

# BLOOD PHYSIOLOGY

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## ❖ Hematology:

- Is a scientific study of the structure and functions of blood in health & disease ( study the normal and abnormal morphology and physiology of blood).

## ❖ Blood:

- Is a highly specialized tissue, which along with the circulatory system is adapted to meet the needs of the body tissues and organ systems.
- Such as exchange of gases, provision of nutrients, and removal of waste products.

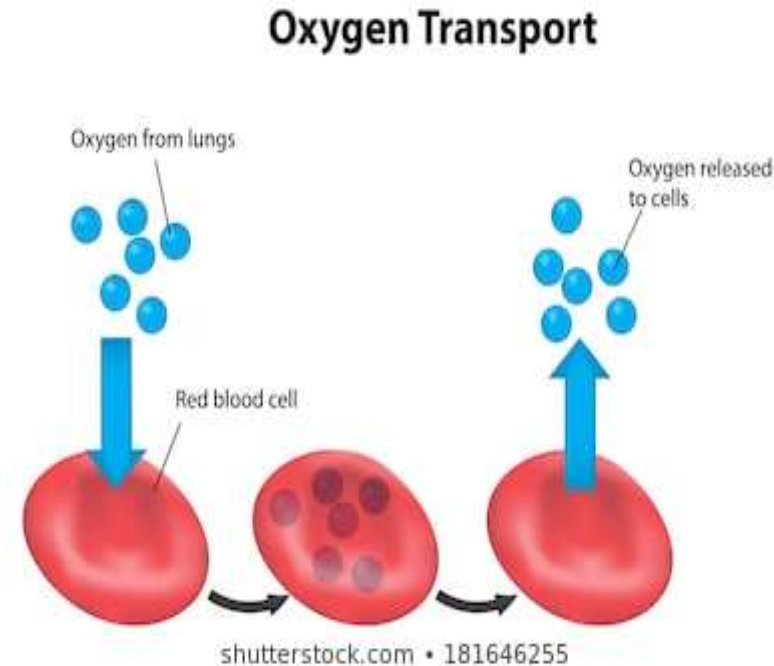
# ❖ General Functions of blood

## 1.Transportation:

- blood is the primary transport medium of the body.

- a.  $O_2$  enters the blood from the lungs and is carried to cells, and  $CO_2$  produced by cells is carried by the blood to the lungs from where it is expelled.

- b. The blood from the gastrointestinal tract to cells transports ingested nutrients; electrolytes & water, and waste products are transported from cells to kidneys for elimination in urine.



## 2.Maintenance:

blood plays a crucial role in maintaining homeostasis (constancy of internal environment).

a. many of the hormones and enzymes that regulate body processes, are found in blood which act as buffers which help keep the blood's PH within its normal limits of ( 7.35 – 7.45).

b. The osmotic composition of blood is also critical for maintaining the normal fluid & electrolyte balance.

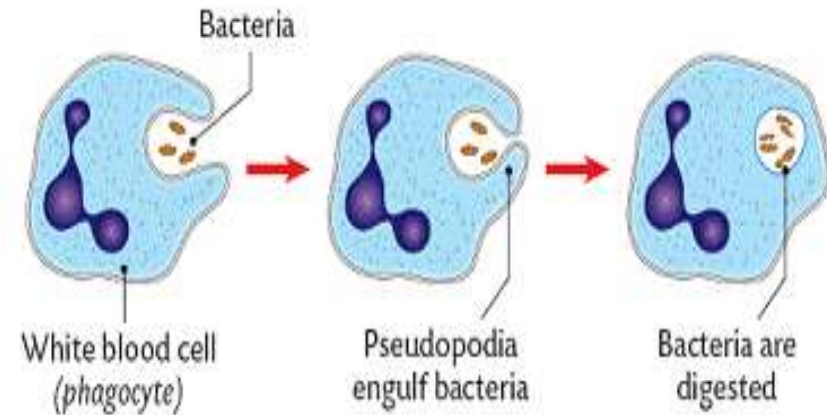
c. Temperature regulation: because blood can hold heat, it is involved with temperature regulation transporting heat from the interior to the surface of the body, where the heat is released.



### 3. Protection:

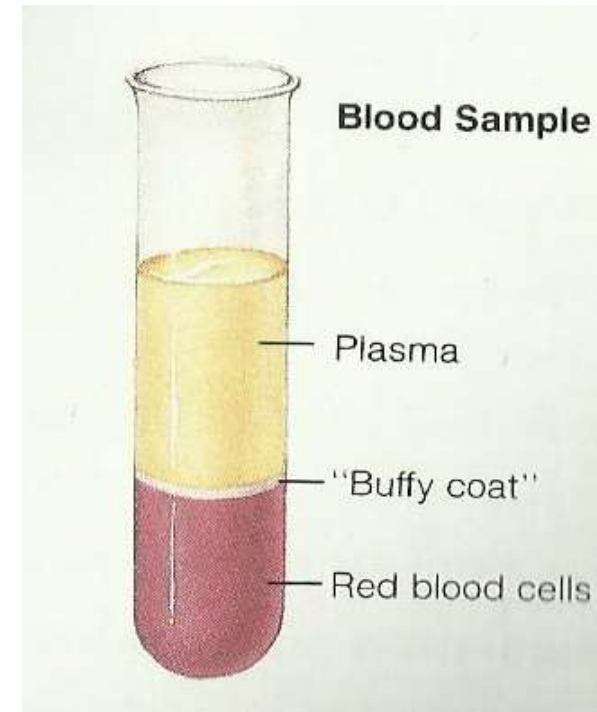
- protecting against foreign substances such as microorganisms and toxins.

- Blood clotting also provides protection against excessive fluid & cell loss when blood vessels are damaged.



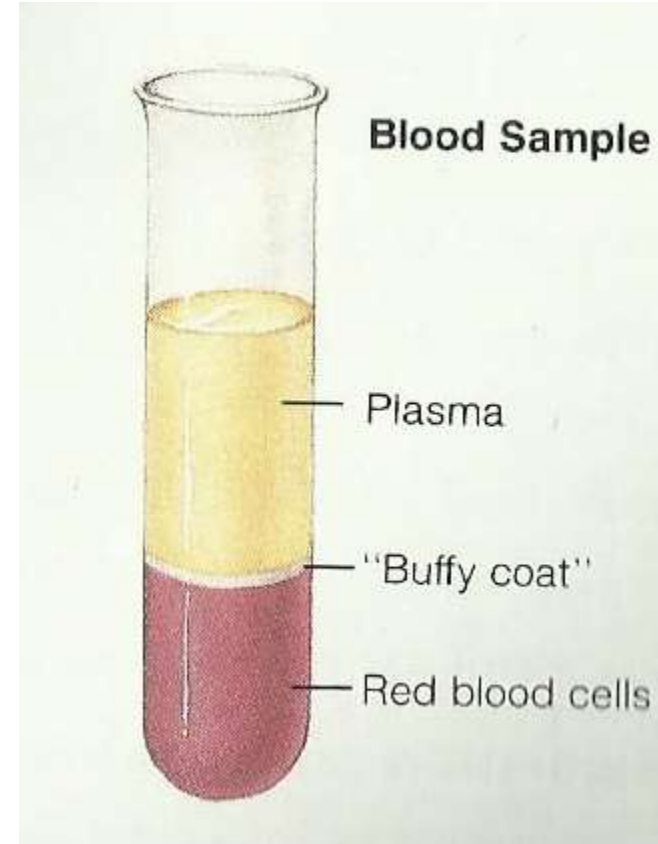
# ❖ Composition of Blood

- The normal total circulating blood volume is **8%** of the body weight of a **70 kg** man (i.e. 5600 ml).
- Blood is a type of connective tissue, consisting of:
  1. **Plasma: the fluid portion of blood.**
  2. **Blood cells: the solid portion of blood.**
    - a) **Specialized cells (erythrocytes and Leukocytes).**
    - b) **Cell fragments (platelets thrombocytes).**

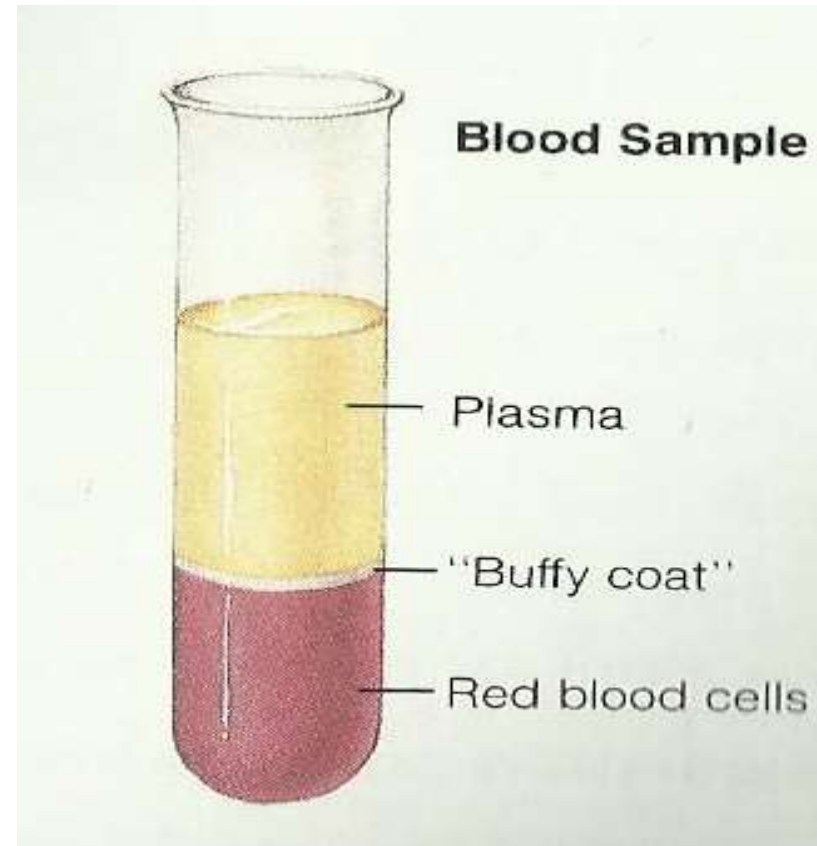


## ❖ PLASMA:

- Is a yellowish liquid component of blood that holds the blood cells of whole blood in suspension.
- It is the liquid part of the blood that carries cells and proteins throughout the body.
- The normal plasma volume is 55% of total blood volume.
- Plasma remains fluid only if an anticoagulant is added to the blood.



- Blood plasma is separated from the blood by spinning a tube of fresh blood containing an anticoagulant in a centrifuge until the blood cells fall to the bottom of the tube.
- The blood plasma is then poured or drawn off.



# ❖ Composition of Plasma

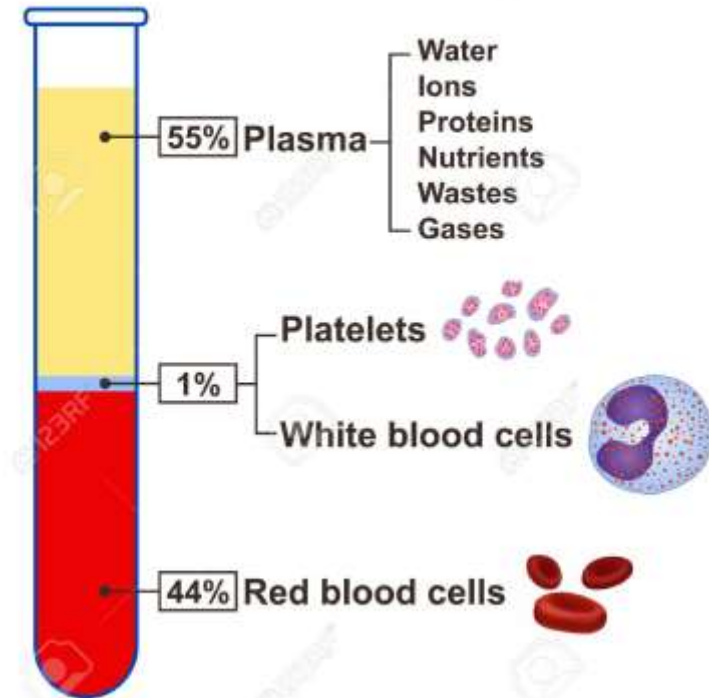
□ Plasma: is a pale yellow fluid that consists of:

1) 91% water: which acts as a solvent and suspending medium for blood component

2) 2% other solutes such as:

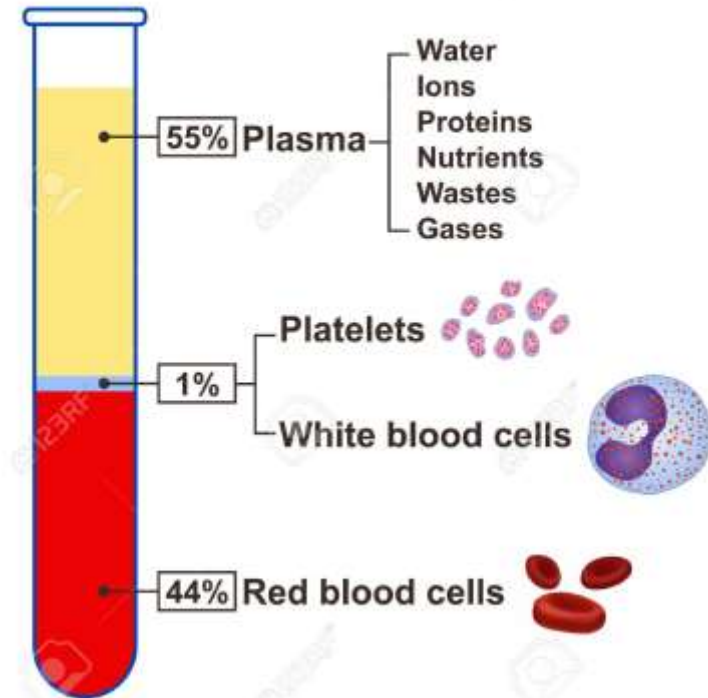
- Ions (involved in osmosis, membrane potential and acid-base balance).
- Nutrients (as a source of energy).
- Vitamins (promote enzyme activity).

## Components of Blood



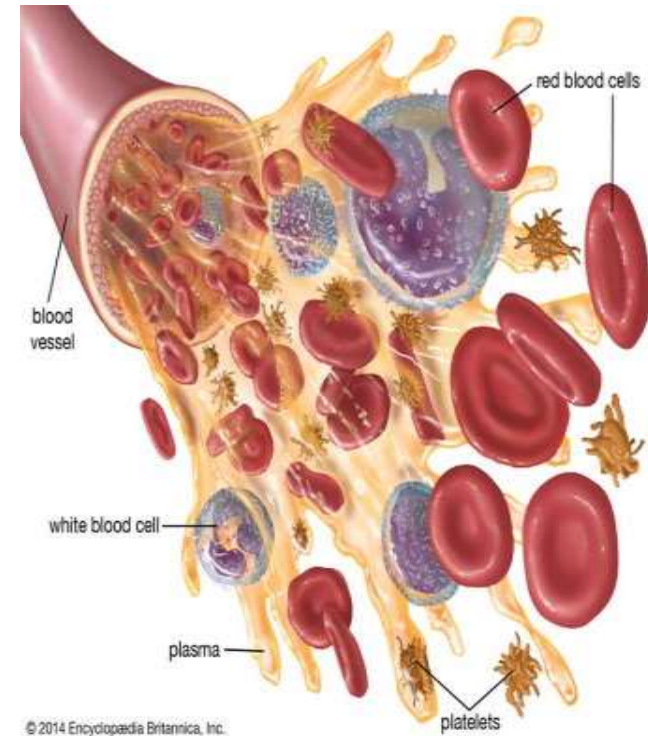
- Gases (such as  $O_2$  necessary for aerobic respiration, and  $CO_2$  waste product of aerobic respiration).
  - Regulatory substances (such as hormones).
  - Waste products (such as urea, uric acid, etc. which are excreted by the kidneys).
- 3) 7% plasma proteins: which include albumin, globulins, and fibrinogen.

## Components of Blood



# ❖ Plasma functions:

1. Transport medium for delivering nutrients to the cells of the various organs of the body.
2. Transporting waste products derived from cellular metabolism to the kidneys, liver, and lungs for excretion.
3. Transport system for blood cells.

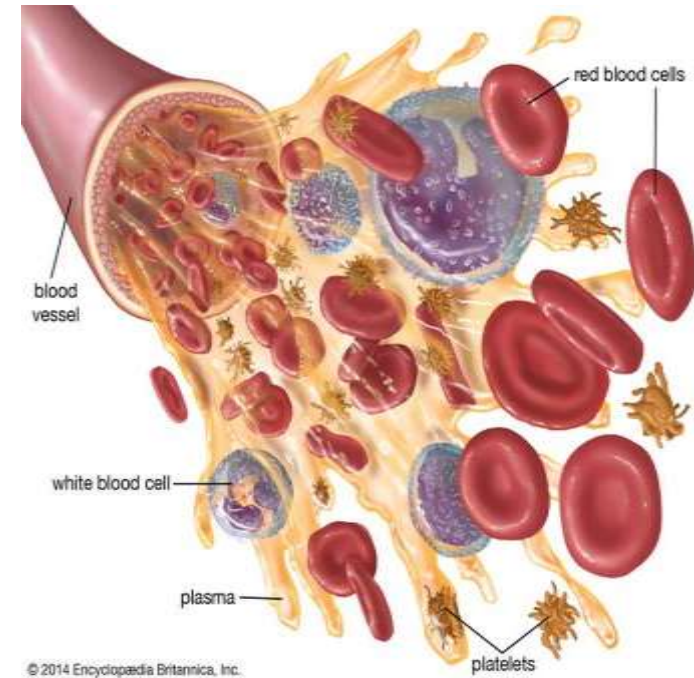




4. Maintaining normal blood pressure.

5. Distribute heat throughout the body.

6. Maintain **homeostasis**, or biological stability, including **acid-base balance** in the blood and body.



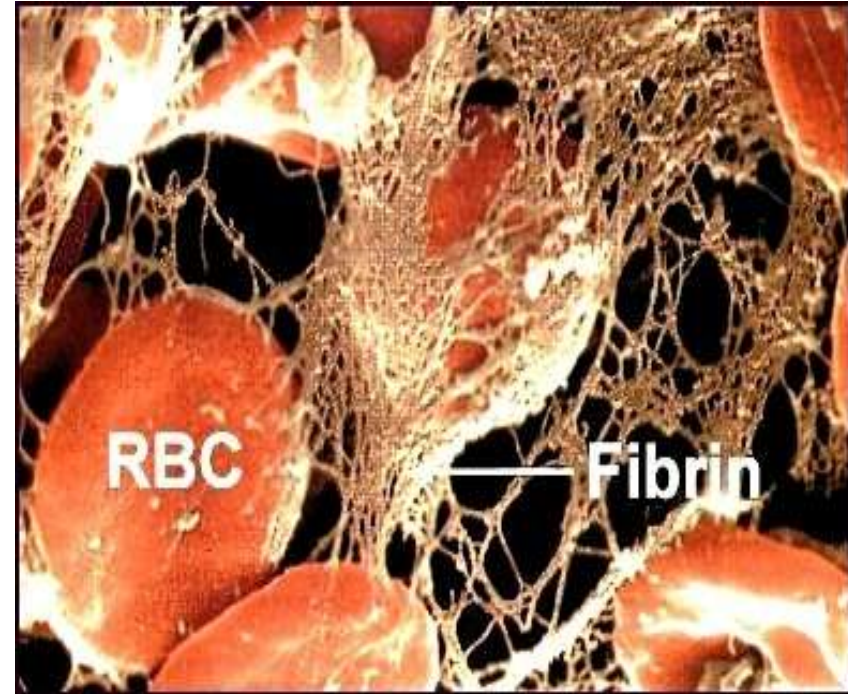


# ❖ Functions of plasma proteins

- Five major functions of plasma proteins.

1) Coagulation: fibrinogen is responsible for blood clots.

- There are plasma proteins known as fibrinolytic factors such as plasminogen, which prevent formation of spontaneous clots in the blood vessels.

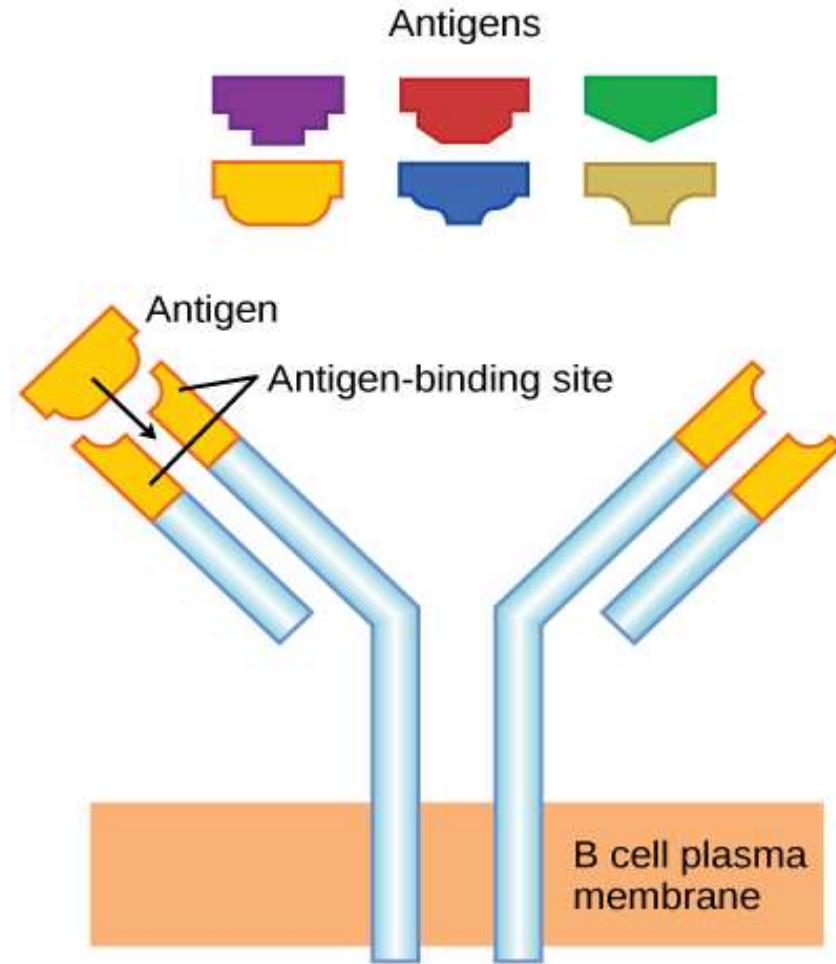


**2. Transport: many plasma proteins acts as carriers; such as; Albumin & globulins acts as carrier proteins.**

**3. Inflammation: Plasma also contains a number of proteins that play a major role in the production of inflammatory responses resulting from infection, allergy, or autoimmune disease. e.g.  $\beta$ - globulins.**

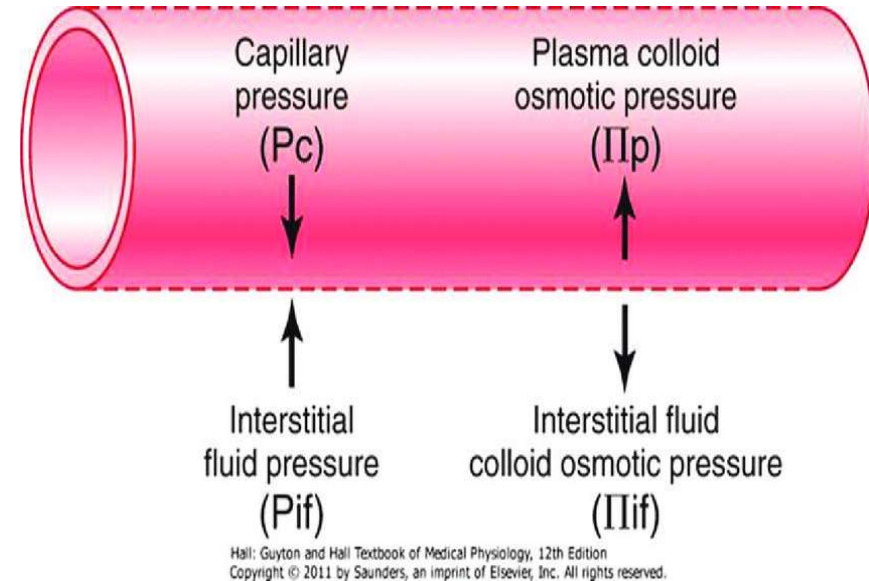
## 4. Immunity:

▪ Immunoglobulin's (IgA, IgD, IgE, IgG, and IgM.) or antibodies: Formed by  $\beta$  – lymphocytes & play a major role in the body's defense against invading pathogens.

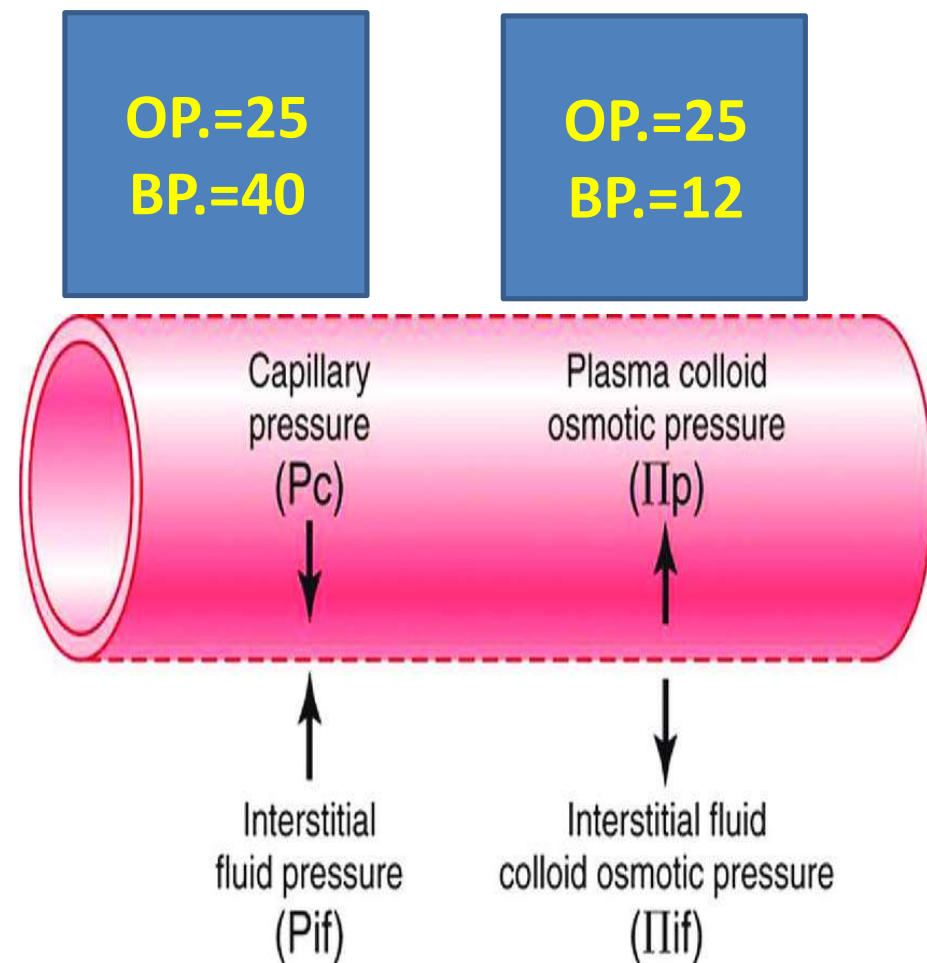


## 5) Transvascular exchange of water:

- This is mainly the function of albumins.
- The osmotic (oncotic) pressure of albumins maintains the delicate balance between the two fluid compartments.

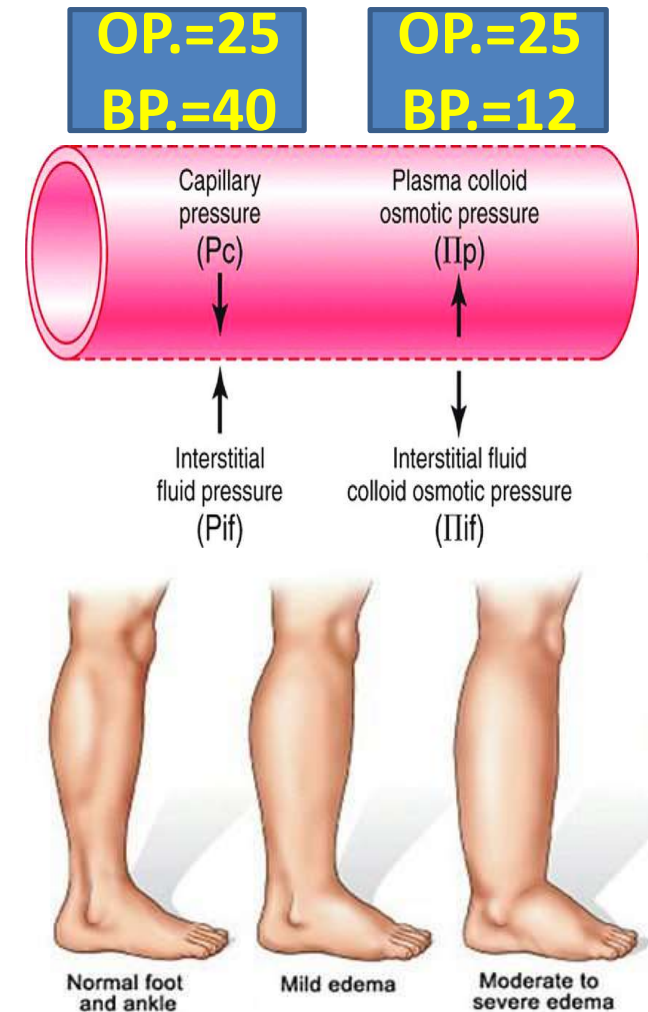


- About 60% of capillary oncotic pressure is due to plasma protein albumin, which is about 25 mmHg at arterial and venous ends of capillary and tends to cause osmosis of fluid inward through the capillary.
- Filtration is occurred at arterial end of capillary because capillary hydrostatic pressure, which is about 40 mmHg, exceeds the oncotic pressure, while at the venous end, reabsorption of water occurs because oncotic pressure exceeds capillary hydrostatic pressure, which is about 12 mmHg.



- If there is abnormal imbalance of forces at capillary wall, odema result.

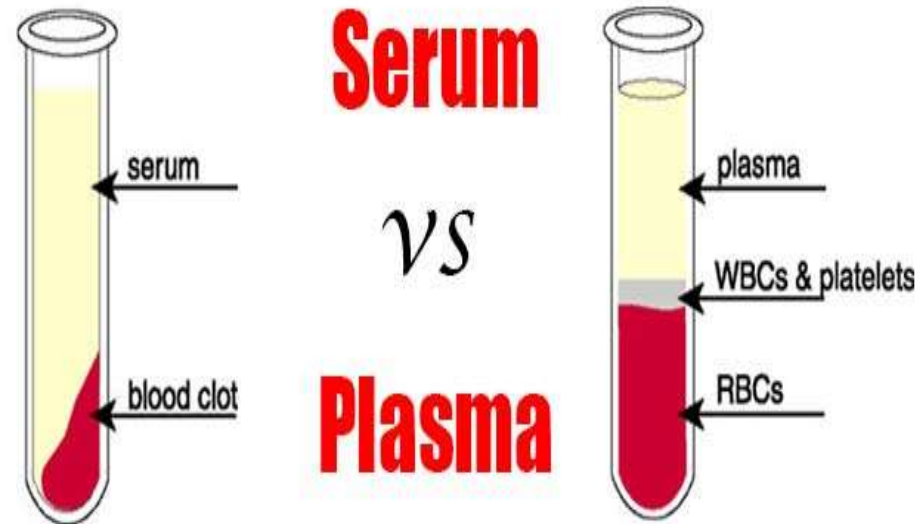
- **Odema** : Is the failure of reabsorption of tissue fluids ( i.e. the filtration rate is exceed the reabsorption rate).



## ❖ Serum

- If whole blood is allowed to clot and the clot is removed, the remaining fluid is called serum.
- Serum has essentially the same composition as plasma except that its clotting factors:

- 1) Fibrinogen (factor I).
- 2) Prothrombin (factor II).
- 3) Labile factor (factor V).
- 4) Antihemophilic factor VIII.



*Serum = Plasma – Clotting Factors*



# **PHYSIOLOGY OF RBC; AND ERYTHROPOIETIN**

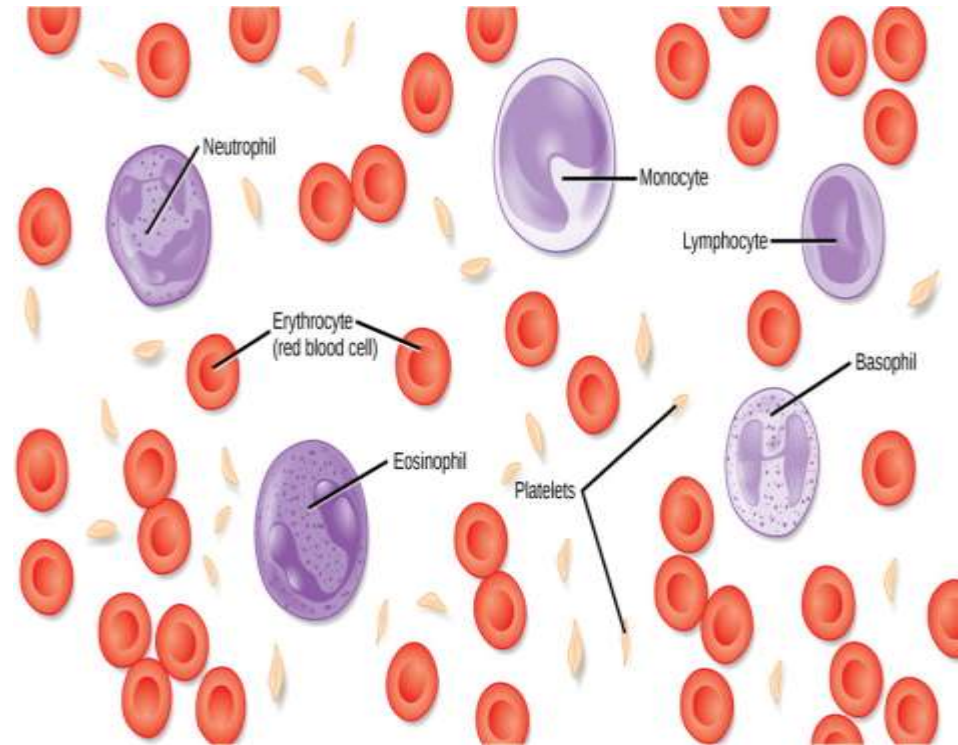


# ❖ Blood cells

1) Red blood cells  
(RBC's) or  
erythrocytes.

2) White blood cells  
(WBC's) or  
leukocytes.

3) Cell fragments  
called platelets or  
thrombocytes.



## ❖ Red blood cells;(RBC) Erythrocytes.

- The major function of red blood cells (*erythrocytes*) is:
  - i. Transport *hemoglobin*, which in turn carries oxygen from the lungs to the tissues.
  - ii. The red blood cells contain a large quantity of *carbonic anhydrase*, (an enzyme) that catalyzes the **reversible** reaction between carbon dioxide (CO<sub>2</sub>) and water to form carbonic acid (H<sub>2</sub>CO<sub>3</sub>).
  - iii. The red blood cells are responsible for most of the acid-base buffering power of whole blood.

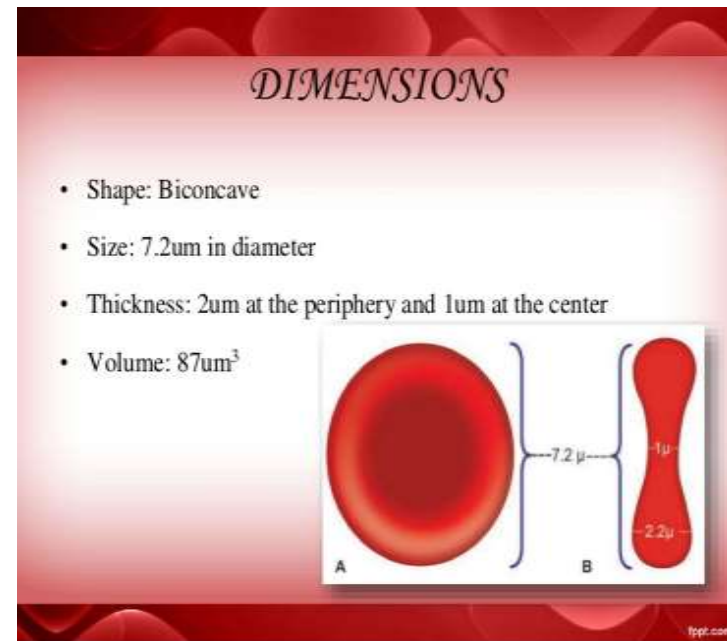


Carbonic Anhydrase



## ❖ Shape and size of red blood cells.

- Normal red blood cells are biconcave discs having a mean diameter of about **7.8  $\mu\text{m}$**  and a thickness of **2.5  $\mu\text{m}$**  at the thickest point and **1  $\mu\text{m}$**  or less in the center.
- The average volume of the red blood cell is **(90 – 95)  $\mu\text{m}^3$** .
- The shapes of red blood cells can change remarkably as the cells squeeze through capillaries; the red blood cell is a “bag” that can be deformed into almost any shape.

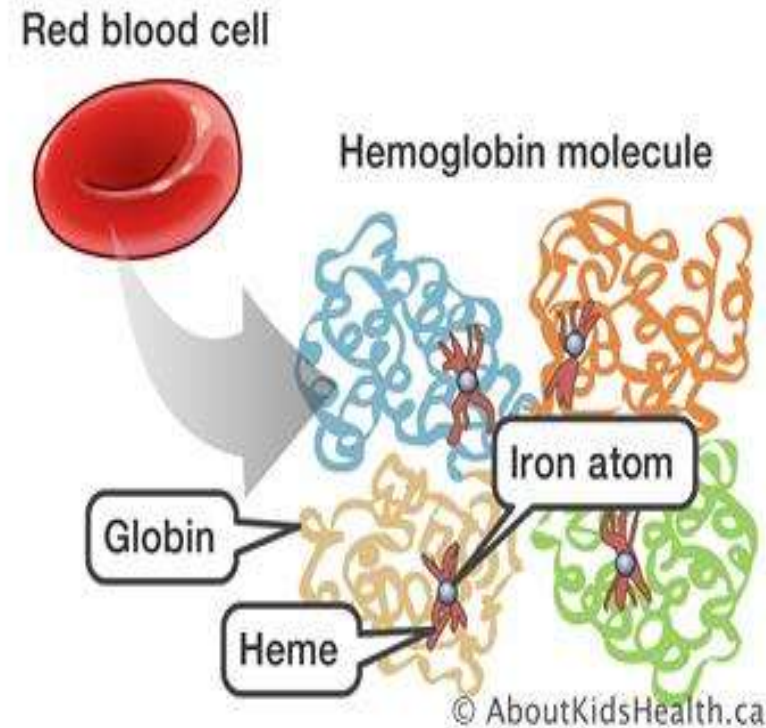


## ❖ Concentration of Red Blood Cells in the Blood.

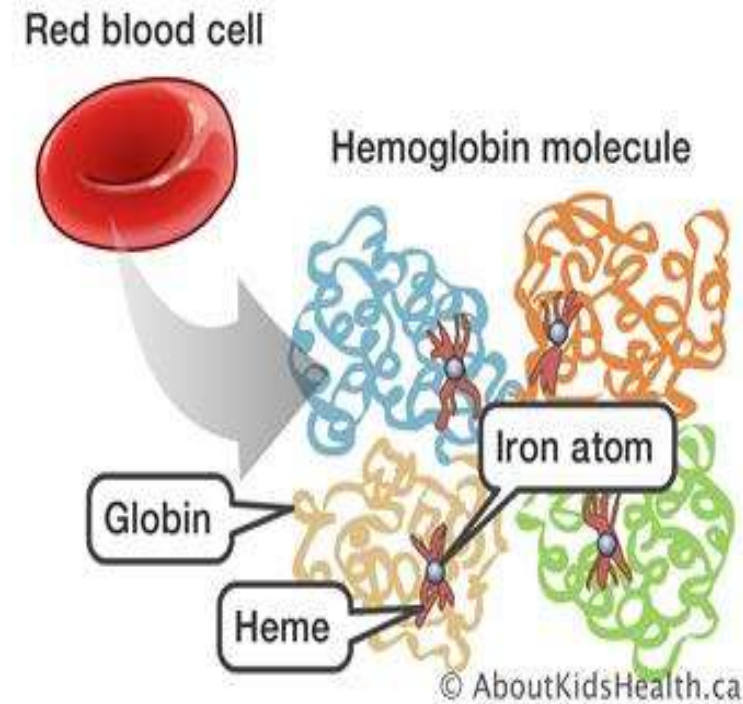
- In normal men, the average number of red blood cells per cubic millimeter is 5,200,000 ( $\pm 300,000$ ).
- in normal women, it is 4,700,000 ( $\pm 300,000$ ).

## ❖ Quantity of Hemoglobin in the Cells.

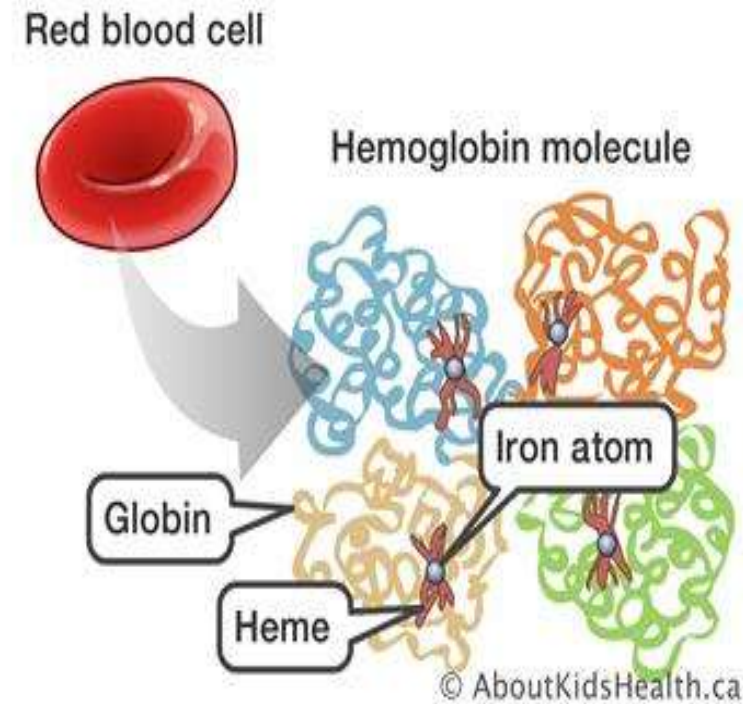
- Red blood cells have the ability to concentrate **hemoglobin** in the cell fluid up to about **34 grams** in each **100 ml.** of cells.



- The whole blood of men contains an average of **15 grams** of hemoglobin **per 100 ml.** of cells;
- For women, it contains an average of **14 grams** per **100 ml.** of cells.
- Each **gram** of pure hemoglobin is capable of combining with **1.34 ml.** of oxygen.



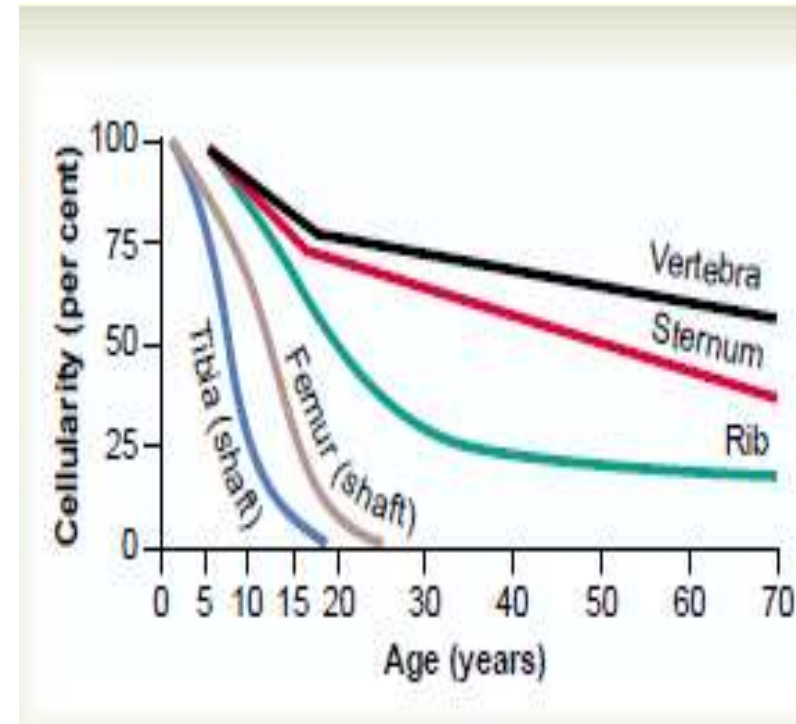
- Therefore:
  - In a normal man, a maximum of about 20 milliliters of oxygen can be carried in combination with hemoglobin in each 100 ml. of blood.
  - In a normal woman, 19 ml. of oxygen can be carried in combination with hemoglobin in each 100 ml. of blood.





