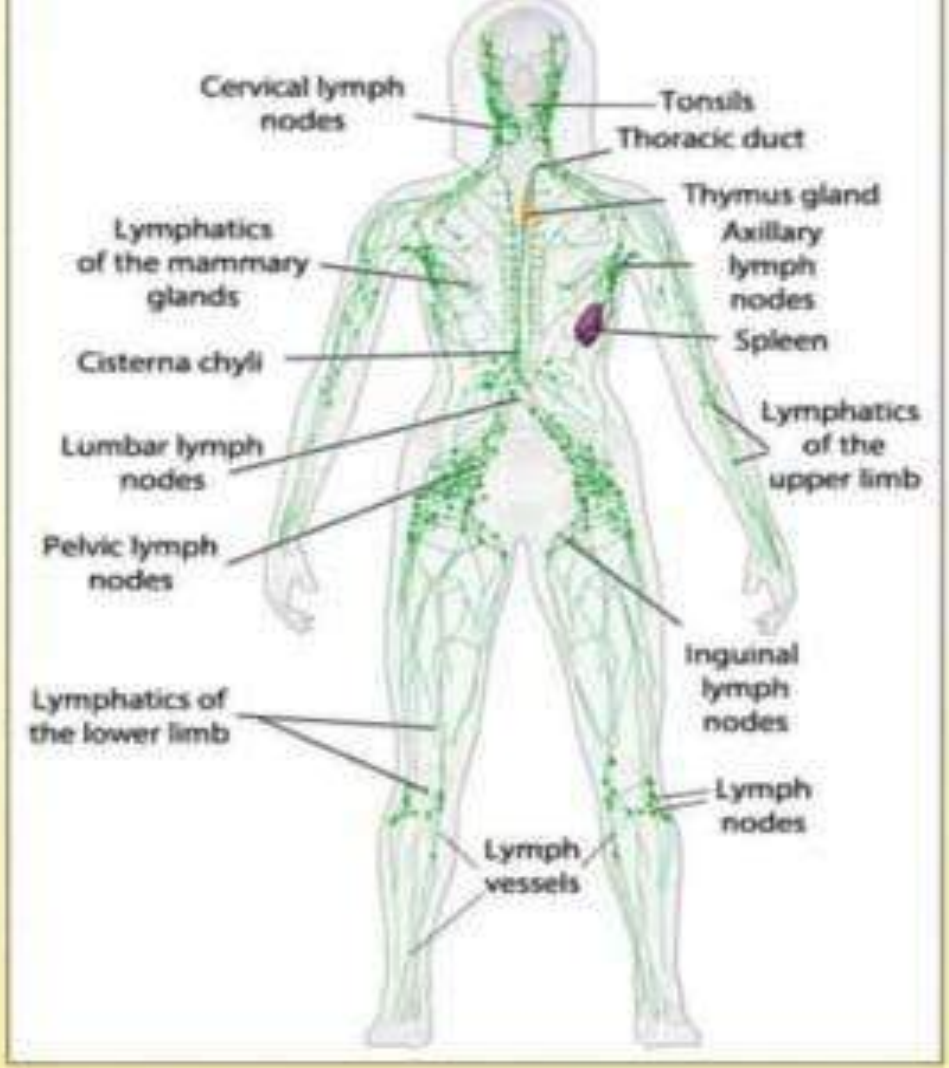
NAME- KHUSHBOO SHAIKH
TOPIC- LYMPHATIC SYSTEM


Cervical lymph nodes
Tonsils
Thoracic duct
Thymus gland
Lymphatics of the mammary glands
Axillary lymph nodes
Spleen
Cisterna chyli
Lymphatics of the upper limb
Lumbar lymph nodes
Pelvic lymph nodes
Inguinal lymph nodes
Lymphatics of the lower limb
Lymph nodes
Lymph vessels

The **lymphatic system** is associated with the blood and the cardiovascular system. Both systems transport vital fluids throughout the body and both have a system of vessels that transport these fluids.

The lymphatic system transports a fluid called lymph through special vessels called lymphatic capillaries and lymphatic trunks. This lymph eventually gets returned to the blood circulation.

In addition to fluid control, our lymphatic system is essential to helping us to destroy a large number of microorganisms that can invade our bodies and cause disease and even death.

The lymphatic system consists of

Lymph,

Lymphatic vessels,

Lymph nodes,

& lymphatic organs.

The **lymphatic** organs are the **bone marrow, tonsils, the spleen, the thymus gland,** and **Peyer's patches.**

Lymph

Lymph is usually clear, transparent and milky fluid flowing through lymphatic vessels. It appears milky due to presence of absorbed fats. Lymph differs from blood because lymph does not contain red blood corpuscles and the protein content is lower.

Composition of Lymph

1. Water
2. The plasma proteins: serum albumin, serum globulin, and serum fibrinogen,
3. Mineral salts: Na^+, K^+, Ca^{+2}, HCO_3, SO_4
4. Organic substances: urea, creatinine, neutral fats and glucose
5. WBCs: Lymphocytes

Functions of lymphatic system

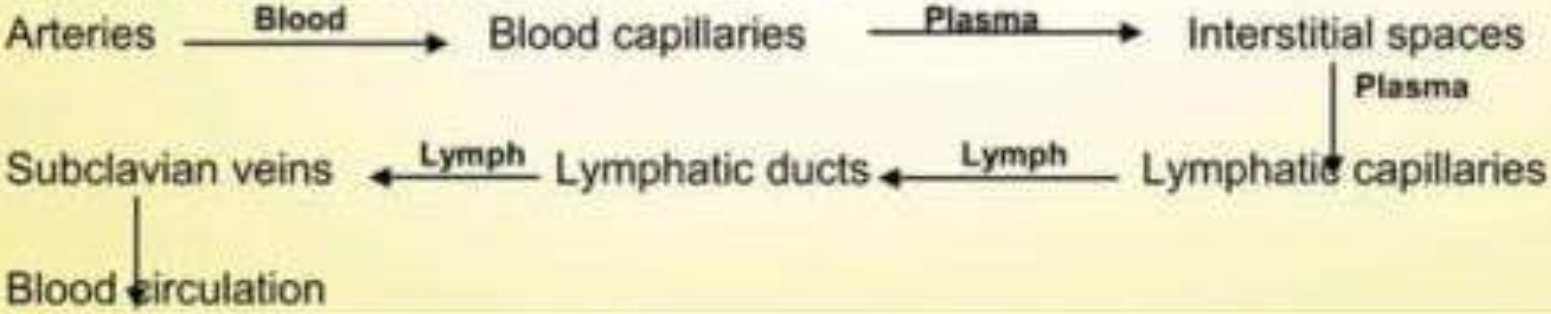
- **Tissue drainage:** Everyday about 21 litres of plasma move from the blood capillaries into interstitial space in between tissue cells to form interstitial fluid. Most of interstitial fluid gets reabsorbed into capillaries but 3 to 4 litres of fluid are drained into lymphatic capillaries. Now this fluid is referred as **lymph**.
- **Transporting dietary fats and vitamins:** Fats and lipid soluble vitamins absorbed by lacteals and villi of gastrointestinal tract and transported to the liver and adipose tissues.

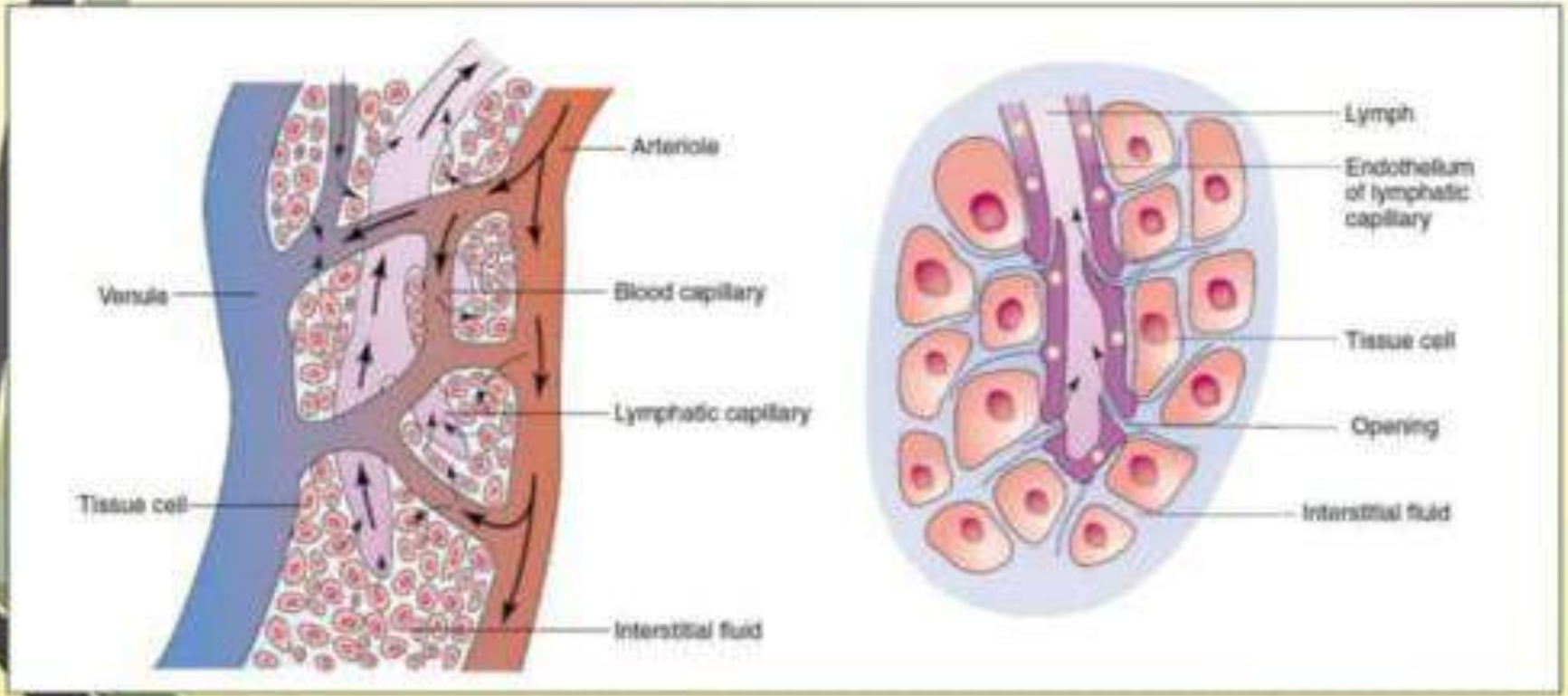
- **Returns plasma protein molecules to blood:** ~25-50% of plasma proteins leak out of capillaries each day they cannot get back into blood capillaries instead lymphatic capillaries pick them up and return them to the blood.
- **Immunity:** the lymphatic organs carry out production and maturation of lymphocytes, the white blood cells that are primarily responsible for immunity and defence mechanism.
- **Haematopoiesis:** some WBC's (lymphocytes, monocytes) are made in lymphatic tissues (not bone marrow).

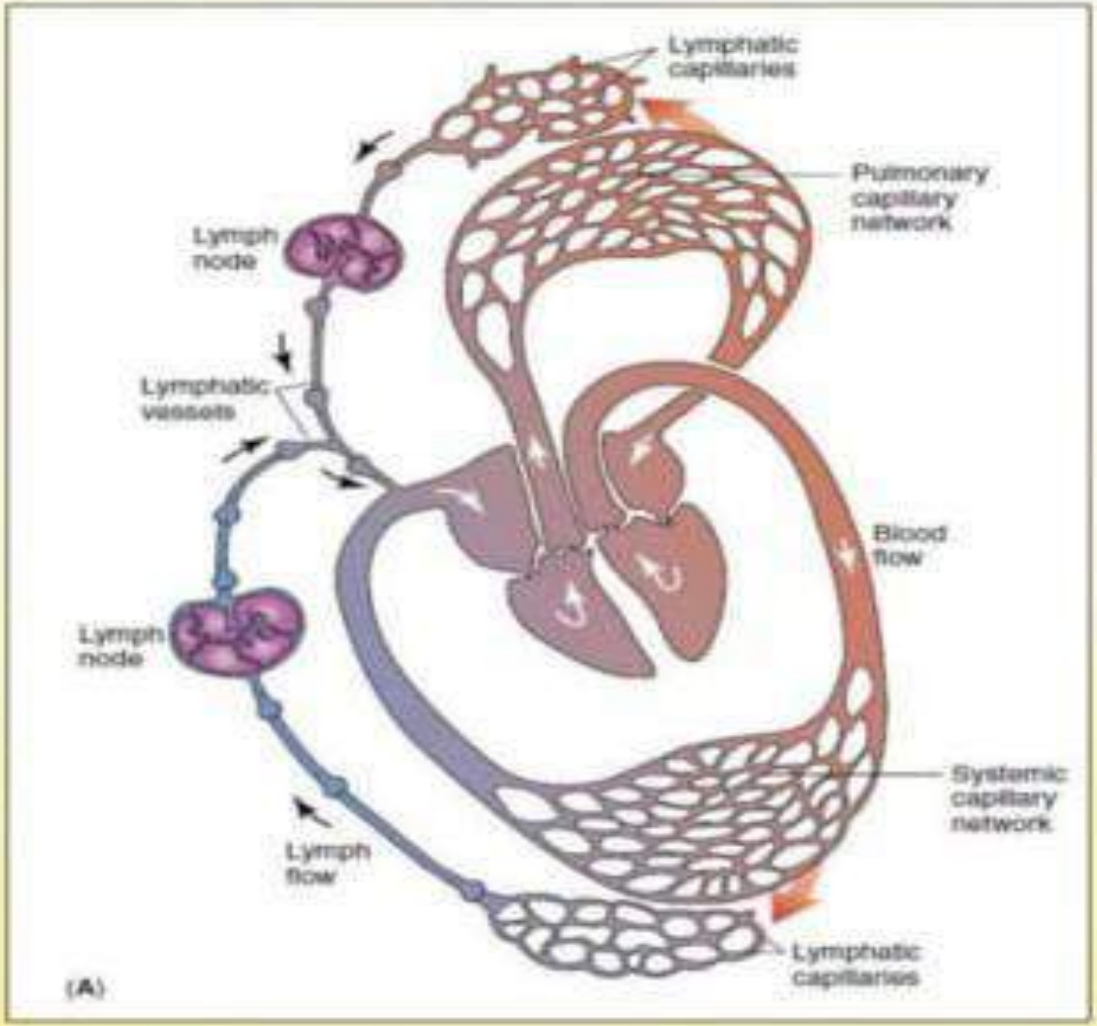
Formation and flow of lymph

Every day about 21 litres of plasma move from the blood capillaries into interstitial space in between tissue cells to form interstitial fluid. Most of interstitial fluid gets reabsorbed into capillaries but 3 to 4 litres of fluid are drained into lymphatic capillaries. Now this fluid is referred as **lymph**.

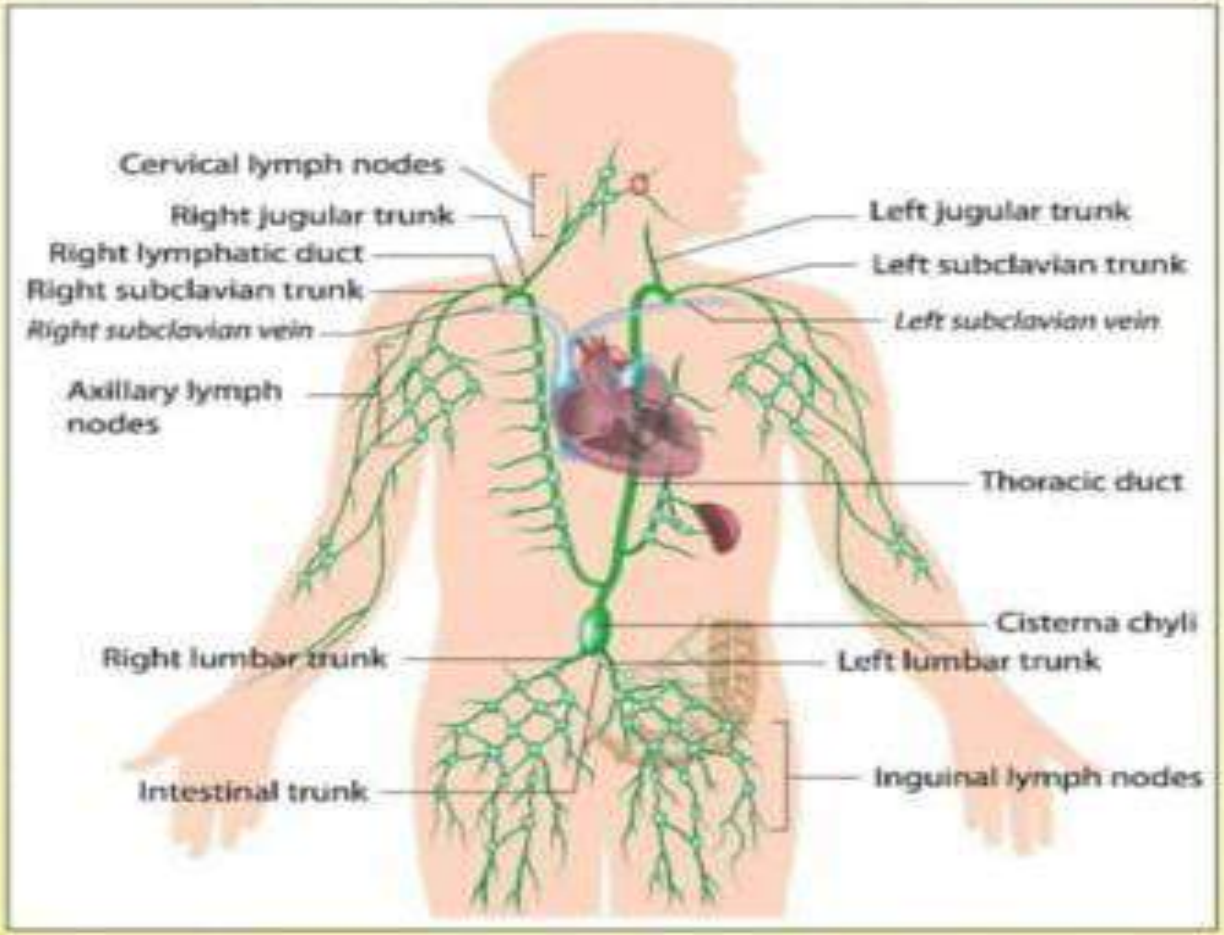
Ultimately, lymph drains **into venous blood** through the **right and left lymphatic duct** at the junction of the **internal jugular vein** and **subclavian veins**. Thus the sequence of fluid flow is as follows:

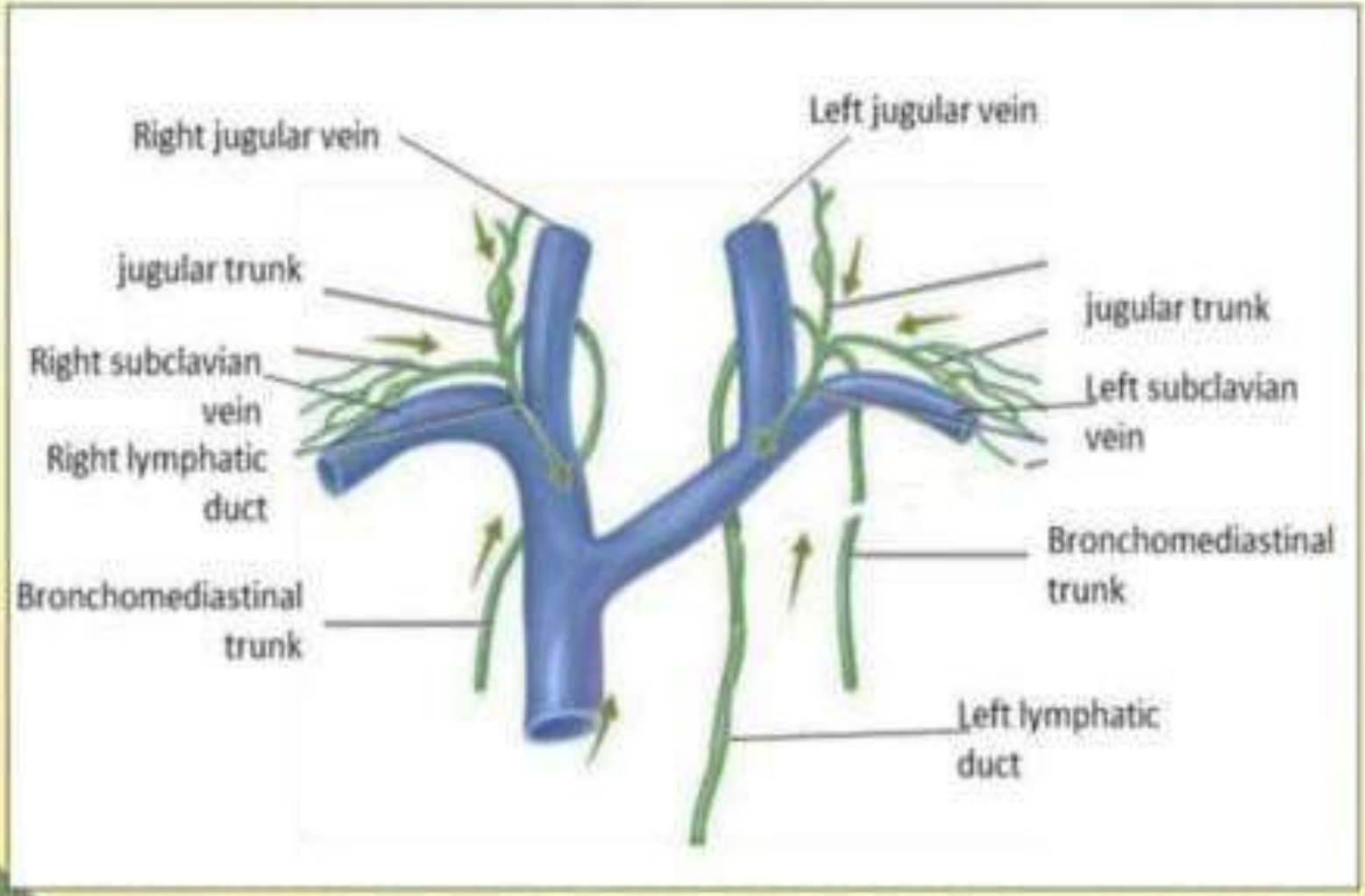



Arteriole
Venule
Blood capillary
Lymphatic capillary
Tissue cell
Interstitial fluid
Lymph
Endothelium of lymphatic capillary
Tissue cell
Opening
Interstitial fluid


Lymphatic capillaries
Pulmonary capillary network
Lymph node
Lymphatic vessels
Blood flow
Lymph node
Systemic capillary network
Lymph flow
Lymphatic capillaries
(A)

- The flow of lymph from interstitial tissue spaces to the lymphatic capillaries, lymphatic ducts and finally to the subclavian veins is maintained primarily by the skeletal muscle contractions.
- Contractions of skeletal muscles compress lymphatic vessels and force lymph toward the right and left subclavian veins. The respiratory pump alternately expands and compresses the lymph vessels in the chest cavity and keeps the lymph moving. One-way valves within the lymphatic vessels prevent backflow of lymph.


Cervical lymph nodes
Right jugular trunk
Right lymphatic duct
Right subclavian trunk
Right subclavian vein
Axillary lymph nodes
Left jugular trunk
Left subclavian trunk
Left subclavian vein
Thoracic duct
Cisterna chyli
Right lumbar trunk
Left lumbar trunk
Intestinal trunk
Inguinal lymph nodes


Right jugular vein
Left jugular vein
jugular trunk
jugular trunk
Right subclavian vein
Left subclavian vein
Right lymphatic duct
Bronchomediastinal trunk
Bronchomediastinal trunk
Left lymphatic duct

Lymph trunks and ducts

- Lymph passes from lymphatic capillaries into lymphatic vessels and through lymph nodes. Lymphatic vessel exiting lymph nodes pass lymph into another node. The exiting lymphatic vessel united to form **lymph trunks.** The principal trunks are the **lumbar, intestinal, bronchomediastinal, subclavian and jugular trunks.** The principle trunks eventually pass their lymph into venous blood through two main channels, the **thoracic duct** and **the right lymphatic duct.**

Left lymphatic duct (thoracic duct)

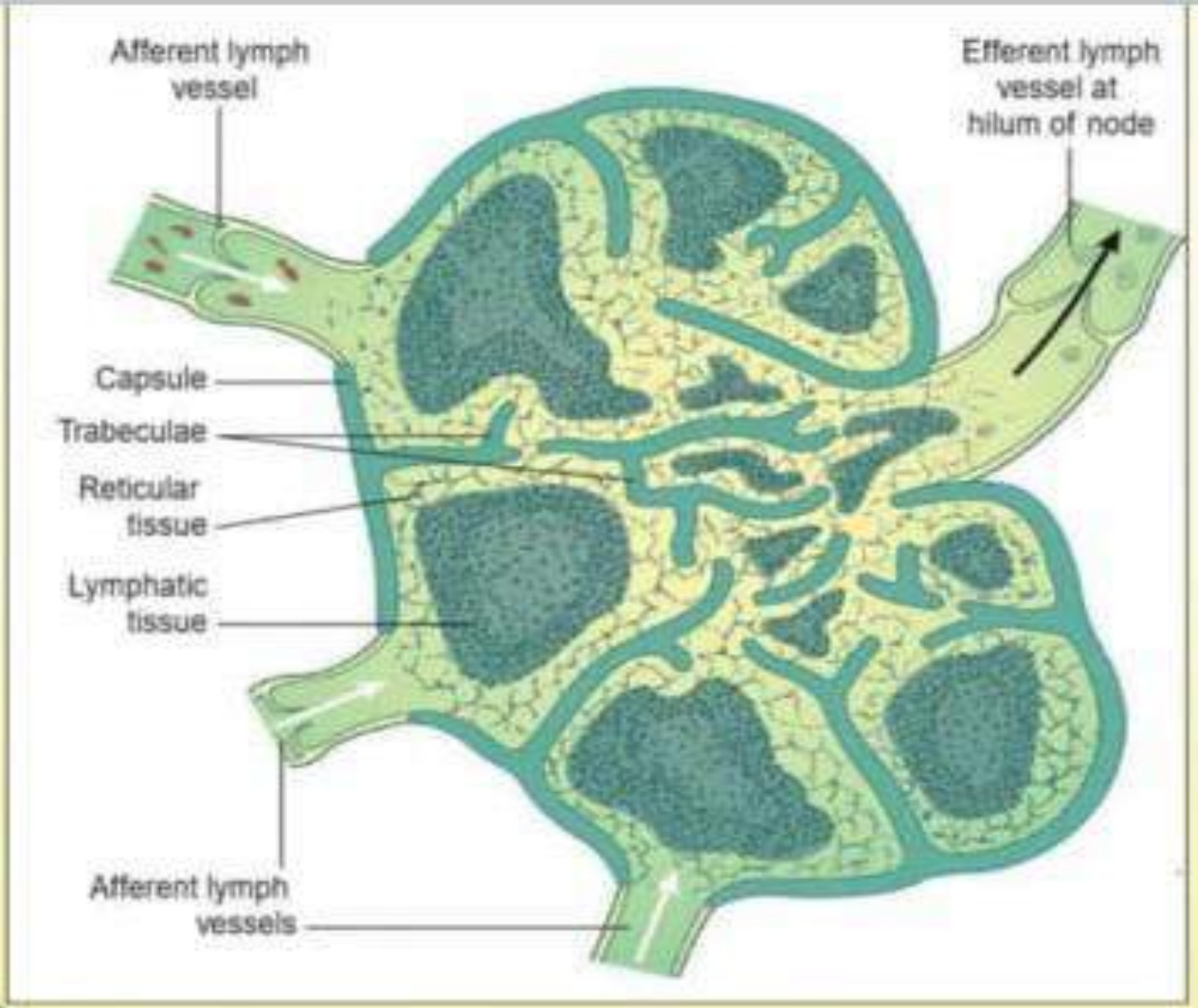
- The left lymphatic duct is about 45 cm in length and begins as a **cisterna chyli** in front of second lumbar vertebra. The thoracic duct is the main collecting duct of lymphatic system. It receives lymph from the left side of the head, neck and chest, the upper left extremity and the entire body below the ribs. Left lymphatic duct (thoracic duct) drains the lymph into **left subclavian vein**.

Right lymphatic duct

- The right lymphatic duct is about 1.25 cm long and drains lymph from the upper right side of the body. The right lymphatic duct collects lymph from right upper extremity; right side of the thorax, right lung, right side of the heart, and liver. Right lymphatic duct opens into **right subclavian vein.**

Lymph nodes

- Lymph nodes are oval to bean-shaped organs of lymphatic system distributed throughout the body including the gastrointestinal tract, armpits, and neck. They are also known as **lymph glands**.
- They range in size from 1 to 25 mm in length, looking like small seeds or almonds. Each lymph node is covered by a **capsule** of fibrous connective tissue.
- The capsular extensions are called as **trabeculae** that contain lymphatic sinuses, reticular fibers and lymphatic tissue. The lymph node is divided into two specialized regions: the **cortex** and **medulla**.


Afferent lymph vessel
Efferent lymph vessel at hilum of node
Capsule
Trabeculae
Reticular tissue
Lymphatic tissue
Afferent lymph vessels

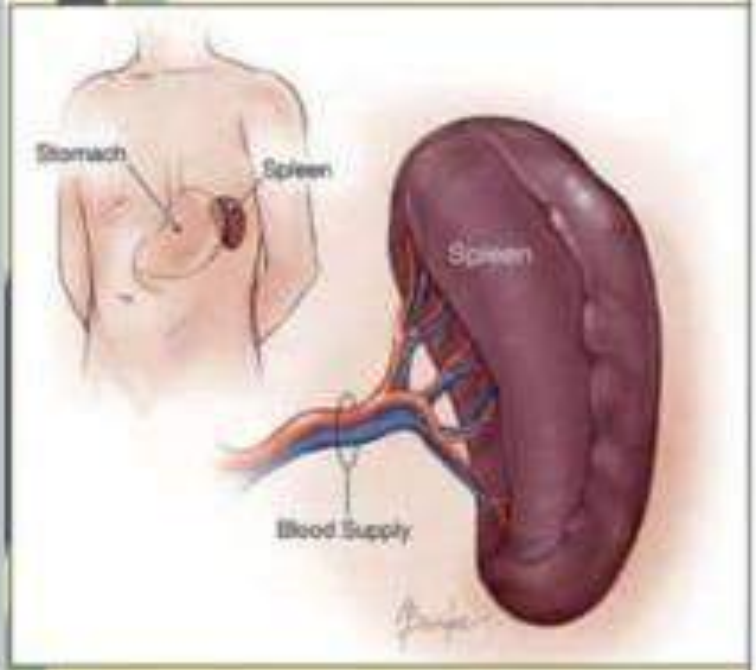
- The outer **cortex** contains densely packed lymphocytes arranged in masses called **follicles**. The outer rim of each follicle contains T-lymphocytes, B-lymphocytes, macrophages and follicular dendritic cells.
- The inner **medulla** consists of **medullary cords** containing macrophages, plasma cells and lymphocytes.
- Lymphatic vessels that enter the lymph node are called afferent lymphatic vessels. Lymph flows through the sinuses in the cortex and then into medulla and exits the lymph node via efferent lymphatic vessels.

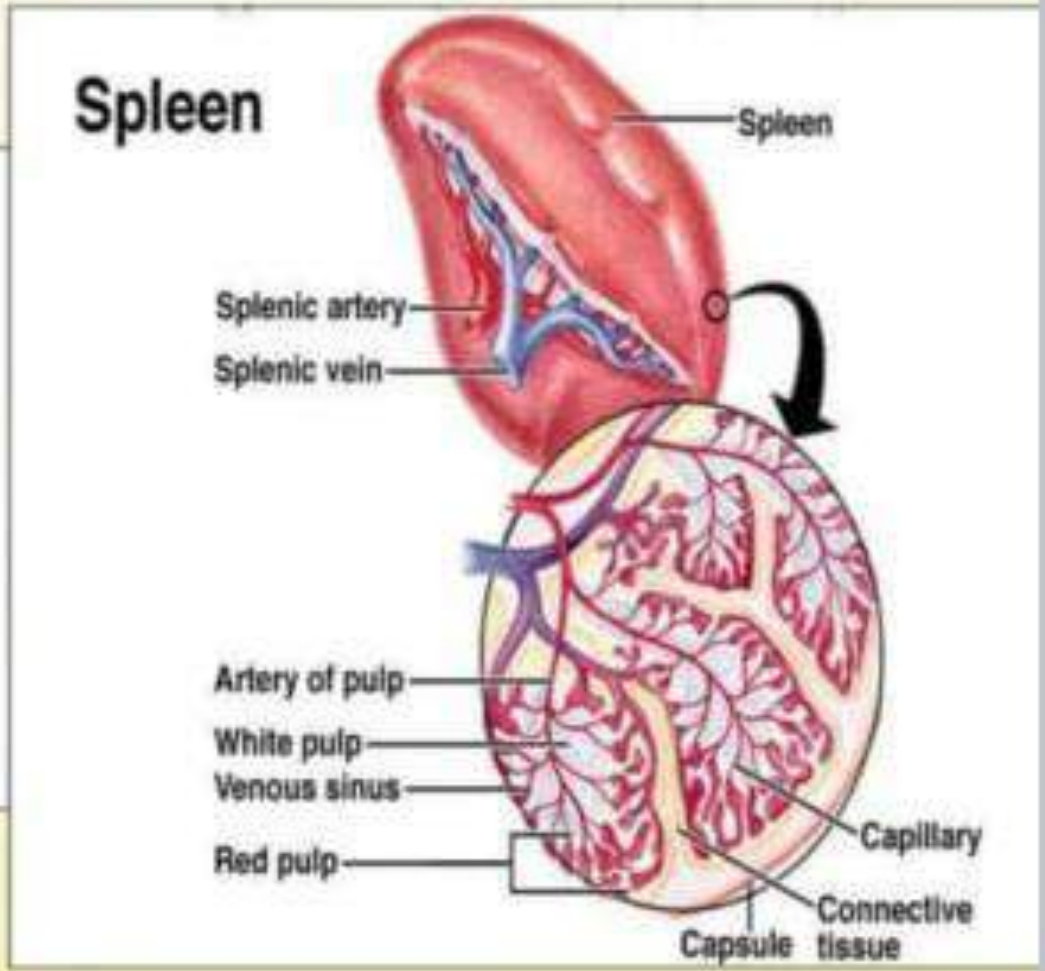
Functions of lymph node

- The lymph node filters foreign substances and cancer cells from lymph as it passes back towards the cardiovascular system. These substances trapped by the reticular fibers within the lymph node.
- The microphages destroy these foreign substances by phagocytosis and lymphocytes promote destruction of others by immune responses.
- The proliferation of plasma cells, B- lymphocytes and T-lymphocytes take place within the lymph node.

SPLEEN

- The spleen is oval in shape and is the single largest organ of lymphatic system in the body. It measures about 12 cm in length. It is found in the left upper corner of the abdominal cavity in between stomach and diaphragm. The spleen consists of two different kinds of tissue called white pulp and red pulp.
- The **white pulp** is made up of lymphatic tissue mostly lymphocytes.
- The **red pulp** consists of venous sinuses and splenic cords. Splenic cords consist of red blood cells, macrophages, B- and T-lymphocytes, plasma cells and granulocytes.
- Blood supply: splenic artery
- Venous drainage: splenic vein


Stomach
Spleen
Spleen
Blood Supply


Spleen
Spleen
Splenic artery
Splenic vein
Artery of pulp
White pulp
Venous sinus
Red pulp
Capillary
Connective tissue
Capsule

Functions of spleen

- **Storage of blood:** The spleen contains about 350 ml of blood and functions as a blood reservoir. During haemorrhage, the spleen will release blood into the blood circulation.
- **Immune response:** Spleen contains plasma cells; B- and T-lymphocytes which are get activated to produce antibodies against foreign antigens.
- **Phagocytosis**: Spleen contains fixed macrophages that phagocytize pathogens or other foreign material in the blood.
- **Haemolysis**: The macrophages of the spleen also phagocytize old red blood cells and form bilirubin. By way of portal circulation, the bilirubin is sent to the liver for excretion in bile.
- **Erythropoiesis:** the spleen and liver are important sites of blood cell production in fetal development.

Glossary

- **Interstitial space** – is a space between two cells
- **Extracellular Fluid** – usually denotes all body fluid outside the cells e.g. plasma, lymph, cerebrospinal fluid,
- **Intracellular fluid** – (within the cell) the fluid inside the cell e.g. Cytoplasm
- **Reservoir** - storage space for fluids.
- **Macrophage** – are a type of WBC that engulfs and digests cellular debris, foreign substances, microbes, cancer cells, and anything else.

