrites. These impulses are transmitted to spinal cord through the axons of these neurons.

Fast pain fibers

Fast pain sensation is carried by A_δ type afferent fibers which synapse with neurons of marginal nucleus in the posterior gray horn.

Slow pain fibers

Slow pain sensation is carried by C type afferent fibers which synapse with neurons of substantia gelatinosa of Rolando in the posterior gray horn (Fig. 88-4).

Second Order Neurons

The neurons of marginal nucleus and substantia gelatinosa of Rolando form the second order

neurons. Fibers from these neurons ascend in the form of the lateral spinothalamic tract.

Third Order Neurons

The third order neurons are in thalamic nucleus, reticular formation. Axons from these neurons reach the sensory area of cerebral cortex.

Center for Pain Sensation

The center for pain sensation is in the postcentral gyrus of parietal cortex. Fibers reaching hypothalamus are concerned with arousal mechanism due to pain stimulus.

■ PATHWAY OF PAIN SENSATION FROM FACE

Pain sensation from face is carried by trigeminal nerve (Chapter 89).

■ PATHWAY OF PAIN SENSATION FROM VISCERA

The pain sensation from thoracic and abdominal viscera is transmitted by sympathetic (thoracolumbar) nerves. Pain from esophagus, trachea and pharynx is carried by vagus and glossopharyngeal nerves.

■ PATHWAY OF PAIN SENSATION FROM PELVIC REGION

Pain sensation from deeper structures of pelvic region is conveyed by sacral parasympathetic nerves.

■ VISCERAL PAIN

Pain from viscera is unpleasant. It is poorly localized.

■ CAUSES OF VISCERAL PAIN

1. *Ischemia*: The substances released during ischemic reactions like bradykinin and proteolytic enzymes stimulate the pain receptors of viscera.

2. *Chemical stimuli*: The chemical substances like acidic gastric juice leaks from ruptured ulcers into peritoneal cavity and produce pain.
3. *Spasm of hollow organs*: Spastic contraction of smooth muscles in gastrointestinal tract and other hollow organs of viscera cause pain by stimulating the free nerve endings.
4. Overdistention of hollow organs also causes pain.

■ REFERRED PAIN

■ DEFINITION

Referred pain is the pain that is perceived at a site adjacent to or away from the site of origin. The deep pain and some visceral pain are referred to other areas. But, the superficial pain is not referred.

■ EXAMPLES OF REFERRED PAIN

1. Cardiac pain is felt at the inner part of left arm and left shoulder
2. Pain in ovary is referred to umbilicus
3. Pain from testis is felt in abdomen
4. Pain in diaphragm is referred to right shoulder
5. Pain in gallbladder is referred to epigastric region
6. Renal pain is referred to loin.

■ MECHANISM OF REFERRED PAIN

Dermatomal Rule

According to dermatomal rule, pain is referred to a structure, which is developed from the same dermatome from which the pain producing structure is developed.

A dermatome includes all the structures or parts of the body, which are innervated by afferent nerve fibers of one dorsal root. For example, the heart and inner aspect of left arm originate from the same dermatome. So, the pain in heart is referred to left arm.

■ ANALGESIA SYSTEM

Analgesia system means the pain control system. The body has its own analgesia system in brain which provides a short term relief from pain. It is also called endogenous analgesia system. It includes gray matter surrounding the III ventricle and aqueduct of Sylvius and reticular formation of brainstem.

The analgesia system has got its own pathway through which it blocks the synaptic transmission of pain sensation in spinal cord and suppresses the pain sensation. In fact analgesic drugs such as opioids act through this system and provide a controlled pain relief.

■ GATE CONTROL THEORY

Gate control theory explains the pain suppression. According to this theory, the pain stimuli transmitted by afferent pain fibers are blocked by gate mechanism located at the posterior gray horn of spinal cord. If the gate is opened, pain is felt. If the gate is closed, pain is suppressed. Brain also plays some important role in the gate control system of the spinal cord.

Significance of Gate Control

Thus, the gating of pain at spinal level is similar to presynaptic inhibition. It forms the basis for relief of pain through rubbing, massage techniques, application of ice packs, acupuncture and electrical analgesia. All these techniques relieve pain by stimulating the release of endogenous pain relievers (opioid peptides) which close the gate and block the pain signals.

■ APPLIED PHYSIOLOGY

1. Analgesia (loss of pain sensation)
2. Hyperalgesia (increased sensitivity to pain sensation)
3. Paralgesia (abnormal pain sensation).

Thalamus

- INTRODUCTION
- THALAMIC NUCLEI
- FUNCTIONS OF THALAMUS
 - RELAY CENTER FOR SENSATIONS
 - CENTER FOR PROCESSING OF SENSORY INFORMATION
 - CENTER FOR DETERMINING QUALITY OF SENSATIONS
 - CENTER FOR SEXUAL SENSATIONS
 - ROLE IN AROUSAL AND ALERTNESS REACTIONS
- APPLIED PHYSIOLOGY

■ INTRODUCTION

Thalamus is a large ovoid mass of gray matter, situated bilaterally in diencephalon. Both thalami form 80% of diencephalon (Fig. 91-1).

■ THALAMIC NUCLEI

Thalamus on each side is divided into five main nuclear groups by means of internal medullary septum.

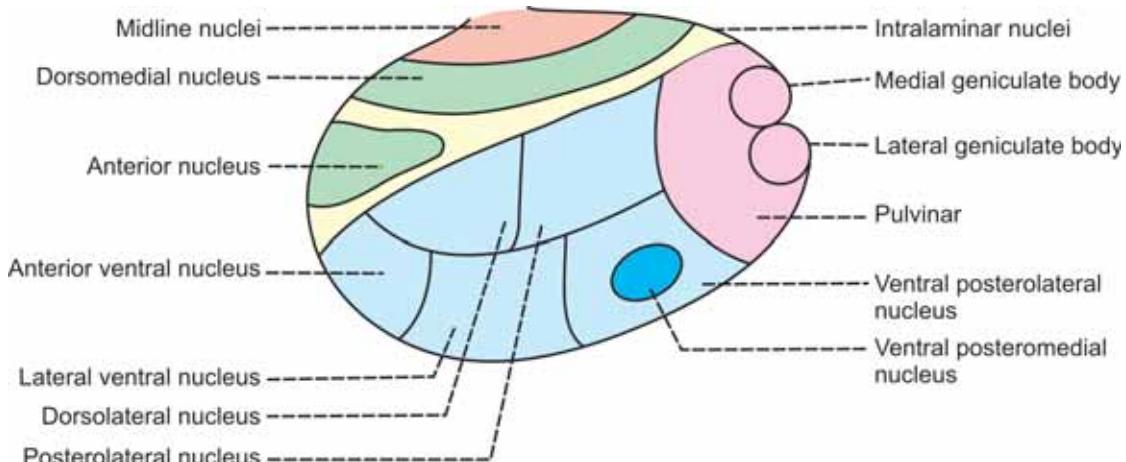


FIGURE 91-1: Thalamic nuclei. Red = Midline nuclei, Yellow = Intralaminar nuclei, Green = Medial mass of nuclei, Blue = Lateral mass of nuclei, Pink = Posterior group of nuclei

■ 1. MIDLINE NUCLEI

It is a group of small nuclei, situated on the medial surface of thalamus near midline.

■ 2. INTRALAMINAR NUCLEI

The intralaminar nuclei are smaller nuclei present in the medullary septum of the thalamus.

■ 3. MEDIAL MASS OF NUCLEI

Medial mass of nuclei is situated medial to septum and it comprises two nuclei.

1. Anterior nucleus
2. Dorsomedial nucleus.

■ 4. LATERAL MASS OF NUCLEI

This group of nuclei is situated lateral to septum. Lateral mass of nuclei is again divided into two subgroups:

- a. Dorsal group of lateral mass with two nuclei:
 1. Dorsolateral nucleus
 2. Posterolateral nucleus
- b. Ventral group of lateral mass with three nuclei:
 1. Anterior ventral nucleus
 2. Lateral ventral nucleus.
 3. Posteroventral nucleus. It consists of two parts:
 - i. Ventral posterolateral nucleus
 - ii. Ventral posteromedial nucleus.

■ 5. POSTERIOR GROUP OF NUCLEI

It is the continuation of lateral mass of nuclei. It has two subgroups:

- a. Pulvinar
- b. Metathalamus which consists of two structures:
 1. Medial geniculate body
 2. Lateral geniculate body.

■ FUNCTIONS OF THALAMUS

Thalamus is primarily concerned with somatic functions and it plays little role in the visceral functions. The various functions of thalamus are:

■ 1. RELAY CENTER FOR SENSATIONS

Thalamus forms the relay center for the sensations. The impulses of almost all the sensations

reach the thalamic nuclei, particularly in the ventral posterolateral nucleus. After being processed in the thalamus, the impulses are carried to cerebral cortex through thalamocortical fibers.

■ 2. CENTER FOR PROCESSING OF SENSORY INFORMATION

Thalamus forms the major center for processing the sensory information. All the peripheral sensory impulses reaching thalamus are integrated and modified before being sent to specific areas of cerebral cortex. This function of thalamus is usually called the processing of sensory information.

Functional Gateway for Cerebral Cortex

Almost all the sensations are processed in thalamus before reaching cerebral cortex. Very little information of somatosensory function is sent directly to cerebral cortex without being processed by the thalamic nuclei. Because of this function, thalamus is usually called a "Functional gateway" for cerebral cortex.

■ 3. CENTER FOR DETERMINING QUALITY OF SENSATIONS

Thalamus is also the center for determining the quality of sensations, that is, to determine the affective nature of sensations. Usually the sensations have two qualities:

- i. The discriminative nature
- ii. The affective nature.

i. The Discriminative Nature

It is the ability to recognize the type, location and other details of the sensations and it is the function of cerebral cortex.

ii. The Affective Nature

The affective nature is the capacity to determine whether a sensation is pleasant or unpleasant and agreeable or disagreeable. Determining the affective nature of sensations is the function of thalamus.

■ 4. CENTER FOR SEXUAL SENSATIONS

Thalamus forms the center for perception of sexual sensations.

■ 5. ROLE IN AROUSAL AND ALERTNESS REACTIONS

Because of its connections with nuclei of reticular formation, thalamus plays an important role in arousal and alertness reactions.

■ 6. CENTER FOR REFLEX ACTIVITY

Since the sensory fibers relay here, thalamus forms the center for many reflex activities.

■ 7. CENTER FOR INTEGRATION OF MOTOR ACTIVITY

Through the connections with cerebellum and basal ganglia, thalamus serves as a center for integration of motor functions.

■ APPLIED PHYSIOLOGY**■ THALAMIC SYNDROME**

Thalamic syndrome is the neurological disease caused by lesion of thalamus. Lesion occurs because of blockage (due to thrombosis) in the thalamogeniculate branch of posterior cerebral artery. The symptoms are:

1. Loss of Sensations

Loss of all sensations (anesthesia) occurs as the sensory relay system in thalamus is affected.

2. Astereognosis

Astereognosis is the loss of ability to recognize a known object by touch with closed eyes. It is due to the loss of tactile and kinesthetic sensations in thalamic syndrome.

3. Ataxia

Ataxia is the incoordination of voluntary movements.

4. Thalamic Phantom Limb

Thalamic phantom limb is the inability to locate the position of a limb with closed eyes. The patient will search for the limb in air.

5. Amelognosia

It is the illusion felt by the patient that his limb is absent.

6. Pain Sensation

Spontaneous pain occurs often. The pain may be so intense, that it even resists the action of powerful sedatives like morphine. Sometimes, the patient feels pain even in the absence of pain stimulus.

7. Involuntary Movements

Thalamic syndrome is always associated with some involuntary motor movements.

- a. Athetosis (slow writhing and twisting movements)
- b. Chorea (quick jerky involuntary movements)
- c. Intention tremor: Tremor is defined as rapid alternate rhythmic and involuntary movement of flexion and extension in the joints of fingers and wrist or elbow. Intention tremor is the tremor that develops while attempting to do any voluntary act. Intention tremor is the common feature of thalamic syndrome.

8. Thalamic Hand or Athetoid Hand

It is the abnormal attitude of the hand in thalamic lesion. It is characterized by moderate flexion at wrist and hyperextension of all fingers.

Hypothalamus

■ INTRODUCTION

■ NUCLEI

■ FUNCTIONS

- SECRETION OF POSTERIOR PITUITARY HORMONES
- CONTROL OF ANTERIOR PITUITARY
- CONTROL OF ADRENAL CORTEX
- CONTROL OF ADRENAL MEDULLA
- REGULATION OF AUTONOMIC NERVOUS SYSTEM
- REGULATION OF HEART RATE
- REGULATION OF BLOOD PRESSURE
- REGULATION OF BODY TEMPERATURE
- REGULATION OF HUNGER AND FOOD INTAKE
- REGULATION OF WATER BALANCE
- REGULATION OF SLEEP AND WAKEFULNESS
- ROLE IN BEHAVIOR AND EMOTIONAL CHANGES
- REGULATION OF SEXUAL FUNCTION
- REGULATION OF RESPONSE TO SMELL
- ROLE IN CIRCADIAN RHYTHM

■ APPLIED PHYSIOLOGY – DISORDERS OF HYPOTHALAMUS

- DIABETES INSIPIDUS
- DYSTROPHIA ADIPOSOGENITALIS
- LAURENCE-MOON-BIEDL SYNDROME
- NARCOLEPSY
- CATAPLEXY

■ INTRODUCTION

Hypothalamus is a diencephalic structure. It is situated just below thalamus in the ventral part

of diencephalon. It is formed by groups of nuclei scattered in the walls and floor of third ventricle. It extends from optic chiasma to mamillary body.

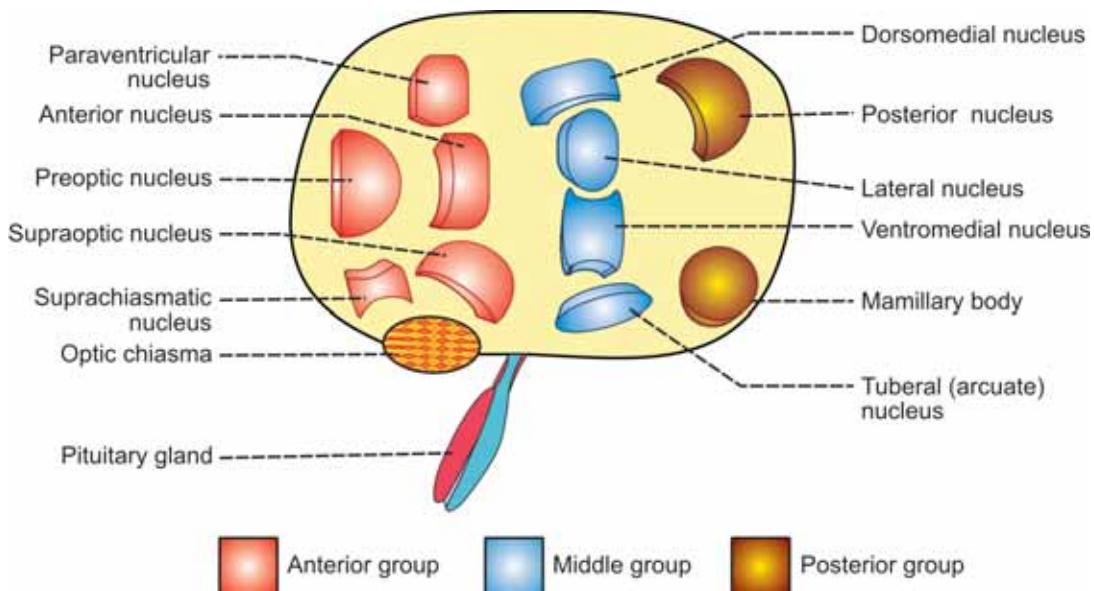


FIGURE 92-1: Nuclei of hypothalamus

■ NUCLEI OF HYPOTHALAMUS

The nuclei of hypothalamus are divided into three groups:

1. Anterior or preoptic group
2. Middle or tuberal group
3. Posterior or mamillary group.

Nuclei of each group are listed in Table 92-1 and represented diagrammatically in Fig. 92-1.

■ FUNCTIONS OF HYPOTHALAMUS

Hypothalamus is the important part of the brain concerned with homeostasis of the body. It regulates many vital functions of the body like endocrine functions, visceral functions,

metabolic activities, hunger, thirst, sleep, wakefulness, emotion, sexual functions, etc (Table 92-2).

■ 1. SECRETION OF POSTERIOR PITUITARY HORMONES

Posterior pituitary hormones namely, antidiuretic hormone (ADH) and oxytocin are secreted by supraoptic and paraventricular nuclei of hypothalamus. These two hormones are transported by means of axonal or axoplasmic flow through the fibers of hypothalamo-hypophyseal tracts to the posterior pituitary (Refer Chapter 45 for details).

TABLE 92-1: Nuclei of hypothalamus

Anterior or Preoptic group	Middle or Tuberal group	Posterior or Mamillary group
<ol style="list-style-type: none"> 1. Preoptic nucleus 2. Paraventricular nucleus 3. Anterior nucleus 4. Supraoptic nucleus 5. Suprachiasmatic nucleus 	<ol style="list-style-type: none"> 1. Dorsomedial nucleus 2. Ventromedial nucleus 3. Lateral nucleus 4. Arcuate (tuberal) nucleus 	<ol style="list-style-type: none"> 1. Posterior nucleus 2. Mamillary body

■ 2. CONTROL OF ANTERIOR PITUITARY

Hypothalamus controls the secretions of anterior pituitary gland by secreting releasing hormones and inhibitory hormones. It secretes seven hormones.

- i. Growth hormone releasing hormone (GHRH)
- ii. Growth hormone releasing polypeptide (GHRP)
- iii. Growth hormone inhibitory hormone (GHIH) or somatostatin
- iv. Thyrotropic releasing hormone (TRH)
- v. Corticotropin releasing hormone (CRH)
- vi. Gonadotropin releasing hormone (GnRH)
- vii. Prolactin inhibitory hormone (PIH).

These hormones are transported from hypothalamus to the anterior pituitary by the hypothalamo-hypophyseal portal blood vessels (Refer Chapter 45 for details).

■ 3. CONTROL OF ADRENAL CORTEX

Hypothalamus controls adrenal cortex through anterior pituitary. Anterior pituitary regulates the adrenal cortex by secreting adrenocorticotrophic hormone (ACTH). ACTH secretion is in turn regulated by corticotropin releasing hormone (CRH) which is secreted by the paraventricular nucleus of hypothalamus (Refer Chapter 49 for details).

■ 4. CONTROL OF ADRENAL MEDULLA

Dorsomedial and posterior hypothalamic nuclei are excited by emotional stimuli. These hypothalamic nuclei, in turn, send impulses to adrenal medulla through sympathetic fibers and cause release of catecholamines, which are essential to cope up with emotional stress (Chapter 50).

■ 5. REGULATION OF AUTONOMIC NERVOUS SYSTEM

Hypothalamus controls the autonomic nervous system (ANS). The sympathetic division of ANS is regulated by posterior and lateral nuclei of hypothalamus. The parasympathetic division of ANS is controlled by anterior group of nuclei.

The influences of cerebral cortex on ANS are executed through hypothalamus (Chapter 103).

■ 6. REGULATION OF HEART RATE

Hypothalamus regulates heart rate through vasomotor center in the medulla oblongata. Stimulation of posterior and lateral nuclei of hypothalamus increases the heart rate. Stimulation of preoptic and anterior nuclei decreases the heart rate (Chapter 64).

■ 7. REGULATION OF BLOOD PRESSURE

Hypothalamus regulates the blood pressure by acting on the vasomotor center. Stimulation of posterior and lateral hypothalamic nuclei increases arterial blood pressure and stimulation of preoptic area decreases the blood pressure (Chapter 65).

■ 8. REGULATION OF BODY TEMPERATURE

The body temperature is regulated by hypothalamus which sets the normal range of body temperature. The set point under normal physiological conditions is 37°C. Hypothalamus has two centers which regulate the body temperature:

- i. Heat loss center that is present in preoptic nucleus of anterior hypothalamus
- ii. Heat gain center that is situated in posterior hypothalamic nucleus.

Regulation of body temperature is explained in Chapter 43.

■ 9. REGULATION OF HUNGER AND FOOD INTAKE

Food intake is regulated by two centers present in hypothalamus:

- i. Feeding center
- ii. Satiety center.

Feeding Center

Feeding center is in the lateral hypothalamic nucleus. In experimental conditions, the stimulation of this center in animals leads to

uncontrolled hunger and increased food intake (hyperphagia) resulting in obesity. The destruction of feeding center leads to loss of appetite (anorexia) and the animal refuses to take food.

Normally feeding center is always active. That means it has the tendency to induce food intake always.

Satiety Center

Satiety center is in the ventromedial nucleus of the hypothalamus. Stimulation of this nucleus in animals causes total loss of appetite and cessation of food intake. Destruction of satiety center leads to hyperphagia and the animal becomes obese. This type of obesity is called hypothalamic obesity.

Satiety center plays important role in regulation of food intake by temporary inhibition of feeding center after food intake.

Mechanism of Regulation of Food Intake

Under normal physiological conditions appetite and food intake are well balanced and continues in a cyclic manner. Feeding center and satiety center of hypothalamus are responsible for regulation of appetite and food intake. These hypothalamic centers are regulated by the following mechanisms:

- i. Glucostatic mechanism
- ii. Lipostatic mechanism
- iii. Peptide mechanism

- iv. Hormonal mechanism
- v. Thermostatic mechanism.

i. Glucostatic Mechanism

The cells of the satiety center function as glucostats or glucose receptors. The glucostats are stimulated by increased blood glucose level during food intake. This develops the feeling of 'fullness'. The satiety center in turn, inhibits the feeding center resulting in stoppage of food intake.

After few hours of food intake, the blood glucose level decreases and satiety center becomes inactive. So, the feeding center is no longer inhibited. Now it becomes active and increases the appetite and induces food intake. After taking food, once again blood glucose level increases and the cycle is repeated (Fig. 92-2).

ii. Lipostatic Mechanism

Leptin is a peptide secreted by adipocytes (cells of adipose tissue). It plays an important role in controlling the food intake and adipose tissue volume. The details of leptin are given in Chapter 52.

When the volume of adipose tissues increases, adipocytes secrete and release a large quantity of leptin into the blood. While circulating through brain, leptin acts on hypothalamus and inhibits the feeding center

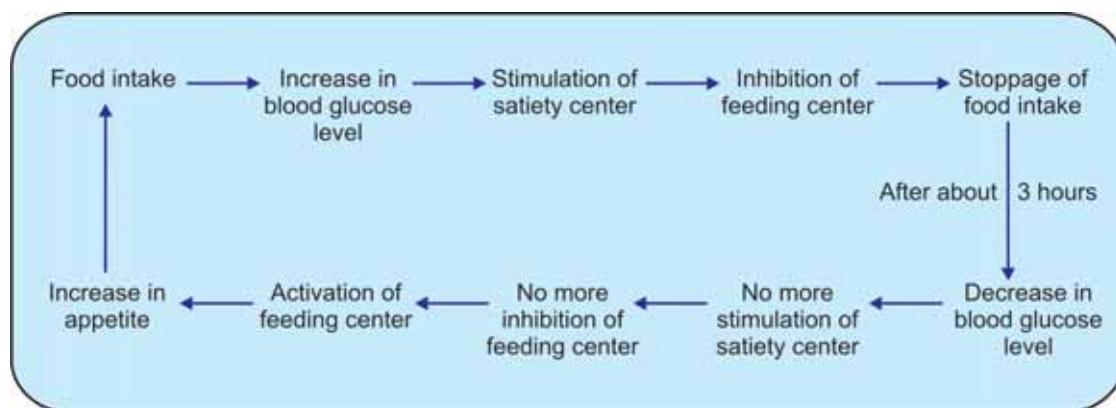


FIGURE 92-2: Glucostatic mechanism

resulting in loss of appetite and stoppage of food intake.

iii. Peptide Mechanism

Some peptides regulate the food intake either by stimulating or inhibiting the feeding center directly or indirectly.

The peptides which increase the food intake are:

- a. Ghrelin
- b. Neuropeptide Y.

Peptides which decrease food intake are:

- a. Leptin
- b. Peptide YY.

iv. Hormonal Mechanism

Some of the endocrine hormones and GI hormones inhibit the food intake by acting through hypothalamus. Such hormones are:

- a. Somatostatin
- b. Oxytocin
- c. Glucagon
- d. Pancreatic polypeptide
- e. Cholecystokinin.

v. Thermostatic Mechanism

Food intake is inversely proportional to body temperature. So in fever, the food intake is decreased due to the influence of preoptic thermoreceptors (see above) on feeding center.

■ 10. REGULATION OF WATER BALANCE

Hypothalamus regulates water content of the body by two mechanisms:

- i. Thirst mechanism
- ii. ADH mechanism.

i. Thirst Mechanism

Thirst center is in the lateral nucleus of hypothalamus. There are some osmoreceptors in the areas adjacent to thirst center. When the ECF volume decreases, the osmolality of ECF is increased. If the osmolarity increases by

1 to 2%, the osmoreceptors are stimulated. Osmoreceptors in turn, activate the thirst center and thirst sensation is initiated. Now, the person feels thirsty and drinks water. Water intake increases ECF volume and decreases the osmolality.

ii. ADH Mechanism

Simultaneously, when the volume of ECF decreases with increased osmolality, the supraoptic nucleus is stimulated and ADH is released. ADH causes retention of water by facultative reabsorption in the renal tubules. It increases the ECF volume and brings the osmolality back to the normal level. On the contrary, when ECF volume is increased, the supraoptic nucleus is not stimulated and ADH is not secreted. In the absence of ADH, more amount of water is excreted through urine and the volume of ECF is brought back to normal.

■ 11. REGULATION OF SLEEP AND WAKEFULNESS

Mamillary body in the posterior hypothalamus is considered as the wakefulness center. Stimulation of mamillary body causes wakefulness and its lesion leads to sleep. Stimulation of anterior hypothalamus also leads to sleep.

■ 12. ROLE IN BEHAVIOR AND EMOTIONAL CHANGES

The behavior of animals and human beings is mostly affected by two responding systems in hypothalamus and other structures of limbic system. These two systems act opposite to one another.

The responding systems are concerned with the affective nature of sensations, i.e. whether the sensations are pleasant or painful. These two qualities are called the Reward (satisfaction) and punishment (aversion or avoidance). Hypothalamus has two centers for behavior and emotional changes are:

- i. Reward center
- ii. Punishment center.

Reward Center

It is situated in medial forebrain bundle and ventromedial nucleus of hypothalamus. Electrical stimulation of these areas in animals pleases or satisfies the animals.

Punishment Center

It is situated in posterior and lateral nuclei of hypothalamus. Electrical stimulation of these

nuclei in animals leads to pain, fear, defense, escape reactions and other elements of punishment.

Role of Reward and Punishment Centers

The importance of the reward and punishment centers lies in the behavioral pattern of the individuals. Almost all the activities of day to day life depend upon reward and punishment. While doing something, if the person is rewarded or

TABLE 92-2: Functions of hypothalamus

Functions	Action/Center	Nuclei/Parts involved
1. Control of anterior pituitary	Releasing hormones Inhibitory hormones	Discrete areas
2. Secretion of posterior pituitary hormones	Oxytocin ADH	Paraventricular nucleus Supraoptic nucleus
3. Control of adrenal cortex	CRH	Paraventricular nucleus
4. Control of adrenal medulla	Catecholamines during emotion	Posterior and dorsomedial nuclei
5. Regulation of ANS	Sympathetic Parasympathetic	Posterior and lateral nuclei Anterior nuclei
6. Regulation of heart rate	Acceleration Inhibition	Posterior and lateral nuclei Preoptic area
7. Regulation of blood pressure	Pressor effect Depressor effect	Posterior and lateral nuclei Preoptic area
8. Regulation of body temperature	Heat gain center Heat loss center	Posterior hypothalamus Anterior hypothalamus
9. Regulation of hunger and food intake	Feeding center Satiety center	Lateral nucleus Ventromedial nucleus
10. Regulation of water intake	Thirst center Water retention by ADH	Lateral nucleus Supraoptic nucleus
11. Regulation of sleep and wakefulness	Sleep Wakefulness	Anterior hypothalamus Mamillary body
12. Regulation of behavior and emotion	Reward center Punishment center	Ventromedial nucleus Posterior and lateral nuclei
13. Regulation of sexual function	Sexual cycle	Tuberal and posterior nuclei
14. Regulation of response to smell	Autonomic responses	Posterior hypothalamus
15. Role in circadian rhythm	Rhythmic changes	Suprachiasmatic nucleus

feels satisfied, he or she continues to do so. If the person feels punished or unpleasant, he or she stops doing so. Thus, these two centers play an important role in the development of the behavioral pattern of a person.

Rage

Rage refers to violent and aggressive emotional expression with extreme anger. It is common in animals when punishment centers in hypothalamus are stimulated. The reactions of rage are expressed by developing a defense posture which includes:

- i. Extension of limbs with lifting of tail
- ii. Hissing and spitting
- iii. Piloerection
- iv. Wide opening of eyeballs with pupillary dilatation
- v. Severe savage attack even by mild provocation.

Sham Rage

Sham rage means false rage. It is an extreme emotional condition that resembles rage and occurs in some pathological conditions in humans. Sham rage is due to release of hypothalamus from the inhibitory influence of cortical control.

■ 13. REGULATION OF SEXUAL FUNCTION

In animals, hypothalamus plays an important role in regulating sexual functions by secreting gonadotropin releasing hormones. Arcuate and posterior hypothalamic nuclei are involved in the regulation of sexual functions.

■ 14. ROLE IN RESPONSE TO SMELL

Posterior hypothalamus along with other structures like hippocampus and brainstem nuclei is responsible for the autonomic responses of body to olfactory stimuli. The responses

include feeding activities and emotional responses like fear, excitement and pleasure.

■ 15. ROLE IN CIRCADIAN RHYTHM

Circadian rhythm is the regular recurrence of physiological processes or activities which occur in cycles of 24 hours. It is also called diurnal rhythm. The term circadian is a Latin word meaning 'around the day'.

The circadian rhythm occurs in response to recurring daylight and darkness. The cyclic changes taking place in various physiological processes are set by means of a hypothetical internal clock that is often called biological clock.

The suprachiasmatic nucleus of hypothalamus plays an important role in setting the biological clock by its connection with retina via retinohypothalamic fibers. Through the efferent fibers it sends circadian signals to different parts and maintains the circadian rhythm of sleep, hormonal secretion, thirst, hunger, appetite, etc.

Whenever body is exposed to a new pattern of daylight/ darkness rhythm, the biological clock is reset provided the new pattern is regular. Accordingly, the circadian rhythm also changes.

■ APPLIED PHYSIOLOGY – DISORDERS OF HYPOTHALAMUS

Following disorders develop in hypothalamic lesion that occurs due to tumors, encephalitis or ischemia.

■ 1. DIABETES INSIPIDUS

Diabetes insipidus is the condition characterized by excretion of large quantity of water through urine. Refer Chapter 45 for details.

■ 2. DYSTROPHIA ADIPOSOGENITALIS

It is characterized by obesity and sexual infantilism, associated with dwarfism (if the condition occurs during growing period). It is also called Fröhlich's syndrome. Refer Chapter 45 for details.

■ 3. LAURENCE-MOON-BIEDL SYNDROME

This disorder of hypothalamus is characterized by moon face (facial contours become round by hiding the bony structures), obesity, polydactylism (having one or more extra fingers or toes), mental retardation and hypogenitalism.

■ 5. NARCOLEPSY

Narcolepsy is a hypothalamic disorder with abnormal sleep pattern. There is sudden attack

of uncontrollable desire for sleep and, the person suddenly falls asleep. It occurs in the daytime.

■ 6. CATAPLEXY

It is the sudden uncontrolled outbursts of emotion associated with narcolepsy. Due to emotional outburst like anger, fear or excitement, the person becomes completely exhausted with muscular weakness. The attack is brief and last for few seconds to a few minutes. The consciousness is not lost.

Cerebellum

- PARTS
 - VERMIS
 - CEREBELLAR HEMISPHERES
- DIVISIONS
- VESTIBULOCEREBELLUM
 - COMPONENTS
 - FUNCTIONS
- SPINOCEREBELLUM
 - COMPONENTS
 - FUNCTIONS
- CORTICOCEREBELLUM
 - COMPONENTS
 - AFFERENT-EFFERENT CIRCUIT
 - FUNCTIONS
- APPLIED PHYSIOLOGY – CEREBELLAR LESIONS
 - DISTURBANCES IN TONE AND POSTURE
 - DISTURBANCES IN EQUILIBRIUM
 - DISTURBANCES IN MOVEMENTS

■ PARTS OF CEREBELLUM

Cerebellum consists of a narrow, worm like central body called vermis and two lateral lobes, the right and left cerebellar hemispheres (Fig. 93-1). The part of vermis on the upper surface of cerebellum is known as superior vermis and the vermis on the under surface of cerebellum is called inferior vermis.

■ VERMIS

The vermis of cerebellum is formed by nine parts. The parts of superior vermis and inferior vermis are listed in Table 93-1.

Nodulus and flocculi are together called flocculonodular lobe. On either side of pyramid, there is another extension named paraflocculus.

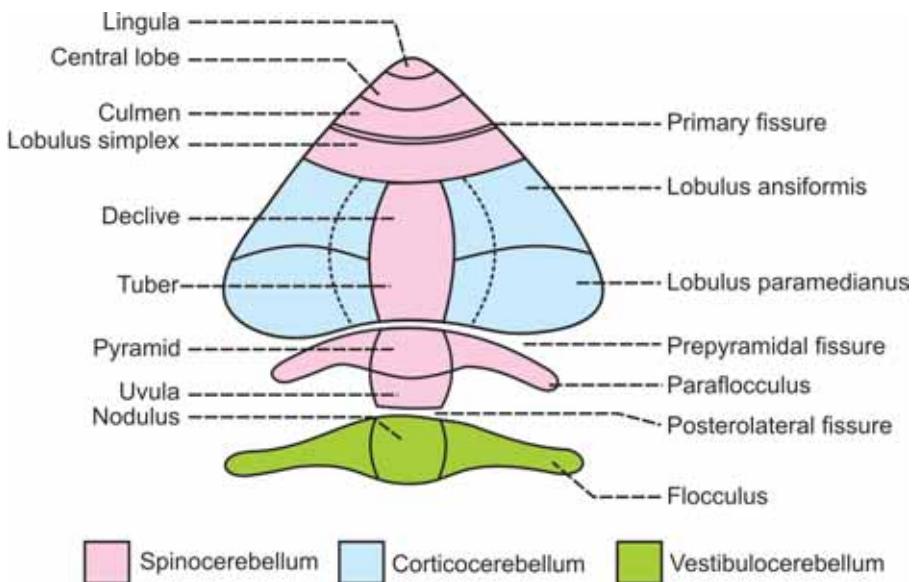


FIGURE 93-1: Parts and functional divisions of cerebellum

TABLE 93-1: Parts of superior and inferior vermis

Superior vermis	Inferior vermis
1. Lingula	6. Tuber
2. Central lobe	7. Pyramid
3. Culmen	8. Uvula
4. Lobulus simplex	9. Nodulus
5. Declive	

TABLE 93-2: Components of divisions of cerebellum

Division	Components
Vestibulocerebellum	Flocculonodular lobe (Nodulus and Flocculi)
Spinocerebellum	Lingula Central lobe Culmen Lobulus simplex Declive Tuber Pyramid Uvula Paraflocculi Medial portions of cerebral hemispheres
Corticocerebellum	Lateral portions of cerebral hemispheres

■ CEREBELLAR HEMISPHERES

The cerebellar hemispheres are the extended portions on either side of the vermis. Each hemisphere has two portions.

1. Lobulus ansiformis or ansiform lobe
2. Lobulus paramedianus or paramedian lobe

■ DIVISIONS OF CEREBELLUM

Based on the functions, the cerebellum is divided into three divisions:

1. Vestibulocerebellum
2. Spinocerebellum
3. Corticocerebellum

■ VESTIBULOCEREBELLUM (ARCHICEREBELLUM)

This part of cerebellum is connected with the vestibular apparatus and so it is known as

vestibulocerebellum. Since, vestibulocerebellum is the phylogenetically oldest part of cerebellum, it is also called archicerebellum.

■ COMPONENTS OF VESTIBULOCEREBELLUM

Vestibulocerebellum includes the flocculonodular lobe that is formed by the nodulus of vermis and its lateral extensions called flocculi (Fig. 93-1 and Table 93-2).

■ FUNCTIONS OF VESTIBULOCEREBELLUM

Vestibulocerebellum regulates tone, posture and equilibrium by receiving impulses from vestibular apparatus regarding gravity and movements (Table 93-3).

Mechanism of Action of Vestibulocerebellum

Normally, the vestibular nuclei of brain stem facilitate the movements of trunk, neck and limbs. The medullary reticular formation inhibits the muscle tone.

After receiving information from vestibular apparatus, the vestibulocerebellum inhibits both vestibular nuclei and medullary reticular formation. As a result, the movements of neck, trunk and limbs are checked and the muscle tone increases. Because of these effects, any

disturbance in posture and equilibrium is corrected.

In the lesion of vestibulocerebellum, there is reduction of muscle tone (hypotonia) and failure to maintain posture and equilibrium.