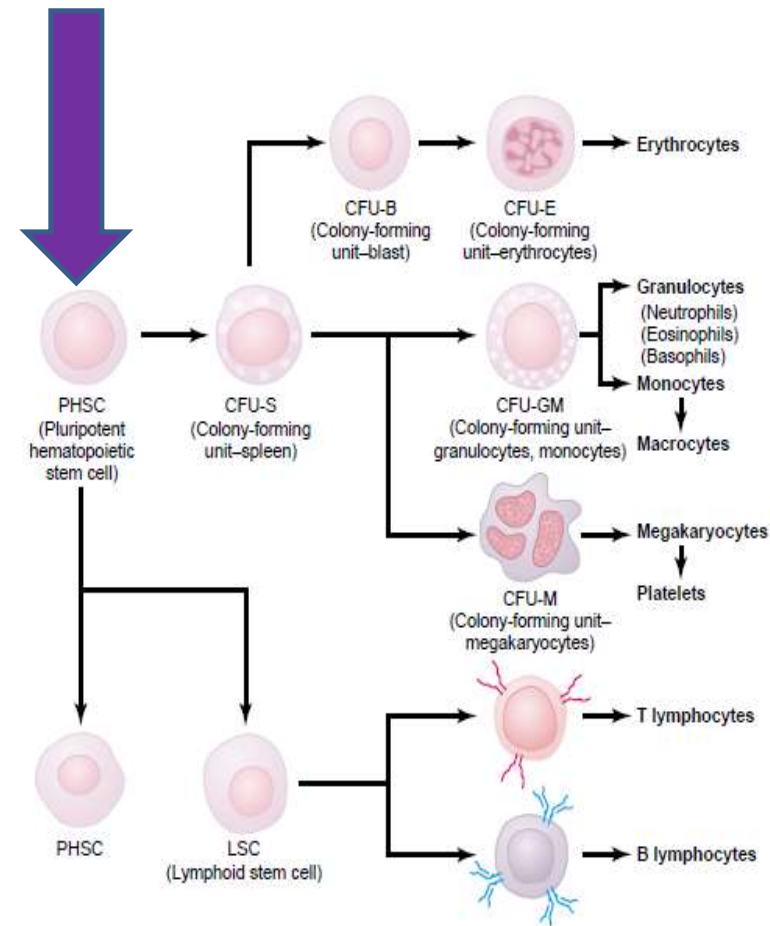
# □ Areas of the Body That Produce Red Blood Cells.

- During the last month or so of gestation and after birth, red blood cells are produced exclusively in the *bone marrow*; all bones produces red blood cells until a person is 5 years old.
- Beyond this age, most red cells continue to be produced in the marrow of the membranous bones, such as the vertebrae, sternum, ribs, and ilia.



# ❖ Genesis of blood cells; Pluripotential hematopoietic stem cell (PHSC).

- The blood cells begin their lives in the bone marrow from a single type of cell called the *pluripotential hematopoietic stem cell*, (PHSC).
- From which all the cells of the circulating blood are eventually derived.

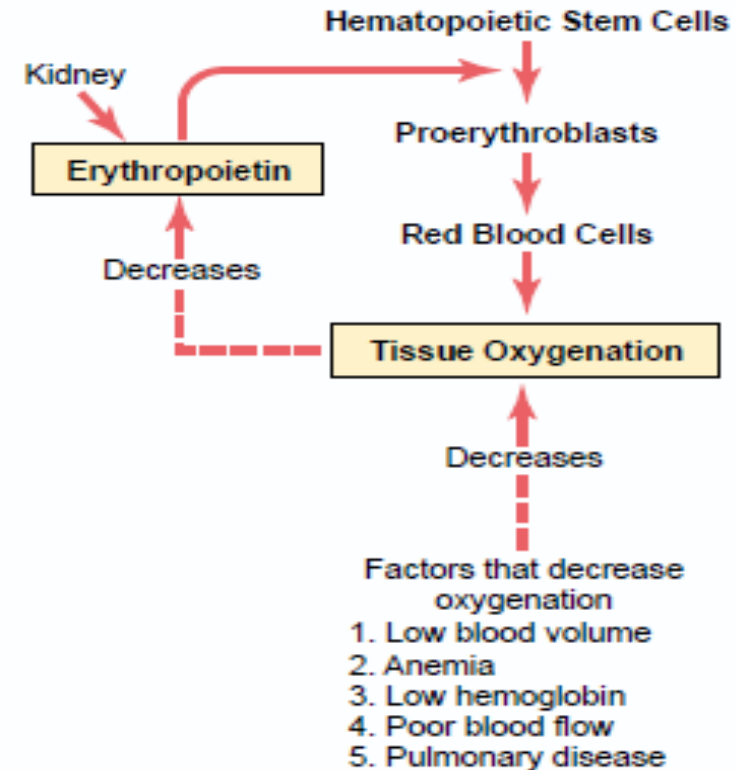




# ❖ Tissue Oxygenation Is the Most Essential Regulator of Red Blood Cell Production:

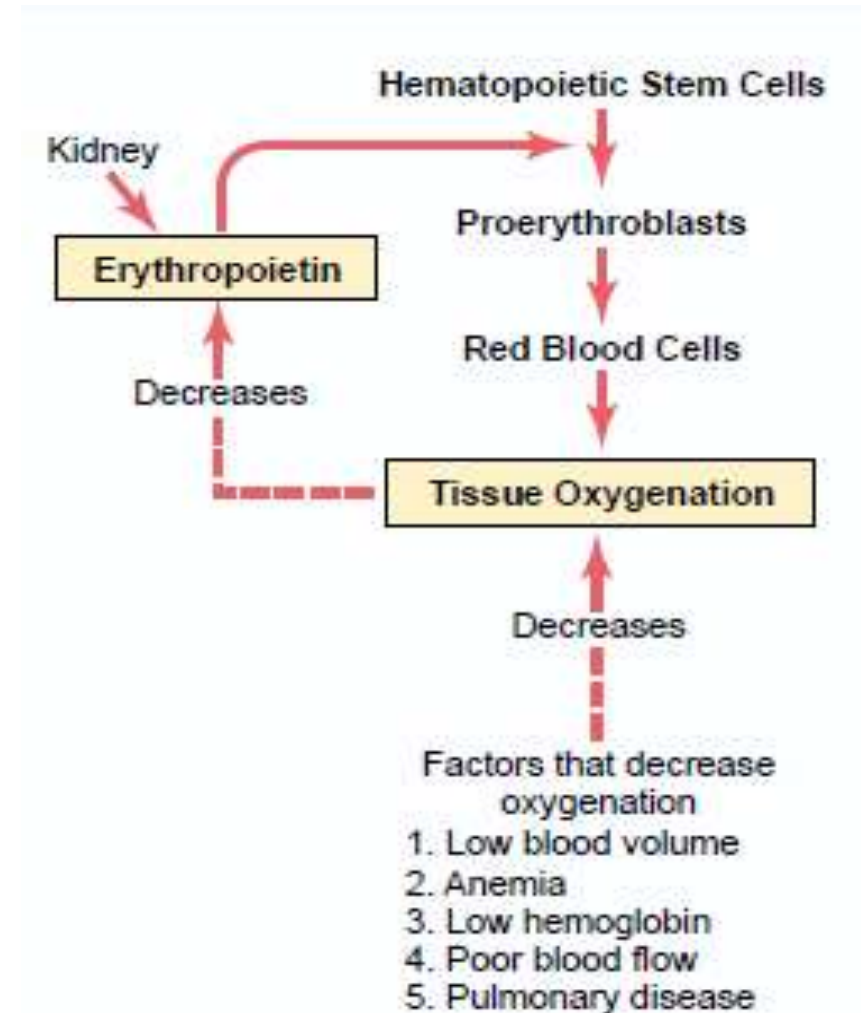
- Any condition that causes the quantity of oxygen transported to the tissues to decrease ordinarily increases the rate of red blood cell production; such as:

- a) Anemic as a result of hemorrhage or any other condition.
- b) Destruction of major portions of the bone marrow by x-ray therapy).
- c) At very *high altitudes*, where the quantity of oxygen in the air is greatly decreased.



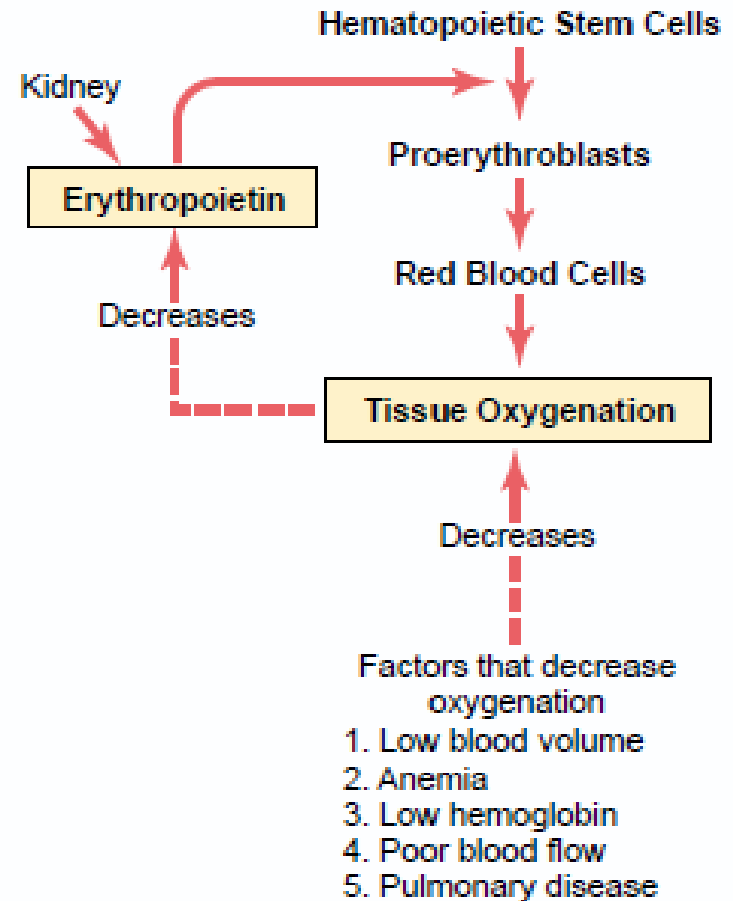
# ❖ Erythropoietin Stimulates Red Cell Production.

- The principal stimulus for red blood cell production in low oxygen states is a circulating hormone called *erythropoietin*.
- Hypoxia causes a marked increase in erythropoietin production, and this will enhance red blood cell production.
- About 90% of all erythropoietin is formed in the **kidneys**.
- The remainder is formed mainly in the **liver**.



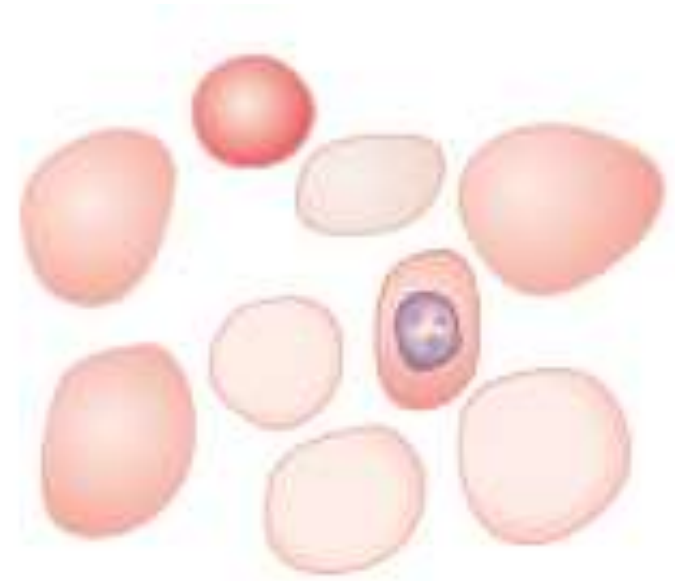
## ❖ Effect of erythropoietin in erythrogenesis:

- When a person is placed in an atmosphere of low oxygen, erythropoietin begins to be formed within **minutes** to **hours**, and it reaches maximum production within **24 hours**.
- Yet almost no new red blood cells appear in the circulating blood until about **5 days** later.



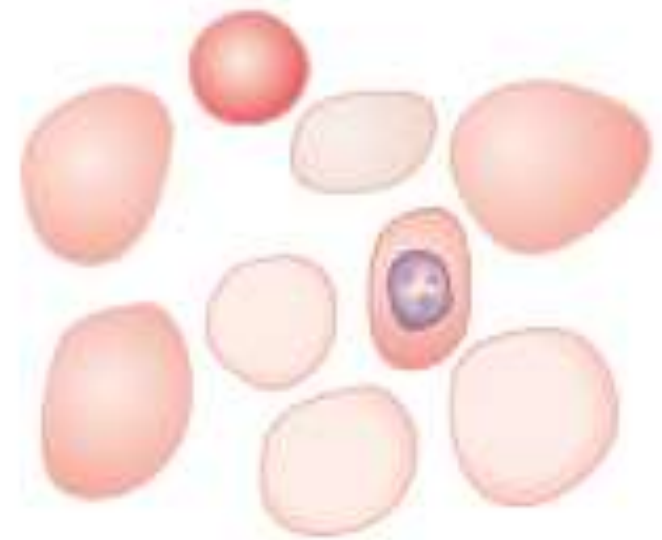
## ❖ Maturation of Red Blood Cells— Vitamin B12 and Folic Acid.

- *Vitamin B12 and folic acid are the most important for final maturation of the red blood cells.*
- Both are essential for the synthesis of DNA.
- Lack both of them causes abnormal and diminished DNA.
- Consequently, failure of nuclear maturation and cell division.



Megaloblastic anemia

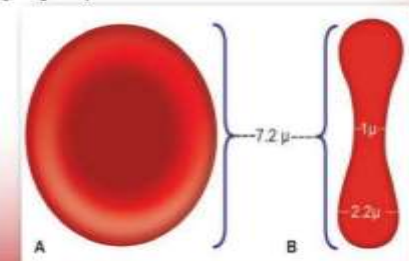
- So; the erythroblastic cells of the bone marrow, in addition to failing to proliferate rapidly, produce mainly larger than normal red cells called *macrocytes*.
- The cell has a flimsy membrane; irregular, large, and oval instead of the usual biconcave disc.
- These cells are capable of carrying oxygen normally, but their fragility causes them to have a short life, (one half - one third ) normal.
- Therefore; deficiency of vitamin B12 or folic acid causes *maturation failure* in the process of erythropoiesis.



Megaloblastic anemia

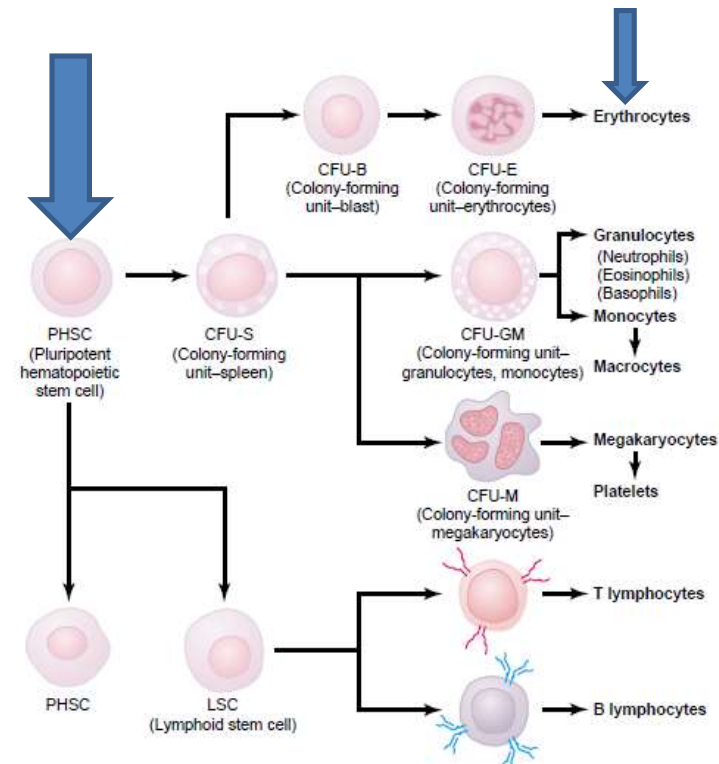
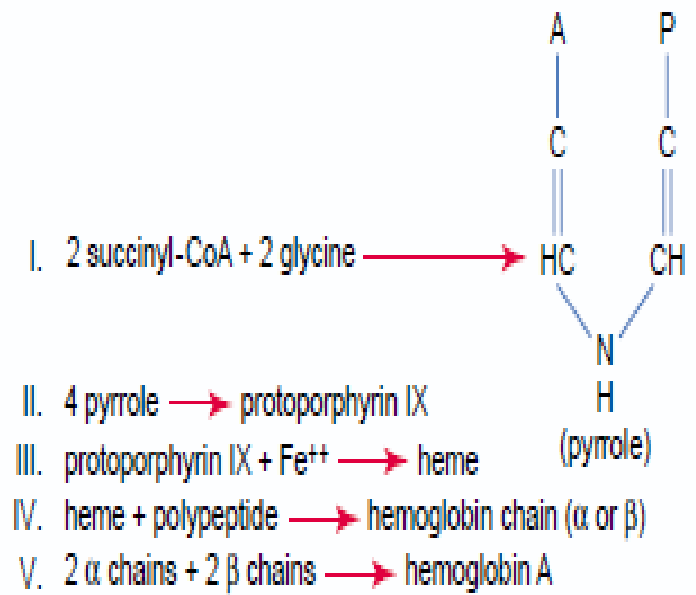
### DIMENSIONS

- Shape: Biconcave
- Size: 7.2um in diameter
- Thickness: 2um at the periphery and 1um at the center
- Volume: 87um<sup>3</sup>



# ❖ Formation of Hemoglobin

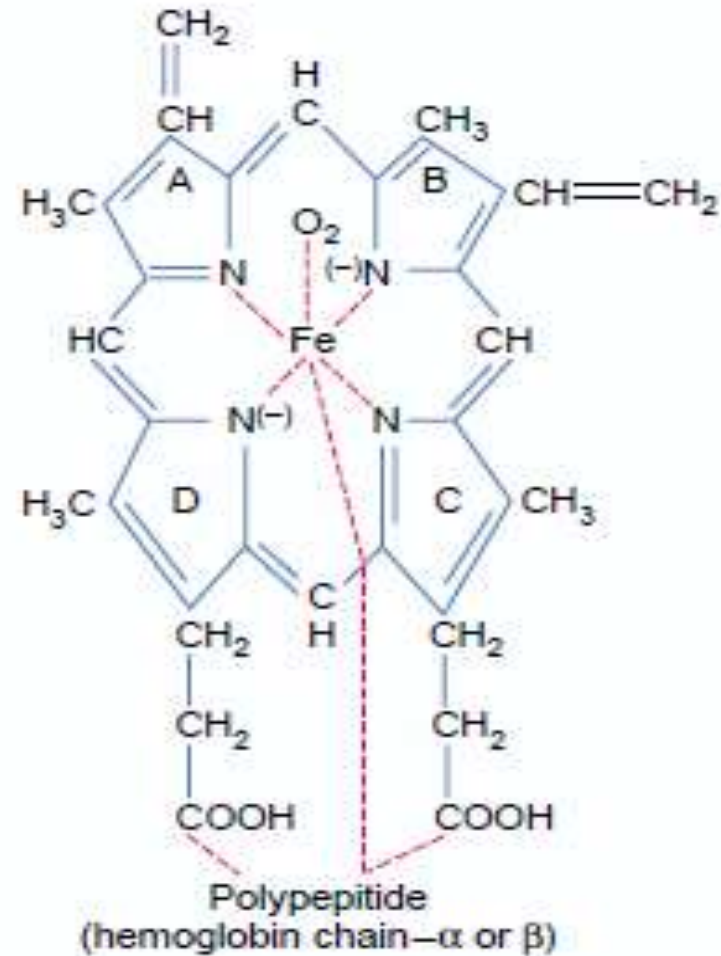
- When **reticulocytes** leave the bone marrow and pass into the blood stream, they continue to form minute quantities of hemoglobin for another day or so until they become mature **erythrocytes**.



## ❖ Combination of Hemoglobin with Oxygen.

- The primary function of hemoglobin in the body is to:

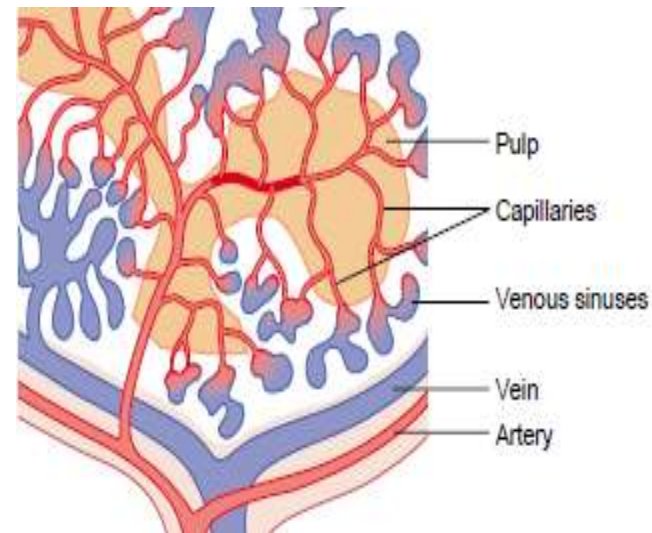
- 1) Combine (loosely and reversibly) with oxygen in the lungs and then to release this oxygen readily in the peripheral tissue capillaries.
- 2) Oxygen binds loosely with one iron atom in the hemoglobin
- 3) The oxygen does not become ionic oxygen but is carried as molecular oxygen (composed of two oxygen atoms), where it is released into the tissue fluids.





## ❖ Life span and destruction of red blood cells:

- The average Life Span of the Red Blood Cells is **120** days before being destroyed.
- The mature red cells do not have a nucleus, mitochondria, or endoplasmic reticulum, they do have **cytoplasmic enzymes** that are capable of metabolizing glucose and forming small amounts of adenosine triphosphate (ATP).
- Once the red cell membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation; through the red pulp of the spleen.

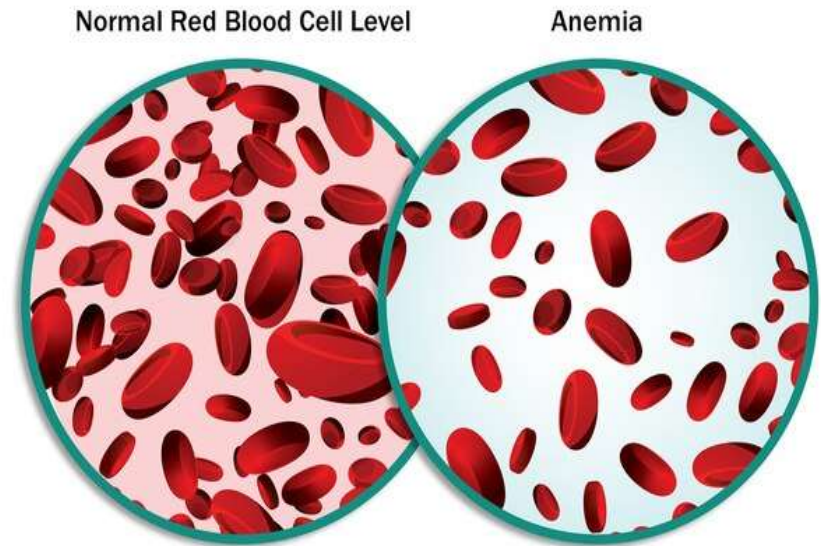


# ❖ Anemias

- Anemia means deficiency of hemoglobin in the blood, which can be caused by either too few red blood cells or too little hemoglobin in the cells.

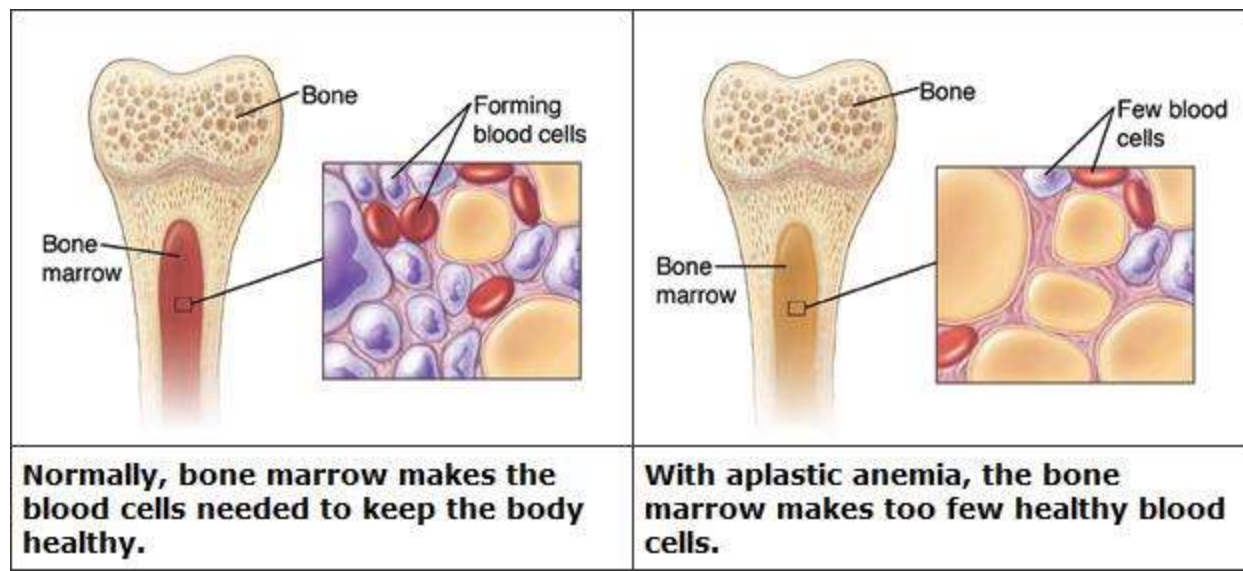
## 1) Blood Loss Anemia.

- After rapid hemorrhage, the body replaces the fluid portion of the plasma in **1 to 3 days**, but this leaves a low concentration of red blood cells.



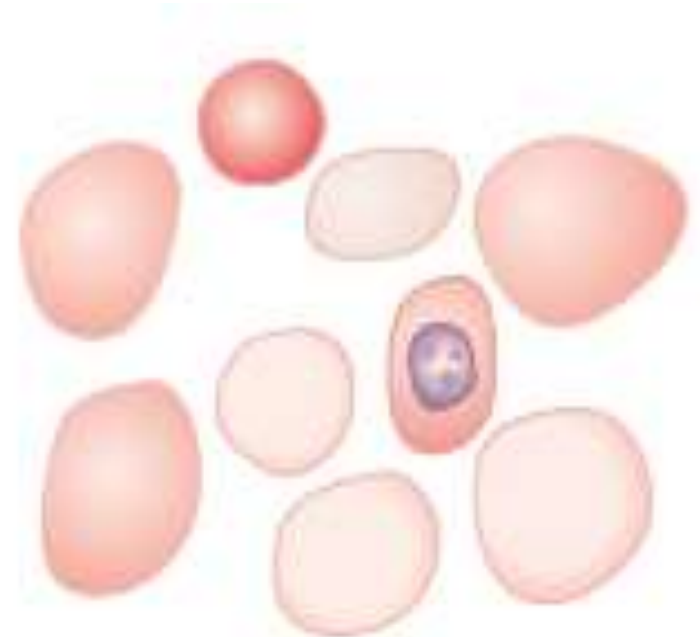
## 2) Aplastic Anemia.

- *Bone marrow aplasia* means lack of functioning bone marrow; due to:
  - **Gamma ray radiation.**
  - **Excessive x-ray treatment.**
  - **Certain industrial chemicals.**
  - **Drugs.**



### 3) Megaloblastic Anemia.

- caused by deficiency of vitamin B12.
  - Folic acid.
  - Intrinsic factor.
- From the stomach mucosa.



Megaloblastic anemia

## 4) Hemolytic anemia.

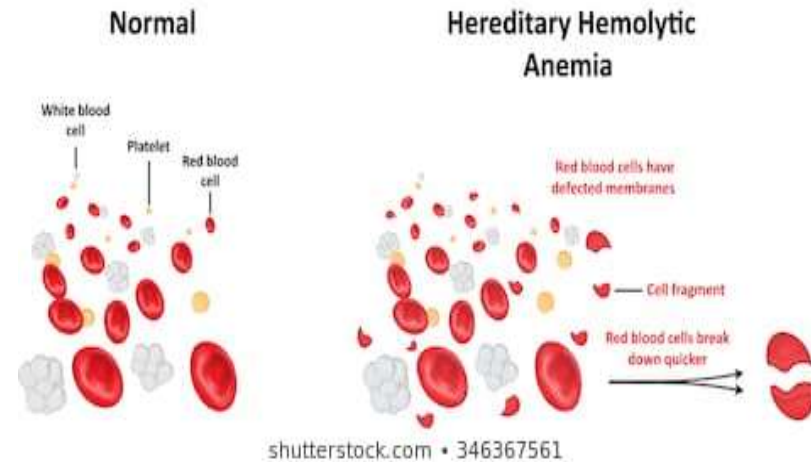
### ➤ Hereditary spherocytosis:

- The red cells are very small and spherical rather than being biconcave discs.

## 5) Sickle cell anemia.

- The cells have an abnormal type of hemoglobin called hemoglobin S, When it exposed to **low concentrations of oxygen**, it precipitates into **long crystals** inside the red blood cell.

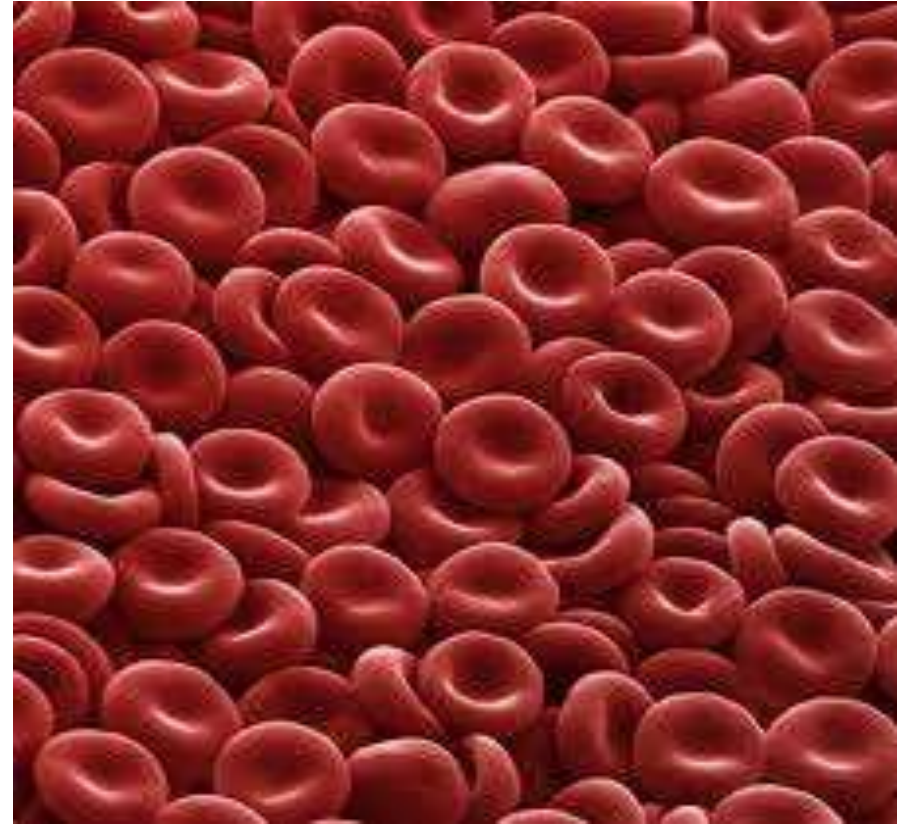
### Hereditary Hemolytic Anemia





## ❖ Polycythemia; Secondary Polycythemia.

- Whenever the tissues become hypoxic; such as at high altitudes, cardiac failure, the blood-forming organs produce large quantities of red blood cells.
- This condition is called *secondary polycythemia*, and the red cell count commonly rises to 6 to 7 million/mm<sup>3</sup>, about 30 per cent above normal.

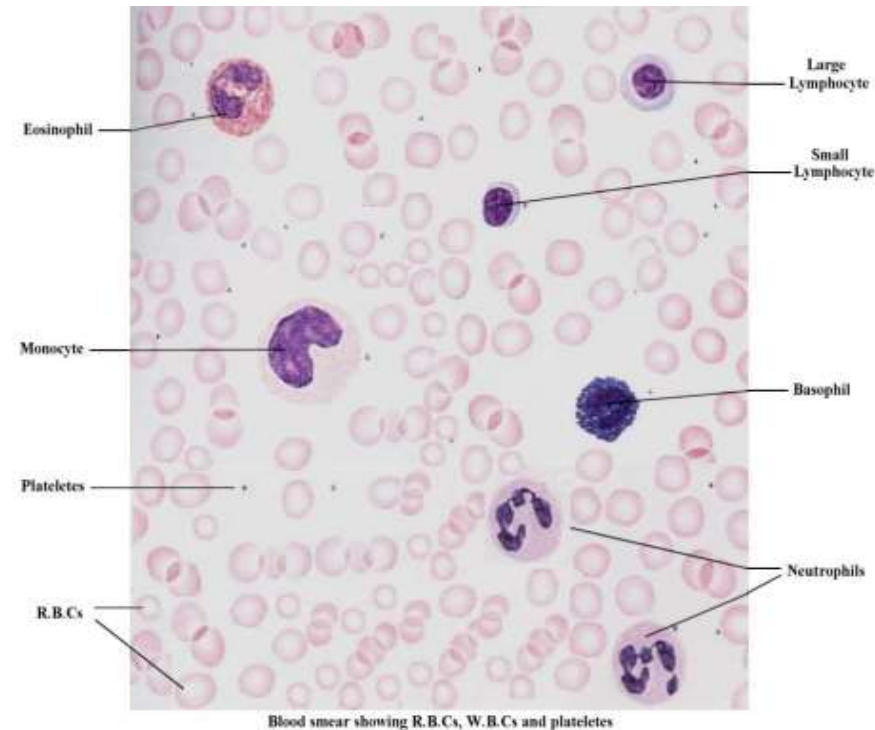


**WHITE BLOOD CELL**

**PHYSIOLOGY**



- Our bodies have a special system for combating the different infectious and toxic agents.
- This is comprised of blood leukocytes (white blood cells) and tissue cells derived from leukocytes.
  - These cells work together in two ways to prevent disease:
    - (1) By actually destroying invading bacteria or viruses by *phagocytosis*.
    - (2) By forming *antibodies* and *sensitized lymphocytes*, one or both of which may destroy or inactivate the invader.



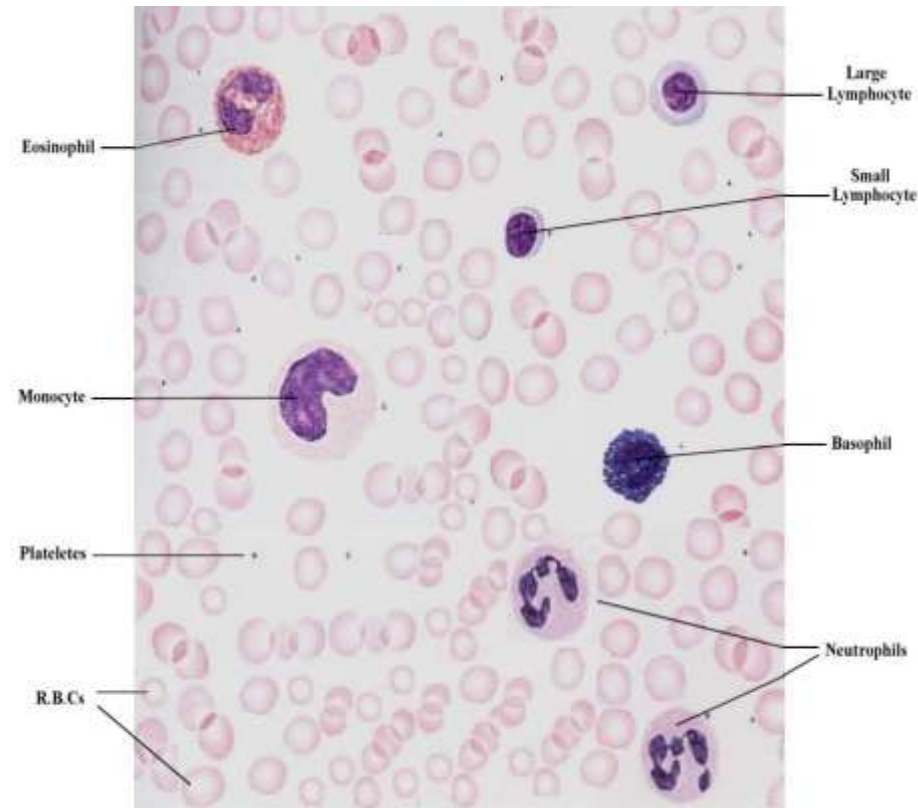
# ❖ Leukocytes (white blood cells)

- They are formed partially in the:

1) Bone marrow (*granulocytes- "neutrophile; eosinophile; basophile" and monocytes and a few lymphocytes*).

2) Lymph tissue (*lymphocytes and plasma cells*).

➤ White blood cells are transported to areas of serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents.



Blood smear showing R.B.Cs, W.B.Cs and platelets

# ❖ Types of White Blood Cells.

- Six types of white blood cells are normally present in the blood.

➤ polymorphonuclear neutrophils.

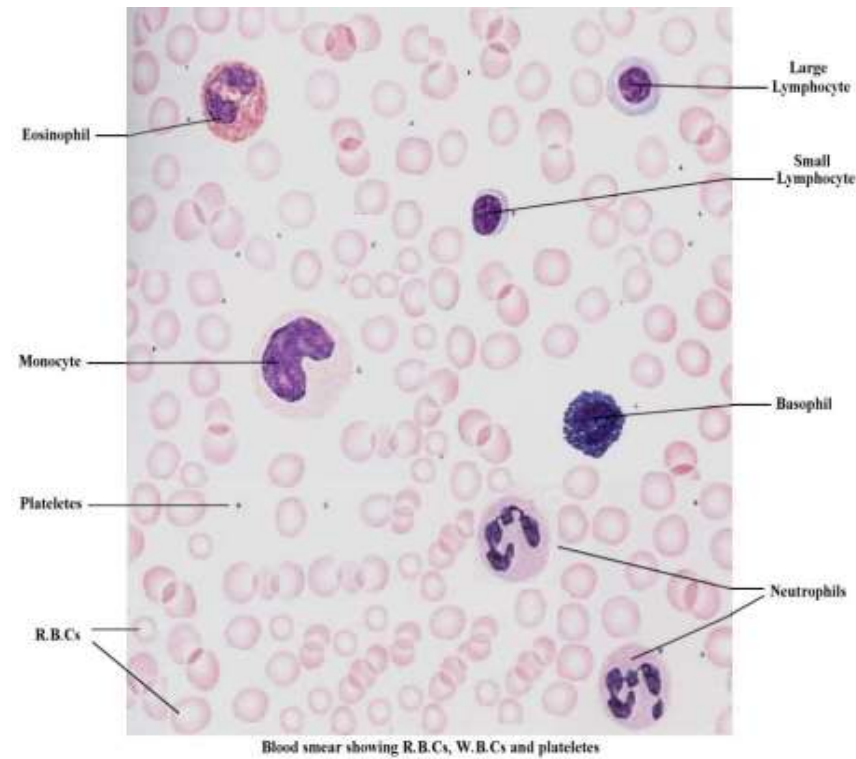
➤ polymorphonuclear eosinophils.

➤ polymorphonuclear basophils.

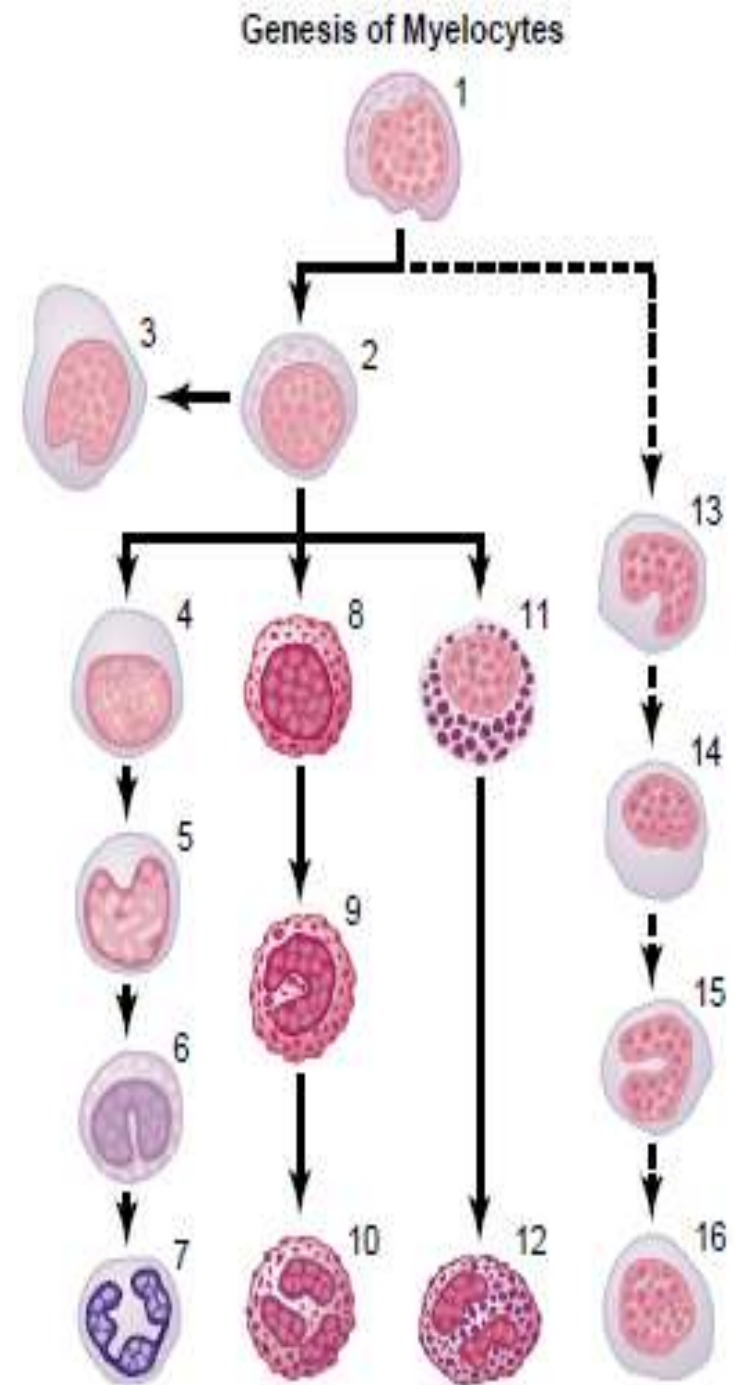
➤ Monocytes.

➤ lymphocytes.

➤ plasma cells.



- The first three types of cells, the polymorphonuclear cells, all have a granular appearance, so it called *granulocytes*, or, in clinical terminology, “polys,” because of the multiplenuclei.
- The granulocytes and monocytes protect the body against invading organisms mainly by ingesting them—that is, by phagocytosis.
- The lymphocytes and plasma cells function mainly in connection with the immune system.