THANK YOU

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

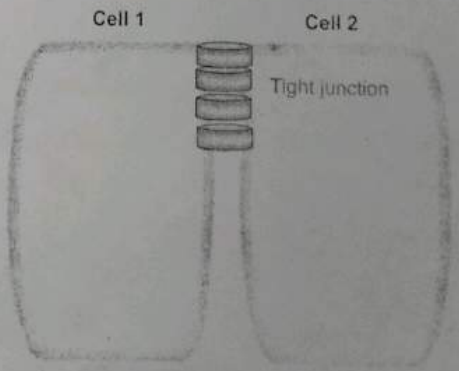


FIGURE 2.1: Tight junction

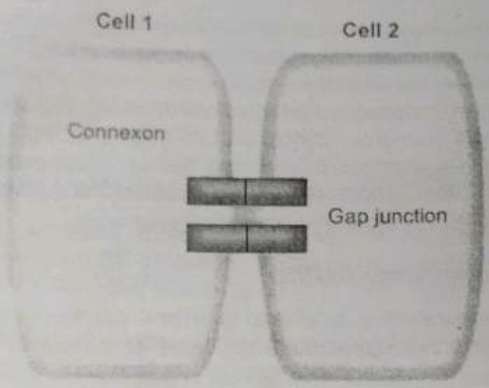


FIGURE 2.2: Gap junction

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)

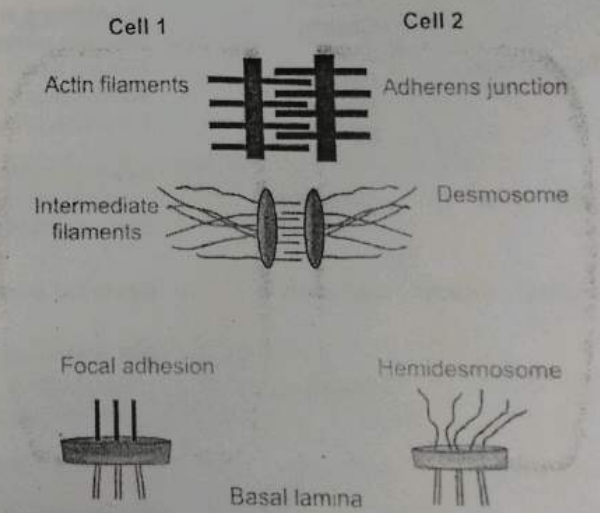


FIGURE 2.3: Anchoring junctions

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

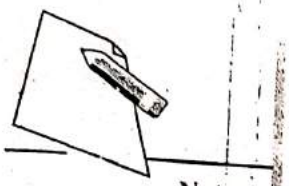
■ CELL ADHESION MOLECULES

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.



Notes

10

MATURATION AND DEVELOPMENT OF LEUCOCYTES

10.1 INTRODUCTION

The leucocytes develop from the multipotent hematopoietic stem cell which then gives rise to a stem cell committed to formation of leucocytes. Both these cells cannot be identified morphologically by routine methods. The various types of leucocytes are granulocytes (neutrophiis, eosinophils and basophils), monocytes and lymphocytes. The three cell types develop separately and accordingly these processes will be discussed separately.

OBJECTIVES

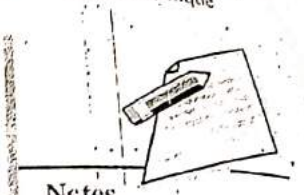
After reading this lesson, you will be able to:

- explain the various stages in the development of leucocytes.
- describe the different types of leucocytes seen normally in PBF.

10.2 MYELOPOIESIS

This is the process of formation of myeloid cells. It is restricted to the bone marrow after birth. The committed progenitor cell for granulocytes and monocytes is the GM-CFU which proliferates and differentiates to form myeloblast and monoblast.

The myeloblast is the earliest morphologically identifiable cell. It is 10-18µm in size. The cytoplasm is scant and basophilic, usually agranular and may contain a few azurophilic cytoplasmic granules in the blast transiting to the next stage



of promyelocyte. It has a large round to oval nucleus with a smooth nuclear membrane. The chromatin is fine, lacy and is evenly distributed throughout the nucleus. Two-five nucleoli can be identified in the nucleus.

The next stage of maturation is the **Promyelocyte**. It is larger than a myeloblast, 12-20 µm with more abundant cytoplasm which has abundant primary azurophilic granules . The nucleus is round to oval, has slightly more condensed chromatin and nucleoli are not prominent.

The next stage is the **Myelocyte** which is identified as being smaller than a promyelocyte, 12-18 µm. The cytoplasm is eosinophilic and an eccentric round to oval nucleus with coarse chromatin and no visible nucleoli can be seen. Specific granules appear in the cytoplasm at this stage and therefore, a myelocyte can be identified as a neutrophilic, eosinophilic or basophilic myelocyte based on the staining properties of the secondary granules. These granules are smaller than the azurophilic granules.

INTEXT QUESTIONS 10.1

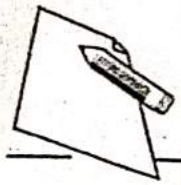
1. Types of leucocytes are ....., ... & .....
2. Types of granulocytes are ....., ... & .....
3. Process of formation of myeloid cells are .....
4. Earliest morphologically identified cell is .....

Metamyelocyte is easily identified by its smaller size, dense and clumped chromatin and an indented, horse shoe shaped nucleus with no nucleoli. The cytoplasm is filled with primary, secondary and tertiary granules but the secondary granules predominate. The presence of granules and their staining properties determine whether it is neutrophilic, eosinophilic or basophilic metamyelocyte.

Neutrophilic metamyelocytes give rise to **band form** in which the nucleus becomes sausage shaped with further condensation of the chromatin.

Finally the **polymorphonuclear neutrophil** is formed which has coarsely clumped nuclear chromatin and 3-5 lobes in the nucleus. The lobes are connected by filamentous strands of chromatin.

Cell division is limited to myeloblast, promyelocyte and myelocyte. With the later stages undergoing differentiation but no further cell division. Hence myeloblasts, promyelocytes and myelocytes comprise the **proliferative or mitotic compartment**. whereas cells from metamylocyte stage onwards comprise the **maturation storage compartment** of the bone marrow.



Notes

The half life of neutrophils in circulation is 6-8 hrs. On completion of the life span, cells may undergo apoptosis or phagocytosis by macrophages, or undergo cell death through mechanisms dependent on reactive oxygen metabolite.

Eosinophils and basophils follow the same pattern of proliferation, differentiation, maturation and storage in the bone marrow. The eosinophils are recognized by their coarse, bright orange reddish granules and a bi or trilobed nucleus. The half life of eosinophils is approx 18 hrs.

Basophils are similar in size to a lymphocyte, have abundant coarse, purplish black granules overlying and obscuring the nucleus. The granules contain histamine, heparin, proteases.

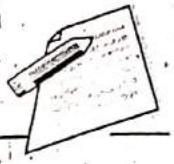
Fig. 10.1: centre row From left to right:myeloblast. promyelocyte, myelocyte, metamyelocyte. band form and mature neutrophil. The top row depicts development of eosinophils and the bottom row development of basophils

Formation of monocytes

The committed progenitor cell GM-CFU also differentiates to form monoblast under the influence of GM-CSF and M-CSF. Monoblast is morphologically similar to myeloblast. Monoblast gives rise to promonocyte which has basophilic cytoplasm, an indented nucleus, fine chromatin, and may contain a nucleolus. They mature into Monocytes which are 15-18 µm in size with a large centrally placed oval or indented nucleus, delicate chromatin and no nucleoli. The cytoplasm is abundant, pale blue in color and has a ground glass appearance due to numerous clear or lilac vacuoles. Monocytes have a short half life in blood of 4.5 to 10 hrs only and migrate from the blood to reside in various tissues as tissue macrophages.

Formation of lymphocytes : Lymphopoiesis

The mature lymphocytes are a heterogenous population of cells that differ from each other in terms of origin, lifespan and preferred sites of location within the lymphoid organ. The earliest identifiable precursor is a Lymphoblast. It is 14-18µm in size, with scant basophilic cytoplasm and high nuclear: cytoplasmic



(N/C) ratio. The nucleus shows coarse clumped chromatin with 1-2 prominent nucleoli. The lymphoblasts mature to prolymphocytes which are smaller cells, 10-12 µm in size with scant cytoplasm, more condensed chromatin and 0-1 nucleoli. The mature lymphocyte can be a small lymphocyte approximately 8-10µm in size with deep purplish blue round or slightly indented nucleus and dense chromatin. Nucleoli are not present. There is a very small rim of basophilic cytoplasm. In the large granular lymphocyte the cytoplasm is more abundant and contains several reddish granules. Both forms are seen in peripheral blood.

Around 60 - 80% of lymphocytes in the peripheral blood are T cells while B cells constitute about 10-15% of peripheral blood lymphocyte population.

For formation of B cells, the lymphoid progenitor gives rise to a Precursor B cell which forms the immature B cell and finally the mature B cell. B lymphocytes are not stored in the BM except for a brief period and are released into circulation to populate the secondary lymphoid organs The B cells occupy the lymphoid follicles.

Each of these stages can be identified by the expression of certain cell surface antigens which can be detected by immunophenotyping. Some of these antigens are described.

Table 10.1

Cell	Antigen
Progenitor B cell	TdT, CD34, CD19,Ig gene rearrangement
Pre B cell	cIg, CD 10, CD 19, CD20
Immature B cell	sIg , CD 19 ,CD20. TdT, CD 34 and CD 10 are not expressed
Mature B cell	coexpression of surface IgD (high) and IgM (low), CD 20, CD 22.

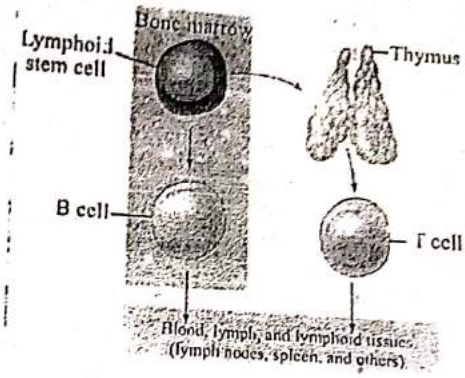
This expression of antigens is used in the classification of leukemias and lymphomas.

The T cells populate the perifollicular cortical areas in the lymph node. They are derived from progenitors which migrate to the thymus where they settle in the corticomedullary junction. The stages in the development of T cells are similar to B cells. The antigens expressed in each of the stages are described now

The earliest progenitor cells committed to the development of T cells express TdT and CD 34.

The immature cortical thymocytes express CD7, TdT, cCD3 and like B lymphocytes undergo TCR gene rearrangement. On further maturation

coexpression of CD 4 and CD8 occurs and later with further maturation the mature T cells express either CD4 or CD 3 antigen.



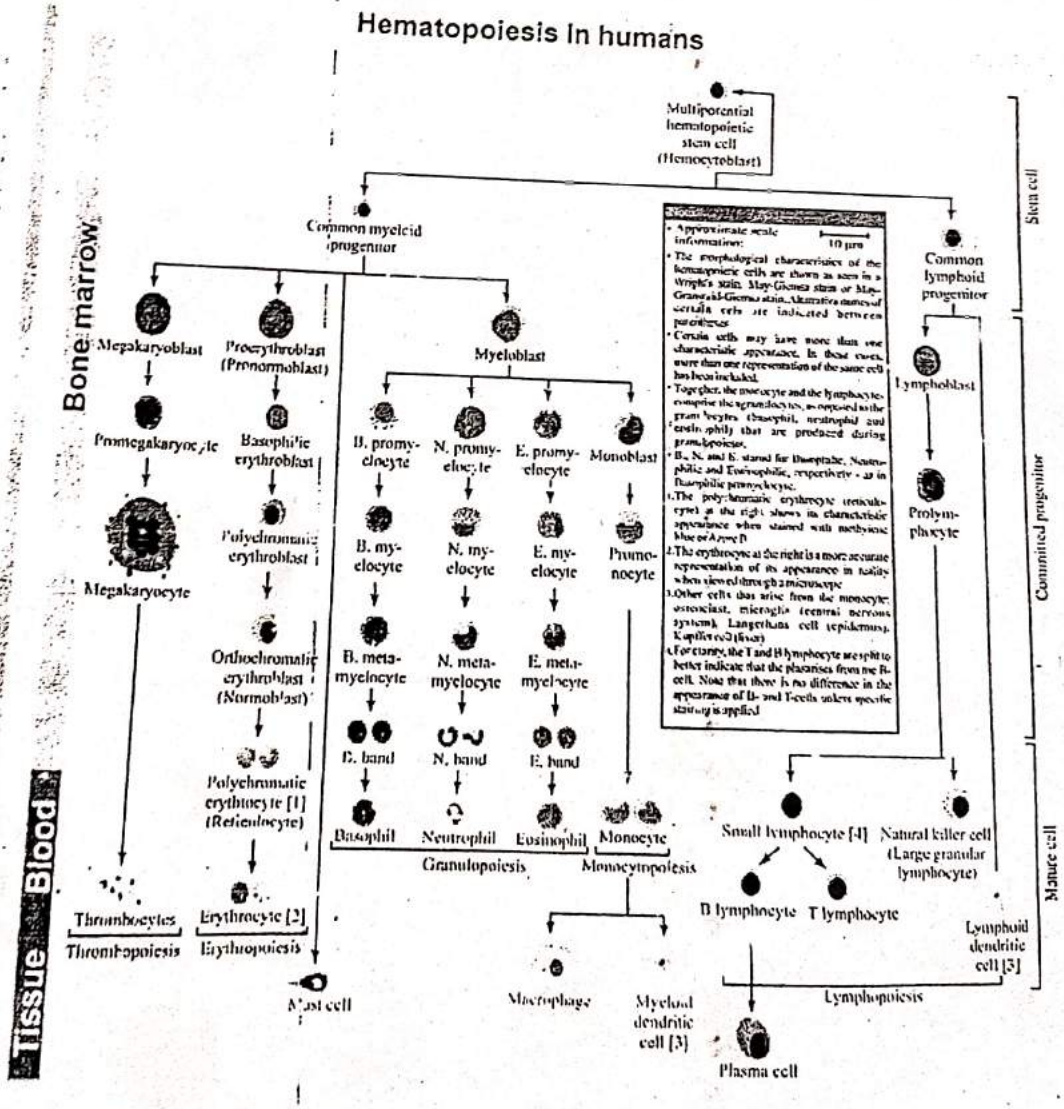


Fig. 10.2: Formation of monocytes, lymphocytes, neutrophil, eosinophil, basophil. red cells and platelets

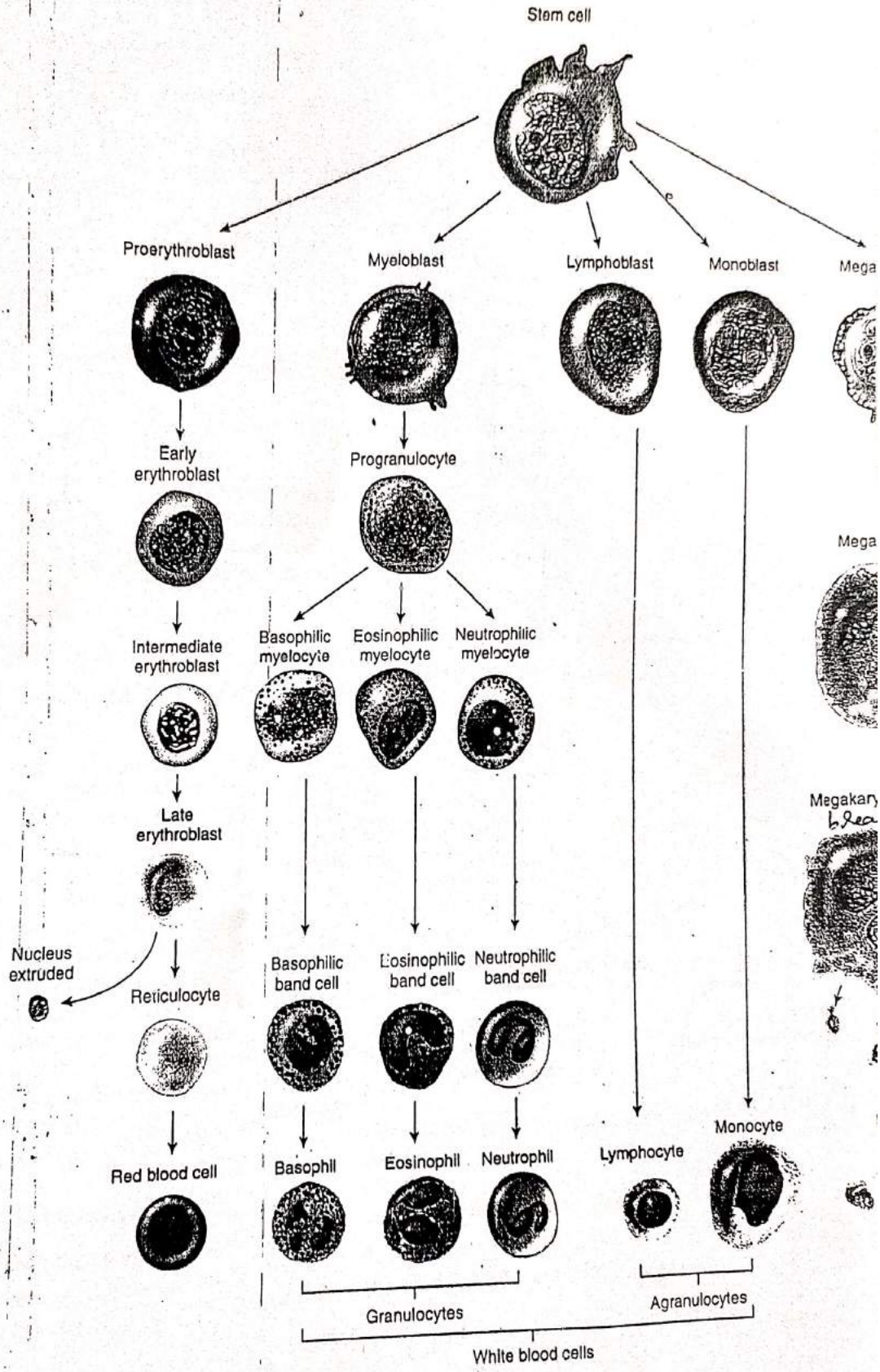


Figure 19.2 Hematopoiesis

Stem cells give rise to the cell lines that produce the formed elements.

Rh FACTOR

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

The persons having D antigen are called 'Rh positive' and those without D antigen are called 'Rh negative'. Among Indian population, 85% of people are Rh positive and 15% are Rh negative. Percentage of Rh positive people is more among black people.

Rh group system is different from ABO group system because, the antigen D does not have corresponding natural antibody (anti-D). However, if Rh positive blood is transfused to a Rh negative person anti-D is developed in that person. On the other hand, there is no risk of complications if the Rh positive person receives Rh negative blood.

INHERITANCE OF Rh ANTIGEN

Rhesus factor is an inherited dominant factor. It may be homozygous Rhesus positive with DD or heterozygous Rhesus positive with Dd (Fig. 19.2). Rhesus negative occurs only with complete absence of D (i.e. with homozygous dd).