■ SPINOCEREBELLUM (PALEOCEREBELLUM)

Spinocerebellum or paleocerebellum is connected with spinal cord and hence the name. It forms the major receiving area of cerebellum for sensory inputs. Spinocerebellum is also phylogenetically older part of cerebellum

■ COMPONENTS OF SPINOCEREBELLUM

Spinocerebellum consists of medial portions of cerebellar hemisphere, paraflocculi and parts of vermis, viz. lingula, central lobe, culmen, lobulus simplex, declive, tuber, pyramid and uvula (Fig. 93-1 and Table 93-2).

■ FUNCTIONS OF SPINOCEREBELLUM

Spinocerebellum regulates tone, posture and equilibrium by receiving sensory impulses from tactile receptors, proprioceptors, visual receptors and auditory receptors. It also receives the cortical impulses via pontine nuclei.

TABLE 93-3: Functions of cerebellum

Functions	Mechanism	Division of cerebellum involved
1. Regulation of tone, posture and equilibrium	By receiving impulses from vestibular apparatus	Vestibulocerebellum
	By receiving impulses from proprioceptors in muscles, tendons and joints, tactile receptors, visual receptors and auditory receptors	Spinocerebellum
2. Regulation of coordinated movements	By: <ol style="list-style-type: none"> Damping action Control of ballistic movements Timing and programming the movements Servomechanism Comparator function 	Corticocerebellum (Neocerebellum)

Spinocerebellum facilitates the discharge from gamma motor neurons. Increased discharge from gamma motor neurons increases the muscle tone. The lesion in spinocerebellum causes stoppage of discharge from the gamma motor neurons resulting in hypotonia and disturbances in posture.

Spinocerebellum also receives impulses from optic and auditory pathway and helps in adjustment of posture and equilibrium in response to visual and auditory impulses.

■ CORTICOCEREBELLUM (NEOCEREBELLUM)

Corticocerebellum is largest part of cerebellum. Because of its connection with cerebral cortex, it is called corticocerebellum or cerebrocerebellum. It is phylogenetically newer part of cerebellum. So, it is also called neocerebellum. It is concerned with planning, programming and coordination

■ COMPONENTS OF CORTICOCEREBELLUM

Corticocerebellum includes the lateral portions of cerebellar hemispheres (Fig. 93-1 and Table 93-2).

■ AFFECTER-EFFERENT CIRCUIT (CEREBRO-CEREBELLO-CEREBRAL CONNECTIONS)

It is a neuronal pathway through which corticocerebellum controls the voluntary movements.

Fibers from motor areas 4 and 6 in frontal lobe of cerebral cortex enter the pontine nuclei. These fibers are called corticopontine fibers (Fig 93-2). From pontine nuclei, the pontocerebellar fibers arise and pass through middle cerebellar peduncle of the opposite side and terminate in the cerebellar cortex. This pathway is called the cerebropontocerebellar tract.

The cerebellar cortex is, in turn, connected to the dentate nucleus. Fibers from the dentate nucleus pass via superior cerebellar peduncle and end in red nucleus of opposite side. These fibers are called dentatorubral fibers. From red nucleus, the rubrothalamic fibers go to thalamus. Thalamus is connected to areas 4 and 6 in motor cortex of cerebrum by thalamocortical fibers. This pathway is called dentatorubrothalamicocortical tract.

■ FUNCTIONS OF CORTICOCEREBELLUM

Corticocerebellum is concerned with the integration and regulation of well coordinated

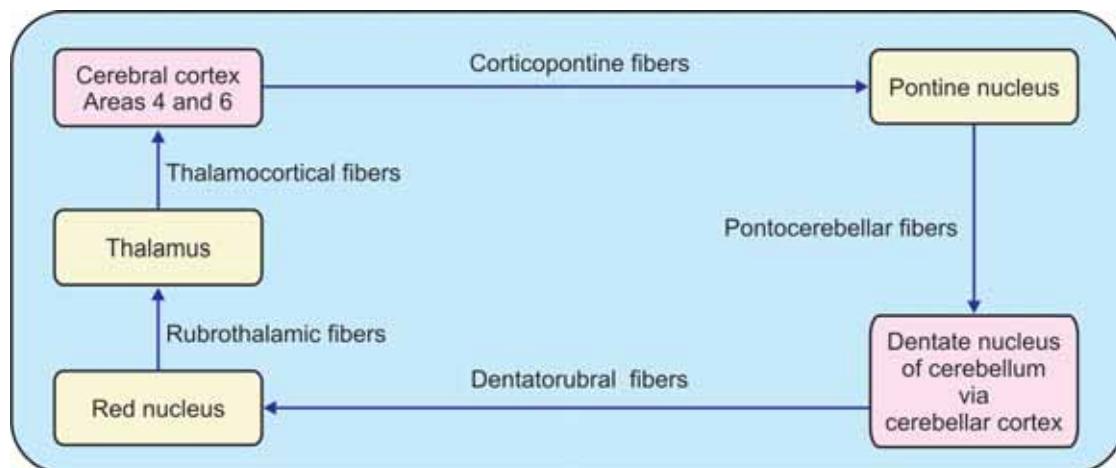


FIGURE 93-2: Schematic representation of cerebro-cerebello-cerebral circuit

muscular activities. It is because of its afferent-efferent connection with cerebral cortex through the cerebro-cerebello-cerebral circuit. Apart from its connections with cerebral cortex, cerebellum also receives feedback signals from the muscles through the nerve fibers of proprioceptors.

Mechanism of Action of Corticocerebellum

1. Damping action

Damping action refers to prevention of exaggerated muscular activity. This helps in making the voluntary movements smooth and accurate. All the voluntary muscular activities are initiated by motor areas of cerebral cortex. Simultaneously, corticocerebellum receives impulses from motor cortex as well as feedback signals from the muscles as soon as the muscular activity starts.

Corticocerebellum, in turn, sends information (impulses) to cerebral cortex to discharge only appropriate signals to the muscles and to cut off any extra impulses. Because of this damping action of corticocerebellum, the exaggeration of muscular activity is prevented and the movements become smooth and accurate. Literally, the word damping means any effect that decreases the amplitude of mechanical oscillation.

2. Control of ballistic movements

Ballistic movements are the rapid alternate movements, which take place in different parts of the body while doing any skilled or trained work like typing, cycling, dancing, etc. Corticocerebellum plays an important role in preplanning the ballistic movements during learning process.

3. Timing and programming the movements

Corticocerebellum plays an important role in timing and programming the movements particularly during learning process. While using a typewriter or while doing any other fast skilled work, a chain of movements occur rapidly in a sequential manner. During the learning process of these skilled works, corticocerebellum plans

the various sequential movements. It also plans schedule of time duration of each movement and the time interval between movements. All the information from corticocerebellum are communicated to sensory motor area of cerebral cortex and stored in the form of memory. So, after the learning process is over, these activities are executed easily and smoothly in sequential manner.

4. Servomechanism

Servomechanism is the correction of any disturbance or interference while performing skilled work. Once the skilled works are learnt, the sequential movements are executed without any interruption. Cerebellum lets the cerebral cortex to discharge the signals, which are already programmed and stored at sensory motor cortex, and, does not interfere much. However, if there is any disturbance or interference, the cortico-cerebellum immediately influences the cortex and corrects the movements.

5. Comparator function

The comparator function of the corticocerebellum is responsible for the integration and coordination of the various muscular activities.

On one side, cerebellum receives the information from cerebral cortex regarding the cortical impulses which are sent to the muscles. On the other side, it receives the feedback information (proprioceptive impulses) from the muscles regarding their actions under the instruction of cerebral cortex.

By receiving the messages from both ends, corticocerebellum compares the cortical commands for muscular activity and the actual movements carried out by the muscles. If any correction is to be done, then, corticocerebellum sends instructions (impulses) to the motor cortex.

Accordingly, the cerebral cortex corrects or modifies the signals to muscles, so that the movements become accurate, precise and smooth. This function of corticocerebellum is known as comparator function.

Simultaneously, it also receives impulses from tactile receptors, eye and ear. Such additional information facilitates the comparator function of corticocerebellum.

■ APPLIED PHYSIOLOGY – CEREBELLAR LESIONS

Cerebellar lesions occur due to tumor, abscess, injury, excess alcohol ingestion. In general, during cerebellar lesions, there are disturbances in posture, equilibrium and the movements. In unilateral lesion, symptoms appear on the affected side because cerebellum controls the same (ipsilateral) side of the body.

■ DISTURBANCES IN TONE AND POSTURE

1. Atonia or Hypotonia

Atonia is the loss of tone and hypotonia is reduction in tone of the muscle. Atonia or hypotonia occurs because of the loss of facilitatory impulses from cerebellum to gamma motor neurons in the spinal cord.

2. Attitude

Attitude of the body changes in unilateral lesion of the cerebellum. The changes in the attitude are:

- i. Rotation of head towards the opposite side (unaffected side)
- ii. Lowering of shoulder on the same side
- iii. Abduction of leg on the affected side. The leg is rotated outward
- iv. The weight of the body is thrown on the leg of unaffected side. So, the trunk is bent with concavity towards the affected side.

3. Deviation Movement

It is the lateral deviation of arms when both the arms are stretched and held in front of the body with closed eyes. In bilateral lesion, both the arms deviate and in unilateral lesion arm of the affected side deviates.

4. Effect on Deep Reflexes

Pendular movements occur while eliciting a tendon jerk particularly the knee jerk (Chapter 87).

■ DISTURBANCES IN EQUILIBRIUM

While Standing

While standing, the legs are spread to provide a broad base. And, the body sways side-to-side with the oscillations of the head.

While Moving – Gait

Gait means the manner of walking. In cerebellar lesion, a staggering, reeling and drunken like gait is observed.

■ DISTURBANCES IN MOVEMENTS

1. Ataxia – lack of coordination of movements.
2. Asynergia – lack of coordination between different groups of muscles
3. Asthenia – weakness, easy fatigability and slowness of muscles
4. Dysmetria – inability to check the exact strength and duration of muscular contractions required for any voluntary act. While reaching for an object, the arm may overshoot (hypermetria) or it may fall short (hypometria) of the object
5. Intention tremor – tremor that occurs while attempting to do any voluntary act. Refer Chapter 91 for details of tremor
6. Astasia – unsteady voluntary movements
7. Nystagmus – to and fro movement of eyeball (Chapter 98)
8. Rebound phenomenon – when the patient attempts to do a movement against a resistance, and if the resistance is suddenly removed, the limb moves forcibly in the direction in which the attempt was made
9. Dysarthria – disturbance in speech
10. Adiadochokinesis – inability to do rapid alternate successive movements such as supination and pronation of arm.

Basal Ganglia

- INTRODUCTION
- COMPONENTS
 - CORPUS STRIATUM
 - SUBSTANTIA NIGRA
 - SUBTHALAMIC NUCLEUS OF LUYS
- FUNCTIONS
 - CONTROL OF MUSCLE TONE
 - CONTROL OF MOTOR ACTIVITY
 - CONTROL OF REFLEX MUSCULAR ACTIVITY
 - CONTROL OF AUTOMATIC ASSOCIATED MOVEMENTS
 - ROLE IN AROUSAL MECHANISM
- APPLIED PHYSIOLOGY – DISORDERS
 - PARKINSON'S DISEASE
 - WILSON'S DISEASE
 - CHOREA
 - ATHETOSIS
 - CHOREOATHETOSIS
 - HUNTINGTON'S DISEASE
 - HEMIBALLISMUS
 - KERNICTERUS

■ INTRODUCTION

Basal ganglia are the scattered masses of gray matter submerged in subcortical substance of cerebral hemisphere (Fig. 94-1). Basal ganglia form the part of extrapyramidal system, which is concerned with integration and the regulation of motor activities.

■ COMPONENTS OF BASAL GANGLIA

Basal ganglia include three primary components:

1. Corpus striatum
2. Substantia nigra
3. Subthalamic nucleus of Luys.

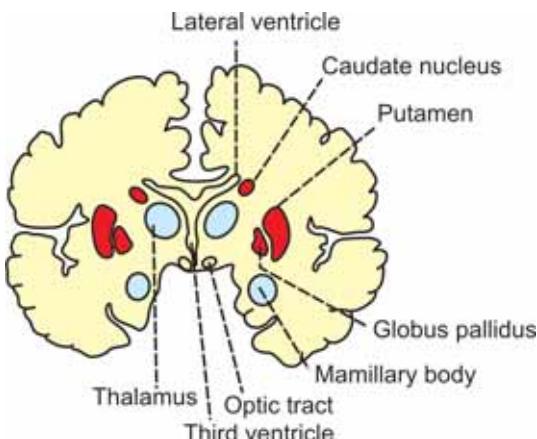


FIGURE 94-1: Basal ganglia

■ CORPUS STRIATUM

It is a mass of gray matter situated at the base of cerebral hemispheres in close relation to the thalamus. It has two parts:

- Caudate nucleus
- Lenticular nucleus which is divided into two portions:
 - Putamen
 - Globus pallidus.

■ SUBSTANTIA NIGRA

Substantia nigra is situated below red nucleus. It is made up of large pigmented and small nonpigmented cells. The pigment contains high quantity of iron.

■ SUBTHALAMIC NUCLEUS OF LUYS

This nucleus is situated lateral to red nucleus and dorsal to substantia nigra.

■ FUNCTIONS OF BASAL GANGLIA

The basal ganglia form the part of extrapyramidal system, which is concerned with motor activities. The various functions of basal ganglia are:

■ 1. CONTROL OF MUSCLE TONE

Basal ganglia control the muscle tone. In fact the gamma motor neurons of spinal cord are responsible for the tone of the muscles. Basal

ganglia decrease muscle tone by inhibiting the gamma motor neurons through descending inhibitory reticular system in brainstem.

■ 2. CONTROL OF MOTOR ACTIVITY

i. Regulation of Voluntary Movements

Voluntary motor activities are initiated by cerebral cortex. However, these movements are controlled by basal ganglia. During lesions of basal ganglia, the control mechanism is lost and so the movements become inaccurate and awkward.

Basal ganglia control the motor activities because of the nervous (neuronal) circuits between basal ganglia and other parts of brain involved in motor activity.

ii. Regulation of Conscious Movements

Basal ganglia regulate the conscious movements. This function of basal ganglia is also known as the cognitive control of activity. For example, when a stray dog barks at a man, immediately the person, understands the situation, turns away and starts running.

iii. Regulation of Subconscious Movements

Basal ganglia regulate the subconscious movements which take place during trained motor activities, i.e. skilled activities such as writing the learnt alphabet, paper cutting, nail hammering, etc.

■ 3. CONTROL OF REFLEX MUSCULAR ACTIVITY

Some of the reflex muscular activities, particularly visual and labyrinthine reflexes are important in the maintenance of posture. Basal ganglia are responsible for the coordination and integration of impulses for these reflex activities.

■ 4. CONTROL OF AUTOMATIC ASSOCIATED MOVEMENTS

Automatic associated movements are the movements in the body, which take place along with some motor activities. Examples are the

swing of the arms while walking, appropriate facial expressions while talking or doing any work. Basal ganglia are responsible for the automatic associated movements.

■ 5. ROLE IN AROUSAL MECHANISM

Globus pallidus and red nucleus are involved in arousal mechanism because of their connections with reticular formation. Extensive lesion in globus pallidus causes drowsiness, leading to sleep.

■ APPLIED PHYSIOLOGY – DISORDERS OF BASAL GANGLIA

■ 1. PARKINSON'S DISEASE

The Parkinson's disease is a slow progressive degenerative disease of nervous system associated with destruction of dopamine producing cells in brain. It is named after the discoverer James Parkinson. It is also called parkinsonism or paralysis agitans.

Causes of Parkinson's Disease

Parkinson's disease occurs due to lack of dopamine caused by damage of basal ganglia. It is mostly due to the destruction of substantia nigra and the nigrostriatal pathway, which has dopaminergic fibers. Damage of basal ganglia usually occurs because of the following causes:

- i. Viral infection of brain like encephalitis
- ii. Cerebral arteriosclerosis
- iii. Injury to basal ganglia
- iv. Destruction or removal of dopamine in basal ganglia. It occurs mostly due to long term treatment with antihypertensive drugs like reserpine. Parkinsonism due to the drugs is known as drug-induced Parkinsonism
- v. Unknown causes: Parkinsonism can occur because of the destruction of basal ganglia due to some unknown causes. This type of Parkinsonism is called idiopathic Parkinsonism.

Signs and Symptoms of Parkinson's Disease

Parkinson's disease develops very slowly and the early signs and symptoms may be unnoticed for months or even for years. Often the symptoms start with a mild noticeable tremor in just one hand. When the tremor becomes remarkable the disease causes slowing or freezing of movements followed by rigidity.

Common signs and symptoms of Parkinson's disease are:

1. Tremor

Refer Chapter 91 for details of tremor. In Parkinson's disease, static tremor or resting tremor occurs during rest. But it disappears while doing any work. It is also called drum beating tremor, as the movements are similar to beating a drum. The thumb moves rhythmically over the index and middle fingers. These movements are called pill rolling movements.

2. Slowness of movements

Over the time, the movements start slowing down (bradykinesia) and it takes a long time even to perform a simple task. Gradually the patient becomes unable to initiate the voluntary activity (akinesia) or the voluntary movements are reduced (hypokinesia). It is because of hypertonicity of the muscles.

3. Poverty of movements

Poverty of movements is the loss of all automatic associated movements. Because of absence of the automatic associate movements, the body becomes statue like. The face becomes mask like, due to absence of appropriate expressions like blinking and smiling.

4. Rigidity

Stiffness of muscles occurs in limbs resulting in rigidity of limbs. The muscular stiffness occurs because of increased muscle tone which is due to the removal of inhibitory influence on gamma

motor neurons. It affects both flexor and extensor muscles equally. So, the limbs become more rigid like pillars. The condition is called lead pipe rigidity. In later stages the rigidity extends to neck and trunk.

5. Gait

Gait refers to manner of walking. The patient loses the normal gait. Gait in Parkinson's disease is called festinant gait. The patient walks quickly in short steps by bending forward as if he is going to catch up the center of gravity.

6. Speech Problems

Many patients develop speech problems. They may speak very softly or sometimes rapidly. The words are repeated many times. Finally the speech becomes slurred and they hesitate to speak.

7. Emotional changes

The persons affected by Parkinson's disease are often upset emotionally.

8. Dementia

In later stages, some patients develop dementia (Chapter 101).

■ 2. WILSON'S DISEASE

Wilson's disease is an inherited disorder characterized by excess of copper in the body tissues. It is also known as progressive hepatolenticular degeneration. This disease develops due to damage of the lenticular nucleus. In addition to symptoms of Parkinson's disease, liver failure and damage to the central nervous system occur.

■ 3. CHOREA

It is an abnormal involuntary movement. Chorea means rapid jerky movements. It mostly involves the limbs. It is due to lesion in caudate nucleus and putamen.

■ 4. ATHETOSIS

It is another type of abnormal involuntary movement, which refers to slow rhythmic and twisting movements. It is because of the lesion in caudate nucleus and putamen.

■ 5. CHOREOATHETOSIS

It is the condition characterized by aimless involuntary muscular movements. It is due to combined effects of chorea and athetosis.

■ 6. HUNTINGTON'S DISEASE

Huntington's disease is an inherited progressive neural disorder due to the degeneration of neurons secreting GABA in corpus striatum and substantia nigra. It is characterized by chorea, hypotonia and dementia.

■ 7. HEMIBALLISMUS

It is a disorder characterized by violent involuntary abnormal movements on one side of the body involving mostly the arm. While walking, the arm swings widely. Hemiballismus occurs due to degeneration of subthalamic nucleus of Luys.

■ 8. KERNICTERUS

Kernicterus is a form of brain damage in infants caused by severe jaundice. Basal ganglia are the mainly affected parts of brain. Refer Chapter 16 for details.

Cerebral Cortex and Limbic System

- INTRODUCTION
- NEOCORTEX AND ALLOCORTEX
- LOBES OF CEREBRAL CORTEX
- CEREBRAL DOMINANCE
- BRODMANN AREAS
- FRONTAL LOBE
 - PRECENTRAL CORTEX
 - PREFRONTAL CORTEX OR ORBITOFRONTAL CORTEX
 - APPLIED PHYSIOLOGY – FRONTAL LOBE SYNDROME
- PARIETAL LOBE
 - SOMESTHETIC AREA I
 - SOMESTHETIC AREA II
 - SOMESTHETIC ASSOCIATION AREA
 - APPLIED PHYSIOLOGY
- TEMPORAL LOBE
 - PRIMARY AUDITORY AREA
 - AUDITOPSYCHIC AREA
 - AREA FOR EQUILIBRIUM
 - APPLIED PHYSIOLOGY – TEMPORAL LOBE SYNDROME
- OCCIPITAL LOBE
 - AREAS OF VISUAL CORTEX
 - APPLIED PHYSIOLOGY
- LIMBIC SYSTEM
 - COMPONENTS
 - FUNCTIONS

■ INTRODUCTION

The cerebral cortex consists of two hemispheres with area of 2.2 sqm. The two cerebral hemi-

spheres are separated by a deep vertical fissure (deep furrow or groove). The separation is complete anteriorly and posteriorly. But in the

middle portion, the fissure extends only up to corpus callosum which is the broad band of commissural fibers, connecting the two hemispheres.

The surface of the cerebral cortex is characterized by complicated pattern of sulci (singular = sulcus) and gyri (singular = gyrus). Sulcus is a slight depression or groove and gyrus is a raised ridge.

Cerebral cortex is formed by outer gray matter and inner white matter. It has different types of nerve cells along with their processes and neuroglia which are arranged in six layers. It is not uniform throughout. It is thickest at the precentral gyrus and thinnest at the frontal and occipital poles.

■ NEOCORTEX AND ALLOCORTEX

The part of the cerebral cortex that has all six layers of structures is called neocortex. It is also called isocortex or neopallium. It is the phylogenetically new structure of cerebral cortex. Neocortex forms the major portion of cerebral cortex.

The remaining part of cerebral cortex has less than six layers of structures. This part of the cortex is called allocortex. It includes archicortex and paleocortex that form the part of limbic system.

■ LOBES OF CEREBRAL CORTEX

In each hemisphere, there are three surfaces lateral, medial and inferior surfaces. The neocortex of each cerebral hemisphere consists of four lobes (Figs 95-1 to 95-3):

1. Frontal lobe
2. Parietal lobe
3. Occipital lobe
4. Temporal lobe.

The lobes of each hemisphere are demarcated by four main fissures and sulci:

1. Central sulcus or Rolandic fissure between frontal and parietal lobes
2. Parieto-occipital sulcus between parietal and occipital lobe
3. Sylvian fissure or lateral sulcus between parietal and temporal lobes
4. Callosom marginal fissure between temporal lobe and limbic area.

■ CEREBRAL DOMINANCE

Cerebral dominance is defined as the dominance of one cerebral hemisphere over the other in the control of cerebral functions. The two cerebral hemispheres are not functionally equivalent.

Cerebral dominance is related to handedness, i.e. preference of the individual to use right

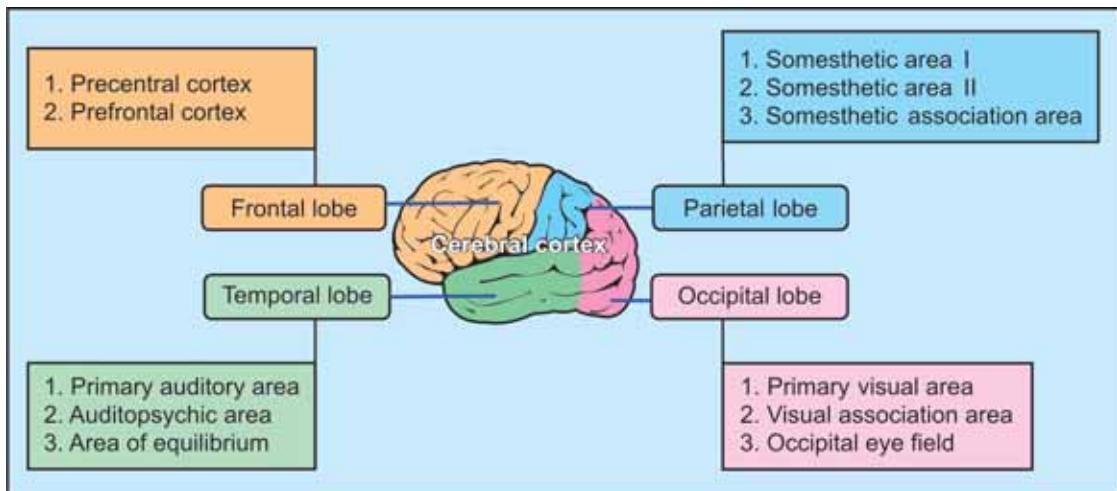


FIGURE 95-1: Parts of cerebral cortex

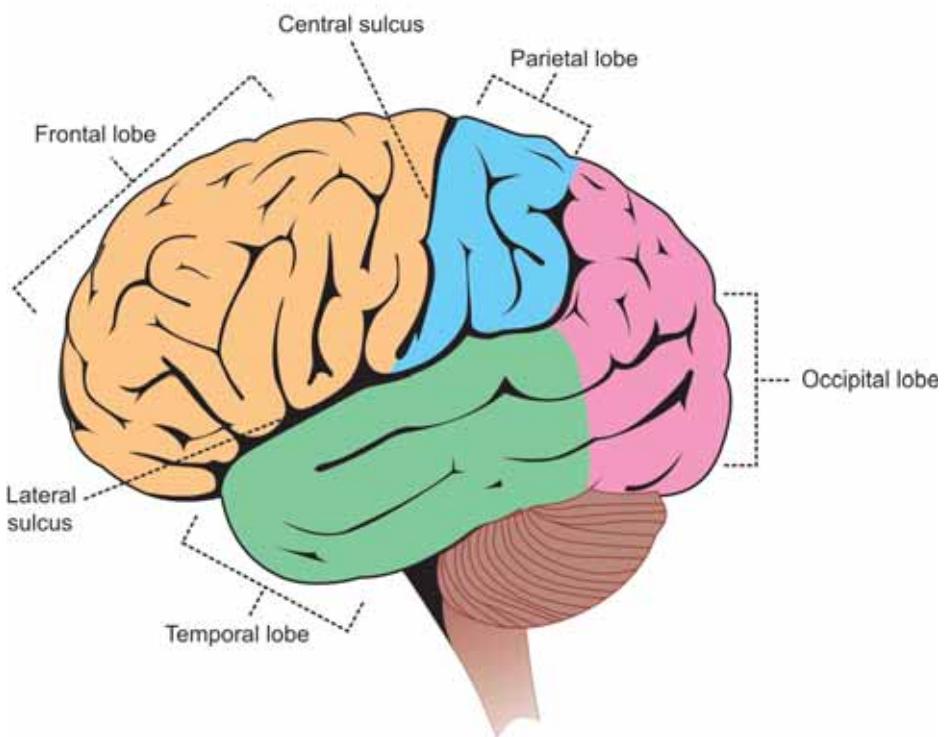


FIGURE 95-2: Lobes of cerebral cortex

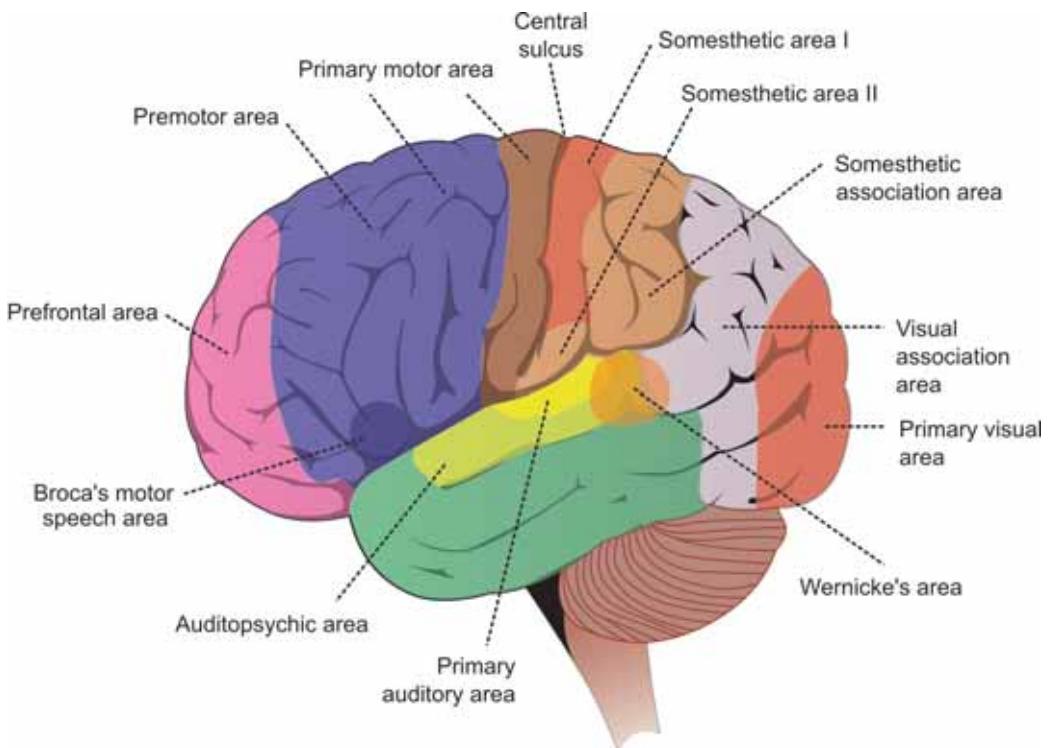
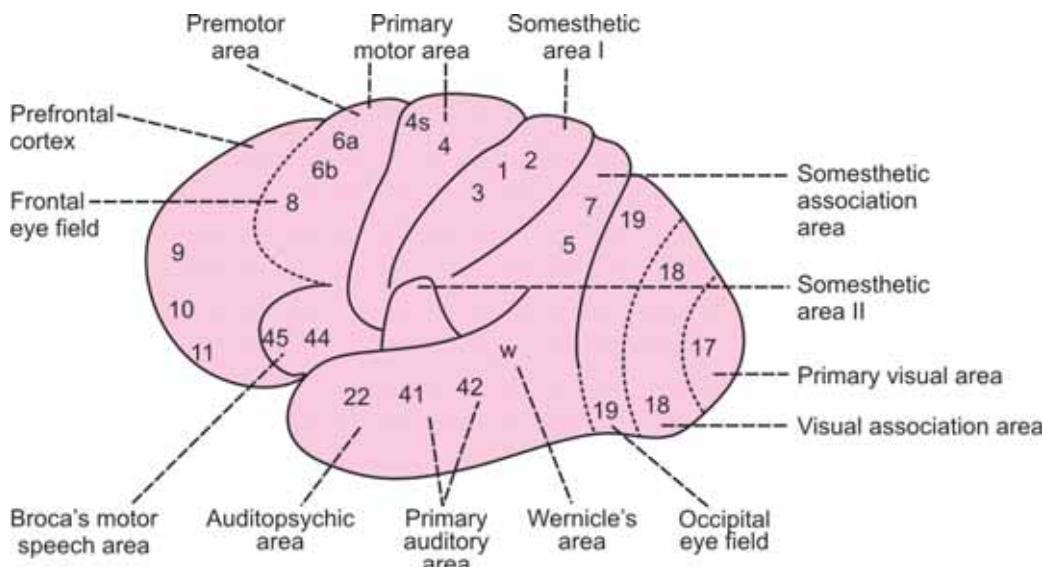


FIGURE 95-3: Functional regions on lateral surface of cerebral cortex



or left hand. More than 90% of people are right handed. In these individuals, the left hemisphere is dominant and it controls the analytical process and language related functions such as speech, reading and writing. Hence, the left hemisphere of these persons is called dominant or categorical hemisphere.

BRODMANN AREAS

Brodmann area is a region of cerebral cortex defined on the basis of organization of neurons. These areas were originally defined and numbered Korbinian Brodmann. Some of these areas were given specific names based on their functions.

FRONTAL LOBE OF CEREBRAL CORTEX

The frontal lobe forms one-third of the cortical surface. It extends from frontal pole to the central sulcus and limited below by the lateral sulcus. The frontal lobe of cerebral cortex is divided into two parts:

- I. Precentral cortex situated posteriorly
- II. Prefrontal cortex situated anteriorly.

■ PRECENTRAL CORTEX

The posterior part of frontal lobe is called precentral cortex. It includes the lip of central sulcus, whole of precentral gyrus and posterior portions of superior, middle and inferior frontal gyri. It also extends to the medial surface.

This part is also called excitomotor cortex or area, since the stimulation of different points in this area causes activity of discrete skeletal muscle. Precentral cortex is further divided into three functional areas (Fig. 95-3):

1. Primary motor area
2. Premotor area
3. Supplementary motor area.

1. Primary Motor Area

It extends throughout the precentral gyrus and the adjoining lip of central sulcus. The areas 4 and 4S are present here (Figs 95-4 and 95-5).

Functions of primary motor area

The primary motor area is concerned with initiation of voluntary movements and speech.

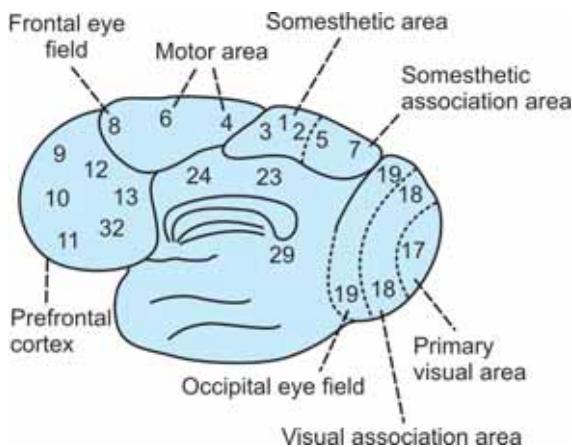


FIGURE 95-5: Medial surface of cerebral cortex

Area 4

It is a tapering strip of area situated in precentral gyrus of frontal lobe (Figs 95-4 and 95-5). Area 4 is the center for movement, as it sends all efferent (corticospinal) fibers of primary motor area. Through the fibers of corticospinal tracts, area 4 activates the lower motor neurons in the spinal cord. It activates both α motor neurons and γ motor neurons simultaneously by the process called coactivation.

Activation of α motor neurons causes contraction of extrafusal fibers of the muscles. Activation of γ motor neurons causes contraction of intrafusal fibers leading to increase in muscle tone.

Localization – homunculus

The muscles of various parts of the body are represented in area 4 in an inverted way from medial to lateral surface. The lower parts of body are represented in medial surface and upper parts of the body are represented in the lateral surface. The order of representation from medial to lateral surface – toes, ankle, knee, hip, trunk, shoulder, arm, elbow, wrist, hand fingers and face. However, parts of the face are not represented in inverted manner (Fig. 95-6).

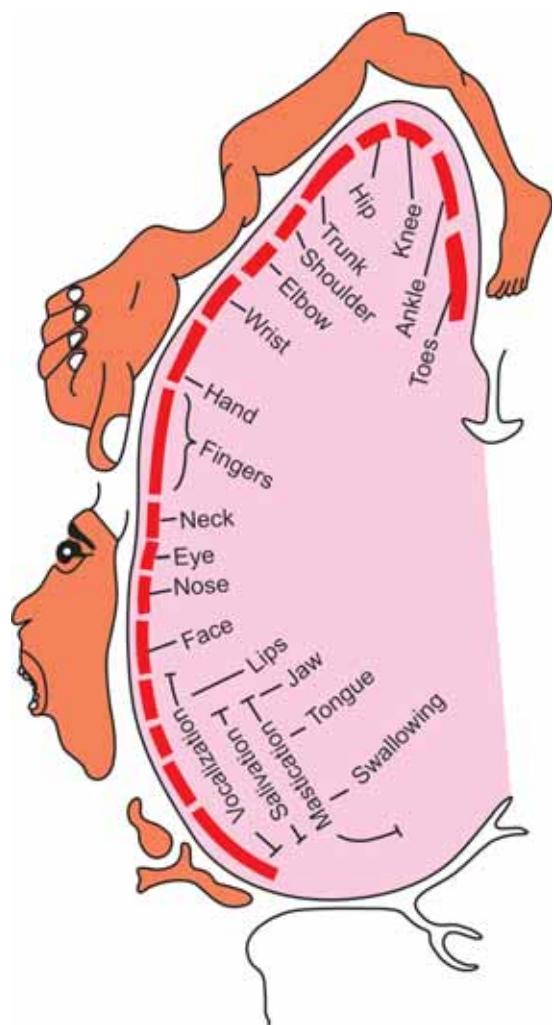


FIGURE 95-6: Topographical arrangement (homunculus) of motor areas in cerebral cortex

Area 4S

Area 4S is called suppressor area. It forms a narrow strip anterior to area 4. It scrutinizes and suppresses the extra impulses produced by area 4 and prevents exaggeration of movements.

2. Premotor Area

This has areas 6, 8, 44 and 45. The premotor area is anterior to primary motor area in the precentral cortex.

Functions of premotor area

The premotor area is concerned with control of postural movements.

Area 6

Area 6 is in the posterior portions of superior, middle and inferior frontal gyri. It is subdivided into 6a and 6b. It gives origin to some of the pyramidal tract fibers.