# ❖ Concentrations of the Different White Blood Cells in the Blood.

- The white blood cells are 7000 cell \microliter of blood.

- The normal percentages of its different types are:

- Neutrophils: 62.0%.

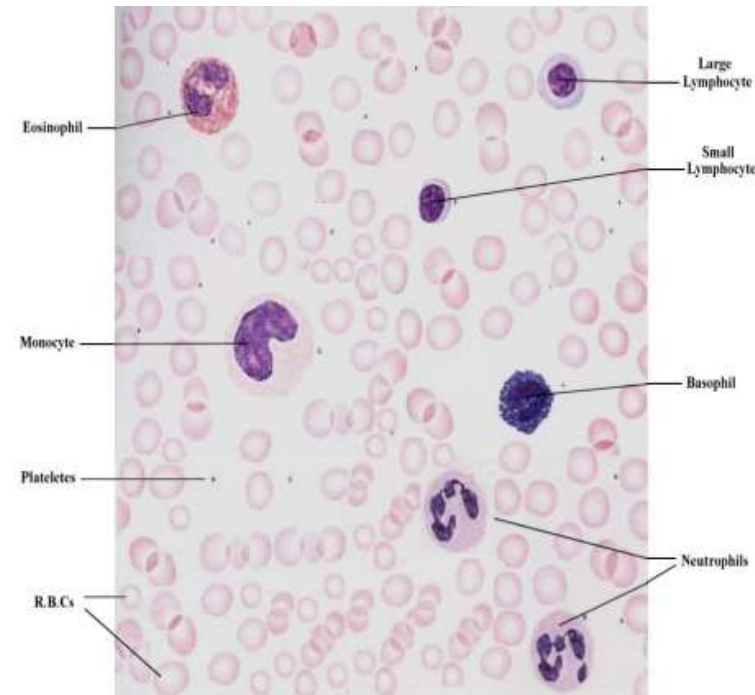
- Eosinophils: 2.3%.

- Basophils: 0.4%.

- Monocytes: 5.3%.

- Lymphocytes: 30.0%.

- Platelets: 300,000\microliter.

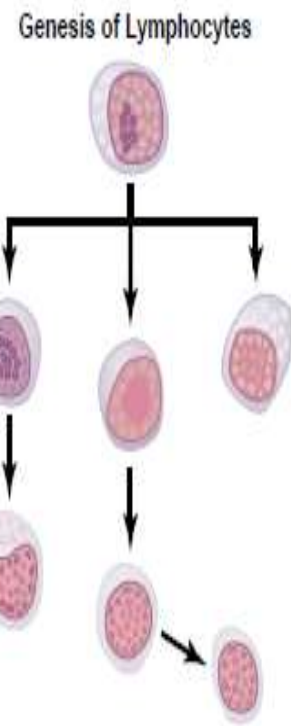
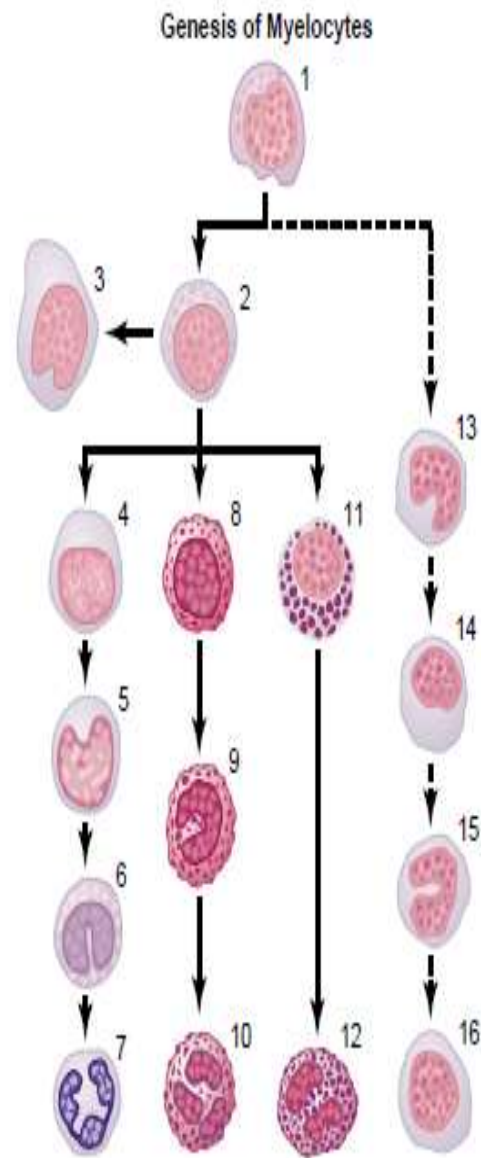


Blood smear showing R.B.Cs, W.B.Cs and platelets

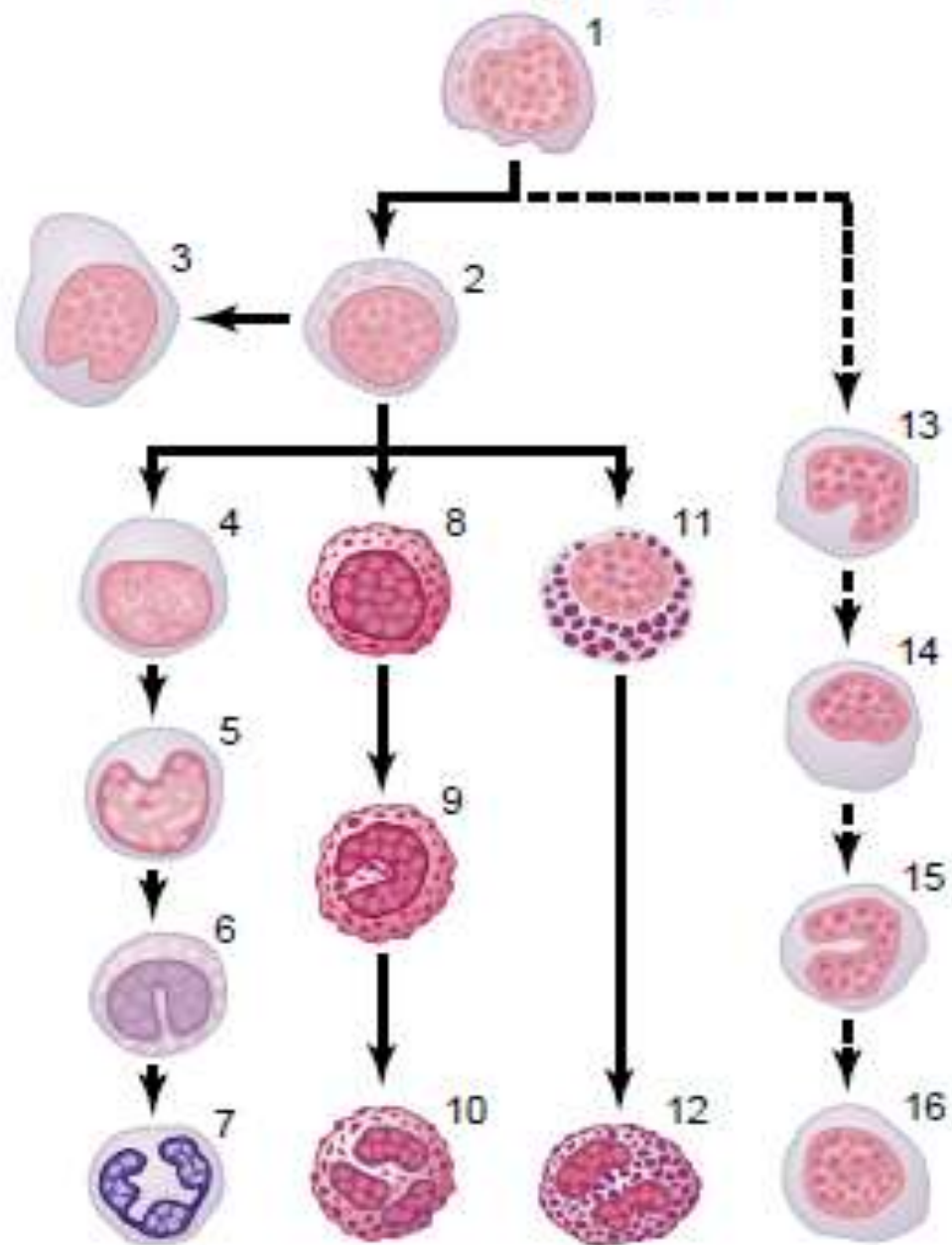


## ❖ Genesis of the White Blood Cells

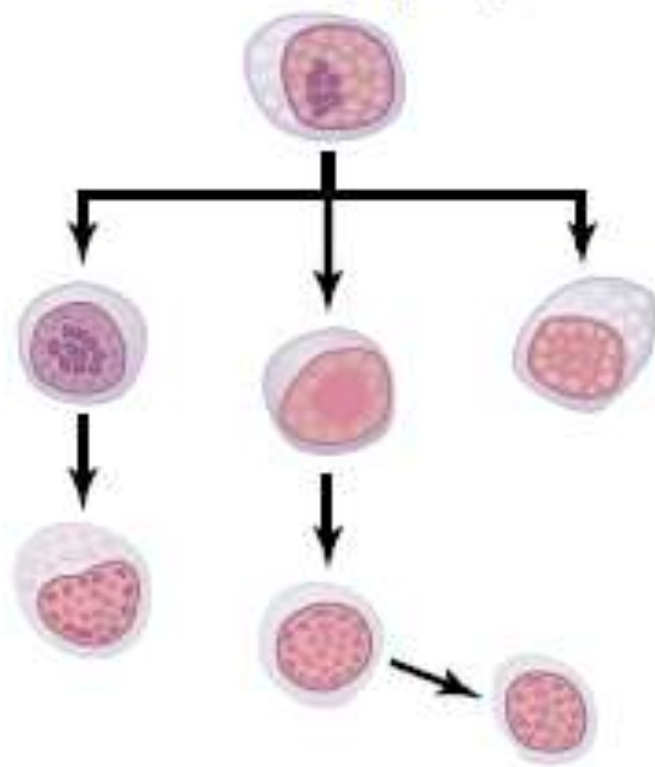
- Early differentiation of the pluripotential hematopoietic stem cell into the different types of committed stem cells.
- Two major lineages of *white blood cells* are formed, the myelocytic and the lymphocytic lineages.
- The *myelocytic lineage*, beginning with the *myeloblast*.
- The *lymphocytic lineage*, beginning with the *lymphoblast*.
- The granulocytes and monocytes are formed only in the bone marrow.
- Lymphocytes and plasma cells are produced mainly in the various lymphogenous tissues—especially the lymph glands, spleen, thymus, tonsils.



### Genesis of Myelocytes

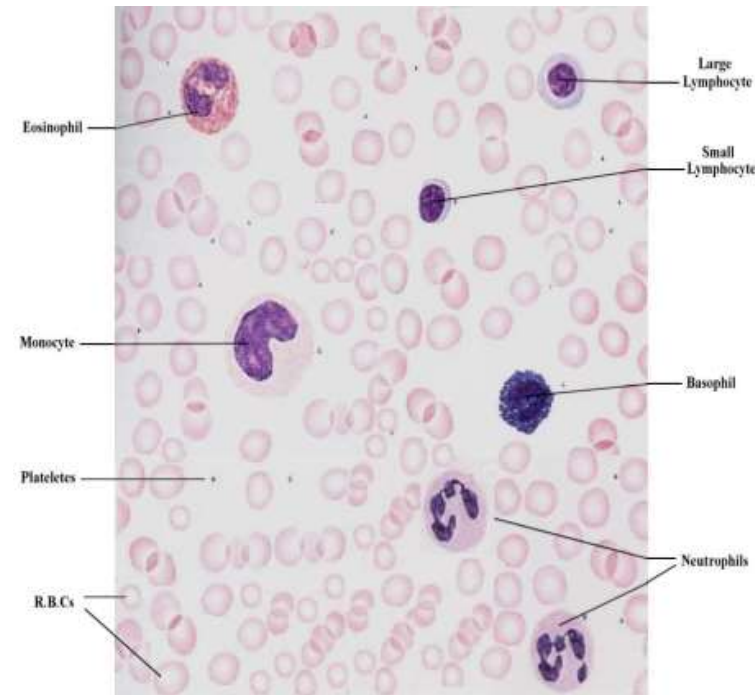


### Genesis of Lymphocytes





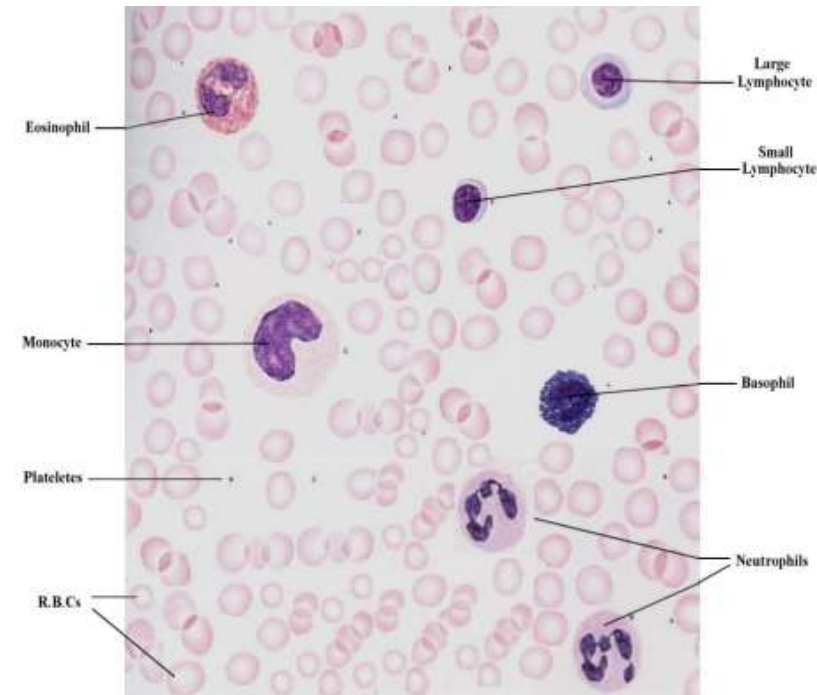
- The white blood cells formed in the bone marrow are stored within the marrow until they are needed in the circulatory system.
- Normally, about three times as many white blood cells are stored in the marrow as circulate in the entire blood.
- The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood.



Blood smear showing R.B.Cs, W.B.Cs and platelets

## ❖❖ Life Span of the White Blood Cells

- The life span of granulocytes is (4 to 8 hours) circulating in the blood and another (4 to 5 days) in tissues where they are needed.
- The monocytes also have a short transit time, (10 to 20 hours) in the blood, before wandering through the capillary membranes into the tissues.
- Once in the tissues, they swell to much larger sizes to become *tissue macrophages*, and, in this form, can live for months unless destroyed while performing phagocytic functions.



Blood smear showing R.B.Cs, W.B.Cs and platelets

- Lymphocytes enter the circulatory system **continually**, along with drainage of lymph from the lymph nodes and other lymphoid tissue.
- After a few hours, they pass out of the blood back into the tissues by **diapedesis**.
- The lymphocytes have life spans of **(weeks or months)**.

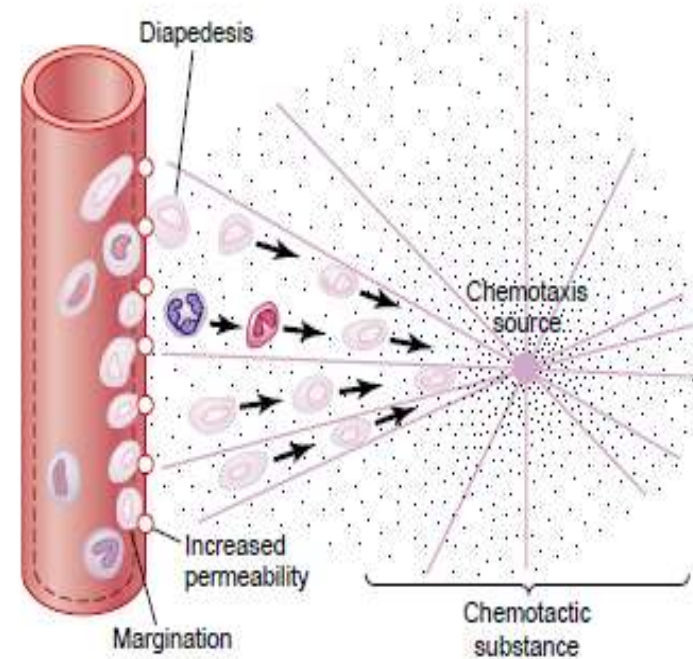
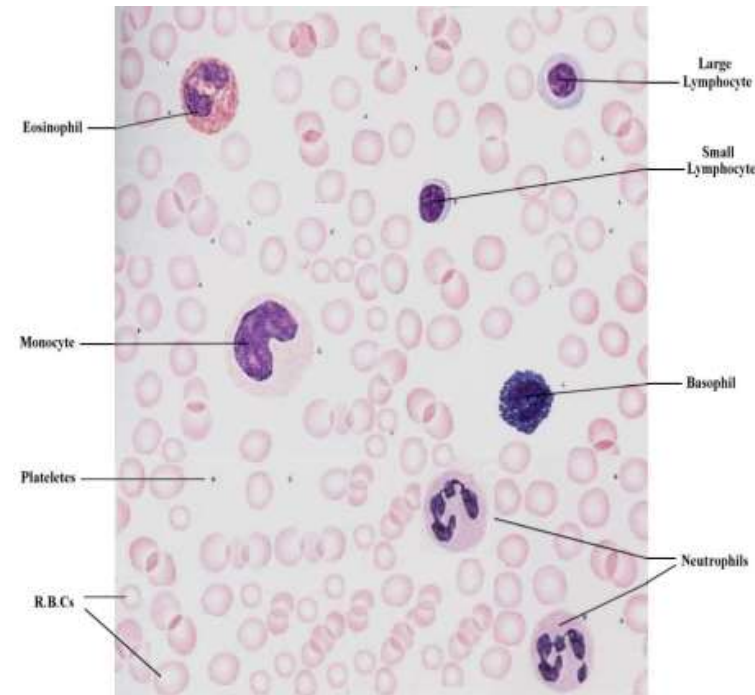


Figure 33-2

Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.

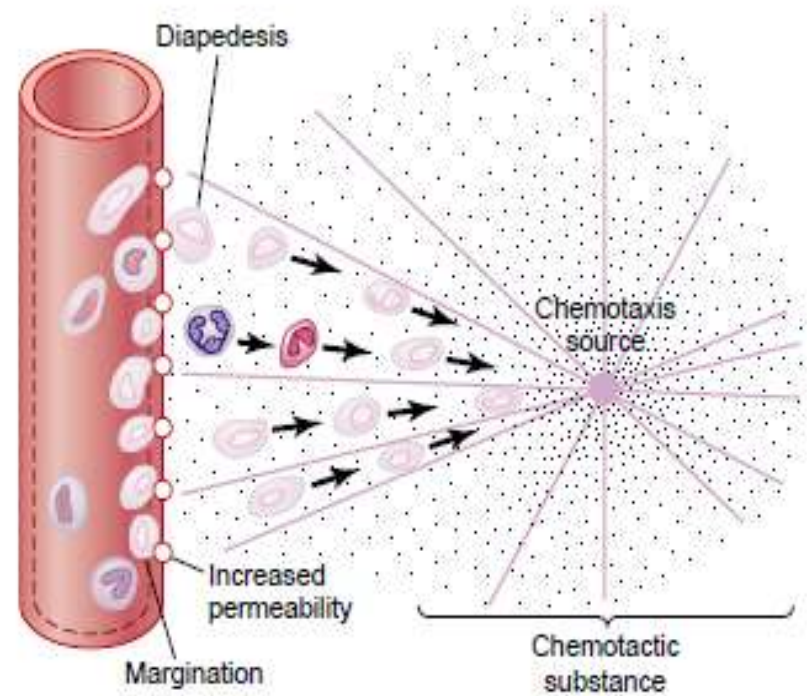
## ❖❖ Neutrophils and Macrophages defend against infections.

- Neutrophils and tissue macrophages attack and destroy invading bacteria, viruses, and other injurious agents.
- The neutrophils are mature cells that can attack and destroy bacteria even in the circulating blood.
- Conversely, the tissue macrophages begin life as: blood monocytes, which are immature cells while still in the blood and have little ability to fight infectious agents at that time.
- Once they enter the tissues, they begin to swell—increasing their diameters as much as fivefold—to as great as (60 to 80  $\mu\text{m}$ ); called *tissue macrophages*.



Blood smear showing R.B.C.s, W.B.C.s and platelets

- ❖ White blood cells enter the tissue spaces by diapedesis.
- Neutrophils and monocytes can squeeze through the pores of the blood capillaries by *diapedesis*.
- That is, even though a pore is much smaller than a cell, a small portion of the cell slides through the pore at a time; the portion sliding through is momentarily constricted to the size of the pore.



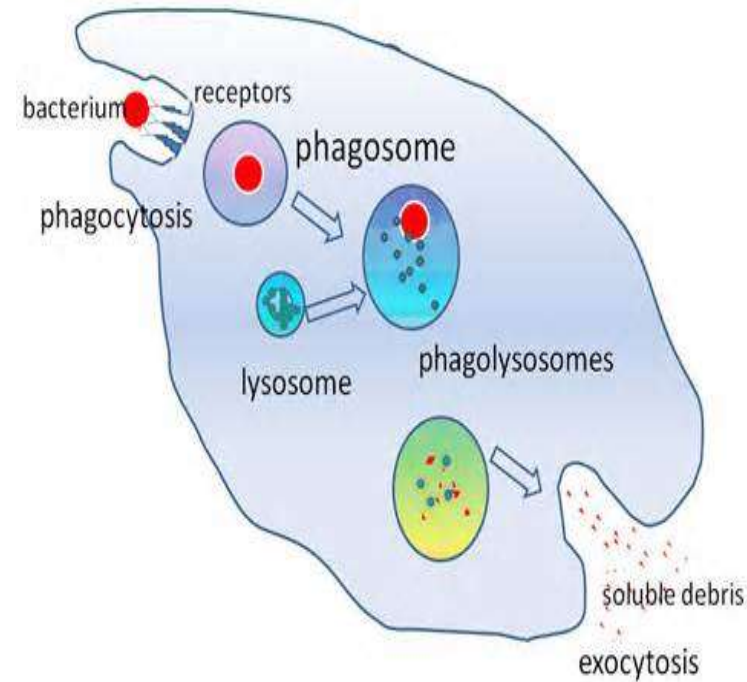
**Figure 33-2**

Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.

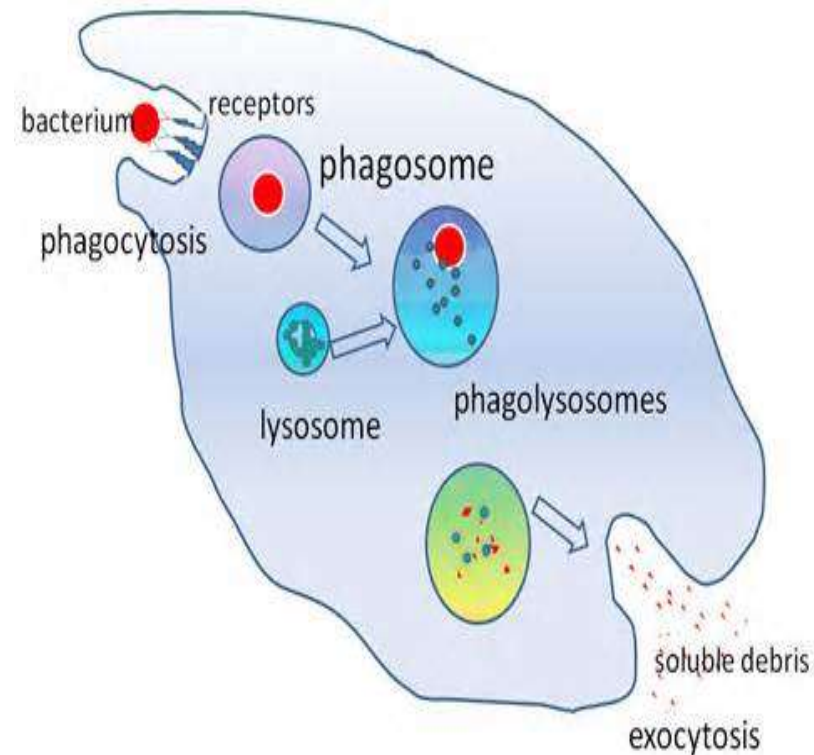


## ❖ Phagocytosis by Neutrophils.

- The neutrophils entering the tissues are already mature cells that can immediately begin phagocytosis.
- The neutrophil first attaches itself to the particle and then projects pseudopodia in all directions around the particle.
- The pseudopodia meet one another on the opposite side and fuse.



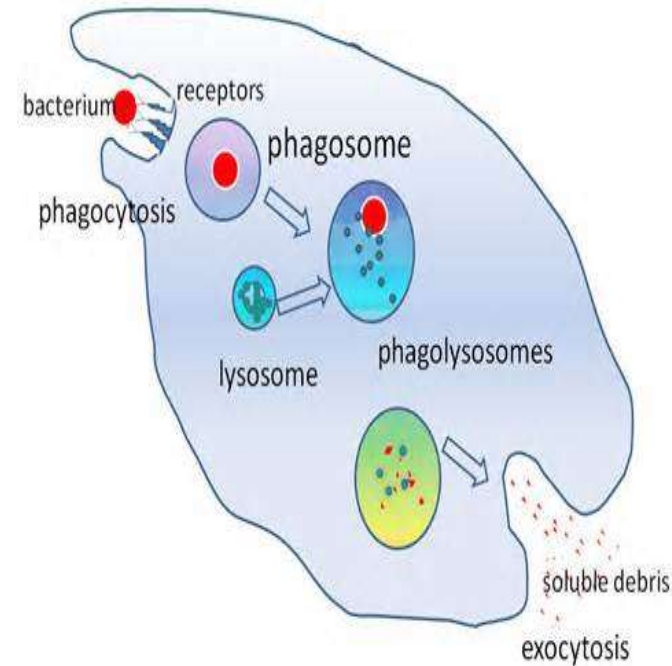
- This creates an enclosed chamber that contains the phagocytized particle.
- Then the chamber invaginates to the inside of the cytoplasmic cavity and breaks away from the outer cell membrane to form a free-floating *phagocytic vesicle* (also called a *phagosome*) inside the cytoplasm.
- A single neutrophil can usually phagocytize (3 to 20 bacteria) before the neutrophil itself becomes inactivated and dies.





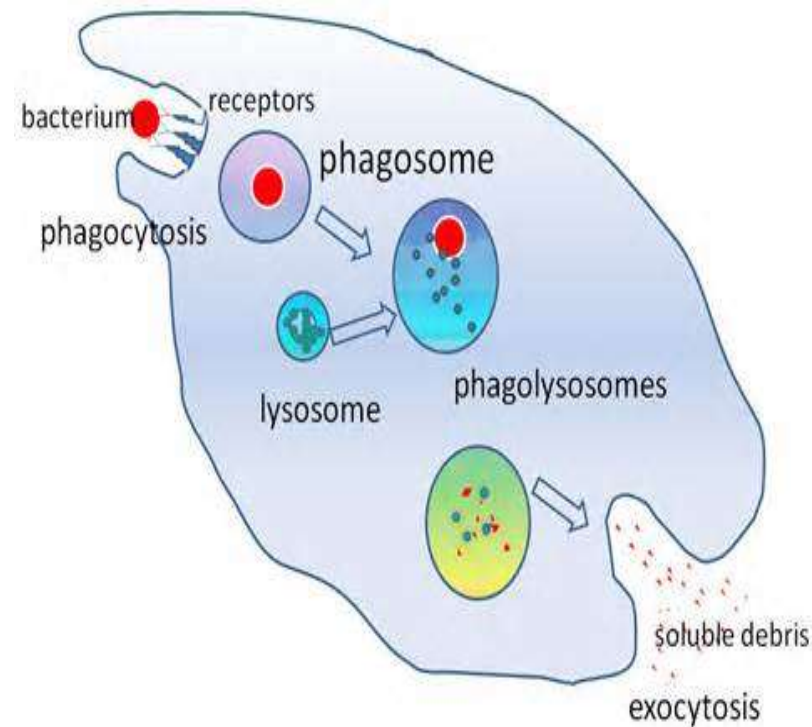
## ❖ Phagocytosis by Macrophages.

- Macrophages are the end stage product of monocytes that enter the tissues from the blood.
- Often capable of phagocytizing as many as **(100 bacteria)**.
- They also have the ability to engulf much larger particles, even whole red blood cells or, occasionally, malarial parasites.
- After digesting particles, macrophages can **extrude** the residual products and often survive and function for many more months.



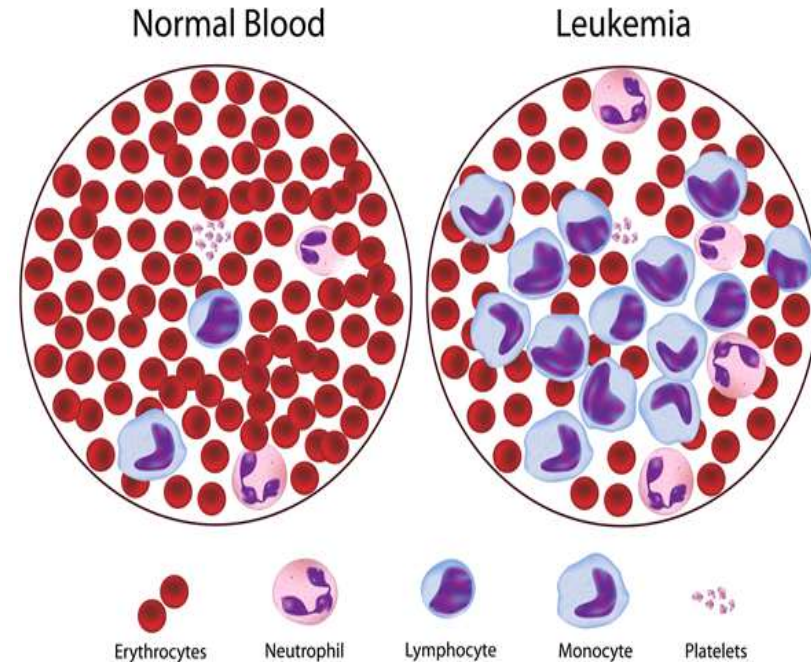
## ❖ Once Phagocytized, Most Particles Are Digested by Intracellular Enzymes.

- Once a foreign particle has been phagocytized, lysosomes will come in contact with the phagocytic vesicle, and their membranes fuse, thereby dumping many digestive enzymes and bactericidal agents into the vesicle.
- Both neutrophils and macrophages contain an abundance of lysosomes filled with *proteolytic enzymes* can digest bacteria and other foreign protein matter.



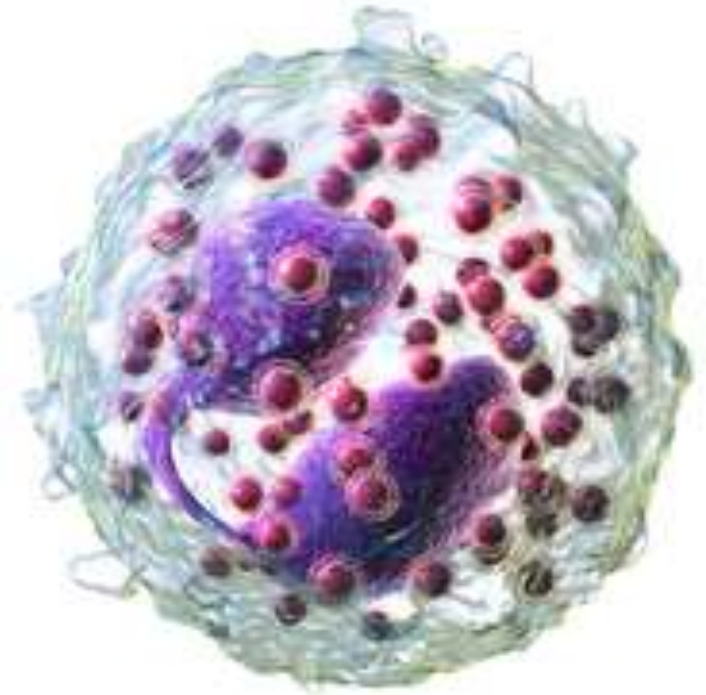
## ❖ Acute Increase in Number of Neutrophils in the Blood "Neutrophilia."

- After the onset of acute, severe inflammation, the number of neutrophils in the blood sometimes increases **fourfold** to **fivefold** from a normal of **(4000 - 5000)** to **(15,000 - 25,000)** neutrophils per microliter.
- This is called *neutrophilia*, which means an increase in the number of neutrophils in the blood.
- Neutrophilia is caused by products of inflammation that enter the blood stream, are transported to the bone marrow, and there act on the stored neutrophils of the marrow to mobilize these into the circulating blood.
- This makes even more neutrophils available to the inflamed tissue area.

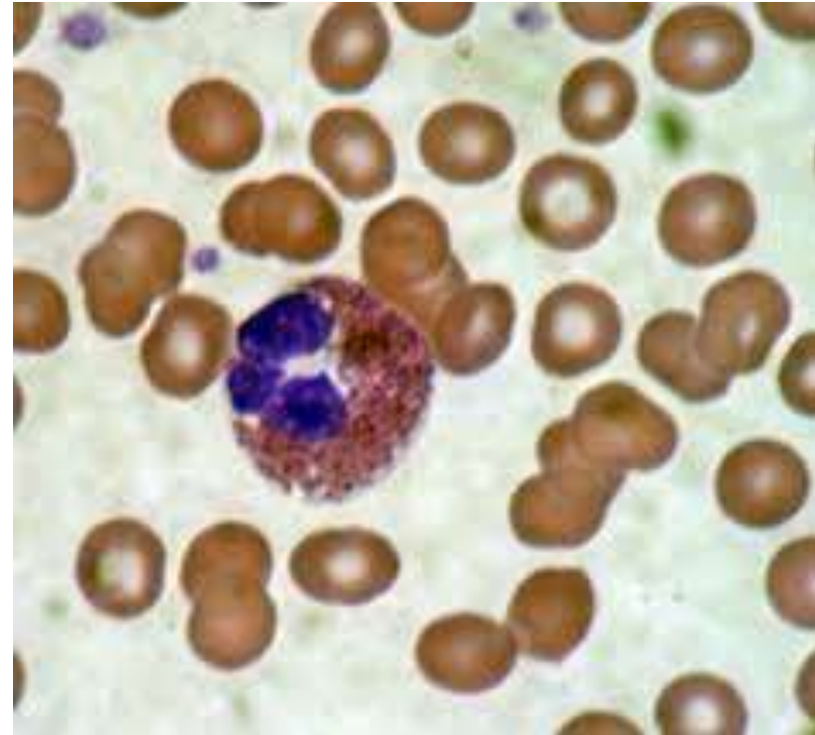


# ❖ Eosinophils

- The eosinophils normally constitute about **2%** of all the blood leukocytes.
- Eosinophils are weak phagocytes, and they exhibit chemotaxis.
- It produced in large numbers in people with **parasitic infections**.
- Eosinophils attach themselves to the parasites by way of special surface molecules and release substances that kill many of the parasites.



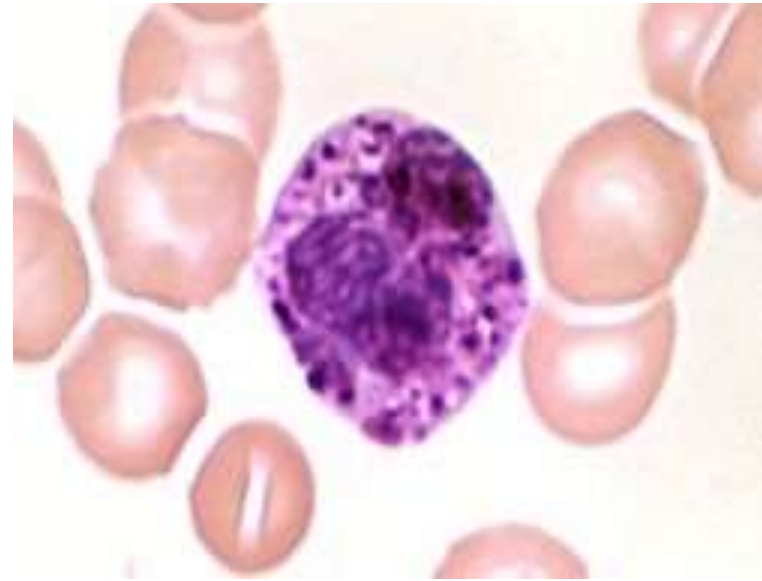
- Eosinophils also have a special propensity to collect in tissues in which **allergic reactions** occur, such as in the peribronchial tissues of the lungs in people with **asthma** and **allergic skin reactions**.



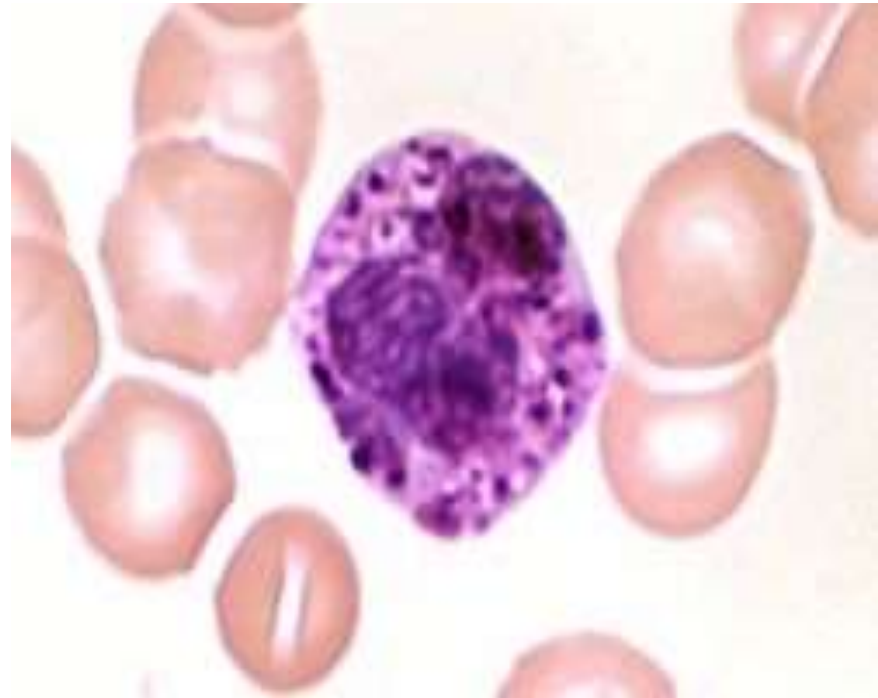


## ❖ Basophils

- The basophils in the circulating blood are similar to the large **tissue mast cells** located immediately outside of the capillaries in the body.
- Both **mast cells** and **basophils** liberate **heparin** into the blood, a substance that can prevent blood coagulation.



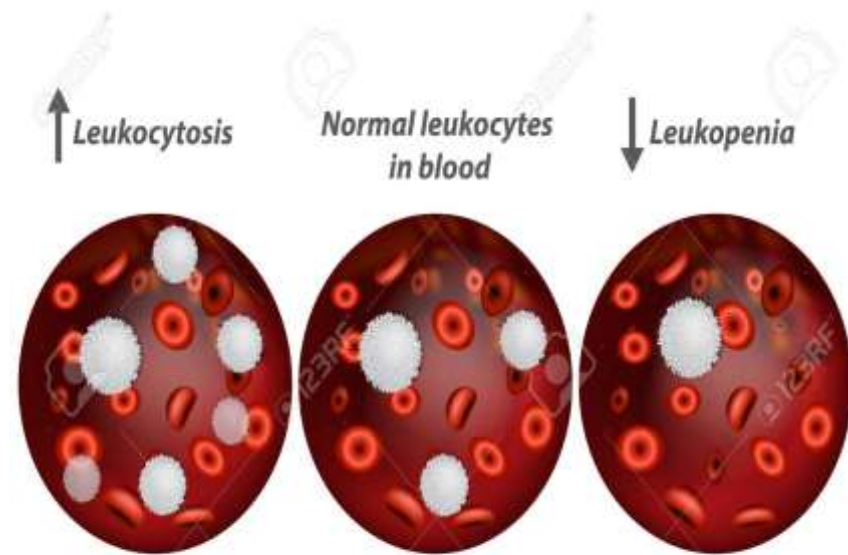
- Both releasing *histamine*, as well as smaller quantities of *bradykinin* and *serotonin*.
- Both play important role in some types of **allergic reactions** because the type of antibody that causes allergic reactions, the **immunoglobulin E (IgE)** type, has a special propensity to become attached to mast cells and basophils.



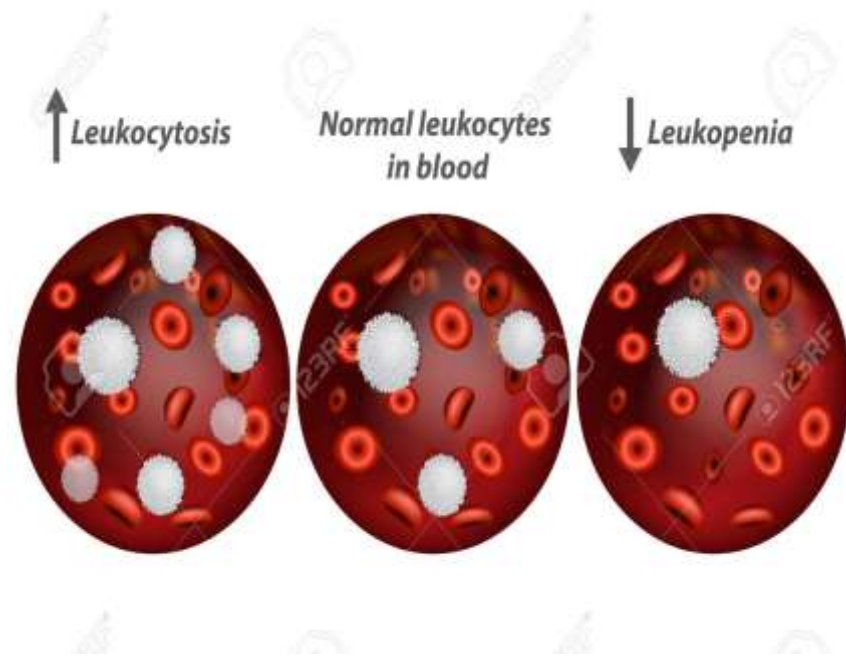


# ❖ Leukopenia

- A clinical condition occurs in which the bone marrow produces very few white blood cells, leaving the body unprotected against many bacteria.
- Normally, the human body lives in symbiosis with many bacteria, because all the mucous membranes of the body are constantly exposed to large numbers of bacteria.



- Any decrease in the number of white blood cells immediately allows invasion of adjacent tissues by bacteria that are already present.
- Within 2 days after the bone marrow stops producing white blood cells, ulcers may appear in the mouth and colon, or the person might develop some form of severe **respiratory infection**.