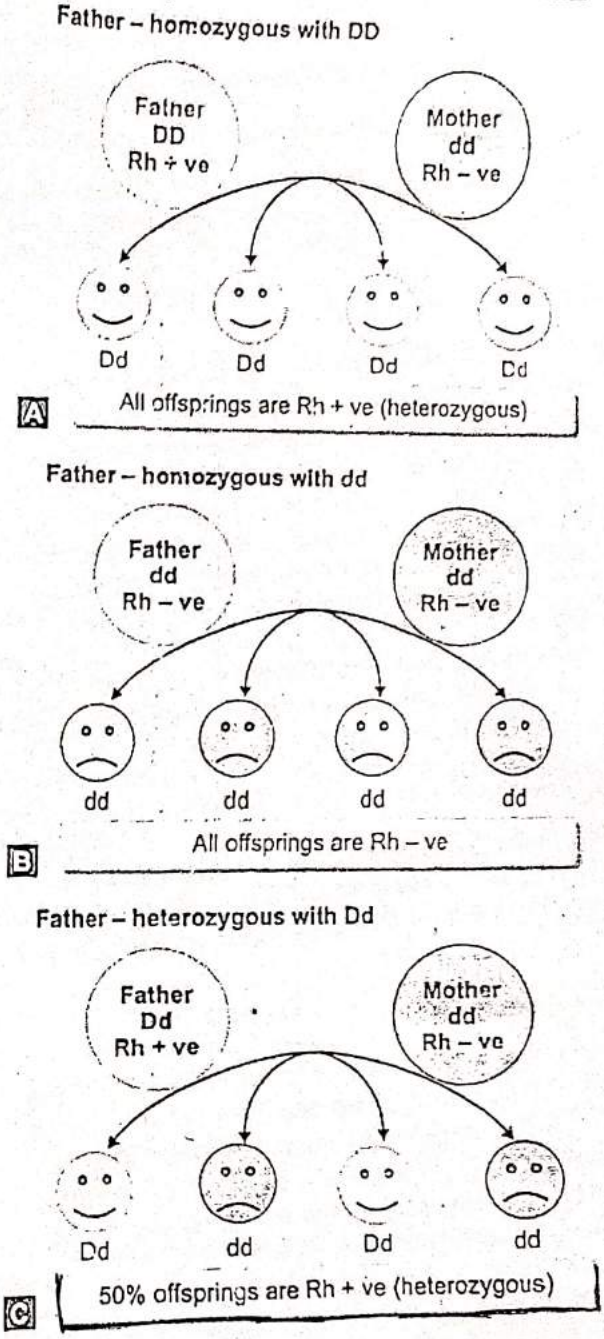


FIGURE 19.2: Inheritance of Rhesus (Rh) antigen. **A.** If father is homozygous with DD. **B.** If father is homozygous with dd. **C.** If father is heterozygous with Dd.

APPLIED PHYSIOLOGY

TRANSFUSION REACTIONS DUE TO ABO INCOMPATIBILITY

Transfusion reactions are the adverse reactions in the body, which occur due to transfusion error that involves transfusion of **incompatible (mismatched) blood**. The reactions may be mild causing only fever and hives (skin disorder characterized by itching) or may be severe leading to renal failure, shock and death.

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

But, if recipient's plasma contains agglutinins against donor's RBCs, the immune system launches a response against the new blood cells. Donor RBCs are agglutinated resulting in transfusion reactions.

Severity of Transfusion Reactions

Severity of transfusion reactions varies from mild (fever and chills) to severe (acute kidney failure, shock and death). Severity depends upon the amount of blood transfused, type of reaction and general health of the patient.

Cause for Transfusion Reactions

Transfusion of incompatible blood produces hemolytic reactions. The recipient's antibodies (IgG or IgM)

adhere to the donor RBCs, which are agglutinated and destroyed. Large amount of free hemoglobin is liberated into plasma. This leads to transfusion reactions.

Signs and Symptoms of Transfusion Reactions

Non-hemolytic transfusion reaction

Non-hemolytic transfusion reaction develops within a few minutes to hours after the commencement of blood transfusion. Common symptoms are fever, difficulty in breathing and itching.

Hemolytic transfusion reaction

Hemolytic transfusion reaction may be acute or delayed. The acute hemolytic reaction occurs within few minutes of transfusion. It develops because of rapid hemolysis of donor's RBCs. Symptoms include fever, chills, increased heart rate, low blood pressure, shortness of breath, bronchospasm, nausea, vomiting, red urine, chest pain, back pain and rigor. Some patients may develop pulmonary edema and congestive cardiac failure.

Delayed hemolytic reaction occurs from 1 to 5 days after transfusion. The hemolysis of RBCs results in release of large amount of hemoglobin into the plasma. This leads to the following complications.

1. *Jaundice*

Normally, hemoglobin released from destroyed RBC is degraded and bilirubin is formed from it. When the serum bilirubin level increases above 2 mg/dL, jaundice occurs Chapter 38).

. *Cardiac Shock*

imultaneously, hemoglobin released into the plasma creases the viscosity of blood. This increases the orkload on the heart leading to **heart failure.** Moreover, xic substances released from hemolyzed cells reduce e arterial blood pressure and develop circulatory shock g. 19.3).

Renal Shutdown

ifunction of kidneys is called renal shutdown. The c substances from hemolyzed cells cause constric- of blood vessels in kidney. In addition, the toxic sub- ces along with free hemoglobin are filtered through nerular membrane and enter renal tubules. Because oor rate of reabsorption from renal tubules, all these tances precipitate and obstruct the renal tubule. suddenly stops the formation of urine (anuria).

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

■ TRANSFUSION REACTIONS DUE TO Rh INCOMPATIBILITY

Generally, Rh incompatibility causes transfusion reactions. Rh incompatibility in fetus causes hemolytic disease leading to erythroblastosis fetalis.

When a Rh negative person receives Rh positive blood for the first time, he/she is not affected much, since the reactions do not occur immediately. But, the Rh antibodies develop within 1 month. The transfused RBCs, which are still present in the recipient's blood, are agglutinated. These agglutinated cells are lysed by macrophages. So, a delayed transfusion reaction occurs. But it is usually mild and does not affect the recipient. However, antibodies developed in the recipient remain in the body forever. So, when this person receives Rh positive blood for the second time, the donor RBCs are agglutinated and severe transfusion reactions occur immediately (Fig. 19.4). These reactions are similar to the reactions of ABO incompatibility (see above).

Hemolytic Disease of Fetus and Newborn: Erythroblastosis Fetalis

Hemolytic disease is a disease in fetus and newborn, characterized by abnormal hemolysis of RBCs. It is due to Rh incompatibility, i.e. the difference between the Rh blood group of the mother and baby. Hemolytic disease leads to erythroblastosis fetalis.

Erythroblastosis fetalis is a hemolytic disease in fetus, characterized by the presence of erythroblasts

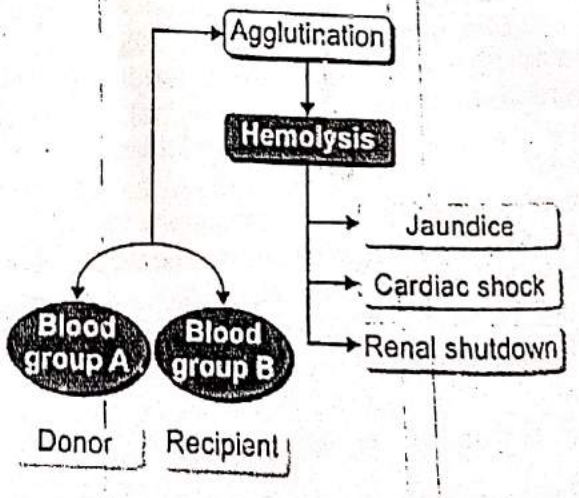


FIGURE 19.3: Complications of mismatched blood transfusion.

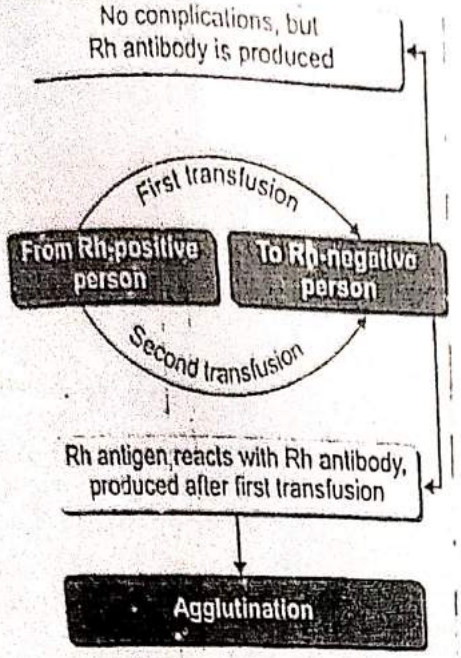


FIGURE 19.4: Rhesus (Rh) incompatibility.

in blood. When a mother is Rh negative and fetus is Rh positive (Rh factor being inherited from the father), usually the first child escapes the complications of Rh incompatibility. This is because the Rh antigen cannot pass from fetal blood into the mother's blood through the placental barrier.

However, at the time of parturition (delivery of the child), the Rh antigen from fetal blood may leak into mother's blood because of placental detachment. During postpartum period, i.e. within a month after delivery, the mother develops Rh antibody in her blood.

When the mother conceives for the second time and if the fetus happens to be Rh positive again, the Rh antibody from mother's blood crosses placental barrier and enters the fetal blood. Thus, the Rh antigen cannot cross the placental barrier, whereas Rh antibody can cross it.

Rh antibody which enters the fetus causes agglutination of fetal RBCs resulting in hemolysis.

Severe hemolysis in the fetus causes jaundice. To compensate the hemolysis of a greater number of RBCs, there is rapid production of RBCs, not only from bone marrow but also from spleen and liver. Now, many large and immature cells in proerythroblastic stage are released into circulation. Because of this, the disease is called erythroblastosis fetalis.

Complications of Erythroblastosis Fetalis

1. Severe anemia.
2. Hydrops fetalis.
3. Kernicterus.

1. *Severe Anemia*

Excessive hemolysis results in anemia and the infant dies when anemia becomes severe.

2. *Hydrops Fetalis*

Hydrops fetalis is a serious condition in fetus, characterized by edema. Severe hemolysis results in the development of edema, enlargement of liver and spleen and cardiac failure. When this condition becomes more severe, it may lead to intrauterine death of fetus.

3. *Bilirubin Encephaiopathy: Kernicterus*

Bilirubin encephalopathy is a neurological disorder characterized by brain damage in infants caused by severe jaundice. If the baby survives anemia in erythroblastosis fetalis (see above), encephalopathy develops because of high bilirubin content.

Bilirubin encephalopathy is often called as kernicterus. The term kernicterus refers to yellow staining of brain tissues caused by bilirubin.

Blood-brain barrier is not well developed in infants as in the adults (Chapter 160). So, the bilirubin enters the brain and causes permanent brain damage. Most commonly affected parts of brain are basal ganglia, hippocampus, geniculate bodies, cerebellum and cranial nerve nuclei.

Features of encephalopathy:

i. When brain damage starts, the babies become lethargic and sleepy. They have high-pitched cry, hypotonia and arching of head backwards.
ii. As the disease progresses, they develop hypertonia and opisthotonus (Chapter 152).
iii. Advanced signs of the disease are inability to suckle milk, irritability and crying, bicycling movements, choreoathetosis (Chapter 148), spasticity (Chapter 32), seizures (Chapter 158), fever and coma.

Prevention or Treatment for Erythroblastosis Fetalis

i. If mother is found to be Rh negative and fetus is Rh positive, anti D (antibody against D antigen; IgG should be administered to the mother at 28th and 34th weeks of gestation, as prophylactic measure. If Rh negative mother delivers Rh positive baby, then anti D should be administered to the mother within 48 hours of delivery. This develops passive immunity and prevents the formation of Rh antibodies in mother's blood. So, the hemolytic disease of newborn does not occur in a subsequent pregnancy

ii. If the baby is born with erythroblastosis fetalis, the treatment is given by means of exchange transfusion (Chapter 20). Rh negative blood is transfused into the infant, replacing infant's own Rh positive blood. It will now take at least 6 months for the infant's new Rh positive blood to replace the transfused Rh negative blood. By this time, all the molecules of Rh antibody derived from the mother get destroyed.

OTHER BLOOD GROUPS

In addition to ABO blood groups and Rh factor, many more blood group systems were found such as Lewis blood group and MNS blood groups. However, these systems of blood groups do not have much clinical importance.

LEWIS BLOOD GROUP

Lewis blood group was first found in a subject named Lewis. The antibody that was found in this lady reacted with the antigens found on RBCs and in body fluids such as saliva, gastric juice, etc. The antigens, which are named Lewis antigens are formed in the tissues, released in the body secretions and then absorbed by the RBC membrane. Because of secretion along with body secretions, these antigens are also known as secretor antigens. Presence of Lewis antigens in children leads to some complications such as retarded growth. Sometimes, it causes transfusion reactions also.

BOMBAY GROUP: H ANTIGEN

H antigen is the precursor of ABO group antigens, i.e. antigen A and antigen B. H antigen is present in RBCs of all individuals. If a person has the gene for A antigen or B antigen or both, these antigens are formed from H antigen. If there is no gene for A and B antigens, the person will not have A or B antigen in spite of having H antigen. The blood of this person belongs to O group.

Rarely, in some persons A, B and H antigens are absent in red blood cells. This group is called Bombay group, since it was first discovered in KEM Hospital in Bombay in the year 1952.

Serum of this Bombay group contains anti A, anti B and anti H antibodies. Sera of these persons will agglutinate the RBCs of all other groups except Bombay group as the red cells of Bombay group do not contain H antigen. While typing the blood group these persons are seen as O group as antigens are absent in RBCs. So, RBCs are agglutinated while typing. However, during crossmatching sera of this group will agglutinate the RBCs of all other groups.

P BLOOD GROUP: P NULL BLOOD GROUP

The P blood group system is a rare one and was discovered in 1927. In 2018, doctors of Manipal have identified P null type phenotype first time in India.

This system is on the basis of presence of any one of P, P1 and Pk antigens on surface of red blood cells. These antigens located on epithelial lining of urinary system form the adhesion sites for the bacteria E. coli that cause urinary tract infection.

Antibodies against P, P1 and Pk antigens can cause acute intravascular hemolytic reaction during incompatible blood transfusion. Particularly antibodies against P and Pk antigens can cause severe erythroblastosis fetalis. In women, these antibodies cause spontaneous abortion.

MNS BLOOD GROUP

MNS blood groups are determined by their reactions with anti-M, anti-N and anti-S. However, these blood groups rarely cause any trouble like hemolysis following transfusion.

OTHER BLOOD GROUPS

Other blood groups include:

1. Auberger group.
2. Diego group.
3. Duffy group.
4. Lutheran group.
5. Kell group.
6. I group.
7. Kidd group.
8. Sutter group.
9. Xg group.

IMPORTANCE OF KNOWING BLOOD GROUP

Nowadays, knowledge of blood group is very essential medically, socially and judicially. The importance of knowing blood group is:

1. Medically, it is important during blood transfusions and in tissue transplants to save life.
2. Socially, one should know his/her own blood group and become a member of the Blood Donor's Club so that he/she can be approached for blood donation during emergency conditions.
3. It is general among the couples, knowledge of blood groups helps to prevent the complications due to Rh incompatibility and save the child from the disorders like erythroblastosis fetalis.

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Table 19.3 Coagulation Factors

Factor Number	Name (synonym)	Description and Function
	Fibrinogen	Plasma protein synthesized in liver; converted to fibrin in stage 3
II	Prothrombin	Plasma protein synthesized in liver (requires vitamin K); converted to thrombin in stage 2
III	Tissue thromboplastin (tissue factor)	Mixture of lipoproteins released from damaged tissue; required in extrinsic stage 1
IV	Calcium ion	Required throughout entire clotting sequence
V	Proaccelerin (labile factor)	Plasma protein synthesized in liver; activated form functions in stage 2 of both intrinsic and extrinsic clotting pathways
VI		Once thought to be involved but no longer accepted as playing a role in coagulation; apparently the same as activated factor V
VII	Serum prothrombin conversion accelerator (stable factor)	Plasma protein synthesized in liver (requires vitamin K); functions in extrinsic stage 1
VIII	Antihemophilic factor (antihemophilic globulin)	Plasma protein synthesized in megakaryocytes and endothelial cells; required for intrinsic stage 1
IX	Plasma thromboplastin component (Christmas factor)	Plasma protein synthesized in liver (requires vitamin K); required for intrinsic stage 1
X	Stuart factor (Stuart-Prower factor)	Plasma protein synthesized in liver (requires vitamin K); required in stage 2 of both intrinsic and extrinsic clotting pathways
XI	Plasma thromboplastin antecedent	Plasma protein synthesized in liver; required for intrinsic stage 1
XII	Hageman factor	Plasma protein required for intrinsic stage 1
XIII	Fibrin-stabilizing factor	Protein found in plasma and platelets; required for stage 3
Platelet Factors		
I	Platelet accelerator	Same as plasma factor V
II	Thrombin accelerator	Accelerates thrombin (intrinsic clotting pathway) and fibrin production
III		Phospholipids necessary for the intrinsic and extrinsic clotting pathways
IV		Binds heparin, which prevents clot formation

Depending on how prothrombinase is formed in stage 1, two separate pathways for coagulation can occur: the **extrinsic clotting pathway** and the **intrinsic clotting pathway.**

Extrinsic Clotting Pathway

The extrinsic clotting pathway is so named because it begins with chemicals that are outside of, or extrinsic to, the blood (see figure 19.11). In stage 1, damaged tissues release a mixture of lipoproteins and phospholipids called **thromboplastin** (throm-bō-plas'tin), also known as **tissue factor (TF),** or factor III. Thromboplastin, in the presence of Ca^{2+}, forms a complex with factor VII, which activates factor X. On the surface of platelets, activated factor X, factor V, platelet phospholipids, and Ca^{2+} complex to form prothrombinase. In stage 2, prothrombinase converts the soluble plasma protein prothrombin into the enzyme thrombin. During stage 3, thrombin converts the soluble plasma protein fibrinogen into the insoluble protein fibrin. Fibrin forms the fibrous network of the clot. Thrombin also stimulates factor XIII activation, which is necessary to stabilize the clot.

Intrinsic Clotting Pathway

The intrinsic clotting pathway is so named beca
chemicals that are inside, or intrinsic to, the blood
In stage 1, damage to blood vessels can expose co
nective tissue beneath the epithelium lining the b
plasma factor XII comes into contact with collage
tivated and it stimulates factor XI which in turn
Activated factor IX joins with factor VIII, platelet p
Ca^{2+} to activate factor X. On the surface of platele
X, factor V, platelet phospholipids, and Ca^{2+} con
thrombinase. Stages 2 and 3 then are activated, an

Although once considered distinct pathwa
that the extrinsic pathway can activate the clotti
intrinsic pathway. The TF–VII complex from the
can stimulate the formation of activated factors
pathway. When tissues are damaged, thrombop
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thrombin is part of a positive-feedback system i
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IV	Calcium ion	Required throughout entire clotting sequence
V	[illegible]	Plasma protein synthesized in liver; activated form functions in stages 2 of both intrinsic and extrinsic clotting pathways
VI	[illegible]	Once thought to be involved but no longer accepted as playing a role in coagulation; apparently the same as activated factor V
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VIII	Antihemophilic factor (antihemophilic globulin)	Plasma protein synthesized in megakaryocytes and endothelial cells; for intrinsic stage 1
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XII	Hagemen factor	Plasma protein required for intrinsic stage 1
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Although once considered distinct pathway that the extrinsic pathway can activate the clottin intrinsic pathway. The TF–VII complex from the can stimulate the formation of activated factors I pathway. When tissues are damaged, thrombopl leads to the production of thrombin, which can the clotting proteins such as factor XI and proth thrombin is part of a positive-feedback system in production stimulates the production of addi

How Vitamin K Helps to Prevent Bleeding

Many of the factors involved in clot formation require vitamin K for their production (see table 19.3). Humans rely on two sources for vitamin K. About half comes from the diet, and half comes from bacteria within the large intestine. Antibiotics taken to fight bacterial infections sometimes kill these intestinal bacteria, thereby reducing vitamin K levels and resulting in bleeding problems. Vitamin K supplements may be necessary for patients on prolonged antibiotic therapy. Newborns lack these intestinal bacteria, and a vitamin K injection is routinely given to infants at birth. Infants can also obtain vitamin K from food such as milk. Because cow's milk contains more vitamin K than does human milk, breast-fed infants are more susceptible to hemorrhage than bottle-fed infants.