Area 6 has two functions:

- i. It is concerned with coordination of movements initiated by area 4. It helps to make the skilled movements more accurate and smooth
- ii. It is believed to be the cortical center for extrapyramidal system.

Area 8

Area 8 is called frontal eye field. It lies anterior to area 6 in the precentral cortex. The frontal eye field is concerned with conjugate movement of eyeballs.

Areas 44 and 45 – Broca's Area

The Broca's area is the motor area for speech. It is present in left hemisphere (dominant hemisphere) of right handed persons and in the right hemisphere of left handed persons. It is a special region of premotor cortex situated in inferior frontal gyrus.

Broca's area is responsible for movements of tongue, lips and larynx, which are involved in speech.

3. Supplementary Motor Area

It is situated in medial surface of frontal lobe rostral to primary motor area.

Function of supplementary motor area

The exact function of this area is not understood clearly. It is suggested that it is concerned with coordinated skilled movements.

■ PREFRONTAL CORTEX OR ORBITOFRONTAL CORTEX

It is the anterior part of frontal lobe of cerebral cortex, in front of areas 8 and 44. It occupies the medial, lateral and inferior surfaces and includes orbital gyri, medial frontal gyrus and the anterior portions of superior, middle and inferior frontal gyri.

Areas present in prefrontal cortex are 9, 10, 11, 12, 13, 14, 23, 24, 29 and 32. Areas 12, 13, 14, 23, 24, 29 and 32 are in medial surface. Areas 9, 10 and 11 are in lateral surface.

Area 13 is concerned with emotional reactions.

Functions of Prefrontal Cortex

1. It forms the center for the higher functions like emotion, learning, memory and social behavior. Short term memories are registered here
2. It is the center for planned actions
3. It is the seat of intelligence. So, it is also called the organ of mind
4. It is responsible for the personality of the individuals
5. It is responsible for the various autonomic changes during emotional conditions, because of its connections with hypothalamus and brainstem.

■ APPLIED PHYSIOLOGY – FRONTAL LOBE SYNDROME

The injury or ablation of prefrontal cortex leads to a condition called frontal lobe syndrome. The features of this syndrome are:

1. Emotional instability: There is lack of restraint leading to hostility, aggressiveness and restlessness
2. Lack of concentration and lack of fixing attention
3. There is lack of initiation and difficulty in planning any course of action
4. Impairment of recent memory occurs. However, the memory of remote events is not lost

5. Loss of moral and social sense is common and there is loss of love for family and friends
6. There is failure to realize the seriousness of the condition. The subject has the sense of well being and also has flight of ideas
7. Apart from behavioral changes, there are some functional abnormalities also
 - i. Hyperphagia (increased food intake)
 - ii. Loss of control over sphincter of the urinary bladder or rectum
 - iii. Disturbances in orientation
 - iv. Slight tremor.

■ PARIETAL LOBE

Parietal lobe extends from central sulcus and merges with occipital lobe behind and temporal lobe below. This lobe is separated from occipital lobe by parieto-occipital sulcus and from temporal lobe by Sylvian sulcus. Parietal lobe is divided into three functional areas:

- A. Somesthetic area I
- B. Somesthetic area II
- C. Somesthetic association area.

In addition to these three areas, a part of sensory motor area is also situated in parietal lobe (see below).

■ SOMESTHETIC AREA I

It is also called somatosensory area I or primary somesthetic or primary sensory area. It is present in the posterior lip of central sulcus, in the postcentral gyrus and in the paracentral lobule.

Areas

This part of parietal lobe has three areas which are called areas 3, 1 and 2. The anterior part of this forms area 3 and posterior part forms areas 1 and 2.

Localization – Homunculus

The different sensory areas of the body are represented in postcentral gyrus (primary sensory area) in an inverted manner as in the motor area. The toes are represented in lowest

part of medial surface, legs at the upper border of hemispheres, then from above downwards knee, thigh, hip, trunk, upper limb, neck and face. The representation of face is not inverted. The representation of parts of face from above downwards is eyelids, nose, cheek, upper lip and lower lip (Fig. 95-7).

Functions

1. The somesthetic area I is responsible for perception and integration of cutaneous and kinesthetic sensations. It receives sensory impulses from cutaneous receptors (touch,

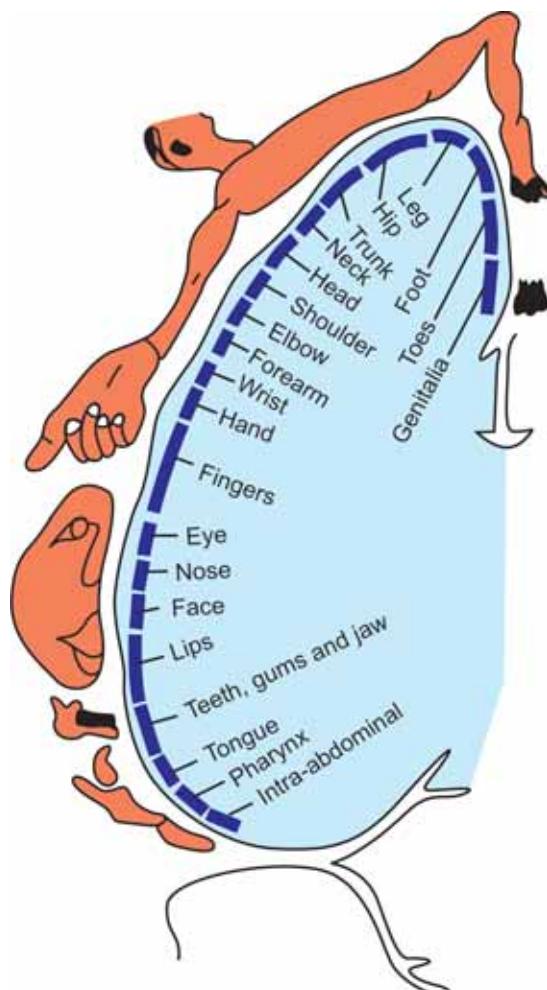


FIGURE 95-7: Topographical arrangement (homunculus) of sensory areas in cerebral cortex

pressure, pain, temperature) and proprioceptors of opposite side through thalamic radiation. Area 1 is concerned with sensory perception. The areas 2 and 3 are involved in the integration of these sensations.

2. This area sends sensory feedback to the premotor area. It is also concerned with the movements of head and eyeballs.
3. Discriminative functions: In addition to perception of cutaneous and kinesthetic sensation, this area is also responsible for recognizing the discriminative features of sensations.

■ SOMESTHETIC AREA II

It is situated in postcentral gyrus below the area of face of somesthetic area I. A part of this is buried in Sylvian sulcus. It is also known as somatosensory area II.

This area receives sensory impulses from somesthetic area I and from thalamus directly. Though the exact role of this area is not clear, it is concerned with perception of sensation. Thus, the sensory parts of body have two representations — in somesthetic area I and area II.

■ SOMESTHETIC ASSOCIATION AREA

This area is situated posterior to postcentral gyrus, above the auditory cortex and in front of visual cortex. It has two areas – 5 and 7. It is concerned with synthesis of various sensations perceived by somesthetic area I. Thus, the somesthetic association area forms the center for combined sensations like stereognosis. The lesion of this area causes astereognosis.

Sensormotor Area

The sensory area of cortex is not limited to postcentral gyrus in parietal lobe. It extends anteriorly into motor area in precentral gyrus of frontal lobe. Similarly, the motor area is extended from precentral gyrus posteriorly into postcentral gyrus.

Thus, the precentral and postcentral gyri are knit together by association neurons and are functionally interrelated. So, this area is called sensormotor area.

The function of sensory motor area is to store the timing and programming of various sequential movements of complicated skilled movements which are planned by neocerebellum (Chapter 93).

■ APPLIED PHYSIOLOGY

Lesion or ablation of parietal lobe (sensory cortex) results in the following disturbances:

1. Contralateral disturbance of cutaneous sensations
2. Disturbances in kinesthetic sensations
3. Loss of tactile localization and discrimination.

■ TEMPORAL LOBE

Temporal lobe of cerebral cortex includes three functional areas

- A. Primary auditory area
- B. Auditopsychic area
- C. Area for equilibrium.

■ PRIMARY AUDITORY AREA

Primary auditory area includes:

1. Area 41
2. Area 42
3. Wernicke's area.

Areas 41 and 42 are situated in anterior transverse gyrus and lateral surface of superior temporal gyrus. Wernicke's area is in upper part of superior temporal gyrus posterior to areas 41 and 42.

Functions

Primary auditory area is concerned with perception of auditory impulses, analysis of pitch and determination of intensity and source of sound.

Areas 41 and 42 are concerned only with the perception of auditory impulses. Wernicke's area is responsible for the interpretation of sound. It carries out this function with the help of auditopsychic area (area 22).

■ AUDITOPSYCHIC AREA

It is the area 22 and it occupies the superior temporal gyrus. This area is concerned with

interpretation of auditory sensation along with Wernicke's area.

■ AREA FOR EQUILIBRIUM

This area is in the posterior part of superior temporal gyrus. It is concerned with the maintenance of equilibrium of the body. Stimulation of this area causes dizziness, swaying, falling and feeling of rotation.

■ APPLIED PHYSIOLOGY – TEMPORAL LOBE SYNDROME

Temporal lobe syndrome is otherwise known as Kluver-Bucy syndrome. It is observed in animals, particularly monkeys after the bilateral ablation of temporal lobe along with amygdaloid and uncus. It occurs in human beings during bilateral lesions of these structures. The manifestations of this syndrome are:

1. Aphasia: Disturbance in speech
2. Auditory disturbances: Such as frequent attacks of tinnitus, auditory hallucinations with sounds like buzzing, ringing or humming.
Tinnitus means noise in the ear. Hallucination means feeling of a particular type of sensation without any stimulus
3. Disturbances in smell and taste sensations
4. Dreamy states: The patients are not aware of their own activities and, have the feeling of unreality
5. Visual hallucinations associated with hemianopia.

■ OCCIPITAL LOBE – VISUAL CORTEX

Occipital lobe is also called the visual cortex.

■ AREAS OF OCCIPITAL LOBE

The occipital lobe consists of three functional areas:

1. Primary visual area – area 17
2. Visual association area – area 18
3. Occipital eye field – area 19.

Functions

1. Primary visual area – area 17 is concerned with perception of visual impulses

2. Visual association area – area 18 is concerned with interpretation of visual impulses
3. Occipital eye field – area 19 is concerned with movement of eyes.

■ APPLIED PHYSIOLOGY

Lesion in the upper or lower part of visual cortex results in hemianopia. Bilateral lesion leads to total blindness. Refer Chapter 106 for details.

■ LIMBIC SYSTEM OR LIMBIC LOBE

Limbic system or limbic lobe is a complex system of cortical and subcortical structures that form a ring around the hilus of cerebral hemisphere (Fig. 95-8). Limbus means ring.

■ COMPONENTS

Structures of limbic system are classified into four groups:

- I. Achicortical structures
- II. Paleocortical structures
- III. Juxtaglomerular structures
- IV. Subcortical structures.

The structures of each group are given in Fig. 95-9.

■ FUNCTIONS

1. *Olfaction*

The pyriform cortex and amygdaloid nucleus form the olfactory centers.

2. *Regulation of Endocrine Glands*

Hypothalamus plays an important role in regulation of endocrine secretion (Chapter 45).

3. *Regulation of Autonomic Functions*

Hypothalamus plays an important role in regulating the autonomic functions (Chapter 92) such as heart rate, blood pressure, water balance and body temperature.

4. *Regulation of Food Intake*

Along with amygdaloid complex, the feeding center and satiety center present in hypothalamus regulate food intake (Chapter 92).

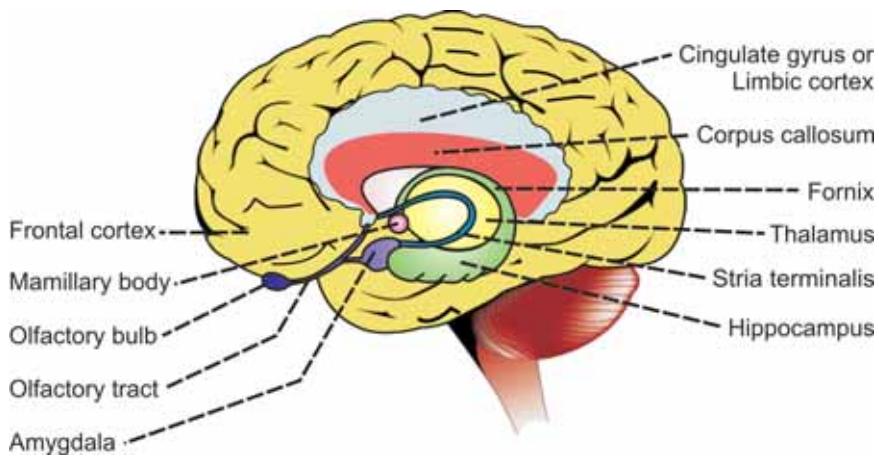


FIGURE 95-8: Major components of limbic system

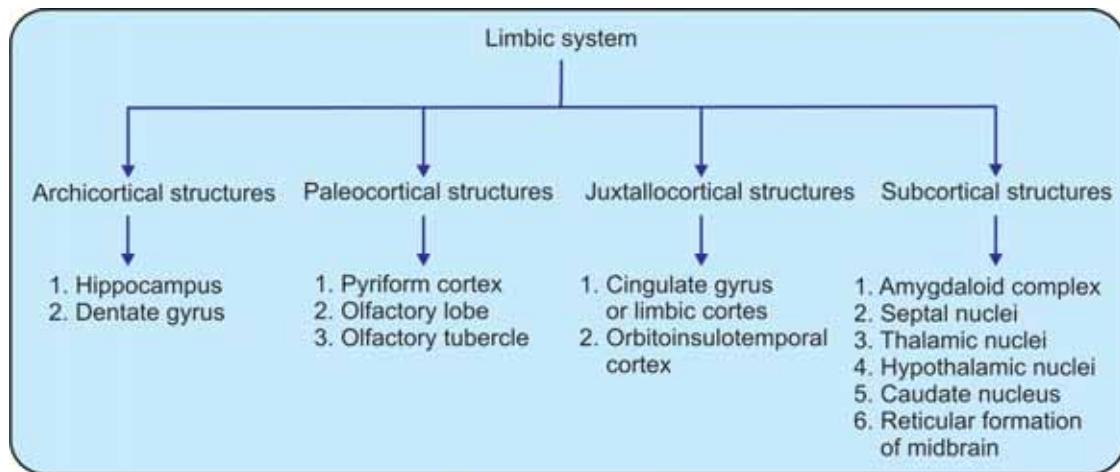


FIGURE 95-9: Components of limbic system

5. Control of Circadian Rhythm

Hypothalamus is taking major role in the circadian fluctuations of various physiological activities.

6. Regulation of Sexual Functions

Hypothalamus is responsible for maintaining sexual functions.

7. Role in Emotional State

The emotional state of a person is maintained by hippocampus along with hypothalamus.

8. Role in Memory

Hippocampus and Papez circuit play an important role in memory (Chapter 101).

9. Role in Motivation

Reward and punishment centers present in hypothalamus and other structures of limbic system are responsible for motivation and the behavior pattern of human beings (Chapter 92).

Refer Chapter 92 for details of the hypothalamic functions.

Reticular Formation

- DEFINITION
- SITUATION
- DIVISIONS
- FUNCTIONS

- ASCENDING RETICULAR ACTIVATING SYSTEM (ARAS)
- DESCENDING RETICULAR SYSTEM

■ DEFINITION

Reticular formation is a diffused mass of neurons and nerve fibers forming an ill-defined meshwork of reticulum in the central portion of the brainstem.

■ SITUATION OF RETICULAR FORMATION

The reticular formation is situated in brainstem. It extends downwards into spinal cord and upwards up to thalamus and subthalamus.

■ DIVISIONS OF RETICULAR FORMATION

Reticular formation is divided into three divisions based on the location in brainstem:

1. Medullary reticular formation
2. Pontine reticular formation
3. Midbrain reticular formation.

Each division of reticular formation has its own collection of nuclei.

■ FUNCTIONS OF RETICULAR FORMATION

Based on functions, the reticular formation along with its connections is divided into two systems.

- I. Ascending reticular activating system
- II. Descending reticular system.

■ ASCENDING RETICULAR ACTIVATING SYSTEM (ARAS)

ARAS begins in lower part of brainstem, extends upwards through pons, midbrain, thalamus and finally projects throughout the cerebral cortex. It projects into cerebral cortex via subthalamus and thalamus.

The ARAS receives fibers from the sensory pathways via long ascending spinal tracts (Fig. 96-1).

Functions of ARAS

1. ARAS is concerned with arousal phenomenon, alertness, maintenance of attention

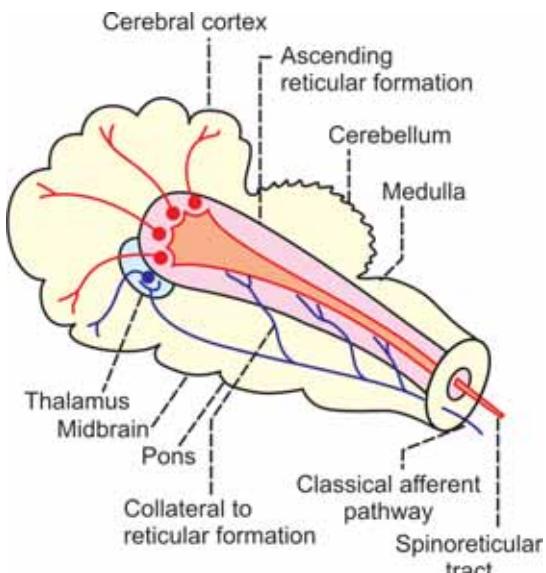


FIGURE 96-1: Ascending reticular formation

and wakefulness. Hence, it is called ascending reticular activating system. Stimulation of midbrain reticular formation produces wakefulness by generalized activation of entire brain including cerebral cortex, thalamus, basal ganglia and brainstem. Any type of sensory impulses such as impulses of proprioception, pain, auditory, visual, taste, and olfactory sensations cause sudden activation of the ARAS producing arousal phenomenon in animals and human beings. Even the impulses of visceral sensations activate this system. The sympathetic stimulation and adrenaline cause arousal by affecting midbrain

2. ARAS also causes emotional reactions
3. ARAS plays an important role in regulating the learning processes and the development of conditioned reflexes.

Mechanism of Action of ARAS

The impulses of all the sensations reach the cerebral cortex through two channels:

1. Classical or specific sensory pathways
2. Ascending reticular activating system or nonspecific sensory pathway

1. Classical or specific sensory pathways

Classical sensory pathways are the pathways which transmit the sensory impulses from receptors to cerebral cortex via thalamus. Some of the pathways carry impulses of a particular sensation only. For example, the auditory stimulus transmitted by the auditory pathway reaches the auditory cortex via thalamus and causes perception of sound. Such classical sensory pathways are called specific sensory pathways.

2. Ascending reticular activating system or nonspecific sensory pathway

All the sensory pathways send collaterals to diffused areas of ARAS. It also receives afferents from spinal cord directly in the form of spinoreticular tract. ARAS in turn sends the impulses to almost all the areas of cerebral cortex and other parts of brain. Hence, this pathway is called the nonspecific sensory pathway.

The nonspecific projection of ARAS into the cortex is responsible for the arousal, alertness and wakefulness. The sensory impulses transmitted directly to cortex via classical pathway causes perception of only the particular sensation. Whereas, the impulses transmitted to cortex via ARAS do not cause the perception of any particular sensation but cause the generalized activation of almost all the areas of cerebral cortex and other parts of brain. This leads to reactions of arousal, alertness and wakefulness.

The ARAS in turn is controlled by the feedback signals from cerebral cortex. Also, an inhibitory system controls the activities of ARAS. The inhibitory system involves posterior hypothalamus, intralaminar and anterior thalamic nuclei and medullary area at the level of tractus solitarius.

The tumor or lesion in ARAS leads to sleeping sickness or coma. The impact of head injury on ARAS also causes coma.

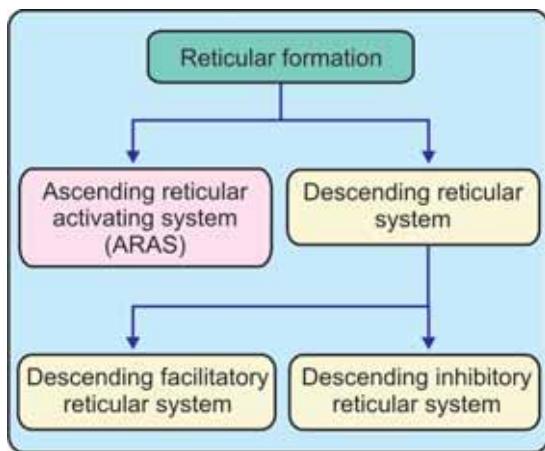


FIGURE 96-2: Functional divisions of reticular formation

■ DESCENDING RETICULAR SYSTEM

The descending reticular system includes reticular formation in brainstem, the reticulospinal tract and reticular formation in spinal cord.

It modifies the activities of spinal motor neurons. Functionally, descending reticular system is divided into two subdivisions (Fig. 96-2):

- I. Descending facilitatory reticular system
- II. Descending inhibitory reticular system.

Descending Facilitatory Reticular System

Descending facilitatory reticular system is present in upper and lateral reticular formation. Its functions are:

1. *Facilitation of somatomotor activities by:*
 - i. Exciting the gamma motor neurons in spinal cord and increasing muscle tone
 - ii. Accelerating movements of the body
 - iii. Causing wakefulness and alertness.
2. *Facilitation of vegetative functions:*
Descending facilitatory reticular system is the center for facilitation of the autonomic functions such as cardiac function, blood pressure, respiration, gastrointestinal function and body temperature.

Descending Inhibitory Reticular System

Descending inhibitory reticular system is located in a small area in lower and medial reticular formation. Its functions are:

1. *Control of somatomotor activities by:*
 - i. Inhibiting gamma motor neurons of spinal cord and decreasing muscle tone
 - ii. Inhibiting the α motor neurons of spinal cord and producing smooth and accurate voluntary movements
 - iii. Controlling the reflex movements.
2. *Control of vegetative functions:*

The descending inhibitory reticular system is the center for inhibition of several autonomic functions such as cardiac function, blood pressure, respiration, gastrointestinal function and body temperature.

Posture and Equilibrium

- DEFINITION
- PROPRIOCEPTORS
 - MUSCLE SPINDLE
 - GOLGI TENDON ORGAN
 - PACINIAN CORPUSCLE
 - FREE NERVE ENDING
- BASIC PHENOMENA OF POSTURE
 - MUSCLE TONE
 - STRETCH REFLEX
- POSTURAL REFLEXES
 - CLASSIFICATION OF POSTURAL REFLEXES
 - STATIC REFLEXES
 - STATOKINETIC REFLEXES

■ DEFINITION

Subconscious adjustment of tone in the different muscles in relation to every movement is known as the posture. The significance of posture is to make the movement smooth and accurate and to maintain the line of gravity constant or to keep the body in equilibrium with the line of gravity. Posture is not the active movement. It is the passive movement associated with redistribution of tone in different groups of related muscles.

Proprioceptors play a major role in the maintenance of posture and equilibrium.

■ PROPRIOCEPTORS

Proprioceptors are the receptors, which give response to change in the position of different parts of the body. These receptors are also called kinesthetic receptors.

Proprioceptors are situated in labyrinth, muscles, tendon of the muscles, joints, ligaments and fascia.

Different proprioceptors are:

1. Muscle spindle
2. Golgi tendon organ
3. Pacinian corpuscle
4. Free nerve ending
5. Proprioceptors in labyrinth

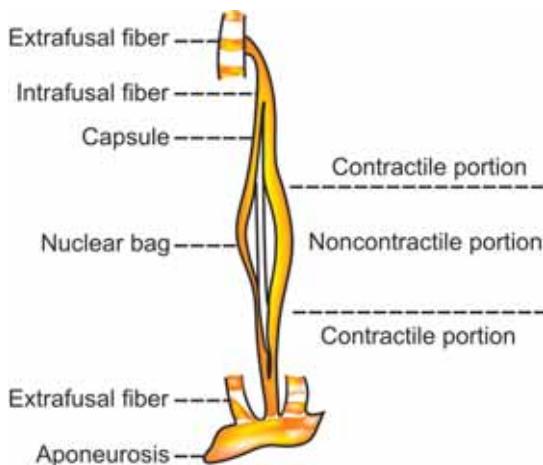


FIGURE 97-1: Muscle spindle

Proprioceptors in labyrinth are described in the next chapter.

■ MUSCLE SPINDLE

Muscle spindle is a spindle shaped proprioceptor situated in the skeletal muscle. It is formed by modified skeletal muscle fibers called intrafusal muscle fibers.

Structure of Muscle Spindle

The muscle spindle has a central bulged portion and two tapering ends. Each muscle spindle is formed by 5 to 12 intrafusal muscle fibers. All these fibers are enclosed by a capsule, which is formed by connective tissue. The intrafusal fibers are attached to the capsule on either end. The capsule is attached to either side of extrafusal fibers or the tendon of the muscle. Thus, the intrafusal fibers are placed parallel to the extrafusal fibers.

The intrafusal fibers are thin and striated (Fig. 97-1). The central portion of the intrafusal fibers does not contract because it has only few or no actin and myosin filaments. So, this portion acts only as a receptor. Only the end portion of the intrafusal fibers can contract. The discharge from the gamma motor neurons causes the contraction of the intrafusal fibers.

Types of Intrafusal Fibers

The muscle spindle is formed by two types of intrafusal fibers.

1. *Nuclear bag fiber*

The central portion of this fiber is enlarged like a bag and contains many nuclei. Hence, it is called the nuclear bag fiber.

2. *Nuclear chain fiber*

In this fiber, the central portion is not bulged and the nuclei are arranged in the center in the form of a chain. The nuclear chain fiber is attached to the side of end portion of the nuclear bag fiber.

Nerve Supply to Muscle Spindle

The muscle spindle is innervated by both sensory and motor nerves. It is the only receptor in the body, which has both sensory and motor nerve supply.

Sensory nerve supply

Each muscle spindle receives two types of sensory nerve fibers:

1. *Primary sensory nerve fiber:* It belongs to type I α (A α) nerve fiber. Each sensory (afferent) nerve fiber has two branches. One of the branches supplies the central portion of nuclear bag fiber (Fig. 97-2). The other branch ends in the central portion of the nuclear chain fiber. The branches end in the form of rings around the central portion of the nuclear bag and nuclear chain fibers. Therefore, these nerve endings are called annulospiral endings.
2. *Secondary sensory nerve fiber:* It is a type II (A β) nerve fiber. It innervates only the nuclear chain fiber and ends near the end portion of nuclear chain fiber like the petals of the flower. So, the nerve ending is called the flower spray ending.

Motor nerve supply

Motor nerve fiber supplying the muscle spindle belongs to gamma motor neuron (A γ) type.

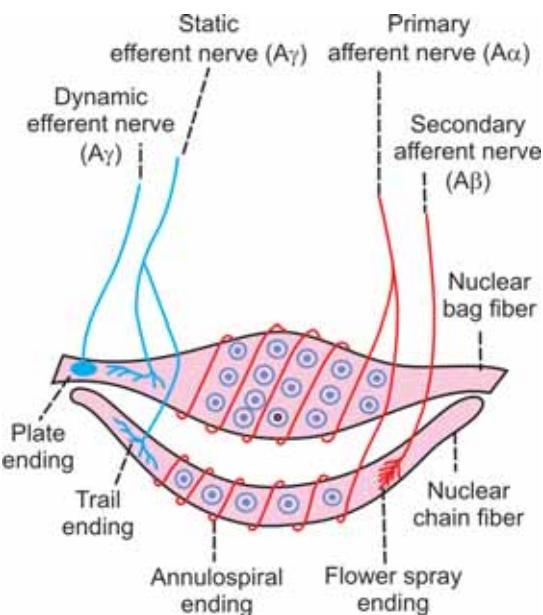


FIGURE 97-2: Nerve supply to muscle spindle. Red = Afferent (sensory) nerve fibers. Blue = Efferent (motor) nerve fibers. Letters in parenthesis indicate the type of nerve fibers

1. *Motor nerve supply to nuclear bag fiber:* The gamma motor nerve fiber supplying nuclear bag fiber ends as motor end plate. This nerve ending is called plate ending. Functionally, it is known as dynamic gamma efferent (motor) nerve fiber.
2. *Motor nerve supply to nuclear chain fiber:* The gamma motor nerve fiber supplying the nuclear chain fiber divides into many branches, which form a network called trail ending. Functionally, it is known as static gamma efferent (motor) nerve fiber. Sometimes, it gives a branch to nuclear bag fiber also.

Functions of Muscle Spindle

Muscle spindle gives response to change in the length of the muscle. It detects how much the muscle is being stretched and sends this information to central nervous system via sensory nerve fibers. The information is processed in central nervous system to determine the position of different parts of the body.

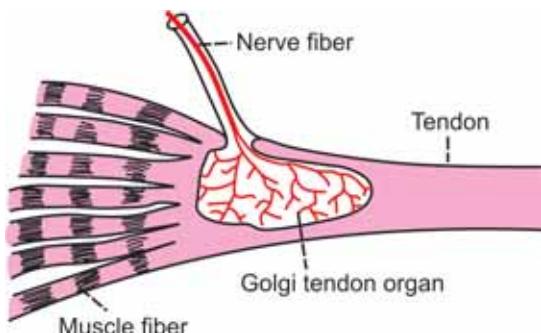


FIGURE 97-3: Golgi tendon apparatus

By detecting the change in length of the muscle, the spindle plays an important role in stretch reflex and maintenance of muscle tone (see below).

■ GOLGI TENDON ORGAN

Golgi tendon organ is situated in the tendon of skeletal muscle near the attachment of extrafusal fibers. It is placed in series between the muscle fibers and the tendon. Golgi tendon organ is formed by a group of nerve endings covered by a connective tissue capsule (Fig. 97-3).

Nerve Supply to Golgi Tendon Organ

The sensory nerve fiber supplying Golgi tendon organ belongs to Ib type.

Functions of Golgi Tendon Organ

The Golgi tendon organ gives response to the change in the force or tension developed in the skeletal muscle during contraction.

■ PACINIAN CORPUSCLE

Pacinian corpuscle is a mechanoreceptor that senses pressure and vibration. It is situated in the deeper layers of skin. It is also situated in the tissues surrounding the joints such as fascia over the muscle, tendons, and joint capsule. The pacinian corpuscles situated in these tissues send information about joint position to central nervous system.

■ FREE NERVE ENDING

Free nerve ending is the receptor for pain sensation situated in skin, muscles, tendon, fascia and joints. It is stimulated during some specific joint positions. In turn, it sends information about joint position to central nervous system.

■ BASIC PHENOMENA OF POSTURE

The basic phenomena for maintenance of posture are the muscle tone and stretch reflex.

■ MUSCLE TONE

Definition

Muscle tone is defined as the state of continuous and passive partial contraction of the muscle with certain vigor and tension. It is also called tonus.

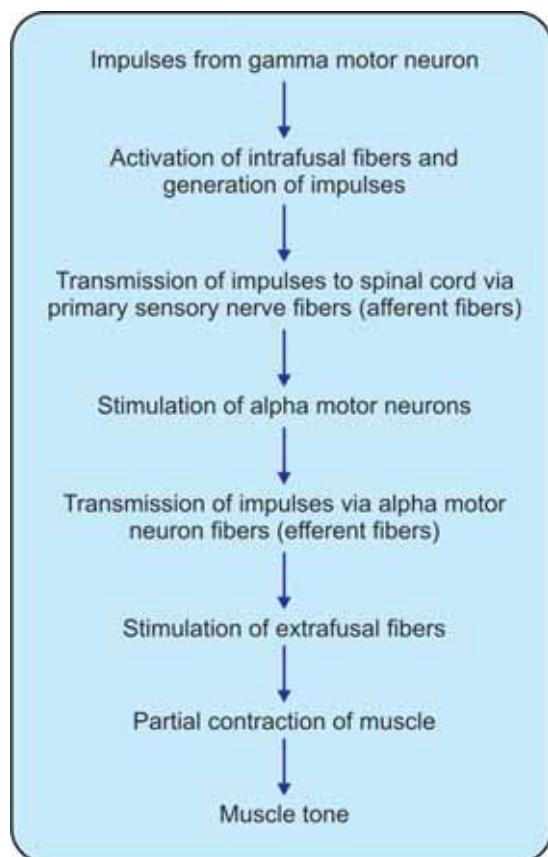


FIGURE 97-4: Schematic diagram showing development of muscle tone

It is also defined as resistance offered by the muscle to stretch.

Significance of Muscle Tone

Muscle tone plays an important role in maintenance of posture. Change in muscle tone enables movement of different parts of the body. Muscle tone is present in all the skeletal muscles. However, it is more in the antigravity muscles such as extensors of lower limb, trunk muscles and neck muscles.

Development of Muscle Tone

Gamma motor neurons and muscle spindle are responsible for the development and maintenance of muscle tone (Figs 97-4 and 97-5).

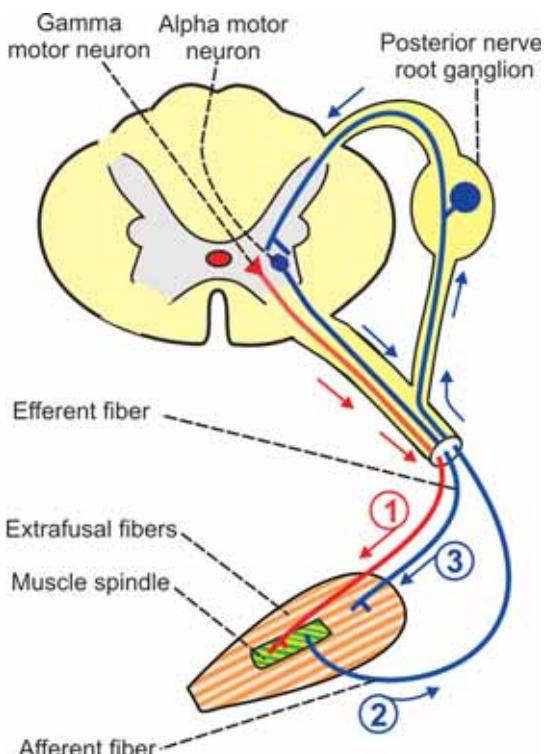


FIGURE 97-5: Development of muscle tone.
1. Impulses from γ motor neuron stimulate muscle spindle. 2. Afferent impulses from muscle spindle to α motor neuron. 3. Efferent impulses from α motor neuron produce contraction of extrafusal fibers and develop muscle tone

The muscle tone is purely a reflex process. This reflex is a spinal segmental reflex. It is developed by continual synchronous discharge of motor impulses from the gamma motor neurons present in the anterior gray horn of the spinal cord.

Regulation of Muscle Tone

Though the muscle tone is developed by discharges from gamma motor neurons, it is maintained continuously and regulated by some supraspinal centers situated in different parts of brain. Some of these centers increase the muscle tone by sending facilitatory impulses while other centers decrease the muscle tone by inhibitory impulses.

■ STRETCH REFLEX

Stretch reflex is the reflex contraction of muscle when it is stretched. It is also called myotatic reflex. It is a monosynaptic reflex and the quickest of all the reflexes. The extensor muscles, particularly the antigravity muscles exhibit a severe and prolonged contraction during stretch reflex.

Stimulation of muscle spindle elicits the stretch reflex. The intrafusal muscle fibers are situated parallel to the extrafusal muscle fibers and are attached to the tendon of the muscle by means of capsule. So, stretching of the muscle causes stretching of the muscle spindle also. This stimulates the muscle spindle and it discharges the sensory impulses. These impulses are transmitted via the primary and secondary sensory nerve fibers to the alpha motor neurons in spinal cord. Alpha motor neurons in turn send motor impulse to muscles through their fibers and cause contraction of extrafusal fibers.

Stretch reflex is the basic reflex involved in maintenance of posture. It is particularly responsible to maintain the body in an upright position.

■ POSTURAL REFLEXES

Postural reflexes are the reflexes which are responsible for the maintenance of posture. The afferent impulses for the maintenance of posture

arise from proprioceptors, vestibular apparatus and retina of the eye and reach the centers in central nervous system. The centers, which maintain the posture, are located at different levels of central nervous system particularly cerebral cortex, cerebellum, brainstem and spinal cord. These centers send motor impulses to the different groups of skeletal muscles so that appropriate movements occur to maintain the posture.

■ CLASSIFICATION OF POSTURAL REFLEXES

The postural reflexes are generally classified into two groups:

- A. Static reflexes
- B. Statokinetic reflexes

■ STATIC REFLEXES

Static reflexes are the postural reflexes that maintain posture at rest. Static reflexes are of four types:

- I. General static reflexes or righting reflexes
- II. Local static reflexes or supporting reflexes
- III. Segmental static reflexes
- IV. Statotonic or attitudinal reflexes

I. General Static Reflexes or Righting Reflexes

General static reflexes are otherwise called righting reflexes because these reflexes help to maintain an upright position of the body. Righting reflexes help to govern the orientation of the head in space, position of the head in relation to the body and appropriate adjustment of the limbs and eyes in relation to the position of the head, so that upright position of the body is maintained.

