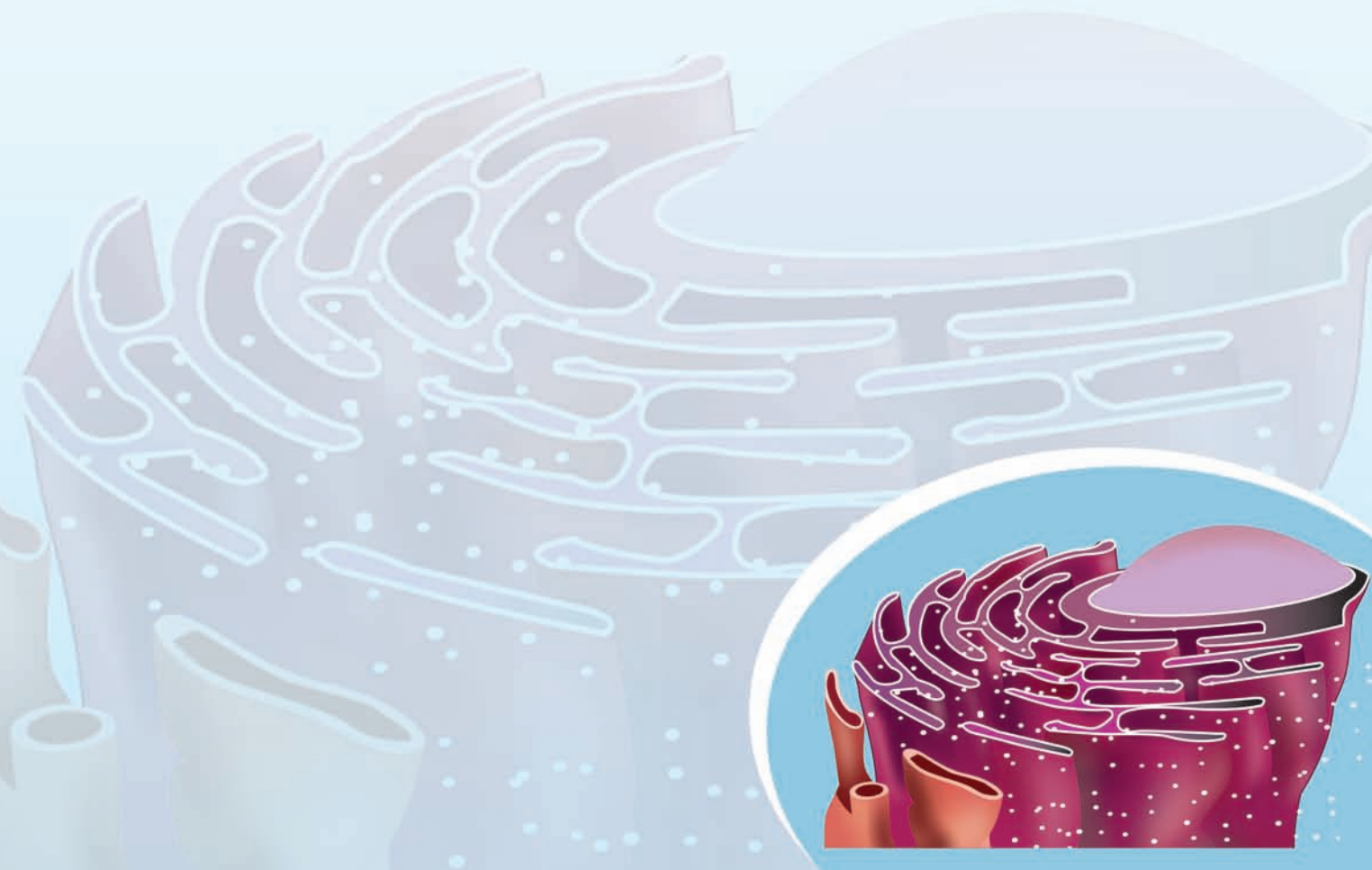
# Section 1

# General Physiology


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# Cell

Chapter 1


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## INTRODUCTION

### CELL

All the living things are composed of cells. A single cell is the smallest unit that has all the characteristics of life. Cell is defined as the structural and functional unit of the living body.

#### *General Characteristics of Cell*

Each cell in the body:

1. Needs nutrition and oxygen
2. Produces its own energy necessary for its growth, repair and other activities
3. Eliminates carbon dioxide and other metabolic wastes
4. Maintains the medium, i.e. the environment for its survival
5. Shows immediate response to the entry of invaders like bacteria or toxic substances into the body
6. Reproduces by division. There are some exceptions like neuron, which do not reproduce.

### TISSUE

Tissue is defined as the group of cells having similar function. There are many types of tissues in the body. All 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).

## ■ ORGAN

An organ is defined as the structure that is formed by two or more primary types of tissues, which execute the functions of the organ. Some organs are composed of all the four types of primary tissues. The organs are of two types, namely tubular or **hollow organs** and compact or **parenchymal organs.** Some of the organs in the body are brain, heart, lungs, stomach, intestine, liver, gallbladder, pancreas, kidneys, endocrine glands, etc.

## ■ SYSTEM

The organ system is defined as group of organs that work together to carry out specific functions of the body.

Each system performs a specific function. Digestive system is concerned with digestion of food particles. Excretory system eliminates unwanted substances. Cardiovascular system is responsible for transport of substances between the organs. Respiratory system is concerned with the supply of oxygen and removal of carbon dioxide. Reproductive system is involved in the reproduction of species. Endocrine system is concerned with growth of the body and regulation and maintenance of normal life. Musculoskeletal system is responsible for stability and movements of the body. Nervous system controls the locomotion and other activities including the intellectual functions.

## ■ STRUCTURE OF THE CELL

Each cell is formed by a **cell body** and a membrane covering the cell body called the cell membrane. Cell body has two parts, namely nucleus and cytoplasm surrounding the nucleus (Fig. 1.1). Thus, the structure of the cell is studied under three headings:

1. Cell membrane
2. Cytoplasm
3. Nucleus.

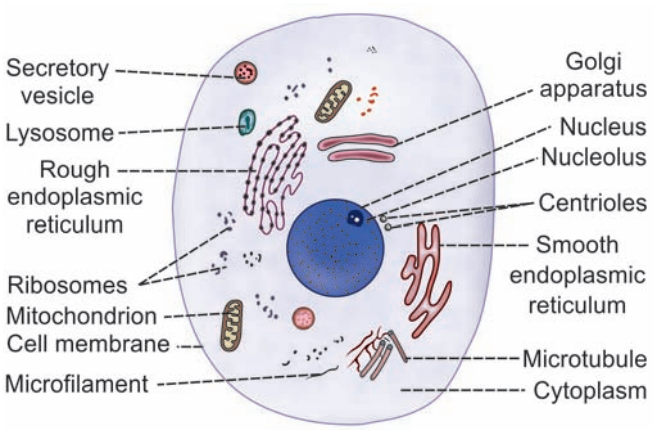



**FIGURE 1.1:** Structure of the cell

## ■ CELL MEMBRANE

Cell membrane is a protective sheath, enveloping the cell body. It is also known as **plasma membrane** or **plasmalemma**. This membrane separates the fluid outside the cell called extracellular fluid (ECF) and the fluid inside the cell called intracellular fluid (ICF). The cell membrane is a semipermeable membrane. So, there is free exchange of certain substances between ECF and ICF. Thickness of the cell membrane varies from 75 to 111Å (Fig. 1.2).

## ■ COMPOSITION OF CELL MEMBRANE

Cell membrane is composed of three types of substances:

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

## ■ STRUCTURE OF CELL MEMBRANE

On the basis of structure, cell membrane is called a **unit membrane** or a three-layered membrane. The electron microscopic study reveals three layers of cell membrane, namely, one central **electron-lucent layer** and two **electron-dense layers.** The two electron-dense layers are placed one on either side of the central layer. The central layer is a lipid layer formed by lipid substances. The other two layers are protein layers formed by proteins. Cell membrane contains some carbohydrate molecules also.

### *Structural Model of the Cell Membrane*

1. *Danielli-Davson model*

'Danielli-Davson model' was the first proposed basic model of membrane structure. It was proposed by James F Danielli and Hugh Davson in 1935. And it was accepted by scientists for many years. This model was basically a **'sandwich of lipids'** covered by proteins on both sides.

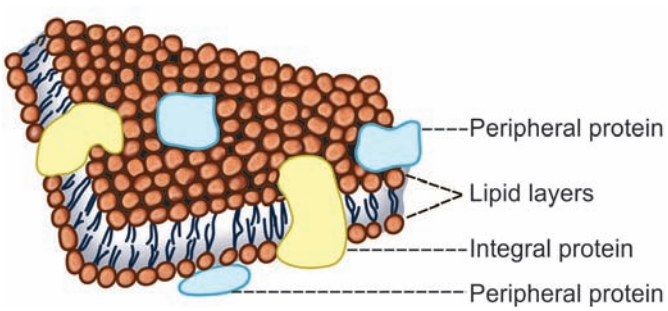



**FIGURE 1.2:** Diagram of the cell membrane

2. *Unit membrane model*

In 1957, JD Robertson replaced 'Danielli-Davson model' by 'Unit membrane model' on the basis of electron microscopic studies.

3. *Fluid mosaic model*

Later in 1972, SJ Singer and GL Nicholson proposed 'The fluid mosaic model'. According to them, 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). This model is accepted by the scientists till now. In this model, the proteins are found to float in the lipid layer instead of forming the layers of the sandwich-type model.

### Lipid Layers of the Cell Membrane

The central lipid layer is a bilayered structure. This is formed by a thin film of lipids. The characteristic feature of lipid layer is that, it is fluid in nature and not a solid structure. So, the portions of the membrane move from one point to another point along the surface of the cell. The materials dissolved in lipid layer also move to all areas of the cell membrane.

Major lipids are:

1. Phospholipids
2. Cholesterol.

1. *Phospholipids*

Phospholipids are the lipid substances containing phosphorus and fatty acids. **Aminophospholipids, sphingomyelins, phosphatidylcholine, phosphatidyletholamine, phosphatidylglycerol, phosphatidylserine** and **phosphatidylinositol** are the phospholipids present in lipid layer of cell membrane.

Phospholipid molecules are arranged in two layers (Fig. 1.3). Each phospholipid molecule resembles the headed pin in shape. The outer part of the phospholipid molecule is called the **head portion** and the inner portion is called the **tail portion.**

Head portion is the polar end and it is soluble in water and has strong affinity for water **(hydrophilic).** Tail portion is the non-polar end. It is insoluble in water and repelled by water **(hydrophobic).**

Two layers of phospholipids are arranged in such a way that the hydrophobic tail portions meet in the center of the membrane. Hydrophilic head portions of outer layer face the ECF and those of the inner layer face ICF (cytoplasm).

2. *Cholesterol*

Cholesterol molecules are arranged in between the phospholipid molecules. Phospholipids are soft and oily structures and cholesterol helps to 'pack' the phospholipids in the membrane. So, cholesterol is responsible for the structural integrity of lipid layer of the cell membrane.

### Functions of Lipid Layer in Cell Membrane

Lipid layer of the cell membrane is a semipermeable membrane and allows only the fat-soluble substances to pass through it. Thus, the fat-soluble substances like oxygen, carbon dioxide and alcohol can pass through this lipid layer. The water-soluble substances such as glucose, urea and electrolytes cannot pass through this layer.

### Protein Layers of the Cell Membrane

Protein layers of the cell membrane are electron-dense layers. These layers cover the two surfaces of the central lipid layer. Protein layers give protection to the central lipid layer. The protein substances present in these layers are mostly glycoproteins.

Protein molecules are classified into two categories:

1. Integral proteins or transmembrane proteins.
2. Peripheral proteins or peripheral membrane proteins.

1. *Integral proteins*

Integral or transmembrane proteins are the proteins that pass through entire thickness of cell membrane from one side to the other side. These proteins are tightly bound with the cell membrane.

Examples of integral protein:

i. Cell adhesion proteins
ii. Cell junction proteins
iii. Some carrier (transport) proteins
iv. Channel proteins
v. Some hormone receptors
vi. Antigens
vii. Some enzymes.

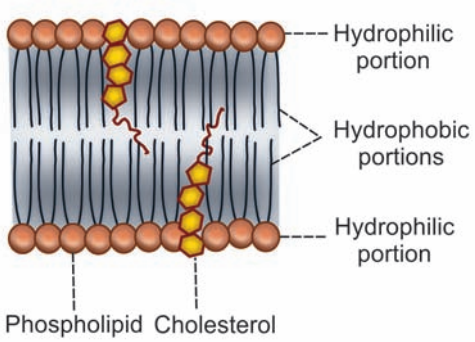



**FIGURE 1.3:** Lipids of the cell membrane

2. *Peripheral proteins*

Peripheral proteins or peripheral membrane proteins are the proteins which are partially embedded in the outer and inner surfaces of the cell membrane and do not penetrate the cell membrane. Peripheral proteins are loosely bound with integral proteins or lipid layer of cell membrane. So, these protein molecules dissociate readily from the cell membrane.

Examples of peripheral proteins:

i. Proteins of cytoskeleton
ii. Some carrier (transport) proteins
iii. Some enzymes.

### *Functions of Proteins in Cell Membrane*

1. Integral proteins provide the structural integrity of the cell membrane
2. Channel proteins help in the diffusion of water-soluble substances like glucose and electrolytes
3. Carrier or transport proteins help in the transport of substances across the cell membrane by means of active or passive transport
4. Pump: Some carrier proteins act as pumps, by which ions are transported actively across the cell membrane
5. Receptor proteins serve as the receptor sites for hormones and neurotransmitters
6. Enzymes: Some of the protein molecules form the enzymes and control chemical (metabolic) reactions within the cell membrane
7. Antigens: Some proteins act as antigens and induce the process of antibody formation
8. Cell adhesion molecules or the integral proteins are responsible for attachment of cells to their neighbors or to basal lamina.

### *Carbohydrates of the Cell Membrane*

Some of the carbohydrate molecules present in cell membrane are attached to proteins and form **glycoproteins (proteoglycans).** Some carbohydrate molecules are attached to lipids and form glycolipids.

Carbohydrate molecules form a thin and loose covering over the entire surface of the cell membrane called **glycocalyx**.

### *Functions of Carbohydrates in Cell Membrance*

1. Carbohydrate molecules are negatively charged and do not permit the negatively charged substances to move in and out of the cell
2. Glycocalyx from the neighboring cells helps in the tight fixation of cells with one another
3. Some carbohydrate molecules function as 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

Cytoplasm of the cell is the jelly-like material formed by 80% of water. It contains a clear liquid portion called **cytosol** and various particles of different shape and size. These particles are proteins, carbohydrates, lipids or electrolytes in nature. Cytoplasm also contains many organelles with distinct structure and function.

Cytoplasm is made up of two zones:

1. Ectoplasm: Peripheral part of cytoplasm, situated just beneath the cell membrane
2. Endoplasm: Inner part of cytoplasm, interposed between the ectoplasm and the nucleus.

# ■ ORGANELLES IN CYTOPLASM

Cytoplasmic organelles are the cellular structures embedded in the cytoplasm. Organelles are considered as small organs of the cell. Some organelles are bound by limiting membrane and others do not have limiting membrane (Box 1.1). Each organelle is having a definite structure and specific functions (Table 1.1).

# ■ ORGANELLES WITH LIMITING MEMBRANE

## ■ ENDOPLASMIC RETICULUM

Endoplasmic reticulum is a network of tubular and microsomal vesicular structures which are interconnected with one another. It is covered by a limiting membrane which is formed by proteins and bilayered lipids. The lumen

**BOX 1.1: Cytoplasmic organelles**

| 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 |
| **Organelles without limiting membrane** |
| 1. Ribosomes |
| 2. Cytoskeleton |

of endoplasmic reticulum contains a fluid medium called **endoplasmic matrix.** The diameter of the lumen is about 400 to 700Å. The endoplasmic reticulum forms the link between nucleus and cell membrane by connecting the cell membrane with the nuclear membrane.

### *Types of Endoplasmic Reticulum*

Endoplasmic reticulum is of two types, namely rough endoplasmic reticulum and smooth endoplasmic reticulum. Both the types 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.

### *Rough Endoplasmic Reticulum*

It is the endoplasmic reticulum with rough, bumpy or bead-like appearance. Rough appearance is due to the attachment of granular ribosomes to its outer surface. Hence, it is also called the **granular endoplasmic**

**TABLE 1.1: Functions of cytoplasmic organelles**

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

**reticulum** (Fig. 1.4). Rough endoplasmic reticulum is vesicular or tubular in structure.

### *Functions of Rough Endoplasmic Reticulum*

1. *Synthesis of proteins*

Rough endoplasmic reticulum is concerned with the synthesis of proteins in the cell. It is involved with the synthesis of mainly those proteins which are secreted from the cells such as insulin from β-cells of islets of Langerhans in pancreas and antibodies from B lymphocytes.

Ribosomes arrange the amino acids into small units of proteins and transport them into the rough endoplasmic reticulum. Here, the carbohydrates are added to the protein units forming the **glycosylated proteins** or **glycoproteins,** which are arranged in the form of reticular vesicles. These vesicles are transported mainly to Golgi apparatus for further modification and processing. Few vesicles are transported to other cytoplasmic organelles.

2. *Degradation of worn-out organelles*

Rough endoplasmic reticulum also plays an important role in the 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.** Autophagosome is digested by lysosomal enzymes (see below for details).

### *Smooth Endoplasmic Reticulum*

It is the endoplasmic reticulum with smooth appearance. It is also called **agranular reticulum.** It is formed by many interconnected tubules. So, it is also called **tubular endoplasmic reticulum.**

### *Functions of Smooth Endoplasmic Reticulum*

1. *Synthesis of non-protein substance*

Smooth endoplasmic reticulum is responsible for synthesis of non-protein substances such as cholesterol and steroid. This type of endoplasmic reticulum is abundant in cells that are involved in the synthesis of lipids, phospholipids, lipoprotein substances, steroid hormones, sebum, etc. In most of the other cells, smooth endoplasmic reticulum is less extensive than the rough endoplasmic reticulum.

2. *Role in cellular metabolism*

Outer surface of smooth endoplasmic reticulum contains many enzymes which are involved in various metabolic processes of the cell.

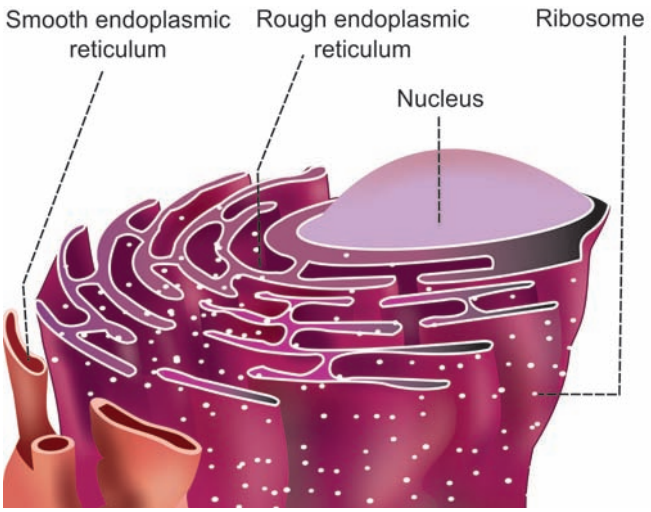



**FIGURE 1.4:** Endoplasmic reticulum

3. *Storage and metabolism of calcium*

Smooth endoplasmic reticulum is the major site of storage and metabolism of calcium. In skeletal muscle fibers, it releases calcium which is necessary to trigger the muscle contraction.