The absorption of vitamin K, which is a fat-soluble vitamin, from the intestine requires the presence of bile. Disorders like obstruction of bile flow to the intestine can interfere with vitamin K absorption and lead to insufficient clotting. Liver diseases that result in the decreased synthesis of clotting factors can also lead to insufficient clot formation.

Control of Clot Formation

Without control, coagulation would spread from the point of initiation to the entire circulatory system. Furthermore, vessels in a healthy person contain rough areas that can stimulate clot formation, and small amounts of prothrombin are constantly being converted into thrombin. To prevent unwanted clotting, the blood contains several **anticoagulants** (an'tē-kō-ag'ū-lantz), which prevent coagulation factors from initiating clot formation. Only when coagulation factor concentrations exceed a given threshold does coagulation occur. At the site of injury, so many coagulation factors are activated that the anticoagulants are unable to prevent clot formation. Away from the injury site, however, the activated coagulation factors are diluted in the blood, anticoagulants neutralize them, and clotting is prevented.

Examples of anticoagulants in the blood are antithrombin, heparin, and prostacyclin. **Antithrombin,** a plasma protein produced by the liver, slowly inactivates thrombin. **Heparin,** produced by basophils and endothelial cells, increases the effectiveness of antithrombin because heparin and antithrombin together rapidly inactivate thrombin. **Prostacyclin** (pros-tă-sī'klin) is a prostaglandin derivative produced by endothelial cells. It counteracts the effects of thrombin by causing vasodilation and by inhibiting the release of coagulation factors from platelets.

Anticoagulants are also important when blood is outside the body. They prevent the clotting of blood used in transfusions and laboratory blood tests. Examples include heparin, **ethylenediaminetetraacetic** (eth'il-ēn-dī'ă-mēn-tet-ră-ă-sē'tik) **acid (EDTA),** and sodium citrate. EDTA and sodium citrate prevent clot formation by binding to Ca^{2+}, thus making the ions inaccessible for clotting reactions.

The Danger of Unwanted Clots

When platelets encounter damaged or diseased areas on the walls blood vessels or the heart, an attached clot called a thrombus (throm'bŭs) may form. A thrombus that breaks loose and begins to through the circulation is called an embolus (em'bō-lŭs). Both thro and emboli can result in death if they block vessels that supply blo essential organs, such as the heart, brain, or lungs. Abnormal coagulation can be prevented or hindered by the injection of anticoagulants like heparin, which acts rapidly. Coumadin (koo'mă- or warfarin (war'fă-rin), acts more slowly than heparin. Coumadin prevents clot formation by suppressing the production of vitamin K–dependent coagulation factors (II, VII, IX, and X) by the liver. Interestingly, coumadin was first used as a rat poison by causing ra bleed to death. In small doses, warfarin is a proven, effective anticoagulant in humans. Caution is necessary with anticoagulant treatment, however, because the patient can hemorrhage internall bleed excessively when cut.

Clot Retraction and Dissolution

The fibrin meshwork constituting the clot adheres to the wall blood vessel. Once a clot has formed, it begins to condens denser, compact structure through a process known as **clot tion.** Platelets contain the contractile proteins actin and which operate in a similar fashion to that of actin and my smooth muscle (see chapter 9). Platelets form small extensi attach to fibrin. Contraction of the extensions pulls on the fib is responsible for clot retraction. As the clot condenses, a flui **serum** (sēr'ŭm) is squeezed out of it. Serum is plasma from fibrinogen and some of the clotting factors have been remov

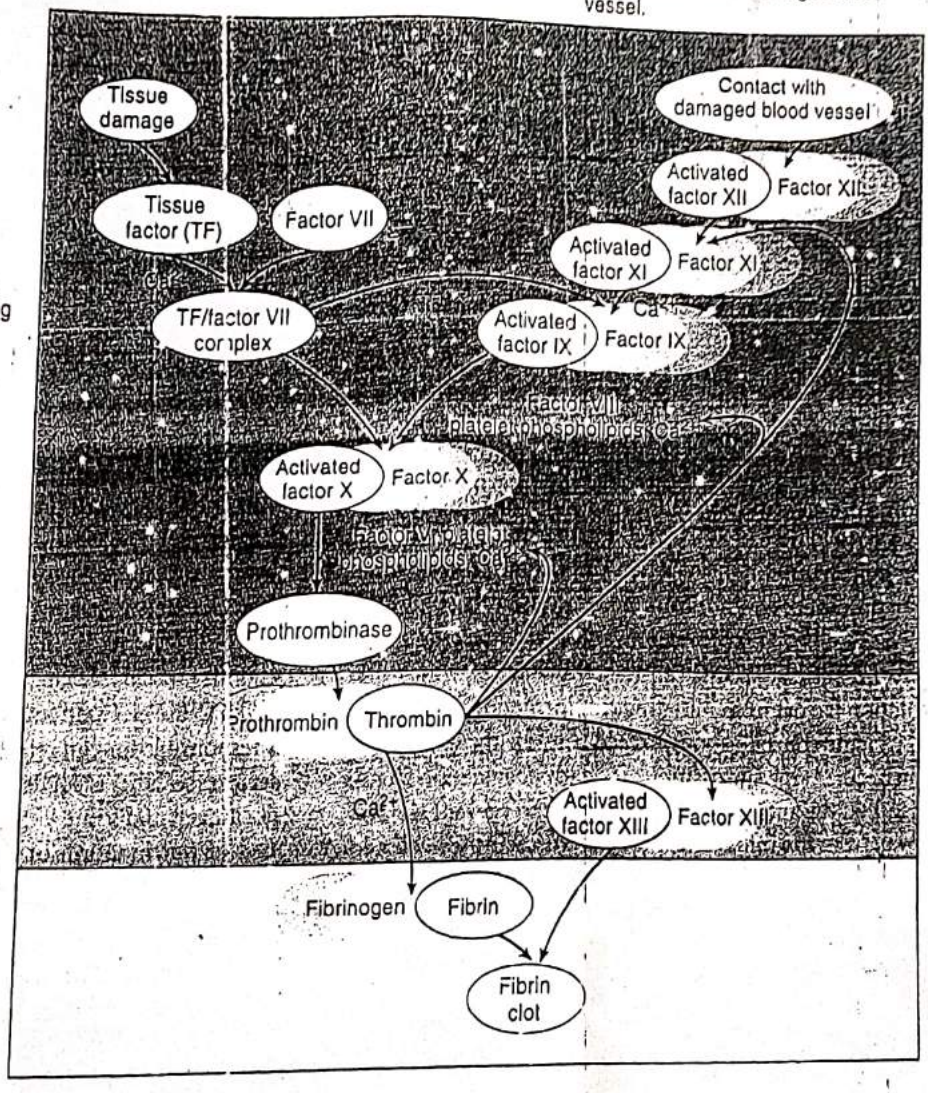
Consolidation of the clot pulls the edges of the da blood vessel together, which can help to stop the flow of bl duce infection, and enhance healing. The damaged vesse paired by the movement of fibroblasts into the damaged a the formation of new connective tissue. In addition, epithe around the wound proliferate and fill in the torn area.

The clot usually is dissolved within a few days after mation by a process called **fibrinolysis** (fī-bri-nol'i-sis), w volves the activity of **plasmin** (plaz'min), an enzyr hydrolyzes fibrin. Plasmin is formed from inactive plasm which is a normal blood protein. It's activated by thrombi XII, tissue plasminogen activator (t-PA), urokinase, and ly enzymes released from damaged tissues (figure 19.12). In c that are caused by blockage of a vessel by a clot, such as a tack, dissolving the clot can restore blood flow and reduce to tissues. For example, streptokinase (a bacterial enzyme) urokinase can be injected into the blood or introduced at site by means of a catheter. These substances convert plas to plasmin, which breaks down the clot.

Stage 1 can be activated in two ways:

Extrinsic clotting pathway starts with tissue factor, which is released outside of the plasma in damaged tissue.

Intrinsic clotting pathway starts when inactive factor XII, which is in the plasma, is activated by coming into contact with a damaged blood vessel.



age 1: Damage to tissue or ood vessels activates clotting tors that activate other clotting tors, which leads to the duction of prothrombinase. e activated factors are within *ite ovals*, whereas the ctive precursors are shown *yellow ovals*.

e 2: Prothrombin is activated othrombinase to form nbin.

3: Fibrinogen is activated ombin to form fibrin, which the clot.

ure 19.11 Clot Formation

has a positive-feedback effect on coagulation by elet activation.

a vascular spasm? Name two factors that produce is the sour e of thromboxanes and endothelin? the function of a platelet plug? Describe the process let plug formation. How are platelets an importa t clot formation?

20. *What is a clot and what is its function?*
21. *What are coagulation factors?*
22. *Clotting is divided into three stages. Describe the final event that occurs in each stage.*
23. *What is the difference between extrinsic and intrinsic activation of clotting?*

Mononuclear phagocyte system

In immunology, the **mononuclear phagocyte system** or **mononuclear phagocytic system** (**MPS**) (also known as the **reticuloendothelial system** or **macrophage system**) is a part of the immune system that consists of the phagocytic cells[1] located in reticular connective tissue. The cells are primarily monocytes and macrophages, and they accumulate in lymph nodes and the spleen. The Kupffer cells of the liver and tissue histiocytes are also part of the MPS. The mononuclear phagocyte system and the monocyte macrophage system refer to two different entities, often mistakenly understood as one.

"Reticuloendothelial system" is an older term for the mononuclear phagocyte system, but it is used less commonly now, as it is understood that most endothelial cells are not macrophages.[2]

The mononuclear phagocyte system is also a somewhat dated concept trying to combine a broad range of cells, and should be used with caution.[3]

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Cell types and locations

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Cell Name	Location
Adipose tissue macrophages	Adipose tissue
Monocyte	Bone Marrow/Blood
Kupffer cell	Liver
Sinus histiocytes	Lymph node
Alveolar macrophage(dust cell)	Pulmonary alveolus of Lungs
Tissue macrophages (Histiocyte) leading to Giant cells	Connective Tissues
Langerhans cell	Skin and Mucosa
Microglia	Central Nervous System
Hofbauer cell	Placenta
Intraglomerular mesangial cell	Kidney
Osteoclasts	Bone
Epithelioid cells	Granulomas
Red Pulp Macrophage (Sinusoidal lining cells)	Red pulp of Spleen
Peritoneal macrophages	Peritoneal cavity

Functions

- Formation of new red blood cells (RBCs) and white blood cells (WBCs).
- Destruction of senescent RBCs.
- Formation of plasma proteins.
- Formation of bile pigments.
- Storage of iron. In the liver, Kupffer cells store excess iron from catabolism of heme from the breakdown of red blood cells. In bone marrow and spleen, iron is stored in MPS cells mostly as ferritin; in iron overload states, mos of the iron is stored as hemosiderin.
- Clearance of Heparin via Heparinases

Hematopoiesis

The various cell types of the mononuclear phagocyte system are all part of the myeloid lineage from the CFU-GEMI (precursor of granulocytes, erythrocytes, monocytes and megakaryocytes.)

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External links

- Immunology at MCG *1/reticulo (http://www.lib.mcg.edu/edu/esimmuno/ch1/reticulo.htm)*

MONONUCLEAR PHAGOCYTE SYSTEM

Mononuclear phagocyte system, also called macrophage system or reticulo-endothelial system, class of cells that occur in widely separated parts of the human body and that have in common the property of phagocytosis, whereby the cells engulf and destroy bacteria, viruses, and other foreign substances and ingest worn-out or abnormal body cells. German pathologist Karl Albert Ludwig Aschoff introduced the term reticulo-endothelial system in 1924, collating the cells based on their phagocytic activity. The later reclassification of phagocytic mononuclear cells, however, resulted in the exclusion of endothelial cells and fibroblasts from the system; hence, Aschoff's term was replaced in the latter part of the 20th century with the name mononuclear phagocyte system.

Mononuclear phagocytic cells are derived from precursor cells in the bone marrow. These precursors develop into monocytes and dendritic cells, phagocytic cells that are released into the bloodstream. Some monocytes and dendritic cells remain in the general blood circulation, but most of them enter body tissues. In tissues, monocytes develop into much larger phagocytic cells known as macrophages. The great majority of macrophages remain as stationary cells within tissue, where they filter out and destroy foreign particles. Some of them break away, however, and wander through the circulation and within the intercellular spaces.

Cells of the mononuclear phagocyte system differ in appearance and name because of their various locations. For example, dendritic cells are found in many tissues, including the lungs, the skin, and the gastrointestinal tract, as well as throughout the lymphatic system. Histiocytes are found in numerous subcutaneous tissues. Kupffer cells line the sinusoids of the liver. Microglia occur in nervous tissue, and alveolar macrophages are found in the air spaces of the lungs.

Each phagocytic cell can engulf and destroy microorganisms, cells, and even tiny fragments of foreign objects, such as bits of splinters and suture materials. Several mobile macrophages can surround larger foreign objects and coalesce into a single phagocytic cell. Thus, by their phagocytosis of foreign substances, macrophages, monocytes, and dendritic cells form an important first line of defense against harmful particles that have reached the body's interior.

Cells of the mononuclear phagocyte system also participate in immune reactions, in which a complex set of events is targeted at a specific foreign substance. Through phagocytosis, macrophages reveal antigens (surface molecules) on foreign substances. Antigens stimulate immune reactions that are directed by white blood cells known as lymphocytes. B lymphocytes (or B cells) synthesize and secrete antibodies with the help of T lymphocytes (or T cells; T cells are also capable of other immunological reactions not involving antibody production). The production of antibodies, in turn, greatly stimulates the phagocytic activity of the cells of the mononuclear phagocyte system.

The mononuclear phagocyte system also plays an important role in the destruction of worn-out red blood cells and the recycling of iron. Specialized macrophages, primarily those residing in

the bone marrow, liver, and spleen, break down old red blood cells and metabolize the hemoglobin (the oxygen-carrying pigment of red blood cells), thereby freeing the iron compound heme for the production of new red blood cells.

Disorders associated with the mononuclear phagocyte system include anemia caused by the excessive destruction of red blood cells. There are also malignant tumours related to mononuclear phagocytes that can be either localized or widespread throughout the body; the excessive proliferation of histiocytes, for example, occurs in malignant histiocytosis and monocytic leukemia. Niemann-Pick disease and Gaucher disease are hereditary disorders characterized by abnormal products of lipid metabolism within cells of the mononuclear phagocyte system.

Mononuclear phagocyte system

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Functions

- Formation of new red blood cells (RBCs) and white blood cells (WBCs).
- Destruction of old RBCs and WBCs
- Formation of antibodies.
- Formation of plasma proteins.
- Formation of bile pigments.
- Storage of iron. In the liver, Kupffer cells store excess iron from catabolism of heme from the breakdown of red blood cells. In bone marrow and spleen, iron is stored in MPS cells mostly as ferritin; in iron overload states, most of the iron is stored as hemosiderin.

The reticuloendothelial system (RES) is an essential component of the immune system, comprised of phagocytic cells located in different organs of the human body. Phagocytic cells capable of engulfing substances, such as bacteria and viruses, rendering them incapable of causing harm to the body. They also ingest abnormal cells and old cells, thus clearing the body of their harmful presence.

Phagocytic cells are derived from the bone marrow stem cells and become monocytes, which circulate in the blood. Most of these monocytes migrate to different tissues inside the body. When they are no longer in the blood circulation, they are called macrophages. Macrophages are generally larger than monocytes and are mostly located in tissues such as the lymph nodes, liver, spleen, brain, and subcutaneous tissues.

The appearance of macrophages differ depending on the organs in which they reside, where they are also given specific names. They are called Kupffer cells when they are found in the liver. In the brain they are known as microglia. When found in the lymph nodes, bone marrow, and spleen, they are named reticular cells. Tissue histiocytes or fixed macrophages are the names used when they are located in the subcutaneous tissues, and while in the lungs they are known as alveolar cells.

Cells of the reticuloendothelial system often remain fixed to these organs, and they function as the first line of protection and defense of the body. They mostly filter and destroy objects which are foreign to the body, such as bacteria, viruses, and bits of sutures or threads used during surgery. Some macrophages are mobile, and they can group together to become one big phagocytic cell in order to ingest larger foreign particles.

The functions of the reticuloendothelial system are not only limited to the ingestion of these foreign substances. The reticuloendothelial system is also important in presenting these substances to other cells of the immune system, such as the lymphocytes. Lymphocytes in turn secrete specific antibodies which can directly destroy specific bacteria and viruses. They are cells capable of remembering specific foreign substances, and render protection by attacking these specific bacteria and viruses every time they enter the body.

One other vital function of the reticuloendothelial system is carried out by the spleen. The spleen is a specialized organ capable of removing old and deformed cells from blood circulation. It is also capable of breaking down worn-out or old red blood cells (RBC) and keeping the hemoglobin part of the RBC to be used again by the body.

Uzma Fatima A. Kolnal Dr. Nataraj

CHAPTER 2

The Cell and Tissues

The human body is made up of many trillion cells. Each individual cell is capable to carry its own functions. Their normal functions are:

1. **Organization:** The cell controls all its organelles and their activities.
2. **Nutrition:** The cell is capable of generating energy for its own functions.
3. **Protection:** The cell is able to fight against the external & internal environmental changes.
4. **Reproduction:** The cell is able to reproduce its identical when the need arises (repair).
5. **Excretion/regulation:** The cell is capable of maintaining its internal environment.
6. **Irritability:** The cells are sensitive to their external environment.

A cell is a structural and functional unit of the body.