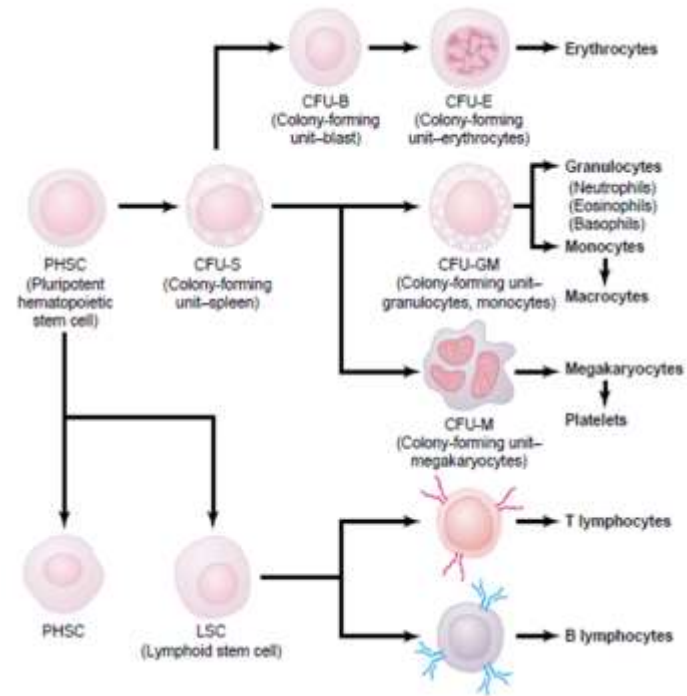
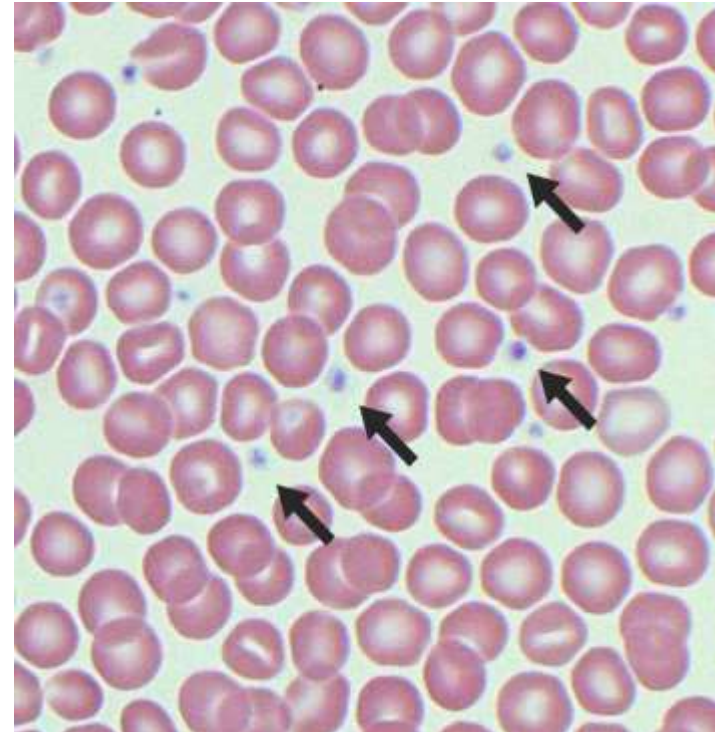
# **BLOOD CLOTTING MECHANISM**

# ❖ Hemostasis:

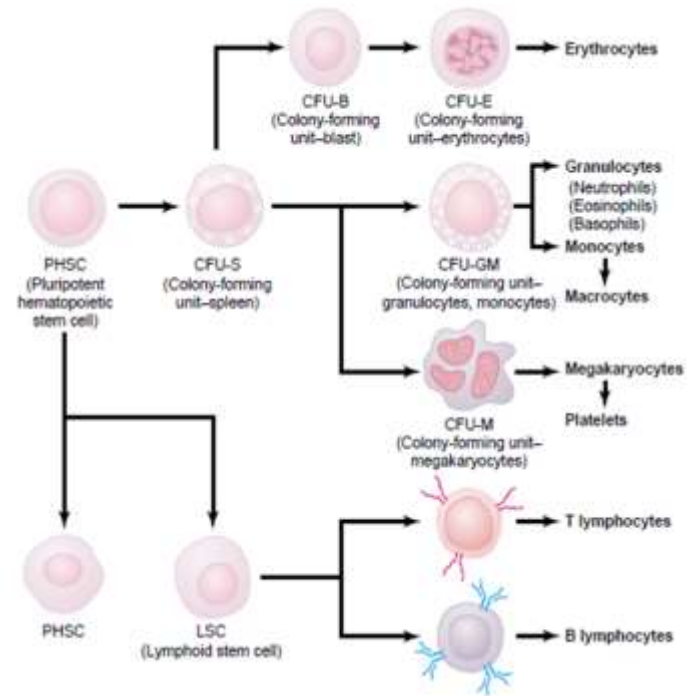
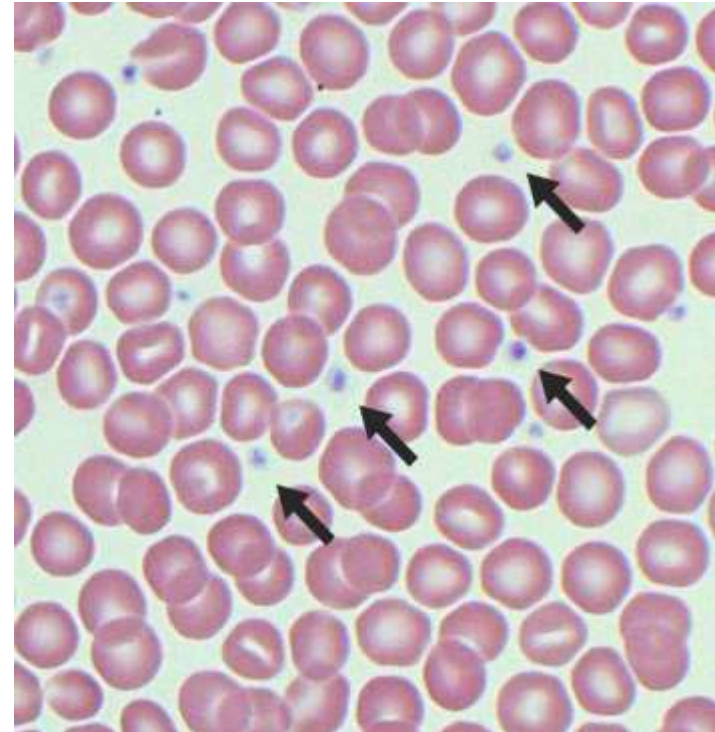
- Hemostasis means prevention of blood loss. Whenever a vessel is severed or ruptured,

## 1. Physical and Chemical Characteristics of Platelets:

- Platelets (*thrombocytes*) are minute discs **1 to 4  $\mu\text{m}$**  in diameter.

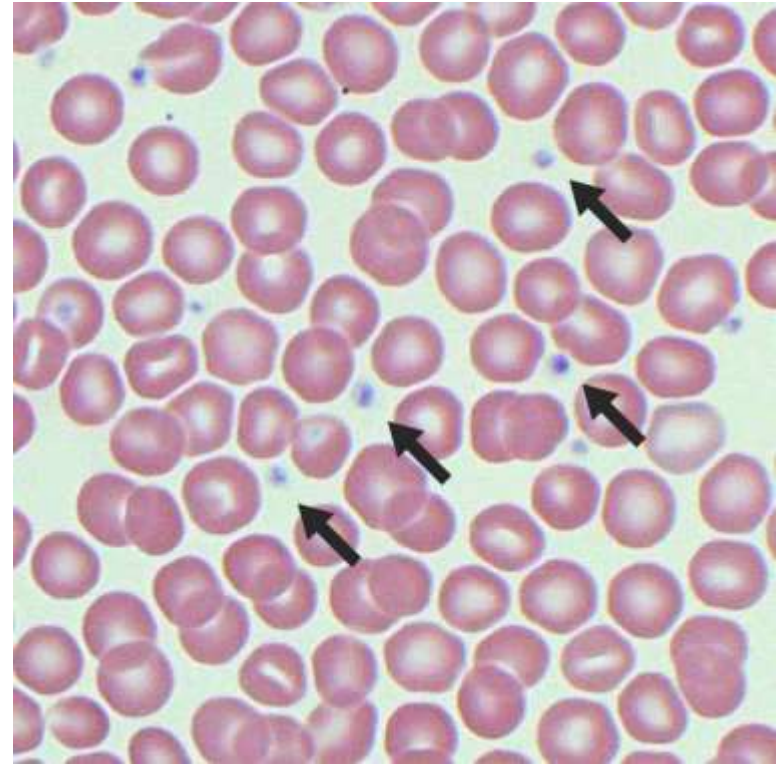


- They are formed in the bone marrow from *megakaryocytes*, which are extremely large cells of the hematopoietic series in the marrow.
- The *megakaryocytes* fragment develop into the minute platelets either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries.



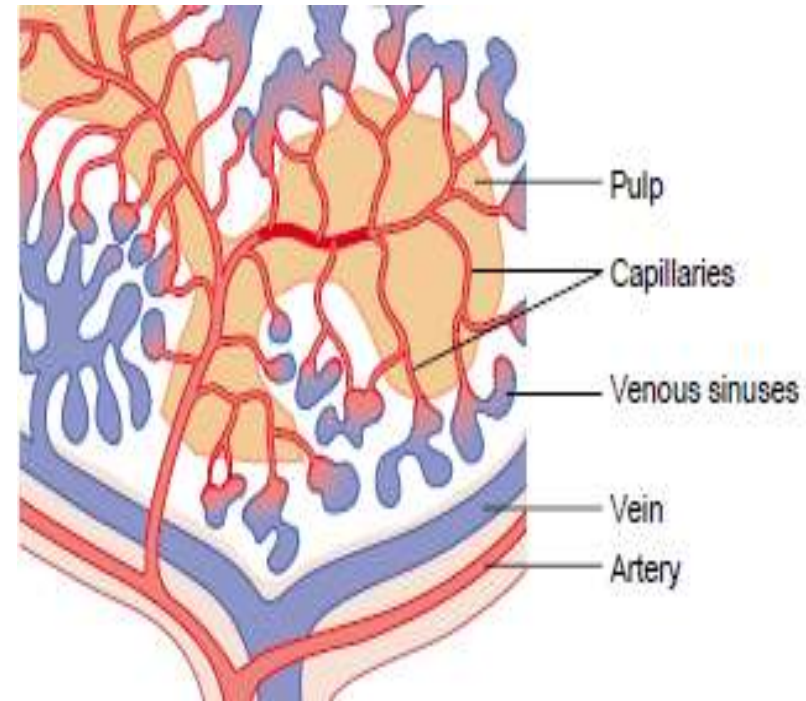


- The normal concentration of platelets in the blood is between 150,000 and 300,000 per microliter.
- The platelet is an active structure.
- It has a half life in the blood of 8 to 12 days.
- Then it is eliminated from the circulation mainly by the tissue macrophage system.





- More than one half of the platelets are removed by **macrophages** in the spleen, where the blood passes through a latticework of tight trabeculae.
- Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce.



□ In their cytoplasm are such active factors as:

(1) Actin and myosin molecules, which are contractile proteins similar to those found in muscle cells.

(2) Residuals of both the *endoplasmic reticulum* and the *Golgi apparatus* that synthesize various enzymes and especially store large quantities of calcium ions.



3) Mitochondria and enzyme systems that are capable of forming *adenosine triphosphate* (ATP) and *adenosine diphosphate* (ADP).

(4) Enzyme systems that synthesize *prostaglandins*, which are local hormones.

(5) Fibrin -stabilizing factor.

(6) A growth factor.



## ➤ The cell membrane of the platelets:

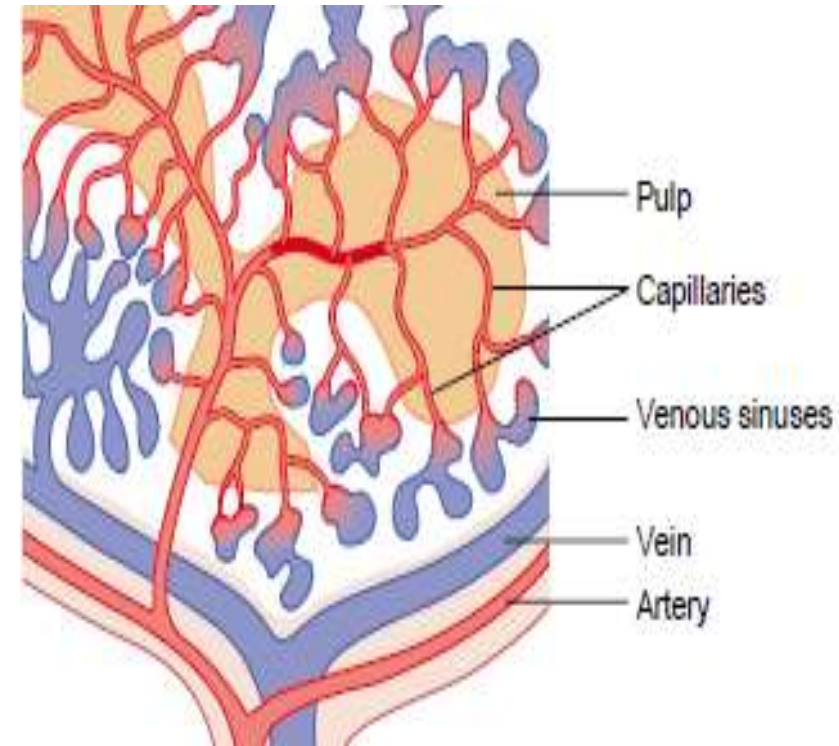
○ Its surface is coated by:

1. *Glycoproteins* that repulses adherence to normal endothelium; and yet causes adherence to *injured* areas of the vessel wall.

2. Phospholipids that activate multiple stages in the blood-clotting process.



- مكرر It has a half life in the blood of 8 to 12 days.
- Then it is eliminated from the circulation mainly by the tissue macrophage system.
- More than one half of the platelets are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae.



# ❖ Events in Hemostasis

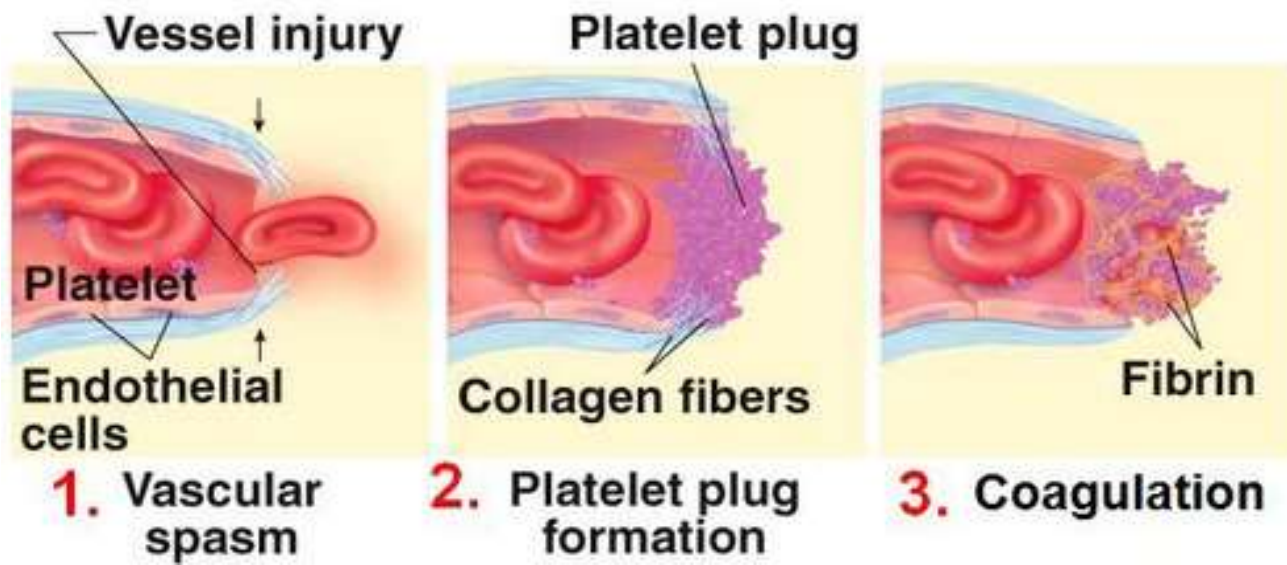
- **Hemostasis:** means prevention of blood loss.
- Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms:

(1) Vascular constriction.

(2) Formation of a platelet plug.

(3) Formation of a blood clot as a result of blood coagulation.

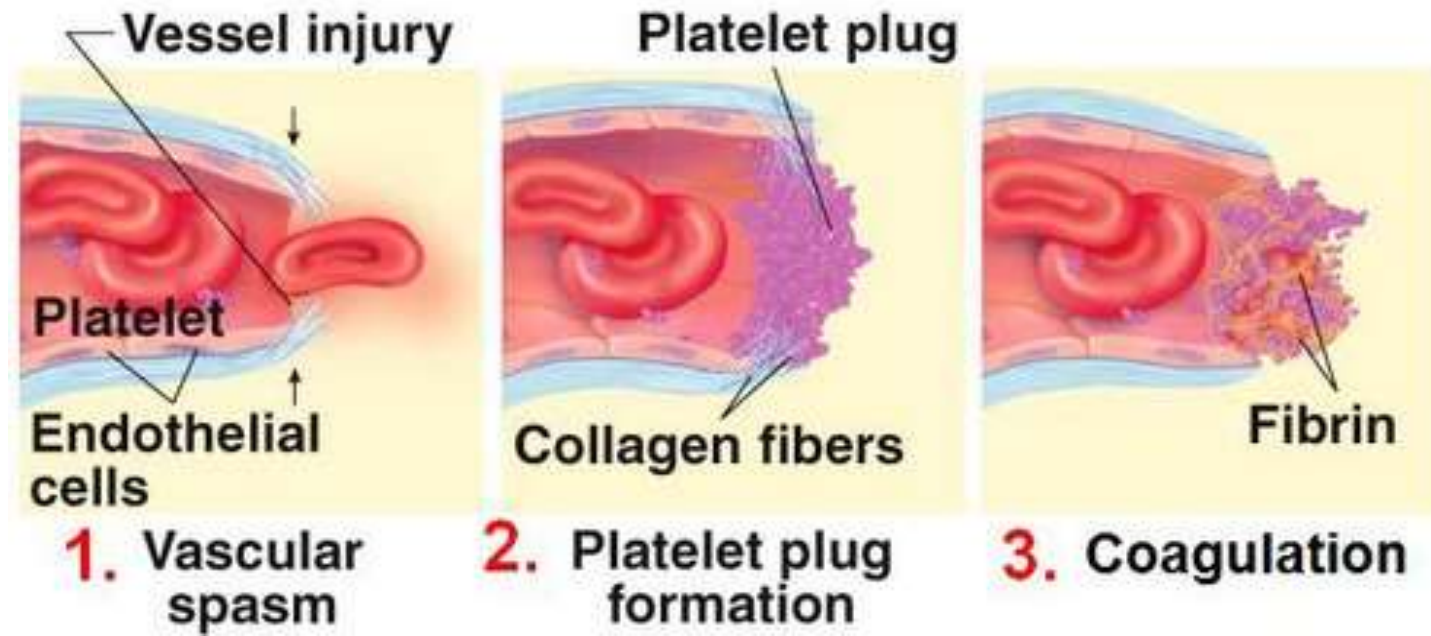
(4) Eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.





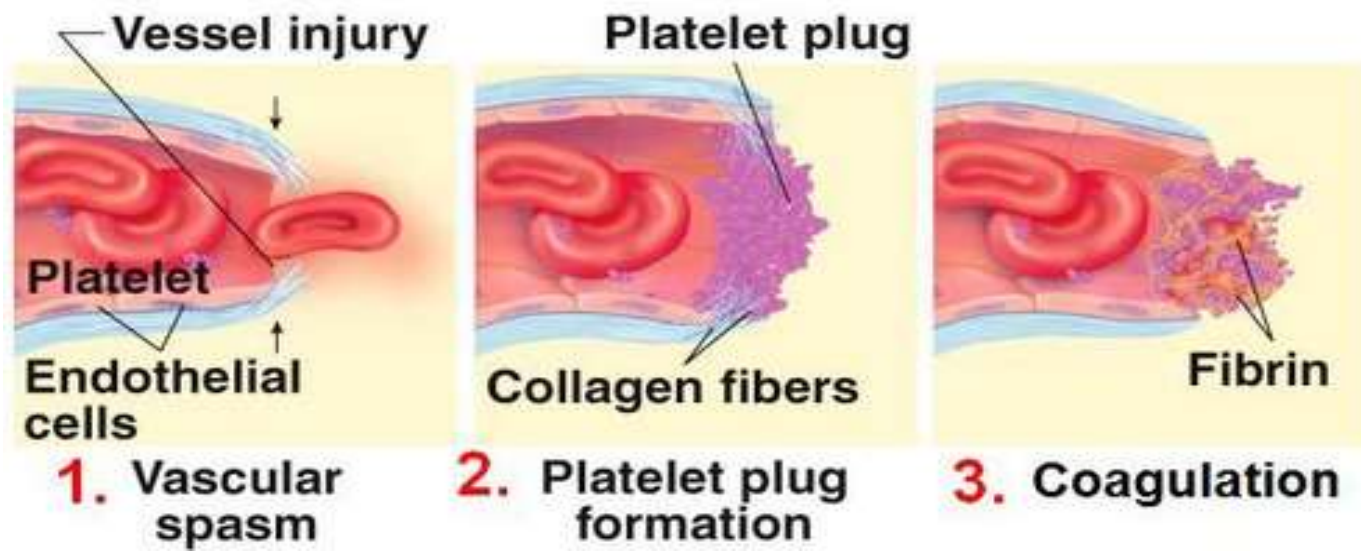
# 1) Vascular Constriction

- Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall itself causes the smooth muscle in the wall to contract; this will reduce the flow of blood from the ruptured vessel.
- The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

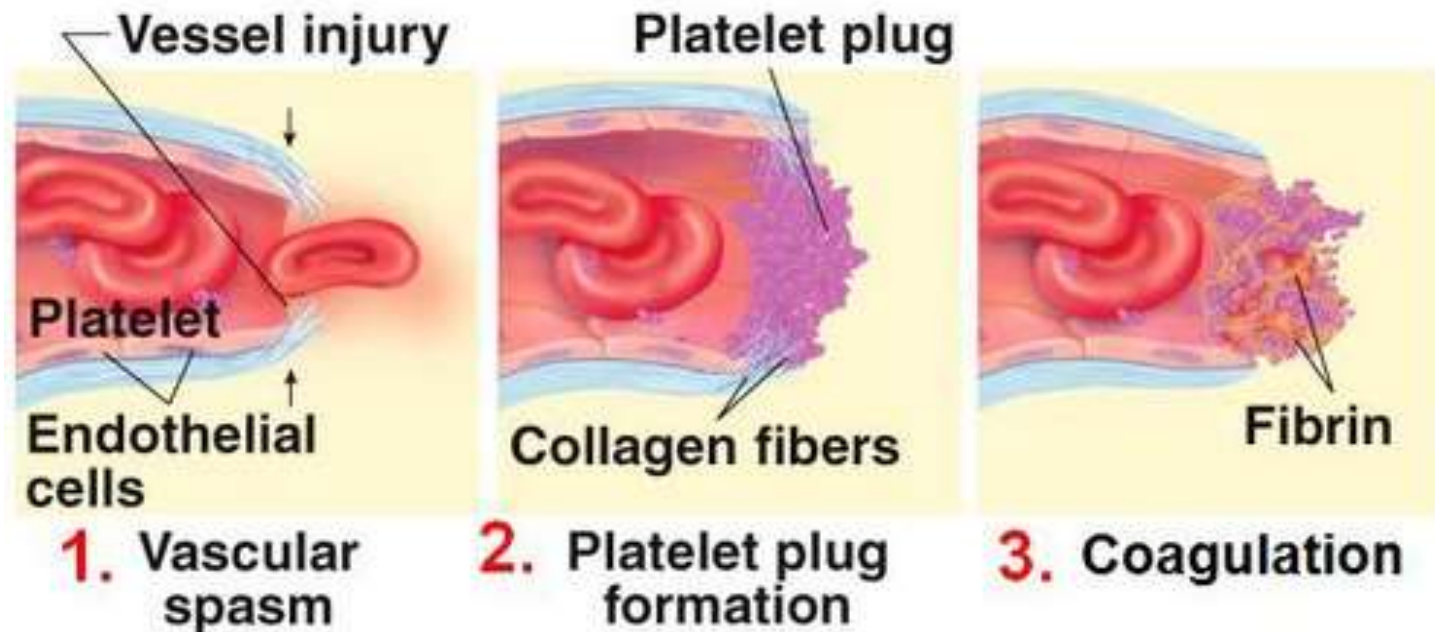


## 2) Formation of the Platelet Plug:

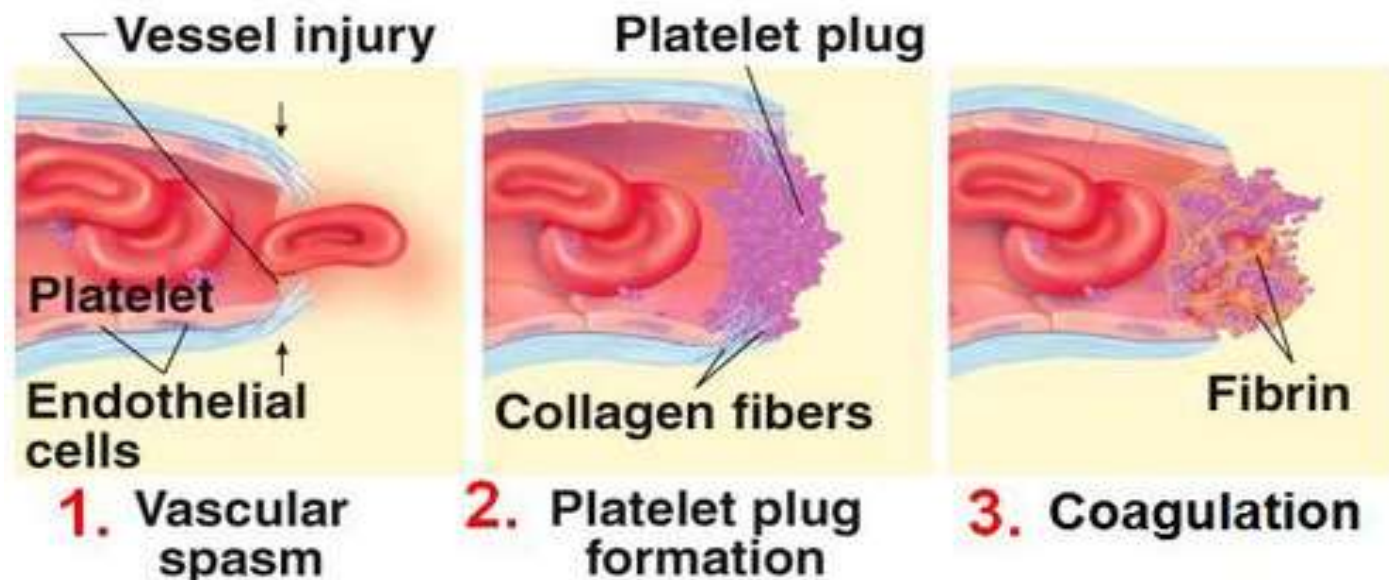
- Platelet repair of vascular openings is based on several important functions of the platelet itself.
- When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets themselves immediately change their own characteristics drastically.



- They begin to **swell**; they assume **irregular** forms with numerous **irradiating pseudopods** protruding from their surfaces; they become **sticky** so that they adhere to collagen in the tissues



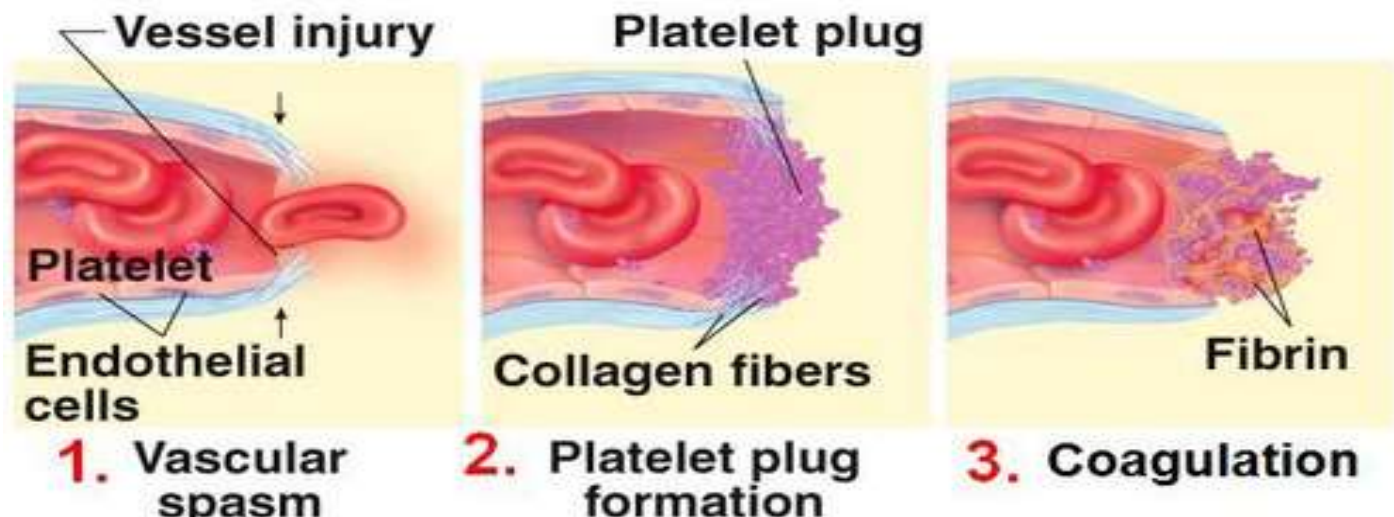
- The damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a *platelet plug*.
- This is at first a loose plug, but it is usually successful in blocking blood loss.
- Then, during the subsequent process of blood coagulation, *fibrin threads* form.
- These attach tightly to the platelets, thus constructing an *unyielding plug*.





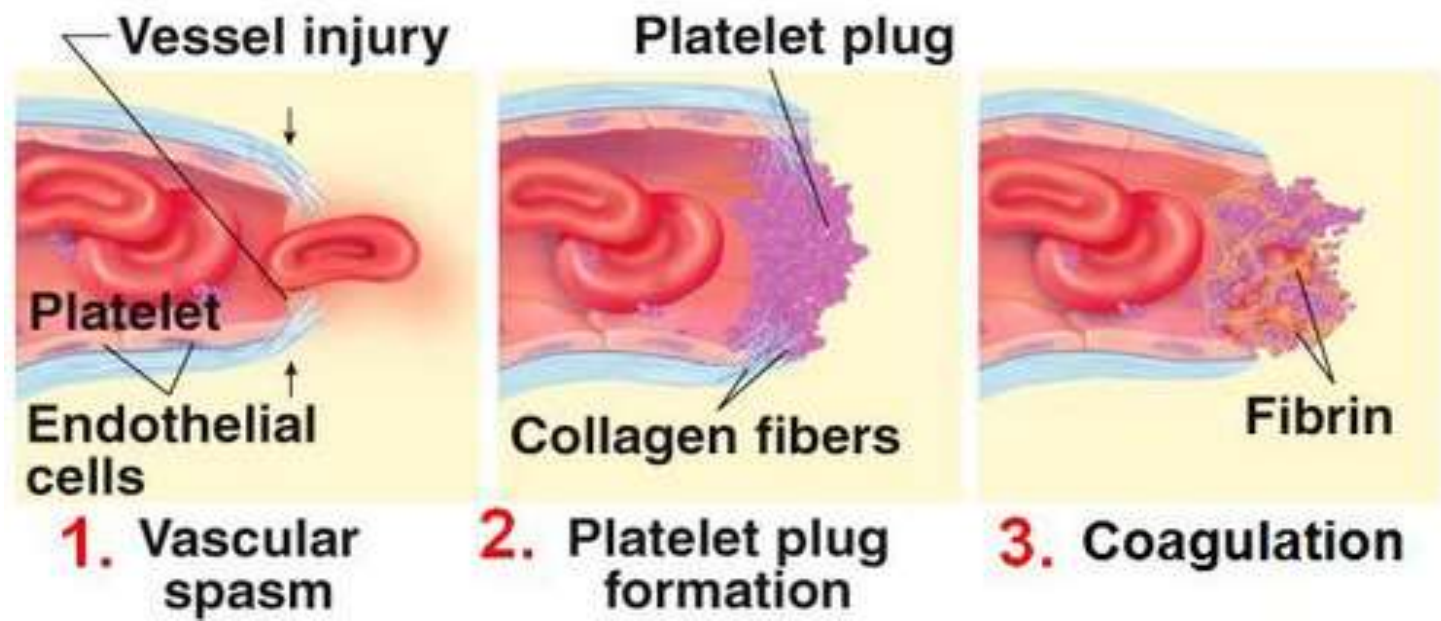
## ❖ Importance of the Platelet Mechanism for Closing Vascular Holes:

- The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels that occur many thousands of times daily.
- A person who has few blood platelets develops each day literally (exactly) thousands of small hemorrhagic areas under the skin and throughout the internal tissues, but this does not occur in the normal person.



### 3) Blood Coagulation in the Ruptured Vessel:

- The third mechanism for hemostasis is formation of the blood clot.
- Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process.





## 4) Fibrous Organization of the Blood Clot:

- Once a blood clot has formed:

- (1) It can become invaded by *fibroblasts*, which subsequently form connective tissue all through the clot.
- The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed.
  - This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.

## ❖ General Mechanism:

- All research workers in the field of blood coagulation agree that clotting takes place in three essential steps:

(1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors.

➤ The net result is formation of a complex of activated substances collectively called *prothrombin activator*.

(2) The prothrombin activator catalyzes conversion of *prothrombin* into *thrombin*.

(3) The thrombin acts as an enzyme to convert *fibrinogen* into *fibrin fibers* that enmesh platelets, blood cells, and plasma to form the clot.

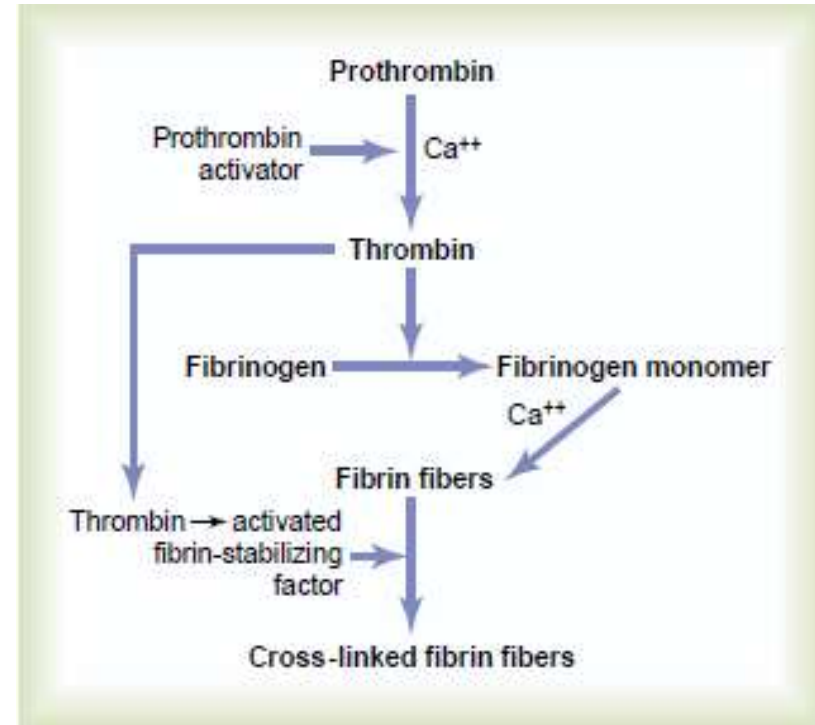


Figure 36-2

Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.

## ❖ Conversion of Prothrombin to Thrombin

- **First:** prothrombin activator is formed as a result of rupture of a blood vessel or as a result of damage to special substances in the blood.
- **Second:** the prothrombin activator, in the presence of sufficient amounts of ionic  $\text{Ca}^{++}$ , causes conversion of prothrombin to thrombin.
- **Third:** the thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds.

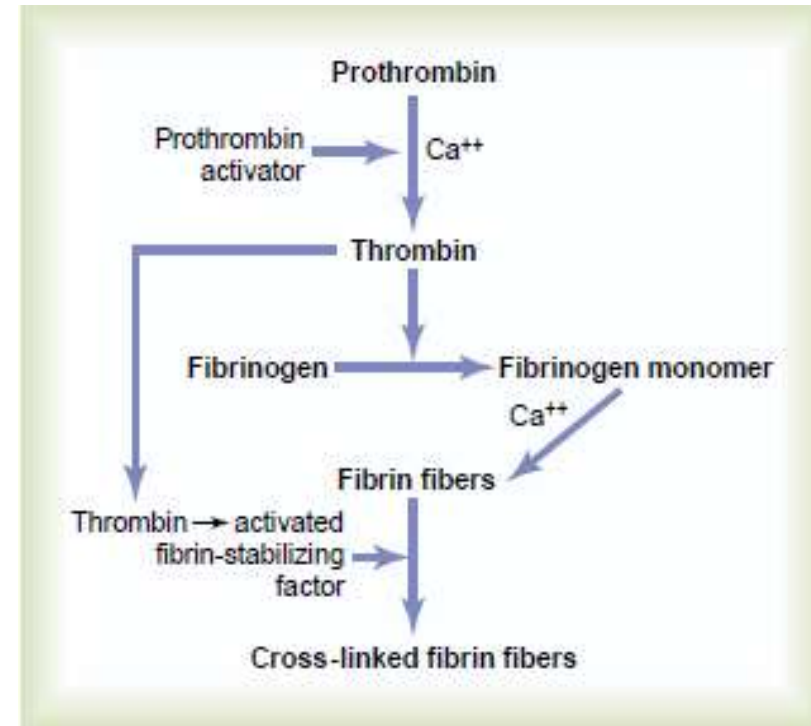


Figure 36-2

Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.

- Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point, because these terminal steps normally occur rapidly to form the clot itself.
- Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue.

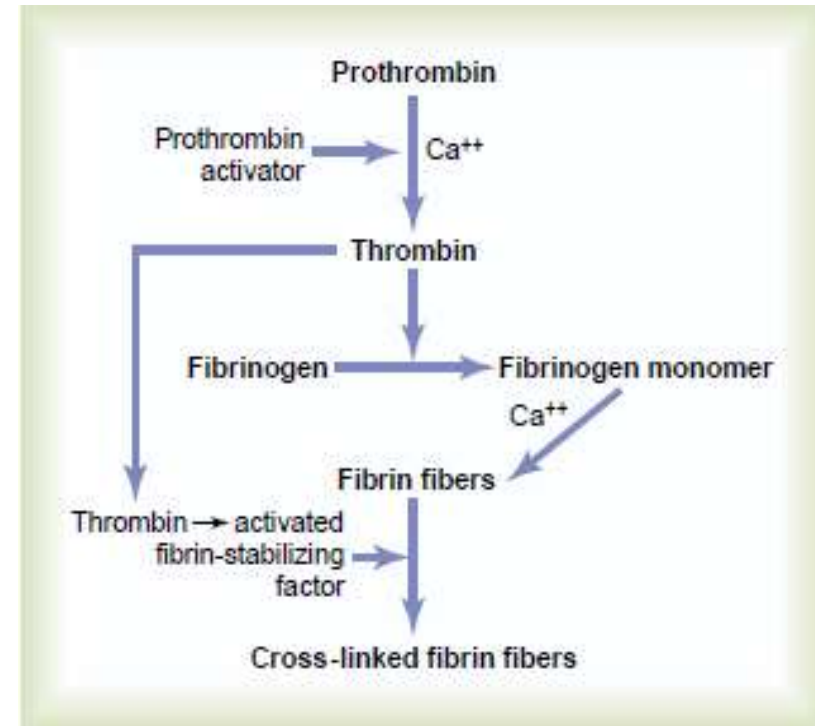
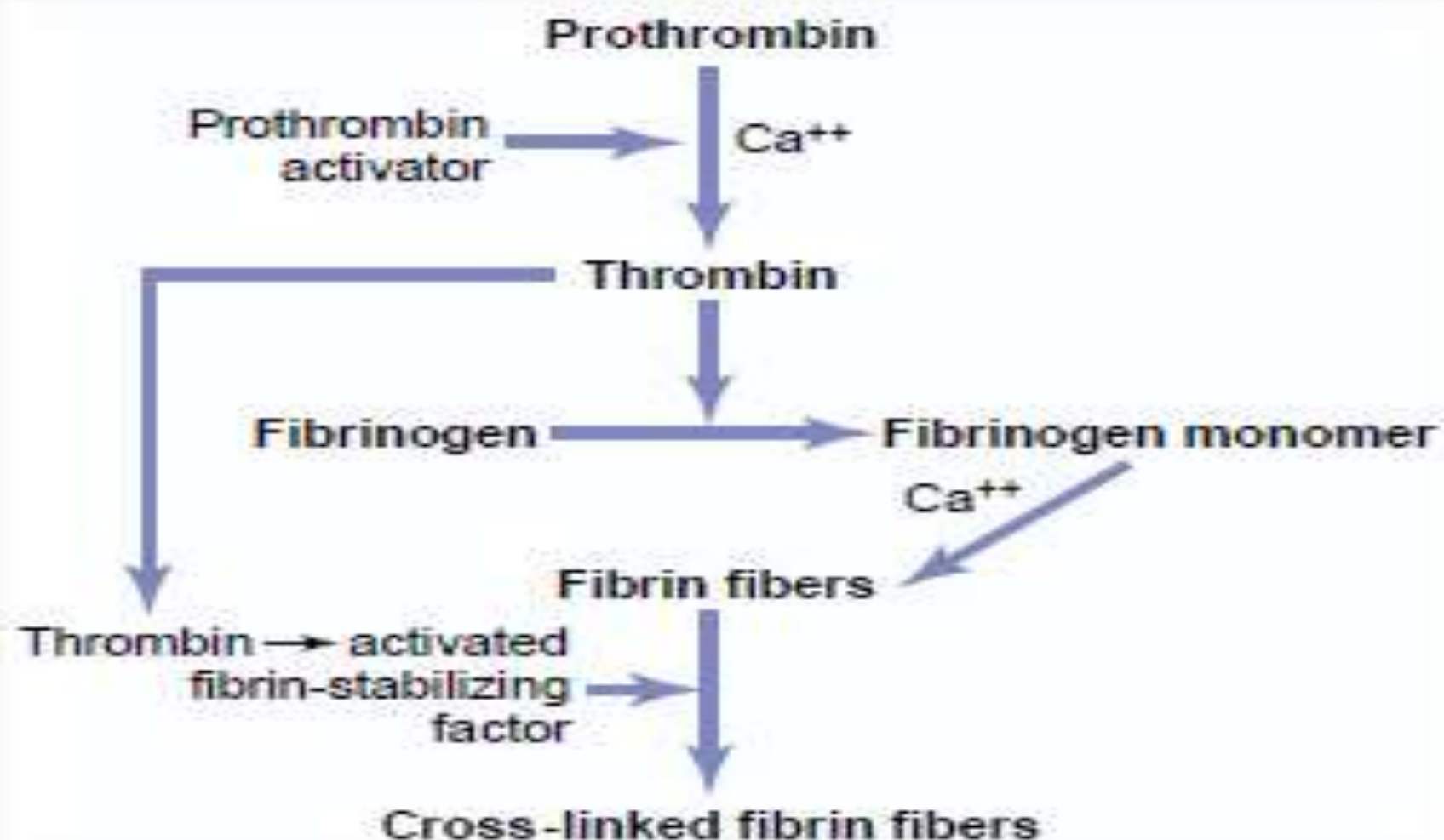


Figure 36-2

Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.



**Figure 36-2**

Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.