4. *Catabolism and detoxification*

Smooth endoplasmic reticulum is also concerned with catabolism and detoxification of toxic substances like some drugs and **carcinogens** (cancer-producing substances) in the liver.

## ■ GOLGI APPARATUS

Golgi apparatus or Golgi body or Golgi complex is a membrane-bound organelle, involved in the processing of proteins. It is present in all the cells except red blood cells. It is named after the discoverer Camillo Golgi. Usually, each cell has one Golgi apparatus. Some of the cells may have more than one Golgi apparatus. Each Golgi apparatus consists of 5 to 8 flattened membranous sacs called the **cisternae.**

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. 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 (Fig. 1.5).

### *Functions of Golgi Apparatus*

Major functions of Golgi apparatus are processing, packing, labeling and delivery of proteins and other molecules like lipids to different parts of the cell.

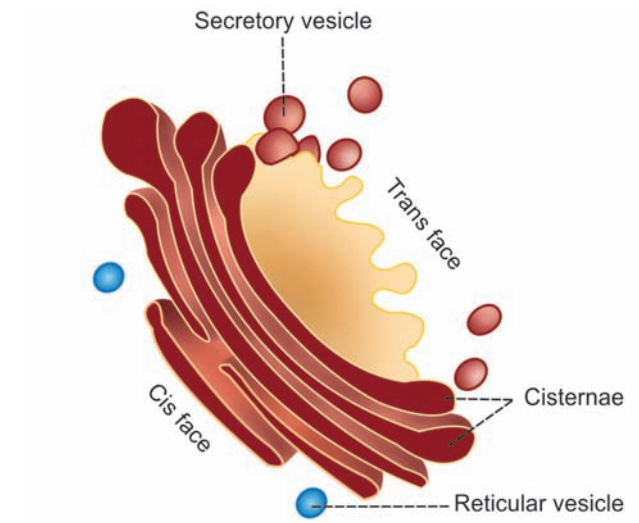



**FIGURE 1.5:** Golgi apparatus

1. *Processing of materials*

Vesicles containing glycoproteins and lipids are transported into Golgi apparatus. Here, the glycoproteins and lipids are modified and processed.

2. *Packaging of materials*

All the processed materials are packed in the form of secretory granules, secretory vesicles and lysosomes, which are transported either out of the cell or to another part of the cell. Because of this, Golgi apparatus is called the **'post office of the cell'.**

3. *Labeling and delivery of materials*

Finally, the Golgi apparatus sorts out the processed and packed materials and labels them (such as phosphate group), depending upon the chemical content for delivery (distribution) to their proper destinations. Hence, the Golgi apparatus is called **'shipping department of the cell'.**

## ■ LYSOSOMES

Lysosomes are the membrane-bound vesicular organelles found throughout the cytoplasm. The lysosomes are formed by Golgi apparatus. The enzymes synthesized in rough endoplasmic reticulum are processed and packed in the form of small vesicles in the Golgi apparatus. Then, these vesicles are pinched off from Golgi apparatus and become the lysosomes.

Among the organelles of the cytoplasm, the lysosomes have the thickest covering membrane. The membrane is formed by a bilayered lipid material. It has many small granules which contain hydrolytic enzymes.

### *Types of Lysosomes*

Lysosomes are of two types:

1. Primary lysosome, which is pinched off from Golgi apparatus. It is inactive in spite of having hydrolytic enzymes
2. Secondary lysosome, which is the active lysosome. It is formed by the fusion of a primary lysosome with phagosome or endosome (see below).

### *Functions of Lysosomes*

Lysosomes are often called **'garbage system'** of the cell because of their degradation activity. About 50 different hydrolytic enzymes, known as acid **hydroxylases** are present in the lysosomes, through which lysosomes execute their functions.

*Important lysosomal enzymes*

1. Proteases, which hydrolyze the proteins into amino acids
2. Lipases, which hydrolyze the lipids into fatty acids and glycerides
3. Amylases, which hydrolyze the polysaccharides into glucose
4. Nucleases, which hydrolyze the nucleic acids into mononucleotides.

*Mechanism of lysosomal function*

Lysosomal functions involve two mechanisms:

1. Heterophagy: Digestion of extracellular materials engulfed by the cell via endocytosis
2. Autophagy: Digestion of intracellular materials such as worn-out cytoplasmic organelles.

*Specific functions of lysosomes*

1. *Degradation of macromolecules*

Macromolecules are engulfed by the cell by means of endocytosis (phagocytosis, pinocytosis or receptor-mediated endocytosis: Chapter 3). The macromolecules such as bacteria, engulfed by the cell via phagocytosis are called **phagosomes** or **vacuoles.** The other macromolecules taken inside via pinocytosis or receptor-mediated endocytosis are called **endosomes.** The **primary lysosome** fuses with the phagosome or endosome to form the **secondary lysosome.** The pH in the secondary lysosome becomes acidic and the lysosomal enzymes are activated. The bacteria and the other macromolecules are digested and degraded by these enzymes. The secondary lysosome containing these degraded waste products moves through cytoplasm and

fuses with cell membrane. Now the waste products are eliminated by exocytosis.

2. *Degradation of worn-out organelles*

The rough endoplasmic reticulum wraps itself around the worn-out organelles like mitochondria and form the vacuoles called **autophagosomes.** One primary lysosome fuses with one autophagosome to form the secondary lysosome. The enzymes in the secondary lysosome are activated. Now, these enzymes digest the contents of autophagosome.

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

Lysosomes in the cells of the secretory glands remove the excess secretory products by degrading the secretory granules.

4. *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 (which contain the particular secretory product of the cell).

Examples of secretory lysosomes:

i. Lysosomes in the cytotoxic T lymphocytes and natural killer (NK) cells secrete perforin and **granzymes,** which destroy both viral-infected cells and tumor cells. Perforin is a pore-forming protein that initiates cell death. Granzymes belong to the family of serine proteases (enzymes that dislodge the peptide bonds of the proteins) and cause the cell death by **apoptosis**
ii. Secretory lysosomes of melanocytes secrete melanin
iii. Secretory lysosomes of mast cells secrete serotonin, which is a vasoconstrictor substance and inflammatory mediator.

## ■ PEROXISOMES

Peroxisomes or microbodies are the membrane limited vesicles like the lysosomes. Unlike lysosomes, peroxisomes are pinched off from endoplasmic reticulum and not from the Golgi apparatus. Peroxisomes contain some oxidative enzymes such as catalase, urate oxidase and D-amino acid oxidase.

### *Functions of Peroxisomes*

Peroxisomes:

i. Breakdown the fatty acids by means of a process called beta-oxidation: This is the major function of peroxisomes
ii. Degrade the toxic substances such as hydrogen peroxide and other metabolic products by means of **detoxification.** A large number of peroxisomes are present in the cells of liver, which is the major organ for detoxification. Hydrogen peroxide is formed from poisons or alcohol, which enter the cell. Whenever hydrogen peroxide is produced in the cell, the peroxisomes are ruptured and the oxidative enzymes are released. These oxidases destroy hydrogen peroxide and the enzymes which are necessary for the production of hydrogen peroxide
iii. Form the major site of oxygen utilization in the cells
iv. Accelerate gluconeogenesis from fats
v. Degrade purine to uric acid
vi. Participate in the formation of myelin
viii. Play a role in the formation of bile acids.

## ■ CENTROSOME AND CENTRIOLES

Centrosome is the membrane-bound cellular organelle situated almost in the center of cell, close to nucleus. It consists of two cylindrical structures called centrioles which are made up of proteins. Centrioles are responsible for the movement of chromosomes during cell division.

## ■ SECRETORY VESICLES

Secretory vesicles are the organelles with limiting membrane and contain the secretory substances. These vesicles are formed in the endoplasmic reticulum and are processed and packed in Golgi apparatus. Secretory vesicles are present throughout the cytoplasm. When necessary, these vesicles are ruptured and secretory substances are released into the cytoplasm.

## ■ MITOCHONDRION

Mitochondrion (plural = mitochondria) is a membrane-bound cytoplasmic organelle concerned with production of energy. It is a rod-shaped or oval-shaped structure with a diameter of 0.5 to 1 µ. It is covered by a bilayered membrane (Fig. 1.6). The outer membrane is smooth and encloses the contents of mitochondrion. This membrane contains various enzymes such as acetyl-CoA synthetase and glycerolphosphate acetyltransferase.

The inner membrane is folded in the form of shelf-like inward projections called **cristae** and it covers the inner matrix space. Cristae contain many enzymes and other protein molecules which are involved in respiration and synthesis of adenosine triphosphate (ATP). Because of these functions, the enzymes and other protein molecules

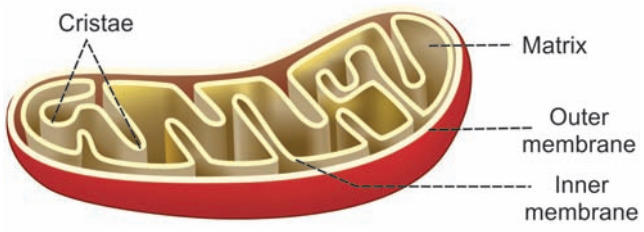



**FIGURE 1.6:** Structure of mitochondrion

in cristae are collectively known as respiratory chain or electron transport system.

*Enzymes and other proteins of respiratory chain*

i. Succinic dehydrogenase
ii. Dihydronicotinamide adenine dinucleotide (NADH) dehydrogenase
iii. Cytochrome oxidase
iv. Cytochrome C
v. ATP synthase.

Inner cavity of mitochondrion is filled with matrix which contains many enzymes. Mitochondrion moves freely in the cytoplasm of the cell. It is capable of reproducing itself. Mitochondrion contains its own deoxyribonucleic acid (DNA), which is responsible for many enzymatic actions. In fact, mitochondrion is the only organelle other than nucleus, which has its own DNA.

### *Functions of Mitochondrion*

1. *Production of energy*

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

2. *Synthesis of ATP*

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

3. *Apoptosis*

Cytochrome C and second mitochondria-derived activator of caspases (SMAC)/diablo secreted in mitochondria are involved in apoptosis (see below).

4. *Other functions*

Other functions of mitochondria include storage of calcium and detoxification of ammonia in liver.

## ■ ORGANELLES WITHOUT LIMITING MEMBRANE

### ■ RIBOSOMES

Ribosomes are the organelles without limiting membrane. These organelles are granular and small dot-like structures with a diameter of 15 nm. Ribosomes are made up of 35% of proteins and 65% of ribonucleic acid (RNA). RNA present in ribosomes is called ribosomal RNA (rRNA). Ribosomes are concerned with protein synthesis in the cell.

### *Types of Ribosomes*

Ribosomes are of two types:

i. Ribosomes that are attached to rough endoplasmic reticulum
ii. Free ribosomes that are distributed in the cytoplasm.

### *Functions of Ribosomes*

Ribosomes are called **'protein factories'** because of their role in the synthesis of proteins. Messenger RNA (mRNA) carries the **genetic code** for protein synthesis from nucleus to the ribosomes. The ribosomes, in turn arrange the amino acids into small units of proteins.

Ribosomes attached to rough endoplasmic reticulum are involved in the synthesis of proteins such as the enzymatic proteins, hormonal proteins, lysosomal proteins and the proteins of the cell membrane.

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

### ■ CYTOSKELETON

Cytoskeleton is the cellular organelle present throughout the cytoplasm. It determines the shape of the cell and gives support to the cell. It is a complex network of structures with varying sizes. In addition to determining the shape of the cell, it is also essential for the cellular movements and the response of the cell to external stimuli.

Cytoskeleton consists of three major protein components:

1. Microtubule
2. Intermediate filaments
3. Microfilaments.

### 1. *Microtubules*

Microtubules are the straight, hollow and tubular structures of the cytoskeleton. These organelles without the limiting membrane are arranged in different bundles. Each tubule has a diameter of 20 to 30 nm. Length of microtubule varies and it may be 1000 times more than the thickness.

Structurally, the microtubules are formed by bundles of globular protein called **tubulin** (Fig. 1.7). Tubulin has two subunits, namely α-subunit and β-subunit.

*Functions of microtubules*

Microtubules may function alone or join with other proteins to form more complex structures like cilia, flagella or centrioles and perform various functions.
Microtubules:

i. Determine the shape of the cell
ii. Give structural strength to the cell
iii. Act like conveyer 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. Are responsible for the movement of centrioles and the complex cellular structures like cilia.

### 2. *Intermediate Filaments*

Intermediate filaments are the structures that form a network around the nucleus and extend to the periphery of the cell. Diameter of each filament is about 10 nm. The intermediate filaments are formed by rope-like polymers, which are made up of **fibrous proteins** (Fig. 1.8).

*Subclasses of intermediate filaments*

Intermediate filaments are divided into five subclasses:

i. Keratins (in epithelial cells)
ii. Glial filaments (in astrocytes)
iii. Neurofilaments (in nerve cells)
iv. Vimentin (in many types of cells)
v. Desmin (in muscle fibers).

*Functions of intermediate filaments*

Intermediate filaments help to maintain the shape of the cell. These filaments also connect the adjacent cells through desmosomes.

### 3. *Microfilaments*

Microfilaments are long and fine thread-like structures with a diameter of about 3 to 6 nm. These filaments are made up of non-tubular contractile proteins called actin and myosin. Actin is more abundant than myosin.

Microfilaments are present throughout the cytoplasm. The microfilaments present in ectoplasm contain only actin molecules (Fig. 1.9) and those present in endoplasm contain both actin and myosin molecules.

*Functions of microfilaments*

Microfilaments:

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

## ■ NUCLEUS

Nucleus is the most prominent and the largest cellular organelle. It has a diameter of 10 µ to 22 µ and occupies about 10% of total volume of the cell.

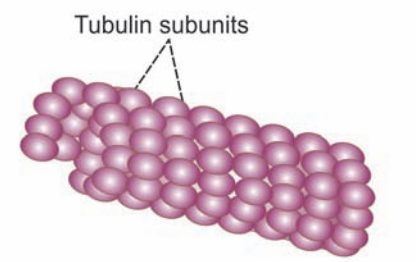



**FIGURE 1.7:** Microtubule

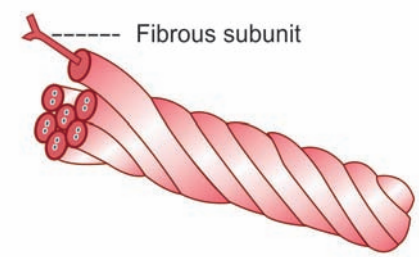



**FIGURE 1.8:** Intermediate filament

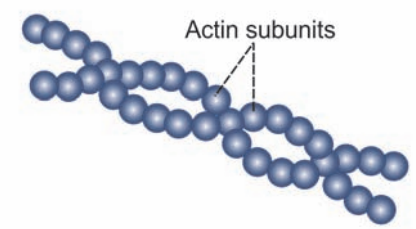



**FIGURE 1.9:** Microfilament of ectoplasm

Nucleus is present in all the cells in the body except the red blood cells. The cells with nucleus are called **eukaryotes** and those without nucleus are known as **prokaryotes**. Presence of nucleus is necessary for cell division.

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

## ■ STRUCTURE OF NUCLEUS

Nucleus is covered by a membrane called **nuclear membrane** and contains many components. Major components of nucleus are **nucleoplasm, chromatin** and nucleolus.

### *Nuclear Membrane*

Nuclear membrane is double layered and porous in nature. This allows the nucleoplasm to communicate with the cytoplasm. The outer layer of nuclear membrane is continuous with the membrane of endoplasmic reticulum. The space between the two layers of nuclear membrane is continuous with the lumen of endoplasmic reticulum.

Pores of the nuclear membrane are guarded (lined) by protein molecules. Diameter of the pores is about 80 to 100 nm. However, it is decreased to about 7 to 9 nm because of the attachment of protein molecules with the periphery of the pores. Exchange of materials between nucleoplasm and cytoplasm occurs through these pores.

### *Nucleoplasm*

Nucleoplasm is a highly viscous fluid that forms the ground substance of the nucleus. It is similar to cytoplasm present outside the nucleus.

Nucleoplasm surrounds chromatin and nucleolus. It contains dense fibrillar network of proteins called the nuclear matrix and many substances such as nucleotides and enzymes. The nuclear matrix forms the structural framework for organizing chromatin. The soluble liquid part of nucleoplasm is known as nuclear hyaloplasm.

### *Chromatin*

Chromatin is a thread-like material made up of large molecules of DNA. The DNA molecules are compactly packed with the help of a specialized basic protein called histone. So, chromatin is referred as **DNA-histone complex.** It forms the major bulk of nuclear material.

DNA is a double helix which wraps around central core of eight histone molecules to form the fundamental packing unit of chromatin called **nucleosome.** Nucleosomes are packed together tightly with the help of a histone molecule to form a chromatin fiber.

Just before cell division, the chromatin condenses to form chromosome.

### *Chromosomes*

Chromosome is the rod-shaped nuclear structure that carries a complete blueprint of all the hereditary characteristics of that species. A chromosome is formed from a single DNA molecule coiled around histone molecules. Each DNA contains many genes.

Normally, the chromosomes are not visible in the nucleus under microscope. Only during cell division, the chromosomes are visible under microscope. This is because DNA becomes more tightly packed just before cell division, which makes the chromosome visible during cell division.

All the dividing cells of the body except reproductive cells contain 23 pairs of chromosomes. Each pair consists of one chromosome inherited from mother and one from father. The cells with 23 pairs of chromosomes are called **diploid cells.** The reproductive cells called gametes or sex cells contain only 23 single chromosomes. These cells are called **haploid cells.**

### *Nucleolus*

Nucleolus is a small, round granular structure of the nucleus. Each nucleus contains one or more nucleoli. The nucleolus contains RNA and some proteins, which are similar to those found in ribosomes. The RNA is synthesized by five different pairs of chromosomes and stored in the nucleolus. Later, it is condensed to form the subunits of ribosomes. All the subunits formed in the nucleolus are transported to cytoplasm through the pores of nuclear membrane. In the cytoplasm, these subunits fuse to form ribosomes, which play an essential role in the formation of proteins.

## ■ FUNCTIONS OF NUCLEUS

Major functions of nucleus are the control of cellular activities and storage of hereditary material. Several processes are involved in the nuclear functions.

Functions of nucleus:

1. Control of all the cell activities that include metabolism, protein synthesis, growth and reproduction (cell division)
2. Synthesis of RNA
3. Formation of subunits of ribosomes
4. Sending genetic instruction to the cytoplasm for protein synthesis through messenger RNA (mRNA)

5. Control of the cell division through genes
6. Storage of hereditary information (in genes) and transformation of this information from one generation of the species to the next.

## DEOXYRIBONUCLEIC ACID

Deoxyribonucleic acid (DNA) is a nucleic acid that carries the genetic information to the offspring of an organism. DNA forms the chemical basis of hereditary characters. It contains the instruction for the synthesis of proteins in the ribosomes. Gene is a part of a DNA molecule.

DNA is present in the nucleus (chromosome) and mitochondria of the cell. The DNA present in the nucleus is responsible for the formation of RNA. RNA regulates the synthesis of proteins by ribosomes. DNA in mitochondria is called **non-chromosomal DNA.**

## STRUCTURE OF DNA

DNA is a double-stranded complex nucleic acid. It is formed by deoxyribose, phosphoric acid and four types of bases. Each DNA molecule consists of two polynucleotide chains, which are twisted around one another in the form of a double helix. The two chains are formed by the sugar deoxyribose and phosphate. These two substances form the backbone of DNA molecule. Both chains of DNA are connected with each other by some organic bases (Fig. 1.10).