When a cat, held with its back downwards, is allowed to fall through the air, it lands upon its paws, with the head and body assuming the normal attitude in a flash. A fish resists any attempt to turn it from its normal position and if it is placed in water upon its back, it flips almost instantly into the normal swimming position. All these actions occur because of the righting reflexes.

The righting reflexes consist of a chain of reactions which occur one after another in an orderly sequence. Each reflex causes the development of the succeeding one.

The righting reflexes are divided into five types:

1. Labyrinthine righting reflexes acting upon the neck muscles
2. Neck righting reflexes acting upon the body
3. Body righting reflexes acting upon the head
4. Body righting reflexes acting upon the body
5. Optical righting reflexes.

The first four reflexes are easily demonstrated on a thalamic animal or a normal animal, which is blindfolded.

Sequential events of righting reflexes

1. When the animal is placed upon its back, the labyrinthine reflexes acting upon the neck muscles turn the head into its normal position in space, in relation to the body
2. The proprioceptive reflexes of the neck muscles then bring the body into its normal position in relation to the position of head
3. When resting upon a rigid support, these reflexes are reinforced by the body righting reflexes on head as well as on the body

4. If the animal happens to be a labyrinthectomized one, then it makes an attempt to recover its upright position as a result of operation of the optical righting reaction. If the optical righting reflexes are abolished by covering the eyes, the righting ability is lost.

Optical righting reflexes are also demonstrated in 3 or 4 weeks old baby. When laid down on belly, i.e. prone position, the baby tries to raise the head to a vertical position.

Centers for righting reflexes

The centers for the first four righting reflexes are in the red nucleus situated in midbrain. The center for the optical righting reflexes is in the occipital lobe of cerebral cortex (Table 97-1).

II. Local Static Reflexes or Supporting Reflexes

Local static reflexes or the supporting reactions support the body in different positions against the gravity and also protect the limbs against hyperextension or hyperflexion.

The supporting reactions are classified into two types:

1. Positive supporting reflexes
2. Negative supporting reflexes.

TABLE 97-1: Static postural reflexes

Reflex	Center
General static reflexes (Righting reflexes)	1. Labyrinthine righting reflexes acting upon the neck muscles
	2. Neck righting reflexes acting upon body
	3. Body righting reflexes acting upon head
	4. Body righting reflexes acting upon body
	5. Optical righting reflexes
Local static reflexes	1. Positive supporting reflexes
	2. Negative supporting reflexes
Segmental static reflexes	1. Crossed extensor reflex
Statotonic or attitudinal reflexes	1. Tonic labyrinthine and neck reflexes acting on limbs
	2. Labyrinthine and neck reflexes acting upon eyes

1. Positive supporting reflexes

Positive supporting reflexes are the reactions, which help to fix the joints and make the limbs rigid like pillars, so that limbs can support the weight of the body against gravity.

The positive supporting reflexes are developed while standing. The body is supported against gravity while standing by the simultaneous reflex contractions of both extensor and flexor muscles and other opposing muscles. The impulses for these reflexes arise from proprioceptors present in the muscles, joints and tendons and the exteroceptors, particularly pressure receptors present in deeper layers of the skin of sole.

2. Negative supporting reflexes

Relaxation of the muscles and unfixing of the joints enable the limbs to flex and move to a new position. It is called negative supporting reaction. It is brought about by raising the leg off the ground and plantar flexion of toes and ankle. When the leg is lifted off the ground, the exteroceptive impulses are stopped. When the toes and ankle joints are plantar flexed, the stretch stimulus for the plantar muscles is stopped. It causes unlocking of the limbs and facilitates new movement.

The centers for the supporting reflexes are located in the spinal cord.

III. Segmental Static Reflexes

The segmental static reflexes are essential for walking. During walking, in one leg, the flexors are active and the extensors are inhibited. On the opposite leg, the flexors are inhibited and extensors are active. Thus, the flexors and extensors of the same limb are not active simultaneously. It is known as crossed extensor reflex. It is due to the reciprocal inhibition and the neural mechanism responsible for this reflex is called reciprocal innervation.

The centers for these reflexes are situated in the spinal cord.

IV. Statotonic or Attitudinal Reflexes

Statotonic or attitudinal reflexes are developed according to the attitude of the body and are of two types:

1. Tonic labyrinthine and neck reflexes acting on the limbs
 2. Labyrinthine and neck reflexes acting upon the eyes.
1. *Tonic labyrinthine and neck reflexes acting on the limbs*

These reflexes maintain the movements of limbs in accordance to the position of the head. When the head of an animal is dorsiflexed, all the four limbs are extended and, when the head is ventriflexed, all the four limbs are flexed.

2. *Labyrinthine and neck reflexes acting upon the eyes*

According to the changes in the position of the head and neck, the eyes also move. These reflexes arise from labyrinth and neck muscles. Turning the head downward causes upward movement of the eyes. The eyes remain in this position as long as the position of the head is retained.

The centers for the statotonic reflexes are present in the medulla oblongata.

■ STATOKINETIC REFLEXES

Statokinetic reflexes are the postural reflexes that maintain posture during movement. These reflexes are concerned with both angular (rotatory), and linear (progressive) movements. The vestibular apparatus is responsible for these reflexes (Chapter 98).

Vestibular Apparatus

- INTRODUCTION
- LABYRINTH
- FUNCTIONAL ANATOMY OF VESTIBULAR APPARATUS
- RECEPTOR ORGAN OF VESTIBULAR APPARATUS
- NERVE SUPPLY TO VESTIBULAR APPARATUS
- FUNCTIONS OF VESTIBULAR APPARATUS
- APPLIED PHYSIOLOGY

■ INTRODUCTION

Vestibular apparatus is the part of labyrinth or inner ear. It plays an important role in maintaining posture and equilibrium through statokinetic reflexes. The other part of labyrinth is the cochlea, which is concerned with sensation of hearing.

■ LABYRINTH

Labyrinth (inner ear) consists of two structures, bony labyrinth and membranous labyrinth.

Bony labyrinth is a series of cavities or channels present in the petrous part of temporal bone. Membranous labyrinth is situated inside bony labyrinth (Fig. 98-1). The space between bony labyrinth and membranous labyrinth is filled with a fluid called perilymph which is similar to ECF in composition.

The membranous labyrinth consists of two portions:

1. Cochlea which is concerned with sensation of hearing (Chapter 110)

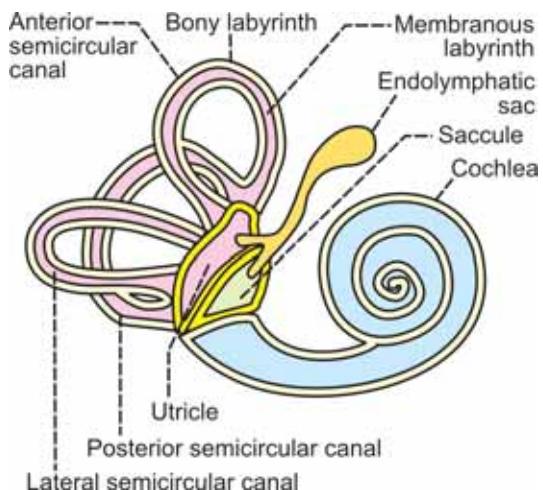


FIGURE 98-1: Labyrinth

2. Vestibular apparatus which is concerned with posture and equilibrium.

The membranous labyrinth is filled with a fluid called endolymph which is similar to ICF in composition.

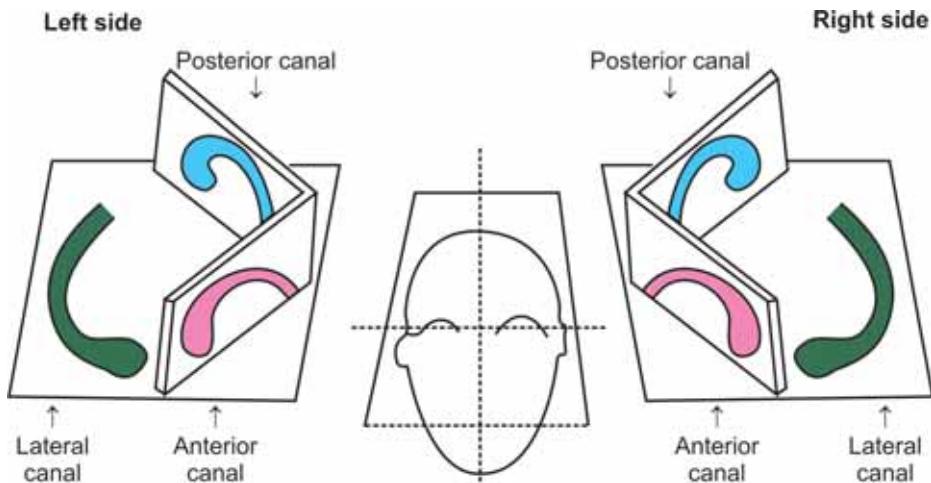


FIGURE 98-2: Position of semicircular canals

■ FUNCTIONAL ANATOMY OF VESTIBULAR APPARATUS

Vestibular apparatus is formed by three semicircular canals and otolith organ or vestibule.

■ SEMICIRCULAR CANALS

The semicircular canals are:

1. Anterior or superior canal
2. Posterior canal
3. Lateral or horizontal or external canal.

The anterior and posterior canals are situated vertically and the lateral canal is situated in horizontal plane (Fig. 98-2).

Ampulla

There are two ends for each semicircular canal. One end is narrow and the other end is enlarged. The enlarged end is called ampulla. The ampulla contains the receptor organ of semicircular canals known as crista ampullaris. The ampulla of all the three canals and narrow end of horizontal canal open directly into the utricle. The narrow ends of anterior and posterior canals open into the utricle jointly, by forming the common crus. Thus, all the three semicircular canals open into the utricle by means of five openings. Utricle opens into saccule.

■ OTOLITH ORGAN

Otolith organ or vestibule is formed by utricle and saccule.

■ RECEPTOR ORGAN IN VESTIBULAR APPARATUS

The receptor organ in semicircular canal is called crista ampullaris and that in otolith organ is called macula. These receptor organs contain the proprioceptors.

■ RECEPTOR ORGAN IN SEMICIRCULAR CANAL – CRISTA AMPULLARIS

Crista ampullaris is situated inside the ampulla of semicircular canals. The crest is formed by a receptor epithelium (neuroepithelium) which consists of hair cells and supporting cells (Fig. 98-3).

Hair Cells

Hair cells are the receptor cells (proprioceptors) of crista ampullaris. There are two types of hair cells, type I and type II hair cells. Hair cells of semicircular canals, utricle and saccule receive both afferent and efferent nerve terminals.

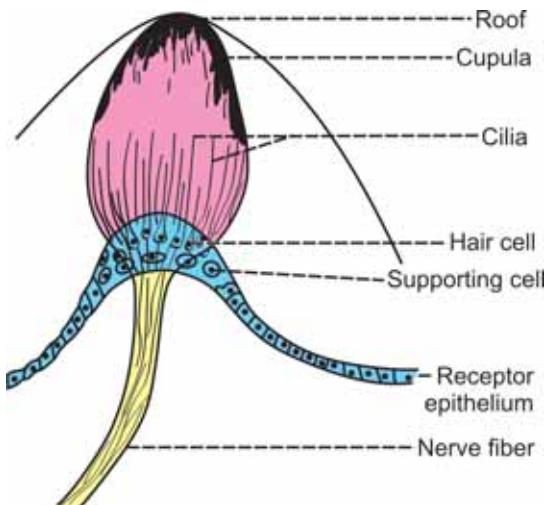


FIGURE 98-3: Crista ampullaris

Type I hair cells

Type I hair cells are flask shaped. The afferent nerve terminates in the form of a calyx that surrounds the cell body. The efferent nerve terminal ends on the surface of the calyx.

Type II hair cells

These cells have a cylindrical or test tube shape. Both afferent and efferent nerve fibers terminate on the surface cell body without forming calyx.

Cilia of hair cells

The apex of each hair cell has a cuticular plate. From this plate, about 40 to 60 cilia arise which are called stereocilia. Each stereocilium is attached at its tip to the neighboring taller one by means of a fine process called tip link. Because of the tip links, all the stereocilia are held together. One of the cilia is very tall which is named as kinocilium (Fig. 98-4).

Cupula

From crista ampullaris, a domeshaped gelatinous structure extends up to the roof of the ampulla. It is known as cupula. The cupula

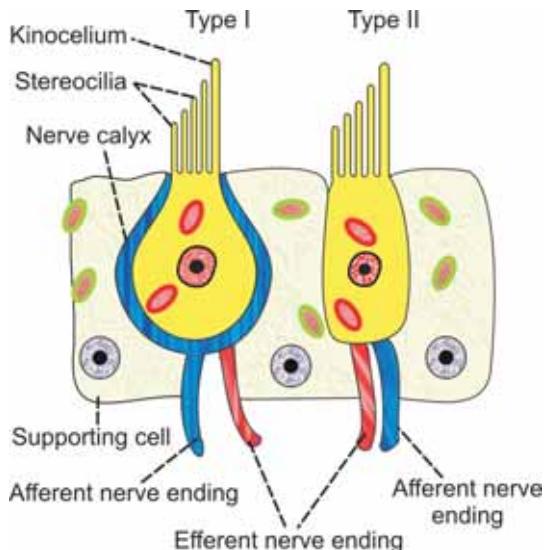


FIGURE 98-4: Hair cells of vestibular apparatus

encloses the cilia of hair cells. The cilia of hair cells are projected in the cupula.

■ RECEPTOR ORGAN IN OTOLITH ORGAN – MACULA

The receptor organ in otolith organ is called macula. Like crista ampullaris, the macula is also formed by neuroepithelium and supporting cells. The neuroepithelium of macula also has two types of hair cells, the type I and type II hair cells (Fig. 98-5).

Otolith Membrane

Like crista ampullaris, macula is also covered by a gelatinous membrane called otolith membrane. It is a flat structure and not dome shaped like cupula. The stereocilia and kinocilium of each hair cell are embedded in otolith membrane. Otolith membrane contains some crystals, which are called ear dust, otoconia or statoconia. The otoconia are mainly constituted by calcium carbonate.

Situation of Macula

In utricle, the macula is situated in horizontal plane, so that the cilia from hair cells are in

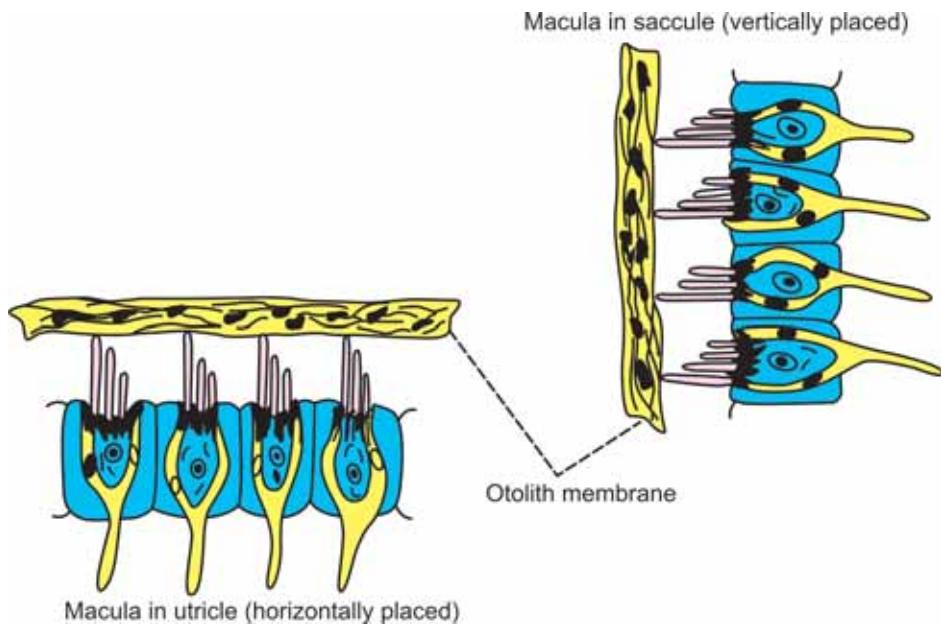


FIGURE 98-5: Macula in otolith organ

vertical direction. In saccule, the macula is in vertical plane and the cilia are in horizontal direction.

■ NERVE SUPPLY TO VESTIBULAR APPARATUS

The impulses from the hair cells of crista ampullaris and maculae are transmitted to medulla oblongata and other parts of central nervous system through the fibers of vestibular division of vestibulocochlear (VIII cranial) nerve.

The first order neurons of the sensory pathway are bipolar in nature. The dendrites of the bipolar cells have close contact with the basal part of hair cells. The axons of the first order neurons (bipolar cells) form the vestibular division of vestibulocochlear nerve.

The hair cells also have efferent nerve fiber which controls the hair cells.

■ FUNCTIONS OF VESTIBULAR APPARATUS

The receptors of semicircular canals give response to rotatory movements or angular acceleration of the head. And, the receptors of utricle

and saccule give response to linear acceleration of head.

Thus, the vestibular apparatus is responsible for detecting the position of head during different movements. It also causes the reflex adjustments in the position of eyeball, head and body during postural changes.

■ FUNCTIONS OF SEMICIRCULAR CANALS

Semicircular canals are concerned with angular (rotatory) acceleration. Semicircular canals sense the rotational movement. Each semicircular canal is sensitive to rotation in a particular plane.

Superior Semicircular Canal

Superior semicircular canal gives response to rotation in anteroposterior plane (transverse axis), i.e. front to back movements like nodding the head while saying 'Yes – yes'.

Horizontal Semicircular Canal

This semicircular canal gives response to rotation in horizontal plane (vertical axis), i.e. side

to side movements (left to right or right to left) like shaking the head while saying 'No – no'.

Posterior Semicircular Canal

This semicircular canal gives response to rotation in the vertical plane (anteroposterior axis) by which head is rotated from shoulder to shoulder.

Mechanism of Stimulation of Receptor Cells in Semicircular Canal

At the beginning of rotation, the receptor cells are stimulated by the movement of endolymph inside the semicircular canals. However, the receptors are stimulated only at the beginning and at the stoppage of rotatory movements. And during rotation at a constant speed, these receptors are not stimulated.

When a person rotates in clockwise direction in horizontal plane (vertical axis), horizontal canal moves in clockwise direction. But, there is no corresponding movement of endolymph inside the canal at the beginning of rotation. Because of the inertia, endolymph remains static. This phenomenon causes relative displacement of endolymph in the direction opposite to that of the rotation of head. That is, the fluid is pushed in anticlockwise direction.

Thus, in the right horizontal semicircular canal, the endolymph flows towards the ampulla and, in the left canal, the fluid moves away from the ampulla (Fig. 98-6). The movement of endolymph in semicircular canal, in turn causes corresponding movement of gelatinous cupula. Thus, in the right horizontal canal, the cupula moves towards the ampulla. Whereas in the left canal the cupula moves away from ampulla. In any semicircular canal, when cupula moves towards the ampulla, the stereocilia of hair cells are pushed towards kinocilium leading to stimulation of hair cells. When the cupula moves away from ampulla, the stereocilia are pushed away from kinocilium and hair cells are not stimulated.

Electrical Potential in Hair Cells – Mechanotransduction

Mechanotransduction is a type of sensory transduction (Chapter 85) in the hair cell (receptor)

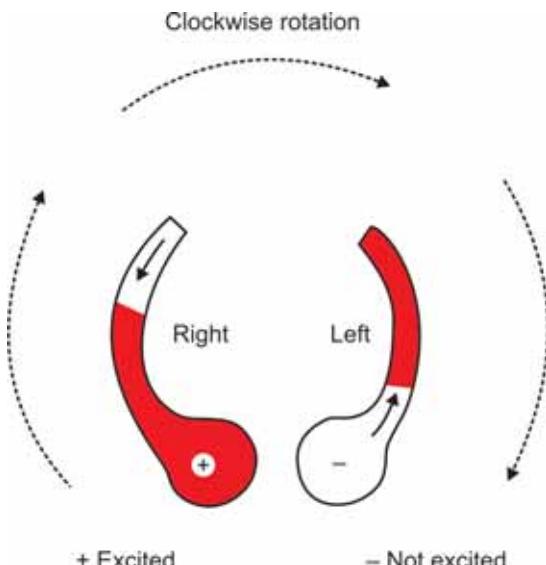


FIGURE 98-6: Movement of fluid and excitation of crista ampullaris in right horizontal semicircular canal during clockwise rotation

by which the mechanical energy (movement of cilia in hair cell) caused by stimulus is converted into action potentials in the vestibular nerve fiber.

The resting membrane potential in hair cells is about -60 mV . The movement of stereocilia of hair cells towards kinocilium causes development of mild depolarization in hair cells up to -50 mV which is called receptor potential.

The receptor potential in hair cells causes generation of action potential in nerve fibers distributed to hair cells.

Movement of stereocilia in the opposite direction (away from kinocilium) causes hyperpolarization of hair cells which stops generation of action potential in the nerve fibers (Fig. 98-7).

Nystagmus

Nystagmus is the rhythmic oscillatory involuntary movements of eyeball. It is common during rotation. It is due to the natural stimulatory effect of vestibular apparatus during rotational acceleration.

Vestibulo-ocular reflex and nystagmus

The nystagmus is a reflex phenomenon that occurs in order to maintain the visual fixation.

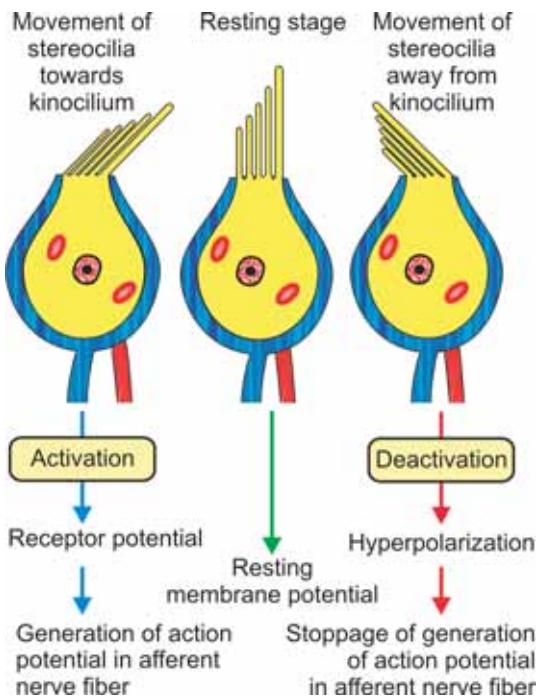


FIGURE 98-7: Mechanotransduction in hair cell of vestibular apparatus. During activation, receptor potential develops in hair cell. It causes development of action potential in afferent nerve fiber.

Since the movements of eyeballs occur in response to the stimulation of vestibular apparatus this reflex is called the vestibulo-ocular reflex.

■ FUNCTION OF OTOLITH ORGAN

Otolith organ is concerned with linear acceleration and detects acceleration in both horizontal and vertical planes. Utricle responds during horizontal acceleration and saccule responds during vertical acceleration.

Function of Utricle

The position of hair cells of macula helps utricle to respond to horizontal acceleration. In the utricle, the macula is situated in horizontal plane

with the hair cells in vertical plane (Fig. 98-5). While moving horizontally, because of inertia the otoconia move in opposite direction and pull the cilia of hair cells resulting in stimulation of hair cells.

For example, when the body moves forward, the otoconia fall back in otolith membrane and pull the cilia of hair cells backward. Pulling of cilia causes stimulation of hair cells. Hair cells send information (impulses) to vestibular, cerebellar and reticular centers. These centers in turn send instructions to various muscles to maintain equilibrium of the body during the forward movement.

Function of Saccule

Macula of saccule is situated in vertical plane with the cilia of hair cells in horizontal plane. While moving vertically, as in the case of utricle, the otoconia of saccule move in opposite direction and pull the cilia resulting in stimulation of hair cells.

For example, while climbing up, the otoconia move down by pulling the cilia downwards. It stimulates the hair cells which in turn send information to the brain centers. And the action follows as in the case of movement in horizontal plane.

■ APPLIED PHYSIOLOGY

■ LABYRINTHECTOMY

Removal of labyrinthine apparatus on both sides leads to complete loss of equilibrium. The equilibrium could be maintained only by visual sensation. The postural reflexes are severely affected. There is loss of hearing sensation too.

Removal of labyrinthine apparatus on one side causes less effect on postural reflexes. However, severe autonomic symptoms such as nausea, vomiting and diarrhea occur.

■ MOTION SICKNESS

Motion sickness is defined as the syndrome of physiological response during movement (travel) to which the person is not adapted. It can occur while traveling in any form of vehicle like automobile, ship, aircraft or spaceship. The motion sickness that occurs while traveling in a watercraft is called seasickness.

Cause

Motion sickness is due to excessive and repeated stimulation of vestibular apparatus

Symptoms

1. Nausea and vomiting
2. Sweating
3. Diarrhea
4. Excess salivation
5. Discomfort
6. Headache
7. Disorientation

The responses of motion sickness can be prevented by avoiding greasy and bulky food before travel and by taking antiemetic drugs (drugs preventing nausea and vomiting).

Electroencephalogram and Epilepsy

- ELECTROENCEPHALOGRAM
 - DEFINITION
 - METHOD OF RECORDING EEG
 - WAVES OF EEG
 - ECG DURING SLEEP
- EPILEPSY
 - DEFINITION
 - TYPES OF EPILEPSY

■ ELECTROENCEPHALOGRAM

■ DEFINITION

Electroencephalography is the study of electrical activities of brain. Electroencephalogram (EEG) is the graphical recording of electrical activities of brain. EEG is useful in the diagnosis of neurological disorders such as epilepsy and sleep disorders.

■ METHOD OF RECORDING EEG

Electroencephalograph is the instrument used to record EEG. The electrodes called scalp electrodes from the instrument placed over unopened skull or over the brain after opening the skull, or by piercing into the brain.

■ WAVES OF EEG

EEG has three types of waves (Fig. 99-1):

1. Alpha waves
2. Beta waves
3. Delta waves.

In children, in addition to these waves, theta waves appear.

Alpha Waves

Alpha waves are rhythmical waves, which appear at a frequency of 8 to 12 waves/second with the amplitude of 50 μ V. The alpha waves are synchronized regular waves.

Alpha waves are obtained in inattentive brain or mind as in drowsiness, light sleep or narcosis with closed eyes. These waves are abolished by any type of stimuli or mental effort and diminished when eyes are opened.

Alpha waves are most marked in parieto-occipital area.

Alpha block

Alpha block is the replacement of synchronized alpha waves in EEG by desynchronized and low voltage waves when the eyes are opened. The desynchronized waves do not have specific frequency. It occurs due to any form of sensory

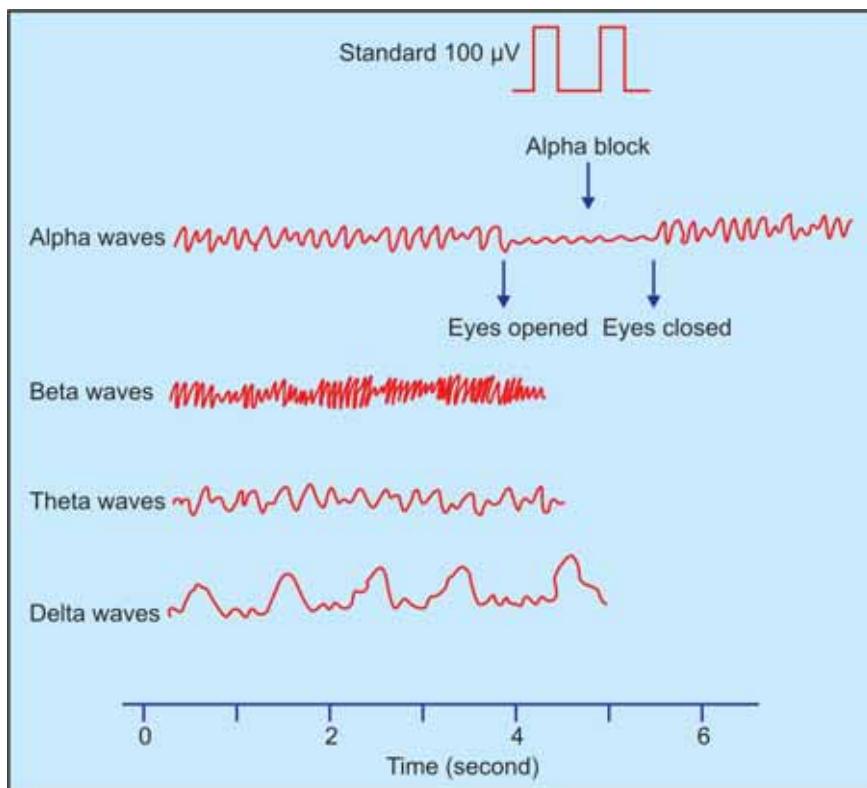


FIGURE 99-1: Waves of EEG

stimulation or mental concentration, such as solving arithmetic problems.

Beta Waves

Beta waves are high frequency waves of 15 to 60/second. But, their amplitude is low, i.e. 5 to 10 μ V. Beta waves are desynchronized waves and are recorded during mental activity or mental tension or arousal state. These waves are not affected by opening the eyes.

Delta Waves

Delta waves are low frequency and high amplitude waves. Frequency of these waves is 1 to 5/second and the amplitude is 20 to 200 μ V. Delta waves are common in early childhood during waking hours. In adults, these waves appear mostly during deep sleep.

Theta Waves

Theta waves are obtained generally in children below 5 years of age. These waves are of low frequency and low voltage waves. The frequency of theta waves is 4 to 8/second and the amplitude is about 10 μ V.

■ EEG DURING SLEEP

The changes in the EEG pattern during sleep are described in Chapter 100.

■ EPILEPSY

■ DEFINITION

Epilepsy is a brain disorder characterized by convulsive seizures or loss of consciousness or both. Convulsion refers to uncontrolled involuntary muscular contractions. Convulsive seizure

means sudden attack of uncontrolled involuntary muscular contractions. It occurs due to paroxysmal (sudden and usually recurring periodically) uncontrolled discharge of impulses from neurons of brain particularly cerebral cortex.

The person with epilepsy remains normal in between seizures. The epileptic attack develops only when the excitability of the neuron is increased, causing excessive neuronal discharge. The persons affected by epilepsy are known as epileptics.

■ TYPES OF EPILEPSY

Epilepsy is divided into two categories:

1. Generalized epilepsy
2. Localized epilepsy.

Generalized Epilepsy

Generalized epilepsy is the type of epilepsy that occurs due to excessive discharge of impulses from all parts of the brain. It is also called general onset seizure or general onset epilepsy.

Generalized epilepsy is subdivided into three types:

1. Grand mal
2. Petit mal
3. Psychomotor epilepsy.

Grand mal

Grand mal is characterized by sudden loss of consciousness followed by convulsion. Just before the onset of convulsions, the person feels the warning sensation in the form of some hallucination. It is called epileptic aura.

In EEG recording, fast waves with a frequency of 15 to 30 per second are seen during initial stage. Later slow and large waves appear. In between seizures, the EEG shows delta waves in all types of epileptics.

The cause of grand mal epilepsy is the excess neural activity in all parts of the brain.

Petit mal

In this type of epilepsy, the person becomes unconscious suddenly without any warning. The unconsciousness lasts for a very short period of 3 to 30 seconds. Convulsions do not occur. However, the muscles of face show twitch like contractions and there is blinking of eyes. Afterwards, the person recovers automatically and becomes normal. The frequency of attack may be once in many months or many attacks may appear in rapid series. It usually occurs in late childhood and disappears completely at the age of 30 or above.

The EEG recording shows slow and large waves during the attack. Each wave is followed by a sharp spike. Delta waves appear in between the seizures.

The causes of petit mal are head injury, stroke, brain tumor and brain infection.

Psychomotor epilepsy

It is characterized by emotional outbursts such as abnormal rage, sudden anxiety, fear or discomfort. There is amnesia or a confused mental state for some period. Some persons have the tendency to attack others bodily or rub their own face vigorously. In most cases, the persons are not aware of their activities.

The EEG recordings show low frequency rectangular waves, ranging between 2 and 4 per second.

The causes of the psychomotor epilepsy are the abnormalities in temporal lobe and tumor in hypothalamus and other regions of limbic system like amygdala and hippocampus.

Localized Epilepsy

The epilepsy that occurs because of excessive discharge of impulses from one part of brain is called localized epilepsy. The contractions usually start in the mouth region and spread down towards the legs. This type of seizure is also known as Jacksonian epilepsy.

Localized epilepsy is caused by brain tumor.

Physiology of Sleep

- DEFINITION
- SLEEP REQUIREMENT
- PHYSIOLOGICAL CHANGES DURING SLEEP
- TYPES OF SLEEP
- STAGES OF SLEEP AND EEG PATTERN
- MECHANISM OF SLEEP
- APPLIED PHYSIOLOGY – SLEEP DISORDERS

■ DEFINITION

Sleep is the natural periodic state of rest for mind and body with closed eyes characterized by partial or complete loss of consciousness. Loss of consciousness leads to decreased response to external stimuli and decreased body movements. The depth of sleep is not constant throughout the sleeping period. It varies in different stages of sleep.

■ SLEEP REQUIREMENT

Sleep requirement is not constant. However, the average sleep requirement per day at different age groups is:

1. Newborn infants — 18 to 20 hours
2. Growing children — 12 to 14 hours
3. Adults — 7 to 9 hours
4. Old persons — 5 to 7 hours

■ PHYSIOLOGICAL CHANGES DURING SLEEP

1. Plasma volume decreases by about 10%
2. Heart rate reduces to about 45 to 60 beats/min

3. Systolic pressure falls to about 90 to 110 mm Hg. If sleep is disturbed by exciting dreams, the pressure is elevated above 130 mm Hg
4. Rate and force of respiration are decreased. Cheyne-Stokes type of periodic breathing may develop
5. Salivary secretion decreases during sleep. Contraction of empty stomach is more vigorous
6. Urine formation decreases. The specific gravity of urine increases
7. Sweat secretion increases
8. Lacrimal secretion decreases
9. Muscle tone reduces
10. Some reflexes particularly the knee jerk, are abolished. Babinski's sign becomes positive.

■ TYPES OF SLEEP

The sleep is of two types:

1. Rapid eye movement sleep or REM sleep
2. Non-rapid eye movement sleep, NREM sleep or non-REM sleep.

■ 1. RAPID EYE MOVEMENT SLEEP (REM SLEEP)

REM sleep is the type of sleep associated with rapid conjugate movements of the eyeballs which occurs frequently. Though the eyeballs move, the sleep is deep. So, it is also called paradoxical sleep. It occupies about 20 to 30% of sleeping period. Functionally, REM sleep is very important because, it plays an important role in consolidation of memory. Dreams occur during this period.

■ 2. NON-RAPID EYE MOVEMENT SLEEP (NREM OR NON-REM SLEEP)

NREM sleep is the type of sleep without the movements of eyeballs. It is also called slow wave sleep. The dreams do not occur in this type of sleep and it occupies about 70 to 80% of total sleeping period. The non-REM sleep is followed by REM sleep.

The differences between the two types of sleep are given in Table 100-1.

TABLE 100-1: REM sleep and non-REM sleep

Characteristics	REM sleep	Non REM sleep
1. Rapid eye movement	Present	Absent
2. Dreams	Present	Absent
3. Muscle twitching	Present	Absent
4. Heart rate	Fluctuating	Stable
5. Blood pressure	Fluctuating	Stable
6. Respiration	Fluctuating	Stable
7. Body temperature	Fluctuating	Stable
8. Neurotransmitter	Noradrenaline	serotonin

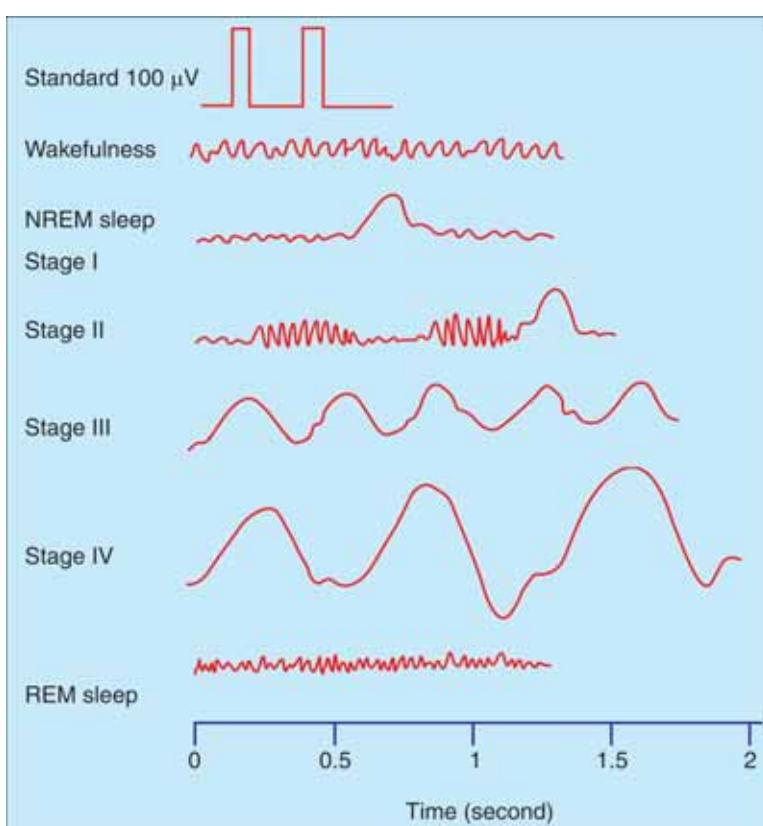


FIGURE 100-1: EEG during wakefulness, different stages of NREM sleep and REM sleep

■ STAGES OF SLEEP AND EEG PATTERN

■ RAPID EYE MOVEMENT SLEEP

During REM sleep, the EEG shows irregular waves with high frequency and low amplitude. These waves are desynchronized waves.