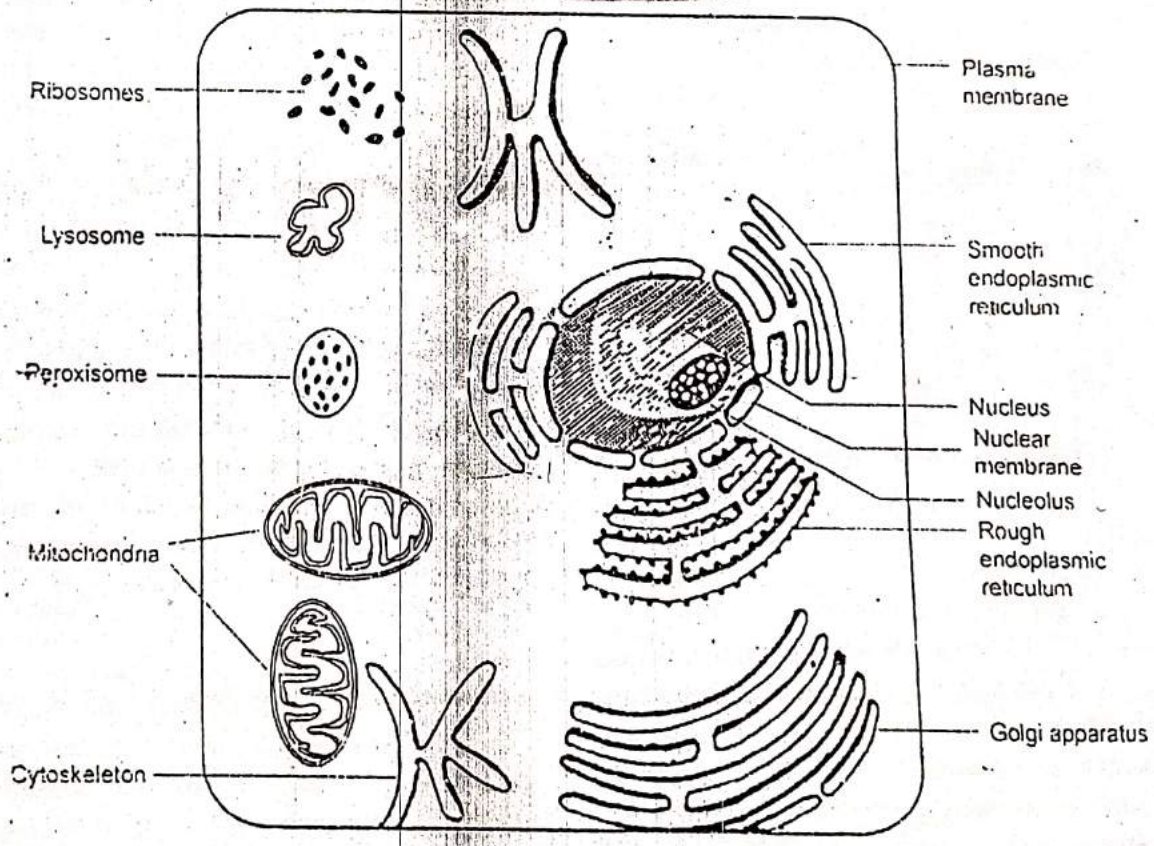

Fig. 2.1: A typical cell.

In a multitrillion cellular animal body, there is a division of labor for which some cells get modified so to carry a specific function and for the same they have to sacrifice one or the other general function e.g., the nerve cells are specialized for the conduction of impulses and they have lost their power of regeneration. Thus, the cells in an animal body though differ in their structure but most of them carry common structures known as the organelles.

The cytoplasm without organelles, is known as cytosol that contains mainly dissolved proteins, electrolytes and glucose.

CELL ORGANELLES

Cell Membrane or Plasma Membrane

It is made up of lipids and proteins with a thickness of 7.5 nm (75 Angstrom unit). The major lipids are phospholipid which are made up of:

1. Hydrophilic end is of phosphate portion which is relatively soluble in water.
2. Hydrophobic end is of lipid portion which is insoluble in water.

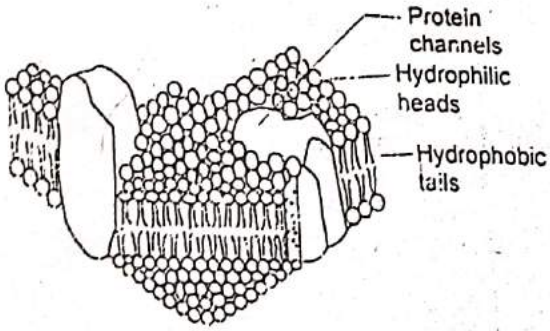

Fig. 2.2: Structure of cell membrane.

These two ends are recognized as head and tail respectively. These molecules are present in two layers in such a way that their heads or the hydrophilic ends remain towards the ECF and the ICF whereas, their tails or the hydrophobic ends remain inside facing each other. Proteins are embedded in the membrane as integral and peripheral proteins. The proteins, in the membrane, function as cell adhesion molecules, carriers, pumps, enzymes, ion channels and receptors.

ECF - Extracellular fluid
ICF - Intracellular fluid

The charged, hydrophilic portions of protein are located on the surface and the uncharged, hydrophobic portions of proteins are located in the interior of the membrane. Cell membrane is semipermeable, allowing selected substances to pass through it. A similar membrane is present around the nucleus.

Basement Membrane or Basal Lamina

Underlying most cells there is a thin, fuzzy layer plus some fibrils that collectively make the basal lamina. It is the extracellular matrix made up of many proteins that hold cells together, regulate their development and determine their growth. These are specific proteins e.g., collagens, laminins, fibronectin, tenascin and proteoglycans.

Nucleus

When a cell is cut in such a way that its one part does not have nucleus, the part without nucleus dies out without dividing. A nucleus is maximally made up of **chromosomes**. Each chromosome is made up of a giant molecule of DNA. The DNA strand is about 2 m long (Fig. 2.7). DNA strand at intervals is wrapped around a core of histone proteins to form a nucleosome. The whole complex of DNA and proteins is called chromatin. It carries a complete blue print for all the heritable species. Generally, each nucleus contains a **nucleolus**, a patchwork of granules rich in RNA. Its number become more in the growing cells. Nucleolus is the site of synthesis of ribosomes. The nucleus is enveloped within a nuclear membrane similar to that of the cell membrane, which is also permeable to ions and some specific messenger molecules.

Mitochondria

It is sausage shaped organelle, which is the **power generating unit** of the cell. Its number in the cytoplasm shows the degree of cellular activity which is proportional to its number. It is made up of two layers of membrane. The inner membrane is folded to form shelves

(cristae). The space inside the inner membrane is called the matrix space and the space between the two membranes is called as intracristal space. The outer membrane is studded with the enzymes concerned with the biological oxidation so as to provide raw materials for the reactions taking place inside the mitochondria. The inner membrane is studded with enzymes concerned with glucose (G), amino acids (AA) and fatty acids (FA) catabolism so as to liberate energy.

$$G/AA/FA \xrightleftharpoons{\text{ATP synthase}} \text{Energy} + CO_2 + H_2O$$

In this process energy is stored as ATP, which is the principal source of energy and the ATP is synthesized by the process of oxidative phosphorylation.

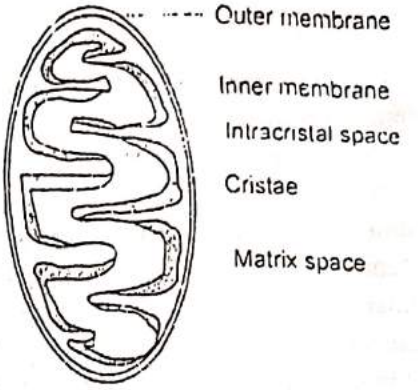

Fig. 2.3: Mitochondria

Mitochondria contain DNA and this is responsible for synthesis of some key compo-

In a multitrillion cell-body, a cell is a structural and functional unit.

Functions of a cell: 1. Organization 2. Irritability 3. Nutrition 4. Protection 5. Reproduction 6. Excretion

Cell organells & their functions

- **Cell membrane:** Protection and transport of elements across it
- **Nucleus:** The controller of the cell, has all programme in coded form (DNA)
- **Endoplasmic reticulum** studded with ribosomes: Seat for protein synthesis
- **Mitochondria:** The power-house; seat of energy production
- **Golgi bodies:** Store-house for synthesized protein and processing thereafter
- **Peroxisomes:** Contains enzymes for catabolic and anabolic reactions
- **Centrosome:** Gets activated at the time of cell division
- **Lysosomes:** Contains digestive enzymes for enemy and autolysis
- **Cytoplasm:** Composed of water, ions and elements
- **Cytoskeleton and molecular motors:** Provides framework and movements

In many multitrillon cellular human body there is a division of labor for which some cells get modified to do special functions leaving behind their either of the usual functions e.g.,

Cells	Specialized for	Lost power of
1. Nerve cells	Conduction of impulses	Regeneration
2. Secretory cells	Secretion	Contraction and reproduction
3. Adipose cells	Storage	Contraction and secretion
4. Muscle cells	Contraction	Diminished reproduction

Fig. 2.4: Cell organelles and functions.

nents of pathway for oxidative phosphorylation. This mitochondrial DNA is of maternal origin being contributed by ovum.

Lysosomes

These are large, irregular structures, which are surrounded by a membrane and they contain a variety of enzymes e.g., ribonuclease, deoxyribonuclease, phosphatase, glycosidase, collagenase and cathepsins. They are like the digestive system of the cell, which are capable to digest most of the engulfed material. In gout, the phagocytes ingest uric acid crystals, which triggers the extracellular release of lysosomal enzymes. These enzymes contribute to the inflammatory response in the joints.

When the lysosome enzymes are absent congenitally, it leads to the lysosomal storage disease e.g.,

- Cathepsin K deficiency: Pyknodysostosis.
- Glycosylasparaginase deficiency: Aspartylglycosaminuria.
- Tay-Sachs disease results from inability to catabolize GM_2 gangliosides due to deficiency of lysosomal enzyme hexosaminidase.

Peroxisomes

Peroxisomes are specific protein containing bodies of 0.5 µm diameter, surrounded by a membrane. Each of them contains about 40 different enzymes concerned with the catalysis of many catabolic and anabolic reactions. Peroxisome specific proteins are concerned with the transport of certain substances into and out of the peroxisomes.

A mutation of one of the genes coding for a peroxisome membrane transporter causes defective beta-oxidation of very long-chained fatty acids – X linked adrenoleukodystrophy that is fatal in childhood.

Cytoskeleton

It's a system of fibres which serves two functions:

1. Maintenance of the cellular structure and
2. It permits the cell to change its shape and to move about.

Primarily, it is made up of microtubules, microfilaments and proteins that anchor them and tie them together.

The microtubules are long, hollow structures with 5 nm thick walls and its cavity is of 15 nm diameter. They provide the tracks for transport of vesicles, organelles and chromosomes (during mitotic division) by forming spindles.

The microtubules are made up of proteins especially tubulin (α and β units).

Intermediate filaments are 8-14 nm in diameter and are made up of various subunits. Their exact function is not known.

Microfilaments are 4-6 in diameter and are long solid fibers. They are made up of actin. Actin and its mRNA is present in all types of cells. It is the most abundant protein in mammalian cells. In vivo, actin molecules (G-actin) polymerizes to form F-actin, the long filamentous chains that are the microfilaments.

The proteins and various organelles in the cytoplasm, move along microtubules propelled by the molecular motors. These motors are 100-500 kDa (kiloDalton) ATPases that get attached with the protein or the organelle (going to be moved) e.g., kinesin, dynein, myosin.

Endoplasmic Reticulum

It is a complex series of tubules in the cytoplasm. The walls of tubule are made up of membrane. In rough endoplasmic reticulum, on the cytoplasmic surface of the membrane, the ribosomes are found attached so this surface appears granular. This is the site of protein synthesis. In smooth endoplasmic reticulum, granules are absent and is the site of steroid synthesis and detoxification processes in cells.

Ribosomes

They are 22-32 nm in diameter, contain many different proteins. They are the sites of all types of protein synthesis.

Golgi Apparatus

These are the specialized globular structures which primarily are the storehouse for the synthesized proteins and then it is involved in *processing of these stored proteins* e.g., the conjugated proteins – lipoproteins, glycoproteins and hemoglobins.

Centrosomes

In the cytoplasm, near the nucleus, a structure is present which is made up of two centrioles surrounded by amorphous pericentriolar material. The centrioles are short cylindrical in shape and are arranged at right angles to each other. The centrioles are made up of microtubules in group of three, run longitudinally in its wall. There are nine of these triplets spaced at regular intervals. When a cell undergoes division process, the centrosomes duplicate themselves and the pair moves apart to form the poles of the mitotic spindle.

Cell Adhesion Molecules (CAMs)

These are specialized protein molecules which serve to:

1. Fasten cells to their neighbours.
2. Fasten cells to the basal lamina.
3. Transmit signals into and out of the cell.

These molecules play an important role in inter-cellular connections. The binding may caused by either of the following manner:

A. The molecule may pass through the cell membrane and are anchored to the cytoskeleton inside the cell.

B. The molecule binds to like molecules on other cells (homophilic binding).

C. The molecule binds to other molecules on other cells (heterophilic binding).

D. The molecule binds to laminins – large cross-shaped molecules with multiple receptors in extracellular matrix.

INTERCELLULAR CONNECTIONS

There are two categories of intercellular connections:

a. Connection that fasten cells to one another and to surrounding tissues.

b. Connection that permits transfer of ions and molecules from one cell to another.

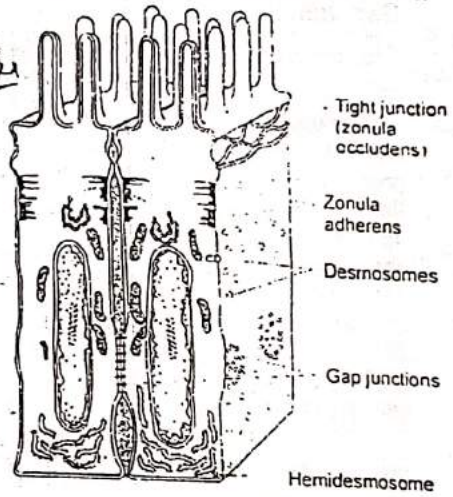

Fig. 2.5 Intercellular junctions.

Connections that Fasten Cells

There are two distinct groups:

1. Connections or junctions that tie cells together so to provide strength and stability to tissues:

- Tight junctions or Zonula occludens: They specially surround the apical margins of the cells in epithelia of intestinal mucosa, walls of renal tubules & allow passage of some ions and solute in variable degree. They prevent the movement of proteins in the plane of the membrane.
- Zonula adherens: In epithelial cells it is usually a continuous structure on the basal side of the zonula occludens. It is the major

site of attachment for intracellular microfilaments.

- **Desmosomes:** They appear as patches characterized by apposed thickening of the membrane of two adjacent cells.

2. Connections or junctions that attach cells to their basal lamina:
   - Hemidesmosome.
   - Focal adhesion.

These two are labile structures that are associated with actin filaments inside the cell and they help in cell movement.

Gap Junctions

They are connections that permit transfer of ions.

The usual intercellular space of 25 nm get reduced to 2-3 nm and hexagonal arrays of protein units (connexons) from each cell are lined up with one another. These units are made up of six subunits surrounding a channel of about 2 nm diameter. These very channels are used for exchange of ions and molecules (with mol. wt. 1000) from one cell to another cell. These junctions permit the rapid propagation of electrical activity from cell to cell. In cardiac muscles the action potential is conducted through them. The diameter of connexon channels is regulated by intracellular calcium ions, pH and voltage. A high concentration of calcium ion reduces diameter of the channels.

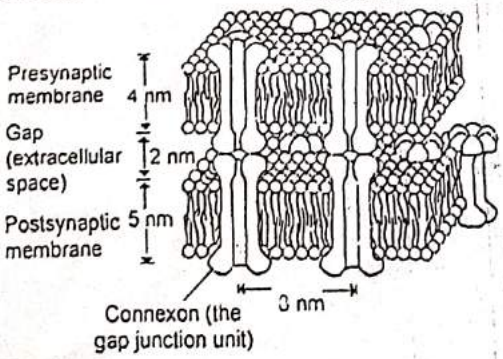

Fig. 2.6: Gap junctions.

INTERCELLULAR COMMUNICATION

Most cells communicate with each other via chemical messengers. At tissue level, chemicals move from cell to cell via the gap junctions where chemicals do not enter in ECF. Besides, there are three general types of intercellular communication system where chemical messenger moves via ECF.

1. **Neural communication:** The neurotransmitters are released at synaptic junctions from nerve cells and act across a narrow synaptic cleft on a postsynaptic cell.
2. **Endocrine communication:** The hormones and growth factors reach cells via the circulating blood.
3. **Paracrine communication:** The products of cells diffuse out in the ECF to affect neighboring cells.

CELL CYCLE

There is an orderly occurrence of events during the mitotic division in a cell. The specific proteins called cyclins and the cyclin-dependent proteokinases regulate this cycle. When DNA gets damaged, its entry into the mitosis process is inhibited, so to provide time for repair of the damaged DNA. *Failure to repair the damaged DNA leads to cancer.*

Apoptosis

In addition to dividing and growing under the genetic control, cells can die and be absorbed under the genetic control. This process is called as programmed cell death or apoptosis (Greek word which means leaves falling from a tree). It can also be called as 'cell suicide' in the sense that the cell's own genes play an active role in its demise (the necrosis is 'cell murder'). Apoptosis is common during the development as well in the adulthood e.g.,

1. **Central nervous system:** A large number of neurons and glial cells are produced and die during the remodeling of the CNS (during the development and the synapse formation).
2. **The immune system:** The apoptosis gets rid of inappropriate clones of immunocytes

and is responsible for the lytic effects of glucocorticoids on lymphocytes.

3. It helps in removal of the webs formed between the fingers in fetal life.
4. It helps in regression of duct systems in the course of sexual development in fetus.
5. In adult females, it participates in the cyclic break down of the endometrium that leads to menstruation.
6. It is responsible for the death of enterocytes sloughed off the tips of the intestinal villi.

The abnormal apoptosis probably occurs in autoimmune diseases, neurodegenerative diseases and the cancer.

DEOXYRIBONUCLEIC ACID (DNA)

DNA is found in bacteria, nuclei of eukaryotic cells and mitochondria. It is made up of two long nucleotide chains, which are bound together by hydrogen bonds (between their bases) in such a way that they produce a **helical** shape. The helical shape is supported by a central histone core. Both the chains are composed of phosphoric acid, deoxyribose sugar and nitrogenous purine and pyrimidine bases – adenine (A), guanine (G), thymine (T) and cytosine (C). It is estimated that each DNA molecule has 3×10^9 pairs of the bases. The width of each helix is 2.0 nm and the length is 3.4 nm whereas the total length of each DNA molecule is about 2.0 meter. Each chromosome contains a segment of the DNA double helix. The sequence of purine and pyrimidine bases in a chain encodes the **genetic messages**. DNA is a component of chromosomes that *carry the genetic message – the blue print for all the heritable characters of the cell.* A **gene** is the amount of information necessary to specify a single protein molecule. There are 50 thousand to one lac genes in the 3 billion base pairs that make up the human genome. The protein coding genes (called as **exons**) contribute 3% in the human genome whereas the remaining 97% is junk DNA (called as **introns**). The characteristic of human DNA (in structure) is variable from individual to individual.

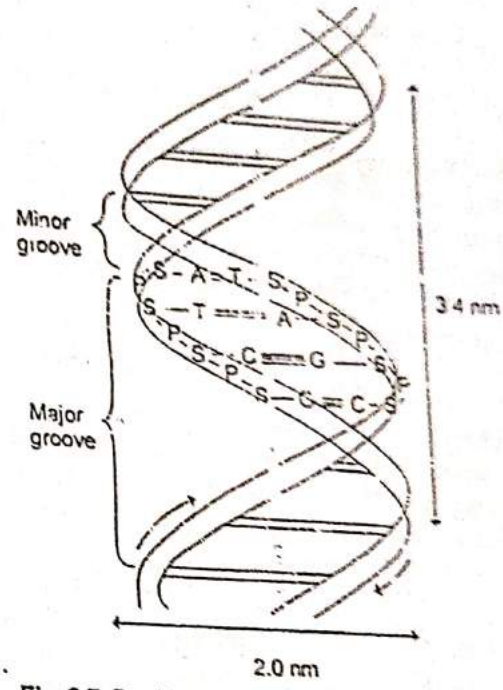

Fig. 2.7: Double helical structure of DNA molecule.