Each chain of DNA molecule consists of many nucleotides. Each nucleotide is formed by:

1. Deoxyribose – sugar
2. Phosphate
3. One of the following organic (nitrogenous) bases:
   - Purines – Adenine (A)
   - Guanine (G)
   - Pyrimidines – Thymine (T)
   - Cytosine (C)

The strands of DNA are arranged in such a way that both are bound by specific pairs of bases. The adenine of one strand binds specifically with thymine of opposite strand. Similarly, the cytosine of one strand binds with guanine of the other strand.

DNA forms the component of chromosomes, which carries the hereditary information. The hereditary information that is encoded in DNA is called **genome.** Each DNA molecule is divided into discrete units called genes.

## GENE

Gene is a portion of DNA molecule that contains the message or code for the synthesis of a specific protein from amino acids. It is like a book that contains the information necessary for protein synthesis. Gene is considered as the basic hereditary unit of the cell.

In the nucleotide of DNA, three of the successive base pairs are together called a triplet or a **codon.** Each codon codes or forms code word (information) for one amino acid. There are 20 amino acids and there is separate code for each amino acid. For example, the triplet CCA is the code for glycine and GGC is the code for proline.

Thus, each gene forms the code word for a particular protein to be synthesized in ribosome (outside the nucleus) from amino acids.

## GENETIC DISORDERS

A genetic disorder is a disorder that occurs because of the abnormalities in an individual's genetic material (genome). Genetic disorders are either hereditary disorders or due to defect in genes.

### *Causes of Gene Disorders*

Genetic disorders occur due to two causes:

1. *Genetic variation:* Presence of a different form of gene
2. *Genetic mutation:* Generally, mutation means an alteration or a change in nature, form, or quality. Genetic mutation refers to change of the DNA sequence within a gene or chromosome of an organism, which results in the creation of a new character.

### *Classification of Genetic Disorders*

Genetic disorders are classified into four types:

1. Single gene disorders
2. Multifactorial genetic disorders
3. Chromosomal disorders
4. Mitochondrial DNA disorders.

1. *Single Gene Disorders*

Single gene disorders or Mendelian or monogenic disorders occur because of variation or mutation in one single gene. Examples include sickle cell anemia and Huntington's disease.

2. *Multifactorial Genetic Disorders*

Multifactorial genetic disorders or polygenic disorders are caused by combination of environmental factors and mutations in multiple genes. Examples are coronary heart disease, Alzheimer's disease, arthritis and diabetes.

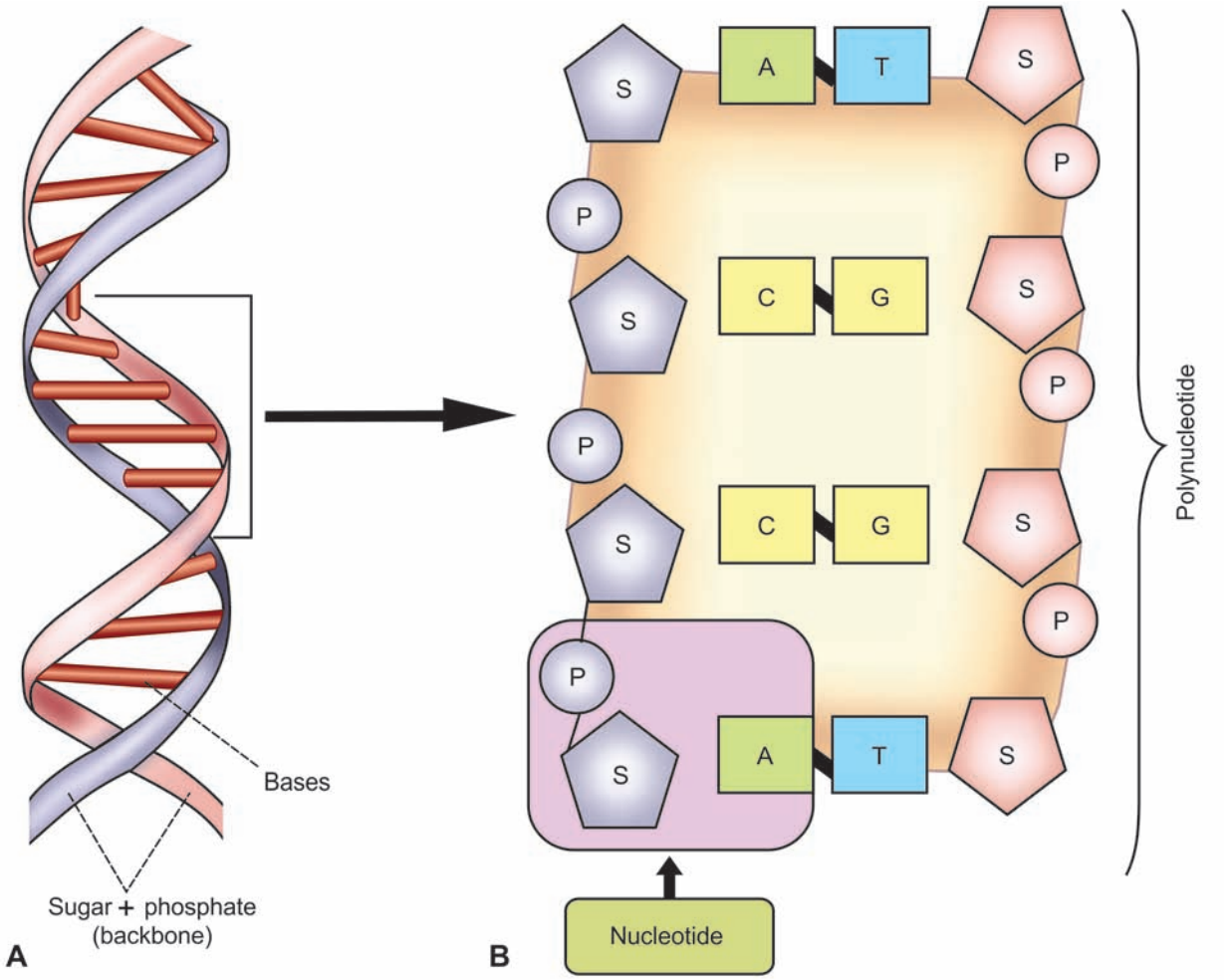



**FIGURE 1.10:** Structure of DNA. **A.** Double helical structure of DNA; **B.** Magnified view of the components of DNA. A = Adenine, C = Cytocine, G= Guanine, P = Phosphate, S = Sugar, T = Thymine.

3. *Chromosomal Disorders*

Chromosomal disorder is a genetic disorder caused by abnormalities in chromosome. It is also called chromosomal abnormality, anomaly or aberration. It often results in genetic disorders which involve physical or mental abnormalities. Chromosomal disorder is caused by numerical abnormality or structural abnormality.

Chromosomal disorder is classified into two types:

i. Structural abnormality (alteration) of chromosomes which leads to disorders like chromosome instability syndromes (group of inherited diseases which cause malignancies)
ii. Numerical abnormality of chromosomes which is of two types:
   a. **Monosomy** due to absence of one chromosome from normal diploid number. Example is Turner's syndrome, which is characterized by physical disabilities
   b. **Trisomy** due to the presence of one extra chromosome along with normal pair of chromosomes in the cells. Example is **Down syndrome,** which is characterized by physical disabilities and mental retardation.

4. *Mitochondrial DNA Disorders*

Mitochondrial DNA disorders are the genetic disorders caused by the mutations in the DNA of mitochondria (non-chromosomal DNA). Examples are **Kearns-Sayre syndrome** (neuromuscular disorder characterized by myopathy, cardiomyopathy and paralysis of ocular muscles) and **Leber's hereditary optic neuropathy** (disease characterized by degeneration of retina and loss of vision).

## RIBONUCLEIC ACID

Ribonucleic acid (RNA) is a nucleic acid that contains a long chain of nucleotide units. It is similar to DNA but contains ribose instead of deoxyribose. Various functions coded in the genes are carried out in the cytoplasm of the cell by RNA. RNA is formed from DNA.

### STRUCTURE OF RNA

Each RNA molecule consists of a single strand of polynucleotide unlike the double-stranded DNA. Each nucleotide in RNA is formed by:

1. Ribose – sugar.
2. Phosphate.
3. One of the following organic bases:
   - Purines – Adenine (A)
   - Purines – Guanine (G)
   - Pyrimidines – Uracil (U)
   - Pyrimidines – Cytosine (C).

Uracil replaces the thymine of DNA and it has similar structure of thymine.

### TYPES OF RNA

RNA is of three types. Each type of RNA plays a specific role in protein synthesis. The three types of RNA are:

#### 1. *Messenger RNA (mRNA)*

Messenger RNA carries the genetic code of the amino acid sequence for synthesis of protein from the DNA to the cytoplasm.

#### 2. *Transfer RNA (tRNA)*

Transfer RNA is responsible for decoding the genetic message present in mRNA.

#### 3. *Ribosomal RNA (rRNA)*

Ribosomal RNA is present within the ribosome and forms a part of the structure of ribosome. It is responsible for the assembly of protein from amino acids in the ribosome.

## GENE EXPRESSION

Gene expression is the process by which the information (code word) encoded in the gene is converted into functional gene product or document of instruction (RNA) that is used for protein synthesis.

Gene expression involves two steps:

1. Transcription.
2. Translation.

### TRANSCRIPTION OF GENETIC CODE

The word transcription means copying. It indicates the copying of genetic code from DNA to RNA. The proteins are synthesized in the ribosomes which are present in the cytoplasm. However, the synthesis of different proteins depends upon the information (sequence of codon) encoded in the genes of the DNA which is present in the nucleus. Since DNA is a macromolecule, it cannot pass through the pores of the nuclear membrane and enter the cytoplasm. But, the information from DNA must be sent to ribosome. So, the gene has to be transcribed (copied) into mRNA which is developed from DNA.

Thus, the first stage in the protein synthesis is transcription of genetic code, which occurs within the nucleus. It involves the formation of mRNA and simultaneous copying or transfer of information from DNA to mRNA. The mRNA enters the cytoplasm from the nucleus and activates the ribosome resulting in protein synthesis. The formation of mRNA from DNA is facilitated by the enzyme RNA polymerase.

### TRANSLATION OF GENETIC CODE

Translation is the process by which protein synthesis occurs in the ribosome of the cell under the direction of genetic instruction carried by mRNA from DNA. Or, it is the process by which the mRNA is read by ribosome to produce a protein. This involves the role of other two types of RNA, namely tRNA and rRNA.

The mRNA moves out of nucleus into the cytoplasm. Now, a group of ribosomes called **polysome** gets attached to mRNA. The sequence of **codons** in mRNA are exposed and recognized by the complementary sequence of base in tRNA. The complementary sequence of base is called **anticodon.** According to the sequence of bases in anticodon, different amino acids are transported from the cytoplasm into the ribosome by tRNA that acts as a carrier. With the help of rRNA, the protein molecules are assembled from amino acids. The protein synthesis occurs in the ribosomes which are attached to rough endoplasmic reticulum.

## GROWTH FACTORS

Growth factors are proteins which act as cell signaling molecules like cytokines (Chapter 17) and hormones (Chapter 65). These factors bind with specific surface receptors of the target cell and activate proliferation, differentiation and/or maturation of these cells.

Often, the term growth factor is interchangeably used with the term **cytokine.** But growth factors are distinct

from cytokines. Growth factors act on the cells of the growing tissues. But cytokines are concerned with the cells of immune system and hemopoietic cells.

Many growth factors are identified. The known growth factors are:

1. Platelet-derived growth factor – PDGF (Chapter 18)
2. Colony stimulating factors – CSF (Chapter 16)
3. Nerve growth factors – NGF (Chapter 134)
4. Neurotropins (Chapter 134)
5. Erythropoietin (Chapter 10)
6. Thrombopoietin (Chapter 18)
7. Insulin-like growth factors – IGF (Chapter 66)
8. Epidermal growth factor – present in keratinocytes and fibroblasts. It inhibits growth of hair follicles and cancer cells
9. Basic fibroblast growth factor – present in blood vessels. It is concerned with the formation of new blood vessels
10. Myostatin – present in skeletal muscle fibers. It controls skeletal muscle growth
11. Transforming growth factors (TGF) – present in transforming cells (cells undergoing differentiation) and in large quantities in tumors and cancerous tissue. TGF is of two types:
    i. TGF-α secreted in brain, keratinocytes and macrophages. It is concerned with growth of epithelial cells and wound healing
    ii. TGF-β secreted by hepatic cells, T lymphocytes, B lymphocytes, macrophages and mast cells. When the liver attains the maximum size in adults, it controls liver growth by inhibiting proliferation of hepatic cells. TGF-β also causes immunosuppression.

## ■ CELL DEATH

Cell death occurs by two distinct processes:

1. Apoptosis
2. Necrosis.

### ■ APOPTOSIS

Apoptosis is defined as the natural or **programed death** of the cell under genetic control. Originally, apoptosis refers to the process by which the leaves fall from trees in autumn (In Greek, apoptosis means 'falling leaves'). 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. In contrast to necrosis, apoptosis usually does not produce inflammatory reactions in the neighboring tissues.

#### *Functional Significance of Apoptosis*

The purpose 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 beyond repair by a virus or a toxin
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 74)
iv. The cell that looses the contact with neighboring cells or basal lamina in the epithelial tissue dies by apoptosis. This is essential for the death of old enterocytes that shed into the lumen of intestinal glands (Chapter 41)
v. It plays an important role in the cyclic sloughing of the inner layer of endometrium, resulting in menstruation (Chapter 80)
vi. Apoptosis removes the autoaggressive T cells and prevents autoimmune diseases.

#### *Activation of Apoptosis*

Apoptosis is activated by either withdrawal of positive signals (survival factors) or arrival of negative signals.

*Withdrawal of positive signals*

Positive signals are the signals which are necessary for the long-time survival of most of the cells. The positive signals are continuously produced by other cells or some chemical stimulants. Best examples of chemical stimulants are:

i. Nerve growth factors (for neurons)
ii. Interleukin-2 (for cells like lymphocytes).

The absence or withdrawal of the positive signals activates apoptosis.

*Arrival of negative signals*

Negative signals are the external or internal stimuli which initiate apoptosis. The negative signals are produced during various events like:

1. Normal developmental procedures
2. Cellular stress
3. Increase in the concentration of intracellular oxidants
4. Viral infection
5. Damage of DNA
6. Exposure to agents like chemotherapeutic drugs, X-rays, ultraviolet rays and the death-receptor ligands.

*Death-receptor ligands and death receptors*

Death-receptor ligands are the substances which bind with specific cell membrane receptors and initiate the process of apoptosis. The common death-receptor ligands are tumor necrosis factors (TNF- α, TNF- β) and Fas ligand (which binds to the receptor called Fas).

Death-receptors are the cell membrane receptors which receive the death-receptor ligands. Well-characterized death receptors are TNF receptor-1 (TNFR1) and TNF-related apoptosis inducing ligand (TRAIL) receptors called DR4 and DR5.

*Role of mitochondria in apoptosis*

External or internal stimuli initiate apoptosis by activating the proteases called **caspases** (cysteinyl-dependent aspartate-specific proteases). Normally, caspases are suppressed by the inhibitor protein called **apoptosis inhibiting factor (AIF).**

When the cells receive the apoptotic stimulus, mitochondria releases two protein materials. First one is **Cytochrome C** and the second protein is called second mitochondria-derived activator of caspases (SMAC) or its homologudiablo.

SMAC/diablo inactivates AIF so that the inhibitor is inhibited. During this process, SMAC/diablo and AIF aggregate to form **apoptosome** which activates caspases. Cytochrome C also facilitates caspase activation.

### *Apoptotic Process*

Cell shows sequence of characteristic morphological changes during apoptosis, viz.:

1. Activated caspases digest the proteins of cyto-skeleton and the cell shrinks and becomes round
2. Because of shrinkage, the cell losses the contact with neighboring cells or surrounding matrix
3. Chromatin in the nucleus undergoes degradation and condensation
4. Nuclear membrane becomes discontinuous and the DNA inside nucleus is cleaved into small fragments
5. Following the degradation of DNA, the nucleus breaks into many discrete nucleosomal units, which are also called chromatin bodies
6. Cell membrane breaks and shows bubbled appearance
7. Finally, the cell breaks into several fragments containing intracellular materials including chromatin bodies and organelles of the cell. Such cellular fragments are called vesicles or apoptotic bodies
8. Apoptotic bodies are engulfed by phagocytes and dendritic cells.

### *Abnormal Apoptosis*

Apoptosis within normal limits is beneficial for the body. However, too much or too little apoptosis leads to abnormal conditions.

*Common abnormalities due to too much apoptosis:*

1. Ischemic-related injuries
2. Autoimmune diseases like:
   i. Hemolytic anemia
   ii. Thrombocytopenia
   iii. Acquired immunodeficiency syndrome (AIDS)
3. Neurodegenerative diseases like Alzheimer's disease.

*Common abnormalities due to too little apoptosis:*

1. Cancer
2. Autoimmune lymphoproliferative syndrome (ALPS).

## ■ NECROSIS

Necrosis (means 'dead' in Greek) is the uncontrolled and **unprogramed 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.

### *Necrotic Process*

Necrosis results in lethal disruption of cell structure and activity. The cell undergoes a series of characteristic changes during necrotic process, viz.

1. Cell swells causing damage of the cell membrane and appearance of many holes in the membrane
2. Intracellular contents leak out into the surrounding environment
3. Intracellular environment is altered
4. Simultaneously, large amount of calcium ions are released by the damaged mitochondria and other organelles
5. Presence of calcium ions drastically affects the organization and activities of proteins in the intracellular components
6. Calcium ions also induce release of toxic materials that activate the lysosomal enzymes
7. Lysosomal enzymes cause degradation of cellular components and the cell is totally disassembled resulting in death
8. Products broken down from the disassembled cell are ingested by neighboring cells.

### *Reaction of Neighboring Tissues after Necrosis*

Tissues surrounding the necrotic cells react to the breakdown products of the dead cells, particularly the derivatives of membrane phospholipids like the arachidonic acid. Along with other materials, arachidonic acid causes the following inflammatory reactions in the surrounding tissues:

1. Dilatation of capillaries in the region and thereby increasing local blood flow
2. Increase in the temperature leading to reddening of the tissues
3. Release of histamine from these tissues which induces pain in the affected area
4. Migration of leukocytes and macrophages from blood to the affected area because of increased capillary permeability
5. Movement of water from blood into the tissues causing local edema
6. Engulfing and digestion of cellular debris and foreign materials like bacteria by the leukocytes and macrophages
7. Activation of immune system resulting in the removal of foreign materials
8. Formation of pus by the dead leukocytes during this process
9. Finally, tissue growth in the area and wound healing.

## ■ CELL ADAPTATION

Cell adaptation refers to the changes taking place in a cell in response to environmental changes.

Normal functioning of the cell is always threatened by various factors such as stress, chemical agents, diseases and environmental hazards. Yet, the cell survives and continues the function by means of adaptation. Only during extreme conditions, the cell fails to withstand the hazardous factors which results in destruction and death of the cell.

Cellular adaptation occurs by any of the following mechanisms.

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

## ■ ATROPHY

Atrophy means decrease in size of a cell. Atrophy of more number of cells results in decreased size or wasting of the concerned tissue, organ or part of the body.

### *Causes of Atrophy*

Atrophy is due to one or more number of causes such as:

i. Poor nourishment
ii. Decreased blood supply
iii. Lack of workload or exercise
iv. Loss of control by nerves or hormones
v. Intrinsic disease of the tissue or organ.