■ NON-RAPID EYE MOVEMENT SLEEP

NREM sleep is divided into four stages, based on the EEG pattern. During the stage of wakefulness, i.e. while lying down with closed eyes and relaxed mind, the alpha waves of EEG appear. When the person proceeds to drowsy state, the alpha waves diminish (Fig. 100-1).

Stage I: Stage of Drowsiness

Alpha waves are diminished and abolished. EEG shows only low voltage fluctuations and infrequent delta waves.

Stage II: Stage of Light Sleep

It is characterized by spindle bursts at a frequency of 14 per second, superimposed by low voltage delta waves.

Stage III: Stage of Medium Sleep

During this stage, the spindle bursts disappear. Frequency of delta waves decreases to 1 or 2 per second and amplitude increases to about 100 µV.

Stage IV: Stage of Deep Sleep

Delta waves become more prominent with low frequency and high amplitude.

■ MECHANISM OF SLEEP

Sleep occurs due to the activity of some sleep inducing centers in brain.

■ SLEEP CENTERS

Complex pathways between the reticular formation of brainstem, diencephalon and cerebral cortex are involved in the onset and maintenance of sleep. However, two centers are located in brainstem, which induce sleep:

1. Raphe nucleus which is responsible for non-REM sleep
2. Locus ceruleus which is responsible for REM sleep

Inhibition of ascending reticular activating system also results in sleep.

Higher Intellectual Functions

- HIGHER INTELLECTUAL FUNCTIONS
- LEARNING
 - DEFINITION
 - TYPES
- MEMORY
 - DEFINITION
 - TYPES
 - PHYSIOLOGICAL BASIS
 - APPLIED PHYSIOLOGY
- CONDITIONED REFLEXES
 - DEFINITION
 - TYPES
- SPEECH
 - DEFINITION
 - MECHANISM
 - NERVOUS CONTROL
 - APPLIED PHYSIOLOGY

■ HIGHER INTELLECTUAL FUNCTIONS

Higher intellectual functions are very essential to make up the human mind. These functions are also called higher brain or cortical functions. Cerebral cortex is responsible for these functions. The important higher intellectual functions are learning, memory, conditioned reflexes and speech.

■ LEARNING

■ DEFINITION

Learning is defined as the process by which new information is acquired.

■ TYPES OF LEARNING

Learning is of two types:

1. Non-associative learning
2. Associative learning.

1. Non-associative Learning

It involves response of a person to only one type of stimulus. It is based on two factors:

i. Habituation

Habituation means getting used to something to which a person is constantly exposed. When a person is exposed to a stimulus repeatedly, he starts ignoring the stimulus slowly. During the first experience, the event (stimulus) is novel and evokes a response. However, it evokes less response when it is repeated. Finally, the person is habituated to the event and ignores it.

ii. Sensitization

Sensitization means a state in which the body becomes more sensitive to a stimulus. When a stimulus is applied repeatedly, habituation occurs. But if the same stimulus is combined with another type of stimulus, which may be pleasant or unpleasant, the person becomes more sensitive to the original stimulus.

For example, a woman gets habituated to different sounds around her and sleep is not disturbed by these sounds. However, she suddenly wakes up when her baby cries because she is sensitized to the crying sound of her baby.

2. Associative Learning

It involves learning about relations between two or more stimuli at a time. The classic example of associative learning is the conditioned reflex (see below).

■ MEMORY

■ DEFINITION

Memory is defined as the ability to recall the past experience. It is also defined as retention of learned materials.

■ TYPES OF MEMORY

Memory is classified into two types:

1. Explicit memory
2. Implicit memory.

1. Explicit Memory

Explicit memory is otherwise known as declarative memory or recognition memory. It is defined as the memory that involves conscious recollection of past experience. It consists of memories regarding the events which occurred in the external world around us. The information stored may be about a particular event that happened at a particular time and place. Examples: Recollection of a birthday party celebrated three days ago; the events taken place while taking breakfast, etc.

Explicit memory involves hippocampus and medial part of temporal lobe.

2. Implicit Memory

Implicit memory is otherwise known as nondeclarative memory or skilled memory. It is defined as the memory in which past experience is utilized without conscious awareness. It helps to perform various skilled activities properly. For example, cycling, driving, playing tennis, dancing, typing, etc. are performed automatically without awareness.

Implicit memory involves the sensory and motor pathways.

Memory is also classified into:

1. Short term memory
2. Long term memory

1. Short Term Memory

Short term memory is the recalling the events that happened very recently, i.e. within hours or days. It is also known as recent memory. For example, telephone number that is known today may be remembered till tomorrow. If it is not recalled repeatedly, it may be forgotten on third day.

2. Long Term Memory

It is otherwise called remote memory. It is the recalling of the events of weeks, months, years or sometimes lifetime. Examples are recalling first day of schooling, birthday celebration of previous year, picnic enjoyed last week, etc.

■ PHYSIOLOGICAL BASIS OF MEMORY

Memory is stored in brain by the alteration of synaptic transmission between the neurons involved in memory. Storage of memory may be facilitated or habituated.

Facilitation

It is the process by which the memory storage is enhanced. It involves increase in synaptic transmission and increased postsynaptic activity.

Habituation

It is the process by which the memory storage is attenuated (attenuation = decrease in strength, effect or value). It involves reduction in synaptic transmission and slow stoppage of postsynaptic activity.

Basis for Short Term Memory

Basic mechanism of memory is the development of new neuronal circuits by the formation of new synapses and facilitation of synaptic transmission. The number of presynaptic terminals and the size of the terminals are also increased.

Basis for Long Term Memory

When the neuronal circuit is reinforced by constant activity, the memory is consolidated and encoded into different areas of the brain. This encoding makes memory a permanent or long term memory.

Sites of Encoding

Hippocampus and the Papez circuit (the closed circuit between hippocampus, thalamus, hypothalamus and corpus striatum) are the main sites for memory encoding. Frontal and parietal areas are also involved in memory storage.

Consolidation of Memory

The process by which a short term memory is crystallized into a long term memory is called memory consolidation

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF MEMORY

1. Amnesia – loss of memory
2. Dementia – progressive deterioration of intellect, emotional control and social behavior and associated with loss of memory
3. Alzheimer's Disease – progressive neurodegenerative disease due to death of neurons in brain.

■ CONDITIONED REFLEXES

■ DEFINITION

Conditioned reflex is the acquired reflex that requires learning, memory and recall of previous experience. It forms the basis of learning.

The unconditioned reflex is the inborn reflex which does not need previous experience.

■ TYPES OF CONDITIONED REFLEXES

The conditioned reflexes are of two types:

- A. Classical conditioned reflexes
- B. Instrumental conditioned reflexes.

Classical Conditioned Reflexes

The Classical conditioned reflexes are those reflexes, which are established by a conditioned stimulus followed by an unconditioned stimulus.

Method of study – Pavlov's bell-dog experiments

The classical conditioned reflexes are demonstrated by the classical bell-dog experiments (salivary secretion experiments) done by Ivan Pavlov and his associates.

In dogs, the duct of parotid gland or submandibular gland was taken outside through cheek or chin respectively and the salivary secretion was measured in drops by means of an electrical recorder.

Types of classical conditioned reflexes

Classical conditioned reflexes are classified into two groups:

- I. Positive or excitatory conditioned reflexes
- II. Negative conditioned reflexes.

I. Positive conditioned reflexes

Positive conditioned reflexes are of three types:

1. Primary conditioned reflex: It is the reflex developed with one unconditioned stimulus and one conditioned stimulus. The dog is fed with food (unconditioned stimulus). Simultaneously a flash of light (conditioned stimulus) is also shown. Both the stimuli are repeated for some days. After the development of reflex, the flash of light (conditioned stimulus) alone causes salivary secretion without food (unconditioned stimulus).
2. Secondary conditioned reflex: It is the reflex developed with one unconditioned stimulus and two conditioned stimuli. After establishment of a conditioned reflex with one conditioned stimulus, another conditioned stimulus is applied along with the first one. For example, the animal is fed with food (unconditioned reflex) and simultaneously a flash of light (first conditioned stimulus), and a bell sound (second conditioned stimulus) are applied. After the development of the reflex, the second conditioned stimulus – the bell sound alone can cause salivary secretion
3. Tertiary conditioned reflex: In this reflex, a third conditioned stimulus is added and, the reflex is established. But, the reflex with more than three conditioned stimuli is not possible.

II. Negative conditioned reflexes

In negative conditioned reflexes the established conditioned reflexes are inhibited by some factors. For example, some disturbing factors like sudden entrance of a stranger or sudden noise can abolish the conditioned reflex and inhibit salivary secretion.

Instrumental or Operant Conditioned Reflexes

The instrumental or operant conditioned reflexes are the reflexes in which the behavior of the person is instrumental. This type of reflexes is developed by the conditioned stimulus followed by a reward or punishment.

For example, if the animal is rewarded by a banana by pressing a bar, the animal repeatedly presses the bar. If the animal is given a tasty food along with electric shock, the animal starts avoiding that food.

The instrumental conditioned reflexes play an important role during the learning processes of a child. These conditioned reflexes are also responsible for behavior pattern of an individual.

■ SPEECH

■ DEFINITION

Speech is defined as the expression of thoughts by production of articulate sound, bearing a definite meaning. When a sound is produced verbally, it is called the speech. If it is expressed by visual symbols, it is known as writing.

■ MECHANISM OF SPEECH

Speech depends upon the coordinated activities of central speech apparatus and peripheral speech apparatus. The central speech apparatus consists of higher centers, i.e. the cortical and subcortical centers. The peripheral speech apparatus includes larynx or sound box, pharynx, mouth, nasal cavities, tongue and lips.

■ NERVOUS CONTROL OF SPEECH

Speech is controlled by the following cortical areas.

A. Motor Areas

1. Broca's area

It is area 44. It is also called speech center. It is situated in lower part of lateral surface of pre-frontal cortex. This area controls the movements of structures concerned with vocalization.

2. Upper frontal motor area

It is situated in the paracentral gyrus over the medial surface of the cerebral hemisphere. It controls the coordinated movements concerned with writing.

B. Sensory Areas

1. Auditopsychic area

Auditopsychic area is situated in the superior temporal gyrus. It is concerned with storage of memories of spoken words.

2. Visuropsychic area

It is present in angular gyrus of the parietal cortex. It is concerned with storage of memories of the visual symbols.

C. Wernicke's Area

This area is situated in the upper part of temporal lobe. It is responsible for understanding the auditory and visual information about any word.

■ APPLIED PHYSIOLOGY – DISORDERS OF SPEECH

1. Aphasia

Aphasia is the loss or impairment of speech. It is due to damage of speech centers which occurs during stroke, head injury, cerebral tumors, brain infections and degenerative disease like Parkinson's disease.

Head's classification of aphasia

Henry Head has classified aphasia into four types:

1. Verbal aphasia: Disability in the formation of words
2. Syntactical aphasia: Inability to arrange words in proper sequence
3. Semantic aphasia: Inability to recognize the significance of words
4. Nominal aphasia: Difficulty in naming the object due to failure in recognizing the meaning of words.

2. Dysarthria or Anarthria

Dysarthria or anarthria is the difficulty or inability to speak because of paralysis of muscles involved in articulation. The spoken and written words are understood. It is caused by damage of brain areas or the nerves that control muscles involved in speech. It occurs in conditions like stroke, brain injury and degenerative disease.

3. Dysphonia

Dysphonia is a voice disorder characterized by hoarseness and a sore or dry throat. Hoarseness means the difficulty in producing sound while trying to speak or a change in the pitch or loudness of voice. It occurs due to diseases of vocal cords or larynx.

4. Stammering

Stammering or stuttering is a speech disorder in which the normal flow of speech is disturbed by repetitions or stoppage of sound and words. It is associated with some unusual facial and body movements. Stammering is due to genetic factors, brain damage, neurological disorders or anxiety.

Cerebrospinal Fluid

- INTRODUCTION
- PROPERTIES AND COMPOSITION
- FORMATION
- CIRCULATION
- ABSORPTION
- PRESSURE EXERTED BY CSF
- FUNCTIONS
- COLLECTION
- BLOOD-BRAIN BARRIER
- BLOOD – CEREBROSPINAL FLUID BARRIER
- APPLIED PHYSIOLOGY

■ INTRODUCTION

Cerebrospinal fluid (CSF) is the clear, colorless and transparent fluid that circulates through ventricles of brain, subarachnoid space and central canal of spinal cord. It is a part of ECF.

■ PROPERTIES AND COMPOSITION OF CSF

Properties

Volume	:	150 ml
Rate of formation	:	0.3 ml per minute
Specific gravity	:	1.005
Reaction	:	Alkaline.

Composition

Composition of CSF is given in Fig. 102-1. CSF also contains some lymphocytes which are added when it flows in the spinal cord.

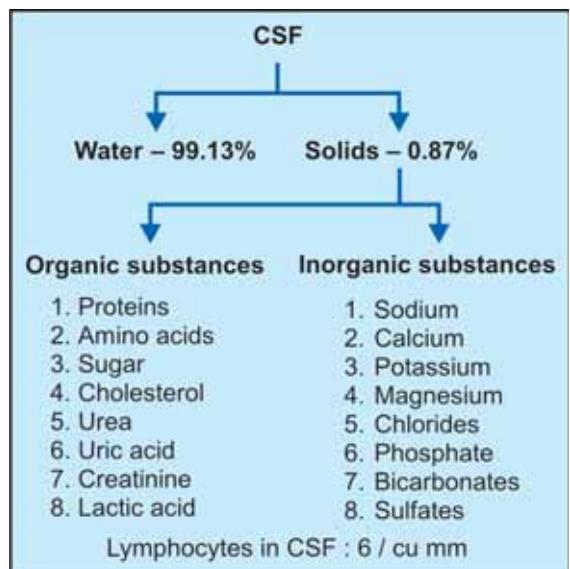


FIGURE 102-1: Composition of cerebrospinal fluid

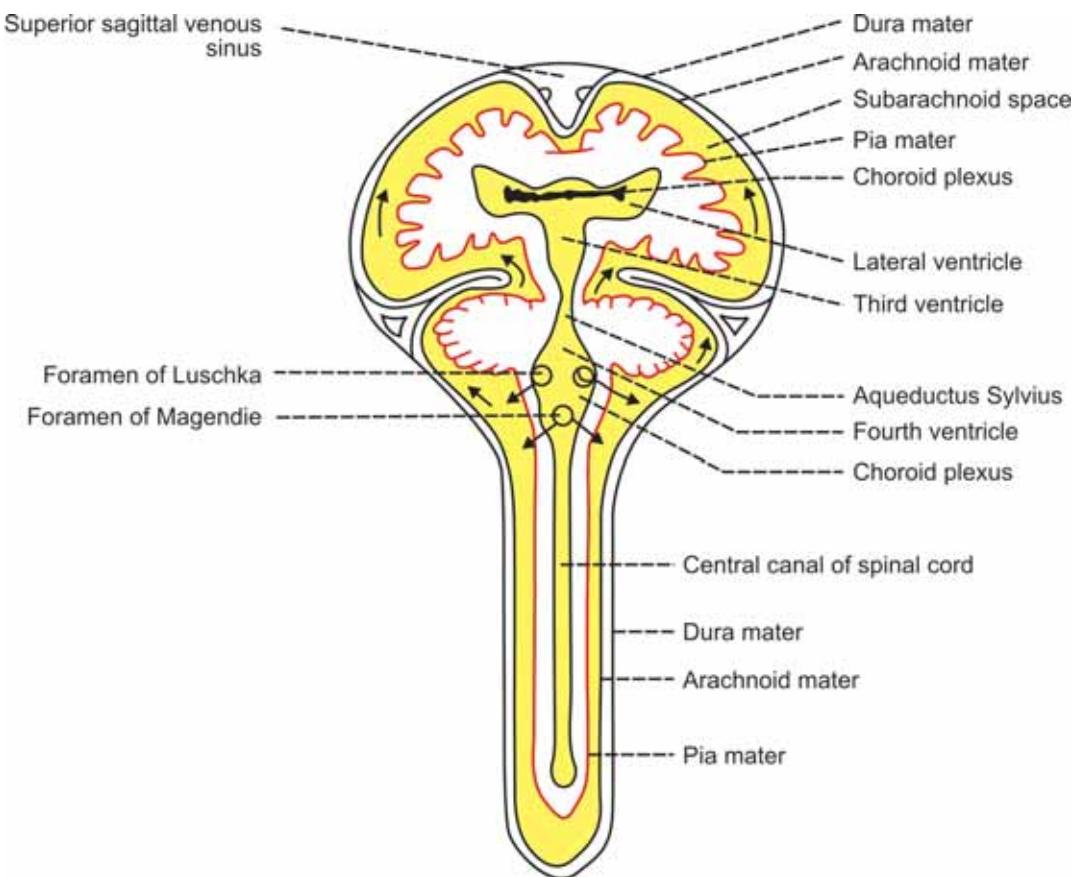


FIGURE 102-2: Circulation of cerebrospinal fluid

■ FORMATION OF CSF

CSF is formed by the choroid plexuses (tuft of capillaries) situated within the ventricles. It is formed by the process of secretion which involves active transport.

■ CIRCULATION OF CSF

Major quantity of CSF is formed in the lateral ventricles and passes through the foramen of Monro into the third ventricle (Figs 102.2 and 102.3). From here, it passes to the fourth ventricle through aqueductus Sylvius. From fourth ventricle, it enters into the cisterna magna and cisterna lateralis through foramen of Magendie (central opening) and foramen of Luschka (lateral opening). The cisternal fluid circulates through the subarachnoid space over spinal cord and cerebral hemispheres.

■ ABSORPTION OF CSF

CSF is mostly absorbed by the arachnoid villi into dural sinuses and spinal veins. Small amount is absorbed into cervical lymphatics and perivascular spaces. The mechanism of absorption is by filtration. Normally, about 500 ml of CSF is formed everyday and an equal amount is absorbed.

■ PRESSURE EXERTED BY CSF

The pressure exerted by CSF varies in different position, viz.

Lateral recumbent position = 10 to 18 cm of H₂O

Lying position = 13 cm of H₂O

Sitting position = 30 cm of H₂O.

Certain events like coughing, crying and compression of internal jugular vein increase the pressure.

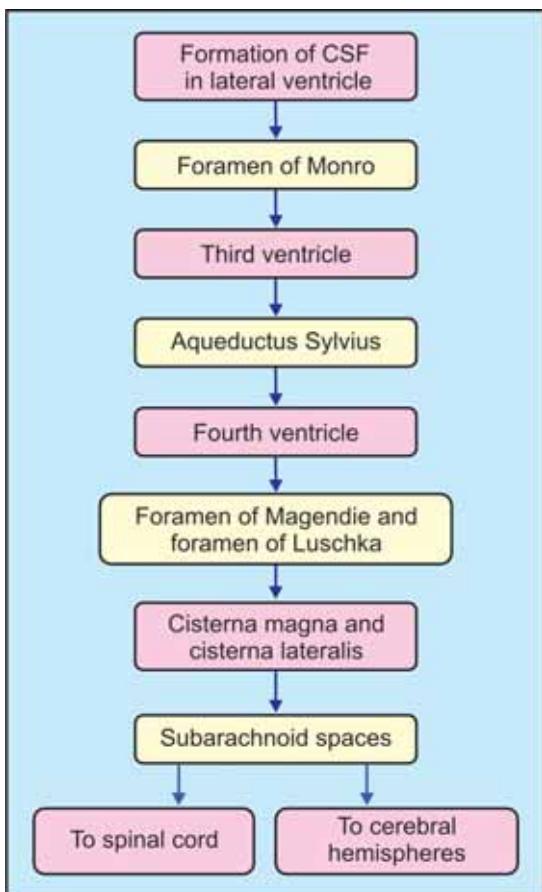


FIGURE 102-3: Schematic diagram of CSF circulation

■ FUNCTIONS OF CSF

1. Protective Function

CSF acts as fluid buffer and protects the brain from shock. Since, the specific gravity of brain and CSF is more or less same, brain floats in CSF. When head receives a blow, CSF acts like a cushion and prevents the movement of brain against the skull bone and thereby prevents the damage of brain.

2. Regulation of Cranial Content Volume

Regulation of cranial content volume is essential because, if the cranial contents increase in

volume, the brain may be affected. The increase in cranial content volume is prevented by greater absorption of CSF.

3. Medium of Exchange

CSF is the medium through which many substances, particularly the nutritive substances and waste materials are exchanged between blood and brain tissues.

■ COLLECTION OF CSF

CSF is collected either by cisternal puncture or lumbar puncture. In cisternal puncture, the CSF is collected by passing a needle between the occipital bone and atlas, so that it enters the cisterna magna. In lumbar puncture, the needle is introduced into the subarachnoid space in the lumbar region, between the third and fourth lumbar spines.

■ BLOOD-BRAIN BARRIER

Blood-brain barrier (BBB) is a neuroprotective structure that prevents the entry of many substances and pathogens into the brain tissues from blood. The barrier exists in the capillary membrane of all parts of the brain except in some areas of hypothalamus.

BBB is formed by tight junctions in the endothelial cells of the brain capillaries. The cytoplasmic foot processes of astrocytes (neuroglial cells) develop around the capillaries and reinforce the barrier.

■ FUNCTIONS OF BLOOD-BRAIN BARRIER

BBB acts as both a mechanical barrier and a transport mechanisms. It prevents harmful chemical substances and permits metabolic and essential materials into the brain tissues.

Substances which can pass through Blood-Brain Barrier

1. Oxygen
2. Carbon dioxide

3. Water
4. Glucose
5. Amino acids
6. Electrolytes
7. Lipid soluble drugs such as L-dopa, 5-HT and tetracycline
8. Lipid soluble anesthetic gases such as ether and nitrous oxide
9. Other lipid soluble substances.

Substances which cannot pass through Blood-Brain Barrier

1. Injurious chemical agents
2. Pathogens such as bacteria
3. Drugs such as penicillin and the catecholamines
4. Bile pigments.

■ BLOOD-CEREBROSPINAL FLUID BARRIER

It is the barrier between the blood and cerebrospinal fluid that exists at the choroid plexus. The function of this barrier is similar to that of the BBB. It does not allow the movement of many substances from blood to cerebrospinal fluid. It allows the movement of only those substances, which are allowed by BBB.

■ APPLIED PHYSIOLOGY – HYDROCEPHALUS

The abnormal accumulation of CSF in the skull associated with enlargement of head is called hydrocephalus. Hydrocephalus along with increased intracranial pressure causes headache and vomiting. In severe conditions, it leads to atrophy of brain, mental weakness and convulsions.

Autonomic Nervous System

- INTRODUCTION
- SYMPATHETIC DIVISION
- PARASYMPATHETIC DIVISION
- FUNCTIONS
- NEUROTRANSMITTERS

■ INTRODUCTION

The autonomic nervous system (ANS) is primarily concerned with the regulation of visceral or vegetative functions of the body. So, it is also called vegetative or involuntary nervous system.

■ DIVISIONS OF ANS

Autonomic nervous system is divided into two divisions:

1. Sympathetic division
2. Parasympathetic division.

The differences between both the divisions of ANS are given in Table 103-1.

■ SYMPATHETIC DIVISION

It is otherwise called thoracolumbar outflow because, the preganglionic neurons are situated in lateral gray horns of 12 thoracic and first two lumbar segments of spinal cord. The fibers arising from here are called preganglionic fibers. The preganglionic fibers leave the spinal cord through anterior nerve root and white rami

communicants, and terminate in the post-ganglionic neurons, which are situated in the sympathetic ganglia.

Sympathetic division supplies smooth muscle fibers of all the visceral organs such as blood vessels, heart, lungs, glands, gastrointestinal organs, etc.

■ SYMPATHETIC GANGLIA

The ganglia of sympathetic division are classified into three groups:

- I. Paravertebral or sympathetic chain ganglia
- II. Prevertebral or collateral ganglia
- III. Terminal or peripheral ganglia.

I. Paravertebral or Sympathetic Chain Ganglia

Paravertebral or sympathetic chain ganglia are present on either side of vertebral column. These ganglia are connected with each other by longitudinal fibers to form the sympathetic chains (Fig. 103-1). Both the chains extend from skull to coccyx.

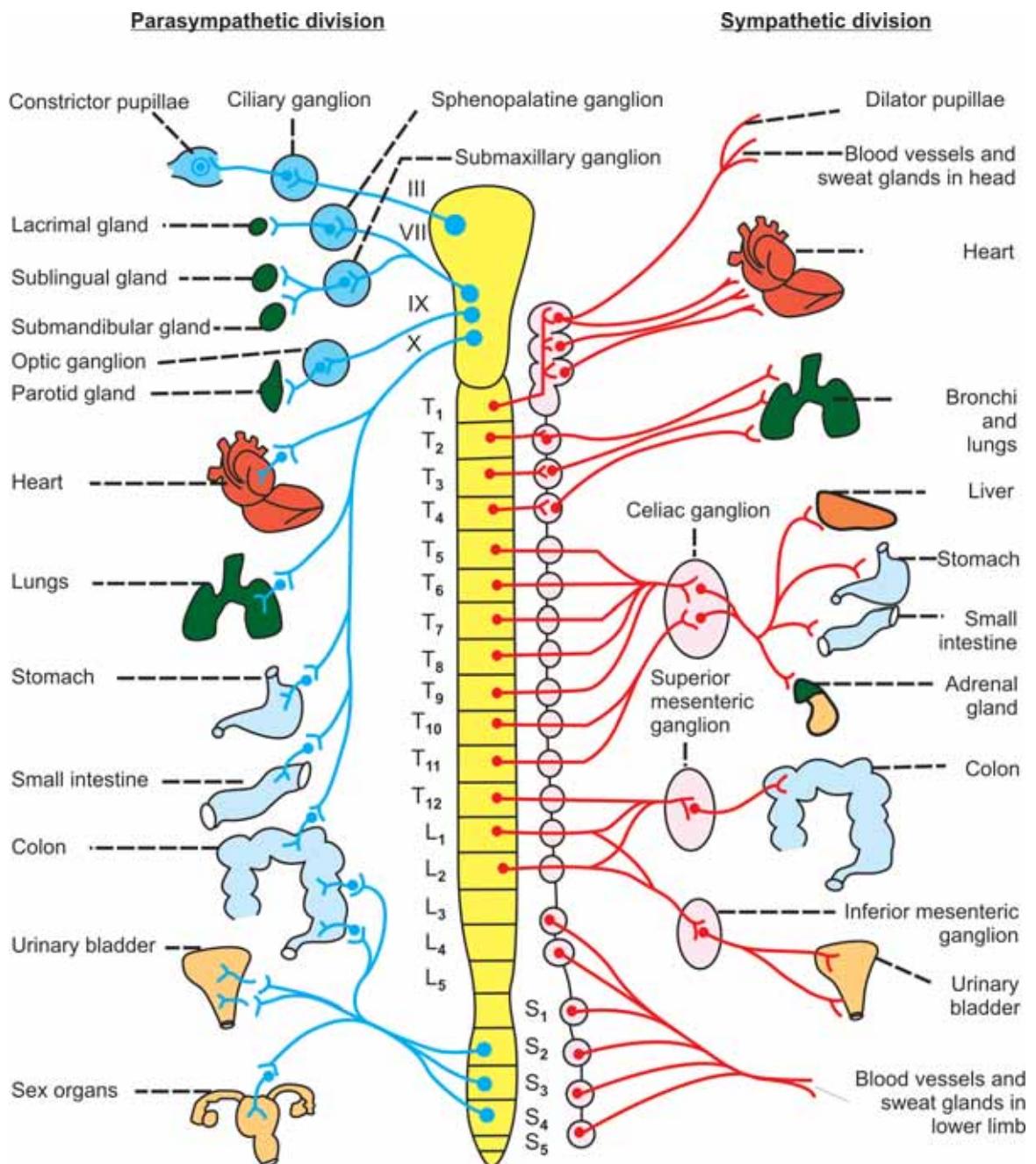


FIGURE 103-1: Autonomic nervous system

Ganglia of the sympathetic chain (trunk) on each side are divided into four groups:

1. Cervical ganglia – 8 in number
2. Thoracic ganglia – 12 in number
3. Lumbar ganglia – 5 in number
4. Sacral ganglia – 5 in number.

II. Prevertebral or Collateral Ganglia

Prevertebral ganglia are situated in thorax, abdomen and pelvis in relation to aorta and its branches.

The prevertebral ganglia are:

1. Celiac ganglion
2. Superior mesenteric ganglion
3. Inferior mesenteric ganglion.

The prevertebral ganglia receive preganglionic fibers from T₅ to L₂ segments. The postganglionic fibers from these ganglia supply the visceral organs of thorax, abdomen and pelvis.

III. Terminal or Peripheral Ganglia

Terminal ganglia are situated within or close to structures innervated by them. Heart, bronchi, pancreas and urinary bladder are innervated by the terminal ganglia.

Sympathoadrenergic System

Sympathoadrenergic system is a functional and phylogenetic unit that includes sympathetic division and adrenal medulla. Adrenal medulla is a modified sympathetic ganglion.

■ PARASYMPATHETIC DIVISION

The parasympathetic division of ANS is otherwise called craniosacral outflow because, the fibers of this division arise from brainstem and sacral segments of spinal cord. The cranial portion of parasympathetic division innervates the blood vessels of the head and neck and many thoracoabdominal visceral organs.

The sacral portion of parasympathetic division innervates the smooth muscles forming the walls of viscera and the glands such

as large intestine, liver, spleen, kidneys, bladder, genitalia, etc.

■ CRANIAL NERVES OF PARASYMPATHETIC DIVISION

The cranial nerves of the parasympathetic division are:

1. Oculomotor (III) nerve
2. Facial (VII) nerve
3. Glossopharyngeal (IX) nerve
4. Vagus (X) nerve.

The fibers of sacral outflow arise from second to fourth sacral (S₂ to S₄) segments of spinal cord.

■ FUNCTIONS OF ANS

The ANS is concerned with regulation of vegetative functions, which are beyond voluntary control. By controlling the various vegetative functions, ANS plays an important role in maintaining the constant internal environment (homeostasis).

Almost all the visceral organs are supplied by both sympathetic and parasympathetic divisions of ANS and, the two divisions produce antagonistic effects on each organ. When the fibers of one division supplying to an organ is sectioned or affected by lesion, the effects of fibers from other division on the organ become more prominent.

The actions of the sympathetic and parasympathetic fibers on various structures are given in Table 103-1.

■ NEUROTRANSMITTERS OF ANS

The different nerve fibers of ANS execute the functions by releasing some neurotransmitter substances.

■ SYMPATHETIC FIBERS

1. Preganglionic fibers: Acetylcholine (Ach)
2. Postganglionic noradrenergic fibers: Norepinephrine
3. Postganglionic cholinergic fibers: Ach

TABLE 103-1: Actions of sympathetic and parasympathetic divisions of ANS

Effector organ		Sympathetic division	Parasympathetic division
1. Eye	Ciliary muscle	Relaxation	Contraction
	Pupil	Dilatation	Constriction
2. Lacrimal glands		Decrease in secretion	Increase in secretion
3. Salivary secretion		Decrease in secretion and vasoconstriction	Increase in secretion and vasodilatation
4. Gastrointestinal tract	Motility	Inhibition	Acceleration
	Secretion	Decrease	Increase
	Sphincters	Constriction	Relaxation
	Smooth muscles	Relaxation	Contraction
5. Gallbladder		Relaxation	Contraction
6. Urinary bladder	Detrusor muscle	Relaxation	Contraction
	Internal sphincter	Constriction	Relaxation
7. Sweat glands		Increase in secretion	-----
8. Heart rate and force		Increase	Decrease
9. Blood vessels		Constriction of all blood vessels except those in heart and skeletal muscle	Dilatation
10. Bronchioles		Dilatation	Constriction

The postganglionic sympathetic cholinergic nerve fibers supply sweat glands and blood vessels in heart and skeletal muscle.

■ PARASYMPATHETIC FIBERS

1. Preganglionic fibers: Ach
2. Postganglionic fibers: Ach

QUESTIONS IN NERVOUS SYSTEM

■ LONG QUESTIONS

1. What is synapse? Explain the structure, functions and properties of synapse.
2. Define and classify reflex action. Explain reflex arc and the properties of reflexes.
3. Name the ascending tracts of the spinal cord and, explain spinothalamic tracts.
4. What are the tracts of Spinal cord? Describe the spinocerebellar tracts.
5. Give an account of tracts in the posterior white funiculus of spinal cord.
6. Enumerate the descending tracts of spinal cord. Describe in detail the pyramidal tracts. Write a note on the effects of upper and lower motor neuron lesions.
7. What are the thalamic nuclei? Describe the functions and effects of lesions of thalamus.
8. Name the hypothalamic nuclei. Explain the functions and effects of lesions of hypothalamus.
9. What are the different divisions of cerebellum? Explain the functions of each division. Add a note on cerebellar lesions.
10. What are the components of basal ganglia? Give an account of functions and disorders of basal ganglia.
11. Name lobes of cerebral cortex? Describe the functions of each lobe. Add a note on frontal lobe syndrome.
9. Cutaneous receptors.
10. Generator (receptor) potential.
11. EPSP.
12. IPSP.
13. Synaptic transmission.
14. Reflex arc.
15. Properties of reflexes.
16. Superficial reflexes.
17. Deep reflexes.
18. Babinski's sign.
19. Upper/lower motor neuron lesion.
20. Pathway for fine touch sensations.
21. Pathway for pressure sensation.
22. Pathway for temperature sensations.
23. Pathway for conscious kinesthetic sensations.
24. Pathway for subconscious kinesthetic sensations.
25. Pathway for pain sensations.
26. Functions of thalamus.
27. Thalamic syndrome.
28. Functions of hypothalamus.
29. Regulation of food intake.
30. Disorders of hypothalamus.
31. Corticocerebellum (Neocerebellum).
32. Spinocerebellum (Paleocerebellum).
33. Vestibulocerebellum
34. Functions of basal ganglia.
35. Parkinsonism.
36. Frontal lobe of cerebral cortex.
37. Parietal lobe (or sensory areas) of cerebral cortex.
38. Functions of limbic system.
39. Muscle spindle.
40. Muscle tone
41. Righting reflexes.
42. Semicircular canal.
43. Otolith organ.
44. Motion sickness.
45. EEG.

■ SHORT QUESTIONS

1. Structure of neuron.
2. Myelin sheath.
3. Classification of nerve fibers.
4. Properties of nerve fibers.
5. Action potential in nerve fiber.
6. Saltatory conduction.
7. Wallarian degeneration.
8. Neuroglia.

- 46. Epilepsy.
- 47. EEG pattern during sleep.
- 48. REM and non-REM sleep.
- 49. Learning.
- 50. Memory.
- 51. Conditioned reflexes.
- 52. Speech disorders.
- 53. CSF.
- 54. Blood-brain barrier.
- 55. Role of ANS in the regulation of cardiovascular functions.
- 56. Role of ANS in the regulation of gastrointestinal activity.
- 57. Functions of sympathetic division of ANS.
- 58. Functions of parasympathetic division of ANS.

SECTION 11

Special Senses

CHAPTERS —

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Structure of the Eye

- SPECIAL SENSES
- FUNCTIONAL ANATOMY OF THE EYEBALL
- WALL OF THE EYEBALL
- FUNDUS OCULI
- INTRAOCULAR FLUIDS
- INTRAOCULAR PRESSURE
- LENS
- OCULAR MUSCLES
- OCULAR MOVEMENTS
- APPLIED PHYSIOLOGY

■ SPECIAL SENSES

Special senses or special sensations are the complex sensations which involve specialized sense organs. These sensations are different from somatic sensations that arise from skin, muscles, tendons and joints (Chapter 89).

Special senses are:

1. Sensation of vision
2. Sensation of hearing
3. Sensation of taste
4. Sensation of smell.

■ FUNCTIONAL ANATOMY OF THE EYEBALL

■ MORPHOLOGY

Human eyeball (bulbus oculi) is approximately globe shaped with a diameter of about 24 mm. It is slightly flattened from above downwards. The center of anterior curvature of the eyeball

is called the anterior pole, and the center of posterior curvature is called the posterior pole. The line joining the two poles is called optic axis. The line joining a point in cornea little medial to anterior pole and the fovea centralis situated lateral to posterior pole is known as visual axis. The light rays pass through the visual axis of eyeball (Fig. 104-1).

■ ORBITAL CAVITY

Except the anterior 1/6, the eyeball is situated in the bony orbital cavity or eye socket. A thick layer of areolar tissue is interposed between the bone and the eye. It serves as a cushion to protect the eyeball from external force. Eyeballs are attached to orbital cavity by ocular muscles.