**THANK  
YOU**

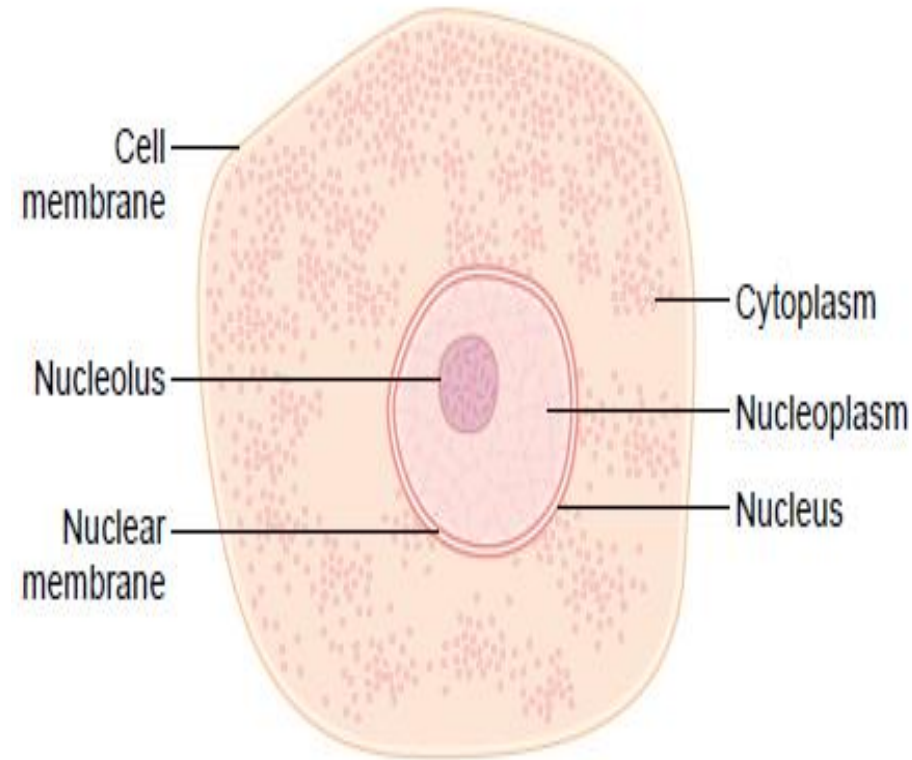


# CELL PHYSIOLOGY

د. محمد عيسى السبعراوي  
ماجستير فسلجة طبية

# ❖ Organization of the Cell

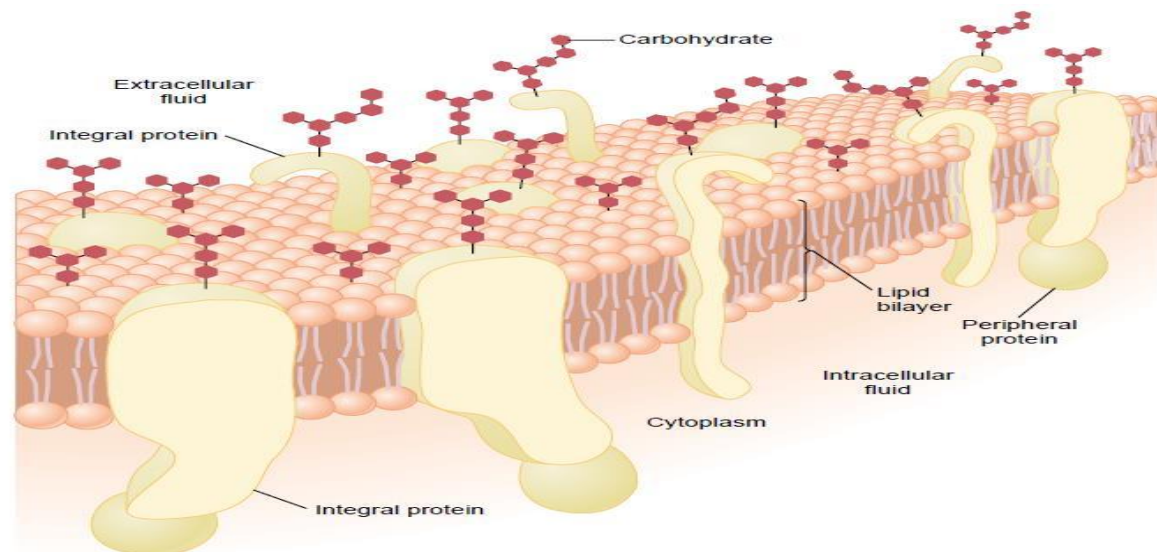
- A typical cell formed by two major parts the *nucleus* and the *cytoplasm*.
- The nucleus is separated from the cytoplasm by a *nuclear membrane*.
- The cytoplasm is separated from the surrounding fluids by a *cell membrane*, also called the *plasma membrane*.
- The different substances that make up the cell are collectively called *protoplasm*.



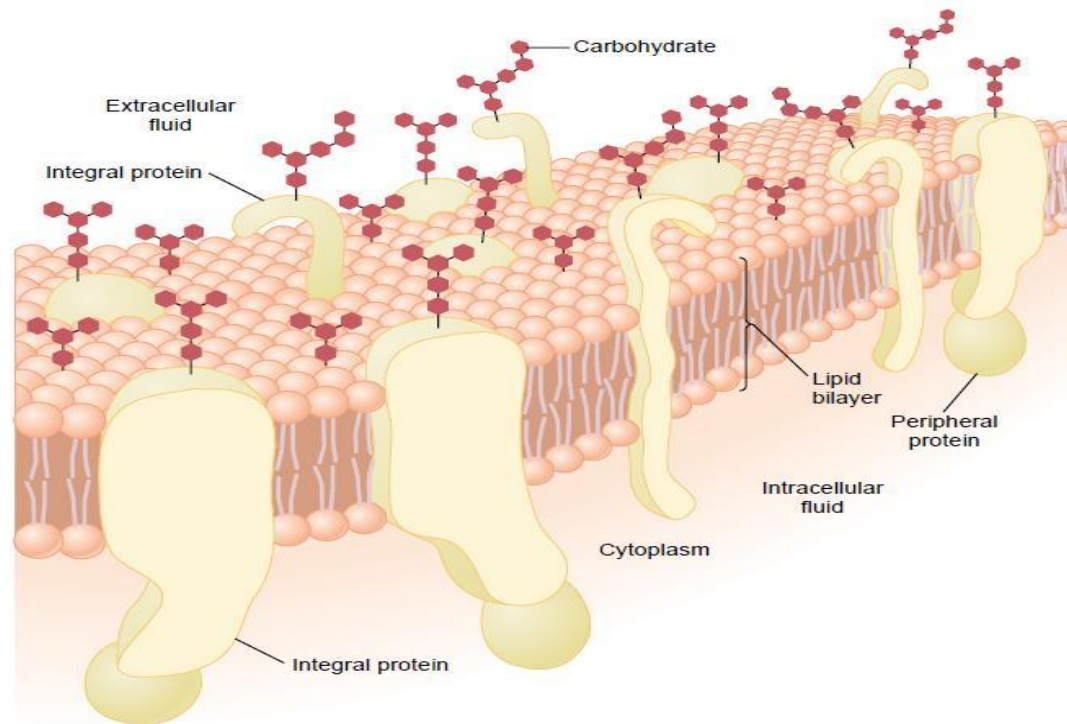
# ❖ Physical Structure of the Cell:

## ☐ Membranous Structures of the Cell

- Most organelles of the cell are covered by membranes composed primarily of **lipids** and **proteins**.
- These membranes include the *cell membrane*, *nuclear membrane*, *membrane of the endoplasmic reticulum*, and *membranes of the mitochondria*, *lysosomes*, and *Golgi apparatus*.
- The lipids of the membranes provide a barrier that **impedes** the movement of **water** and **water-soluble substances** from one cell compartment to another because water is not soluble in lipids.

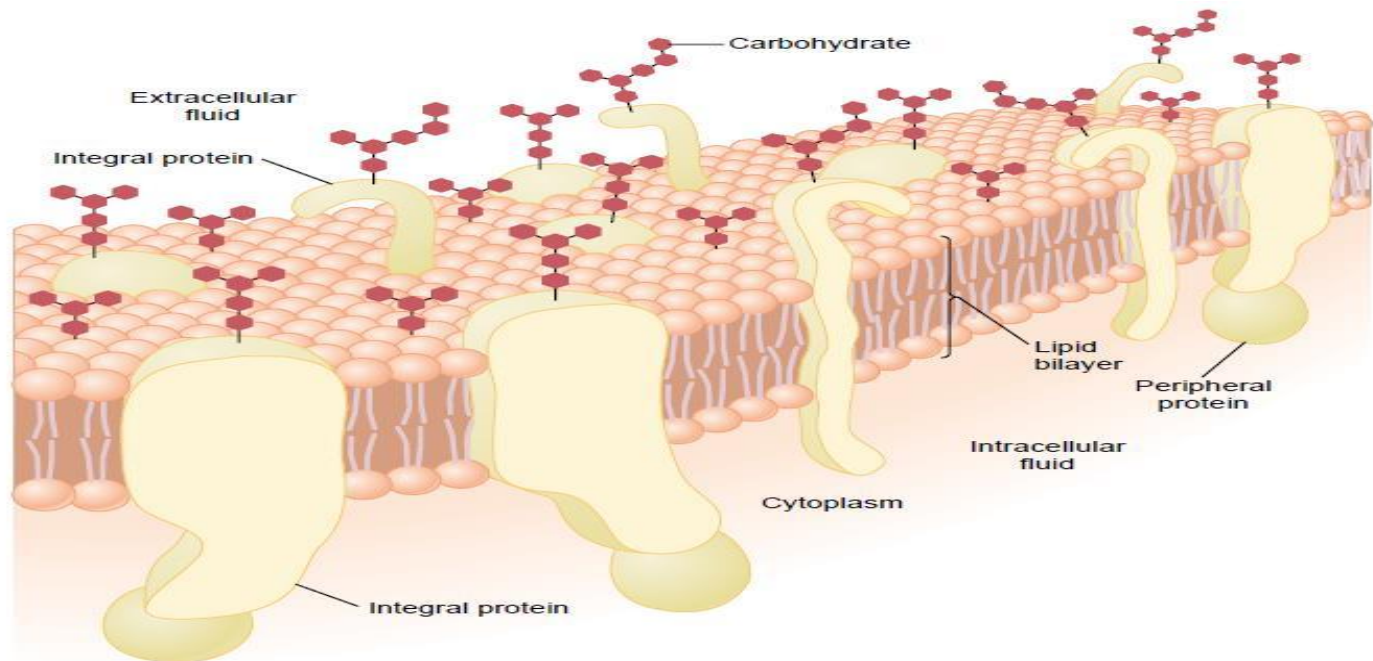


- Protein molecules in the membrane often do **penetrate** all the way through the membrane, thus providing specialized **pathways**, often organized into actual **pores**, for passage of specific substances through the membrane.
- Also, many other membrane proteins are *enzymes* that catalyze a multitude of different chemical reactions.



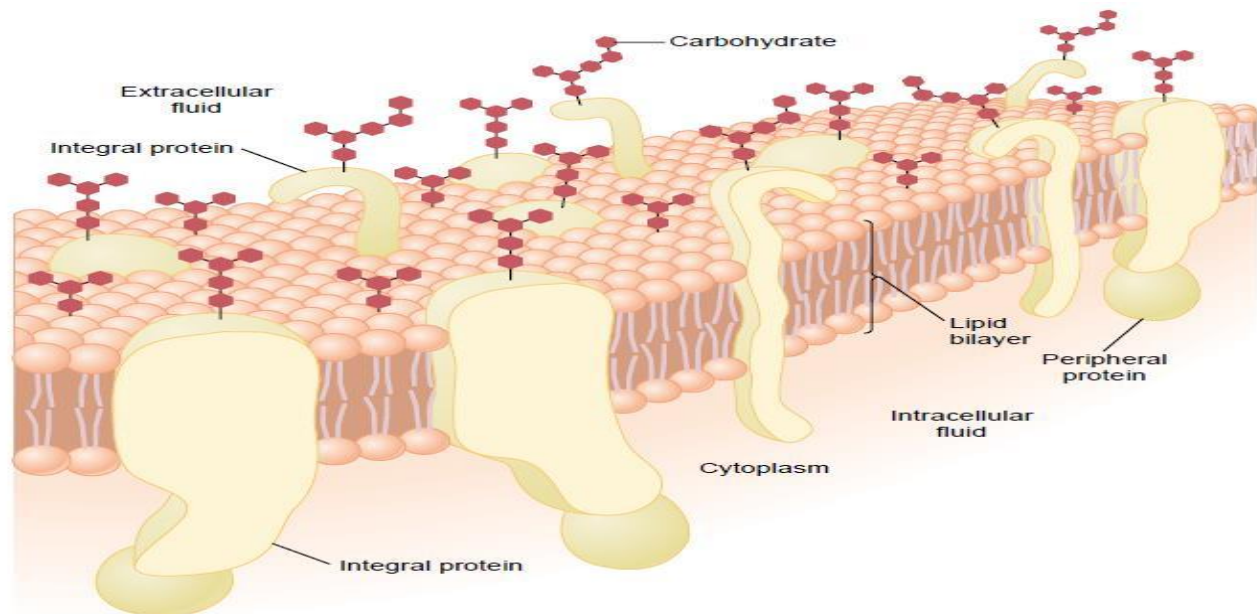
# ❖ Cell Membrane

- The cell membrane which envelops the cell, is a thin, pliable, elastic structure only 7.5 to 10 nanometers thick.
- It is composed almost entirely of proteins and lipids (proteins 55%; phospholipids 25%; cholesterol 13%; other lipids 4% and carbohydrates 3%).



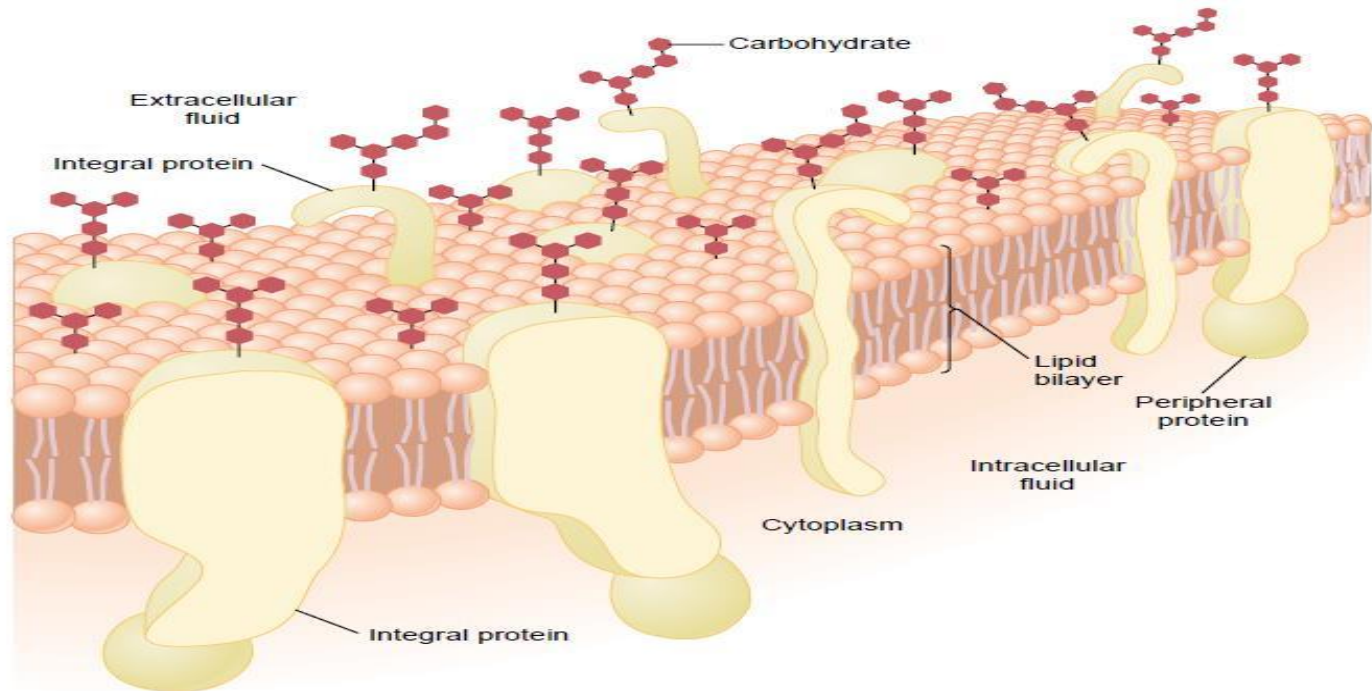
# ❖ Lipid Barrier of the Cell Membrane Impedes Water Penetration:

- The basic structure of cell membrane is a *lipid bilayer*, which is a thin, double-layered film of lipids.
- Interspersed in this lipid film are large globular protein molecules.
- The basic lipid bilayer is composed of phospholipid molecules.
- One end of each phospholipid molecule is soluble in water; that is **hydrophilic**.
- The other end is soluble only in fats; that is **hydrophobic**.



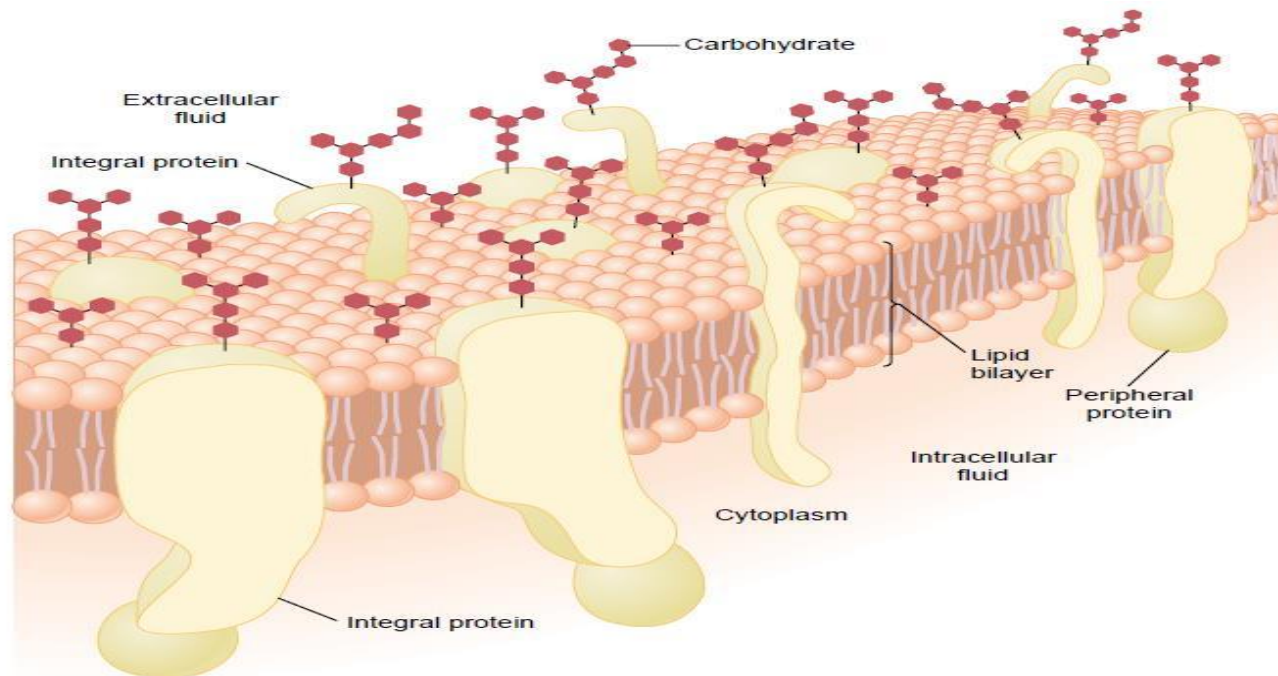


- The lipid layer of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea.
- Conversely, fat-soluble substances, such as oxygen, carbon dioxide, and alcohol, can penetrate this portion of the membrane with ease.

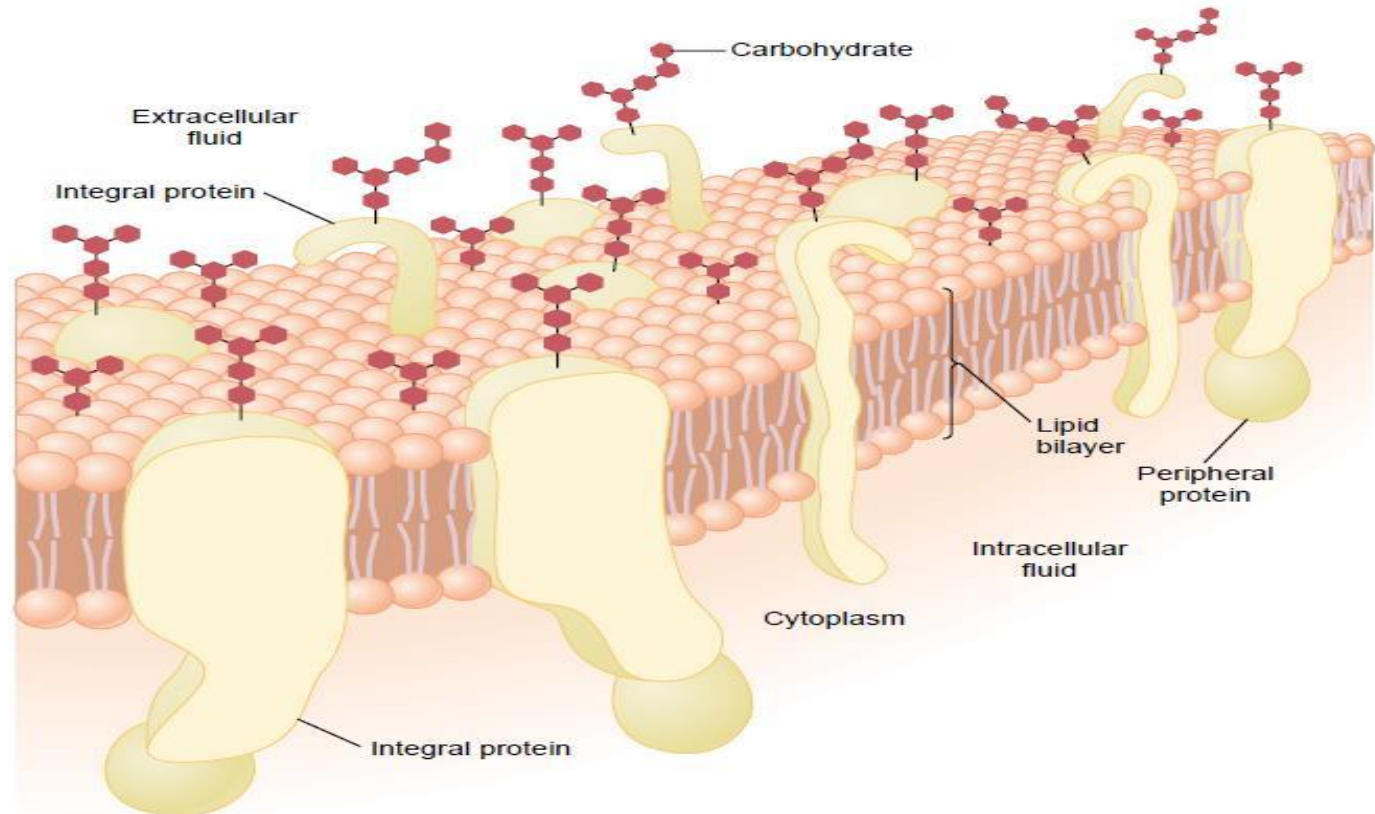


## ❖ Cell Membrane Proteins.

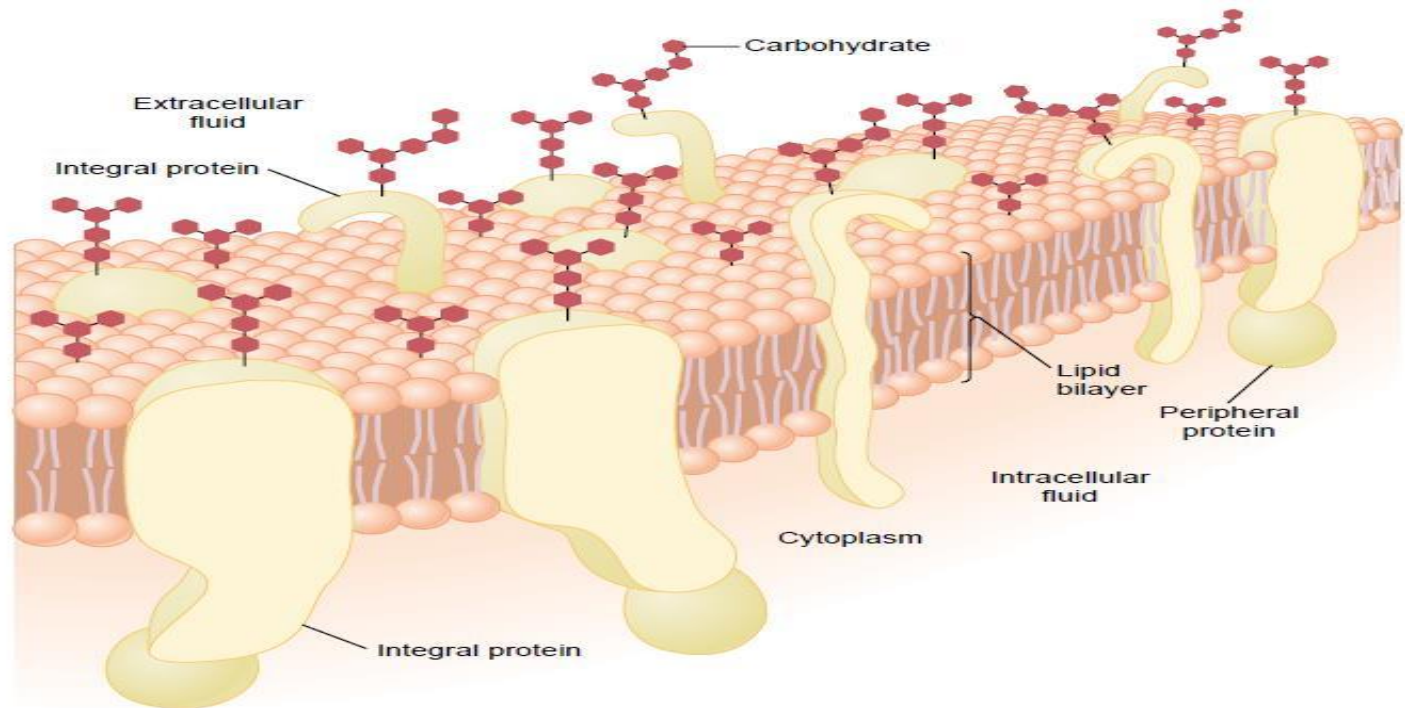
- There are globular masses floating in the lipid bilayer. These are membrane proteins, most of which are *glycoproteins*. Two types of proteins are present:
- **integral proteins** that protrude all the way through the membrane.
- **peripheral proteins** that are attached only to one surface of the membrane and do not penetrate all the way through.



- Many of the integral proteins provide structural *channels* (or *pores*) through which water molecules and water-soluble substances, especially ions, can diffuse between the extracellular and intracellular fluids.
- These protein channels also have selective properties that allow preferential diffusion of some substances over others.



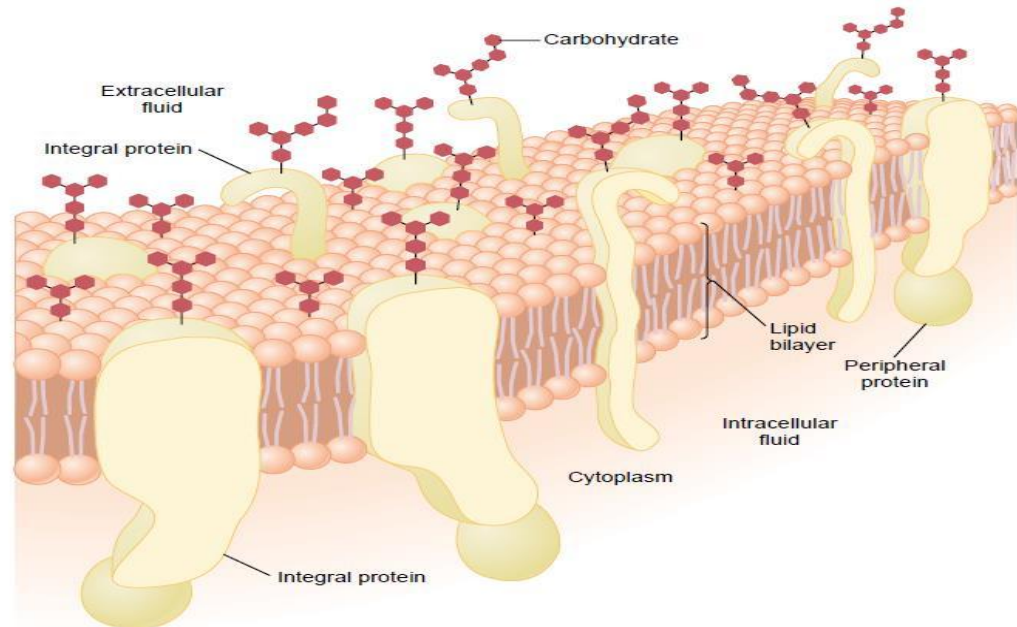
- Other integral proteins act as *carrier proteins* for transporting substances that otherwise could not penetrate the lipid bilayer.
- Sometimes these even transport substances in the direction opposite to their natural direction of diffusion, which is called “active transport.”



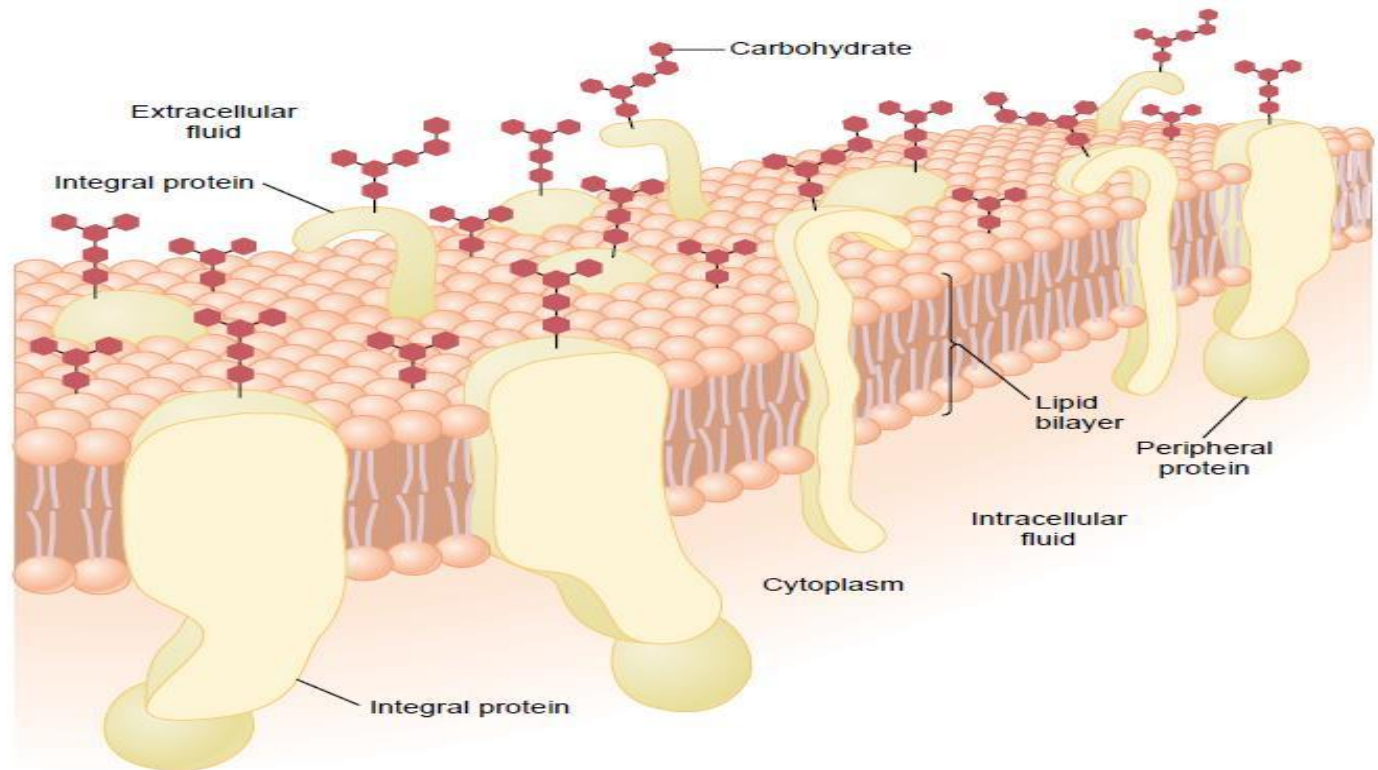


➤ Still other integral membrane protein act as *enzymes*.

➤ Integral membrane proteins can also serve as a *receptors* for water-soluble chemicals, such as peptide hormones, that do not easily penetrate the cell membrane.



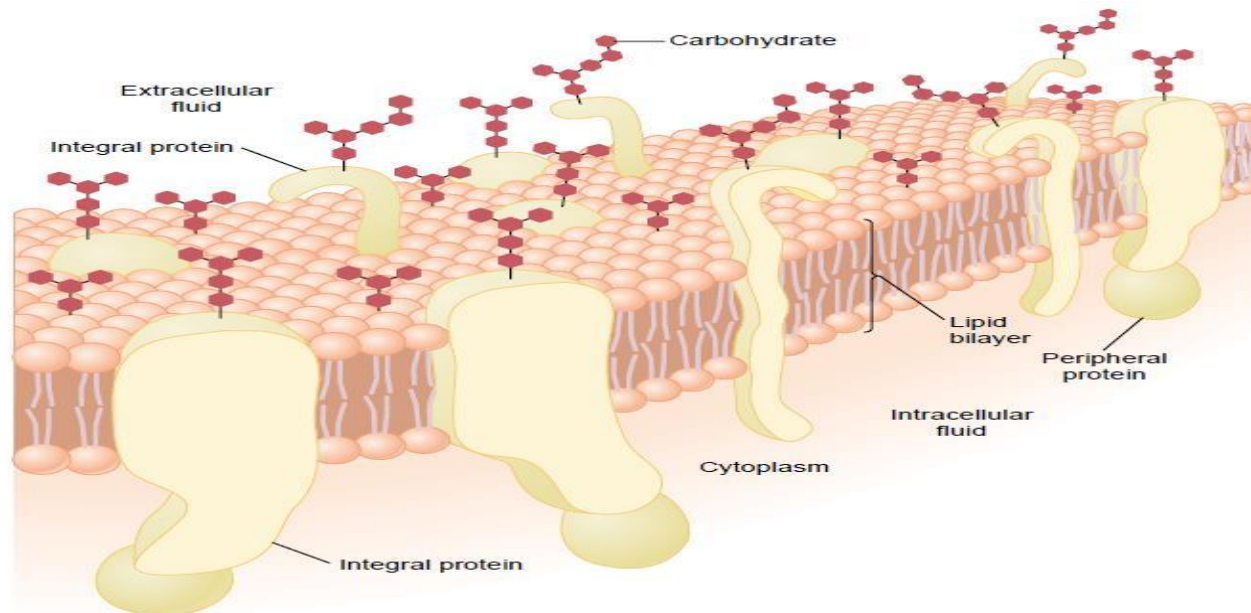
- integral proteins spanning the cell membrane provide a means of conveying information about the environment to the cell interior.
- Peripheral protein molecules are often attached to the integral proteins, their function almost entirely as enzymes or as controllers of transport of substances through the cell membrane “pores.”





## ❖ Membrane Carbohydrates—The Cell “Glycocalyx .”

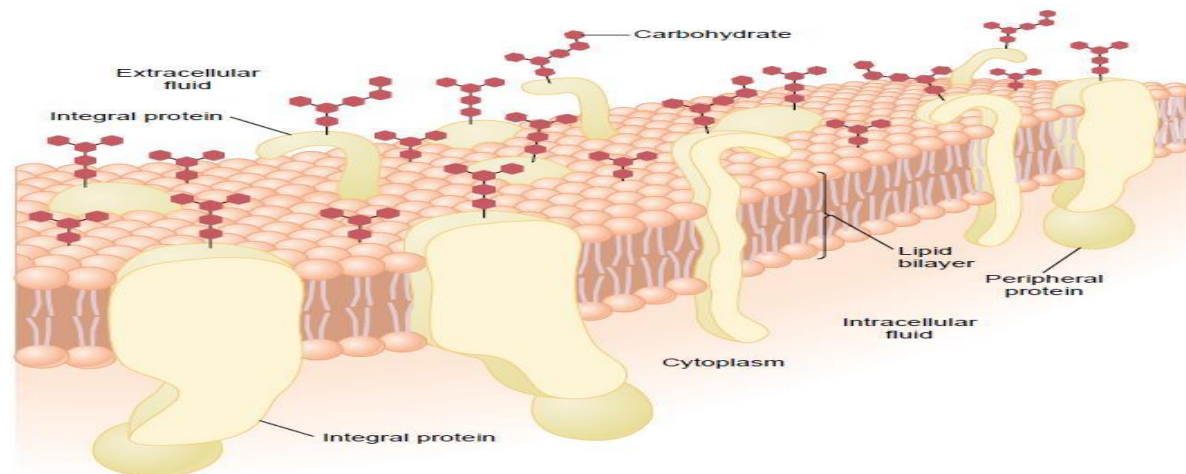
- Membrane carbohydrates occur almost invariably in combination with proteins or lipids in the form of *glycoprotein* or *glycolipids* .
- The entire outside surface of the cell often has a loose carbohydrate coat called the *glycocalyx* .



❖ The carbohydrate moieties attached to the outer surface of the cell have several important functions:

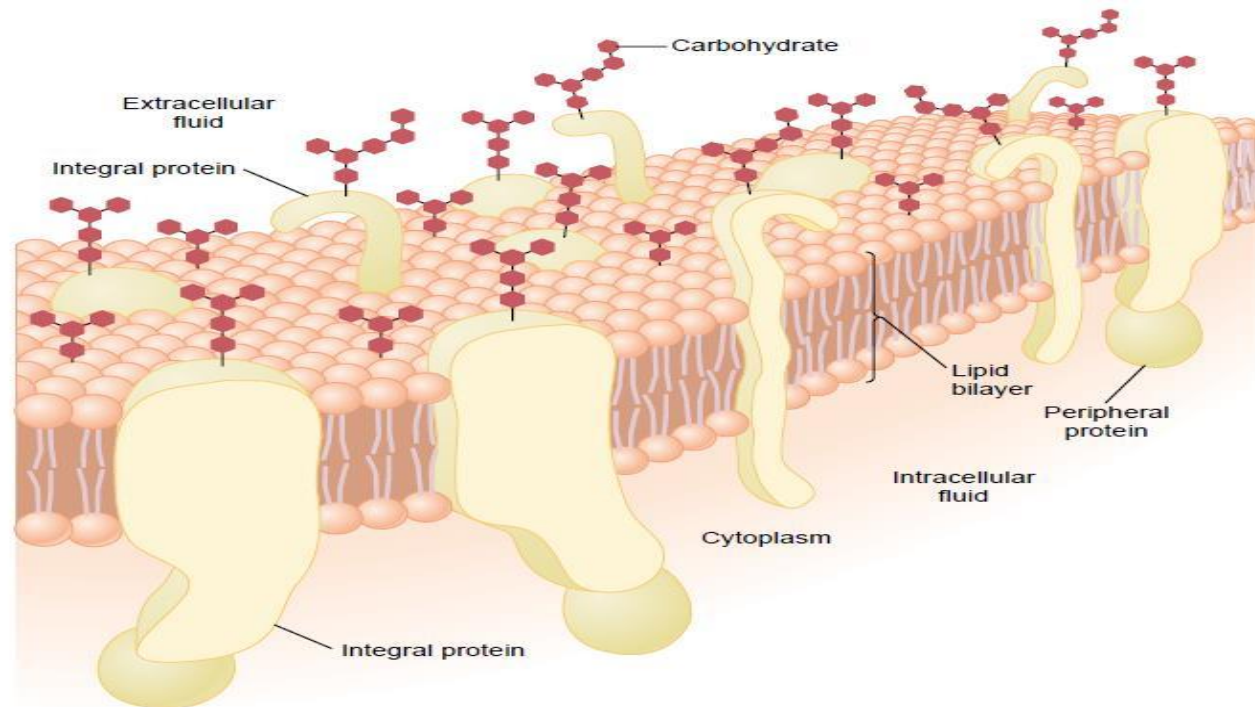
(1) Many of them have a negative electrical charge, which gives most cells an overall negative surface charge that repels other negative objects.

(2) The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cells to one another.



(3) Many of the carbohydrates act as *receptor substances* for binding hormones, such as insulin; when bound, this combination activates attached internal proteins that, in turn, activate a cascade of intracellular enzymes.

(4) Some carbohydrate moieties enter into immune reactions.



# ❖ Cytoplasm and Its Organelles:

It consist of five important organelles:

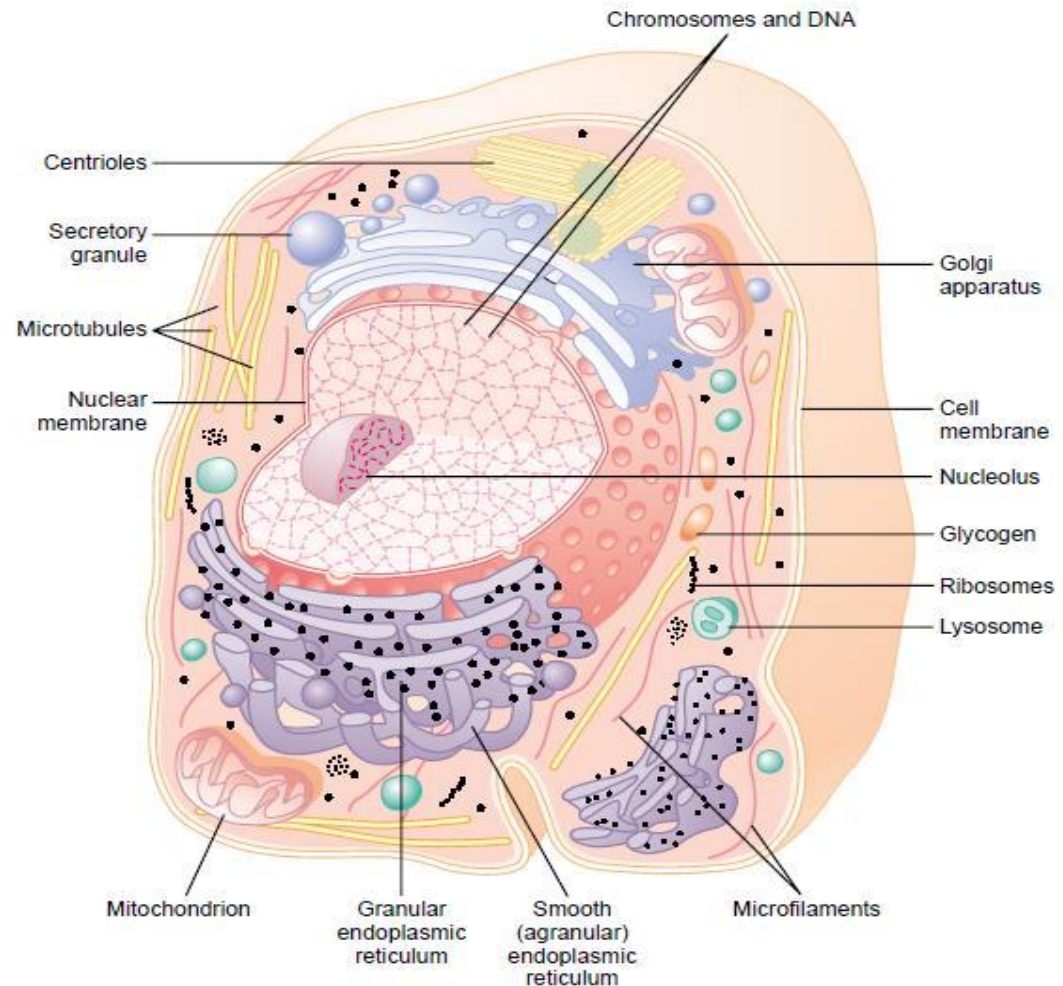
➤ Endoplasmic reticulum.

➤ The Golgi apparatus

➤ Mitochondria.

➤ Lysosomes.