### *Types of Atrophy*

Atrophy is of two types, physiological atrophy and pathological atrophy. Examples of physiological atrophy are the atrophy of thymus in childhood and tonsils in adolescence. The pathological atrophy is common in skeletal muscle, cardiac muscle, sex organs and brain.

## ■ HYPERTROPHY

Hypertrophy is the increase in the size of a cell. Hypertrophy of many cells results in enlargement or overgrowth of an organ or a part of the body. Hypertrophy is of three types.

### 1. *Physiological Hypertrophy*

Physiological hypertrophy is the increase in size due to increased workload or exercise. The common physiological hypertrophy includes:

i. *Muscular hypertrophy:* Increase in bulk of skeletal muscles that occurs in response to strength training exercise
ii. *Ventricular hypertrophy:* Increase in size of ventricular muscles of the heart which is advantageous only if it occurs in response to exercise.

### 2. *Pathological Hypertrophy*

Increase in cell size in response to pathological changes is called pathological hypertrophy. Example is the ventricular hypertrophy that occurs due to pathological conditions such as high blood pressure, where the workload of ventricles increases.

### 3. *Compensatory Hypertrophy*

Compensatory hypertrophy is the increase in size of the cells of an organ that occurs in order to compensate the loss or dysfunction of another organ of same type. Examples are the hypertrophy of one kidney when the other kidney stops functioning; and the increase in muscular strength of an arm when the other arm is dysfunctional or lost.

## ■ HYPERPLASIA

Hyperplasia is the increase in number of cells due to increased cell division (mitosis). It is also defined as abnormal or unusual proliferation (multiplication) of cells due to constant cell division. Hyperplasia results in gross enlargement of the organ. Hyperplasia involves constant cell division of the normal cells only. Hyperplasia is of three types.

### 1. *Physiological Hyperplasia*

Physiological hyperplasia is the momentary adaptive response to routine physiological changes in the body. For example, during the proliferative phase of each menstrual cycle, the endometrial cells in uterus increase in number.

### 2. *Compensatory Hyperplasia*

Compensatory hyperplasia is the increase in number of cells in order to replace the damaged cells of an organ or the cells removed from the organ.

Compensatory hyperplasia helps the tissues and organs in regeneration. It is common in liver. After the surgical removal of the damaged part of liver, there is increase in the number of liver cells resulting in regeneration. Compensatory hyperplasia is also common in epithelial cells of intestine and epidermis.

### 3. *Pathological Hyperplasia*

Pathological hyperplasia is the increase in number of cells due to abnormal increase in hormone secretion. It is also called hormonal hyperplasia. For example, in gigantism, hypersecretion of growth hormone induces hyperplasia that results in overgrowth of the body.

## ■ DYSPLASIA

Dysplasia is the condition characterized by the abnormal change in size, shape and organization of the cell. Dysplasia is not considered as true adaptation and it is suggested as related to hyperplasia. It is common in epithelial cells of cervix and respiratory tract.

## ■ METAPLASIA

Metaplasia is the condition that involves replacement of one type of cell with another type of cell. It is of two types.

### 1. *Physiological Metaplasia*

Replacement of cells in normal conditions is called physiological metaplasia. Examples are transformation of cartilage into bone and transformation of monocytes into macrophages.

### 2. *Pathological Metaplasia*

Pathological metaplasia is the irreversible replacement of cells due to constant exposure to harmful stimuli. For example, chronic smoking results in transformation of normal mucus secreting ciliated columnar epithelial cells into non-ciliated squamous epithelial cells, which are incapable of secreting mucus. These transformed cells may become cancerous cells if the stimulus (smoking) is prolonged.

# ■ CELL DEGENERATION

Cell degeneration is a process characterized by damage of the cells at cytoplasmic level, without affecting the nucleus. Degeneration may result in functional impairment or deterioration of a tissue or an organ. It is common in metabolically active organ like liver, heart and kidney. Degenerative changes are reversible in most of the cells.

### *Causes for Cell Degeneration*

Common causes for cell degeneration:

1. Atrophy, hypertrophy, hyperplasia and/or dysplasia of cell

2. Fluid accumulation in the cell
3. Fat infiltration into the cell
4. Calcification of cellular organelles.

## CELL AGING

Cell aging is the gradual structural and functional changes in the cells that occur over the passage of time. It is now suggested that cell aging is due to damage of cellular substances like DNA, RNA, proteins and lipids, etc. when the cell becomes old. When more cellular substances are damaged, the cellular function decreases. This causes deterioration of tissues, organs or parts of the body. Finally, the health of the body starts declining and this leads to death. So, the cell aging determines the health and life span of the body.

## STEM CELLS

Stem cells are the primary cells capable of reforming themselves through mitotic division and differentiating into specialized cells. These cells serve as repair system of the body and are present in all multicellular organisms.

### TYPES OF STEM CELLS

Stem cells are of two types:

1. Embryonic stem cells derived from embryo
2. Adult stem cells derived from adults.

#### 1. *Embryonic Stem Cells*

Embryonic stem cells are derived from the inner cell mass of a blastocyst which is an early stage of embryo. It takes about 4 to 5 days after fertilization to reach the blastocyst stage and it has about 30 to 50 cells. Embryonic stem cells have two important qualities:

i. Self-renewal capacity
ii. Pluripotent nature, i.e. these cells are capable of differentiating into all types of cells in ectodermal, endodermal and mesodermal layers.

Because of these two qualities, the embryonic stem cells can be used therapeutically for regeneration or replacement of diseased or destroyed tissues. In fact, embryonic pluripotent stem cells are now cultured and lot of research is going on to explore the possibility of using these cells in curing the disorders like diabetes mellitus by cell replacement technique. But, ethical issues arise because the embryo has to be destroyed to collect the stem cells.

*Stem cells from umbilical cord blood*

Stem cells in umbilical cord blood are collected from the placenta or umbilical cord. Use of these stem cells for research and therapeutic purposes does not create any ethical issue because it does not endanger the life of the fetus or newborn. Because of vitality and easy availability, the umbilical cord blood stem cells are becoming a potent resource for transplant therapies. Nowadays, these stem cells are used to treat about 70 diseases and are used in many transplants worldwide.

#### 2. *Adult Stem Cells*

Embryonic stem cells do not disappear after birth. But remain in the body as adult stem cells and play a role in repair of damaged tissues. However, their number becomes less. Adult stem cells are the undifferentiated multipotent progenitor cells found in growing children and adults. These are also known as **somatic stem cells** and are found everywhere in the body. These cells are capable of dividing and reforming the dying cells and regenerating the damaged tissues. So, these stem cells can also be used for research and therapeutic purposes.

Adult stem cells are collected from bone marrow. Two types of stem cells are present in bone marrow:

i. **Hemopoietic stem cells,** which give rise to blood cells (Chapter 10)
ii. **Bone marrow stromal cells,** which can differentiate into cardiac and skeletal muscle cells.

### ADVANTAGES OF STEM CELLS

Adult stem cells from bone marrow are used in bone marrow transplant to treat leukemia and other blood disorders since 30 years. Recently, it is known that these stem cells can develop into nerve cells, liver cells, skeletal muscle cells and cardiac muscle cells.

Recent discoveries also reveal that the stem cells are present in several tissues which include blood, blood vessels, skeletal muscle, liver, skin and brain. It is also found that these cells are capable of differentiating into multiple cell types. So, the cell-based therapy using stem cells may be possible to treat many diseases such as heart diseases, diabetes, Parkinson's disease, Alzheimer's disease, spinal cord injury, stroke and rheumatoid arthritis.

# Cell Junctions

Chapter 2

- DEFINITION AND CLASSIFICATION
- OCCLUDING JUNCTIONS
  - TIGHT JUNCTION
  - APPLIED PHYSIOLOGY
- COMMUNICATING JUNCTIONS
  - GAP JUNCTION
  - CHEMICAL SYNAPSE
  - APPLIED PHYSIOLOGY
- ANCHORING JUNCTIONS
  - ADHERENS JUNCTION
  - FOCAL ADHESION
  - DESMOSOME
  - HEMIDESMOSOME
  - APPLIED PHYSIOLOGY
- CELL ADHESION MOLECULES
  - TYPES

## DEFINITION AND CLASSIFICATION

Cell junction is the connection between the neighboring cells or the contact between the cell and extracellular matrix. It is also called **membrane junction.**

Cell junctions are classified into three types:

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

## OCCLUDING JUNCTIONS

Cell junctions which prevent intercellular exchange of substances are called occluding junctions, i.e. these junctions prevent the movement of ions and molecules from one cell to another cell. Tight junctions belong to this category.

### TIGHT JUNCTION

Tight junction is the intercellular occluding junction that prevents the passage of large molecules. It is also called **zonula occludens.** It is the region where the cell membranes of the adjacent cells fuse together firmly. This type of junction is present in the **apical margins** of epithelial and endothelial cells in intestinal mucosa, wall of renal tubule, capillary wall and choroid plexus.

#### *Structure of Tight Junction*

Tight junction is made up of a **ridge** which has two halves. One half of the ridge is from one cell and another half is from the other cell. Both halves of the ridge fuse with each other very tightly and occupy the space between the two cells (Fig. 2.1). Each half of the ridge consists of **tight junction strands.**

*Proteins of tight junction*

Proteins involved in the formation of tight junctions are classified into two types:

1. Tight junction **membrane proteins** or integral membrane proteins, such as occludin, claudin and **junctional adhesion molecules (JAMs)**

2. **Scaffold** (framework or platform) proteins or peripheral membrane proteins or cytoplasmic **plaque proteins** such as cingulin, symplekin and ZO-1, 2, 3.

Tight junction membrane protein molecules are anchored in the strands of the ridge and attach with their counterparts of neighboring cell, so that both the cells are held together. The scaffold (platform) proteins are attached with the tight junction membrane proteins and strengthen the anchoring in the ridges.

### *Functions of Tight Junction*

1. *Strength and stability:* The tight junction holds the neighboring cells of the tissues firmly and thus provides strength and stability to the tissues.
2. *Selective permeability* **(gate function):** The tight junction forms a selective barrier for small molecules and a total barrier for large molecules.

   In the epithelial and endothelial cells, tight junction is the most apical intercellular junction, which functions as selective (semipermeable) diffusion barriers between the neighboring cells. This function is called barrier or gate function. **Barrier function** of tight junction regulates the interchange of ions, water and varieties of macromolecules between the cells. The magnitude of this function varies in different tissues. In some epithelial cells, few substances pass through the tight junction (by diffusion or active transport). In other cells, no substance passes through the tight junction.
3. *Fencing function:* Tight junction prevents the lateral movement of proteins (integral membrane proteins) and lipids in cell membrane and thus acts as a fence. The fencing function maintains the different composition of proteins and lipids between the apical and basolateral plasma membrane domains. Because of this function, the tight junction is sometimes referred as impermeable junction.
4. *Maintenance of cell polarity:* Fencing function of the tight junction maintains the cell polarity by keeping the proteins in the apical region of the cell membrane.
5. *Blood-brain barrier:* Tight junction in the brain capillaries forms the blood-brain barrier, which prevents the entrance of many substances from capillary blood into brain tissues. Only lipid-soluble substances like drugs and steroid hormones can pass through the blood-brain barrier.

## ■ APPLIED PHYSIOLOGY

Diseases caused by mutation of genes encoding proteins of tight junction:

1. Hereditary deafness
2. Ichthyosis (scaly skin)
3. Sclerosing cholangitis (inflammation of bile duct causing obstruction)
4. Hereditary hypomagnesemia (low level of magnesium in the blood)
5. Synovial sarcoma (soft tissue cancer)

Functions of tight junction are affected by some bacteria and viruses also.

## ■ COMMUNICATING JUNCTIONS

Cell junctions which permit the intercellular exchange of substances are called communicating junctions, i.e. these junctions permit the movement of ions and molecules from one cell to another cell. Gap junction and chemical synapse are the communicating junctions.

## ■ GAP JUNCTION

Gap junction is the intercellular junction that allows passage of ions and smaller molecules between the cells. It is also called **nexus.** It is present in heart, basal part of epithelial cells of intestinal mucosa, etc.

### *Structure of Gap Junction*

Membranes of the two adjacent cells lie very close to each other and the intercellular space is reduced from the usual size of 2.5 to 3 nm. Cytoplasm of the two cells is connected by the channels formed by the membranes of both cells. So, the molecules move from one cell to another cell directly through these channels, without having contact with extracellular fluid (ECF).

Each channel consists of two halves. Each half belongs to one of the two adjacent cells. Each half of the

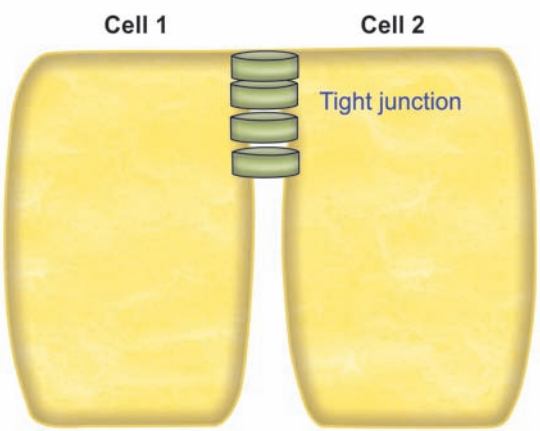



**FIGURE 2.1:** Tight junction

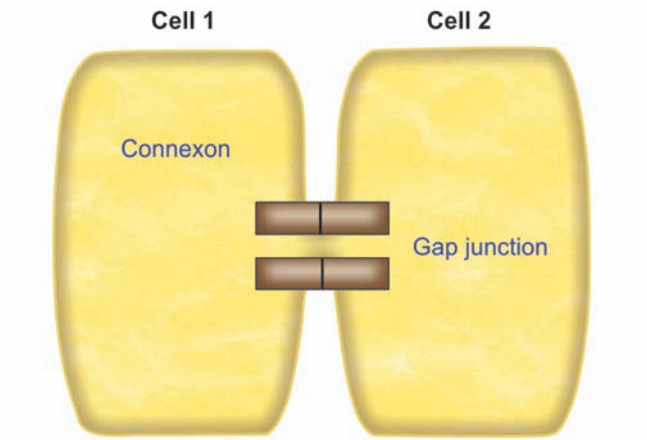



**FIGURE 2.2:** Gap junction

channel is surrounded by 6 subunits of proteins which are called **connexins** or **connexons** (Fig. 2.2).

### *Functions of Gap Junction*

1. Diameter of the channel in the gap junction is about 1.5 to 3 nm. So, the channel permits the passage of glucose, amino acids, ions and other substances, which have a molecular weight less than 1,000
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.

### *Regulation of the Diameter of Channels in Gap Junction*

In the gap junctions, the diameter of each channel is regulated by the intracellular calcium ions. When the concentration of intracellular calcium ion increases, the protein subunits of connexin surrounding the channel come close to each other by sliding. Thus, the diameter of the channel decreases. The diameter of the channel is also regulated by pH, electrical potential, hormones or neurotransmitter.

## ■ 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 140).

## ■ APPLIED PHYSIOLOGY

Mutation in the genes encoding the connexins causes diseases such as:

1. Deafness
2. Keratoderma (thickening of skin on palms and soles)
3. Cataract (opacity of lens in eye)
4. Peripheral neuropathy (damage to the nerves of peripheral nervous system)
5. Charcot-Marie-Tooth disease (a form of neuropathy)
6. Heterotaxia (abnormal arrangement of organs or parts of the body in relation to left-right symmetry).

## ■ ANCHORING JUNCTIONS

Anchoring junctions are the junctions, which provide strength to the cells by acting like mechanical attachments, i.e. these junctions provide firm structural attachment between two cells or between a cell and the extracellular matrix (Fig. 2.3). Anchoring junctions are responsible for the **structural integrity** of the tissues and are present in the tissues like heart muscle and epidermis of skin, which are subjected to severe mechanical stress.

The firm attachment between two cells or between a cell and the **extracellular matrix** is provided by either actin filaments or the intermediate filaments. Depending upon this, anchoring junctions are classified into four types:

1. Actin filament attachment
   i. Adherens junction (cell to cell)
   ii. Focal adhesion (cell to matrix)
2. Intermediate filament attachment
   i. Desmosome (cell to cell)
   ii. Hemidesmosome (cell to matrix)

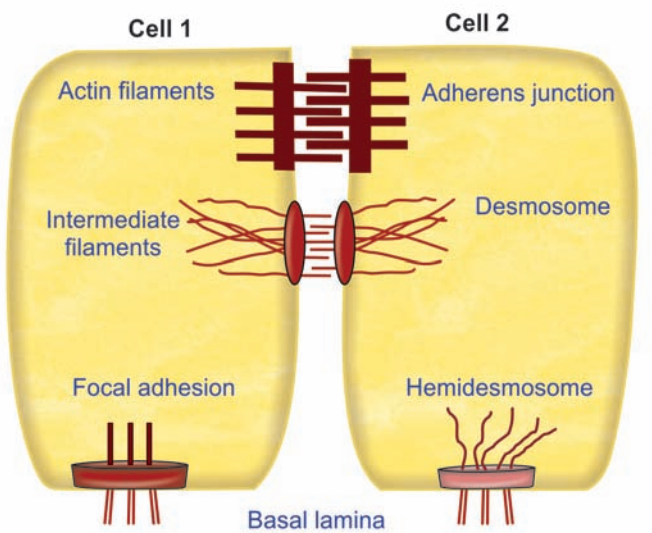



**FIGURE 2.3:** Anchoring junctions

## ■ ADHERENS JUNCTION

Adherens junction is the cell to cell junction, which connects the actin filaments of one cell to those of another cell. In some places like epithelial linings, this junction forms a continuous adhesion **(zonula adherens)** just below the tight junctions. In adherens junction, the membranes of the adjacent cells are held together by some transmembrane proteins called cadherins.

Adherens junction provides strong mechanical attachments of the adjacent cells. Adherens junction is present in the **intercalated disks** between the branches of cardiac muscles (Chapter 89). During the contractions and relaxation of heart, the cardiac muscle fibers are held together tightly by means of this junction. The adherens junction present in epidermis helps the skin to withstand the mechanical stress.

## ■ FOCAL ADHESION

Focal adhesion is the cell to matrix junctions, which connects the actin filaments of the cell to the extracellular matrix. In epithelia of various organs, this junction connects the cells with their basal lamina. The transmembrane proteins, which hold the cell membrane and the matrix are called **integrins.**

## ■ DESMOSOME

Desmosome is a cell to cell junction, where the intermediate filaments connect two adjacent cells. Desmosome is also called **macula adherens.** The membranes of two adjacent cells, which oppose each other, are thickened and become spot-like patches. Intermediate filaments are attached with the thickened patches. Some of these filaments are parallel to the membrane and others are arranged in radiating fashion. Desmosomes function like tight junctions. The transmembrane proteins involved in desmosome are mainly cadherins.

## ■ HEMIDESMOSOME

Hemidesmosome is a cell to matrix junction, which connects the intermediate filaments of the cell to the extracellular matrix. This type of cell junction is like half desmosome and the thickening of membrane of only one cell occurs. So, this is known as hemidesmosome or half desmosome. Mostly, the hemidesmosome connects the cells with their **basal lamina.** The proteins involved in this are integrins (Table 2.1).