■ EYELIDS

Eyelids protect the eyeball from foreign particles coming in contact with its surface and cutoff the

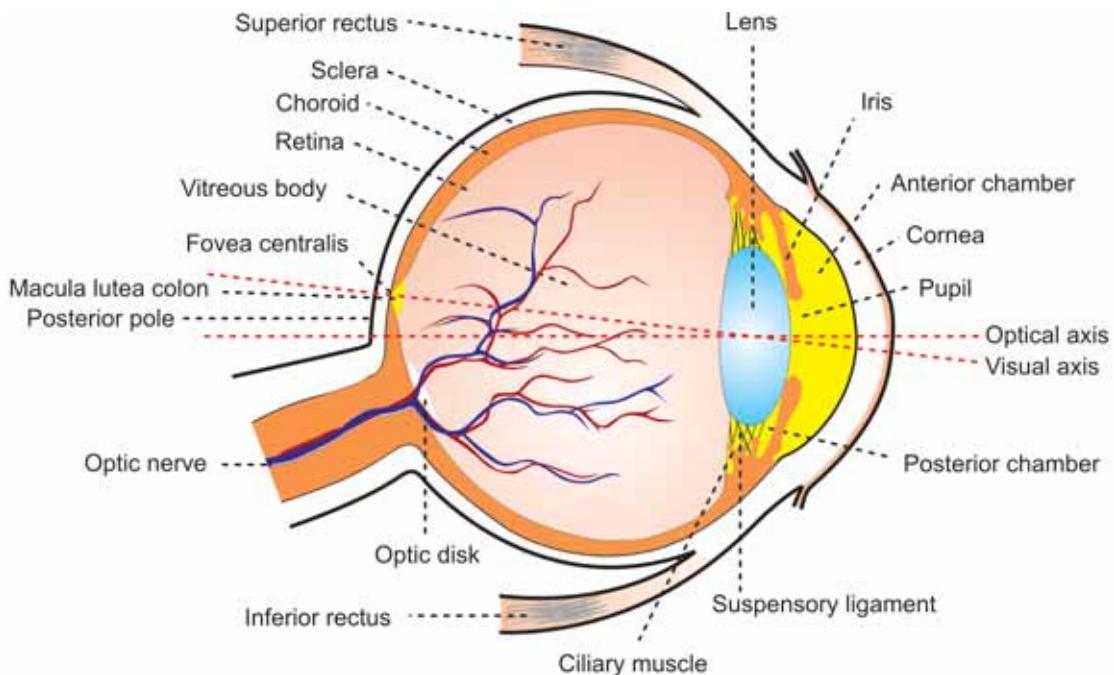


FIGURE 104-1: Structure of eyeball

light during sleep. The eyelids are opened and closed voluntarily as well as reflexly.

The margins of eyelids have sensitive hairs called the cilia. Each cilium arises from a follicle, which is surrounded by a sensory nerve plexus. When the dust particle comes in contact with cilia, these sensory nerves are activated resulting in rapid blinking of eyelids. It prevents the dust particles from reaching the eyeball.

The opening between the two eyelids is called palpebral fissure. In adults, it is about 25 mm long. Its width is about 12 to 15 mm when opened.

■ CONJUNCTIVA

It is a thin mucous membrane, which covers the exposed part of the eye. After covering the anterior surface, the conjunctiva is reflected into the inner surfaces of the eyelids. The part of conjunctiva covering the eyeball is called the bulbar portion. The part covering the eyelid is called the palpebral portion.

■ LACRIMAL GLAND

The lacrimal gland is situated in the shelter of bone, forming the upper and outer border of wall of the eye socket. From the lacrimal gland, tear flows over the surface of conjunctiva and drains into nose via lacrimal ducts, lacrimal sac and nasolacrimal duct. Tear is a hypertonic fluid. Due to its continuous washing and lubrication, the conjunctiva is kept moist and is protected from infection. Tear also contains lysozyme that kills bacteria.

■ WALL OF THE EYEBALL

The wall of the eyeball is composed of three layers namely outer, middle and inner layers (Fig. 104-2).

■ OUTER LAYER OR TUNICA EXTERNA OR TUNICA FIBROSA

The outer layer preserves the shape of eyeball. The anterior 1/6 is transparent and is known as

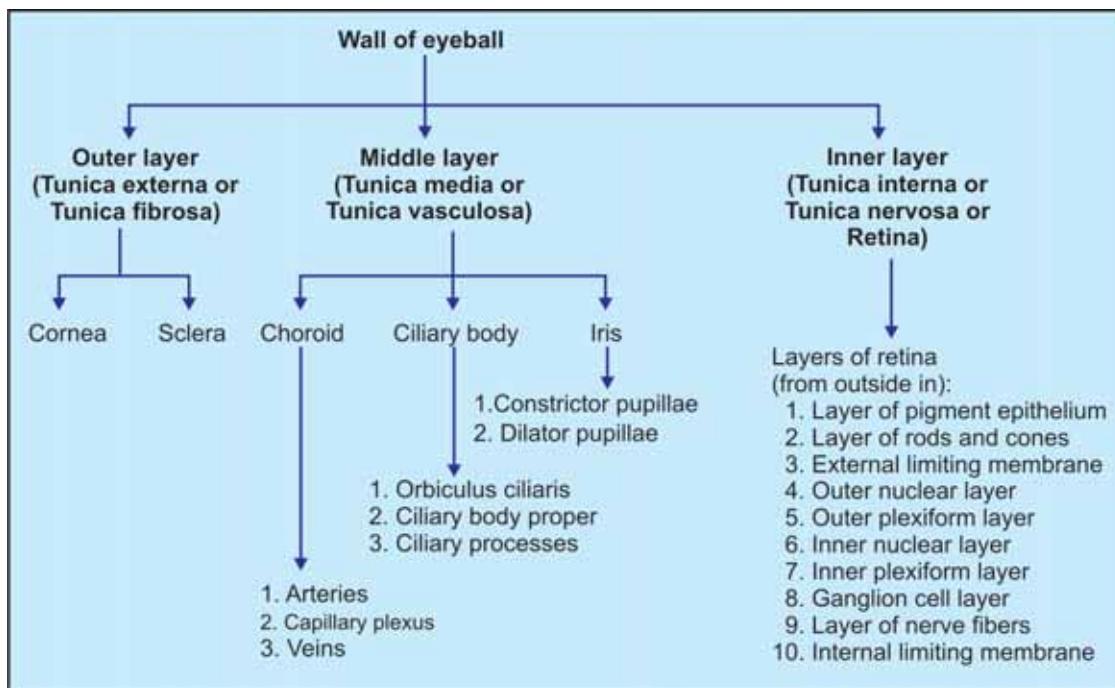


FIGURE 104-2: Wall of the eyeball

cornea. It covers the iris and the pupil. It is continuous with the sclera. The posterior 5/6 of this coat is tough, fibrous and opaque and it is called the sclera.

MIDDLE LAYER OR TUNICA MEDIA OR TUNICA VASCULOSA

The middle layer surrounds the eyeball completely except for a small opening in front known as the pupil. This layer comprises three structures.

1. Choroid
2. Ciliary body
3. Iris.

1. Choroid

Choroid is the thin vascular layer of eyeball situated between sclera and retina. It forms posterior 5/6 of middle layer. The choroid is extended anteriorly up to the insertion of ciliary muscle (the level of ora serrata). Choroid is composed of a rich capillary plexus, numerous small arteries and veins.

2. Ciliary Body

Ciliary body is the thickened anterior part of middle layer of eye situated between choroid and iris. It is situated in front of ora serrata.

It is in the form of a ring. Its outer surface is separated from the sclera by perichoroidal space. The inner surface of the ciliary body faces the vitreous body and lens. The suspensory ligaments from the lens are attached to ciliary body. The anterior surface of ciliary body faces towards the center of cornea. From the surface, the iris arises. Ciliary body has three parts:

- i. Orbiculus ciliaris
- ii. Ciliary body proper
- iii. Ciliary processes.

3. Iris

Iris is the thin colored curtain like structure of eyeball. It forms the anterior most part of middle layer. It is like a thin circular diaphragm, placed in front of the lens. It has a circular opening in the center called pupil. Iris is a muscular structure and has two muscles:

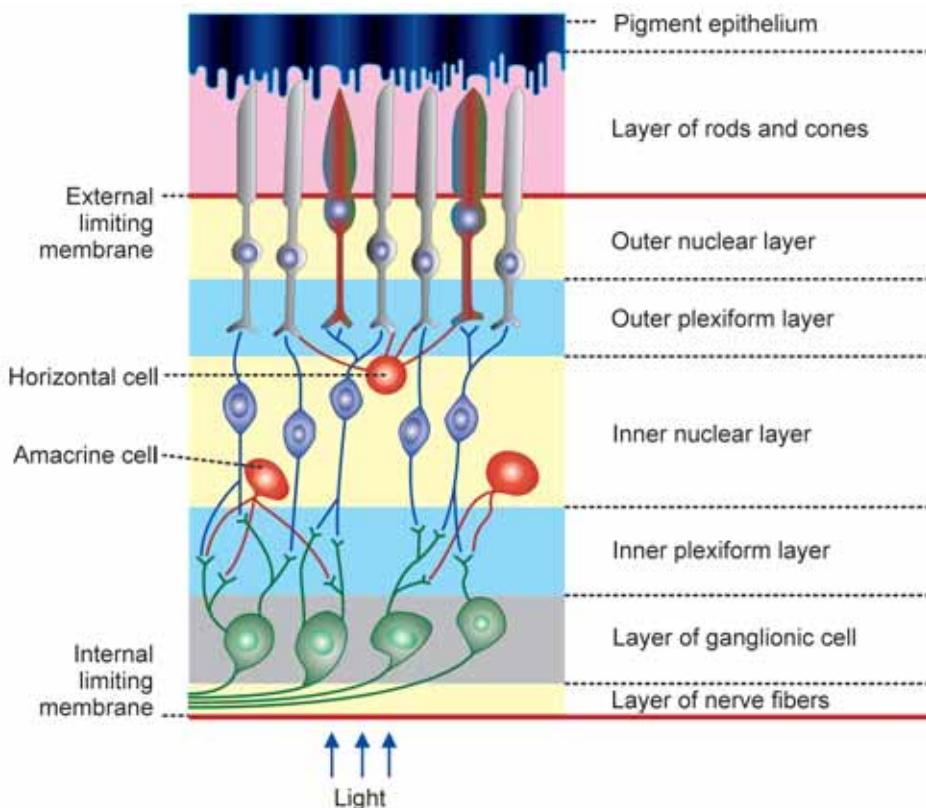


FIGURE 104-3: Layers of retina

- i. Constrictor papillae or sphincter pupillae. Contraction of this muscle causes constriction of pupil
- ii. Dilator papillae or pupillary dilator muscle. Contraction of this muscle causes dilation of pupil.

The activities of these muscles of iris increase or decrease the diameter of the pupil and regulate the amount of light entering the eye. Thus, iris acts like the diaphragm of a camera.

Iris separates the space between cornea and lens into two chambers namely, the anterior and posterior chambers. Both the chambers communicate with each other through pupil. The lateral border of anterior chamber is angular in shape. It is called iris angle or angle of anterior chamber.

■ INNER LAYER OR TUNICA INTERNA OR TUNICA NERVOSA OR RETINA

Retina is the light sensitive membrane that forms the innermost layer of eyeball. It extends from the margin of optic disk to just behind the ciliary body. Here, it ends abruptly as a dentated border known as ora serrata. Retina has the receptors of vision. Structurally, retina is made up of 10 layers (Fig. 104-3).

1. Layer of pigment epithelium
2. Layer of rods and cones
3. External limiting membrane
4. Outer nuclear layer
5. Outer plexiform layer
6. Inner nuclear layer
7. Inner plexiform layer
8. Ganglion cell layer

9. Layer of nerve fibers
10. Internal limiting membrane.

1. Layer of Pigment Epithelium

It is the outermost layer situated adjacent to choroid. It is a single layer of hexagonal epithelial cells which contain the pigment melanin.

2. Layer of Rods and Cones

This layer lies between pigment epithelial layer and external limiting membrane. The rods and cones are the light sensitive portions of the visual receptor cells, the rod cells and the cone cells. The receptor cells are arranged in a parallel fashion and are perpendicular to the inner surface of the eyeball.

3. External Limiting Membrane

It is a thin layer, formed by the chief supporting elements of retina called the Müller's fibers.

4. Outer Nuclear Layer

The fibers and granules of rods and cones are present in this layer. The granules of rods and cones contain nucleus.

5. Outer Plexiform Layer

This layer contains reticular meshwork formed by the terminal fibers of rods and cones and the dendrites from bipolar cells, situated in the inner nuclear layer.

6. Inner Nuclear Layer

The inner nuclear layer contains small oval shaped flattened bipolar cells. The axons of the bipolar cells go inside and synapse with dendrites of ganglionic cells in the inner plexiform layer. The dendrites synapse with fibers of rods and cones in the outer plexiform layer. This layer also contains nuclei of Müller's supporting fibers and some association neurons called horizontal cells and amacrine cells.

7. Inner Plexiform Layer

This layer of retina consists of synapses between dendrites of ganglionic cells and axons of bipolar cells.

8. Ganglion Cell Layer

Multipolar cells are present in this layer. The axons from ganglion cells are in the inner surface of the retina. These axons form the optic nerve. The dendrites of the ganglion cells synapse with axons of bipolar cells in the inner plexiform layer.

9. Layer of Nerve Fibers

It is formed by nonmyelinated axons of ganglionic cells. After taking origin, the axons run horizontally to a short distance. Afterwards, the fibers converge towards the optic disk and form the optic nerve.

10. Internal Limiting Membrane

It is the inner most layer of retina and it separates retina from the vitreous body. It is a hyaline membrane formed by the opposition of expanded ends of Müller's fibers.

■ FUNDUS OCULI OR FUNDUS

Fundus oculi or fundus is the posterior part of interior of eyeball (Fig. 104-4). It is examined by ophthalmoscope. It has two important structures:

1. Optic disk
2. Macula lutea with fovea centralis.

■ OPTIC DISK – BLIND SPOT

Optic disk is a pale disk situated near the center of the posterior wall of eyeball. It is formed by the convergence of axons from ganglion cells, while forming the optic nerve. The optic disk contains all the layers of retina except rods and cones. Therefore, it is insensitive to light, i.e. the object is not seen if the image falls upon this area. Because of this, the optic disk is known as blind spot.

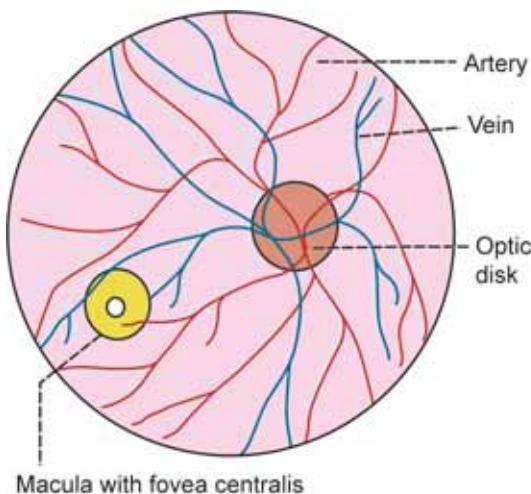


FIGURE 104-4: Fundus oculi

■ MACULA LUTEA

Macula lutea is a small yellowish area situated lateral to optic disk in retina. It is also called yellow spot. The yellow color of macula lutea is due to the presence of a yellow pigment. Macula lutea has fovea centralis in its center.

Fovea Centralis

Fovea centralis is a minute depression in the center of macula lutea. The fovea is the region of the most acute vision because it contains only cones. When one looks at an object, the eyeballs are directed towards the object, so that, the image of that object falls on the fovea of each eye and the person can see the object very clearly. It is known as foveal vision.

The vision in other parts of retina is called peripheral or extrafoveal vision. It is less sensitive and enables the subject to gain only a dim and an ill-defined impression of surroundings.

■ INTRAOCULAR FLUIDS

Two types of fluids are present in the eye:

1. Vitreous humor
2. Aqueous humor.

■ VITREOUS HUMOR

Vitreous humor or vitreous body is a viscous fluid present behind the lens in the space between the lens and retina. It is a highly viscous and gelatinous substance. It is formed by a fine fibrillar network of proteoglycan molecules. Vitreous humor helps maintain the shape of the eyeball.

■ AQUEOUS HUMOR

It is a thin fluid present in front of retina. It fills the space between the lens and cornea. This space is divided into anterior and posterior chambers by iris. Both the chambers communicate with each other through pupil.

Aqueous humor is formed by ciliary processes. After formation, aqueous humor reaches the posterior chamber. From here it reaches the anterior chamber via pupil.

From anterior chamber, the aqueous humor passes through the angle between cornea and iris, meshwork of trabeculae and canal of Schlemm and reaches the venous system via anterior ciliary vein.

Functions of aqueous humor

Aqueous humor:

1. Maintains shape of the eyeball
2. Maintains the intraocular pressure
3. Provides nutrients, oxygen and electrolytes to the avascular structures like lens and cornea
4. Removes metabolic end products from lens and cornea.

■ INTRAOCULAR PRESSURE

Intraocular pressure is the measure of fluid pressure in the eye exerted by aqueous humor. The normal intraocular pressure varies between 12 and 20 mm Hg. It is measured by tonometer. When intraocular pressure increases to about 60 to 70 mm Hg, glaucoma occurs. Refer Applied Physiology in this chapter for details.

■ LENS

The lens of the eyeball is crystalline in nature. It is situated behind the pupil. It is a biconvex, transparent and elastic structure. It is avascular and receives its nutrition mainly from the aqueous humor.

Lens refracts light rays and helps to focus the image of the objects on retina. The focal length of human lens is 44 mm and its refractory power is 23D.

Lens is supported by the suspensory ligaments (zonular fibers) which are attached with ciliary bodies.

■ CHANGES IN THE LENS DURING OLD AGE

In old age, the elastic property of lens is decreased due to the physical changes in lens and its capsule. It causes presbyopia.

In old age, lens becomes opaque and this condition is called cataract.

■ OCULAR MUSCLES

■ MUSCLES OF THE EYEBALL

The muscles of the eyeball are of two types:

1. Intrinsic muscles
2. Extrinsic muscles.

1. *Intrinsic Muscles*

The intrinsic muscles are formed by smooth muscle fibers and are controlled by the autonomic nerves. The intrinsic muscles of the eye are constrictor pupillae, dilator pupillae and ciliary muscle.

2. *Extrinsic Muscles*

The extrinsic muscles are formed by skeletal muscle fibers and are controlled by the somatic

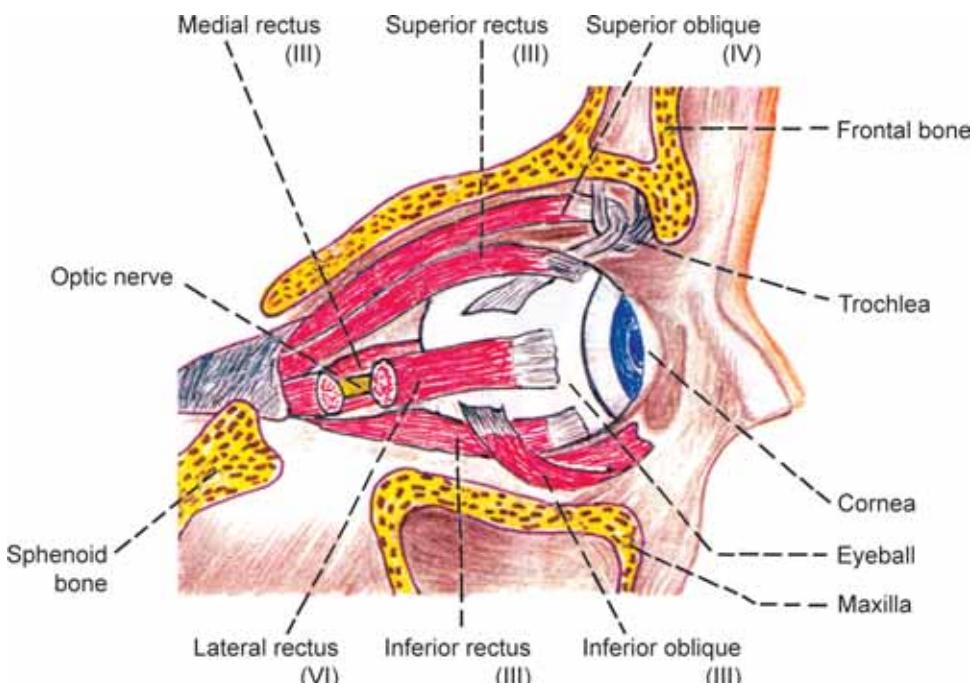


FIGURE 104-5: Extrinsic muscles of eyeball. Numbers in parenthesis indicate the cranial nerve supplying the muscle

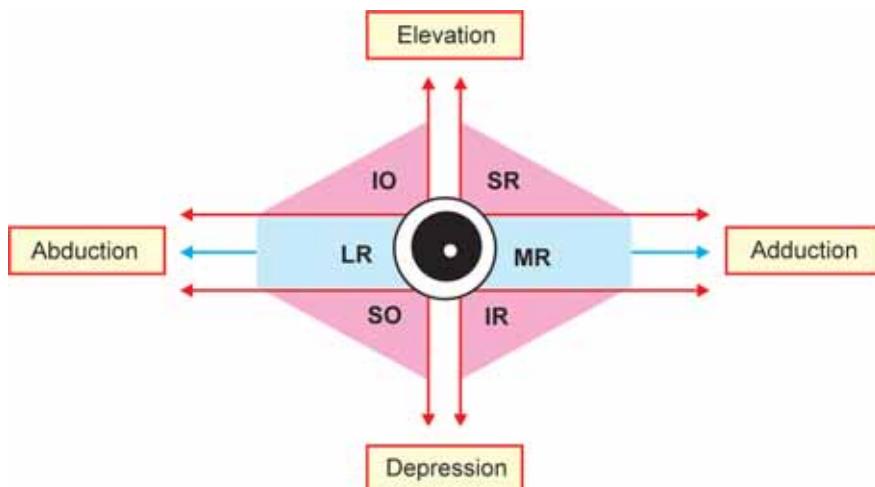


FIGURE 104-6: Diagram showing the movements of right eye. MR = Medial rectus. SO = Superior oblique. LR = Lateral rectus. IO = Inferior oblique. SR = Superior rectus. IR = Inferior rectus

nerves. The eyeball moves within the orbit by six extrinsic skeletal muscles (Fig. 104-5). One end of each muscle is attached to the eyeball and the other end to the wall of orbital cavity. There are four straight muscles (rectus) and two oblique muscles:

1. Superior rectus
2. Inferior rectus
3. Medial or internal rectus
4. Lateral or external rectus
5. Superior oblique
6. Inferior oblique.

■ INNERVATION OF OCULAR MUSCLES

Innervation of Intrinsic Muscles

The intrinsic muscles of eyeball are innervated by both sympathetic and parasympathetic divisions of autonomic nervous system.

Innervation of Extrinsic Muscles

The extrinsic muscles of the eyeball are innervated by somatic motor nerve fibers. The somatic nerve fibers arise from the cranial nerve nuclei in brainstem and reach the ocular muscles via three cranial nerves:

1. Oculomotor (third) nerve which supplies superior rectus, inferior rectus, medial rectus (internal rectus) and Inferior oblique
2. Trochlear (fourth) nerve which supplies the superior oblique
3. Abducent (sixth) nerve which supplies the lateral rectus (external rectus).

■ OCULAR MOVEMENTS

The eyeball moves or rotates within the orbital socket in any of the three primary axes, vertical (abduction and adduction), transverse (elevation and depression) and anteroposterior axis (extorsion and intorsion). Refer Fig. 104-6 and Table 104-1 for details.

■ APPLIED PHYSIOLOGY

■ GLAUCOMA

Glaucoma is a disease characterized by increase in intraocular pressure above 60 mmHg resulting in damage of optic nerve and blindness. Intraocular pressure increases due to the blockage in the drainage of aqueous humor.

TABLE 104-1: Muscles taking part in ocular movements

Movement	Primary muscle	Secondary muscle
1. Abduction	Lateral rectus	Superior oblique Inferior oblique
2. Adduction	Medial rectus	Superior rectus
		Inferior rectus
3. Elevation	Superior rectus	Inferior oblique
4. Depression	Inferior rectus	Superior oblique
5. Extorsion	Inferior oblique	Inferior rectus
6. Intorsion	Superior oblique	Superior rectus

■ CATARACT

Cataract is the opacity or cloudiness in the natural lens of the eye. It is the major cause of blindness worldwide. When the lens becomes cloudy, light rays cannot pass through it easily, and vision is blurred. Cataract develops in old age after 55 to 60 years.

The lens is situated within the sealed capsule. The old cells die and accumulate within the capsule. Over years, the accumulation of cells is associated with accumulation of fluid and denaturation of the proteins in the lens fibers causing cloudiness of lens and blurred image.

Visual Process and Field of Vision

■ VISUAL PROCESS

- INTRODUCTION
- IMAGE FORMING MECHANISM
- NEURAL BASIS OF VISUAL PROCESS
- CHEMICAL BASIS OF VISUAL PROCESS
- ACUITY OF VISION

■ FIELD OF VISION

- DEFINITION
- BINOCULAR AND MONOCULAR VISION
- DIVISIONS OF VISUAL FIELD
- CORRESPONDING RETINAL POINTS
- BLIND SPOT
- VISUAL FIELD AND RETINA
- MAPPING OF VISUAL FIELD

■ VISUAL PROCESS

■ INTRODUCTION

Visual process is the series of actions that take place during visual perception. When the image of an object is focused on retina, the energy in visual spectrum is converted into electrical potentials (impulses) by rods and cones of retina through some chemical reactions. The impulses from rods and cones reach the cerebral cortex through optic nerve. And, the sensation of vision is produced in cerebral cortex. Thus, process of visual sensation is explained on the basis of image formation, and neural and chemical phenomena.

■ IMAGE FORMING MECHANISM

While looking at an object, the light rays from the object are refracted and brought to a focus upon retina. The image falls on the retina in an inverted position and reversed side to side. In spite of this, the object is seen in an upright position. It is because of the role played by cerebral cortex.

The light rays are refracted by the lens and cornea. The refractory power is measured in diopter (D). A diopter is the reciprocal of focal length expressed in meters.

The focal length of cornea is 24 mm and refractory power is 42D. The focal length of lens is 44 mm and refractory power is 23D.

■ NEURAL BASIS OF VISUAL PROCESS

The retina has the visual receptors which are also called photoreceptors. The photo receptors are rods and cones. There are about 6 million cones and 12 million rods in the human eye. The distribution of the photoreceptors varies in different areas of retina. Fovea has only cones and no rods. While proceeding from fovea towards the periphery of retina, the rods increase and the cones decrease in number. At the periphery of the retina, only rods are present and cones are absent.

Functions of Rods

Rods are very sensitive to light and have a low threshold. So, the rods are responsible for dim light vision or night vision or scotopic vision. But, rods do not take part in resolving the details and boundaries of objects (visual acuity) or the color of the objects (color vision). The vision by rod is black, white or in the combination of black and white namely, gray. Therefore, the colored objects appear faded or grayish in twilight.

Functions of Cones

Cones have high threshold for light stimulus. So, the cones are sensitive only to bright light. Therefore, the cone cells are called receptors of bright light vision or photopic vision or day light vision. The cones are also responsible for acuity of vision and the color vision.

■ CHEMICAL BASIS OF VISUAL PROCESS

Photosensitive pigments present in rods and cones are concerned with chemical basis of visual process. The chemical reactions involved in these pigments lead to the development of electrical activity in retina and generation of impulses (action potentials) which are transmitted through optic nerve. The photochemical changes in the visual receptors are called Wald's visual cycle.

Rhodopsin

Rhodopsin is the photosensitive pigment of rod cells. Rhodopsin is made up of a protein called

opsin and a chromophore. The opsin present in rhodopsin is known as scotopsin. Chromophore is a chemical substance that develops color in the cell. The chromophore present in the rod cells is called retinal. The retinal is the aldehyde of vitamin A or retinol.

Photochemical Changes in Rhodopsin

During exposure to light, rhodopsin is bleached and it is split into retinine and the protein called opsin through various intermediate photochemical reactions. The metarhodopsin produced during these reactions is the activated rhodopsin. It is responsible for development of receptor potential in rod cells.

Phototransduction

Visual transduction or phototransduction is the process by which the light energy is converted into receptor potential in visual receptors.

The resting membrane potential in other sensory receptor cells is usually between -70 and -90 mV. However, in the visual receptors in dark, the negativity is reduced and the resting membrane potential is about -40 mV. When light falls on retina, the rhodopsin is converted into metarhodopsin which causes mild hyperpolarization which is called receptor potential in the rod cells.

Thus, the process of receptor potential in visual receptors is different from that of other sensory receptors. When other sensory receptors are excited, the electrical response is in the form of depolarization. But, in visual receptors, the response is in the form of hyperpolarization.

Significance of Hyperpolarization

The hyperpolarization in rod cells leads to the development of response in bipolar cells and ganglionic cells so that the action potentials are transmitted to cerebral cortex via optic pathway.

Photosensitive Pigment in Cone Cells

The photosensitive pigment in the cone cells are porphyropsin, iodopsin and cyanopsin. Only one of these pigments is present in each cone. Each

type of cone pigment is sensitive to a particular light and the maximum response is shown at a particular light and wavelength.

The processes involved in phototransduction in cone cells are similar to those in the rod cells.

Dark Adaptation

Dark adaption is the process by which the person is able to see the objects in dim light. If a person enters a dim lighted room (darkroom) from a bright lighted area, he is blind for some time, i.e. he cannot see any object. After some time his eyes get adapted and he starts seeing the objects slowly. The maximum duration for dark adaptation is about 20 minutes.

Causes for dark adaptation

1. *Resynthesis of rhodopsin:* The time required for dark adaptation is partly determined by the time to resynthesize rhodopsin. In bright light, much of the pigment is being bleached (broken down). But in dim light, it requires some time for the regeneration of certain amount of rhodopsin, which is necessary for optimal rod function.
2. *Dilatation of pupil:* The dilatation of pupil during dark adaptation allows more and more light to enter the eye.

Light Adaptation

Light adaptation is the process in which eyes get adapted to bright light. When a person enters a bright lighted area from a dim lighted area, he feels discomfort due to the dazzling effect of bright light. After some time, when the eyes become adapted to light, he sees the objects around him without any discomfort. It is the mere disappearance of dark adaptation. The maximum period for light adaptation is about 5 minutes.

Causes for light adaptation

1. Reduced sensitivity of rods during light adaptation due to the breakdown of rhodopsin

2. Constriction of pupil which reduces quantity of light rays entering the eye.

Night Blindness

Night blindness is defined as the loss of vision in dim light. It is otherwise called nyctalopia or defective dim light (scotopic) vision.

Causes of night blindness

It is due to the deficiency of vitamin A, which is essential for the function of rods. The deficiency of vitamin A which occurs because of:

1. The diet containing less amount of vitamin A
2. Decreased absorption of vitamin A from the intestine.

Initially, vitamin A deficiency causes defective rod function. Prolonged deficiency leads to anatomical changes in rods and cones, and finally the degeneration of other retinal layers occurs. So, retinal function can be restored, only if treatment is given with vitamin A before the visual receptors start degenerating.

■ ACUITY OF VISION

Definition

Acuity of vision is the ability of the eye to determine the precise shape and details of the object. It is also called visual acuity. Cones of the retina are responsible for acuity of vision. Visual acuity is highly exhibited in fovea centralis, which contains only cones. It is greatly reduced during the refractory errors.

Test for Acuity of Vision

Acuity of vision is tested for distant vision as well as near vision. If there is any difficulty in seeing the distant object or the near object, the defect is known as error of refraction. The refractive errors are described separately in Chapter 109.

Distant vision

Snellen's chart is used to test the acuity of vision for distant vision in the diagnosis of refractive errors of the eye.

Near vision

Jaeger's chart is used to test the visual acuity for near vision.

■ FIELD OF VISION

■ DEFINITION

The part of the external world seen by one eye when it is fixed in one direction is called field of vision or visual field of that eye.

■ BINOCULAR AND MONOCULAR VISION

Binocular Vision

Binocular vision is the vision in which both the eyes are used together so that a portion of external world is seen by the eyes together. In humans and some animals, the eyeballs are placed in front of the head. So, the visual fields of both the eyes overlap. Because of this a portion of the external world is seen by both the eyes.

Monocular Vision

It is the vision in which each eye is used separately. In some animals like dog, rabbit and horse, the eyeballs are present at the sides of head. So, the visual fields of both eyes overlap to a very small extent. Because of this, different portion of the external world is seen by each eye.

■ DIVISIONS OF VISUAL FIELD

The visual field of human eye has an angle of 160° in horizontal meridian and 135° in vertical meridian. The visual field is divided into four parts:

1. Temporal field
2. Nasal field
3. Upper field
4. Lower field.

Temporal and Nasal Fields

The visual field of each eye is divided into two unequal parts namely, outer or temporal field and the inner or nasal field by a vertical line passing through the fixation point (Fig. 105-1). The fixation point is the meeting point of visual axis with the object.

The temporal part of visual field extends up to about 100° but the nasal part extends only up to 60° because it is restricted by nose.

Upper and Lower Fields

The visual field of each eye is also divided into an upper field and a lower field by a horizontal line passing through the fixation point. The extent of the upper field is about 60° as it is restricted by upper eyelid and orbital margin. The extent of lower field is about 75° . It is restricted by cheek. Thus, the visual field is restricted in all the sides except in the temporal part.

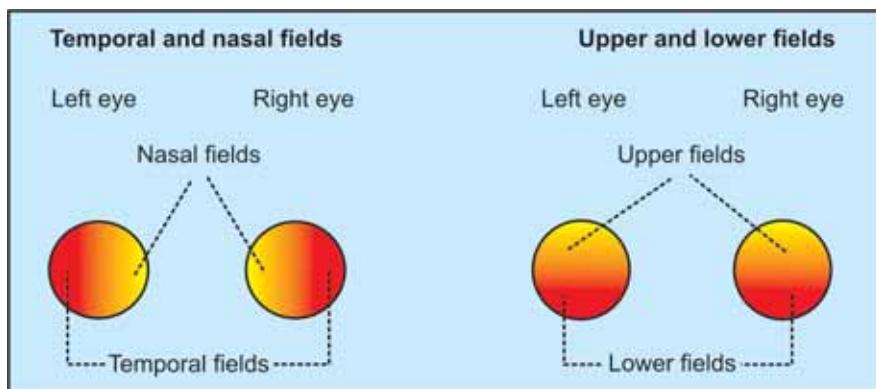


FIGURE 105-1: Divisions of visual field

■ CORRESPONDING RETINAL POINTS

Corresponding retinal points are the area in retina of both eyes on which the light rays from the object falls. It occurs in the binocular vision. The two images developed on retina of both eyes are fused into a single sensation. So, we see the objects with single image.

Diplopia

Diplopia means double vision. Normal single sensation is because of the ocular muscles, which direct the axes of the eyes in such a way, that the light rays from the object fall upon the corresponding points of both retinas. If the light rays do not fall on the corresponding retinal points, diplopia occurs.

■ BLIND SPOT

Blind spot is the small area of retina where visual receptors are absent. The optic disk in the retina does not have any visual receptors and, if the image of any object falls on the optic disk, the

object cannot be seen. So this part of the retina is blind hence the name blind spot.

Normally, the darkness in the visual field due to the blind spot does not cause any inconvenience because, the fixation of each eye is at different angles. Even when one eye is closed or blind, the person is not aware of blind spot. However, one can recognize blind spot by some experimental procedures.

■ VISUAL FIELD AND RETINA

The light rays from different halves of each visual field do not fall on the same halves of the retina. The light rays from temporal part of visual field of an eye fall on the nasal half of retina of that eye. Similarly, the light rays from nasal part of visual field fall on the temporal half of retina of the same side.

■ MAPPING OF VISUAL FIELD

The shape and extent of visual field is mapped out by means of an instrument called perimeter. The visual field is also determined by Bjerrum screen or by confrontation test.

Visual Pathway

- INTRODUCTION
- VISUAL RECEPTORS
- FIRST ORDER NEURONS
- SECOND ORDER NEURONS
- THIRD ORDER NEURONS
- COURSE OF VISUAL PATHWAY
- APPLIED PHYSIOLOGY

■ INTRODUCTION

Visual pathway or optic pathway is the nervous pathway that carries the retinal impulses to cerebral cortex. In binocular vision, the light rays from temporal (outer) half of visual field (Chapter 105) fall upon the nasal part of corresponding retina. Light rays from nasal (inner) half of visual field fall upon the temporal part of retina.

■ VISUAL RECEPTORS

Rods and cones, which are present in the retina of eye, form the visual receptors. Fibers from the visual receptors synapse with dendrites of bipolar cells of inner nuclear layer of retina.

■ FIRST ORDER NEURONS

First order neurons (primary neurons) are bipolar cells in the retina. Axons from the bipolar cells synapse with dendrites of ganglionic cells.

■ SECOND ORDER NEURONS

Second order neurons (secondary neurons) are the ganglionic cells in ganglionic cell layer of

retina. The axons of the ganglionic cells form optic nerve. The optic nerve leaves the eye and terminates in lateral geniculate body.

■ THIRD ORDER NEURONS

The third order neurons are in the lateral geniculate body. Fibers arising from here reach the visual cortex.