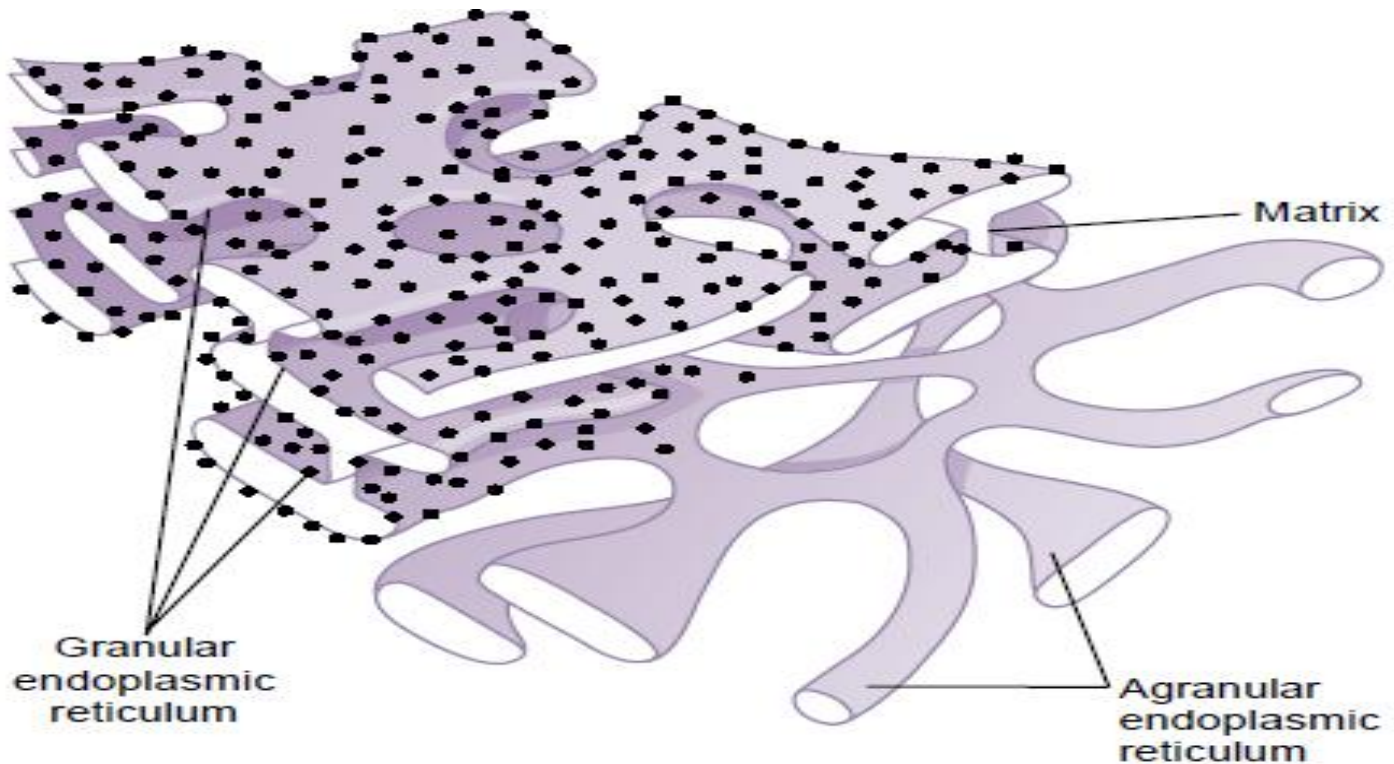
➤ Peroxisomes.



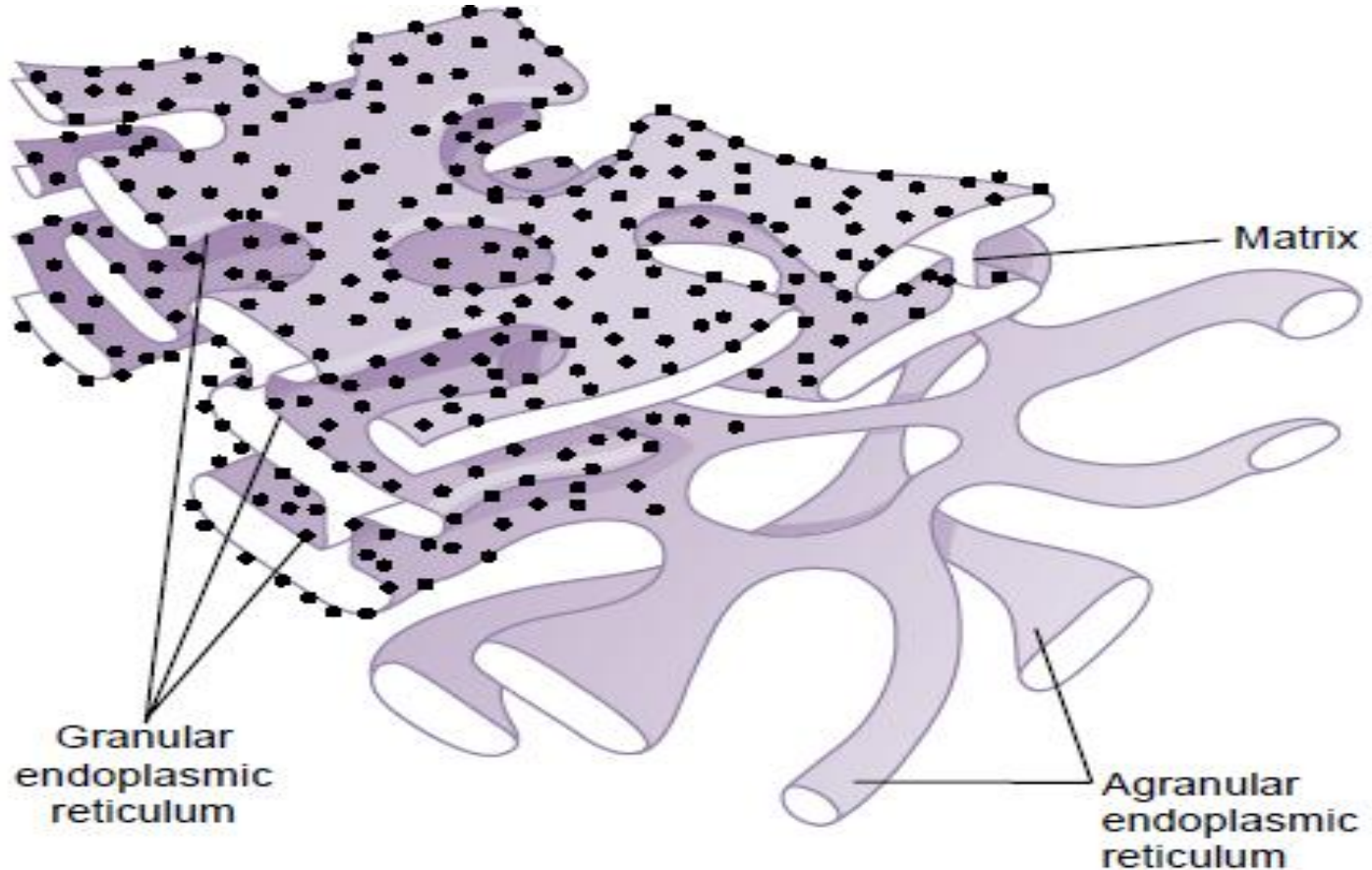


# ❖ Endoplasmic Reticulum

- It's a network of tubular and flat vesicular structures in the cytoplasm; The tubules and vesicles interconnect with one another. Also, their walls are constructed of lipid bilayer membranes that contain large amounts of proteins.

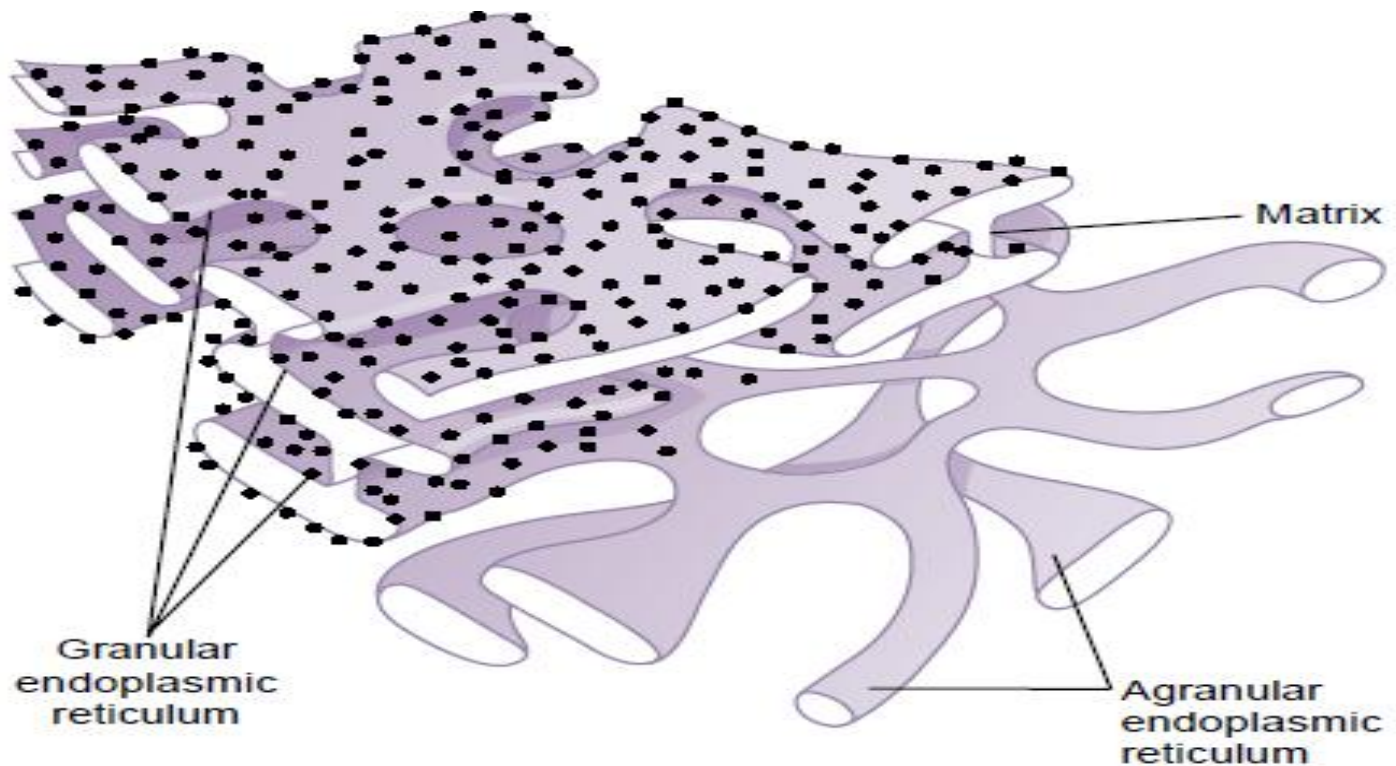


- The space inside the tubules and vesicles is filled with *endoplasmic matrix*, a watery medium.
- The space inside the endoplasmic reticulum is connected with the space between the two membrane surfaces of the nuclear membrane.



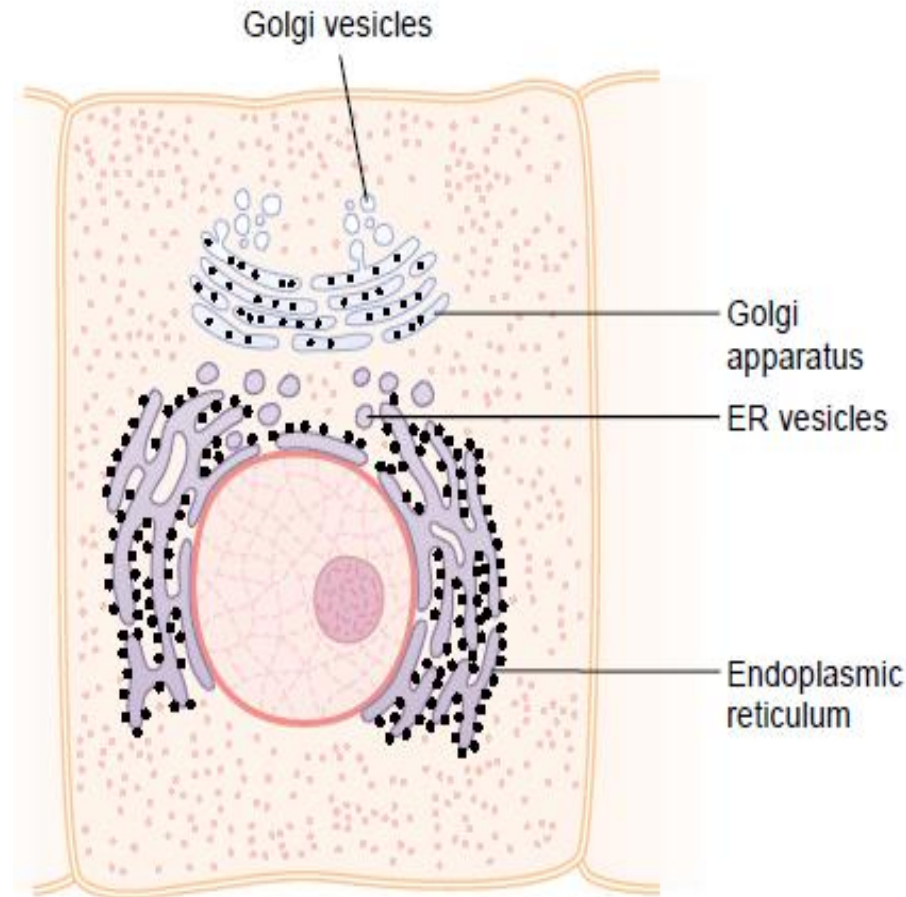


- The vast surface area of this reticulum and the multiple enzyme systems attached to its membranes provide machinery for a major share of the metabolic functions of the cell.



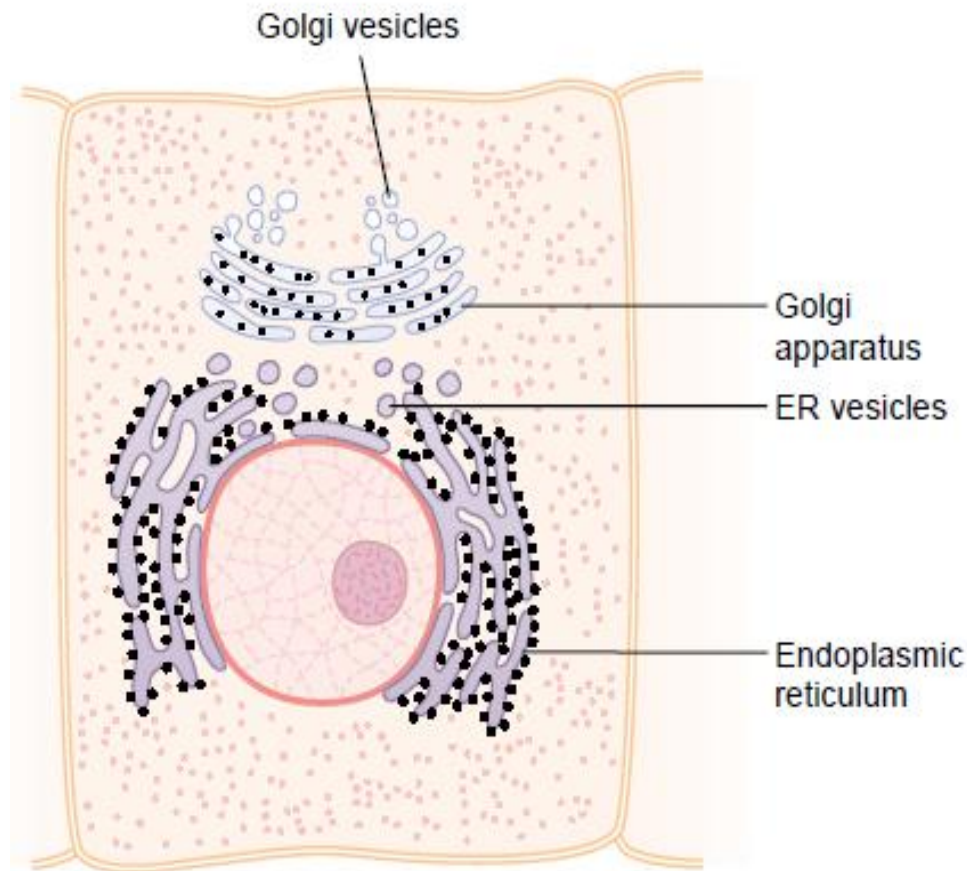
## ❖ Ribosomes and the Granular Endoplasmic Reticulum.

- Attached to the outer surfaces of many parts of the endoplasmic reticulum are large numbers of minute granular particles called *ribosomes*.
- Where these are present, the reticulum is called the *granular endoplasmic Reticulum*.
- They function to synthesize new protein molecules.



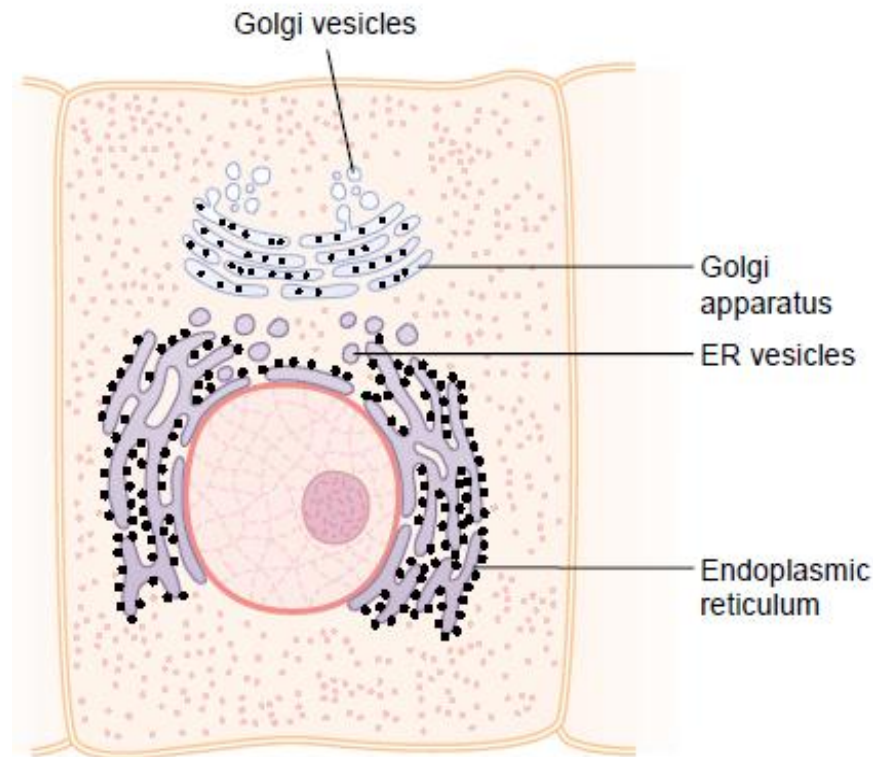
## ❖ A granular Endoplasmic Reticulum.

- Part of the endoplasmic reticulum has no attached ribosomes .
- This part is called the *agranular, or smooth, endoplasmic reticulum*.
- its functions is synthesis of lipid substances.



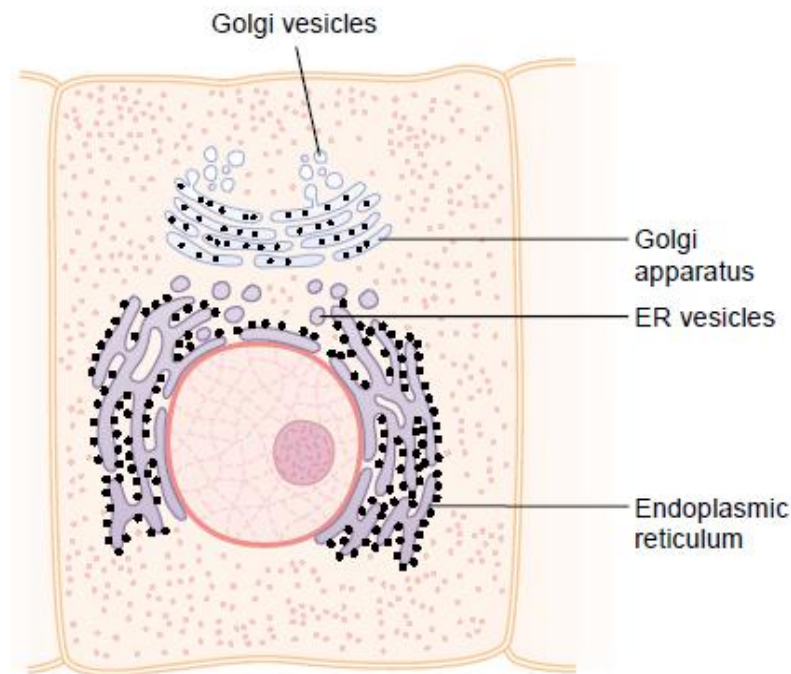
## ❖ Golgi Apparatus:

- Is closely related to the endoplasmic reticulum.
- It has membranes similar to those of the agranular endoplasmic reticulum.
- It usually is composed of four or more stacked layers of thin, flat, enclosed vesicles lying near one side of the nucleus.
- This apparatus is prominent in secretory cells, where it is located on the side of the cell from which the secretory substances are extruded.



➤ The Golgi apparatus functions in association with the endoplasmic reticulum, small “transport vesicles” (endoplasmic reticulum vesicles) continually pinch off from the endoplasmic reticulum then fused with the Golgi apparatus. So, substances entrapped in the ER vesicles are transported to the Golgi apparatus.

➤ The transported substances are then processed in the Golgi apparatus to form lysosomes, secretory vesicles and other cytoplasmic components



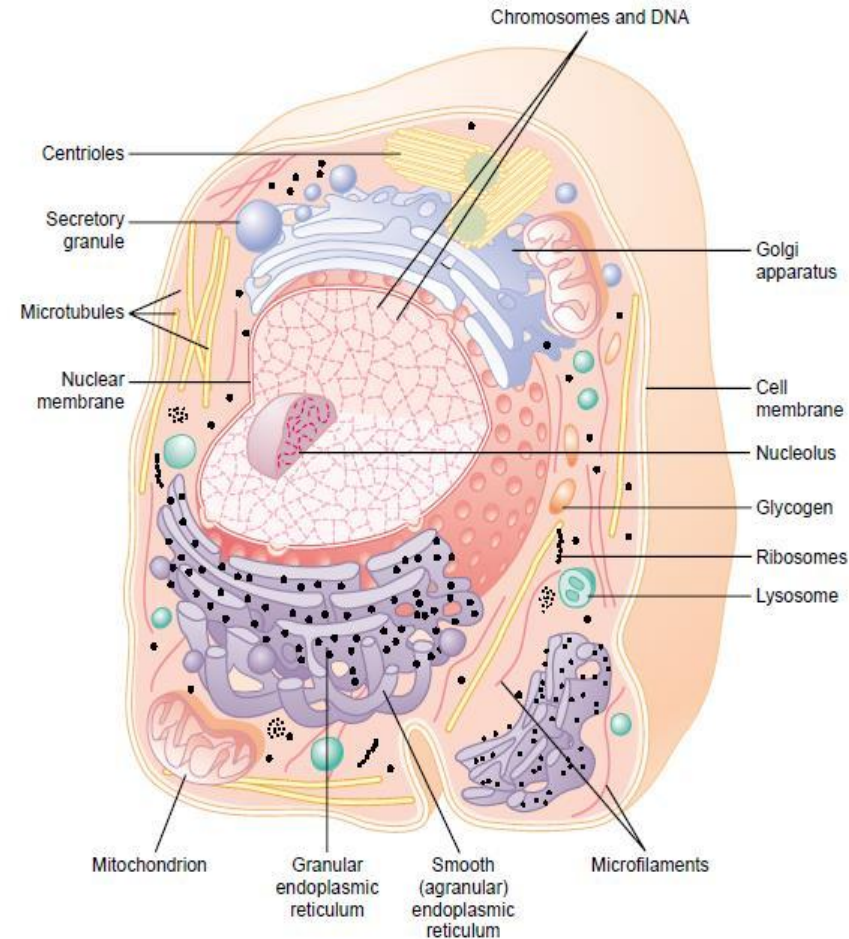


# ❖ Lysosomes

➤ Its vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasm.

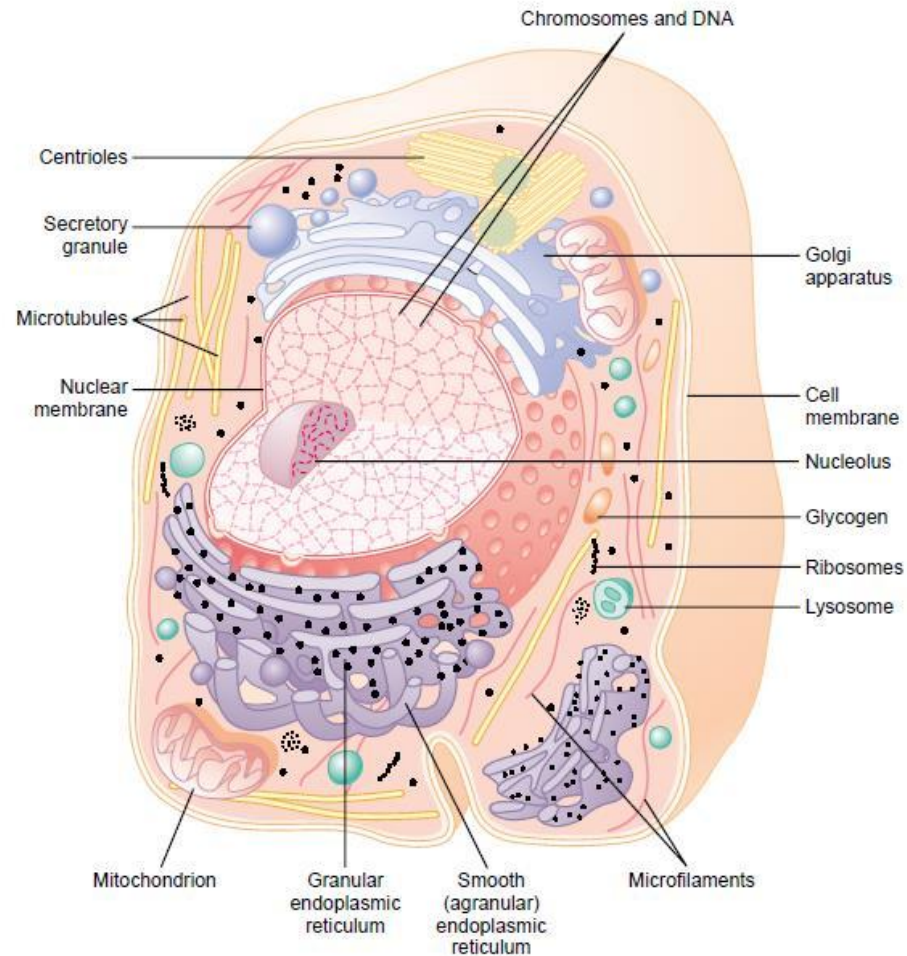
➤ The lysosomes provide an *intracellular digestive system* that allows the cell to digest:

- (1) Damaged cellular structures.
- (2) Food particles that have been ingested by the cell.
- (3) Unwanted matter such as bacteria.



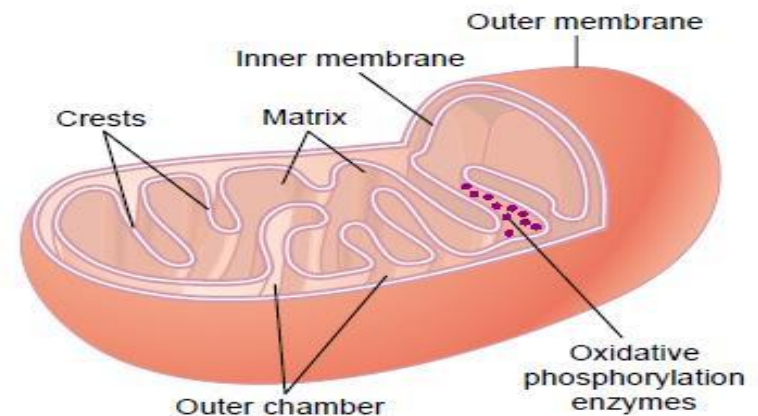


- It is surrounded by a typical lipid bilayer membrane and is filled with large numbers of small granules, which are protein aggregates of as many as 40 different *hydrolase (digestive) enzymes*.
- A hydrolytic enzyme is capable of splitting an organic compound into two or more parts (protein, glycogen, and lipids).
- The membrane surrounding the lysosome prevents the hydrolytic enzymes from their digestive actions.

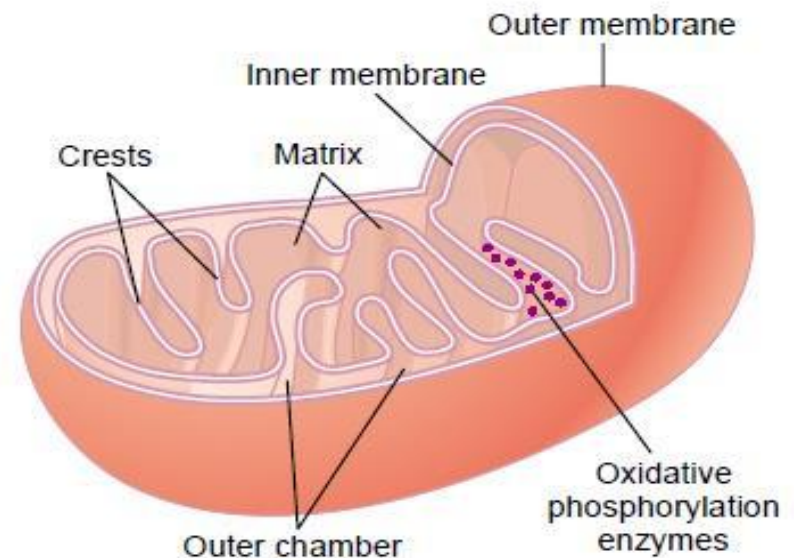


## ❖ Mitochondria:

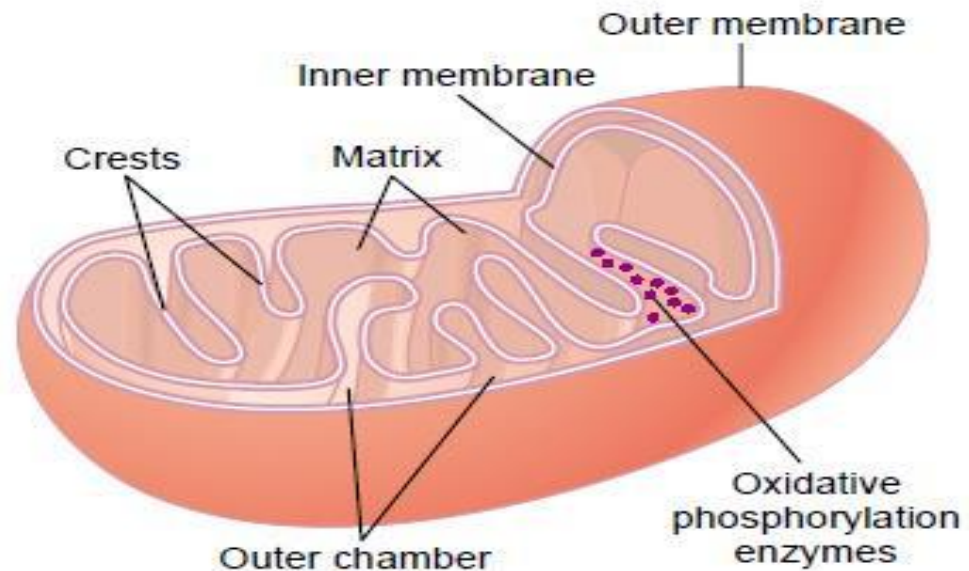
- It also called the “power houses” of the cell.
- Without them, cells would be unable to extract enough energy from the nutrients.
- Mitochondria are present in all areas of each cell’s cytoplasm, but the total varies from less than a **hundred** up to **several thousand**, depending on the amount of energy required by the cell.
- The mitochondria are concentrated in those portions of the cell that are responsible for the major share of its energy metabolism.



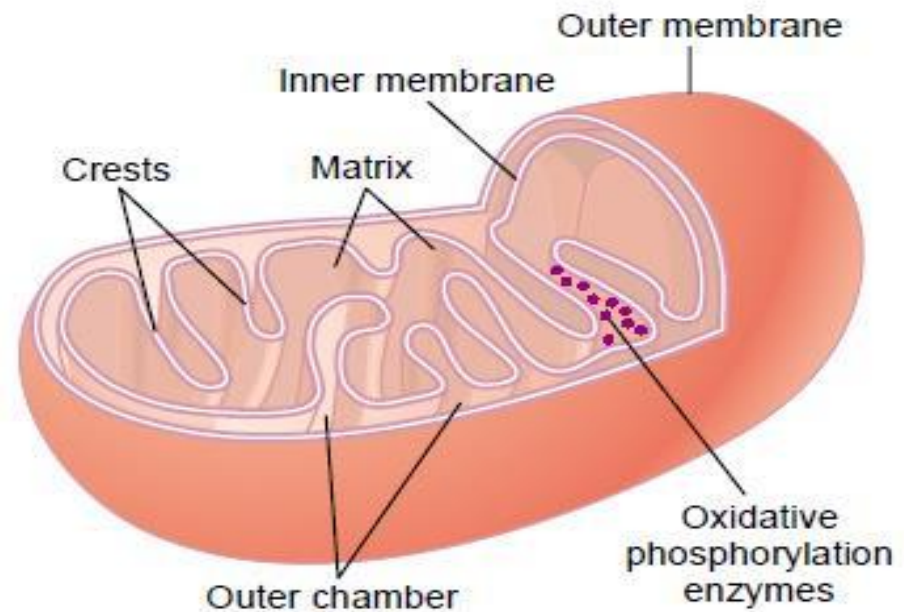
- They are also variable in size and shape.
- Some are only a few hundred nanometers in diameter and globular in shape,
- whereas others are elongated—as large as 1 micrometer in diameter and 7 micrometers long; others are branching and filamentous.



- It is composed mainly of two lipid bilayer–protein membranes: an *outer membrane* and an *inner membrane*.
- Many foldings of the inner membrane form *shelves* onto which *oxidative enzymes* are attached.
- The inner cavity of the mitochondrion is filled with a *matrix* that contains large quantities of dissolved enzymes that are necessary for extracting energy from nutrients.



➤ These enzymes operate in association with the oxidative enzymes on the shelves to cause oxidation of the nutrients, thereby forming carbon dioxide and water and at the same time releasing energy.

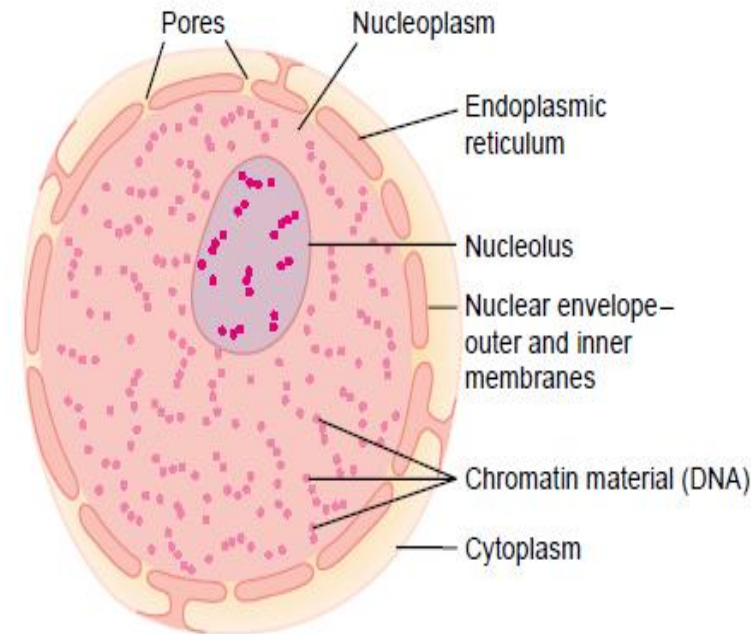


- The liberated energy is used to synthesize a “high-energy” substance called *adenosine triphosphate (ATP)*.
- ATP is then transported out of the mitochondrion, and it diffuses throughout the cell to release its own energy wherever it is needed for performing cellular function.
- Mitochondria are self – replicative, which means that one mitochondrion can form a second one, a third one, and so on, whenever there is a need in the cell for increased amounts of ATP.
- The mitochondria contain *DNA* similar to that found in the cell nucleus. The DNA of the mitochondrion plays a role in controlling replication of the mitochondrion itself.



# ❖ Nucleus:

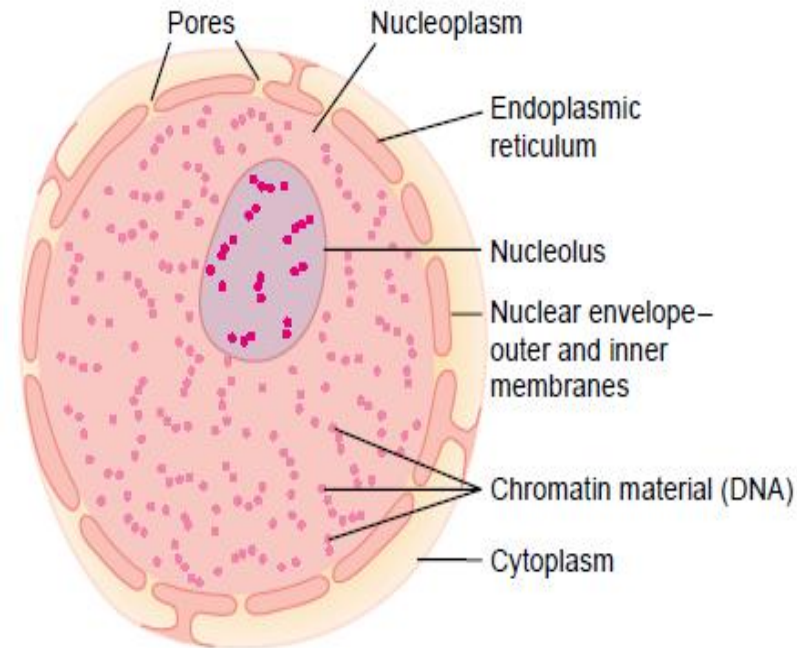
- The nucleus is the control center of the cell.
- The nucleus contains large quantities of DNA, which are the *genes*.
- The genes determine the characteristics of the:
  - Cell's proteins.
  - Intracellular enzymes (that control cytoplasmic and nuclear activities).



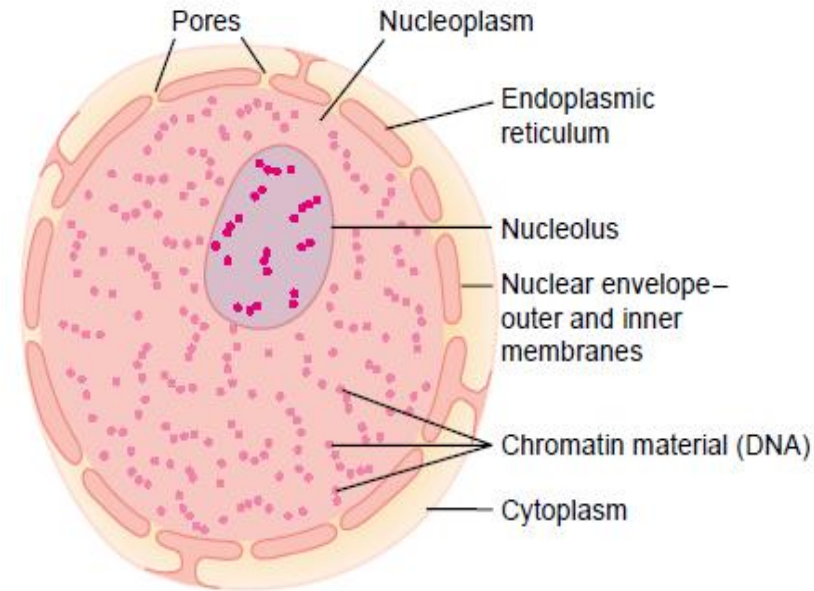
- The genes also control and promote reproduction of the cell itself.
- The genes first reproduce to give two identical sets of genes; then the cell splits by a special process called *mitosis* to form two daughter cells, each of which receives one of the two sets of DNA genes.

# ❖ Nuclear Membrane

- Also called the *nuclear envelope*, is actually two separate bilayer membranes, one inside the other.
- The outer membrane is continuous with the endoplasmic reticulum of the cell cytoplasm
- The space between the two nuclear membranes is also continuous with the space inside the endoplasmic reticulum.

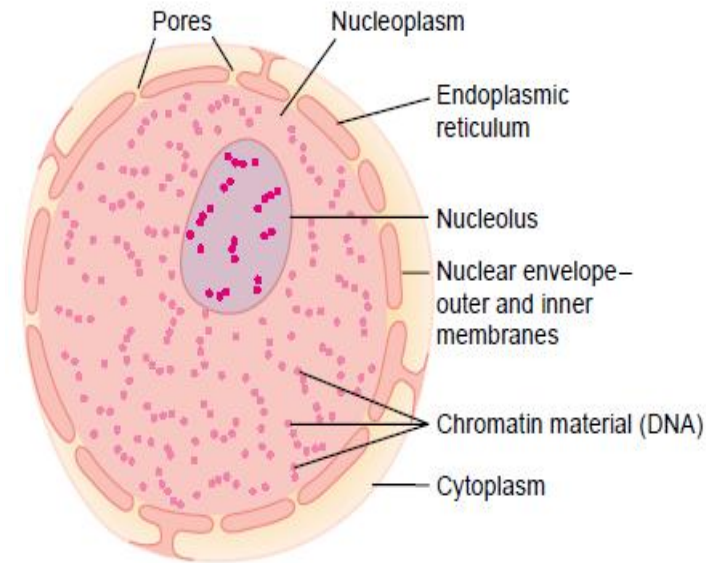


- The nuclear membrane is penetrated by several thousand *nuclear pores*.
- The central area of each pore is about 9 nanometers in diameter.
- This allow molecules up to 44,000 molecular weight to pass through with reasonable ease.



## ❖ Nucleoli:

- The nuclei of most cells contain one or more highly staining structures called *nucleoli*.
- The nucleolus does not have a limiting membrane.
- it is simply an accumulation of large amounts of RNA and proteins of the types found in ribosomes.
- The nucleolus becomes considerably enlarged when the cell is actively synthesizing proteins.

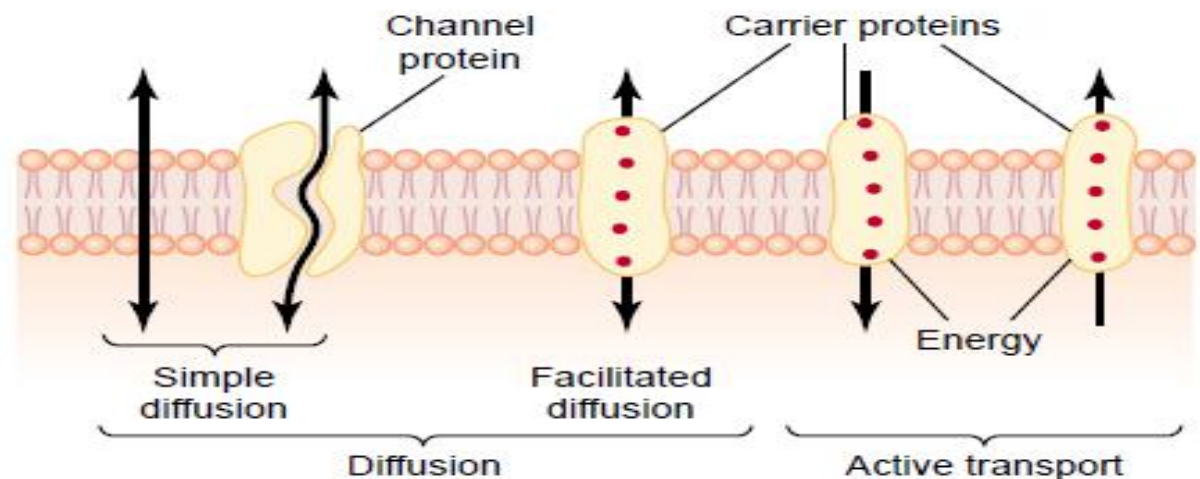


# Transport of substances through the cell membrane:

## ❖ Diffusion” Versus “Active Transport.”

Transport through the cell membrane, either directly through the lipid bilayer or through the proteins, occurs by one of two basic processes:

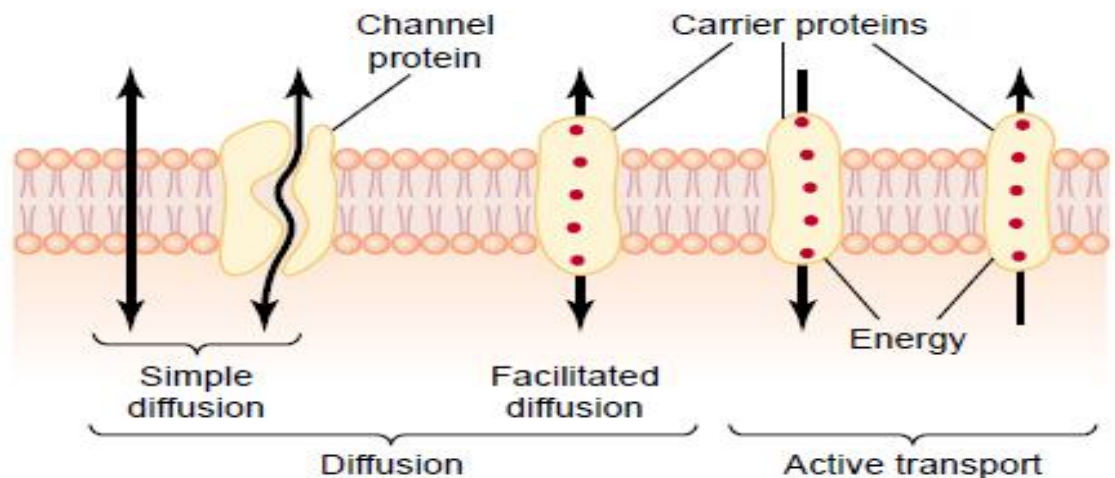
- **Diffusion:** means random molecular movement of substances through intermolecular spaces in the membrane or in combination with a carrier protein. The energy that causes diffusion is the energy of the normal kinetic motion of matter.