## ■ APPLIED PHYSIOLOGY

1. Dysfunction of adherens junction and focal junction in colon due to mutation of proteins results in **colon cancer.** It also leads to **tumor metastasis** (spread of cancer cells from a primary tumor to other parts of the body)
2. Dysfunction of desmosome causes **bullous pemphigoid** (autoimmune disease with tense blistering

**TABLE 2.1: Cell junctions**

| Junction type | Proteins involved | Function | Example |
|---|---|---|---|
| Tight junction | Occludin<br>Claudin<br>JAMs<br>Cingulin<br>Symplekin<br>ZO-1, 2, 3 | Strength and stability to tissues<br>Selective permeability<br>Fencing function<br>Maintenance of cell polarity<br>Formation of blood-brain barrier | Epithelial lining of intestinal mucosa and renal tubule<br>Endothelium in capillary wall and choroid plexus |
| Gap junction | Connexins | Allows passage of small molecules, ions and chemical messengers<br>Propagation of action potential | Epithelial lining<br>Heart<br>Intestine |
| Adherens junction | Cadherins | Cell to cell attachment | Epithelial lining<br>Heart<br>Epidermis |
| Focal adhesions | Integrins | Cell attachment to<br>Basal lamina<br>Extracellular matrix | Epithelial lining |
| Desmosome | Cadherins | Cell to cell attachment | Epithelial lining<br>Skin |
| Hemidesmosome | Integrins | Cell attachment to<br>Basal lamina<br>Extracellular matrix | Epithelial lining |

eruptions of the skin). The patients with this disease develop antibodies against cadherins
3. Dysfunction of hemidesmosome also causes bullous pemphigoid. The patients develop antibodies against integrins.

## CELL ADHESION MOLECULES

Cell adhesion molecules (CAMs) or cell adhesion proteins are the protein molecules, which are responsible for the attachment of cells to their neighbors or to basal lamina (or basal membrane). CAMs form the important structures of intercellular connections and are responsible for structural organization of tissues.

### TYPES OF CELL ADHESION MOLECULES

Cell adhesion molecules are classified into four types:

1. **Cadherins,** which form the molecular limbs between neighboring cells. These CAMs form adherens junction and desomosome
2. **Integrins,** which form the focal adhesion and hemidesmosome
3. **IgG super family,** which form the cell adhesion molecules in nervous system
4. **Selectins,** which act as receptors for carbohydrates (ligand or mucin) and are found in platelets and endothelial cells.

# Transport through Cell Membrane

Chapter 3

- INTRODUCTION
- BASIC MECHANISM OF TRANSPORT
- PASSIVE TRANSPORT
- SPECIAL TYPES OF PASSIVE TRANSPORT
- ACTIVE TRANSPORT
- SPECIAL TYPES OF ACTIVE TRANSPORT
- MOLECULAR MOTORS
- APPLIED PHYSIOLOGY

## INTRODUCTION

All the cells in the body must be supplied with essential substances like nutrients, water, electrolytes, etc. Cells also must get rid of many unwanted substances like waste materials, carbon dioxide, etc. The cells achieve these by means of transport mechanisms across the cell membrane.

Structure of the cell membrane is well suited for the transport of substances in and out of the cell. Lipids and proteins of cell membrane play an important role in the transport of various substances between extracellular fluid (ECF) and intracellular fluid (ICF). Refer Chapter 1 for details of lipids and proteins of the cell membrane.

## BASIC MECHANISM OF TRANSPORT

Two types of basic mechanisms are involved in the transport of substances across the cell membrane:

1. Passive transport mechanism
2. Active transport mechanism.

## PASSIVE TRANSPORT

Passive transport is the transport of substances along the **concentration gradient** or **electrical gradient** or both **(electrochemical gradient)**. It is also known as **diffusion** or **downhill movement.** It does not need energy. Passive transport is like swimming in the direction of water flow in a river. Here, the substances move from region of higher concentration to the region of lower concentration. Diffusion is of two types, namely simple diffusion and facilitated diffusion.

Simple diffusion of substances occurs either through lipid layer or protein layer of the cell membrane. Facilitated diffusion occurs with the help of the carrier proteins of the cell membrane. Thus, the diffusion can be discussed under three headings:

1. Simple diffusion through lipid layer
2. Simple diffusion through protein layer
3. Facilitated or carrier-mediated diffusion.

### SIMPLE DIFFUSION THROUGH LIPID LAYER

Lipid layer of the cell membrane is permeable only to lipid-soluble substances like oxygen, carbon dioxide and alcohol. The diffusion through the lipid layer is directly proportional to the solubility of the substances in lipids (Fig. 3.1A).

### SIMPLE DIFFUSION THROUGH PROTEIN LAYER

Protein layer of the cell membrane is permeable to water-soluble substances. Mainly, electrolytes diffuse through the protein layer.

#### *Protein Channels or Ion Channels*

Throughout the central lipid layer of the cell membrane, there are some **pores.** Integral protein molecules of

protein layer invaginate into these pores from either surface of the cell membrane. Thus, the pores present in the central lipid layer are entirely lined up by the integral protein molecules. These pores are the hypothetical pores and form the channels for the diffusion of water, electrolytes and other substances, which cannot pass through the lipid layer. As the channels are lined by protein molecules, these are called **protein channels** for water-soluble substances.

### *Types of Protein Channels or Ion Channels*

Characteristic feature of the protein channels is the selective permeability. That is, each channel can permit only one type of ion to pass through it. Accordingly, the channels are named after the ions which diffuse through these channels such as sodium channels, potassium channels, etc.

### *Regulation of the Channels*

Some of the protein channels are continuously opened and most of the channels are always closed. Continuously opened channels are called **ungated channels** (Fig. 3.1B). Closed channels are called **gated channels.** These channels are opened only when required (Fig. 3.1C).

### *Gated Channels*

Gated channels are divided into three categories:

i. Voltage-gated channels
ii. Ligand-gated channels
iii. Mechanically gated channels.

i. *Voltage-gated channels*

Voltage-gated channels are the channels which open whenever there is a change in the electrical potential. For example, in the neuromuscular junction, when action potential reaches axon terminal, the calcium channels are opened and calcium ions diffuse into the interior of the axon terminal from ECF (Chapter 32).

Similarly, in the muscle during the **excitation-contraction coupling,** the action potential spreads through the transverse tubules of the sarcotubular system. When the action potential reaches the cisternae, large number of calcium ions diffuse from cisternae into sarcoplasm.

ii. *Ligand-gated channels*

Ligand-gated channels are the type of channels which open in the presence of some hormonal substances. The hormonal substances are called ligands and the channels are called ligand-gated channels. During the transmission of impulse through the neuromuscular junction, acetylcholine is released from the vesicles. The acetylcholine moves through the presynaptic membrane (membrane of the axon terminal) and reaches the synaptic cleft. Then, the acetylcholine molecules cause opening of sodium channels in the postsynaptic membrane and sodium ions diffuse into the neuromuscular junction from ECF.

iii. *Mechanically gated channels*

Mechanically gated channels are the channels which are opened by some mechanical factors. Examples are, channels present in the pressure receptors (Pacinian corpuscles) and the receptor cells (hair cells) of organ

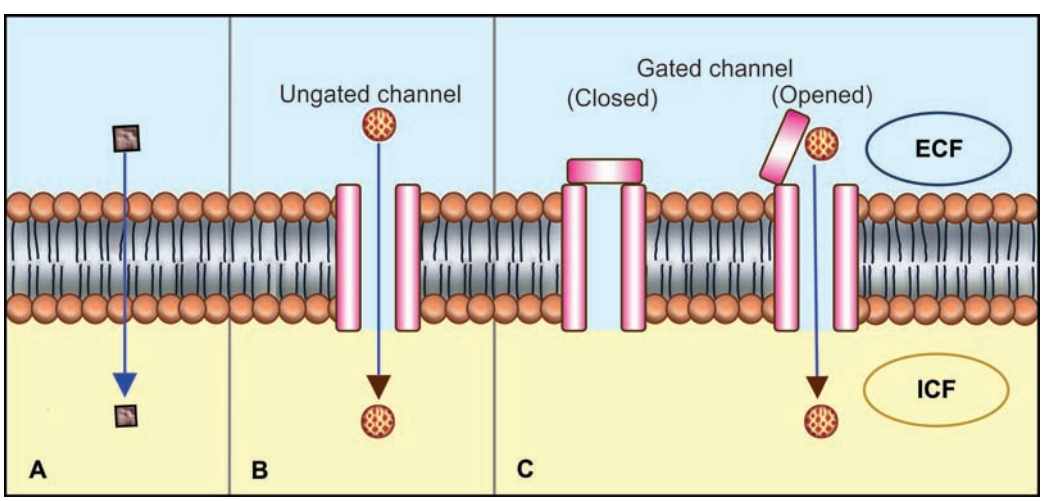



**FIGURE 3.1:** Hypothetical diagram of simple diffusion through the cell membrane.
**A.** Diffusion through lipid layer; **B.** Diffusion through ungated channel; **C.** Diffusion through gated channel.

of Corti and vestibular apparatus. When a Pacinian corpuscle is subjected to pressure, it is compressed resulting in deformation of its core fiber. This deformation causes opening of sodium channel and development of receptor potential (Chapter 139).

Sound waves cause the movement of cilia of hair cells in organ of Corti (cochlea), which is the receptor organ in the ear. Movements of the cilia cause opening of potassium channels leading to the development of receptor potential (Chapter 174). Similar mechanism prevails in hair cells of vestibular apparatus also (Chapter 158).

### *Ion Channel Diseases*

Refer applied physiology of this chapter.

## ■ FACILITATED OR CARRIER-MEDIATED DIFFUSION

Facilitated or carrier-mediated diffusion is the type of diffusion by which the water-soluble substances having larger molecules are transported through the cell membrane with the help of a carrier protein. By this process, the substances are transported across the cell membrane faster than the transport by simple diffusion.

Glucose and amino acids are transported by facilitated diffusion. Glucose or amino acid molecules cannot diffuse through the channels because the diameter of these molecules is larger than the diameter of the channels. Molecule of these substances binds with carrier protein. Now, some conformational change occurs in the carrier protein. Due to this change, the molecule reaches the other side of the cell membrane (Fig. 3.2).

## ■ FACTORS AFFECTING RATE OF DIFFUSION

Rate of diffusion of substances through the cell membrane is affected by the following factors:

### 1. *Permeability of the Cell Membrane*

Rate of diffusion is directly proportional to the permeability of cell membrane. Since the cell membrane is selectively permeable, only limited number of substances can diffuse through the membrane.

### 2. *Temperature*

Rate of diffusion is directly proportional to the body temperature. Increase in temperature increases the rate of diffusion. This is because of the thermal motion of molecules during increased temperature.

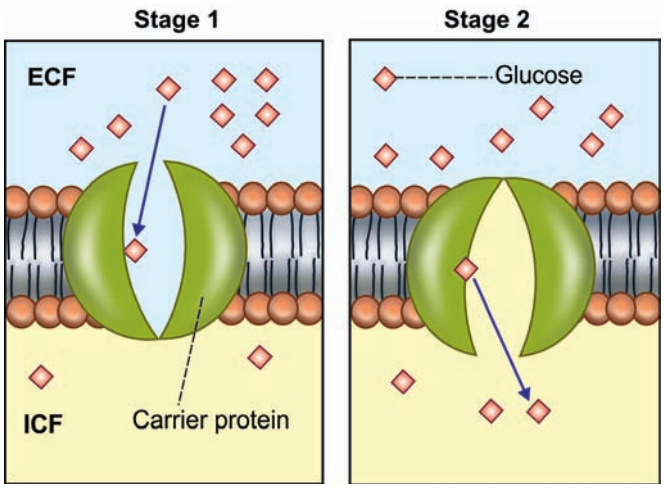



**FIGURE 3.2:** Hypothetical diagram of facilitated diffusion from higher concentration (ECF) to lower concentration (ICF). Stage 1. Glucose binds with carrier protein. Stage 2. Conformational change occurs in the carrier protein and glucose is released into ICF.

### 3. *Concentration Gradient or Electrical Gradient of the Substance across the Cell Membrane*

Rate of diffusion is directly proportional to the concentration gradient or electrical gradient of the diffusing substances across the cell membrane. However, facilitated diffusion has some limitation beyond certain level of concentration gradient.

### 4. *Solubility of the Substance*

Diffusion rate is directly proportional to the solubility of substances, particularly the lipid-soluble substances. Since oxygen is highly soluble in lipids, it diffuses very rapidly through the lipid layer.

### 5. *Thickness of the Cell Membrane*

Rate of diffusion is inversely proportional to the thickness of the cell membrane. If the cell membrane is thick, diffusion of the substances is very slow.

### 6. *Size of the Molecules*

Rate of diffusion is inversely proportional to the size of the molecules. Thus, the substances with smaller molecules diffuse rapidly than the substances with larger molecules.

### 7. *Size of the Ions*

Generally, rate of diffusion is inversely proportional to the size of the ions. Smaller ions can pass through the

membrane more easily than larger ions with the same charge. However, it is not applicable always. For instance, sodium ions are smaller in size than potassium ions. Still, sodium ions cannot pass through the membrane as easily as potassium ions because sodium ions have got the tendency to gather water molecules around them. This makes it difficult for sodium ions to diffuse through the membrane.

### 8. *Charge of the Ions*

Rate of diffusion is inversely proportional to the charge of the ions. Greater the charge of the ions, lesser is the rate of diffusion. For example, diffusion of calcium ($Ca^{++}$) ions is slower than the sodium ($Na^{+}$) ions.

## ■ 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

Bulk flow is the diffusion of large quantity of substances from a region of high pressure to the region of low pressure. It is due to the pressure gradient of the substance across the cell membrane.

Best example for bulk flow is the exchange of gases across the respiratory membrane in lungs. Partial pressure of oxygen is greater in the alveolar air than in the alveolar capillary blood. So, oxygen moves from alveolar air into the blood through the respiratory membrane. Partial pressure of carbon dioxide is more in blood than in the alveoli. So, it moves from the blood into the alveoli through the respiratory membrane (Chapter 124).

### ■ FILTRATION

Movement of water and solutes from an area of high hydrostatic pressure to an area of low hydrostatic pressure is called filtration. Hydrostatic pressure is developed by the weight of the fluid. Filtration process is seen at arterial end of the capillaries, where movement of fluid occurs along with dissolved substances from blood into the interstitial fluid (Chapter 27). It also occurs in glomeruli of kidneys (Chapter 52).

### ■ OSMOSIS

Osmosis is the special type of diffusion. It is defined as the movement of water or any other solvent from an area of lower concentration to an area of higher concentration of a solute, through a semipermeable membrane (Fig. 3.3). The semipermeable membrane permits the passage of only water or other solvents but not the solutes.

Osmosis can occur whenever there is a difference in the solute concentration on either side of the membrane. Osmosis depends upon osmotic pressure.

#### *Osmotic Pressure*

Osmotic pressure is the pressure created by the solutes in a fluid. 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 concentration get dissolved in the solvent. This creates a pressure which is known as osmotic pressure. Normally, the osmotic pressure prevents further movement of water or other solvent during osmosis.

#### *Reverse Osmotic Pressure*

Reverse osmosis is a process in which water or other solvent flows in reverse direction (from the area of higher concentration to the area of lower concentration of the solute), if an external pressure is applied on the area of higher concentration.

#### *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

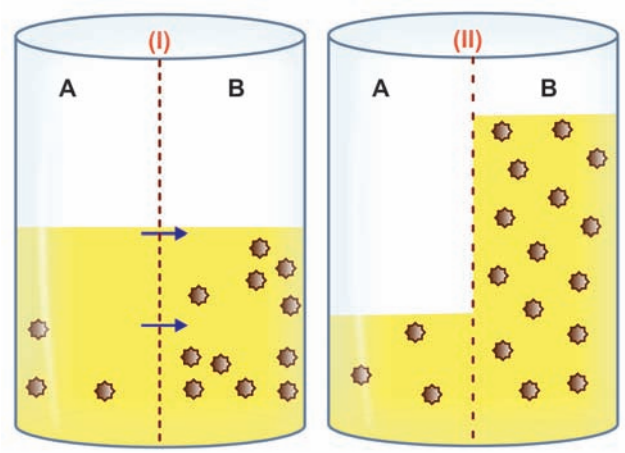



**FIGURE 3.3:** Osmosis. Red objects = solute, Yellow shade = water, Green dotted line = semipermeable membrane. In (I), concentration of solute is high in compartment B and low in compartment A. So, water moves from A to B through semipermeable membrane. In (II), entrance of water into B exerts osmotic pressure.

(proteins) of the plasma is known as oncotic pressure and it is about 25 mm Hg.

### *Types of Osmosis*

Osmosis across the cell membrane is of two types:
1. Endosmosis: Movement of water into the cell
2. Exosmosis: Movement of water out of the cell.

## ■ ACTIVE TRANSPORT

Active transport is the movement of substances against the chemical or electrical or electrochemical gradient. It is like swimming against the water tide in a river. It is also called **uphill transport.** Active transport requires energy, which is obtained mainly by breakdown of high energy compounds like **adenosine triphosphate** (ATP).

### *Active Transport vs Facilitated Diffusion*

Active transport mechanism is different from facilitated diffusion by two ways:
1. Carrier protein of active transport needs energy, whereas the carrier protein of facilitated diffusion does not need energy
2. In active transport, the substances are transported against the concentration or electrical or electrochemical gradient. In facilitated diffusion, the substances are transported along the concentration or electrical or electrochemical gradient.

## ■ CARRIER PROTEINS OF ACTIVE TRANSPORT

Carrier proteins involved in active transport are of two types:
1. Uniport
2. Symport or antiport.

### 1. *Uniport*

Carrier protein that carries only one substance in a single direction is called uniport. It is also known as **uniport pump.**

### 2. *Symport or Antiport*

Symport or antiport is the carrier protein that transports two substances at a time.

Carrier protein that transports two different substances in the same direction is called symport or **symport pump.** Carrier protein that transports two different substances in opposite directions is called antiport or **antiport pump.**

## ■ 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.

## ■ SUBSTANCES TRANSPORTED BY ACTIVE TRANSPORT

Substances, which are transported actively, are in ionic form and non-ionic form. Substances in ionic form are sodium, potassium, calcium, hydrogen, chloride and iodide. Substances in non-ionic form are glucose, amino acids and urea.

## ■ TYPES OF ACTIVE TRANSPORT

Active transport is of two types:
1. Primary active transport
2. Secondary active transport.

## ■ PRIMARY ACTIVE TRANSPORT

Primary active transport is the type of transport mechanism in which 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 means of a common carrier protein called sodium-potassium ($Na^+$-$K^+$) pump. It is also called **$Na^+$-$K^+$ ATPase pump** or **$Na^+$-$K^+$ ATPase.** This pump transports sodium from inside to outside the cell and potassium from outside to inside the cell. This pump is present in all the cells of the body.

$Na^+$-$K^+$ pump is responsible for the distribution of sodium and potassium ions across the cell membrane and the development of resting membrane potential.

*Structure of $Na^+$-$K^+$ pump*

Carrier protein that constitutes $Na^+$-$K^+$ pump is made up of two protein subunit molecules, an $\alpha$-subunit with a molecular weight of 100,000 and a $\beta$-subunit with a molecular weight of 55,000. Transport of $Na^+$ and $K^+$

occurs only by α-subunit. The β-subunit is a glycoprotein the function of which is not clear.

α-subunit of the $Na^+$-$K^+$ pump has got six sites:

i. Three receptor sites for sodium ions on the inner (towards cytoplasm) surface of the protein molecule
ii. Two receptor sites for potassium ions on the outer (towards ECF) surface of the protein molecule
iii. One site for enzyme adenosine triphosphatase (ATPase), which is near the sites for sodium.

*Mechanism of action of $Na^+$-$K^+$ pump*

Three sodium ions from the cell get attached to the receptor sites of sodium ions on the inner surface of the carrier protein. Two potassium ions outside the cell bind to the receptor sites of potassium ions located on the outer surface of the carrier protein (Fig. 3.4, Stage 1).