■ COURSE OF VISUAL PATHWAY

The visual pathway consists of six components:

1. Optic nerve
2. Optic chiasma
3. Optic tract
4. Lateral geniculate body
5. Optic radiation
6. Visual cortex.

■ 1. OPTIC NERVE

It is formed by the axons of ganglionic cells (Fig. 106-1). Optic nerve leaves the eye through optic disk. The fibers from temporal part of retina are in lateral part of the nerve and carry the

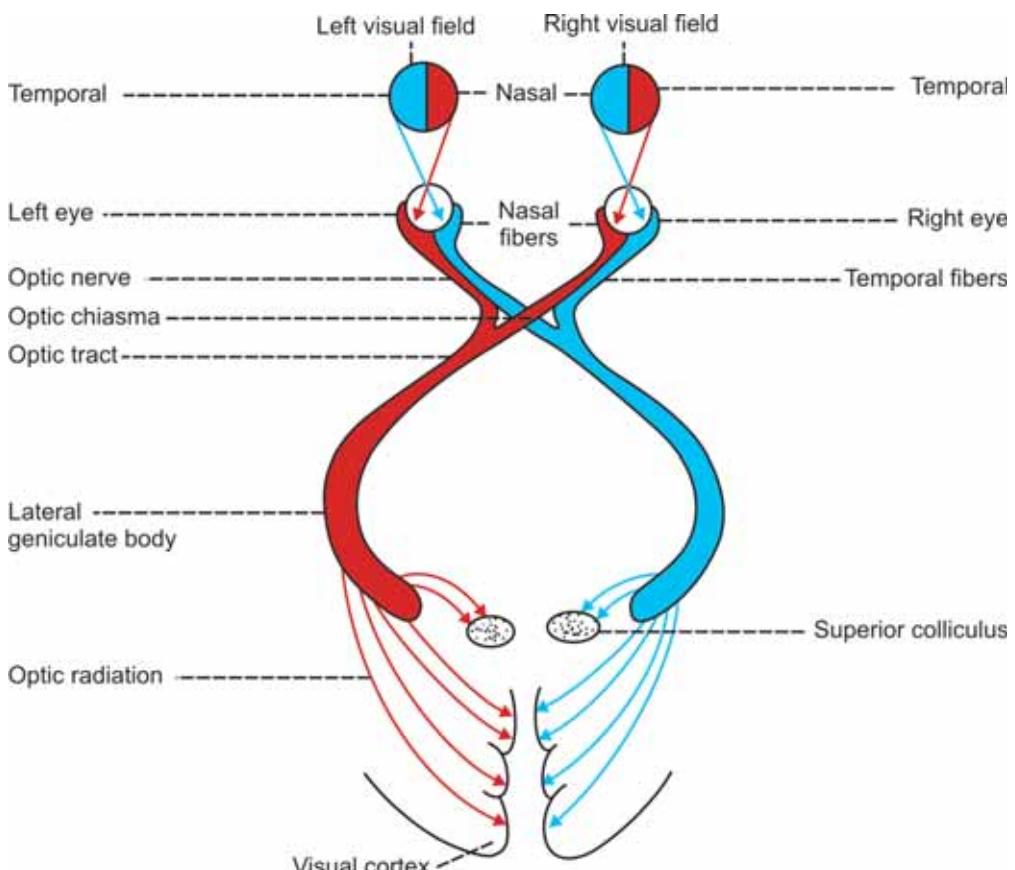


FIGURE 106-1: Visual pathway

impulses from nasal half of visual field of same eye. The fibers from nasal part of retina are in medial part of the nerve and carry the impulses from temporal half of visual field of same eye.

■ 2. OPTIC CHIASMA

The medial fibers of each optic nerve cross the midline and join the uncrossed lateral fibers of opposite side to form the optic tract (Fig. 106-1). The area of crossing of the optic nerve fibers is called optic chiasma.

■ 3. OPTIC TRACT

It is formed by uncrossed fibers of optic nerve on the same side and crossed fibers of optic nerve from the opposite side. All the fibers of optic tract run backward and outward and terminate in the lateral geniculate body in

thalamus. Few fibers just pass through medial geniculate body and run towards superior colliculus in midbrain.

Due to crossing of medial fibers in optic chiasma, the left optic tract carries impulses from temporal part of left retina and nasal part of right retina, i.e. it is responsible for vision in nasal half of left visual field and temporal half of right visual field. The right optic tract contains fibers from nasal half of left retina and temporal half of right retina. It is responsible for vision in temporal half of left visual field and nasal half of right visual field.

■ 4. LATERAL GENICULATE BODY

Majority of the fibers of optic tract terminate in lateral geniculate body, which forms the subcortical center for visual sensation. From here,

the geniculocalcarine tract or optic radiation arises. This tract is the last relay of visual pathway.

Some of the fibers from optic tract do not synapse in lateral geniculate body but, pass through it and terminate in one of the following centers:

- The superior colliculus which is concerned with reflex movements of eyeballs and head in response to optic stimulus
- Pretectal nucleus which is concerned with light reflexes
- Supraoptic nucleus of hypothalamus which is concerned with the retinal control of pituitary.

■ 5. OPTIC RADIATION

Fibers from lateral geniculate body pass through internal capsule and form optic radiation. Optic radiation ends in visual cortex (Fig. 106-2).

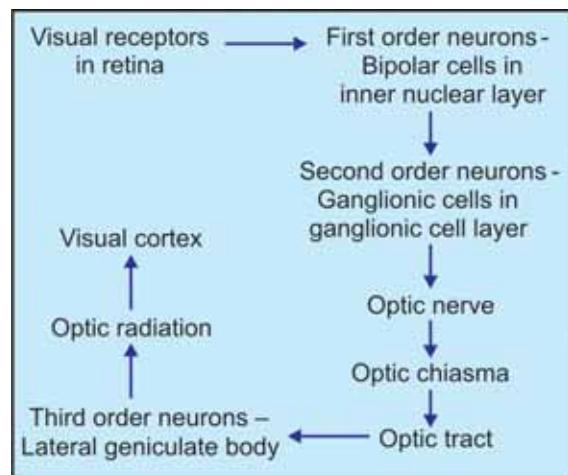


FIGURE 106-2: Schematic representation of visual pathway

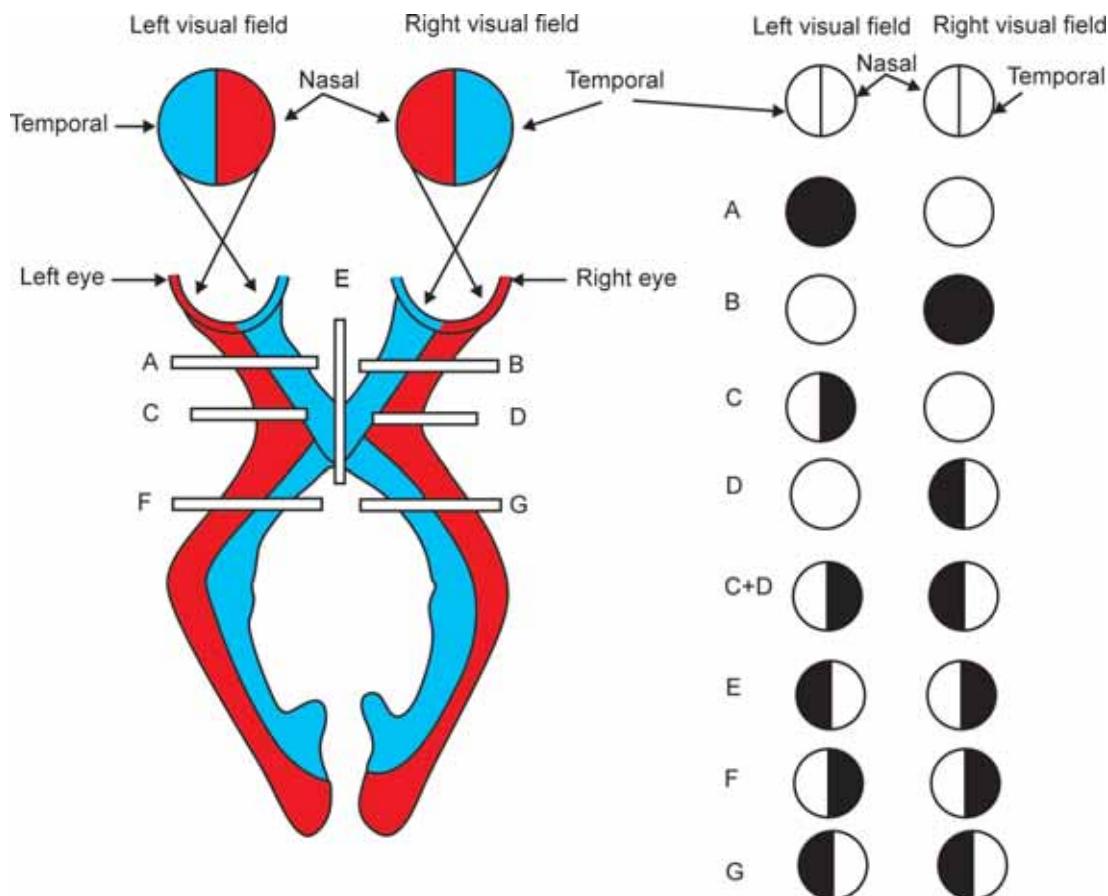


FIGURE 106-3: Effects of lesions of optic pathway. Dark shade in circles indicates blindness

■ 6. VISUAL CORTEX

The primary cortical center for vision is called visual cortex that is located on the medial surface of occipital lobe. It forms the walls and lips of calcarine fissure in medial surface of occipital lobe.

There is definite localization of retinal projections upon visual cortex. In fact, the point to point projection of retina upon visual cortex is well established. The peripheral retinal representation occupies the anterior part of visual cortex. The macular representation occupies the posterior part of visual cortex near the occipital pole.

Areas of Visual Cortex and their Function

Three areas are present in visual cortex:

- i. Primary visual area (area 17) which is concerned with perception of visual impulses
- ii. Visual association area (area 18) which is concerned with interpretation of visual impulses
- iii. Occipital eye field (area 19) which is concerned with movement of eyes.

■ APPLIED PHYSIOLOGY

The injury to any part of optic pathway causes visual defect and the nature of defect depends upon the location and extent of injury. The loss

of vision in one visual field is known as anopia. Loss of vision in one half of visual field is called hemianopia (Fig. 106-3).

Hemianopia is classified into two types:

1. *Homonymous hemianopia*: Loss of vision in the same halves of both visual fields
2. *Heteronymous hemianopia*: Loss of vision in opposite halves of visual field.

■ EFFECT OF LESION AT DIFFERENT LEVELS OF VISUAL PATHWAY

1. Lesion of left optic nerve – total blindness (anopia) of left eye (Fig. 106-3: A)
2. Lesion of right optic nerve – total blindness (anopia) of right eye (Fig. 106-3: B)
3. Lesion of lateral fibers in left side of optic chiasma – left nasal hemianopia (Fig. 106-3: C)
4. Lesion of lateral fibers in right side of optic chiasma – right nasal hemianopia (Fig. 106-3: D)
5. Lesion of lateral fibers in both sides of optic chiasma – binasal hemianopia (Fig. 106-3: C + D)
6. Lesion of medial fibers in optic chiasma – bitemporal hemianopia (Fig. 106-3: E)
7. Lesion of left optic radiation – right homonymous hemianopia (Fig. 106-3: F)
8. Lesion of right optic radiation – left homonymous hemianopia (Fig. 106-3: G).

Pupillary Reflexes

- INTRODUCTION
- LIGHT REFLEX
 - DIRECT LIGHT REFLEX
 - INDIRECT LIGHT REFLEX
 - PATHWAY FOR LIGHT REFLEX
 - CILIOSPINAL REFLEX
- ACCOMMODATION
 - DEFINITION
 - MECHANISM OF ACCOMMODATION
 - ACCOMMODATION REFLEX
 - PATHWAY FOR ACCOMMODATION REFLEX
- APPLIED PHYSIOLOGY – PRESBYOPIA

■ INTRODUCTION

Pupillary reflexes are the visceral reflexes, which alter the size of pupil. Pupillary reflexes are classified into three types:

1. Light reflex
2. Cilioospinal reflex
3. Accommodation reflex.

■ LIGHT REFLEX

It is the reflex in which the pupil constricts when light is flashed into the eyes. It is also called pupillary light reflex. Light reflex is of two types:

■ DIRECT LIGHT REFLEX

Direct light reflex or direct pupillary light reflex is constriction of pupil in an eye when light is thrown into that eye.

■ INDIRECT LIGHT REFLEX

Indirect light reflex or consensual light reflex is constriction of pupil in both eyes when light is thrown into one eye.

PATHWAY FOR LIGHT REFLEX

Afferent Pathway

The pathway for light reflex is slightly deviated from visual pathway. When light falls on the eye, the visual receptors are stimulated. The afferent (sensory) impulses from the receptors pass through the optic nerve, optic chiasma and optic tract. At the midbrain level, few fibers get separated from the optic tract and synapse on the neurons of pretectal nucleus, which lies close to the superior colliculus.

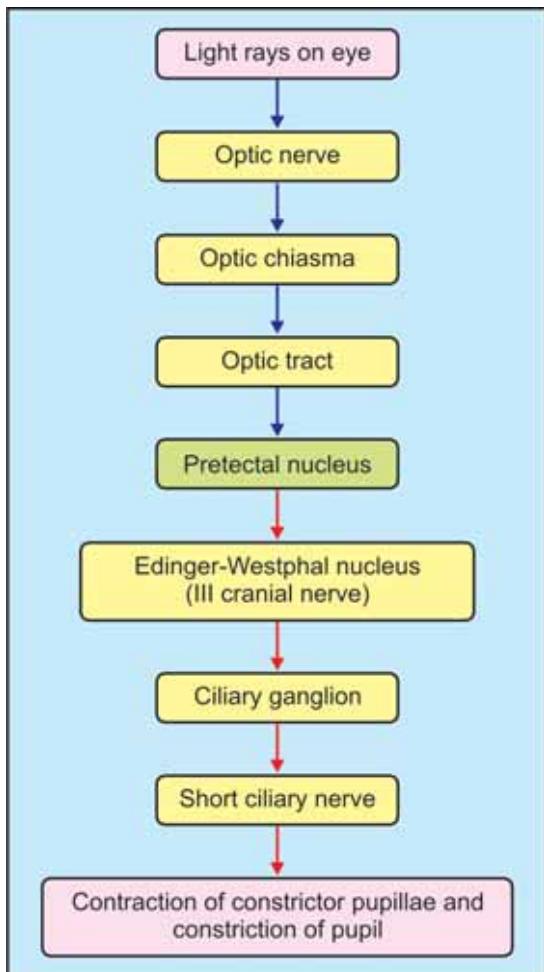


FIGURE 107-1: Pathway for light reflex

Center

The pretectal nucleus of midbrain forms the center for light reflexes.

Efferent Pathway

The efferent (motor) impulses from this nucleus are carried by short fibers to Edinger-Westphal nucleus (parasympathetic nucleus) of oculomotor nerve (third cranial nerve) in midbrain. From Edinger-Westphal nucleus, the preganglionic fibers pass through oculomotor nerve and reach the ciliary ganglion. The postganglionic fibers arising from the ciliary ganglion pass through the short ciliary nerves

and reach the eyeball. These fibers cause contraction of constrictor pupillae muscle of iris (Fig. 107-1) resulting in constriction of pupil.

■ CILIOSPINAL REFLEX

Ciliospinal reflex is the dilatation of pupil in eyes caused by painful stimulation of skin over the neck. It is due to the contraction of dilator pupillae muscle. Sensory impulses pass through cutaneous afferent nerve. The center is in first thoracic spinal segment. The efferent impulses pass through sympathetic fibers and reach dilator pupillae.

■ ACCOMMODATION

■ DEFINITION

Accommodation is the adjustment of the eye to see either near or distant objects clearly. It is the process, by which light rays from near objects or distant objects are brought to a focus on the sensitive part of retina. It is achieved by various adjustments made in the eyeball.

■ MECHANISM OF ACCOMMODATION

Light rays from distant objects are approximately parallel and are less refracted while getting focused on retina. But, the light rays from near objects are divergent. So, to be focused on retina, these light rays should be refracted (converged) to a greater extent.

Accommodation in near vision occurs by means of three adjustments made in the eyeballs:

1. Increase in anterior curvature of the lens so that the refractory power of lens is increased
2. Convergence of both eyeballs which brings the retinal images on to the corresponding points
3. Constriction of pupil that causes:
 - i. Increase in the visual acuity
 - ii. Reduction in the quantity of light entering eye
 - iii. Increase in the depth of focus through more central part of lens as its convexity is increased.

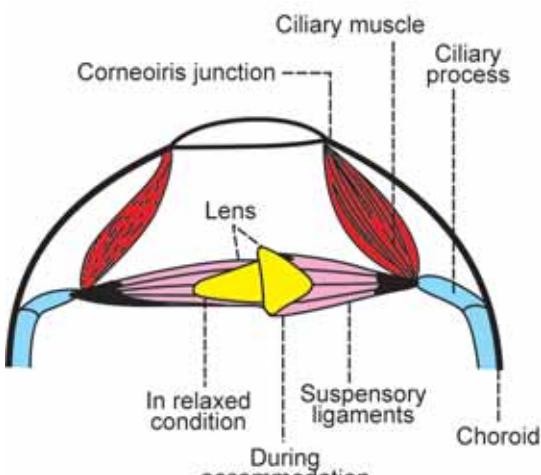


FIGURE 107-2: Accommodation

Young-Helmholtz Theory

This theory describes how the curvature of lens increases and thereby, the refractive power of lens is enhanced. When the eyes are fixed on a distant object (distant vision) lens is flat due to the traction of suspensory ligaments which extend from the capsule of lens and are attached to the ciliary processes. The ciliary processes are attached to choroid through the ciliary muscle (Fig. 107-2).

When the vision is shifted from the distant object to a near object (near vision), ciliary muscle contracts and draws the choroid forward. The ciliary processes are brought closer to lens. The suspensory ligaments are slackened. Now, the tension on the lens is released. The lens, due to its elastic property, bulges forward. The anterior curvature (convexity) of lens increases greatly. A very little change occurs in posterior curvature.

In resting eye, the intraocular pressure sets up tension in choroids and pulls the ciliary processes backward and outward. The suspensory ligaments are tensed up and the lens becomes flat.

■ ACCOMMODATION REFLEX

Accommodation is a reflex action. When a person looks at a near object after seeing a far object, three adjustments are made in the eyeballs:

1. Convergence of the eyeballs due to contraction of the medial recti
2. Constriction of the pupil due to the contraction of constrictor pupillae of iris
3. Increase in the anterior curvature of the lens due to contraction of the ciliary muscle.

Thus, the accommodation reflex involves both skeletal muscle (medial recti) and smooth muscle (ciliary muscle and sphincter pupillae).

■ PATHWAY FOR ACCOMMODATION REFLEX

Afferent Pathway

Visual impulses from retina pass through the optic nerve, optic chiasma, optic tract, lateral geniculate body and optic radiation to visual cortex (area 17) of occipital lobe. From here, the association fibers carry the impulses to frontal lobe (Fig. 107-3).

Center

The center for accommodation lies in frontal eye field (area 8) that is situated in the frontal lobe of cerebral cortex.

Efferent Pathway

1. *Efferent fibers to ciliary muscle and sphincter pupillae:* From area 8, the corticonuclear fibers pass via internal capsule to the Edinger-Westphal nucleus of III cranial nerve. From here, the preganglionic fibers pass through the third cranial nerve to the ciliary ganglion. The postganglionic fibers from

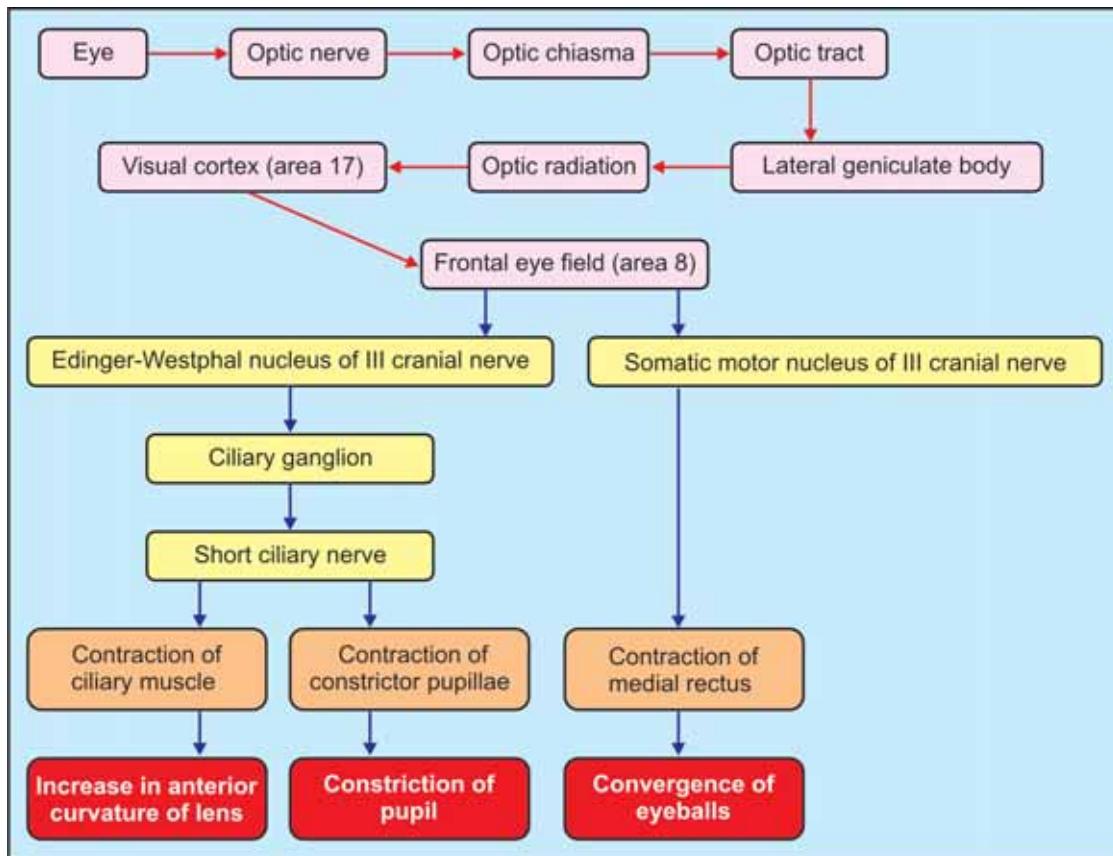


FIGURE 107-3: Pathway for accommodation reflex

ciliary ganglion pass via the short ciliary nerves and supply the ciliary muscle and the constrictor pupillae.

2. *Efferent fibers to medial rectus:* Some of the fibers from frontal eye field terminate in the somatic motor nucleus of oculomotor nerve. The fibers from the motor nucleus supply the medial rectus.

■ APPLIED PHYSIOLOGY – PRESBYOPIA

In old age, the amplitude of accommodation is decreased and the near point is away from the eye. So the near objects cannot be seen clearly. This condition is called presbyopia. Details are given in Chapter 109.

Color Vision

- INTRODUCTION
- VISIBLE SPECTRUM AND SPECTRAL COLORS
- CONES AND COLOR VISION – YOUNG-HELMOLTZ TRICHROMATIC THEORY
- APPLIED PHYSIOLOGY – COLOR BLINDNESS

■ INTRODUCTION

The human eye can recognize about 150 different colors in the visible spectrum. The discrimination and appreciation of colors depend upon the ability of cones in retina.

■ VISIBLE SPECTRUM AND SPECTRAL COLORS

■ SPECTRAL COLORS

When the sunlight or white light is passed through a glass prism, it is separated into different colors. The series of colored light produced by the prism is called the visible spectrum and the colors that form the spectrum are called the spectral colors. The spectral colors are red, orange, yellow, green, blue, indigo and violet (ROYGBIV or VIBGYOR). In the spectrum, the colors occupy the position according to their wavelengths. Wavelength is the distance between two identical points in the wave of light energy. Accordingly, red has got the maximum wavelength of about 8,000 Å and the violet has got the minimum wavelength of about 3,000 Å.

The light rays longer than the red are called infrared rays or the heat waves and the rays shorter than violet are called the ultraviolet rays. But, these two extraordinary types of rays do not evoke the sensation of vision.

■ EXTRASPECTRAL COLORS

Extraspectral colors are the colors other than those present in visible spectrum. These colors are formed by the combination of two or more spectral colors. For example, purple is the combination of violet and red. Pink is the combination of red and white.

■ PRIMARY COLORS

The primary colors are those, which when combined together produce the white. The primary colors are red, green and blue. These three colors in equal proportion give white.

■ COMPLEMENTARY COLORS

Complementary colors are the pair of two colors which produce white when mixed or combined

in proper proportion. Examples of complementary colors are red and greenish blue; orange and cyan blue; yellow and indigo blue; violet and greenish yellow; and purple and green.

■ CONES AND COLOR VISION – YOUNG-HELMHOLTZ TRICHROMATIC THEORY

According to Young- Helmholtz theory, retina has three types of cones and each cone is supplied by a separate fiber of optic nerve. Each cone has its own photosensitive pigment and gives response to one of the primary colors namely, red, green and blue. The different color sensations are produced by the stimulation of various combinations of the three types of cones. White is perceived by equal stimulation of all three types of cones.

■ APPLIED PHYSIOLOGY – COLOR BLINDNESS

Color blindness is the failure to appreciate one or more colors. It is common in 8% of males and only in 0.4% of females, as mostly the color blindness is an inherited sex linked recessive character. In addition to hereditary conditions, color blindness occurs due to acquired conditions also such as ocular diseases or injury or disease of retina.

■ CLASSIFICATION OF COLOR BLINDNESS

Based on Young-Helmholtz trichromatic theory, color blindness is classified into three types.

1. Monochromatism
2. Dichromatism
3. Trichromatism.

1. Monochromatism

Monochromatism is the condition characterized by total inability to perceive color. It is also called total color blindness or achromatopsia. Monochromatism is very rare. The persons with monochromatism are called monochromats. The

retina of monochromats is totally insensitive to color and they see the whole spectrum in only black, white and different shades of gray. So, their vision is similar to black and white photography.

2. Dichromatism

Dichromatism is the color blindness in which the subject can appreciate only two colors. Persons with this defect are called dichromats. They can match the entire spectrum of colors by only two primary colors because the receptors for third color are defective. The defects are classified into three groups:

i. *Protanopia*

Protanopia is the type of dichromatism caused by the defect in the receptor of first primary color, i.e. red. So, the red color cannot be appreciated. The persons having protanopia are called protanopes. They use blue and green to match the colors. Thus, they confuse red with green.

ii. *Deuteranopia*

It is the dichromatism caused due to the defect in the receptor of the second primary color, i.e. green. Deuteranopes use blue and red colors and they cannot appreciate green color.

iii. *Tritanopia*

It is the dichromatism caused due to the defect in the receptor of third primary color, i.e. blue. Tritanopes use red and green colors and they cannot appreciate blue color.

3. Trichromatism

Trichromatism is the color blindness in which the intensity of one of the primary colors cannot be appreciated correctly though the affected persons are able to perceive all the three colors. The persons with this defect are called trichromats. Even the dark shades of one particular color look dull for them. Trichromatism is classified into three types:

i. Protanomaly

Protanomaly is the type of trichromatism in which the perception for red is weak. So to appreciate the red color, the person requires more intensity of red than a normal person.

ii. Deuteranomaly

Deuteranomaly is the trichromatism in which the perception for green is weak.

iii. Tritanomaly

It is the trichromatism with weak perception for blue.

■ TESTS FOR COLOR BLINDNESS

Color blindness is determined by using:

1. Ishihara's color charts
2. Colored wool
3. Edridge-Green lantern

Errors of Refraction

- **EMETROPIA AND AMETROPIA**
 - **MYOPIA OR SHORT SIGHTEDNESS**
 - **HYPERMETROPIA OR LONG SIGHTEDNESS**
- **ANISOMETROPIA**
- **ASTIGMATISM**
- **PRESBYOPIA**

■ EMETROPOIA AND AMETROPIA

Emmetropia is the vision with lens having normal refractive power and eye is called emmetropic eye. Any deviation in the refractive power from normal condition which leads to inadequate focusing on retina is called ametropia and the eye is called ametropic eye. The defect is due to the change in shape of the eyeball.

Ametropia is of two types:

1. Myopia
2. Hypermetropia.

■ MYOPIA OR SHORT SIGHTEDNESS

Myopia is the eye defect characterized by the inability to see the distant object. It is otherwise called short sightedness because the person can see near objects clearly but not the distant objects (Fig. 109-1 and Table 109-1).

Cause

In myopia, the refractive power of the lens is usually normal. But, the anteroposterior diameter

of the eyeball is abnormally long. Therefore, the image is brought to a focus a little in front of retina. In other words, the refractory power of lens is too strong for the length of eyeball. The light rays, after coming to a focus, disperse again so, a blurred image is formed upon retina.

Correction

In myopic eye, in order to form a clear image on the retina, the light rays entering the eye must be divergent and not parallel. Thus, the myopic eye is corrected by using biconcave lens. The light rays are diverged by the concave lens before entering the eye (Fig. 109-1).

■ HYPERMETROPIA OR LONG SIGHTEDNESS

Hypermetropia is the eye defect characterized by the inability to see the near object. It is otherwise known as long sightedness because the person can see the distant objects clearly but not the near objects. It is also called hyperopia.

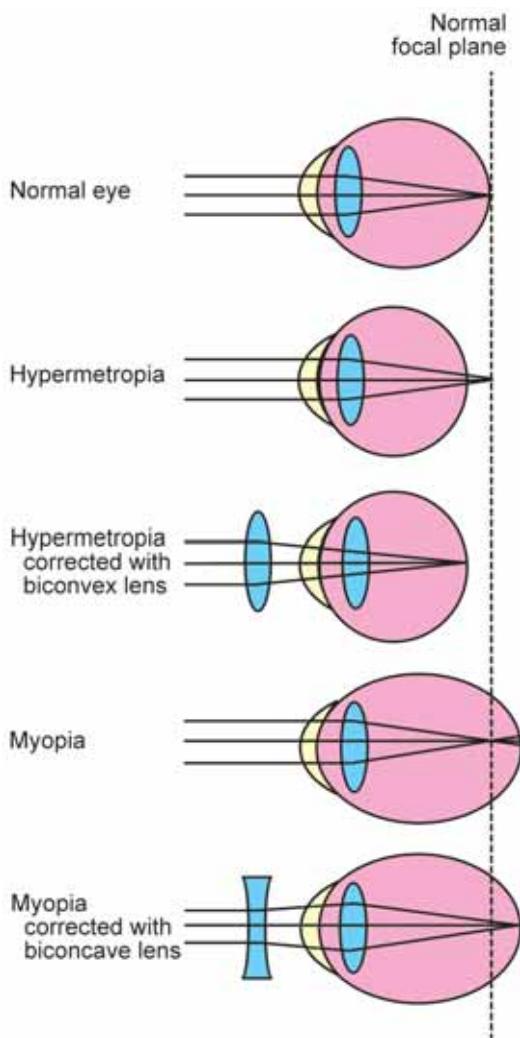


FIGURE 109-1: Errors of refraction

Cause

Hypermetropia is due to decreased anteroposterior diameter of the eyeball. So, even though the refractive power of the lens is normal, the light rays are not converged enough to form a clear image on retina, i.e. the light rays are brought to a focus behind retina. It causes a blurred image of near objects. Hypermetropia occurs in childhood, if the eyeballs fail to develop to the correct size. It is common in old age also.

Correction

Hypermetropia is corrected by using biconvex lens. The light rays are converged by convex lens before entering the eye (Fig. 109-1).

■ ANISOMETROPIA

Anisometropia is the condition in which the two eyes have unequal refractive power. It is corrected by using different appropriate lens for each eye (Table 109-1).

■ ASTIGMATISM

Astigmatism is the condition in which the light rays are not brought to a sharp point upon retina. It is the common optical defect present in all eyes. When it is moderate, it is known as physiological astigmatism. When it is well marked, it is considered abnormal. For example, the stars appear as small dots of light to a person with normal eye. But in astigmatism, the stars appear as radiating short lines of light (A = not; stigma = point).

■ CAUSE OF ASTIGMATISM

The light rays pass through all meridians of a lens. In a normal eye, lens has approximately same curvature in all meridians. So, the light rays are refracted almost equally in all meridians and brought to a focus.

If the curvature is different in different meridians viz. vertical, horizontal and oblique, the refractive power is also different in different meridians. The meridian with greater curvature refracts the light rays more strongly than the other meridians. So, these light rays are brought to a focus in front of the light rays, which pass through other meridians. Such irregularity of curvature of lens causes astigmatism.

■ TYPES OF ASTIGMATISM

Astigmatism is of two types.

1. Regular astigmatism
2. Irregular astigmatism.

TABLE 109-1: Errors of refraction

Type of error	Cause	Correction
Myopia	Increase in anteroposterior diameter of the eyeball	Biconcave lens
Hypermetropia	Decrease in anteroposterior diameter of the eyeball	Biconvex lens
Anisometropia	Difference in refractive power of both eyes	Separate lens (biconcave or biconvex) for each eye as required
Astigmatism	Refractory power of lens is different in different meridians	Cylindrical lens
Regular astigmatism	Refractory power of lens is unequal in different meridians but uniform in one single meridian	
Irregular astigmatism	Refractory power of lens is unequal in different meridians as well as in different points in same meridian	
Presbyopia	Loss of elasticity in lens and weakness of ocular muscles due to old age	Biconvex lens

1. Regular Astigmatism

In this type of astigmatism, the refractive power is unequal in different meridians because of alteration of curvature in one meridian. But, it is uniform in all points throughout the affected meridian.

2. Irregular Astigmatism

Here, the refractive power is unequal not only in different meridians, but it is also unequal in different points of same meridian.

■ CORRECTION OF ASTIGMATISM

Astigmatism is corrected by using cylindrical glass lens having the convexity in the meridians corresponding to that of lens of eye having a lesser curvature, i.e. if the horizontal curvature of lens is less, the person should use cylindrical glass lens with the convexity in horizontal meridian.

■ PRESBYOPIA

Presbyopia is the condition characterized by progressive decrease in the ability of eyes to

focus on near objects with age. It is due to the gradual reduction in the amplitude of accommodation. Presbyopia starts developing after middle age and progresses as the age advances (presbyos = old; ops = eye). In presbyopia, the distant vision is unaffected. Only the near vision is affected. The near point is away from eye. In presbyopia, the anterior curvature of lens does not increase during near vision. So, the light rays from near objects are not brought to a focus on retina.

■ CAUSES OF PRESBYOPIA

- Decreased elasticity of lens is because of the physical changes in lens and its capsule during old age. So, the anterior curvature is not increased during near vision.
- Decreased convergence of eyeballs due to the concomitant weakness of ocular muscles in old age.

■ CORRECTION OF PRESBYOPIA

Presbyopia is corrected by using biconvex lens.

Structure of Ear and Auditory Pathway

■ EXTERNAL EAR

- AURICLE OR PINNA
- EXTERNAL AUDITORY MEATUS

■ MIDDLE EAR

- AUDITORY OSSICLES
- AUDITORY MUSCLES
- EUSTACHIAN TUBE

■ INTERNAL EAR

- COCHLEA
- COMPARTMENTS OF COCHLEA
- ORGAN OF CORTI

■ AUDITORY PATHWAY

- INTRODUCTION
- RECEPTORS
- FIRST ORDER NEURONS
- SECOND ORDER NEURONS
- THIRD ORDER NEURONS
- CORTICAL AUDITORY CENTERS
- APPLIED PHYSIOLOGY – EFFECT OF LESION

■ EXTERNAL EAR

The ear consists of three parts namely, external ear, middle ear and internal ear (Fig. 110-1). The external ear is formed by two parts:

1. Auricle or pinna
2. External auditory meatus.

■ MIDDLE EAR

The middle ear or tympanic cavity is situated within the temporal bone. It is separated from external auditory meatus by a thin semitransparent membrane called tympanic membrane (Fig. 110-2).

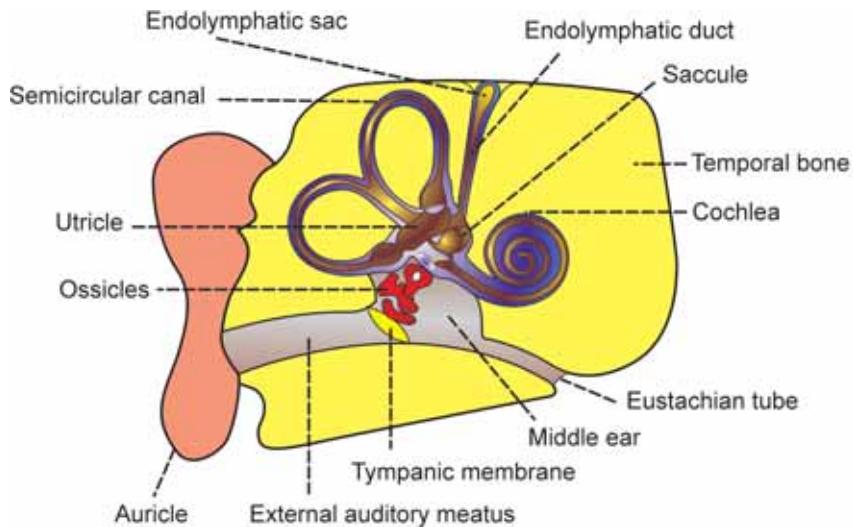


FIGURE 110-1: Diagram showing the structure of ear

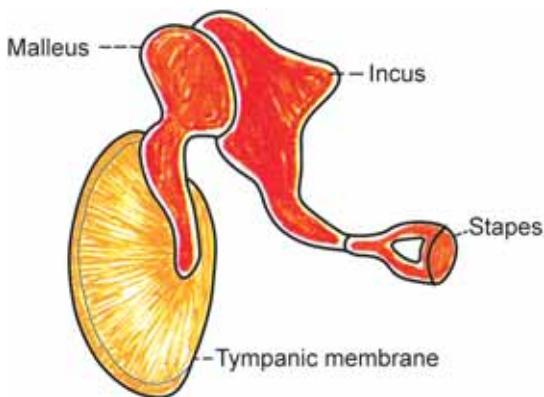


FIGURE 110-2: Tympanic membrane and auditory ossicles

Middle ear consists of the following structures:

1. Auditory ossicles
2. Auditory muscles
3. Eustachian tube.

■ AUDITORY OSSICLES

The auditory ossicles are the three miniature bones, which are arranged in the form of a chain extending across the middle ear from the tympanic membrane to oval window (Fig. 110-2).