## ➤ Active transport:

- Movement of ions or other substances across the membrane in combination with a carrier protein; that causes the substance to move against an energy gradient, such as from a low-concentration state to a high-concentration state.
- This movement requires an additional source of energy besides kinetic energy.



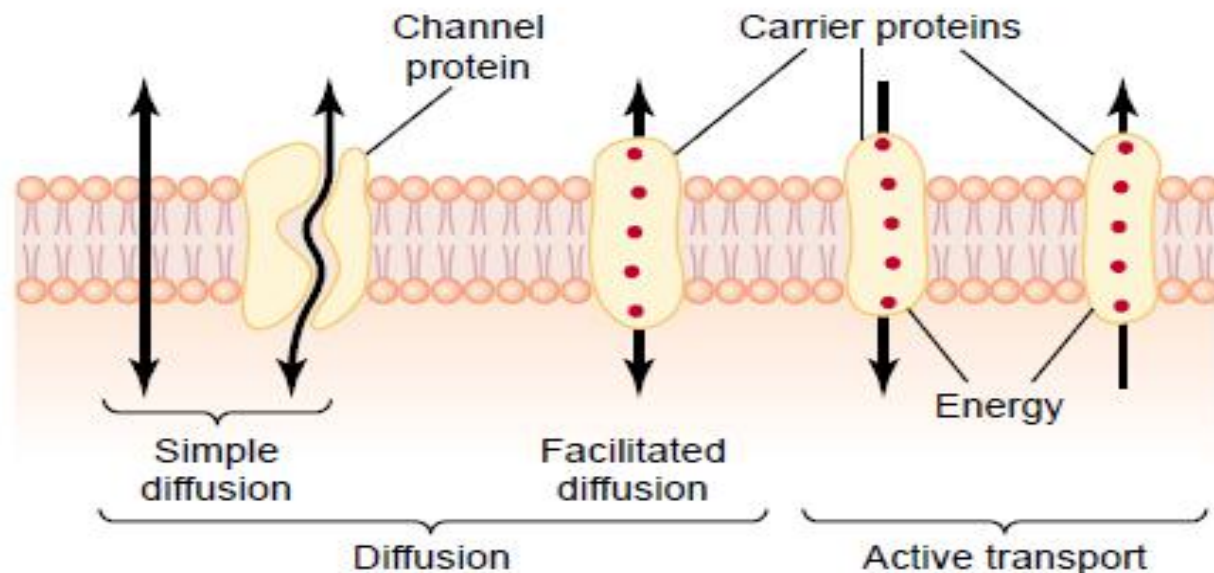
## ❖ Diffusion Through the Cell Membrane

It divided into two subtypes called:

*Simple diffusion* and *facilitated diffusion*.

### ➤ Simple diffusion:

- Means that kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with carrier proteins in the membrane.
- The rate of diffusion is determined by the amount of substance available, the velocity of kinetic motion, and the number and sizes of openings in the membrane through which the molecules or ions can move.

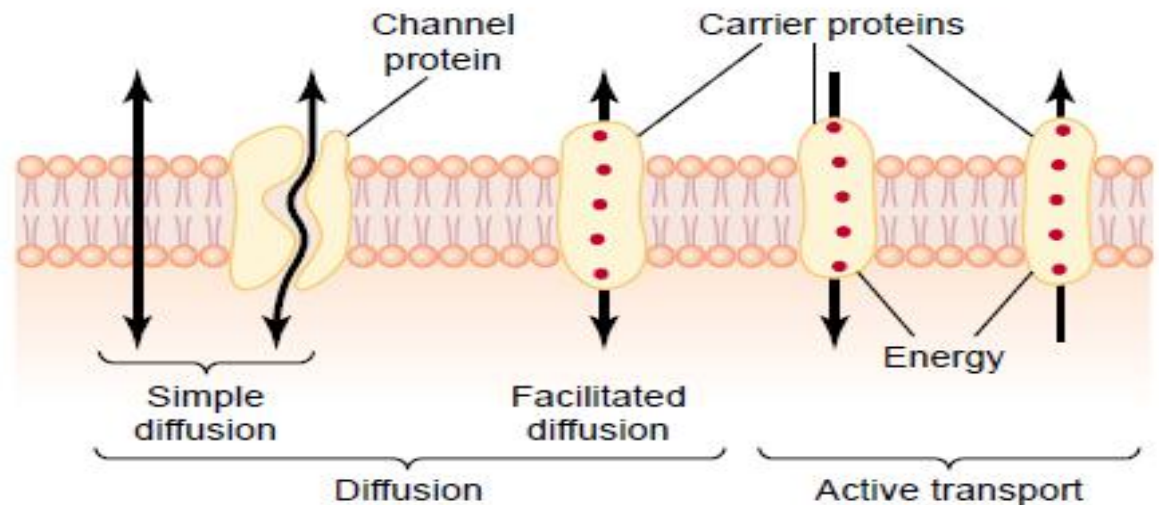


## ➤ Facilitated diffusion:

It requires interaction of a carrier protein which aids passage of the molecules or ions through the membrane by binding chemically with them and shuttling them through the membrane.

Simple diffusion can occur through the cell membrane by two pathways:

- (1) Through the interstices of the lipid bilayer if the diffusing substance is lipid soluble.
- (2) Through watery channels that penetrate all the way through the large transport proteins.



## ❖ Diffusion of Lipid-Soluble Substances Through the Lipid Bilayer.

- One of the most important factors that determines how rapidly a substance diffuses through the lipid bilayer is the *lipid solubility* of the substance. (e g. oxygen, nitrogen, carbon dioxide, and alcohol).

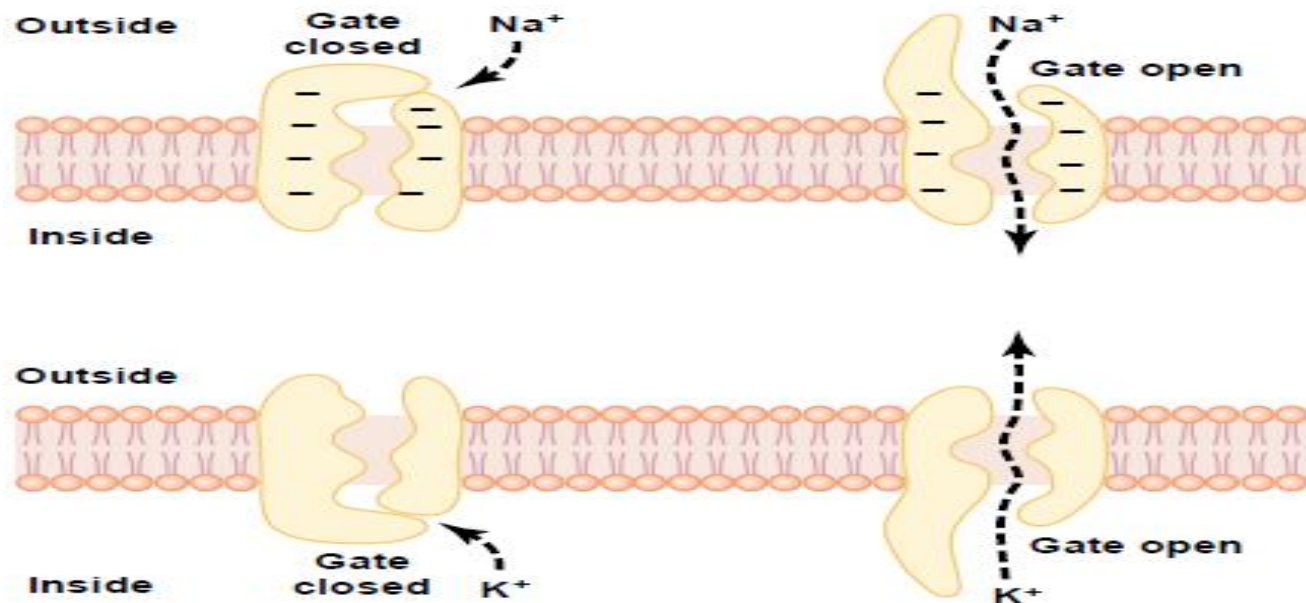
## ❖ Diffusion of Water and Other Lipid-Insoluble Molecules Through Protein Channels.

- Even though water is highly insoluble in the membrane lipids, it readily passes through channels in protein molecules that penetrate all the way through the membrane.
- The total amount of water that diffuses in each direction through the red cell membrane during each second is about 100 times as great as the volume of the red cell itself.

## ❖ Diffusion Through Protein Channels, and “Gating” of These Channels:

The protein channels are distinguished by two important characteristics:

- (1) They are often selectively permeable to certain substances,
- (2) Many of the channels can be opened or closed by *gates*.

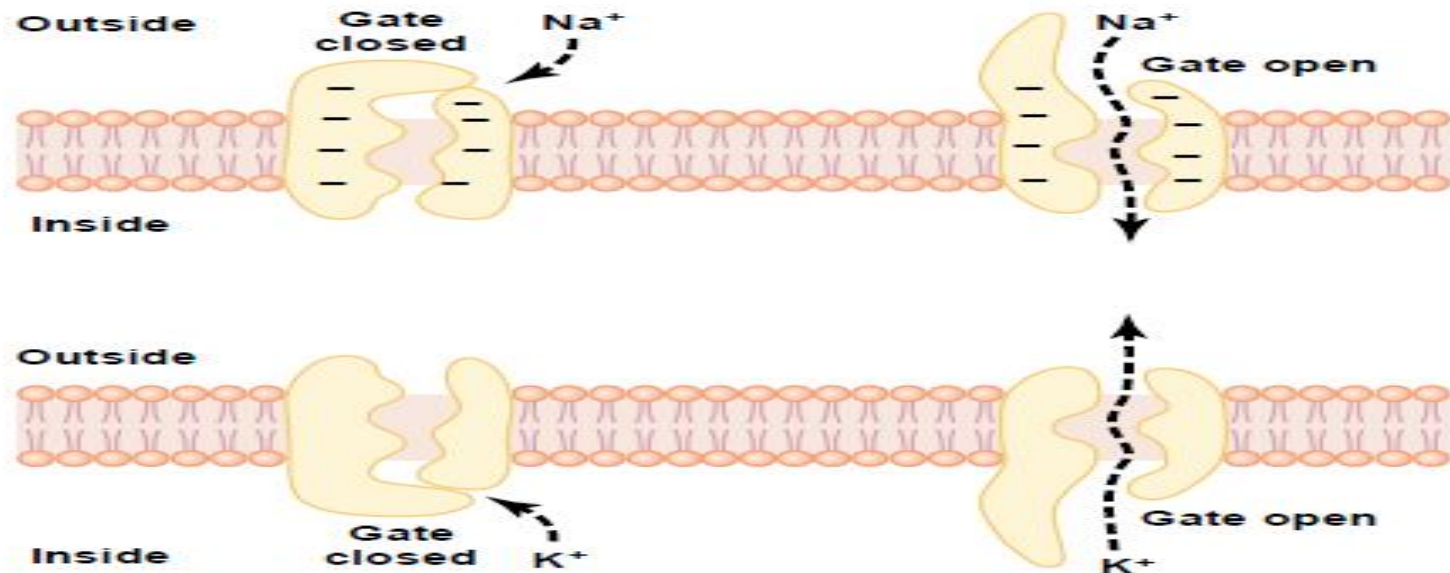




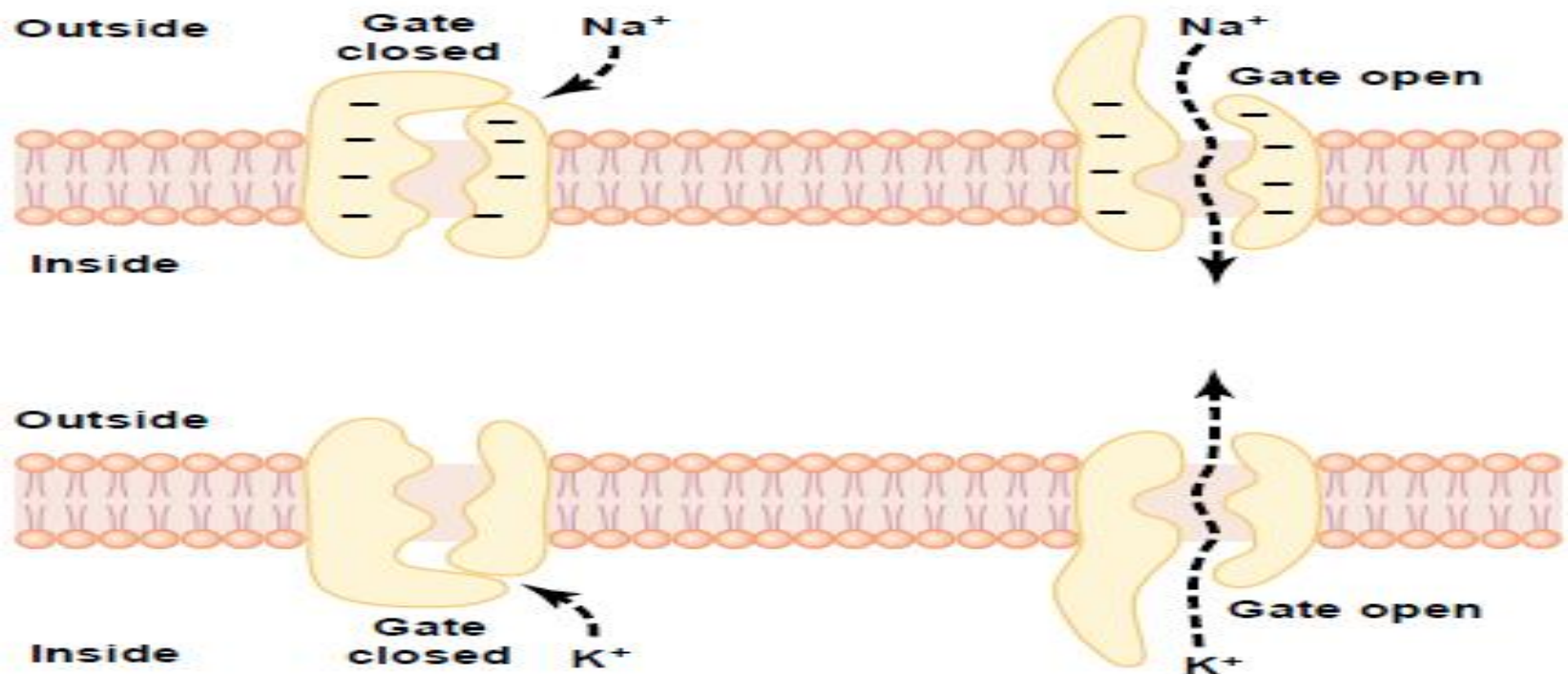
# ❖ Selective Permeability of Protein Channels.

## ➤ Sodium channel

Its only 0.3 by 0.5 nanometer in diameter, but more important, the inner surfaces of this channel are *strongly negatively charged*.

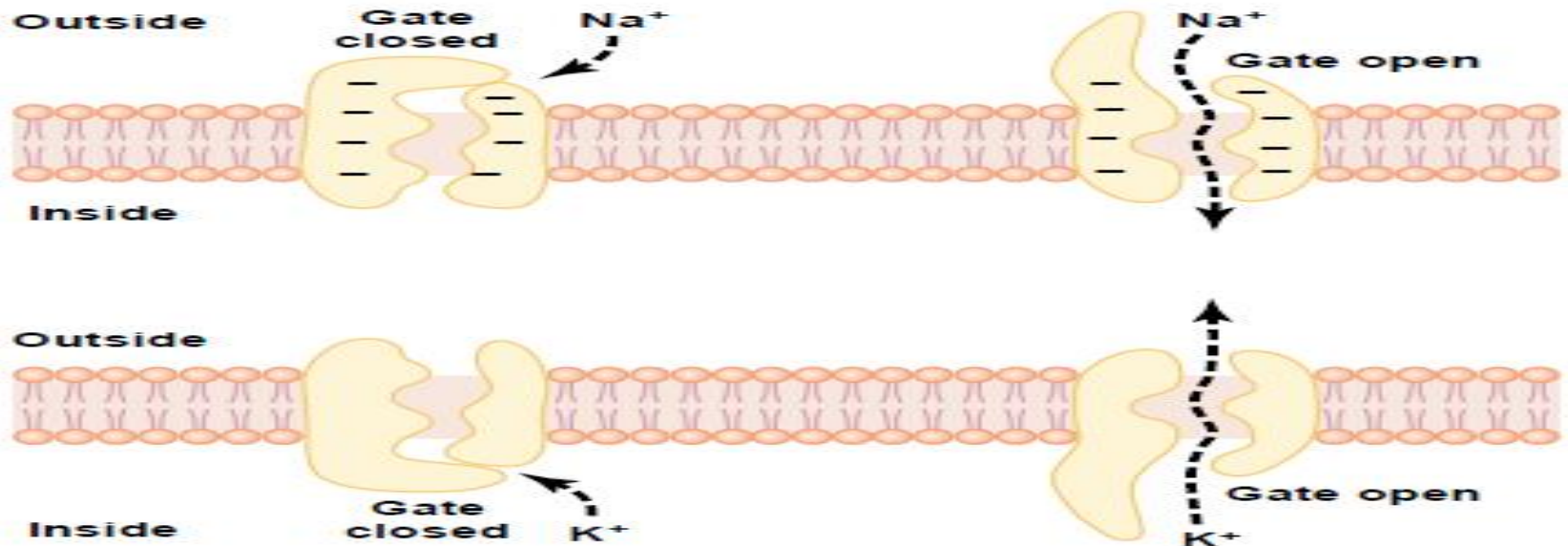


- These strong negative charges can pull small *dehydrated* sodium ions into these channels, actually pulling the sodium ions away from their hydrating water molecules.
- Once in the channel, the sodium ions diffuse in either direction according to the usual laws of diffusion.



## ➤ potassium channels:

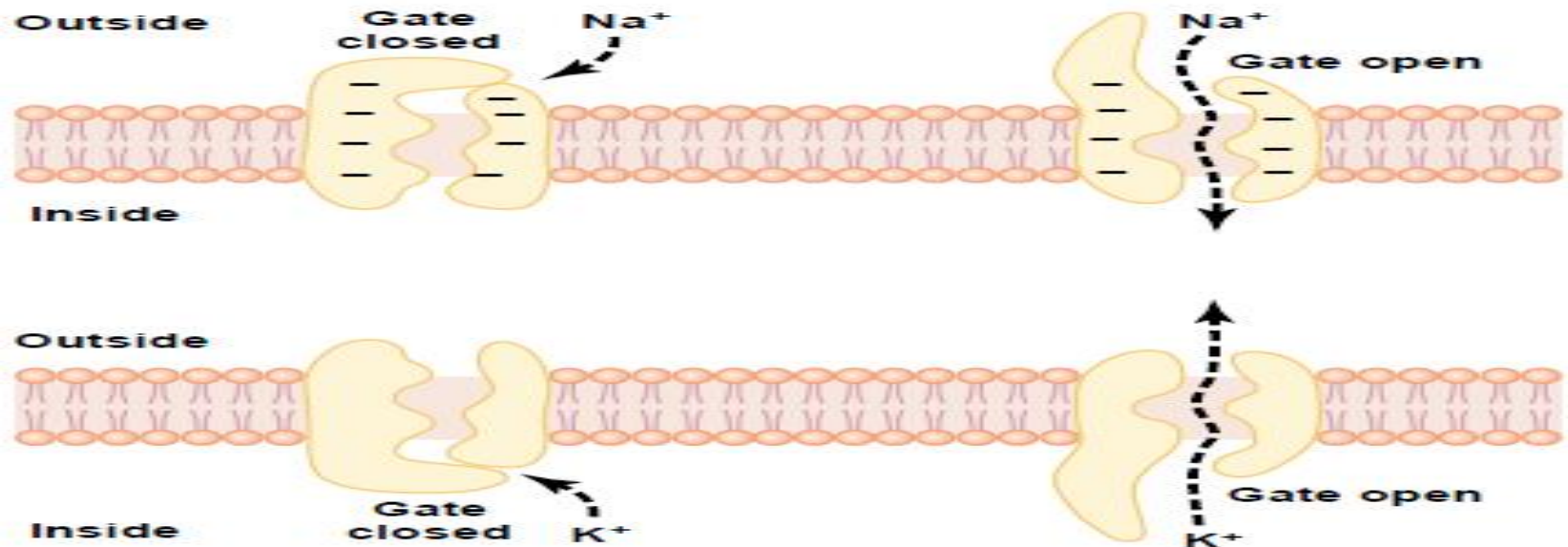
- These channels are slightly smaller than the sodium channels, only 0.3 by 0.3 nanometer, but *they are not negatively charged, and their chemical bonds are different.*
- Therefore, no strong attractive force is pulling ions into the channels, and the potassium ions are not pulled away from the water molecules that hydrate them.



- The hydrated form of the potassium ion is considerably smaller than the hydrated form of sodium because the sodium ion attracts far more water molecules than does potassium.
- Therefore, the smaller hydrated potassium ions can pass easily through this small channel, whereas the larger hydrated sodium ions are rejected, thus providing selective permeability for a specific ion.

## ❖ Gating of Protein Channels.

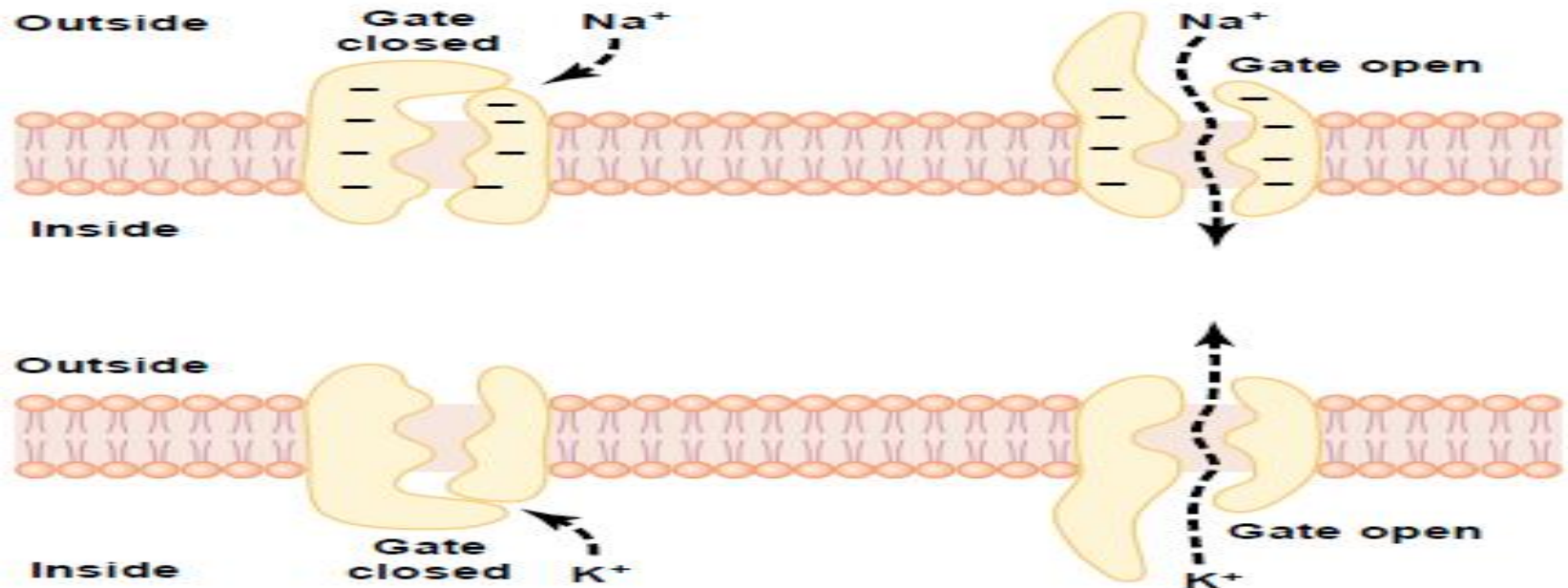
- Gating of protein channels provides a means of controlling ion permeability of the channels.
- Some of the gates are actual gate like extensions of the transport protein molecule, which can close the opening of the channel or can be lifted away from the opening by a conformational change in the shape of the protein molecule itself.



The opening and closing of gates are controlled in two principals:

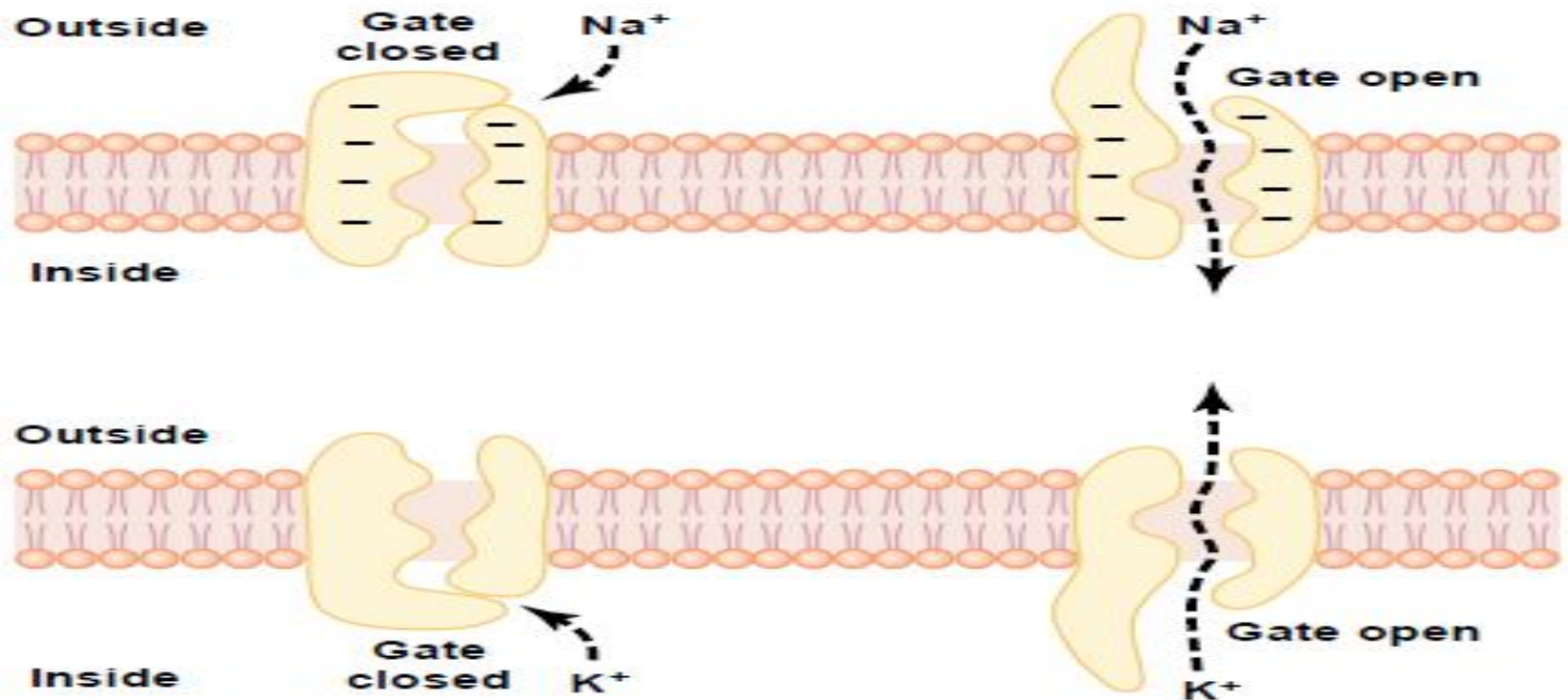
## 1. Voltage gating.

- The molecular conformation of the gate or of its chemical bonds responds to the electrical potential across the cell membrane.
- when there is a strong negative charge on the inside of the cell membrane, this presumably could cause the outside sodium gates to remain tightly closed.
- conversely, when the inside of the membrane loses its negative charge, these gates would open suddenly and allow tremendous quantities of sodium to pass inward through the sodium pores.



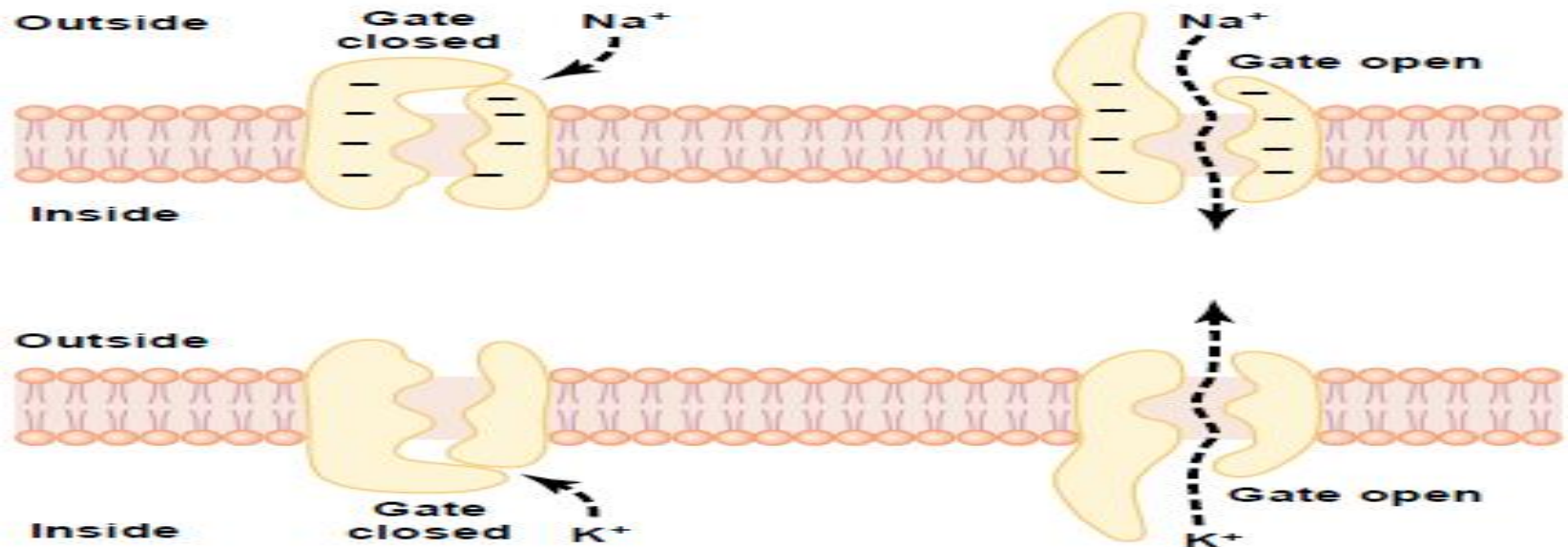


- While the potassium gates are on the intracellular ends of the potassium channels, and they open when the inside of the cell membrane becomes positively charged.



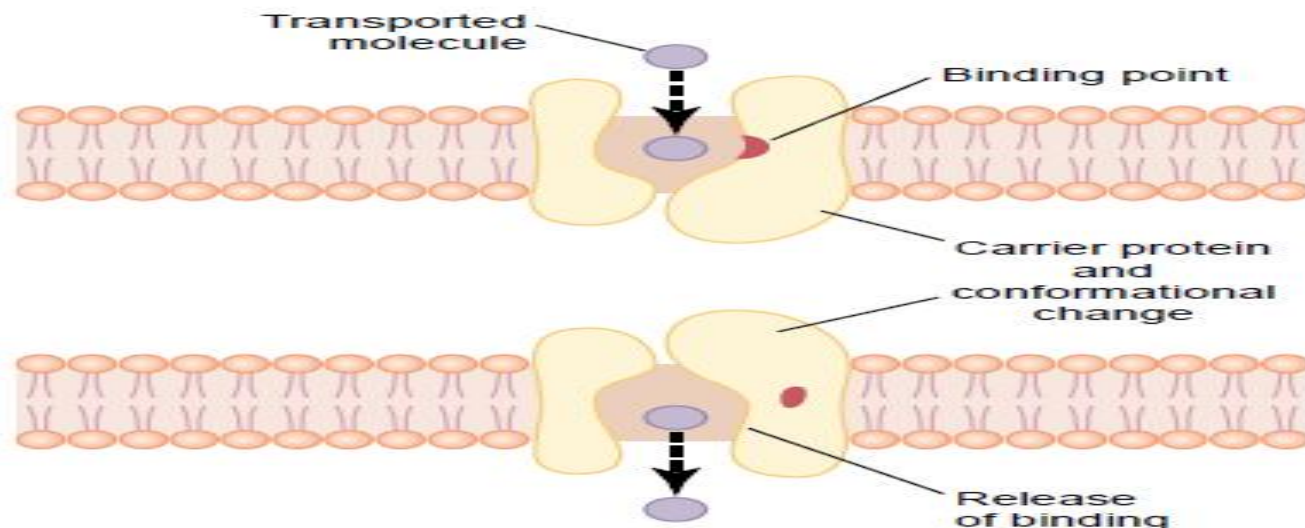
## 2. Chemical (ligand) gating:

- Some protein channel gates are opened by the binding of a chemical substance (a ligand) with the protein; this causes a conformational or chemical bonding change in the protein molecule that opens or closes the gate.
- This is called *chemical gating* or *ligand gating*. (eg. of chemical gating is the effect of acetylcholine on the so-called *acetylcholine channel*).

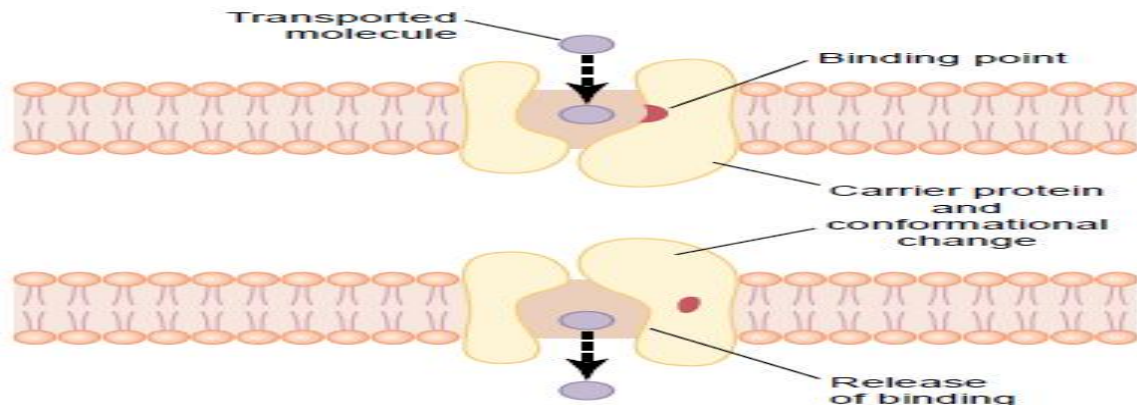


# ❖ Facilitated Diffusion

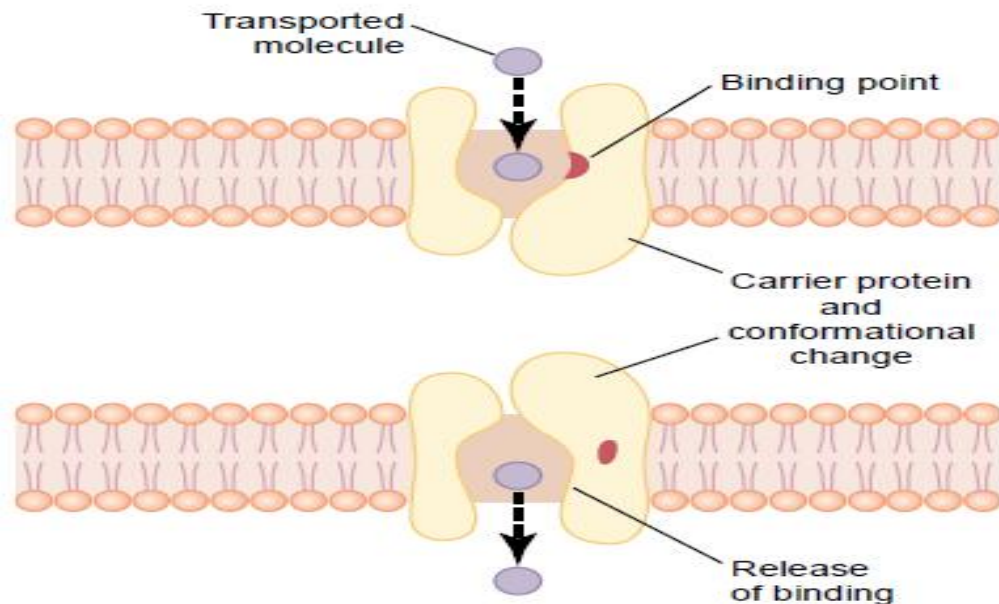
- Facilitated diffusion is also called *carrier-mediated diffusion* because a substance transported in this manner diffuses through the membrane using a specific carrier protein to help.
- The carrier *facilitates* diffusion of the substance to the other side.



- The carrier protein with a pore large enough to transport a specific molecule partway through.
- It also shows a binding “receptor” on the inside of the protein carrier.
- The molecule to be transported enters the pore and becomes bound.
- Then , in a fraction of a second, a conformational or chemical change occurs in the carrier protein, so that the pore now opens to the opposite side of the membrane.
- Because the binding force of the receptor is weak, the thermal motion of the attached molecule causes it to break away and to be released on the opposite side of the membrane.



- Among the most important substances that cross cell membranes by facilitated diffusion are *glucose* and most of the *amino acids*.
- Also, insulin can increase the rate of facilitated diffusion of glucose as much as 10-fold to 20-fold.
- This is the principal mechanism by which insulin controls glucose use in the body.



## ❖ Factors That Affect Net Rate of Diffusion:

### ☐ Concentration Difference :

- The rate at which the substance diffuses *inward* is proportional to the concentration of molecules on the *outside*, because this concentration determines how many molecules strike the outside of the membrane each second.
  - Conversely, the rate at which molecules diffuse *outward* is proportional to their concentration *inside* the membrane.
- Net diffusion  $\propto (C_o - C_i)$  in which  $(C_o)$  is concentration outside and  $(C_i)$  is concentration inside.



## **❑ Membrane Electrical Potential.**

**If an electrical potential is applied across the membrane, the electrical charges of the ions cause them to move through the membrane even though no concentration difference exists to cause movement.**

## ❖ Effect of a Pressure Difference Across the Membrane.

- Considerable pressure difference develops between the two sides of a diffusible membrane.
- This occurs : at the blood capillary membrane in all tissues of the body.
- The pressure is about 20 mm Hg greater inside the capillary than outside.

# ❖ **Primary Active Transport and Secondary Active Transport.**

Active transport is divided into two types according to the source of the energy used to cause the transport.

## **primary active transport:**

The energy is derived directly from breakdown of adenosine triphosphate (ATP).

## **secondary active transport:**

The energy is derived secondarily from energy that has been stored in the form of ionic concentration differences of secondary molecular or ionic substances between the two sides of a cell membrane.

In both instances, transport depends on *carrier proteins that penetrate through the* cell membrane, as is true for facilitated diffusion.

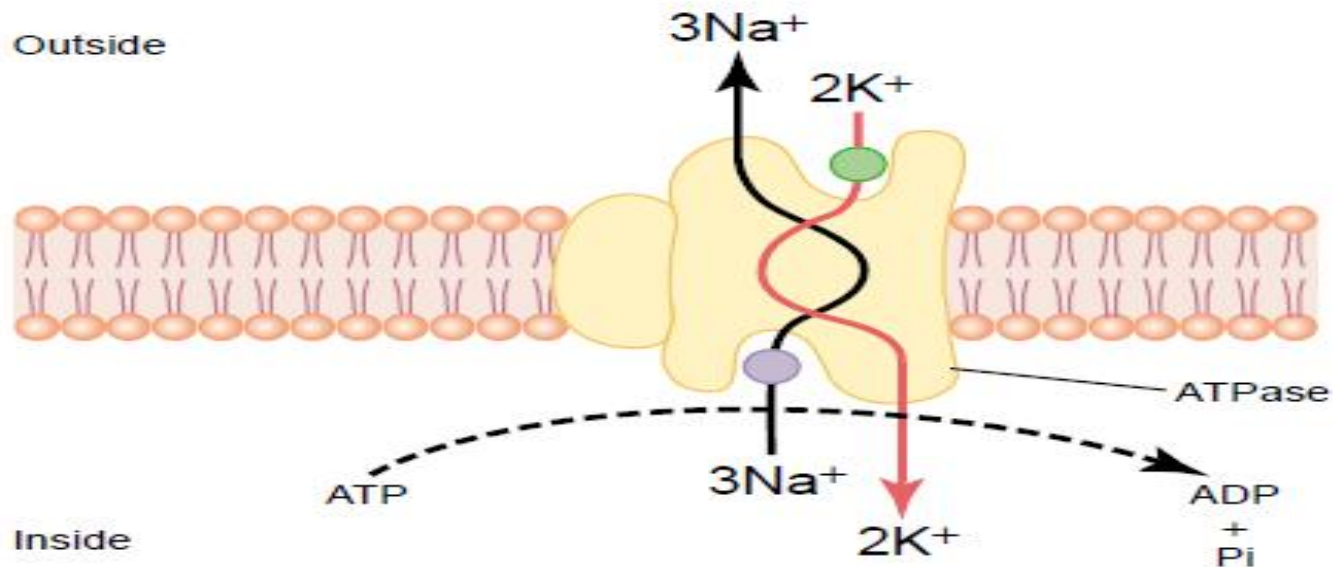
# ❖ “Active Transport” of Substances Through Membranes:

- A large concentration of a substance is required in the intracellular fluid even though the extracellular fluid contains only a small concentration. This is true, for instance, for **potassium ions**.
- Conversely, it is important to keep the concentrations of other ions very low inside the cell even though their concentrations in the extracellular fluid are great. This is especially true for **sodium ions**.

- Some energy source must cause excess movement of potassium ions to the inside of cells and excess movement of sodium ions to the outside of cells.
- When a cell membrane moves molecules or ions against a concentration gradient or against an electrical gradient or pressure gradient the process is called *active transport*.
- Different substances that are actively transported through at least some cell membranes include sodium ions, potassium ions, calcium ions, iron ions, hydrogen ions, chloride ions, iodide ions, urate ions, several different sugars, and most of the amino acids.