Binding of sodium and potassium ions to carrier protein activates the enzyme ATPase. ATPase causes breakdown of ATP into adenosine diphosphate (ADP) with the release of one high energy phosphate. Now, the energy liberated causes some sort of conformational change in the molecule of the carrier protein. Because of this, the outer surface of the molecule (with potassium ions) now faces the inner side of the cell. And, the inner surface of the protein molecule (with sodium ions) faces the outer side of the cell (Fig. 3.4, Stage 2). Now, dissociation and release of the ions take place so that the sodium ions are released outside the cell (ECF) and the potassium ions are released inside the cell (ICF). Exact mechanisms involved in the dissociation and release of ions are not yet known.

*Electrogenic activity of $Na^+$-$K^+$ pump*

$Na^+$-$K^+$ pump moves three sodium ions outside the cell and two potassium ions inside cell. Thus, when the pump works once, there is a net loss of one positively charged ion from the cell. Continuous activity of the sodium-potassium pumps causes reduction in the number of positively charged ions inside the cell leading to increase in the negativity inside the cell. This is called the electrogenic activity of $Na^+$-$K^+$ pump.

*Abnormalities of $Na^+$-$K^+$ Pump*

Refer applied physiology of this Chapter.

### *Transport of Calcium Ions*

Calcium is actively transported from inside to outside the cell by calcium pump. Calcium pump is operated by a separate carrier protein. Energy is obtained from ATP by the catalytic activity of ATPase. Calcium pumps are also present in some organelles of the cell such as sarcoplasmic reticulum in the muscle and the mitochondria of all the cells. These pumps move calcium into the organelles.

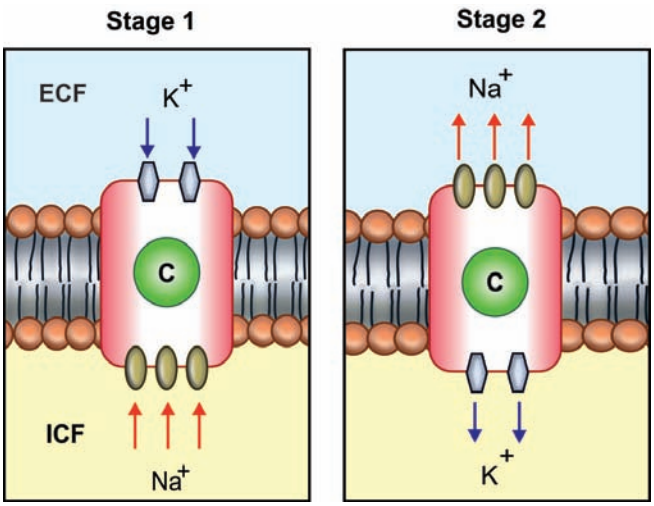



**FIGURE 3.4:** Hypothetical diagram of sodium-potassium pump. C = carrier protein. Stage 1: Three $Na^+$ from ICF and two $K^+$ from ECF bind with 'C'. Stage 2: Conformational change occurs in 'C' followed by release of $Na^+$ into ECF and $K^+$ into ICF

### *Transport of Hydrogen Ions*

Hydrogen ion is actively transported across the cell membrane by the carrier protein called hydrogen pump. It also obtains energy from ATP by the activity of ATPase. The hydrogen pumps that are present in two important organs have some functional significance.

1. *Stomach:* Hydrogen pumps in parietal cells of the gastric glands are involved in the formation of hydrochloric acid (Chapter 38)
2. *Kidney:* Hydrogen pumps in epithelial cells of distal convoluted tubules and collecting ducts are involved in the secretion of hydrogen ions from blood into urine (Chapter 54).

## ■ SECONDARY ACTIVE TRANSPORT

Secondary active transport is the transport of a substance with sodium ion, by means of a common carrier protein. When sodium is transported by a carrier protein, another substance is also transported by the same protein simultaneously, either in the same direction (of sodium movement) or in the opposite direction. Thus, the transport of sodium is coupled with transport of another substance.

Secondary active transport is of two types:

1. Cotransport
2. Counter transport.

### Sodium Cotransport

Sodium cotransport is the process in which, along with sodium, another substance is transported by a carrier protein called symport. Energy for movement of sodium is obtained by breakdown of ATP. And the energy released by the movement of sodium is utilized for movement of another substance.

Substances carried by sodium cotransport are glucose, amino acids, chloride, iodine, iron and urate.

*Carrier protein for sodium cotransport*

Carrier protein for the sodium cotransport has two receptor sites on the outer surface.

Among the two sites, one is for binding of sodium and another site is for binding of other substance.

*Sodium cotransport of glucose*

One sodium ion and one glucose molecule from the ECF bind with the respective receptor sites of carrier protein of the cell membrane. Now, the carrier protein is activated. It causes conformational changes in the carrier protein, so that sodium and glucose are released into the cell (Fig. 3.5).

Sodium cotransport of glucose occurs during absorption of glucose from the intestine and reabsorption of glucose from the renal tubule.

*Sodium cotransport of amino acids*

Carrier proteins for the transport of amino acids are different from the carrier proteins for the transport of glucose. For the transport of amino acids, there are five sets of carrier proteins in the cell membrane. Each one carries different amino acids depending upon the molecular weight of the amino acids.

Sodium cotransport of amino acids also occurs during the absorption of amino acids from the intestine and reabsorption from renal tubule.

### Sodium Counter Transport

Sodium counter transport is the process by which the substances are transported across the cell membrane in exchange for sodium ions by carrier protein called antiport.

Various counter transport systems are:

i. Sodium-calcium counter transport: In this, sodium and calcium ions move in opposite directions with the help of a carrier protein. This type of transport of sodium and calcium ions is present in all the cells

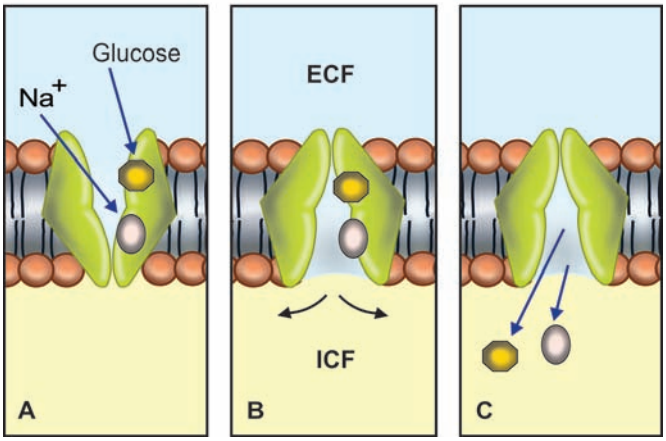



**FIGURE 3.5:** Sodium cotransport. **A.** $Na^+$ and glucose from ECF bind with carrier protein; **B.** Conformational change occurs in the carrier protein; **C.** $Na^+$ and glucose are released into ICF.

ii. Sodium-hydrogen counter transport: In this system, the hydrogen ions are exchanged for sodium ions and this occurs in the renal tubular cells. The sodium ions move from tubular lumen into the tubular cells and the hydrogen ions move from tubular cell into the lumen (Figs 3.6 and 3.7)

iii. Other counter transport systems: Other counter transport systems are sodium-magnesium counter transport, sodium-potassium counter transport, calcium-magnesium counter transport, calcium-potassium counter transport, chloride-bicarbonate counter transport and chloride-sulfate counter transport.

## ■ SPECIAL TYPES OF ACTIVE TRANSPORT

In addition to primary and secondary active transport systems, there are some special categories of active transport which are generally called the vesicular transport.

Special categories of active transport:

1. Endocytosis
2. Exocytosis
3. Transcytosis.

### ■ ENDOCYTOSIS

Endocytosis is defined as a transport mechanism by which the **macromolecules** enter the cell. Macromolecules (substances with larger molecules) cannot pass through the cell membrane either by active or by passive transport mechanism. Such substances are transported into the cell by endocytosis.

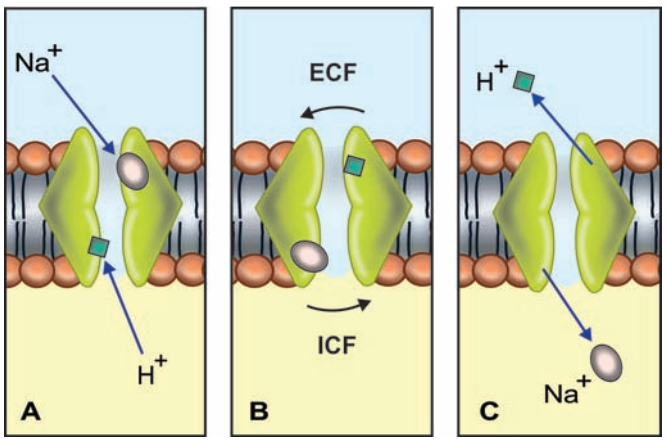



**FIGURE 3.6:** Sodium counter transport. **A.** $Na^+$ from ECF and $H^+$ from ICF bind with carrier protein; **B.** Conformational change occurs in the carrier protein; **C.** $Na^+$ enters ICF and $H^+$ enters ECF.

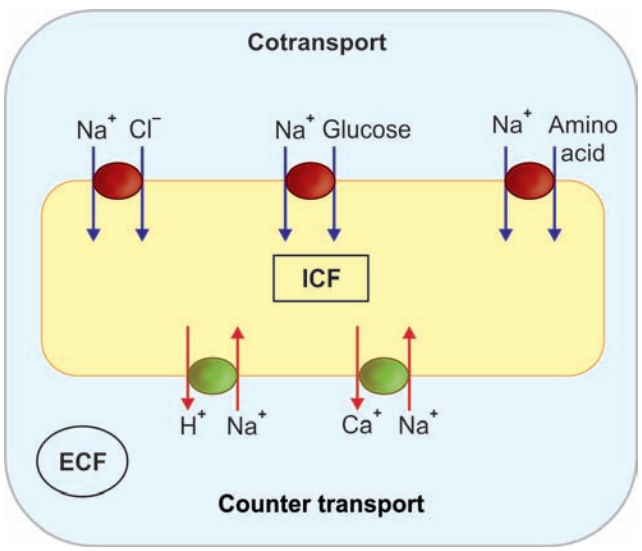



**FIGURE 3.7:** Sodium cotransport and counter transport by carrier proteins

Endocytosis is of three types:

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

### 1. *Pinocytosis*

Pinocytosis is a process by which macromolecules like bacteria and antigens are taken into the cells. It is otherwise called the **cell drinking.**

*Mechanism of pinocytosis*

Pinocytosis involves following events:

i. Macromolecules (in the form of droplets of fluid) bind to the outer surface of the cell membrane
ii. Now, the cell membrane evaginates around the droplets
iii. Droplets are engulfed by the membrane
iv. Engulfed droplets are converted into vesicles and vacuoles, which are called endosomes (Fig. 3.8)
v. Endosome travels into the interior of the cell
vi. Primary lysosome in the cytoplasm fuses with endosome and forms secondary lysosome
vii. Now, hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the endosomal contents.

### 2. *Phagocytosis*

Phagocytosis is the process by which particles larger than the macromolecules are engulfed into the cells. It is also called **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 bacteria or foreign body enters the body, first the phagocytic cell sends cytoplasmic extension **(pseudopodium)** around bacteria or foreign body
ii. Then, these particles are engulfed and are converted into endosome like vacuole. Vacuole is very large and it is usually called the phagosome
iii. Phagosome travels into the interior of cell
iv. Primary lysosome fuses with this phagosome and forms secondary lysosome
v. Hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the phagosomal contents (Fig. 3.9).

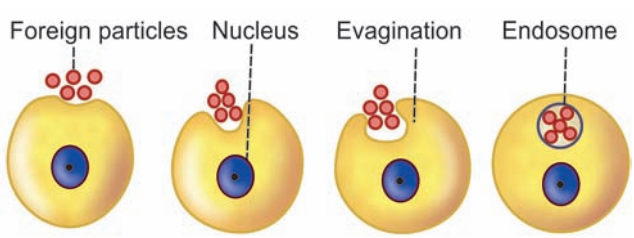



**FIGURE 3.8:** Process of pinocytosis

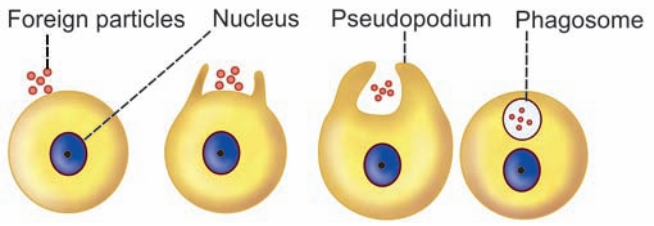



**FIGURE 3.9:** Process of phagocytosis

### 3. *Receptor-mediated Endocytosis*

Receptor-mediated endocytosis is the transport of macromolecules with the help of a receptor protein. Surface of cell membrane has some pits which contain a receptor protein called **clathrin.** Together with a receptor protein (clathrin), each pit is called **receptor-coated pit.** These receptor-coated pits are involved in the receptor-mediated endocytosis (Fig. 3.10).

*Mechanism of receptor-mediated endocytosis*

i. Receptor-mediated endocytosis is induced by substances like ligands (Fig. 3.10-i)
ii. Ligand molecules approach the cell and bind to receptors in the coated pits and form ligand-receptor complex (Fig. 3.10-ii)
iii. Ligand-receptor complex gets aggregated in the coated pits. Then, the pit is detached from cell membrane and becomes the coated vesicle. This coated vesicle forms the endosome (Fig. 3.10-iii)
iv. Endosome travels into the interior of the cell. Primary lysosome in the cytoplasm fuses with endosome and forms secondary lysosome (Fig. 3.10-iv)
v. Now, the hydrolytic enzymes present in secondary lysosome are activated resulting in release of ligands into the cytoplasm (Fig. 3.10-v)
vi. Receptor may move to a new pit of the cell membrane (Fig. 3.10-vi).

Receptor-mediated endocytosis play an important role in the transport of several types of macromolecules into the cells, viz.

i. Hormones: Growth hormone, thyroid stimulating hormone, luteinizing hormone, prolactin, insulin, glucagon, calcitonin and catecholamines
ii. Lipids: Cholesterol and low-density lipoproteins (LDL)
iii. Growth factors (GF): Nerve GF, epidermal GF, platelet-derived GF, interferon
iv. Toxins and bacteria: Cholera toxin, diphtheria toxin, pseudomonas toxin, recin and concanavalin A
v. Viruses: Rous sarcoma virus, semliki forest virus, vesicular stomatitis virus and adenovirus
vi. Transport proteins: Transferrin and transcobalamine
vii. Antibodies: IgE, polymeric IgG and maternal IgG.

Some of the receptor-coated pits in cell membrane are coated with another protein called **caveolin** instead of clathrin. Caveolin-coated pits are concerned with the transport of vitamins into the cell.

## ■ EXOCYTOSIS

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

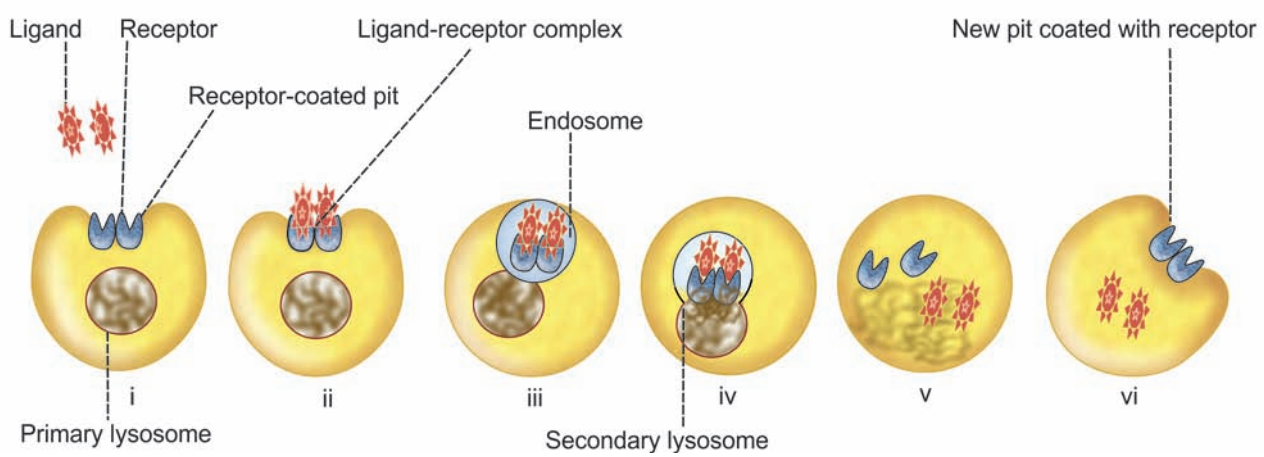



**FIGURE 3.10:** Mechanism of receptor-mediated endocytosis. The numbering of each figure corresponds with the numbers used in the text.

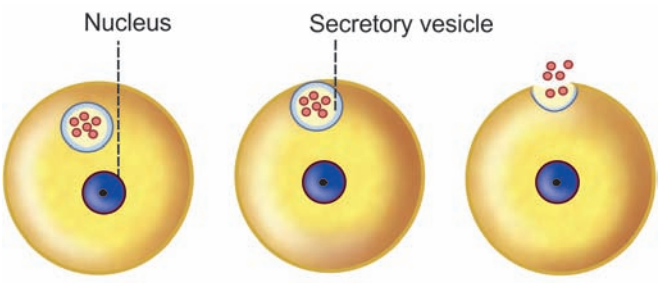



**FIGURE 3.11:** Process of exocytosis

### *Mechanism of Exocytosis*

Exocytosis is involved in the release of secretory substances from cells. Secretory substances of the cell are stored in the form of secretory vesicles in the cytoplasm. When required, the vesicles approach the cell membrane and get fused with the cell membrane. Later, the contents of the vesicles are released out of the cell (Fig. 3.11).

### *Role of Calcium in Exocytosis*

Calcium ions play an important role during the release of some secretory substances such as neurotransmitters. The calcium ions enter the cell and cause exocytosis. However, the exact mechanism of exocytosis is not clear.

## ■ 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.

### *Mechanism of Transcytosis*

Cell encloses the extracellular substance by invagination of the cell membrane to form a vesicle. Vesicle then moves across the cell and thrown out through opposite cell membrane by means of exocytosis. Transcytosis involves the receptor-coated pits as in receptor-mediated endocytosis. Receptor protein coating the pits in this process is caveolin and not clathrin. Transcytosis is also called, vesicle trafficking or cytopempsis.

Transcytosis plays an important role in selectively transporting the substances between two environments across the cells without any distinct change in the composition of these environments. Example of this type of transport is the movement of proteins from capillary blood into interstitial fluid across the endothelial cells of the capillary. Many pathogens like human immunodeficiency virus (HIV) are also transported by this mechanism.

## ■ MOLECULAR MOTORS

Molecular motors are the protein-based molecular machines that perform intracellular movements in response to specific stimuli.

### ■ FUNCTIONS OF MOLECULAR MOTORS

1. Transport of synaptic vesicles containing neurotransmitters from the nerve cell body to synaptic terminal
2. Role in cell division (mitosis and meiosis) by pulling the chromosomes
3. Transport of viruses and toxins to the interior of the cell for its own detriment.

### ■ TYPES OF MOLECULAR MOTORS

Molecular motors are classified into three super families:

1. Kinesin
2. Dynein
3. Myosin.

#### 1. *Kinesin*

Kinesin transports substances by moving over the microtubules. Each kinesin molecule has two heads and a tail portion. One of the heads hydrolyses ATP to obtain energy. By utilizing this energy, the other head swings continuously causing movement of the whole kinesin molecule (Fig. 3.12). End portion of the tail carries the cargo (substances to be transported). Kinesin is responsible for **anterograde transport** (transport of substances towards the positive end of microtubule).