The auditory ossicles are:

1. Malleus
2. Incus
3. Stapes.

1. *Malleus*

It is otherwise called hammer. It has a handle, head and neck. The handle is otherwise known as manubrium. It is attached to the tympanic membrane. The head or capitulum articulates with the body of next bone incus.

2. *Incus*

Incus is also known as anvil. It looks like a premolar tooth. Incus has a body, one long process and one short process. Anterior surface of the body articulates with head of malleus. The tip of the long process is like a knob, called lenticular process and it articulates with the next bone, stapes.

3. *Stapes*

Stapes is also called stirrup. It is the smallest bone present in the body. It has a head, neck, anterior crus, posterior crus and a footplate. Head articulates with incus. Footplate fits into the oval window.

■ AUDITORY MUSCLES

Two skeletal muscles are attached to the ossicles:

1. Tensor tympani
2. Stapedius.

1. *Tensor Tympani*

Tensor tympani muscle arises from cartilaginous portion of eustachian tube. Its tendon is inserted on manubrium of malleus which is in turn attached to tympanic membrane.

Tensor tympani muscle pulls and keeps the tympanic membrane stretched constantly.

2. *Stapedius*

Stapedius is the smallest skeletal muscle in human body with a length of just over 1 mm. It arises from interior pyramid of tympanic cavity. Its tendon is inserted into the posterior surface of neck of stapes.

Stapedius prevents excess movements of stapes. When it contracts, it pulls the neck of stapes backwards and reduces the movement of footplate against the fluid in cochlea.

■ EUSTACHIAN TUBE

Eustachian tube or the auditory tube connects the middle ear with posterior part of nose and forms the passage of air between middle ear and atmosphere. So, the pressure on both sides of tympanic membrane is equalized.

■ INTERNAL EAR

The internal ear or labyrinth is a membranous structure, enclosed by a bony labyrinth in petrous part of temporal bone. It consists of the sense organs of hearing and equilibrium. The sense organ for hearing is the cochlea. And, the sense organ for equilibrium is the vestibular apparatus. Vestibular apparatus is already explained in Chapter 98.

■ COCHLEA

Cochlea is a coiled structure like a snail's shell (cochlea = snail's shell). It consists of two structures:

1. Central conical axis formed by spongy bone called modiolus
2. Bony spiral canal, which winds around the modiolus.

■ COMPARTMENTS OF COCHLEA

Two membranous partitions called basilar membrane and vestibular membrane divide the spiral canal of cochlea into three compartments.

The compartments of spiral canal of cochlea are:

- i. Scala vestibuli
- ii. Scala tympani
- iii. Scala media.

All the three compartments are filled with fluid. Scala vestibuli and scala tympani contain perilymph. The scala media is filled with endolymph.

i. *Scala vestibuli*

Scala vestibuli lies above the scala media. It arises from oval window (fenestra vestibuli) which is closed by the footplate of stapes. It follows the osseous canal up to its apex. At the apex, it communicates with the scala tympani through a small canal called helicotrema.

ii. *Scala tympani*

It lies below the scala media. It is parallel to scala vestibuli and ends at the round window. The round window is closed by a strong thin membrane known as secondary tympanic membrane.

iii. *Scala media*

Scala media is otherwise called cochlear duct. It ends blindly at the apex and at the base of cochlea. The sensory part of cochlea called organ of Corti is situated on the upper surface of basilar membrane (Fig. 110-3).

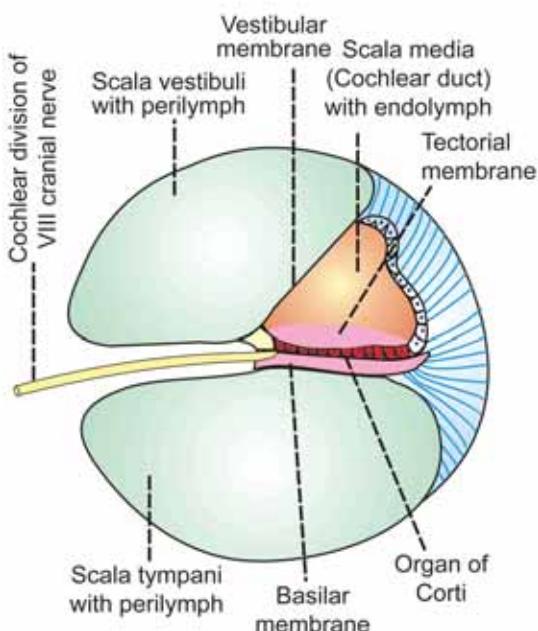


FIGURE 110-3: Cross section of spiral canal of cochlea

■ ORGAN OF CORTI

Organ of Corti is the receptor organ for hearing. It is the neuroepithelial structure in cochlea (Fig. 110-4). It rests upon the lip of spiral lamina and the basilar membrane. It extends throughout the cochlear duct, except for a short distance on either end. The roof of the organ of Corti is formed by gelatinous tectorial membrane.

Structure

The organ of Corti is made up of the sensory elements, called the hair cells and various supporting cells. All the cells of organ of Corti are arranged in order from center towards periphery of the cochlea:

1. Border cells
2. Inner hair cells
3. Inner phalangeal cells
4. Inner pillar cells
5. Outer pillar cells
6. Outer phalangeal cells

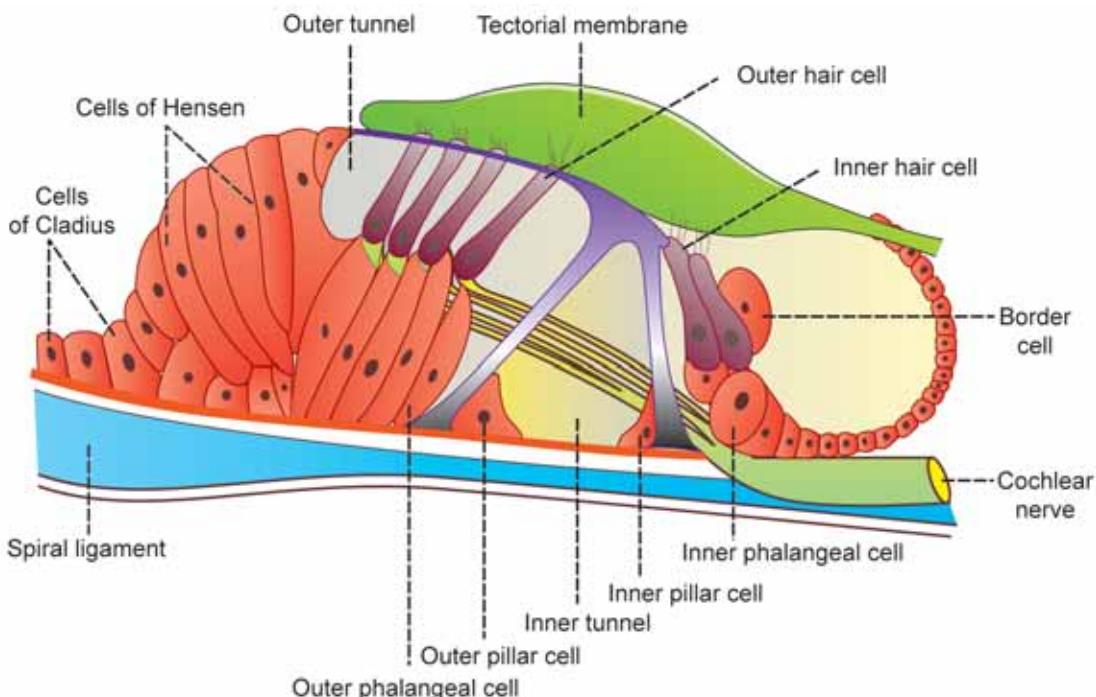


FIGURE 110-4: Organ of Corti

7. Outer hair cells
8. Cells of Hensen
9. Cells of Claudius
10. Tectorial membrane and lamina reticularis.

Hair Cells of Organ of Corti

The hair cells in organ of Corti are the receptors of the auditory sensation. The hair cells are of two types, outer hair cells and inner hair cells.

The surface of the hair cells bears a cuticular plate and a number of short stiff hairs which are called stereocilia. Each hair cell has about 100 stereocilia. One of the stereocilia is larger and it is called kinocilium. The stereocilia are in contact with the tectorial membrane. Sensory nerve fibers are distributed around the hair cells.

AUDITORY PATHWAY

INTRODUCTION

The fibers of auditory pathway pass through cochlear division of vestibulocochlear nerve (VIII cranial nerve). It is also known as auditory nerve.

RECEPTORS

The outer and inner hair cells in organ of Corti are the receptors of the auditory sensation. The afferent nerve fibers which innervate the hair cells form the auditory nerve (see below).

FIRST ORDER NEURONS

The first order neurons of the auditory pathway are the bipolar cells of spiral ganglion situated in the modiolus of cochlea (Fig. 110-5).

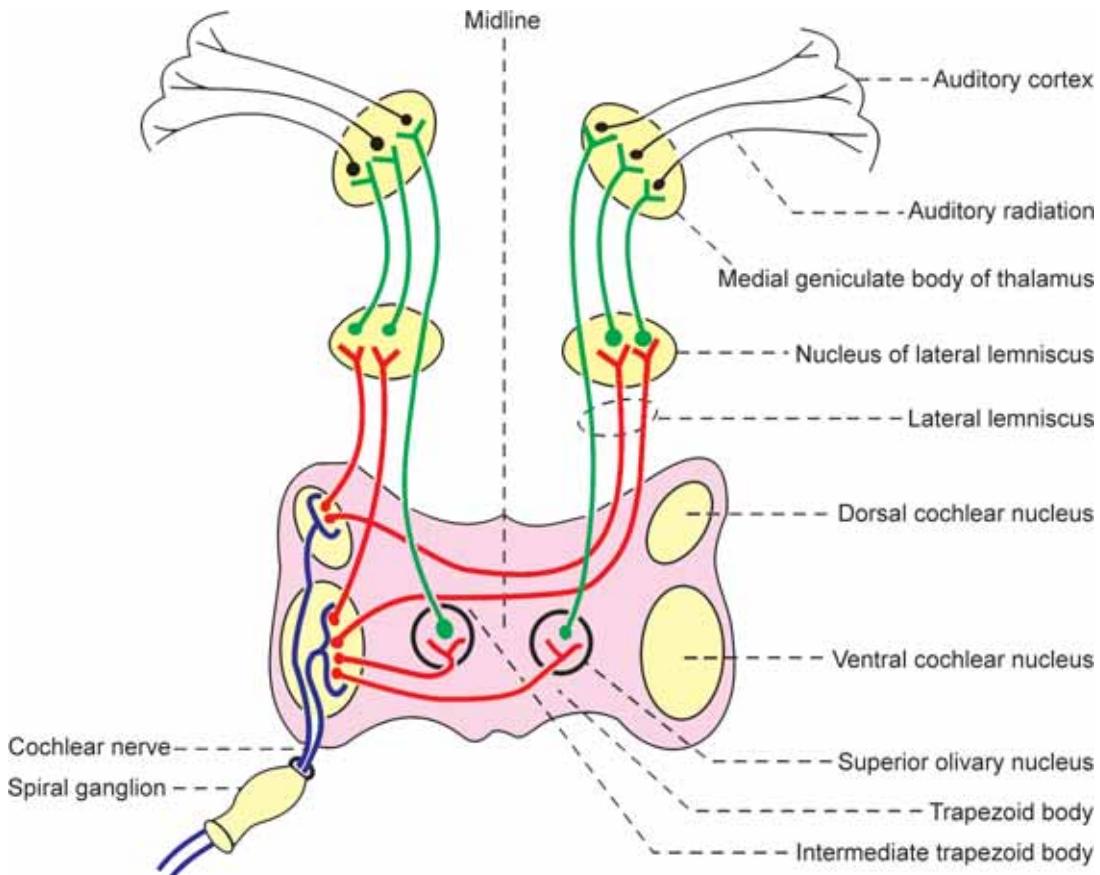


FIGURE 110-5: Auditory pathway. Blue = First order neuron. Red = Second order neuron. Green = Third order neuron. Black = Auditory radiation

The dendrites of the bipolar cells are distributed around the hair cells of organ of Corti. Their axons leave ear as cochlear nerve fibers and enter medulla oblongata. Immediately after entering the medulla oblongata, the fibers divide into two groups which end on ventral and dorsal cochlear nuclei of the same side in medulla oblongata.

■ SECOND ORDER NEURONS

The neurons of dorsal and ventral cochlear nuclei in the medulla oblongata form the second order neurons of auditory pathway. The axons of the second order neurons run in four different directions:

1. First group of fibers cross the midline and run to the opposite side to form trapezoid body and go to the superior olivary nucleus.
2. Second group of the fibers terminate at the superior olivary nucleus of same side via trapezoid body of the same side
3. Third group of fibers run in the lateral lemniscus of the same side and terminate in the nucleus of lateral lemniscus
4. Fourth group of fibers cross the midline as intermediate trapezoid fibers and join the nucleus of lateral lemniscus of opposite side.

■ THIRD ORDER NEURONS

Third order neurons are in the superior olivary nuclei and nucleus of lateral lemniscus. The fibers from here end in medial geniculate body which forms the subcortical auditory center.

Fibers from medial geniculate body go to the temporal cortex, via internal capsule as auditory radiation.

■ CORTICAL AUDITORY CENTERS

The cortical auditory centers are in the temporal lobe of cerebral cortex. The auditory areas are area 41, area 42 and Wernicke's area.

Areas 41 and 42 are the primary auditory areas which are concerned with the perception of auditory impulses. Wernicke's area is responsible for the analysis and interpretation of sound with the help of auditopsychic area.

■ APPLIED PHYSIOLOGY – EFFECT OF LESION

1. Lesion of cochlear nerve causes deafness
2. Unilateral lesion of auditory pathway above the level of cochlear nuclei causes diminished hearing
3. Degeneration of hair cells in organ of Corti leads to gradual loss of hearing that is common in old age
4. Lesion in superior olivary nucleus results in poor localization of sound.

111

Mechanism of Hearing and Auditory Defects

- INTRODUCTION
- ROLE OF EXTERNAL EAR
- ROLE OF MIDDLE EAR
 - ROLE OF TYMPANIC MEMBRANE
 - ROLE OF AUDITORY OSSICLES
 - ROLE OF EUSTACHIAN TUBE
- ROLE OF INNER EAR
 - TRAVELING WAVE
 - EXCITATION OF HAIR CELLS
- ELECTRICAL EVENTS DURING THE PROCESS OF HEARING
 - SOUND TRANSDUCTION
 - RECEPTOR POTENTIAL
- PROPERTIES OF SOUND
- APPRECIATION OF PITCH OF THE SOUND – THEORIES OF HEARING
- APPRECIATION OF LOUDNESS OF SOUND
- LOCALIZATION OF SOUND
- AUDITORY DEFECTS
 - CONDUCTION DEAFNESS
 - NERVE DEAFNESS

■ INTRODUCTION

The sound waves travel through the external auditory meatus and produce vibrations in the tympanic membrane. The vibrations from tympanic membrane travel through malleus and incus and reach the stapes resulting in the movement of stapes. The movements of stapes

produce vibrations in the fluids of cochlea and which stimulate the hair cells in the organ of Corti. This, in turn, causes the generation of action potential (auditory impulses) in the auditory nerve fibers. When the auditory impulses reach the cerebral cortex, the perception of hearing occurs.

■ ROLE OF EXTERNAL EAR

External ear directs the sound waves towards the tympanic membrane. The sound waves produce pressure changes over the surface of tympanic membrane.

■ ROLE OF MIDDLE EAR

■ ROLE OF TYMPANIC MEMBRANE

Due to the pressure changes produced by sound waves, the tympanic membrane vibrates, i.e. it moves in and out of middle ear. Thus, the tympanic membrane acts as a resonator that produces the vibration of sound.

■ ROLE OF AUDITORY OSSICLES

The vibrations set up in tympanic membrane are transmitted through the malleus and incus and reach the stapes, causing to and fro movement of stapes against oval window and against the perilymph present in scala vestibuli of cochlea.

Impedance Matching

Impedance matching is the process, by which the tympanic membrane and auditory ossicles convert the sound energy into the mechanical vibrations in the fluid of internal ear with minimum loss of energy by matching the impedance offered by the fluid.

Impedance means obstruction or opposition to the passage of sound waves. When sound waves reach the inner ear, the fluid (perilymph) in cochlea offers impedance, i.e. the fluid resists the transmission of sound due to its own inertia. Tympanic membrane and the auditory ossicles effectively reduce the sound impedance which is called the impedance matching.

Significance of impedance matching

Impedance matching is the most important function of middle ear. Because of impedance matching the sound waves (stimuli) are transmitted to cochlea with minimum loss of intensity. Without impedance matching conductive deafness occurs.

Types of Conduction

Conduction of sound from external ear to internal ear through middle ear occurs by three routes:

1. Ossicular conduction
2. Air conduction
3. Bone conduction.

1. Ossicular conduction

Ossicular conduction is the conduction of sound waves through middle ear by auditory ossicles. This is the normal way of conduction of the sound waves through middle ear.

2. Air conduction

It is the conduction of sound waves through air in middle ear. It occurs when the auditory ossicles are diseased.

3. Bone conduction

It is the conduction of sound waves by bones. When middle ear is affected, bone conduction occurs. In this type of conduction, the sound waves are transmitted to cochlear fluid by the vibrations set up in the skull bones.

■ ROLE OF EUSTACHIAN TUBE

The Eustachian tube is not concerned with hearing directly. However, it is responsible for equalizing the pressure on either side of tympanic membrane.

■ ROLE OF INNER EAR

■ TRAVELING WAVE

The movement of footplate of stapes against oval window causes movement of perilymph in scala vestibuli. The fluid does not move all the way from oval window towards round window through the helicotrema. It immediately hits the vestibular membrane near oval window and displaces the fluid in scala media (Fig. 111-1). This causes bulging of basal portion of basilar membrane towards scala tympani.

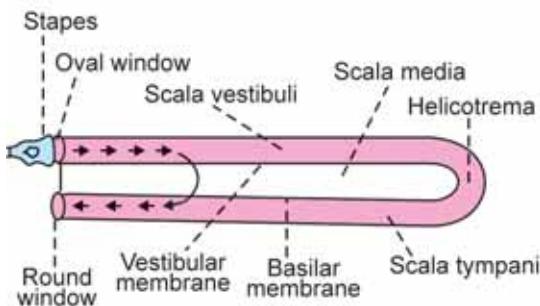


FIGURE 111-1: Diagrammatic representation of cochlea. The arrows show displacement of fluid

The elastic tension developed in the bulged portion of basilar membrane initiates a wave called travelling wave. It travels along basilar membrane towards the helicotrema like that of arterial pulse wave.

■ EXCITATION OF HAIR CELLS

The stereocilia of hair cells in organ of Corti are embedded in tectorial membrane. The hair cells are tightly fixed by cuticular lamina reticularis and the pillar cells of Corti. When the traveling wave produces vibration of basilar membrane, all these structures move as a single unit. It causes movements of stereocilia leading to excitement of hair cells and generation of receptor potential.

■ ELECTRICAL EVENTS DURING THE PROCESS OF HEARING

■ SOUND TRANSDUCTION

Sound transduction is a type of sensory transduction (Chapter 85) in the hair cell (receptor) by which the energy (movement of cilia in hair cell) caused by sound is converted into action potentials in the auditory nerve fiber.

■ RECEPTOR POTENTIAL OR COCHLEAR MICROPHONIC POTENTIAL

Receptor potential or cochlear microphonic potential is the mild depolarization that is developed

in the hair cells of cochlea when sound waves are transmitted to internal ear. The resting membrane potential in hair cells is about -60 mV .

Receptor potential in the hair cells causes generation of action potential in auditory nerve fibers.

■ PROPERTIES OF SOUND

Sound has two basic properties:

1. The pitch which depends upon the frequency of sound waves. Frequency of sound is expressed in hertz. The frequency of sound audible to human ear lies between 20 and 20,000 Hz or cycles/second. The range of greatest sensitivity lies between 2,000 and 3,000 Hz (cycles/second).
2. The loudness or intensity which depends upon the amplitude of sound waves. It is expressed in decibel (dB). The threshold intensity of sound wave is not constant. It varies in accordance to the frequency of the sound.

■ APPRECIATION OF PITCH OF THE SOUND – THEORIES OF HEARING

Though many theories are postulated to explain the mechanism by which the pitch of the sound is appreciated only few theories are accepted so far. The accepted theories are:

1. Place Theory

According to this theory, the nerve fibers from different portions (places) of organ of Corti on basilar membrane give response to sounds of different frequency. Accordingly, the corresponding nerve fiber from organ of Corti gives information to the brain regarding the portion of organ of Corti that is stimulated.

2. Traveling Wave Theory

This theory explains how the traveling wave is generated in the basilar membrane. The generation, movement and disappearance of travel-

ing wave are already described earlier in this chapter.

■ APPRECIATION OF LOUDNESS OF SOUND

Appreciation of loudness of sound depends upon the activities of auditory nerve fibers.

When the loudness of sound increases, it produces longer vibrations which spread over longer area of basilar membrane. This activates large number of hair cells and recruits more number of auditory nerve fibers. So, the frequency of action potential is also increased.

■ LOCALIZATION OF SOUND

Sound localization is the ability to detect the source from where the sound is produced or the direction through which the sound wave is traveling. It is important for survival and it helps to protect us from moving objects such as vehicles. Cerebral cortex and medial geniculate body are responsible for localization of sound.

■ AUDITORY DEFECTS

The auditory defects may be either partial or complete. The auditory defects are of two types:

1. Conduction deafness
2. Nerve deafness.

■ 1. CONDUCTION DEAFNESS

Conduction deafness occurs due to impairment in the transmission of sound waves in external ear or middle ear.

Causes of Conduction Deafness

- i. Obstruction of external auditory meatus with dry wax or foreign bodies
- ii. Thickening of tympanic membrane due to infection
- iii. Perforation of tympanic membrane due to inequality of pressure on either side
- iv. Inflammation of middle ear (otitis media)
- v. Fixation of footplate of stapes against oval window (otosclerosis).

■ 2. NERVE DEAFNESS

Nervous deafness is caused by damage of any structure in cochlea such as hair cell, organ of Corti, basilar membrane or cochlear duct or the lesion in auditory pathway.

Causes of Nerve Deafness

- i. Degeneration of hair cells
- ii. Damage of cochlea by prolonged exposure to loud noise
- iii. Tumor affecting VIII cranial nerve.

Sensation of Taste

- TASTE BUDS
- PATHWAY FOR TASTE
- PRIMARY TASTE SENSATIONS
- DISCRIMINATION OF DIFFERENT TASTE SENSATIONS
- TASTE SENSATIONS AND CHEMICAL CONSTITUTIONS
- TASTE TRANSDUCTION
- APPLIED PHYSIOLOGY

■ TASTE BUDS

Taste buds are the sense organs for taste or gustatory sensation. The taste buds are ovoid bodies with a diameter of 50 to 70 μ .

■ SITUATION OF TASTE BUD

Most of the taste buds are present on the papillae of tongue. Some taste buds are situated in the mucosa of epiglottis, palate, pharynx and proximal part of esophagus. Three types of papillae are located on the tongue:

1. Filiform papillae
2. Fungiform papillae
3. Circumvallate papillae.

1. *Filiform Papillae*

Filiform papillae are small and conical shaped papillae situated over the dorsum of tongue. These papillae contain less number of taste buds (only a few).

2. *Fungiform Papillae*

Fungiform papillae are round in shape and are situated over the anterior surface of tongue near the tip. Numerous fungiform papillae are present. The number of taste buds in each is moderate (up to 10).

3. *Circumvallate Papillae*

Circumvallate papillae are large structures arranged in 'V' shape on the posterior part of tongue and are many in number. Each papilla contains many taste buds (up to 100).

■ STRUCTURE OF TASTE BUD

The taste bud is a bundle of taste receptor cells, with supporting cells embedded in the epithelial covering of the papillae (Fig. 112-1). Each taste bud contains about 40 cells, which are the

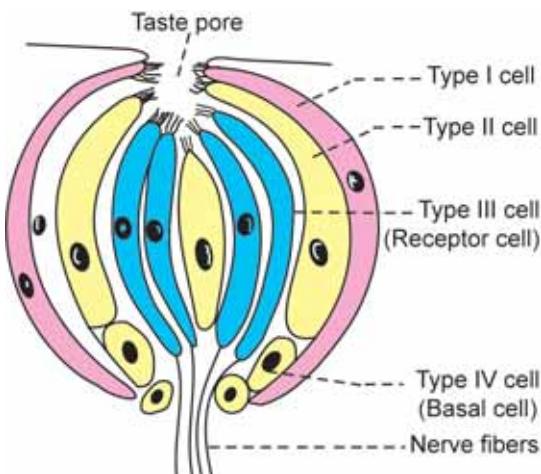


FIGURE 112-1: Taste bud

modified epithelial cells. The cells of taste bud are divided into four groups:

1. Type I cells or sustentacular cells
2. Type II cells
3. Type III cells
4. Type IV cells or basal cells.

Type I cells and type IV cells are supporting cells. Type III cells are the taste receptor cells. Function of type II cell is unknown. Type I, II and III cells have projections called microvilli. The microvilli project into an opening in the epithelium covering the tongue. The opening is called taste pore. All the cells of taste bud are surrounded by epithelial cells.

■ PATHWAY FOR TASTE

Receptors

Receptors for taste sensation are the type III cells of taste buds. Each taste bud is innervated by about 50 sensory nerve fibers and each nerve fiber supplies at least 5 taste buds.

First Order Neurons

First order neurons of taste pathway are in the nuclei of three different cranial nerves. The

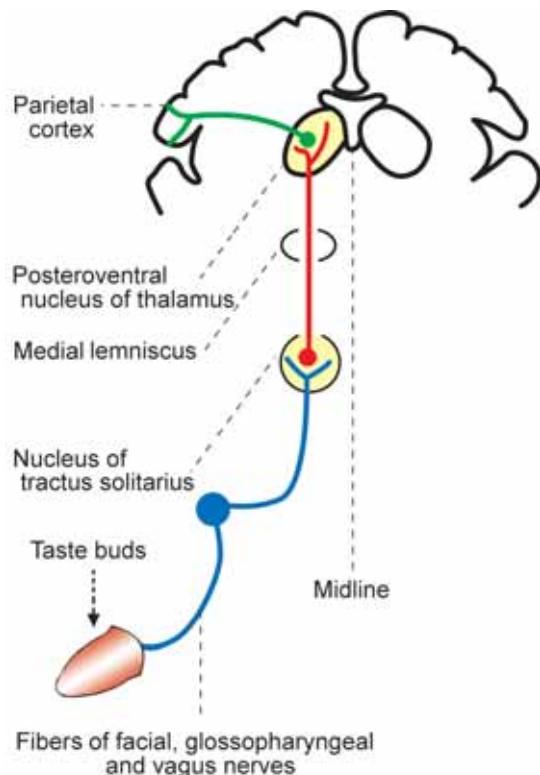


FIGURE 112-2: Pathway for taste sensation

dendrites of the neurons are distributed to the taste buds. After arising from taste buds, the fibers run along the following nerves (Fig. 112-2):

1. Chorda tympani fibers of facial nerve, which run from anterior two-third of tongue
2. Glossopharyngeal nerve fibers, which run from posterior one-third of the tongue
3. Vagal fibers, which run from taste buds in other regions.

Axons of the first order neurons run together in medulla oblongata and terminate in the nucleus of tractus solitarius.

Second Order Neurons

Second order neurons are in the nucleus of tractus solitarius. Axons of the second order neurons run through medial lemniscus and terminate in posteroverentral nucleus of thalamus.

Third Order Neurons

The third order neurons are in the posteroverentral nucleus of thalamus. The axons from the third order neurons project into cerebral cortex.

Taste Center

The center for taste sensation is in the opercular insular cortex (lower part of postcentral gyrus) in parietal lobe of cerebral cortex.

■ PRIMARY TASTE SENSATIONS

The primary or fundamental taste sensations are divided into five types:

1. Sweet
2. Salt
3. Sour
4. Bitter
5. Umami.

Man can perceive more than 100 different tastes. Other taste sensations are just the combination of two or more primary sensations. Sometimes, the taste sensation is combined with other sensations like pain (ginger) or temperature (flavor).

■ TASTE SENSATIONS AND CHEMICAL CONSTITUTIONS

■ 1. SWEET TASTE

Sweet taste is produced mainly by organic substances like monosaccharides, polysaccharides, glycerol, alcohol, aldehydes, ketones and chloroform. The inorganic substances, which produce sweet taste are lead and beryllium.

■ 2. SALT TASTE

Salt taste is produced by chlorides of sodium, potassium and ammonium, nitrates of sodium and potassium. Some sulfates, bromides and iodides also produce salt taste.

■ 3. SOUR TASTE

Sour taste is produced by hydrogen ions in acids and acid salts.

■ 4. BITTER TASTE

Bitter taste is produced by organic substances like quinine, strychnine, morphine, glucosides, picric acid and bile salts and inorganic substances like salts of calcium, magnesium and ammonium.

■ 5. UMAMI

Umami is the recently recognized taste sensation. Umami is a Japanese word meaning 'delicious'. Receptors of this taste sensation respond to monosodium glutamate which is a common ingredient in Asian food.

■ TASTE TRANSDUCTION

Taste transduction is the process in which taste receptor converts chemical energy into action potentials in the taste nerve fiber. Receptors of taste sensation are chemoreceptors, which are stimulated by substances dissolved in mouth by saliva. The dissolved substances act on the microvilli of taste receptors exposed in the taste pore. It causes the development of receptor potential in the receptor cells. This in turn, is responsible for the generation of action potential in the sensory neurons.

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF TASTE SENSATION

1. Ageusia – loss of taste sensation
2. Hypogeusia – decrease in the taste sensation
3. Taste blindness – inability to recognize substances by taste due to genetic disorder
4. Dysgeusia – disturbance in the taste sensation like hallucinations of taste.

Sensation of Smell

- OLFACTORY RECEPTORS
- OLFACTORY PATHWAY
- GENERATOR POTENTIAL IN OLFACTORY RECEPTOR
- CLASSIFICATION OF ODOR
- THRESHOLD FOR OLFACTORY SENSATION
- APPLIED PHYSIOLOGY

■ OLFACTORY RECEPTORS

Olfactory receptors are situated in olfactory mucous membrane that lines upper part of nostril. The olfactory mucous membrane consists of 10 to 20 millions of olfactory receptor cells supported by the sustentacular cells. The mucosa also contains mucus secreting Bowman's glands (Fig. 113-1).

The olfactory receptor cell is a bipolar neuron. The dendrite of this neuron is short. The expanded end of the dendrite is called olfactory rod. From the rod, about 10 to 12 cilia arise. Cilia are nonmyelinated with a length of $2\ \mu$ and a diameter of $0.1\ \mu$. The cilia project to the surface of olfactory mucous membrane.

The mucus secreted by Bowman's glands continuously lines the olfactory mucosa. The mucus contains some proteins, which increase the actions of odoriferous substances on receptor cells.

■ OLFACTORY PATHWAY

Axons of the bipolar olfactory receptors pierce the cribriform plate of ethmoid bone and reach

the olfactory bulb. Here, the axons synapse with dendrites of mitral cells. Different groups of these synapses form globular structures, called olfactory glomeruli.

The axons of mitral cells leave the olfactory bulb and form olfactory tract. The olfactory tract runs backwards and ends in olfactory cortex.

The olfactory cortex includes the structures, which form a part of limbic system. The structures are anterior olfactory nucleus, prepyriform cortex, olfactory tubercle and amygdala.

■ GENERATOR POTENTIAL IN OLFACTORY RECEPTOR

The odoriferous substance stimulates the olfactory receptors resulting in generation of receptor potential.

The receptor potential causes generation of action potential in the axon of the bipolar neuron.

■ CLASSIFICATION OF ODOR

The odor is classified into various types:

1. Aromatic or resinous odor – camphor, lavender, clove and bitter almonds

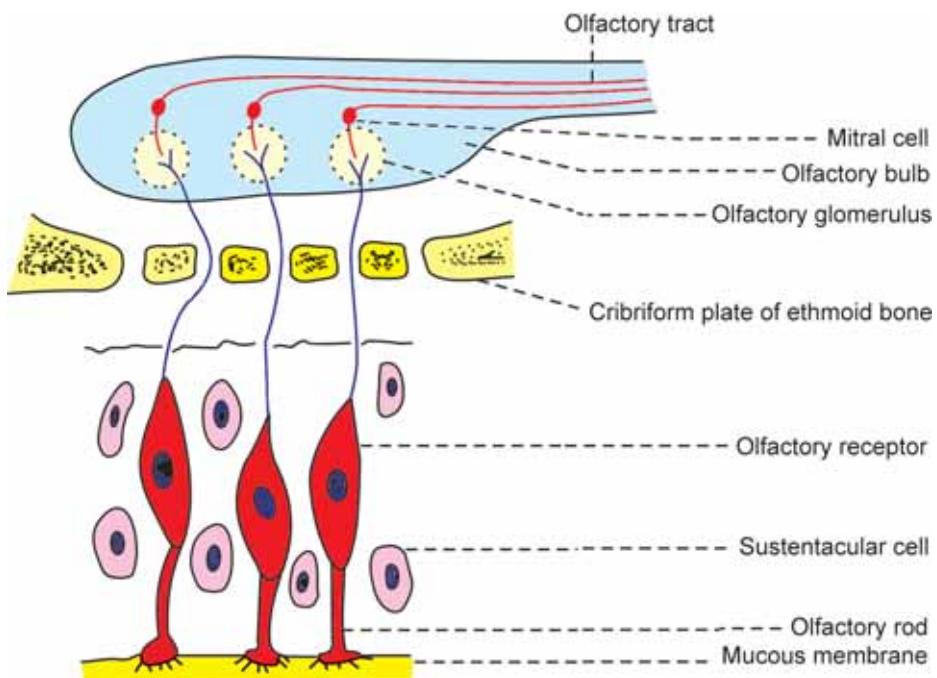


FIGURE 113-1: Olfactory mucous membrane and pathway for olfactory sensation

2. Ambrosial odor – musk
3. Burning odor – burning feathers, tobacco, roasted coffee and meat
4. Ethereal odor – fruits, ethers and bees wax
5. Fragrant or balsamic odor – flowers and perfumes
6. Garlic odor – garlic, onion, and sulfur
7. Goat odor – caproic acid, and sweet cheese
8. Nauseating odor – decayed vegetables and feces
9. Repulsive odor – bed bug.

■ THRESHOLD FOR OLFACTORY SENSATION

Ethyl ether	:	5.8	mg/L of air
Chloroform	:	3.3	mg/L of air
Peppermint oil	:	0.02	mg/L of air

Butyric acid : 0.009 mg/L of air
 Artificial musk : 0.00004 mg/L of air
 Methyl mercaptan : 0.0000004 mg/L of air

Thus, the methyl mercaptan produces olfactory sensation even at a low concentration of 0.0000004 mg/L of air.

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF OLFACTORY SENSATION

1. Anosmia – total loss of sensation of smell
2. Hyposmia – reduced ability to recognize and to detect any odor
3. Hyperosmia or olfactory hyperesthesia – increased or exaggerated olfactory sensation.

QUESTIONS IN SPECIAL SENSES

■ LONG QUESTIONS

1. Draw a diagram of visual pathway and explain it. Add a note on hemianopia.
2. Explain the auditory pathway with suitable diagram. Add a note on auditory defects.
3. Explain the mechanism of hearing.

■ SHORT QUESTIONS

1. Retina.
2. Ocular movements.
3. Visual receptors.
4. Aqueous humor.
5. Intraocular pressure.
6. Dark adaptation.

7. Light adaptation.
8. Nyctalopia.
9. Effects of lesion in optic pathway.
10. Accommodation reflex.
11. Presbyopia.
12. Color blindness.
13. Errors of refraction.
14. Auditory ossicles.
15. Cochlea/organ of Corti.
16. Role of middle ear in hearing / functions of middle ear.
17. Auditory defects.
18. Taste buds.
19. Taste pathway.
20. Olfactory pathway.

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