RIBONUCLEIC ACID (RNA)

It is a cytoplasmic structure, made up of a single chain (like DNA) with one different base – Adenine, Guanine, Uracil and Cytosine. Moreover, it is composed of sugar moiety ribose instead of 2'-deoxyribose.

BIOCHEMICAL PHYSIOLOGY

The compounds are acids, bases or salts.

An **acid** is a substance which provides hydrogen ions, whereas a base is a substance which accepts hydrogen ions.

1. The electrolytes which always exist in ionic form (even in solid state) are known as **strong electrolytes** e.g., sodium chloride (NaCl), sodium bicarbonate (Na_2HCO_3).
2. The electrolytes which get dissociated completely into ions when they are present

in a solution, are known as true electrolytes e.g., hydrochloric acid (HCl).

3. The electrolytes which partially dissociate into ions when they are present in a solution (so their solution contains their undissociated molecules too) are known as weak electrolytes e.g., carbonic acid (H_2CO_3).

Glucose and urea are non-electrolytes or unionized molecules.

Based on electrolysis, the ions are divided into two groups:

1. The positively charged ions are called as cations and
2. The negatively charged ions are called as anions.

The ions and the undissociated molecules of a compound in a solution, together exert a pressure to retain its water content. This pressure is called as osmotic pressure. Thus, the osmotic pressure of a solution depends upon the number of ions and undissociated number of molecules (not on their size and weight). The concentration of osmotically significant particles is expressed as osmolarity. The concentration of osmotically active particles is termed as osmole.

Osmolarity

It is the number of osmoles per liter of solution. The volume of the various solutes in the solution and temperature affect it.

Osmolality

It is the number of osmoles per kilogram of the solvent. The volume and the temperature do not affect it.

The total plasma osmolal concentration is 280-295 mOsm/kg of water.

The total CSF osmolal concentration is 289.0 ± 1 mOsm/kg of water.

One osmole equals the gram molecular weight of a substance divided by the number of freely moving particles that each molecule liberates in the solution e.g.,

One mole NaCl = 1 osmole Na^+ + 1 osmole Cl^-
One mole Na_2SO_4 = 2 osmole Na^+ + 1 osmole SO_4^{--}

Thus each mole of NaCl in solution would supply 2 osmoles while each mole of Na_2SO_4 ($Na^+ + Na^+ + SO_4^{--}$) supplies 3 osmoles.

If a solute is a nonionizing compound (e.g., glucose, urea), the number of its molecules will determine the osmotic pressure. *Plasma is not an ideal solution* because the ionic interactions reduce the number of particles free to exert an osmotic affect.

A mole is the gram molecular weight of a substance i.e., the molecular weight of the substance in grams.

Each mole/mol consists of approximately 6×10^{23} molecules. The mole is the standard unit for expressing the quantity of substance in Systeme International (SI) units.

pH

In pure water, the number of H^+ ions is equal to the number of OH^- ions. In the pure water, at 23°C the concentrations of H^+ ions is 10^{-7} Eq/L of water (the equivalent weight of H^+ is 1, so there is 10^{-7} g hydrogen ions per liter of pure water) hence is the concentration of the OH^- ions.

A solution containing equal number of H^+ and OH^- ions is called as neutral solution (in respect with water) and is expressed as pH = 7. The letter 'p' signifies that the negative logarithm to base 10 of the quantity is employed instead of the quantity itself.

An increase in H^+ ion concentration or a decrease in OH^- ion concentration in a solution makes it acidic whereas reverse of it makes it alkaline. (Details are given in excretory system).

TRANSPORT OF IONS/MOLECULES ACROSS THE CELL MEMBRANE

The cell membrane is made up of a lipid bilayer which is studded with large number of protein

molecules. Many protein molecules penetrate all the way through the membrane. The lipid bilayer is not miscible with ECF and ICF so behaves as barrier for water and water-soluble substances. To maintain body homeostasis movement of most ions across the membrane is essential. The lipid soluble substances e.g., oxygen, carbon dioxide, nitrogen and alcohol easily move out and in through the membrane by diffusion method. The water and water soluble substances move in and out through the protein molecules in following ways:

a. Active transport.
b. Passive transport.

Active Transport

It's a process for transport of molecules and ions 'uphill' against a concentration, pressure and/or electrical gradient. Hence some energy is spent in this process e.g., ions of sodium, potassium, calcium, iron, hydrogen, chloride, iodide, urate, several different sugars and most of amino acids.

There are two mechanisms for active transport:

1. Primary active transport: In this mechanism energy is derived directly from adenosine triphosphate (ATP) or some other high energy phosphate compounds. Its examples are sodium-potassium pump, calcium and hydrogen ions.
2. Secondary active transport: In this mechanism energy is derived secondarily from energy that has been stored in the form of ionic concentration differences on two sides of the membrane e.g.

a. When sodium ions are actively transported out of cells, its large concentration outside the cells (in ECF) represents a storehouse of energy because sodium ions always attempt to diffuse inside the cell membrane. This nature of sodium ion pulls other substances along with sodium – *cotransport*. It's examples are glucose and amino acids.
b. The above described mechanism with sodium, when occurs inside (in ICF) a cell to transport out sodium ion along with other ions, it is called as *counter-transport* e.g., calcium and hydrogen ions.

Passive Transport

It's a process for transport of molecules and ions as per concentration, pressure and/or electrical gradients. Hence no energy is spent in this process e.g., water and water soluble substances through the protein molecules studded in the lipid bilayer of the cell membrane.

Diffusion

It's the random molecular movement of substances molecule by molecule/is the continual movement of molecules in liquids or gases. Generally, it's process to equilibrate concentration of ions and molecules on two sides of the membrane.

It is based on the basic property of soluble molecules in liquids and gases. In molecular state elements are in constant are in constant motion due to generating heat in themselves. Each molecule moves its own way without any particular fashion – zigzag movement. They collide with each other innumerable time. In each collision they either loose or gain heat. It is known as *Brownian movement*. Their movement stops only at absolute zero temperature and their speed enhances with the rise in temperature of liquid or gas. It is divided into:

a. Simple diffusion.
b. Facilitated diffusion.

Simple Diffusion

In this mechanism the molecular kinetic movement of molecules or ions occur through a membrane opening or through intermolecular spaces.

The rate of diffusion depends upon:

a. Amount of substance available for diffusion.
b. The velocity of kinetic motion.

c. The number and sizes of openings in the cell membrane.

The diameter of protein channels varies from 0.12 to 0.8 nm. The passage of substance through these channels depends on three factors:

1. The diameter of the channel.
2. The shape of the protein channel (rounded, oval, square, pentagonal, and hexagonal).
3. The nature of protein molecule's electrical charge along with its inside surfaces.

Most of the protein channels have two common characteristics:

- Most channels are selectively permeable to certain ions & molecules.
- The channels can be opened or closed by gates (molecular conformation) e.g., sodium and potassium.

The protein channels are three types:

1. Simple aqueous ion channels e.g., aquaporins for water molecules that remain open all the time.
2. Gated protein channels are with gate that can be opened or closed. They are of three types:
   a. **Voltage-gated protein channels** where the opening and closing of gate is potential voltage dependent e.g., channels for sodium and potassium ions.
   b. **Ligand-gated protein channels** where a specialized substance in ECF or ICF alternates the opening and closing of the channels.

   External ligands are neurohormones and hormones.

   Internal ligands are intracellular calcium ions, cAMP, lipids and G-protein.
   c. **Mechano-sensitive protein channels** which respond to mechanical stretch. These channels play an important role in cell movement.

Facilitated Diffusion

In this mechanism there is an interaction between a carrier protein and the molecule/ion which is to be transported through the channel. This carrier protein binds chemically to shuttle them through the channel e.g., the carrier molecule for glucose is of 45,000 molecular weight (nature is till not known). Most of the amino acids are also transported through this mechanism. The substances are moved in the direction of their chemical and electrical gradients and no energy input is required.

These transport protein channels are of three types:

a. **Uniports:** They transport one specific substance only.
b. **Symports:** Proteins which require binding of more than one substance and the substances are transported across the membrane together e.g., in intestine sodium

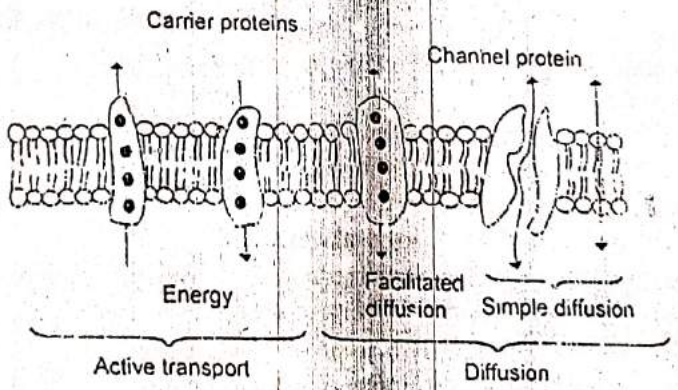

Fig. 2.8: Transport pathways through cell membrane and basic mechanisms of transport.

and glucose molecules get bind with a single protein.

c. **Antiports:** Proteins which exchange one substance for another substance e.g., sodium-potassium ATPase moves three sodium ion out of the cell in exchange for two potassium ions into the cell.

Channelopathies

These are diseases related to disorders of ion channels. These mostly affect the skeletal muscles and brain tissue to produce episodic paralyses or convulsions.

Osmosis

Water moves freely across the cell membrane without changing its concentration either in ECF or ICF. Under certain conditions when water creates a concentration difference in ECF and ICF cause the cell to shrink or swell respectively. These two conditions are called as *ex-osmosis* and *end-osmosis* respectively. These conditions are possible only when the cell membrane is *semi-permeable* i.e., the membrane is allowing permeation of water molecules freely on one side only while the water soluble ions are of much greater size so are unable to move along water molecules or no water soluble ions are present on one side.

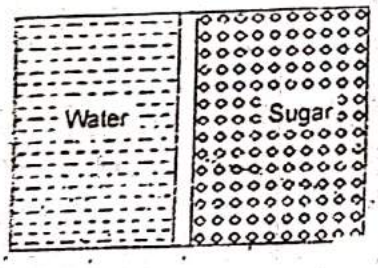

Fig. 2.9: End-osmosis.

When an appropriate pressure is applied in ICF, the movement of water in ICF stops. The amount of pressure that exactly stops water movement is known as osmotic pressure of non-diffusible substance. The osmotic pressure is always exerted by particles present in a solution, and is determined by the number of particles per unit volume of fluid (not by the mass of particles). The osmotic pressure is expressed in terms of osmole.

1 osmole is 1 gram molecular weight of undissociated solute.

Filtration

The ions move across the fenestrated membrane along the hydrostatic pressure gradient e.g., formation of CSF and glomerular filtrate.

Exocytosis and Endocytosis

A solid particle at the surface of the membrane grooves in or out to form a vesicle, which is taken in (endocytosis) or thrown out (exocytosis) of the cell.

Pinocytosis

A similar process to that in exo- & endocytosis but difference is that instead of a solid particle this process takes place with a fluid material.

Phagocytosis

Phagocytosis ('cell eating') is the process by which bacteria, dead tissue or other bits of material are engulfed by cells such as polymorphonuclear leukocytes of the blood. The material makes contact with the cell membrane, which then invaginates. The invagination is pinched off, leaving the engulfed material in the membrane enclosed vacuole and the cell membrane intact.

Transcytosis

Also called **vesicular transport**. It is seen in endothelial cells of capillaries and makes use of coated vesicles. Small amounts of protein are transported out of capillaries across endothelial cells by endocytosis followed by exocytosis on the interstitial side of the cells.

TISSUE

When many similar cells at a site function in a composite manner, collectively they are known as **tissue**.

There are five widely distributed basic tissues which are built up, in varying proportions, to form the organs within the body. They are epithelial, connective, skeletal or sclerous, muscular and nervous.

Epithelial Tissue

It covers the surfaces of the body:

1. The external surface of skin.
2. The internal surface of GIT, respiratory system, urogenital system, closed serous cavities, vessels, acini and ducts of all secreting glands, cavities of brain, heart and the central canal of the spinal cord.

Functions

Primarily protection and/or secretion. The epithelium covering the intestinal villi, has ability to absorb the intestinal contents too. The epithelium, in serous cavities, provides a smooth moist surface.

Types of Epithelial Tissue

1. Simple: It is of the following types:
   a. *Pavement*: Flattened cells of variable shapes and size, present in the alveoli of lungs.

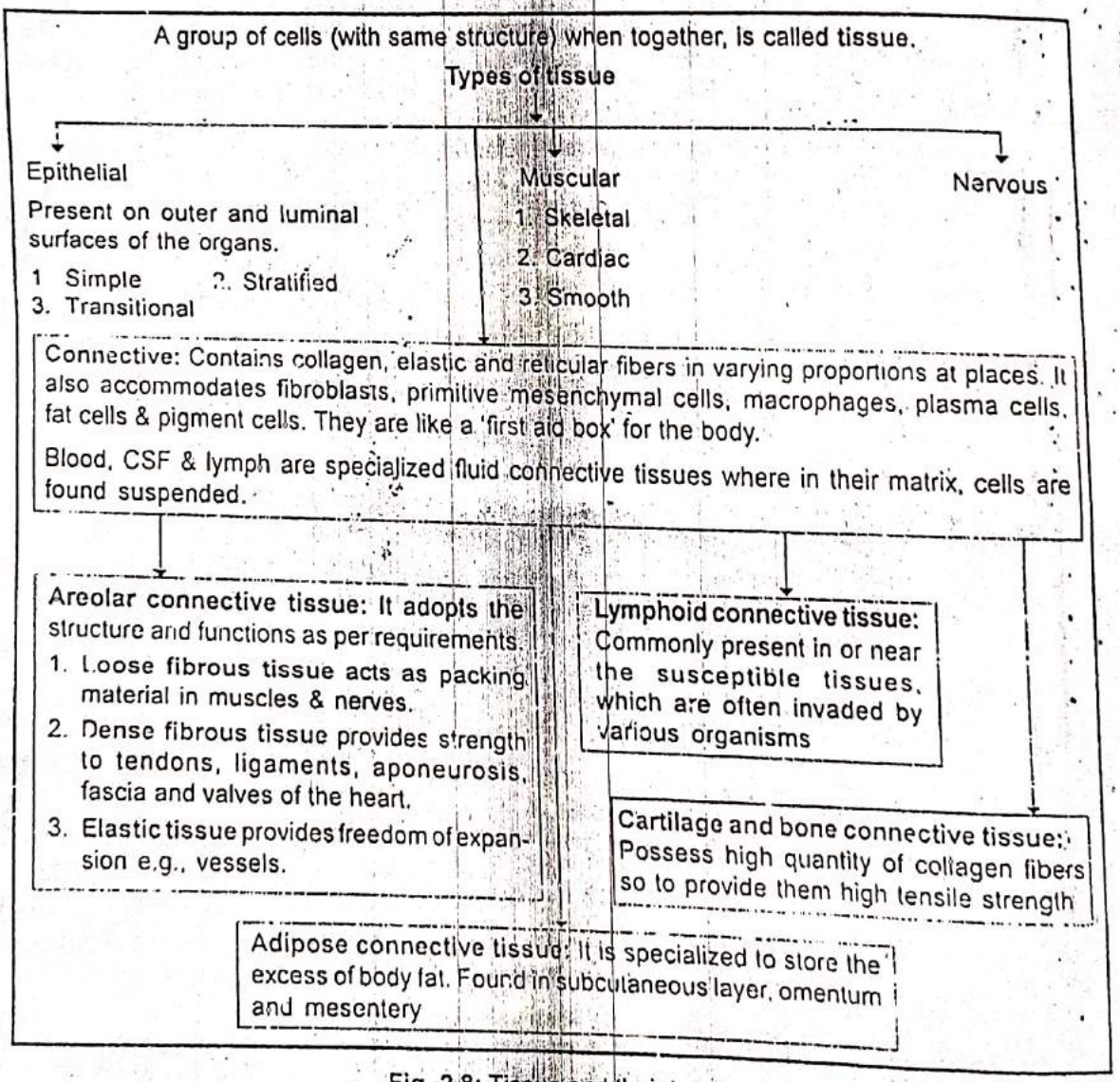

Fig. 2.8: Tissue and their types.

serous membranes, heart cavities, blood and lymphatic vessels.

b. *Columnar*: Cylindrical or rod shaped of secretory nature, present in GIT including the related glands, part of male urethra, vas deferens, renal tubules, prostatic ducts, bulbo-urethral glands, greater vestibular glands and in modified form in ovaries.

c. *Ciliated*: Columnar in shape, present along the respiratory tract up to the respiratory bronchiole (except lower part of pharynx and vocal cord), tympanic cavities, auditory tube, uterine tube, efferent ductules of testes, lobules of epididymis, ventricles of brain, central canal of spinal cord (ependyma).

2. **Stratified:** Several layers of cells arranged one over the other, present in epidermis, part of male urethra and esophagus. Primary function is protection.

3. **Transitional:** Several layers with three distinct varieties of cells, present in ureter and urinary bladder. They provide changeable accommodation.

Connective Tissue

The term 'connective' is misnomer. It does not mean that it connects two cells rather it stands for 'binding'. It consists of cells embedded in matrix, the cytoplasm may or may not contain the fibres.

Common Cells Types

1. **Fibroblasts**, which form fibers in the connective tissue.
2. **Histiocytes** form a group of phagocytic cells of reticulo-endothelial system.
3. **Plasma cells**, uncommon in healthy tissue, numerous in connective tissues present in mucosa and submucosa of the gut and the omentum.
4. **Mast cells**, found mainly in loose connective tissue and in fibrous capsules of organs and around the vessels.
5. **Reticular cells**, are found in the reticular connective tissues for the formation of reticular fibers. These cells are of heterogenous nature i.e., regarded as embryonic cells which give rise to the stem cells for the development of blood cells. They have fibrocytic and phagocytic alliances.
6. **Fat cells**, numerous in the adipose tissues and chiefly meant for the storage.
7. **Pigmented cells**, present in the corium of the skin, iris and choroid of eyes.

Matrix

It is amorphous, viscous, semifluid substance which occupies the intervals between the connective cells and fibers. It contains water, mucopolysaccharide (hyaluronic acid), hyaluronan sulphate, chondroitin sulphate, glycoproteins and a little albumin and globulin.

Functions: The **mucopolysaccharide** forms hydrated gel.

The **matrix** protects and binds together the elements of the connective tissue. It provides medium for the movement of cells and diffusion of metabolites between the cells and the vascular system. It is an important site for the water storage. The matrix amount decreases with age.

Fibers

They are of three types:

a. Collagen or white,
b. Elastic or yellow and
c. Reticular.