#### 2. *Dynein*

Dynein is almost similar to kinesin and transports substances by moving over the microtubules. But it is responsible for **retrograde transport** (transport of substances towards the negative end of microtubule).

#### 3. *Myosin*

Myosin transports substances by moving over microfilaments. Myosins are classified into 18 types according to the amino acid sequence. However, myosin II and V are functionally significant. Myosin II is involved in muscle contraction (Chapter 31). Myosin V is involved in transport of vesicles.

## APPLIED PHYSIOLOGY

### ABNORMALITIES OF SODIUM-POTASSIUM PUMP

Abnormalities in the number or function of $Na^+$-$K^+$ pump are associated with several pathological conditions. Important examples are:

1. Reduction in either the number or concentration of $Na^+$-$K^+$ pump in myocardium is associated with cardiac failure
2. Excess reabsorption of sodium in renal tubules is associated with hypertension.

### CHANNELOPATHIES OR ION CHANNEL DISEASES

Channelopathies or ion channel diseases are caused by mutations in genes that encode the ion channels.

#### 1. *Sodium Channel Diseases*

Dysfunction of sodium channels leads to muscle spasm and **Liddle's syndrome** (dysfunction of sodium channels in kidney resulting in increased osmotic pressure in the blood and hypertension).

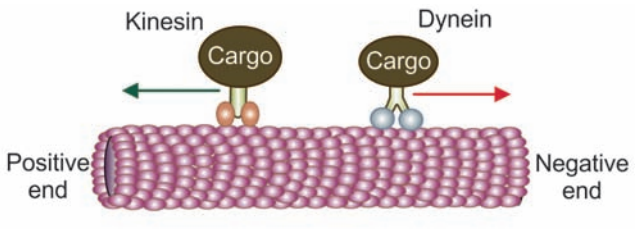



**FIGURE 3.12:** Kinesin and dynein motor molecules

#### 2. *Potassium Channel Diseases*

Potassium channel dysfunction causes disorders of heart, inherited deafness and epileptic seizures in newborn.

#### 3. *Chloride Channel Diseases*

Dysfunction of chloride channels results in formation of renal stones and **cystic fibrosis.** Cystic fibrosis is a generalized disorder affecting the functions of many organs such as lungs (due to excessive mucus), exocrine glands like pancreas, biliary system and immune system.

# Chapter 4

# Homeostasis

- INTRODUCTION
- ROLE OF VARIOUS SYSTEMS OF THE BODY IN HOMEOSTASIS
- COMPONENTS OF HOMEOSTATIC SYSTEM
- MECHANISM OF ACTION OF HOMEOSTATIC SYSTEM
  - NEGATIVE FEEDBACK
  - POSITIVE FEEDBACK

## INTRODUCTION

'Homeostasis' refers to the maintenance of constant internal environment of the body (homeo = same; stasis = standing). Importance of internal environment was notified by the great biologist of 19th century Claude Bernard. He enlightened the fact that 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.

Internal environment in the body is the **extracellular fluid (ECF)** in which the cells live. It is the fluid outside the cell and it constantly moves throughout the body. It includes blood, which circulates in the vascular system and fluid present in between the cells called **interstitial fluid.** ECF contains nutrients, ions and all other substances necessary for the survival of the cells.

Normal healthy living of large organisms including human beings depends upon the constant maintenance of internal environment within the physiological limits. If the internal environment deviates beyond the **set limits,** body suffers from malfunction or dysfunction. Therefore, the ultimate goal of an organism is to have a normal healthy living, which is achieved by the maintenance of internal environment within set limits.

The concept of homeostasis forms basis of physiology because it explains why various physiological functions are to be maintained within a normal range and in case if any function deviates from this range how it is brought back to normal. Understanding the concept of homeostasis also forms the basis for clinical diagnostic procedures. For example, increased body temperature beyond normal range as in the case of fever, indicates that something is wrong in the heat production-heat loss mechanism in the body. It induces the physician to go through the diagnostic proceedings and decide about the treatment.

For the functioning 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. These detectors sense 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.

## ROLE OF VARIOUS SYSTEMS OF THE BODY IN HOMEOSTASIS

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. 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. Nutrients are essential for various activities of the cell and growth of the tissues. These substances also form the source of energy required for various activities of the cells. Nutrients must be digested, absorbed into the blood and supplied to the cells. Digestive system and circulatory system play major roles in the supply of nutrients.
4. Adequate amount of oxygen should be made available to the cells for the metabolism of the nutrients. Simultaneously, the carbon dioxide and other metabolic end products must be removed. Respiratory system is concerned with the supply of oxygen and removal of carbon dioxide. Kidneys and other excretory organs are involved in the excretion of waste products.
5. Many hormones are essential for the metabolism of nutrients and other substances necessary for the cells. 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 are also involved in homeostasis. This system helps the organism to move around in search of food. It also helps to protect the organism from adverse surroundings, thus preventing damage or destruction.
9. Central nervous system, which includes brain and spinal cord also, plays an important role in homeostasis. Sensory system detects the state of the body or surroundings. 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. Autonomic nervous system regulates all the vegetative functions of the body essential for homeostasis.

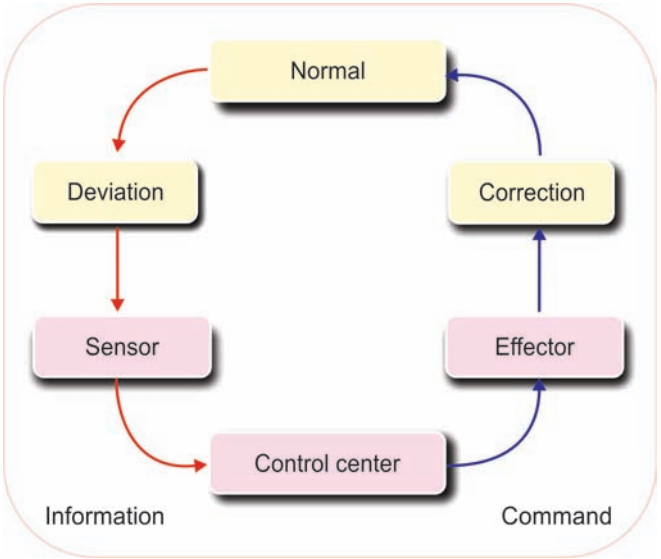



**FIGURE 4.1:** Components of homeostatic system

## ■ COMPONENTS OF HOMEOSTATIC SYSTEM

Homeostatic system in the body acts through self-regulating devices, which operate in a cyclic manner (Fig. 4.1). This cycle includes four components:

1. **Sensors** or **detectors,** which recognize the deviation
2. Transmission of this message to a **control center**
3. Transmission of information from the control center to the effectors for correcting the deviation

   Transmission of the message or information may be an electrical process in the form of impulses through nerves or a chemical process mainly in the form of hormones through blood and body fluids
4. **Effectors,** which correct the deviation.

## ■ MECHANISM OF ACTION OF HOMEOSTATIC SYSTEM

Homeostatic mechanism in the body is responsible for maintaining the normalcy of various body systems. Whenever there is any change in behavioral pattern of any system, the effectors bring back the normalcy either by inhibiting and reversing the change or by supporting and accelerating the change depending upon requirement of the situation. This is achieved by means of **feedback signals.**

Feedback is a process in which some proportion of the output signal of a system is fed (passed) back to the input. This is done more often intentionally in order to control the behavior pattern of the system. Whenever any change occurs, system receives and reacts to two types of feedback:

1. Negative feedback
2. Positive feedback.

## ■ NEGATIVE FEEDBACK

Negative feedback is the one to which the system reacts in such a way as to arrest the change or reverse the direction of change. After receiving a message, effectors send negative feedback signals back to the system. Now, the system stabilizes its own function and makes an attempt to maintain homeostasis.

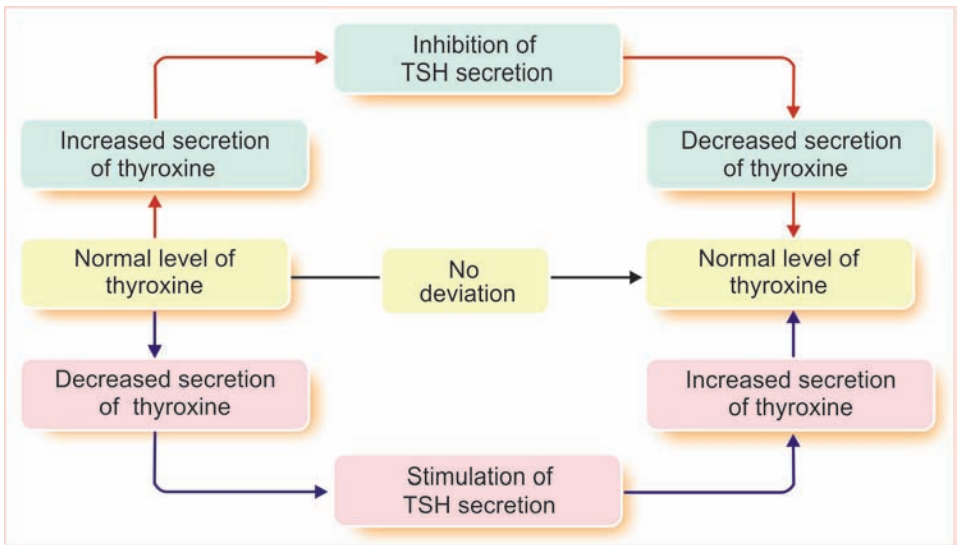



**FIGURE 4.2:** Negative feedback mechanism – secretion of thyroxine.
TSH = Thyroid-stimulating hormone.

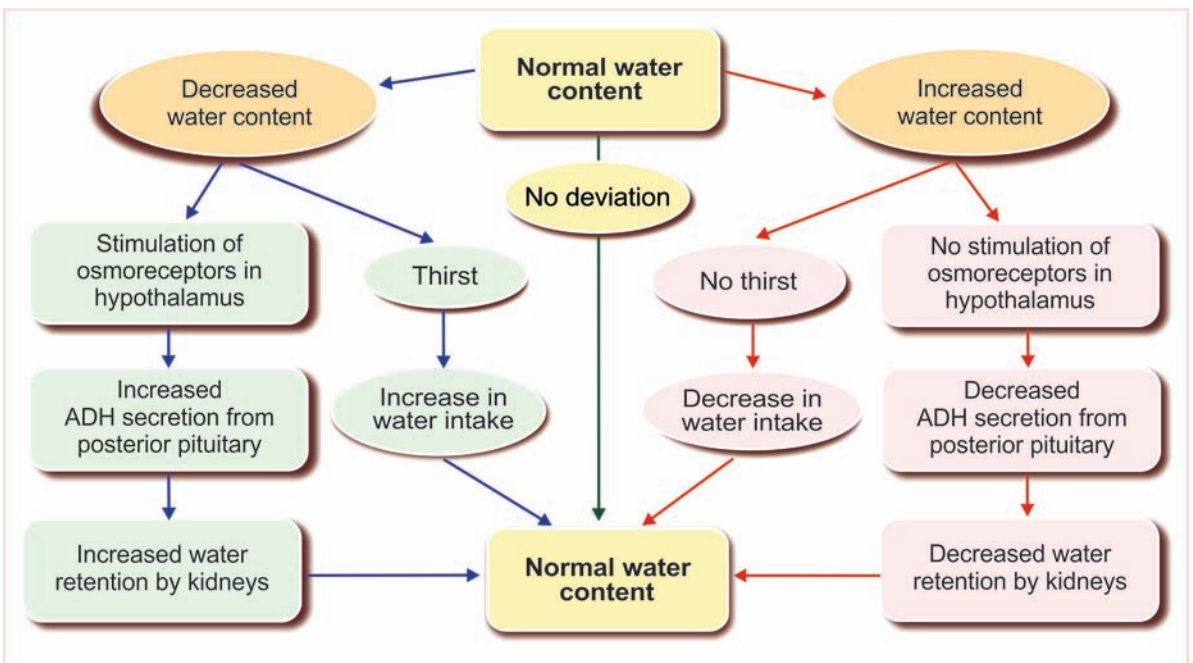



**FIGURE 4.3:** Negative feedback mechanism – maintenance of water balance.
ADH = Antidiuretic hormone.

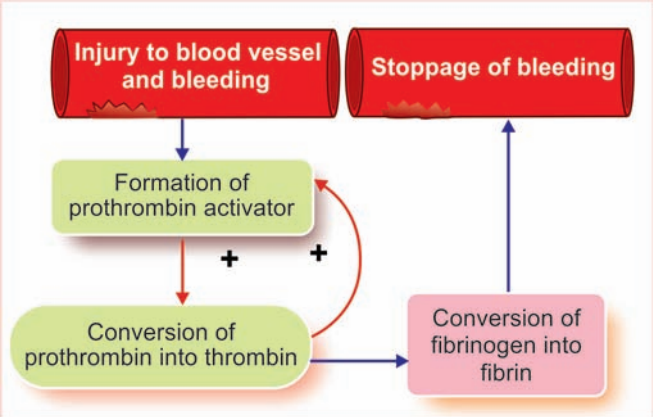



**FIGURE 4.4:** Positive feedback mechanism – coagulation of blood. Once formed, thrombin induces the formation of more prothrombin activator.

Many homeostatic mechanisms in the body function through negative feedback. For example, thyroid-stimulating hormone (TSH) released from pituitary gland stimulates thyroid gland to secrete thyroxine. When thyroxine level increases in blood, it inhibits the secretion of TSH from pituitary so that, the secretion of thyroxin from thyroid gland decreases (Fig. 4.2). On the other hand, if thyroxine secretion is less, its low blood level induces pituitary gland to release TSH. Now, TSH stimulates thyroid gland to secrete thyroxine (Refer Chapter 67 for details). Another example for negative feedback mechanism is maintenance of water balance in the body (Fig. 4.3).

## ■ POSITIVE FEEDBACK

Positive feedback is the one to which the system reacts in such a way as to 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.

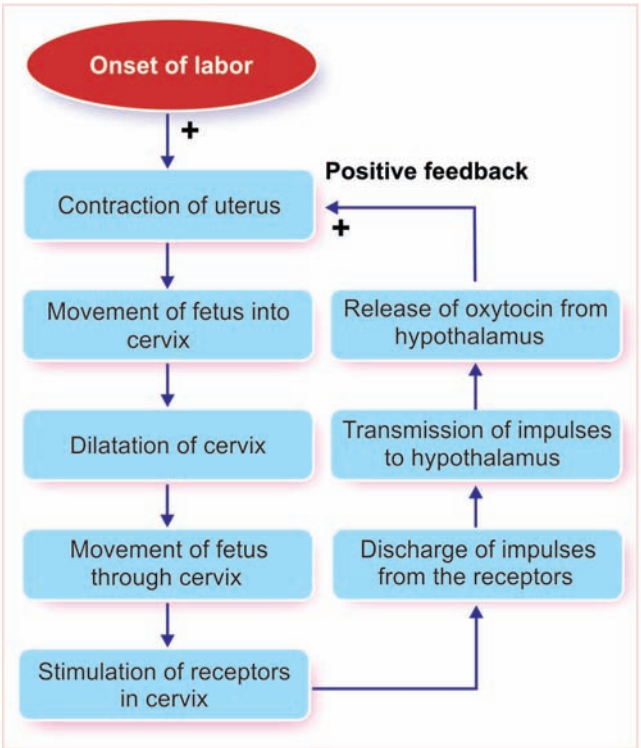



**FIGURE 4.5:** Positive feedback mechanism – parturition

The three stages are:

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

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 20). Other processes where positive feedback occurs are milk ejection reflex (Chapter 66) and parturition (Fig. 4.5) (Chapter 84) and both the processes involve oxytocin secretion.

# Chapter 5

# Acid-base Balance


- INTRODUCTION
- HYDROGEN ION AND pH
- DETERMINATION OF ACID-BASE STATUS
- REGULATION OF ACID-BASE BALANCE
  - DEFINITION
  - REGULATION OF ACID-BASE BALANCE BY RESPIRATORY MECHANISM
  - REGULATION OF ACID-BASE BALANCE BY RENAL MECHANISM
- DISTURBANCES OF ACID-BASE STATUS
  - ACIDOSIS
  - ALKALOSIS
  - RESPIRATORY ACIDOSIS
  - RESPIRATORY ALKALOSIS
  - METABOLIC ACIDOSIS
  - METABOLIC ALKALOSIS
- CLINICAL EVALUATION – ANION GAP


## INTRODUCTION

Acid-base balance is very important for the homeostasis of the body and almost all the physiological activities depend upon the acid-base status of the body. Acids are constantly produced in the body. However, the acid production is balanced by the production of bases so that the acid-base status of the body is maintained.

An acid is the **proton donor** (the substance that liberates hydrogen ion). A base is the **proton acceptor** (the substance that accepts hydrogen ion).

In spite of continuous production of acids in the body, the concentration of free hydrogen ion is kept almost constant at a pH of 7.4 with slight variations.

## HYDROGEN ION AND pH

Hydrogen ion ($H^+$) contains only a single proton (positively charged particle), which is not orbited by any electron. Therefore, it is the smallest ionic particle. However, it is highly reactive. Because of this, the $H^+$ shows severe effects on the physiological activities of the body even at low concentrations. The normal $H^+$ concentration in the extracellular fluid (ECF) is 38 to 42 nM/L.

The pH is another term for $H^+$ concentration that is generally used nowadays instead of 'hydrogen ion concentration'. The pH scale was introduced in order to simplify the mathematical handling of large numbers.

Negative logarithm of $H^+$ concentration is taken for calculating the pH as given below.

$$pH = \log \frac{1}{H^+}$$

An increase in $H^+$ ion concentration decreases the pH (acidosis) and a reduction in $H^+$ concentration increases the pH (alkalosis). An increase in pH by one-fold requires a tenfold decrease in $H^+$ concentration (Table 5.1).

In a healthy person, the pH of the ECF is 7.40 and it varies between 7.38 and 7.42. The maintenance of acid-base status is very important for homeostasis, because even a slight change in pH below 7.38 or above 7.42 will cause serious threats to many physiological functions.

**TABLE 5.1: Hydrogen ion concentration and pH**

| $H^+$ (nM/L) | pH |
|---|---|
| 10,000 | 5.0 |
| 1,000 | 6.0 |
| 100 | 7.0 |
| 10 | 8.0 |
| 1 | 9.0 |

## ■ DETERMINATION OF ACID-BASE STATUS

It is difficult to determine the acid-base status in the ECF by direct methods. So, an indirect method is followed by using **Henderson-Hasselbalch equation.** In this, to determine the pH of a fluid, the concentration of bicarbonate ions ($HCO_3^-$) and the $CO_2$ dissolved in the fluid are measured. The pH is calculated as follows:

$$pH = pK + \log \frac{HCO_3^-}{CO_2}$$

Where, pK is constant with pH of 6.1
Thus,

$$pH = 6.1 + \log \frac{HCO_3^-}{CO_2}$$

In addition to this, the pH of plasma is also determined by using an instrument called pH meter.

Normal acid-base ratio is 1:20, i.e. the ratio of 1 part of $CO_2$ (derived from $H_2CO_3$) and 20 parts of $HCO_3^-$. If this ratio is altered, the pH also is altered leading to either acidosis or alkalosis.

Thus, the pH of arterial blood is an indirect measurement of $H^+$ concentration and it reflects the balance of $CO_2$ and $HCO_3^-$.

## ■ REGULATION OF ACID-BASE BALANCE

Body is under constant threat of acidosis because of the production of large amount of acids. Generally, two types of acids are produced in the body:

1. Volatile acids
2. Non-volatile acids.

### 1. *Volatile Acids*

Volatile acids are derived from $CO_2$. Large quantity of $CO_2$ is produced during the metabolism of carbohydrates and lipids. This $CO_2$ is not a threat because it is almost totally removed through expired air by lungs.

### 2. *Non-volatile Acids*

Non-volatile acids are produced during the metabolism of other nutritive substances such as proteins. These acids are real threat to the acid-base status of the body. For example, sulfuric acid is produced during the metabolism of sulfur containing amino acids such as **cysteine** and **metheonine;** hydrochloric acid is produced during the metabolism of lysine, arginine and histidine. Fortunately, body is provided with the best regulatory mechanisms to prevent the hazards of acid production.

### *Compensatory Mechanism*

Whenever there is a change in pH beyond the normal range, some compensatory changes occur in the body to bring the pH back to normal level. The body has three different mechanisms to regulate acid-base status:

1. Acid-base buffer system, which binds free $H^+$
2. Respiratory mechanism, which eliminates $CO_2$
3. Renal mechanism, which excretes $H^+$ and conserves the bases ($HCO_3^-$).

Among the three mechanisms, the acid-base buffer system is the fastest one and it readjusts the pH within seconds. The respiratory mechanism does it in minutes. Whereas, the renal mechanism is slower and it takes few hours to few days to bring the pH back to normal. However, the renal mechanism is the most powerful mechanism than the other two in maintaining the acid-base balance of the body fluids.

## ■ REGULATION OF ACID-BASE BALANCE BY ACID-BASE BUFFER SYSTEM

### ■ DEFINITION

An acid-base buffer system is the combination of a weak acid **(protonated substance)** and a base – the salt **(unprotonated substance).** Buffer system is the one, which acts immediately to prevent the changes in pH. Buffer system maintains pH by binding with free $H^+$.

### *Types of Buffer Systems*

Body fluids have three types of buffer systems, which act under different conditions:

1. Bicarbonate buffer system
2. Phosphate buffer system
3. Protein buffer system.

### 1. *Bicarbonate Buffer System*

Bicarbonate buffer system is present in ECF (plasma). It consists of the protonated substance, carbonic acid ($H_2CO_3$) which is a weak acid and the unprotonated substance, $HCO_3^-$, which is a weak base. $HCO_3^-$ is in the form of salt, i.e. sodium bicarbonate ($NaHCO_3$).

*Mechanism of action of bicarbonate buffer system*

Bicarbonate buffer system prevents the fall of pH in a fluid to which a strong acid like hydrochloric acid (HCl) is added.

Normally, when HCl is mixed with a fluid, pH of that fluid decreases quickly because the strong HCl dissociates into $H^+$ and $Cl^-$.

But, if bicarbonate buffer system ($NaHCO_3$) is added to the fluid with HCl, the pH is not altered much. This is because the $H^+$ dissociated from HCl combines with $HCO_3^-$ of $NaHCO_3$ and forms a weak $H_2CO_3$. This $H_2CO_3$ in turn dissociates into $CO_2$ and $H_2O$.

$$HCl + NaHCO_3 \rightarrow H_2CO_3 + NaCl$$
$$\downarrow$$
$$CO_2 + H_2O$$

Bicarbonate buffer system also prevents the increase in pH in a fluid to which a strong base like sodium hydroxide (NaOH) is added.

Normally, when a base (NaOH) is added to a fluid, pH increases. It is prevented by adding $H_2CO_3$, which dissociates into $H^+$ and $HCO_3^-$. The hydroxyl group (OH) of NaOH combines with $H^+$ and forms $H_2O$. And $Na^+$ combines with $HCO_3^-$ and forms $NaHCO_3$. $NaHCO_3$ is a weak base and it prevents the increase in pH by the strong NaOH.

As sodium bicarbonate is a very weak base, its association with $H^+$ is poor. So the rise in pH of the fluid is very mild.

*Importance of bicarbonate buffer system*

Bicarbonate buffer system is not powerful like the other buffer systems because of the large difference between the pH of ECF (7.4) and the pK of bicarbonate buffer system (6.1). But this buffer system plays an important role in maintaining the pH of body fluids than the other buffer systems. It is because the concentration of two components ($HCO_3^-$ and $CO_2$) of this buffer system is regulated separately by two different mechanisms.

Concentration of $HCO_3^-$ is regulated by kidney and the concentration of $CO_2$ is regulated by the respiratory system. These two regulatory mechanisms operate constantly and simultaneously, making this system more effective.

## 2. *Phosphate Buffer System*

This system consists of a weak acid, the dihydrogen phosphate ($H_2PO_4$ – protonated substance) in the form of sodium dihydrogen phosphate ($NaH_2PO_4$) and the base, hydrogen phosphate ($HPO_4$ – unprotonated substance) in the form of disodium hydrogen phosphate ($Na_2HPO_4$).

Phosphate buffer system is useful in the intracellular fluid (ICF), in red blood cells or other cells, as the concentration of phosphate is more in ICF than in ECF.

*Mechanism of phosphate buffer system*

When a strong acid like hydrochloric acid is mixed with a fluid containing phosphate buffer, sodium dihydrogen phosphate ($NaH_2PO_4$ – weak acid) is formed. This permits only a mild change in the pH of the fluid.

$$\underset{\text{(strong acid)}}{HCl} + Na_2HPO_4 \rightarrow \underset{\text{(weak acid)}}{NaH_2PO_4} + NaCl$$

If a strong base such as sodium hydroxide (NaOH) is added to the fluid containing phosphate buffer, a weak base called disodium hydrogen phosphate ($Na_2HPO_4$) is formed. This prevents the changes in pH.

$$\underset{\text{(strong base)}}{NaOH} + NaH_2PO_4 \rightarrow \underset{\text{(weak base)}}{NaHPO_4} + H_2O$$

*Importance of phosphate buffer system*

Phosphate buffer system is more powerful than bicarbonate buffer system as it has a pK of 6.8, which is close to the pH of the body fluids, i.e. 7.4. In addition to ICF, phosphate buffer is useful in tubular fluids of kidneys also. It is because more phosphate ions are found in tubular fluid.

In the red blood cells, the potassium ion concentration is higher than the sodium ion concentration. So, the elements of phosphate buffer inside the red blood cells are in the form of potassium dihydrogen phosphate ($KH_2PO_4$) and dipotassium hydrogen phosphate ($K_2HPO_4$).

## 3. *Protein Buffer System*

Protein buffer systems are present in the blood; both in the plasma and erythrocytes.

*Protein buffer systems in plasma*

Elements of proteins, which form the weak acids in the plasma are:

i. C-terminal carboxyl group, N-terminal amino group and side-chain carboxyl group of glutamic acid
ii. Side-chain amino group of lysine
iii. Imidazole group of histidine.

Protein buffer systems in plasma are more powerful because of their high concentration in plasma and because of their pK being very close to 7.4.

*Protein buffer system in erythrocytes (Hemoglobin)*

Hemoglobin is the most effective protein buffer and the major buffer in blood. Due to its high concentration than

the plasma proteins, hemoglobin has about six times more buffering capacity than the plasma proteins. The deoxygenated hemoglobin is a more powerful buffer than oxygenated hemoglobin because of the higher pK. When a hemoglobin molecule becomes deoxygenated in the capillaries, it easily binds with $H^+$, which are released when $CO_2$ enters the capillaries. Thus, hemoglobin prevents fall in pH when more and more $CO_2$ enters the capillaries.

## REGULATION OF ACID-BASE BALANCE BY RESPIRATORY MECHANISM

Lungs play an important role in the maintenance of acid-base balance by removing $CO_2$ which is produced during various metabolic activities in the body. This $CO_2$ combines with water to form carbonic acid.

Since carbonic acid is unstable, it splits into $H^+$ and $HCO_3^-$.

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Entire reaction is reversed in lungs when $CO_2$ diffuses from blood into the alveoli of lungs.

$$H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow CO_2 + H_2O$$

And $CO_2$ is blown off by ventilation (Chapter 125).

When metabolic activities increase, more amount of $CO_2$ is produced in the tissues and the concentration of $H^+$ increases as seen above. Increased $H^+$ concentration increases the pulmonary ventilation (hyperventilation) by acting through the chemoreceptors (Chapter 126). Due to hyperventilation, the excess of $CO_2$ is removed from the body.

## REGULATION OF ACID-BASE BALANCE BY RENAL MECHANISM

Kidney maintains the acid-base balance of the body by the secretion of $H^+$ and by the retention of $HCO_3^-$ (Fig. 5.1). Details are given in Chapter 54.

# APPLIED PHYSIOLOGY – DISTURBANCES OF ACID-BASE STATUS

## ACIDOSIS

Acidosis is the reduction in pH (increase in $H^+$ concentration) below normal range.

Acidosis is produced by:

1. Increase in partial pressure of $CO_2$ in the body fluids particularly in arterial blood
2. Decrease in $HCO_3^-$ concentration.

## ALKALOSIS

Alkalosis is the increase in pH (decrease in $H^+$ concentration) above the normal range (Table 5.2).

Alkalosis is produced by:

1. Decrease in partial pressure of $CO_2$ in the arterial blood
2. Increase in $HCO_3^-$ concentration.

Since the partial pressure of $CO_2$ ($pCO_2$) in arterial blood is controlled by lungs, the acid-base disturbances produced by the change in arterial $pCO_2$ are called the respiratory disturbances.

On the other hand, the disturbances in acid-base status produced by the change in $HCO_3^-$ concentration are generally called the metabolic disturbances.

Thus the acid-base disturbances are:

1. Respiratory acidosis
2. Respiratory alkalosis
3. Metabolic acidosis
4. Metabolic alkalosis.

## RESPIRATORY ACIDOSIS

Respiratory acidosis is the acidosis that is caused by alveolar hypoventilation. During hypoventilation the lungs fail to expel $CO_2$, which is produced in the tissues. $CO_2$ is the major end product of oxidation of carbohydrates, proteins and fats.

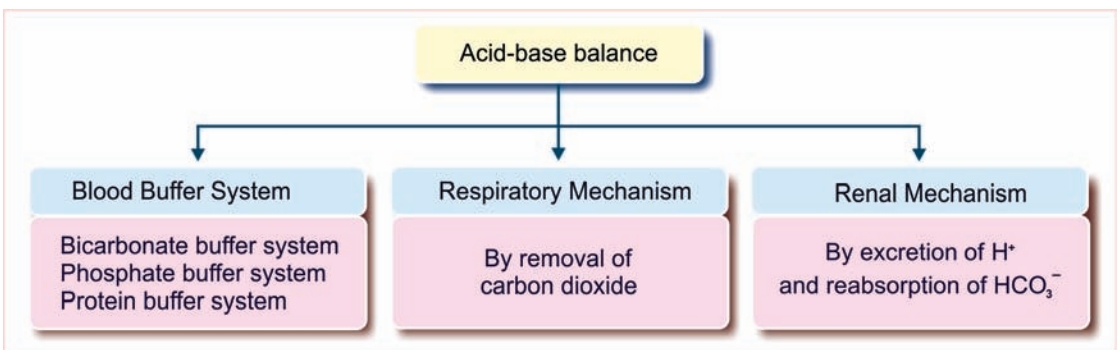



**FIGURE 5.1:** Regulation of acid-base balance

$CO_2$ accumulates in blood where it reacts with water to form carbonic acid, which is called **respiratory acid.** Carbonic acid dissociates into $H^+$ and $HCO_3^-$. The increased $H^+$ concentration in blood leads to decrease in pH and acidosis.

Normal partial pressure of $CO_2$ in arterial blood is about 40 mm Hg. When it increases above 60 mm Hg acidosis occurs.

### *Causes of Excess $CO_2$ in the Body*

Hypoventilation (decreased ventilation) is the primary cause for excess $CO_2$ in the body. Some of the conditions when increase in $pCO_2$ and respiratory acidosis occur due to hypoventilation are listed in Table 5.3.

## ■ RESPIRATORY ALKALOSIS

Respiratory alkalosis is the alkalosis that is caused by alveolar hyperventilation. Hyperventilation causes excess loss of $CO_2$ from the body. Loss of $CO_2$ leads to decreased formation of carbonic acid and decreased release of $H^+$. Decreased $H^+$ concentration increases the pH leading to respiratory alkalosis.

When the partial pressure of $CO_2$ in arterial blood decreases below 20 mm Hg, alkalosis occurs.

### *Causes of Decrease in $CO_2$ in the Body*

Hyperventilation is primary cause for loss of excess $CO_2$ from the body because during hyperventilation, lot of $CO_2$ is expired through respiratory tract leading to decreased $pCO_2$. Some of the conditions when decreased $pCO_2$ and respiratory alkalosis occur due to hyperventilation are given in Table 5.4.

## ■ METABOLIC ACIDOSIS

Metabolic acidosis is the acid-base imbalance characterized by excess accumulation of **organic acids** in the body, which is caused by abnormal metabolic processes. Organic acids such as lactic acid, ketoacids and uric acid are formed by normal metabolism. The quantity of these acids increases due to abnormality in the metabolism.

### *Causes of Metabolic Acidosis*

*Lactic acid*

The amount of lactic acid increases during anaerobic glycolysis in some abnormal conditions such as circulatory shock.

**TABLE 5.2: Biochemical changes in arterial blood during acid-base disturbance**

| Parameter | Acidosis | | Alkalosis | |
|---|---|---|---|---|
| | Respiratory | Metabolic | Respiratory | Metabolic |
| $H^+$ | Increases | Increases | Decreases | Decreases |
| pH | Decreases | Decreases | Increases | Increases |
| $pCO_2$ | Increases | Decreases | Decreases | Increases |
| $HCO_3^-$ | Increases slightly | Decreases very much | Decreases slightly | Increases very much |

**TABLE 5.3: Causes of acidosis**

| Respiratory acidosis | Metabolic acidosis |
|---|---|
| 1. Airway obstruction due to bronchitis, bronchospasm, emphysema, etc. | 1. Lactic acidosis as in circulatory shock |
| 2. Lung diseases like fibrosis, pneumonia, etc. | 2. Ketoacidosis as in diabetes mellitus |
| 3. Respiratory center depression by anesthetics, sedatives, cerebral trauma, tumors, etc. | 3. Uric acidosis as in renal failure |
| 4. Extrapulmonary thoracic diseases like flail chest, kyphosis and scoliosis | 4. Acid poisoning |
| 5. Neural diseases like polymyelitis, paralysis of respiratory muscles | 5. Renal tubular acidosis due to decreased $H^+$ excretion |
| | 6. Loss of excess $HCO_3^-$ due to diarrhea and pancreatic, intestinal, or biliary fistula |

**TABLE 5.4: Causes of alkalosis**

| Respiratory alkalosis | Metabolic alkalosis |
|---|---|
| 1. Hypoxia as in high altitude, severe anemia and pulmonary diseases like edema and embolism | 1. Vomiting and congenital diarrhea |
| 2. Increased respiratory drive due to cerebral disturbances, voluntary hyperventilation and psychological and emotional trauma | 2. Endocrine disorders such as Cushing's syndrome and Conn's syndrome |
| | 3. Diuretic therapy |

**TABLE 5.5: Variations in anion gap**

| Increase in anion gap | Decrease in anion gap |
|---|---|
| 1. Metabolic disorder (inability to metabolize lactic acid) | 1. Hyperchloremic acidosis (increased chloride level in blood) |
| 2. Dehydration | 2. Hypoalbuminemia (low albumin level in blood) |
| 3. Diabetes, starvation, alcoholism (due to increased production of ketoacid) | 3. Multiple myeloma (due to accumulation of anionic proteins) |
| 4. Renal disease (failure to excrete acids – phosphate and sulfate) | 4. Hyponatremia (low blood sodium level) |
| 5. Respiratory disease (production of excess lactic acid due to inadequate oxygen supply to tissues) | 5. Renal disease (loss of excess sodium or potassium through urine) |
| 6. Genetic disorder (involving enzymes of carbohydrate metabolism) | 6. Hyperthyroidism |
| 7. Nutritional deficiencies | 7. Toxicity due to lithium or bromide |

*Ketoacids*

The amount of ketoacids increases because of insulin deficiency as in the case of diabetes mellitus. In diabetes mellitus, glucose is not utilized due to lack of insulin. So, lipids are utilized for liberation of energy resulting in production of excess acetoacetic acid and beta hydroxybutyric acid.

*Uric acid*

The amount of uric acid increases in the body due to the failure of excretion. Normally uric acid is excreted by kidneys. But in renal diseases, the kidneys fail to excrete the uric acid.

Some of the conditions when the metabolic acids increase in the body resulting in metabolic acidosis are listed in Table 5.3.

## ■ METABOLIC ALKALOSIS

Metabolic alkalosis is the acid-base imbalance caused by loss of excess $H^+$ resulting in increased $HCO_3^-$ concentration. Some of the endocrine disorders, renal tubular disorders, etc. cause metabolic disorders leading to loss of $H^+$. It increases $HCO_3^-$ and pH in the body leading to metabolic alkalosis.

Some of the conditions when excess $H^+$ is lost and $HCO_3^-$ content increases leading to metabolic alkalosis are given in Table 5.4.

## ■ CLINICAL EVALUATION OF DISTURBANCES IN ACID-BASE STATUS – ANION GAP

Anion gap is an important measure in the clinical evaluation of disturbances in acid-base status. Only few cations and anions are measured during routine clinical investigations. Commonly **measured cation** is sodium and the **unmeasured cations** are potassium, calcium and magnesium. Usually measured anions are chloride and bicarbonate. The unmeasured anions are phosphate, sulfate, proteins in anionic form such as albumin and other organic anions like lactate.

Difference between concentrations of unmeasured anions and unmeasured cations is called anion gap.

It is calculated as:

$$\text{Anion gap} = [Na^+] - [HCO_3^-] - [Cl^-]$$
$$= 144 - 24 - 108 \text{ mEq/L}$$
$$= 12 \text{ mEq/L}$$

Normal value of anion gap is 9 to 15 mEq/L. It increases when concentration of unmeasured anion increases and decreases when concentration of unmeasured cations decreases.

Anion gap is a useful measure in the differential diagnosis (diagnosis of the different causes) of acid-base disorders particularly the metabolic acidosis. Variations of anion gap are given in Table 5.5.

# 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 regulation of acid-base balance. Add a note on disturbances of acid-base balance.
4. Explain the homeostasis in the body with suitable examples.

## SHORT QUESTIONS

1. Cell membrane.
2. Proteins of cell membrane.
3. Organelles present in the cytoplasm of the cell.
4. Endoplasmic reticulum.
5. Ribosomes.
6. Mitochondria.
7. Golgi apparatus.
8. RNA.
9. DNA.
10. Cellular organelles taking part in protective function.
11. Apoptosis.
12. Cellular necrosis.
13. Tight junctions.
14. Gap junctions.
15. Passive transport.
16. Active transport.
17. Primary active transport.
18. Secondary active transport.
19. Sodium-potassium pump.
20. Simple diffusion through cell membrane.
21. Facilitated diffusion or carrier-mediated diffusion.
22. Ion channels.
23. Factors affecting diffusion.
24. Pinocytosis.
25. Phagocytosis.
26. Transcytosis.
27. Receptor-mediated endocytosis.
28. Homeostasis.
29. Components of homeostasis.
30. Negative feedback.
31. Positive feedback.
32. Acid-base buffer system.
33. Role of blood in the maintenance of acid-base balance or acid-base buffer system.
34. Role of lungs in the maintenance of acid-base balance.
35. Role of kidneys in the maintenance of acid-base balance.
36. Acidosis.
37. Alkalosis.
38. Anion gap.