The **collagen fibers** are composed of the protein collagen which is characterized by the presence of hydroxyproline (present only in collagen and elastin). The fibers are present in bundles to provide support and repair. It is maximally present in white fibrous tissue, tendons, aponeurosis, ligaments, articular capsules, deep fascia, bones and cartilages.

The **elastic fibers** have property of strength, extensibility and elastic recoil activity.

The **reticular fibers** are maximally present in reticular tissue and are believed to be immature collagen fibers.

Types of Connective Tissue

1. **Areolar connective tissue:** It is utilized as the packing material in the body so to provide strength to the body organs/ structures. Maximally present in skeletal muscle, nerves, ligaments and valves.
2. **Elastic areolar tissue:** It contains elastin more so the organ can expand on need e.g., vessels and bladders.
3. **Fatty connective tissue:** It is the store house of fat and are maximally present under the skin and in omentum.
4. **Lymphoid connective tissue:** It is seat of body defense so are maximally found at sites which are vulnerable to foreign attacks e.g., the digestive and the respiratory systems.
5. **Fluid connective tissue:** Blood, lymph and cerebrospinal fluid.

THE BONES AND CARTILAGES

At the time of birth in newborn baby the skeleton contains 50% cartilage and 50% bone. At and after age of 2 years the skeleton contains 65% bone and 35% cartilage.

Functions of Skeleton

1. **Protective:** It provides framework for the body and protects soft tissues and the vital organs.
2. **Mechanical:** It supports the body to assume various postures. It provides attachment to the related muscles and tendons so that the bones behave as levers.
3. **Metabolic:** It participates in tissue metabolism and helps in body's homeostasis for calcium and phosphate balance.
4. **Hematopoietic:** It produces the cell components for the blood.

Classification of Bones

The bones present in the human body are classified on the basis of their size and shape.

1. The long bones e.g., the bones of the l
2. The short bones e.g., the bones of the and ankle.
3. The flat bones e.g., the bones of the mandible and scapula.
4. The irregular bones e.g., the bones vertebral column.
5. The sesamoid bones: These bones more or less rounded nodules of b embedded in certain tendons and us related to articular surfaces. They m pressure, diminish friction and occasion alter the direction of the pull of a mu e.g., patella embedded in the tendon o quadriceps femoris. Two each are pre on the palmar and plantar aspects of hand and foot.

Composition of Bone

The bone is a living tissue with follov properties:

a. Support and protection to soft tissues
b. They are light and strong.
c. They can grow and remodel themselv withstand normal or new stresses.
d. They are the store house for calcium phosphorus.

They are composed of water (9% of total body water) and solids.

Among the solids (dried cortical bone)

- Organic substances (25%).
- Inorganic substances (75%).

Bone contains calcium 99% of the total calcium, phosphorus 88%, magnesium sodium 35%, carbonate 20% of the total contents.

Among the organic substances it con collagen (90-95%) and the ground substa (5-10%) - glycosaminoglycans, glycoprot lipids and peptides.

The bone is composed of a tough or matrix (greatly strengthened by deposi

calcium salts). The compact bone contains matrix 30% and salts 70%.

Bone Salts

The crystalline salts deposited in the organic matrix of bone are composed principally of calcium and phosphorus [Hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$]. Each crystal is 400 Angstrom long, 10-30 Angstrom thick, 100 Angstrom wide and is shaped like a long, flat plate.

The collagen fibers of compact bone are composed of repeating periodic segments every 640 Angstrom along its length. Hydroxyapatite crystals lie adjacent to each segment of fiber bound tightly to it. This intimate bonding prevents 'shear' in the bone i.e., prevents the crystals and collagen fibers from slipping out of place. The collagen fibers of bone, like those of tendons, have great tensile strength, whereas, the calcium salts have great compressional strength.

Bone Cells

The bone cells are of three types and all are derived embryologically, from the primitive mesenchymal reticulum.

Osteoblasts

These cells are concerned with the bone formation and are situated on the outer surface of the bone, the marrow cavity and the epiphyseal plate. These cells arise from the giant multinucleated primitive cells called as osteoprogenitor cells. The conversion of osteoprogenitor cells into the osteoblast cells is accelerated by GH, calcitonin, insulin, testosterone, estrogens and skeletal growth factor whereas is inhibited by cortisol. Their functions are:

1. It has a role in the formation of the bone matrix. They synthesize the bone matrix by secreting type I collagen and a protein called matrix Gla protein (MGP) or osteocalcin. The other proteins involved in the matrix are also produced by the osteoblasts.
2. It has a role in the calcification of bones. The osteoblasts are rich in the enzyme alkaline phosphatase, necessary for the deposition of calcium into the bone matrix. The proteins (Gla protein & osteopontin), which are involved in the calcification, are also produced by the osteoblasts.

After taking part in the process of bone formation, the osteoblasts differentiate into the osteocytes which are trapped inside the lacunae of the calcified bone.

Osteocytes

These are the small, flattened and round cells, which are found embedded into the bone lacunae. Their cytoplasmic processes run into the canaliculi, which contact with others forming the tight junctions. Their functions are:

a. They help to maintain the bone as living tissue as they carry the metabolic activities.
b. Osteocytes maintain the exchange of calcium between the bone and the ECF.

Osteoclasts

These are the giant multinucleated cells present in the lacunae of the bone matrix. They are derived from the hematopoietic stem cells via monocytes. They are responsible for the bone reabsorption during the bone remodeling, for which the lysosomal enzymes are synthesized and released by them.

The entire process of remodeling extends for 100 days in the compact bones whereas, 200 days in the trabecular bone.

Parts and Structure of Bone

In a typical long bone there are three parts:

1. The diaphysis, the mid shaft.
2. The epiphysis, both the ends of the bone.
3. The metaphysis, area between the diaphysis and the epiphysis (spongy bone).

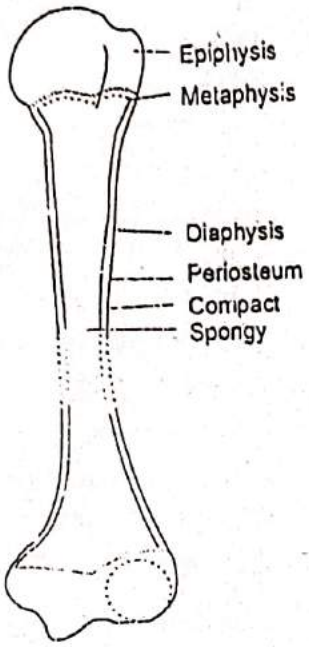

Fig. 2.11: Anterior view of humerus.

The bone is covered by a white fibrous connective tissue layer called periosteum and an inner dense fibrous membrane called endosteum. The muscle, tendons are attached to the periosteum. The heads of bone (epiphysis) are covered by a hyaline cartilage, which forms synovial joint with the adjoining bone.

Longitudinally, bone has two layers:

1. The outer compact bone and
2. The inner spongy bone.

The thickness of these two layers varies from bone to bone.

The epiphysis contains large amount of spongy bone and a thin outer compact bone. In the diaphysis, the compact bone is more than the spongy bone layer.

Compact Bone

It is hard, dense and forms 80% of the bone in the body. Within it, there is a cavity called as the medullary cavity, which contains yellow bone marrow. The compact bone consists of minute cylindrical structures called as osteons of Haversian system formed by the concentric layers of collagen.

There is a canal in its centre, Haversian canal, which contains the blood and lymph vessels and the nerve fibers. The canals communicate with each other by transverse canals called as Volkmann's canal (Fig.2.12). Within the Haversian system, there are small cavities, called as lacunae, inside which the osteocytes are trapped. The osteocytes send long processes called canaliculi to communicate with other canaliculi with tight junctions.

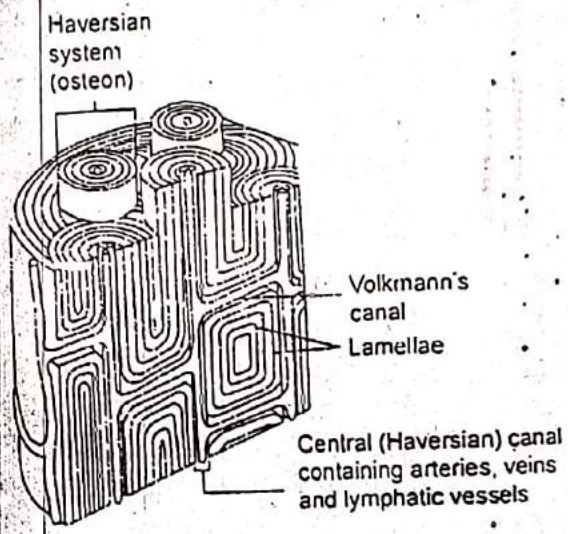

Fig. 2.12: Microscopic structure of compact bone.

Spongy Bone

It is also known as trabecular or cancellous bone, forms 20% of the bone in the body. It is made up of bone spicules which are separated by spaces. It contains the red bone marrow.

Marrow Cavity

The compact bone has a large narrow cavity called the marrow cavity or **medullary cavity**, which contains yellow bone marrow.

General Properties

In a fresh bone, its outer surface is pinkish-white and when it is broken its inner part appears dark red colored. As compared to other tissues of the body, bones are hard with a mild elasticity. As compared to an adult bone, the bone of a child is more elastic. This elastic property of the bones provides them their stress (weight)

bearing capacity. The maximum bearing capacity of a bone is known as the break point of the bone e.g., the longitudinal compression capacity of clavicle is 192 kg, humerus 600 kg and femur 756 kg. The bones have an exclusive property of remodeling throughout the human life. Moreover, they have a compensatory property too i.e., when due to some reasons tibia bone of the leg is removed the weak appearing fibula increases in weight and diameter to compensate for the tibia.

Total number of bones in an adult human body is 206 bones.

Axial skeleton	*Number*
Skull (8 paired and 5 unpaired)	21
Ossicles of both ears	06
Lower jaw – mandible	01
Neck-hyoid	01
Vertebral column:	
Cervical: 7	
Thoracic: 12	26
Lumbar: 5	
Sacral: 1 (5 fused bones)	
Coccyx: 1 (4 or 5 fused bones)	
Chest	
Sternum	01
Ribs (12 pairs)	24
Total	80

Appendicular skeleton	*Number*
Upper Limb (paired)	10
Scapula	
Clavicle	
Upper arm – humerus	
Lower arm – radius and ulna	
Wrist – carpal (8)	16
Hand – metacarpal (5)	10
Fingers – phalanges (14)	28
Lower limb (paired)	10
Pelvis	
Thigh – femur	
Knee – patella	
Leg – tibia, fibula	
Ankle – tarsal (7)	14
Foot – metatarsal (5)	10
Toes – phalanges (14)	28
Total	126

CARTILAGE

The organization and functions of cartilage are more or less similar to that of the bones but the cartilages have no inorganic salts. The cartilage contains chondrocytes found embedded in a matrix of collagen and proteoglycan (glycosaminoglycans – chondroitin-4-sulphate, chondroitin-6-sulphate and keratan sulphate in variable proportions).

The cartilages are of three types:

1. **Hyaline cartilage:** They contain water 75%, collagen 25-70% and glycosaminoglycans 14-40%. They are vascular but without lymphatic and nerve fibers. They are present at the articular ends of the long bones, at the anterior end of the ribs, the external auditory meatus, larynx, trachea and the bronchial tree.
2. **Fibrocartilage:** They contain collagen fibers maximally with glycosaminoglycans 2%. It is present at the sites where great tensile strength with flexibility and rigidity are required e.g., intervertebral discs, knee joint, mandibular joint and pubic symphysis.
3. **Elastic cartilage:** They have elastin 20%, collagen 25%, glycosaminoglycans 14-40% and water e.g., external ear, part of larynx, epiglottis and eustachian tube.

JOINTS

A joint or articulation is formed where two or more bones meet one another. The function of a joint is an important factor in determination of its character and structures.

a. At a joint where a little or no movement is required, union is by the fibrous tissue and hence the joint is called a **fibrous joint.** They are of three types:

1. **Suture joints** e.g., joints between the bones of the cranium.
2. **Gomphoses** or peg and socket joint i.e., insertion of a conical process into a socket

e.g., articulation of the root of teeth with the alveoli of mandible and maxillae.

3. Syndesmosis is a joint in which the opposed bony surfaces are connected by an interosseous ligament e.g., tibio-fibular joint.

b. At a joint where no movement is required, union is by the cartilage and hence is called as **cartilaginous joint** e.g.,

1. **Primary cartilaginous joint** (temporary) replaced by bones between epiphysis and diaphysis of long bones, between the occipital and sphenoid bones.
2. **Secondary cartilaginous joint** where the bony ends are connected to each other by a flattened disc of fibrocartilage e.g., pubic symphysis, manubrium and body of sternum, joints between the vertebral bodies.

c. Synovial joints: At joints where a wider range of movement is necessary a cavity bounded by a fibrous articular capsule between the bones is formed. The contiguous (kissing) bony surfaces are covered with articular cartilage and are not attached to each other. There is a joint cavity containing a viscous fluid, **synovial fluid**. The **synovial membrane** (under the synovial capsule) has two types of cells.

1. Type A cells that are of phagocytic nature.
2. Type B cells that secrete fluid with hyaluronic acid.

The synovial fluid is straw colored viscous fluid which resembles with plasma except that it has a protein concentration 10-20 g/L. All the joints of long bones are the synovial joints e.g., shoulder joint, elbow joint, wrist joint, hip joint, knee joint and ankle joint.

Types of movements at synovial joints are extension, flexion, abduction, adduction and circumduction.

TEETH

Teeth with the help of tongue and jaw movements grind the food and the process is known as **mastication**. The powerful muscles of the jaw play a vital role to produce a force, mastication pressure to teeth. The occlusive pressure between the incisors is about 50 to 100 pounds and that between the molar teeth is 150 to 200 pounds. This much occlusive force is possible because of the projections and facets present in teeth, specially in molars and premolars. The projections and facets between the corresponding upper and lower teeth are present in such a way, that their surfaces fit over each other without leaving any potential space. This tight fitting is called as **occlusion**. (The occlusion property can be tested by placing a piece of paper between the upper and lower set of teeth and asking the person to clinch the same. It will not be easy for you to remove the paper with ease).

Dentition

The human beings develop two sets of teeth during their life time.

a. **Deciduous teeth:** 20 in number.

M_2, M_1, C, I_2, I_1	I_1, I_2, C, M_1, M_2
M_2, M_1, C, I_2, I_1	I_1, I_2, C, M_1, M_2

b. **Permanent teeth:** In general there are 32 teeth divided into four quadrants. Each quadrant is composed of a set of 8 teeth namely – incisors (2), canine (1), premolar (2) and molar (3).

$M_3, M_2, M_1, Pm_2, Pm_1, C, I_2, I_1$	$I_1, I_2, C, Pm_1, Pm_2, M_1, M_2, M_3$
$M_3, M_2, M_1, Pm_2, Pm_1, C, I_2, I_1$	$I_1, I_2, C, Pm_1, Pm_2, M_1, M_2, M_3$

The incisors are for cutting, canine for tearing and premolars and molars for grinding the food.

Development

Like skin, teeth are developed from ectoderm and mesoderm both. Its enamel part is derived from the ectoderm and rest of other parts are derived from the mesoderm. The formation of

...ous teeth starts by the 6th week of the ...terine life as a thickened ridge of ...m called primary dental lamina. Its ...surface is invaginated by a papilla of the ...m called as the dental papilla. The ... organ becomes moulded like a hood or ... The papilla assumes the shape of the ... crown of the tooth and gives rise to the ... and the dentine.

At the same time a solid ectodermal bud ... into the mesoderm. This bud is the ... organ of the permanent tooth. It is ...ated by a mesodermal dental papilla in ... manner as described with deciduous ...th.

...of Eruption

...duous teeth	Age in months
... incisor	6-8
... incisor	8-10
...	12-16
...	16-20
...	20-30
...anent teeth	Age in years
...	6-7
... incisor	6-8
... incisor	7-9
...	9-12
... premolars	9-12
...	11-13
...	17-21

...ucture of Teeth

...ooth consists of three parts:

- ...e crown, projecting beyond the gum.
- ...e root, embedded in the alveolus of ...illa or mandible.
- ...e neck, constricted part between the ...own and the root.

...the centre of all these parts of the tooth ... substance called the **pulp**. Outside the ... a yellow white layer known as **dentine**. ...forms the bulk of the tooth. Covering the ... in the crown region there is a white, hard layer of the **enamel**, while covering the dentine of the root is a thin layer, the cementum which resembles bone in structure. At the apex of the root there are number of foramina in the cementum and dentine, through which the blood vessels and the nerves pass into the pulp.

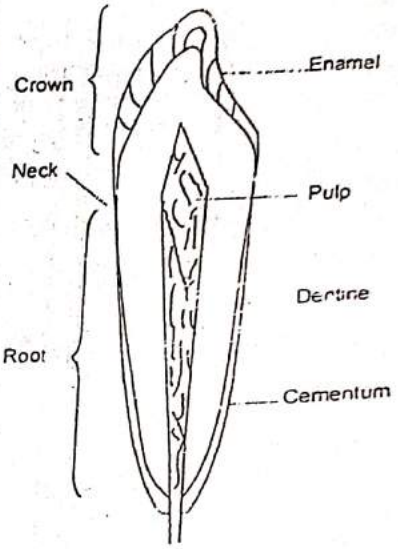

Fig. 2.13: Functional parts of a tooth.

Metabolism

The dentine is deposited and nourished by the **odontoblasts**, which line its inner surface along the wall of the pulp cavity. The calcium salts in dentine make it extremely resistant to compressional forces, the collagen fibers make it tough and resistant to tensional forces that might result when the teeth strike against a solid substance.

The rate of development and eruption of teeth is accelerated by thyroid and growth hormones. The deposition of salts is affected by vitamin D and parathyroid hormones.

The salts of teeth are same to that of the bones. They are composed of hydroxyapatite with carbonate and other cations so as to produce a hard crystalline substance. New salts are constantly being deposited and old salts get

reabsorbed. This deposition and reabsorption process take place mainly in the dentine and the cementum (least in enamel). This exchange of salts takes place with the pulp cavity while in enamel it is between the enamel and the saliva.

Role of Fluorine

In childhood, where the teeth are in process of development, fluorine ions replace many of the hydroxyl ions in the hydroxyapatite crystals that makes the enamel less soluble. It is also toxic to oral bacteria. When a small pit develops in a tooth, it has property to help the tooth in healing by promoting the deposition of calcium salts in the pit.

Dental Caries

The word caries is referred to erosion of tooth that occurs due to action of bacteria, *Streptococcus mutans*. In the process of caries development, a plaque of precipitated products of saliva and food is deposited on any surface of the tooth. The bacteria become inhabitant of the plaque living mainly on the availability of carbohydrates. Because of bacterial metabolism the bacteria release acids (lactic acid) and the proteolytic enzymes. The slowly developing high acidic medium starts dissolving the tooth salts while the rest of harm is done by the proteolytic enzyme.

Erasistratus (300-260 BC) postulated anatomy and physiology of heart, lung, blood vessels, GIT, spinal nerves, muscular contractions and hunger. He is crowned as 'The Father of Physiology'