## ❖ Primary Active Transport Sodium-Potassium Pump:

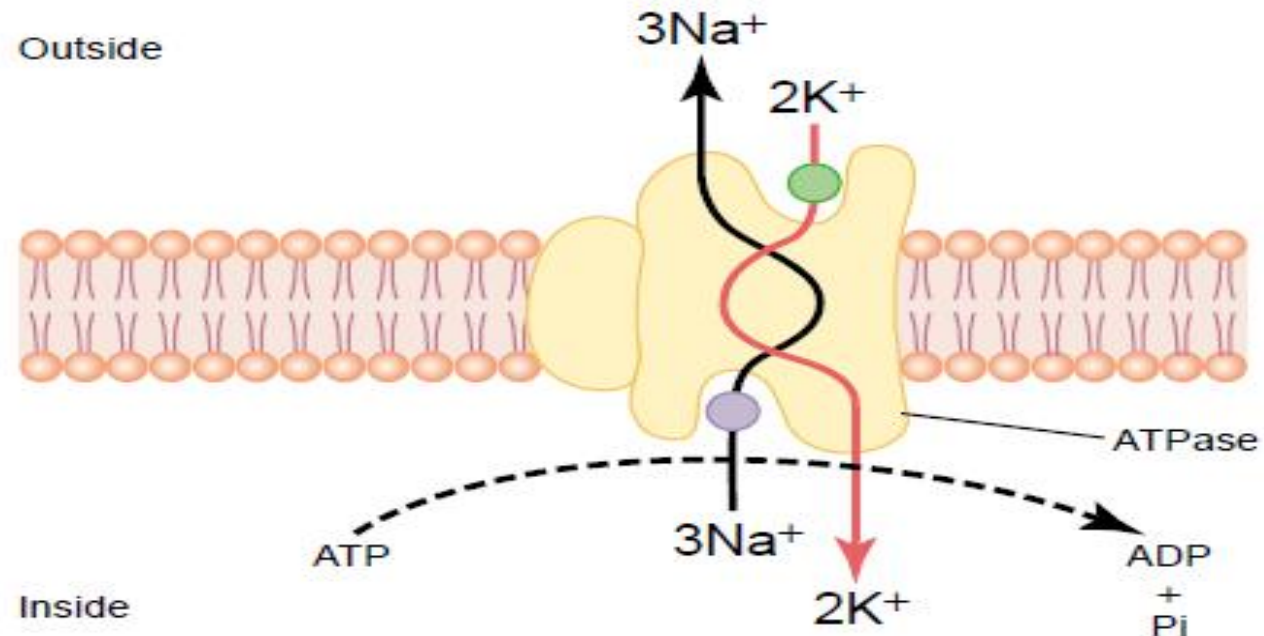
- *Sodium-potassium ( $\text{Na}^+/\text{K}^+$ ) pump*, it pumps sodium ions outward through the cell membrane of all cells and at the same time pumps potassium ions from the outside to the inside.
- This pump is responsible for maintaining the sodium and potassium concentration differences across the cell membrane, as well as for establishing a negative electrical voltage inside the cells.



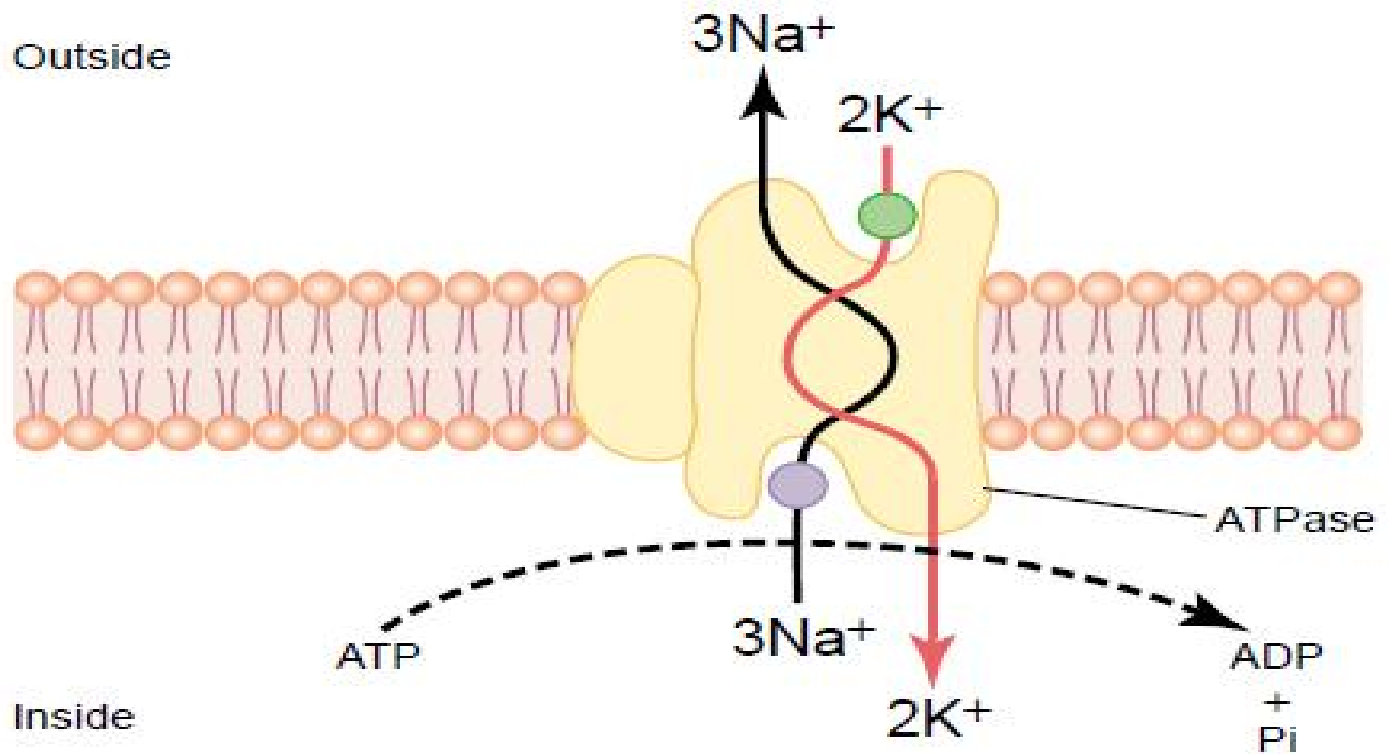


The carrier protein has the followings:

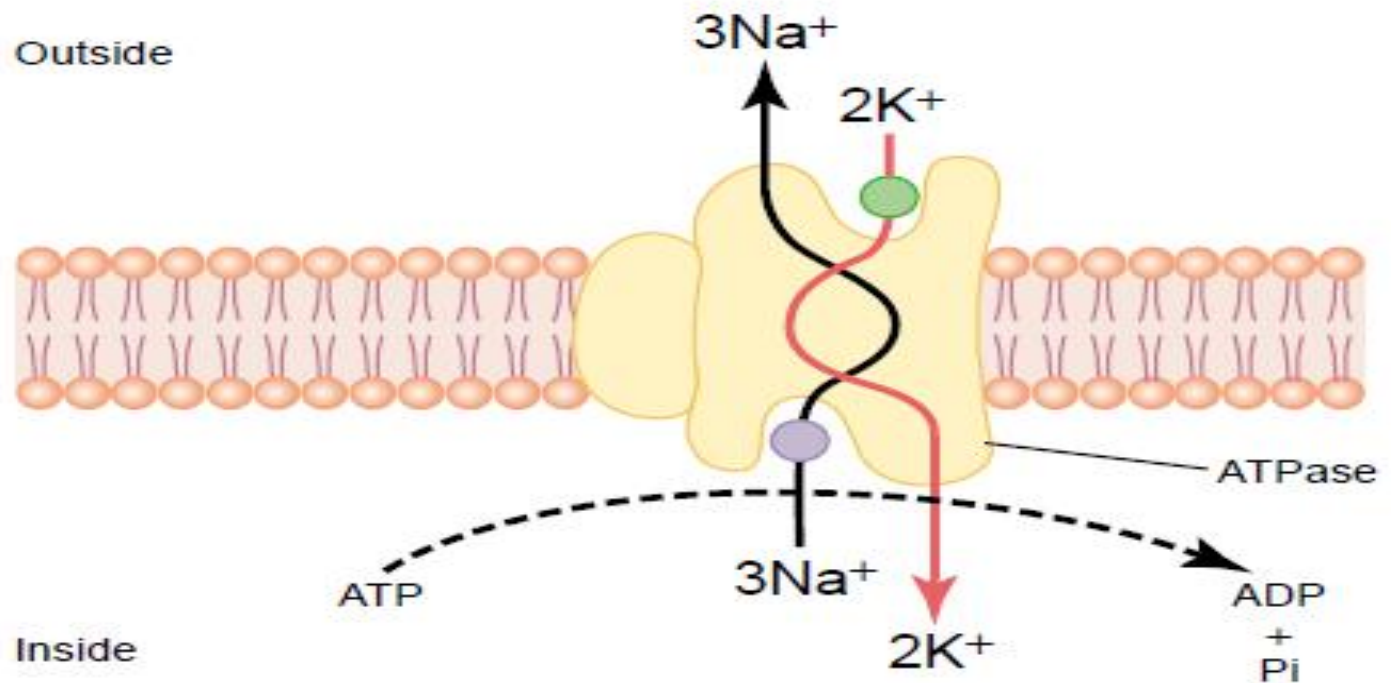
1. It has three *receptor sites for binding sodium ions* on the portion of the protein that protrudes to the inside of the cell.
2. It has two *receptor sites for potassium ions* on the outside.
3. The inside portion of this protein near the sodium binding sites has **ATPase** activity.



- To put the pump into perspective: When two potassium ions bind on the outside of the carrier protein and three sodium ions bind on the inside, the ATPase function of the protein becomes activated.
- This then cleaves one molecule of ATP, splitting it to adenosine diphosphate (ADP) and liberating a high-energy phosphate bond of energy.



➤ This liberated energy is then believed to cause a chemical and conformational change in the protein carrier molecule, extruding the three sodium ions to the outside and the two potassium ions to the inside.



## ❖ Importance of the Na<sup>+</sup>-K<sup>+</sup> Pump for Controlling Cell Volume.

- One of the most important functions of the Na<sup>+</sup>-K<sup>+</sup> pump is to control the volume of each cell.
- Without function of this pump, most cells of the body would swell until they burst.

The mechanism for controlling the volume is as follows:

- Inside the cell are large numbers of proteins and other organic molecules that cannot escape from the cell.
- Most of these are negatively charged and therefore attract large numbers of potassium, sodium, and other positive ions as well.

- All these molecules and ions then cause osmosis of water to the interior of the cell.
- Unless this is checked, the cell will swell indefinitely until it bursts. The normal mechanism for preventing this is the  $\text{Na}^+\text{-K}^+$  pump.
- This device pumps three  $\text{Na}^+$  ions to the outside of the cell for every two  $\text{K}^+$  ions pumped to the interior.
- Also, the membrane is far less permeable to sodium ions than to potassium ions, so that once the sodium ions are on the outside, they have a strong tendency to stay there.

- This represents a net loss of ions out of the cell, which initiates osmosis of water out of the cell as well.
- IF a cell begins to swell for any reason, this automatically activates the  $\text{Na}^+\text{-K}^+$  pump, moving still more ions to the exterior and carrying water with them.
- Therefore, the  $\text{Na}^+\text{-K}^+$  pump performs a continual surveillance role in maintaining normal cell volume.



## ❖ **Electrogenic Nature of the Na<sup>+</sup>-K<sup>+</sup> Pump.**

- **The fact that the Na<sup>+</sup>-K<sup>+</sup> pump moves three Na<sup>+</sup> ions to the exterior for every two K<sup>+</sup> ions to the interior means that a net of one positive charge is moved from the interior of the cell to the exterior for each cycle of the pump.**
- **This creates positivity outside the cell but leaves a deficit of positive ions inside the cell; that is, it causes negativity on the inside.**

## ❖ Primary Active Transport of Calcium Ions

- Another important primary active transport mechanism is the *calcium pump*.
- Calcium ions are normally maintained at extremely low concentration in the intracellular cytosol of virtually all cells in the body, at a concentration about **10,000 times** less than that in the extracellular fluid.
- This is achieved mainly by two primary active transport calcium pumps. One is in the cell membrane and pumps calcium to the outside of the cell.

- The other pumps calcium ions into one or more of the intracellular vesicular organelles of the cell, such as the sarcoplasmic reticulum of muscle cells and the mitochondria in all cells.
- In each of these instances, the carrier protein penetrates the membrane and functions as an enzyme ATPase, having the same capability to cleave ATP as the ATPase of the sodium carrier protein.
- The difference is that; this protein has a highly specific binding site for calcium instead of for sodium.

# ❖ **Primary Active Transport of Hydrogen Ions**

**At two places in the body, primary active transport of hydrogen ions is very important:**

➤ **In the gastric glands of the stomach.**

➤ **In the late distal tubules and cortical collecting ducts of the kidneys.**

## ❖ **Secondary Active Transport— Co-Transport and Counter Transport**

- **When sodium ions are transported out of cells by primary active transport, a large concentration gradient of sodium ions across the cell membrane usually develops.**
- **This gradient represents a storehouse of energy because the excess sodium outside the cell membrane is always attempting to diffuse to the interior.**

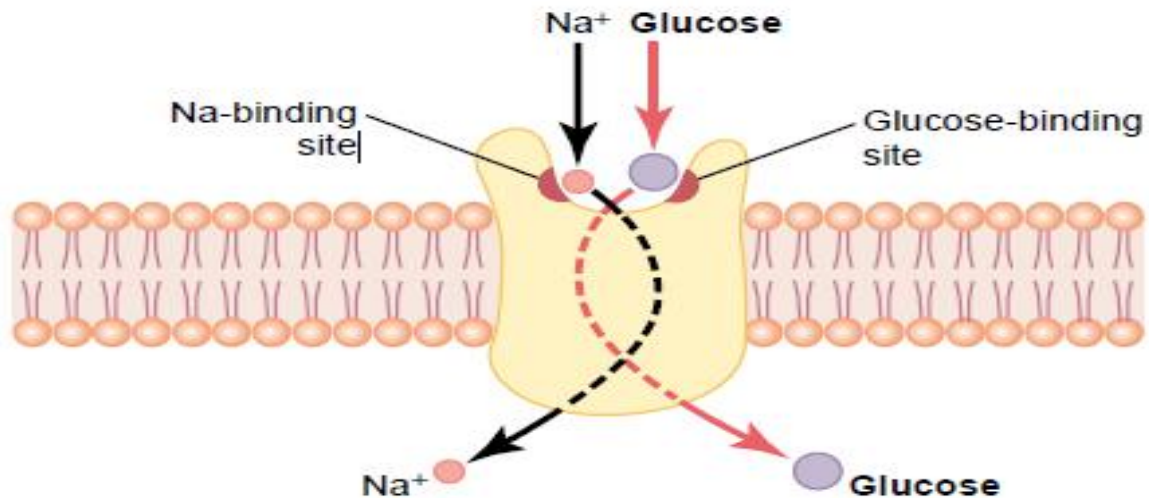
- Under appropriate conditions, this diffusion energy of sodium can pull other substances along with the sodium through the cell membrane.
- This phenomenon is called *co-transport*; it is one form of *secondary active transport*.
- For sodium to pull another substance along with it, a coupling mechanism is required.
- This is achieved by means of still another carrier protein in the cell membrane.



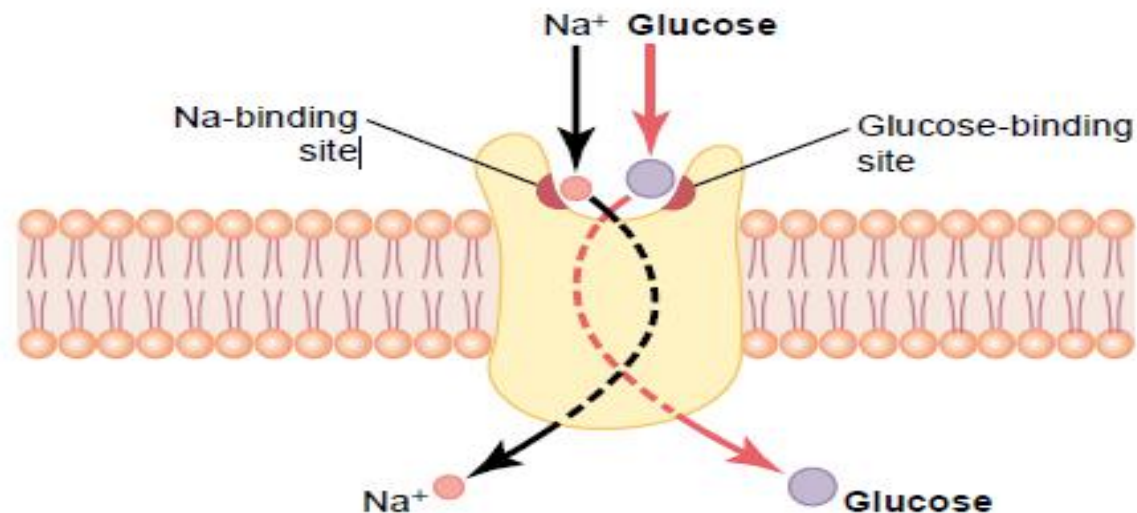
- **The carrier in this instance serves as an attachment point for both the sodium ion and the substance to be co-transported.**
- **Once they both are attached, the energy gradient of the sodium ion causes both the sodium ion and the other substance to be transported together to the interior of the cell.**

## ❖ Counter-transport:

- sodium ions again attempt to diffuse to the interior of the cell because of their large concentration gradient.
- However, this time, the substance to be transported is on the inside of the cell and must be transported to the outside.

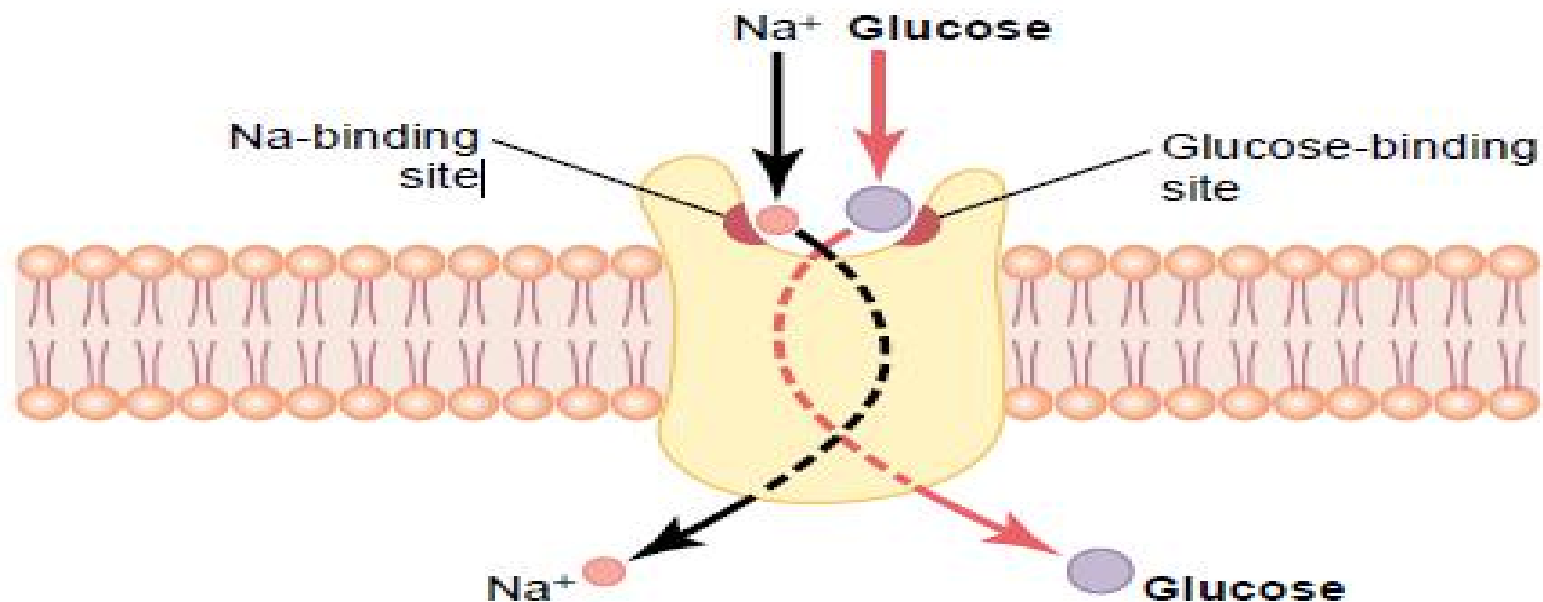


- Therefore, the sodium ion binds to the carrier protein where it projects to the exterior surface of the membrane.
- while the substance to be counter-transported binds to the interior projection of the carrier protein.
- Once both have bound, a conformational change occurs, and energy released by the sodium ion moving to the interior causes the other substance to move to the exterior.

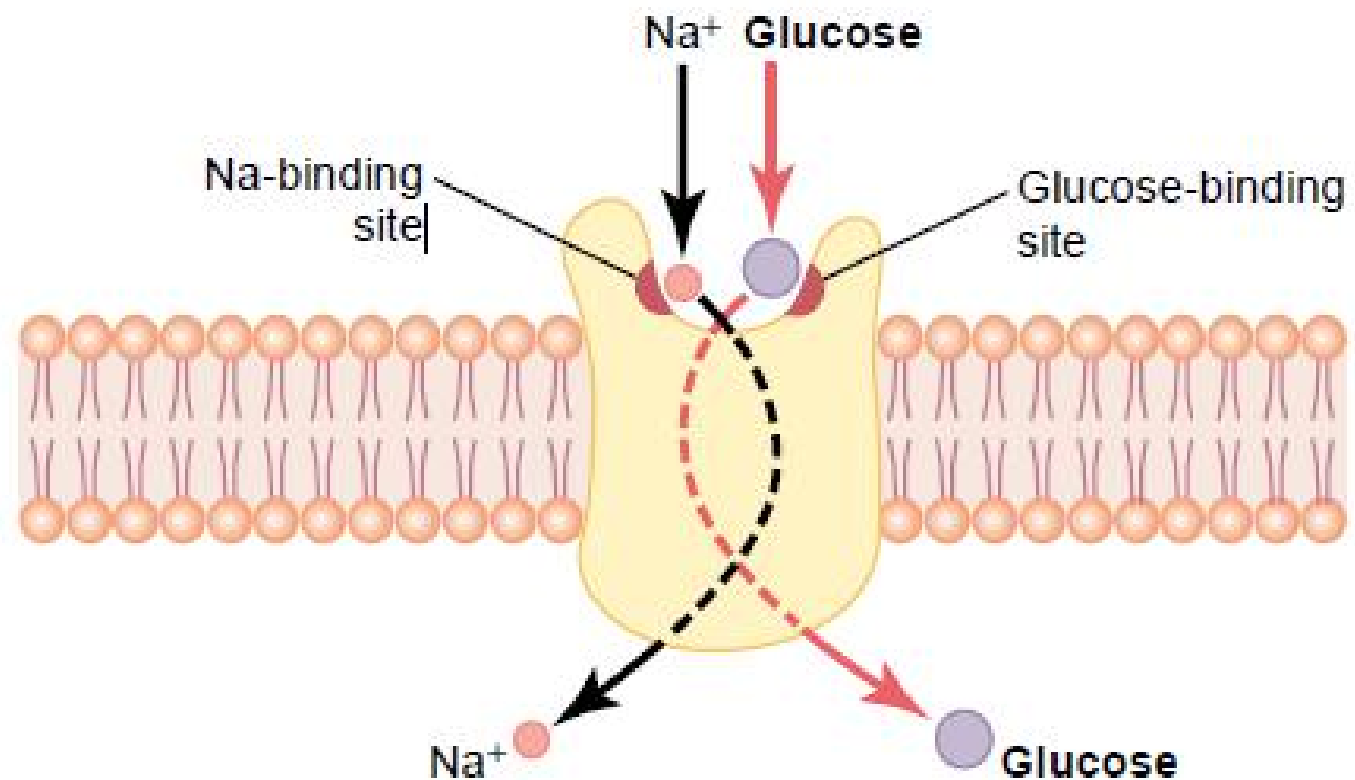


## ❖ Co-Transport of Glucose and Amino Acids:

- Along with Sodium Ions Glucose and many amino acids are transported into most cells against large concentration gradients; the mechanism of this is entirely by co-transport, the transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose. Also, the concentration of sodium ions is very high on the outside and very low inside, which provides energy for the transport.



- When they both become attached, the conformational change takes place automatically, and the sodium and glucose are transported to the inside of the cell at the same time.
- *Sodium co-transport of the amino acids* occurs in the same manner as for glucose.



- Sodium co-transport of glucose and amino acids occurs especially through the **epithelial cells** of the **intestinal tract** and the **renal tubules** of the kidneys to promote absorption of these substances into the blood.
- Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ions, iron ions, and urate ions.



## ❖ Sodium Counter-Transport of Calcium and Hydrogen Ions

- Sodium-calcium counter-transport occurs through all or almost all cell membranes, with sodium ions moving to the interior and calcium ions to the exterior.
- both bound to the same transport protein in a counter transport mode. This is in addition to primary active transport of calcium that occurs in some cells.

- Sodium-hydrogen counter-transport occurs in several tissues, in the *proximal tubules* of the kidneys, where sodium ions move from the lumen of the tubule to the interior of the tubular cell, while hydrogen ions are counter transported into the tubule lumen.
- So it can transport *extremely large numbers of hydrogen ions*, thus making it a key to hydrogen ion control in the body fluids.

## ❖ **Active Transport Through Cellular Sheets:**

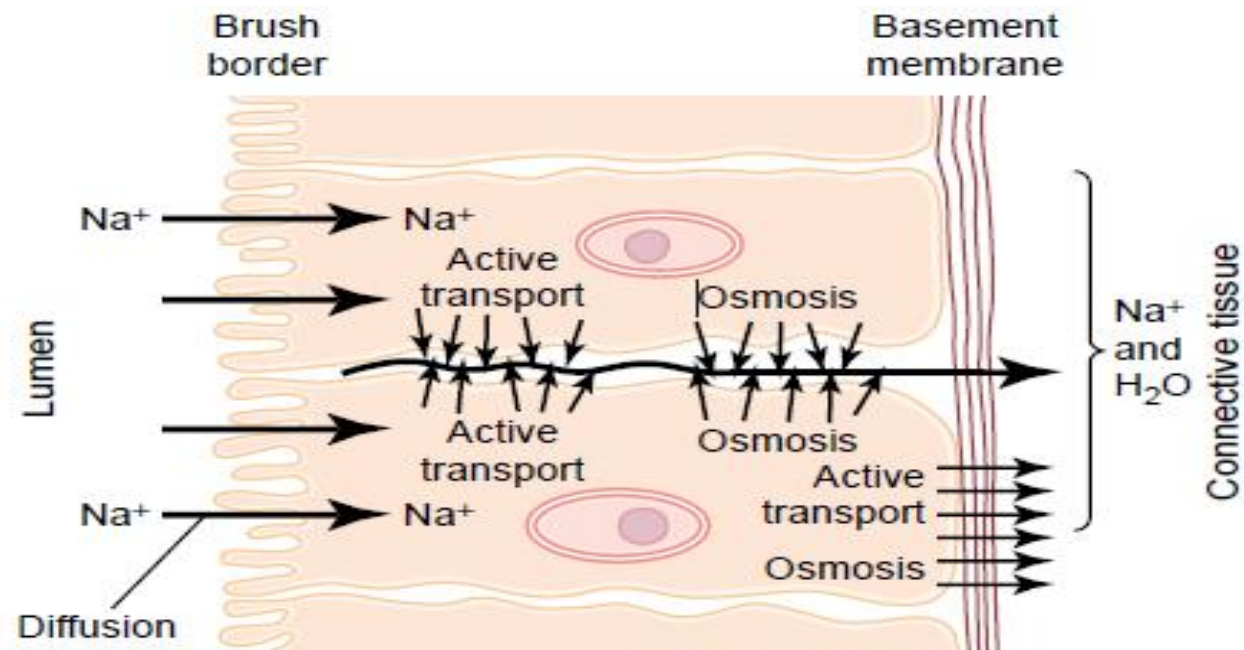
- **At many places in the body, substances must be transported all the way through a cellular sheet instead of simply through the cell membrane.**

**Transport of this type occurs through the:**

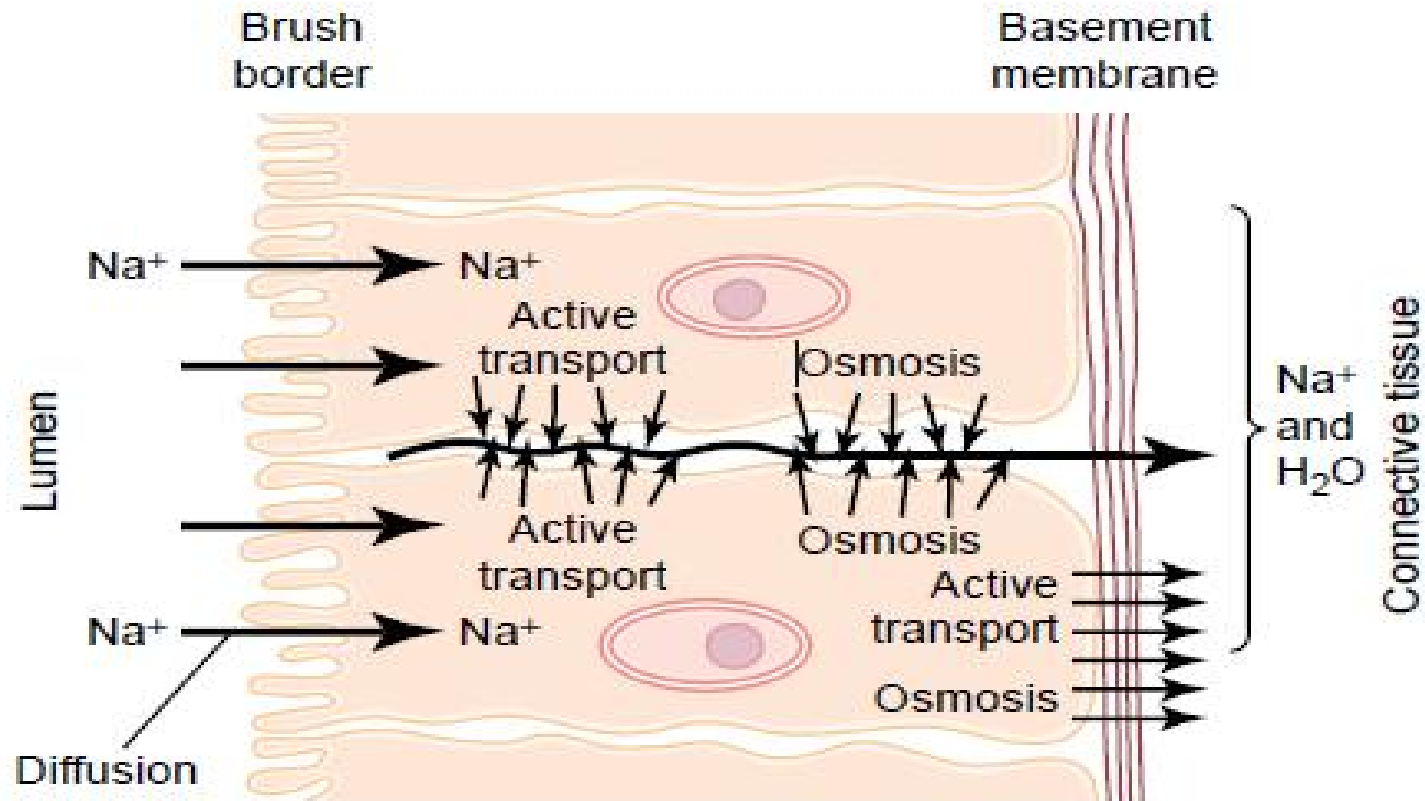
- **Intestinal epithelium.**
- **Epithelium of the renal tubules.**
- **Epithelium of all exocrine glands (salivary glands).**
- **Epithelium of the gallbladder.**
- **Membrane of the choroid plexus of the brain.**

The basic mechanism for transport of a substance through a cellular sheet is:

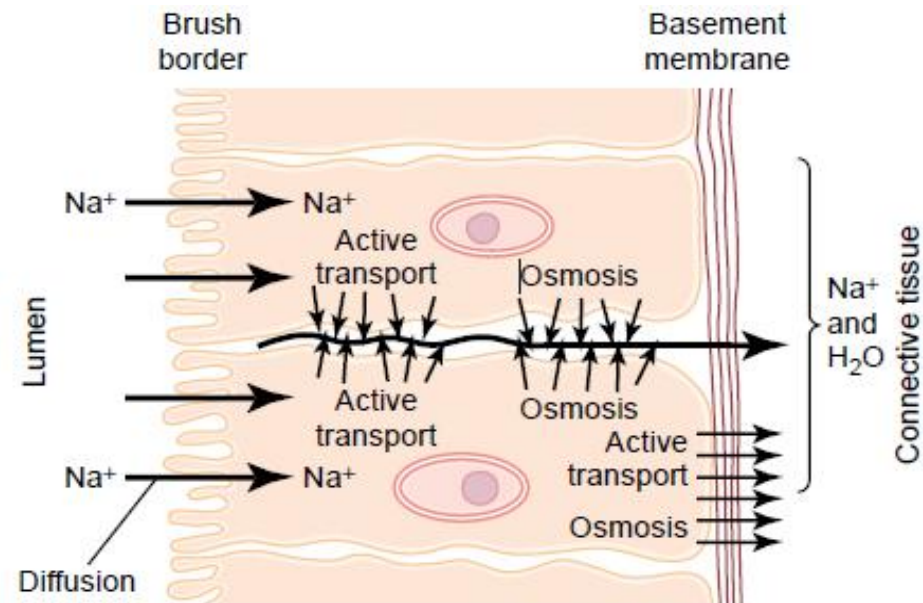
- (1) *Active transport* through the cell membrane *on one side* of the transporting cells in the sheet.
- (2) Either *simple diffusion* or *facilitated diffusion* through the membrane *on the opposite side* of the cell.



- the epithelial cells are connected together tightly at the luminal pole by means of junctions called “kisses.” The brush border on the luminal surfaces of the cells is permeable to both sodium ions and water. Therefore, sodium and water diffuse readily from the lumen into the interior of the cell.

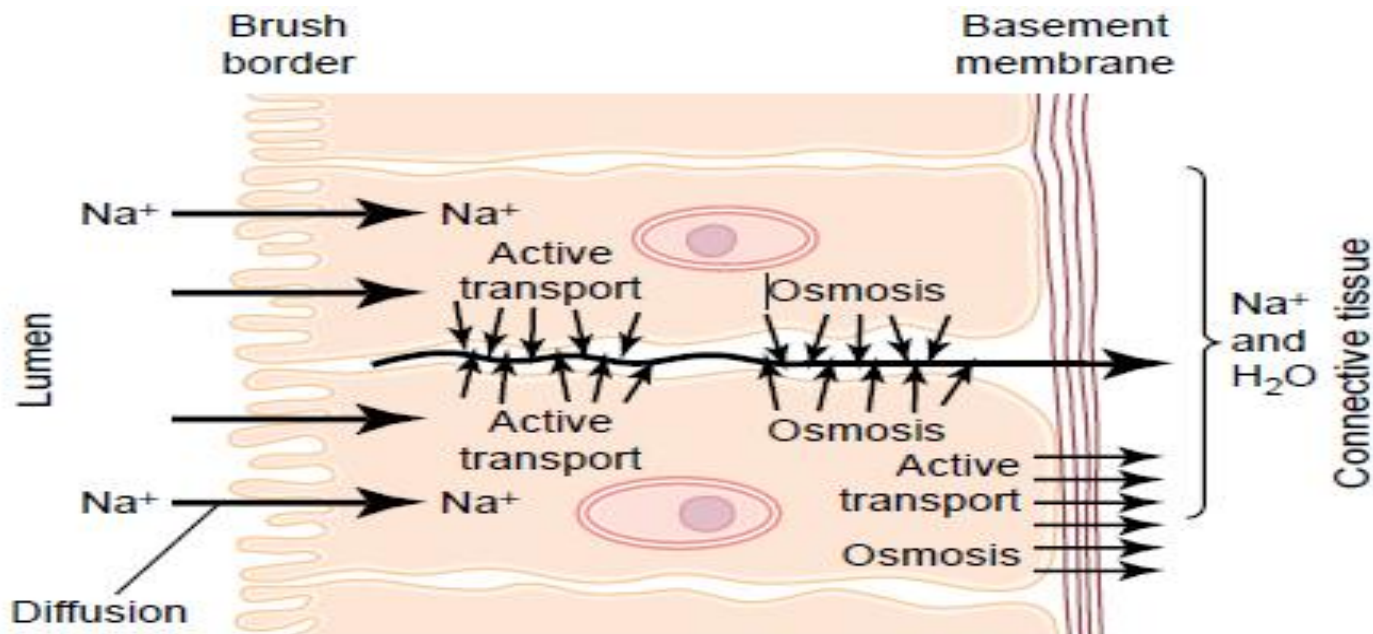


- Then, at the basal and lateral membranes of the cells, sodium ions are actively transported into the extracellular fluid of the surrounding connective tissue and blood vessels.
- This creates a high sodium ion concentration gradient across these membranes, which in turn causes osmosis of water as well.
- Thus, active transport of sodium ions at the basolateral sides of the epithelial cells results in transport not only of sodium ions but also of water.





- These are the mechanisms by which almost all the **nutrients, ions, and other substances** are absorbed into the blood from the intestine.
- They are also the way the same substances are reabsorbed from the glomerular filtrate by the renal tubules.



# **The Body Fluid Compartments: Extracellular; Intracellular and Interstitial Fluid; and Edema**

## ❖ Daily Intake of Water

**Water is added to the body by two major sources:**

- (1) It is ingested in the form of liquids or water in the food, which together normally add about 2100 ml/day to the body fluids.**
- (2) It is synthesized in the body as a result of oxidation of carbohydrates, adding about 200 ml/day. This provides a total water intake of about 2300 ml/day.**

## Daily Intake and Output of Water (ml/day)

---

	Normal	Prolonged, Heavy Exercise
<b>Intake</b>		
Fluids ingested	2100	?
From metabolism	<u>200</u>	<u>200</u>
Total intake	2300	?
<b>Output</b>		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	<u>1400</u>	<u>500</u>
Total output	2300	6600

# ❖ Daily Loss of Body Water

## ➤ Insensible Water Loss:

There is a continuous loss of water by:

- Evaporation from the respiratory tract.
- Diffusion through the skin.

✓ Which together account for about 700 ml/day of water loss under normal conditions.

✓ This is termed *insensible water loss* because we are not consciously aware of it.

➤ The insensible water loss through the skin occurs independently of sweating, the average water loss by diffusion through the skin is about 300 to 400 ml/day.

## ❖ **Fluid Loss in Sweat.**

- The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature.
- The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise, water loss in sweat occasionally increases to 1 to 2 L/hour.

## ❖ **Water Loss in Feces.**

- Only a small amount of water (100 ml/day) normally is lost in the feces.
- This can increase to several liters a day in people with severe diarrhea.



## ❖ Water Loss by the Kidneys.

- The remaining water loss from the body occurs in the urine excreted by the kidneys.
- The most important means by which the body maintains a balance between water and electrolytes intake and output in the body, is by controlling the rates at which the kidneys excrete these substances.
- urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking tremendous amounts of water.

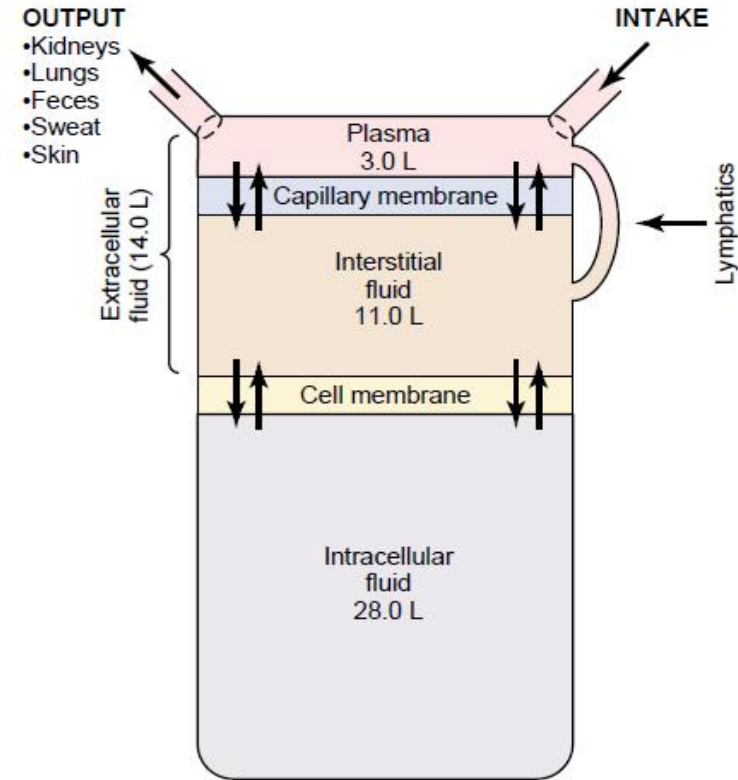
## ❖ Body Fluid Compartments

The total body fluid is distributed mainly between two compartments:

- The *extracellular fluid* .
- The *intracellular fluid*.

### ❑ The extracellular fluid:

- ✓ Is divided into the *interstitial fluid* and the *blood plasma* .
- ✓ In the average 70-kilogram adult human, the total body water is about 60 per cent of the body weight, or about 42 liters .
- ✓ This percentage can change, depending on age, gender, and degree of obesity.

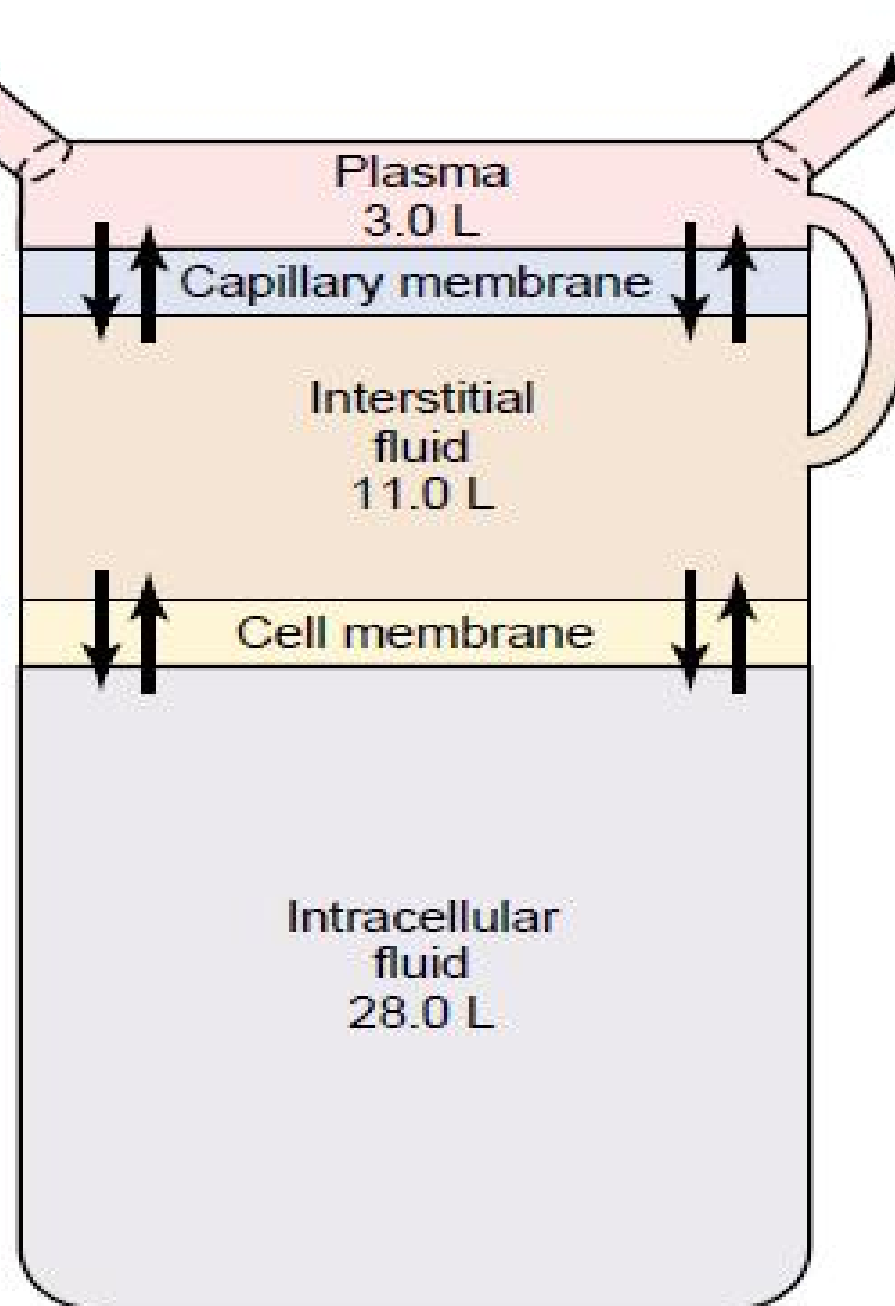


## OUTPUT

- Kidneys
- Lungs
- Feces
- Sweat
- Skin

## INTAKE

Extracellular  
fluid (14.0 L)



Lymphatics

Intracellular  
fluid  
28.0 L

Cell membrane

Interstitial  
fluid  
11.0 L

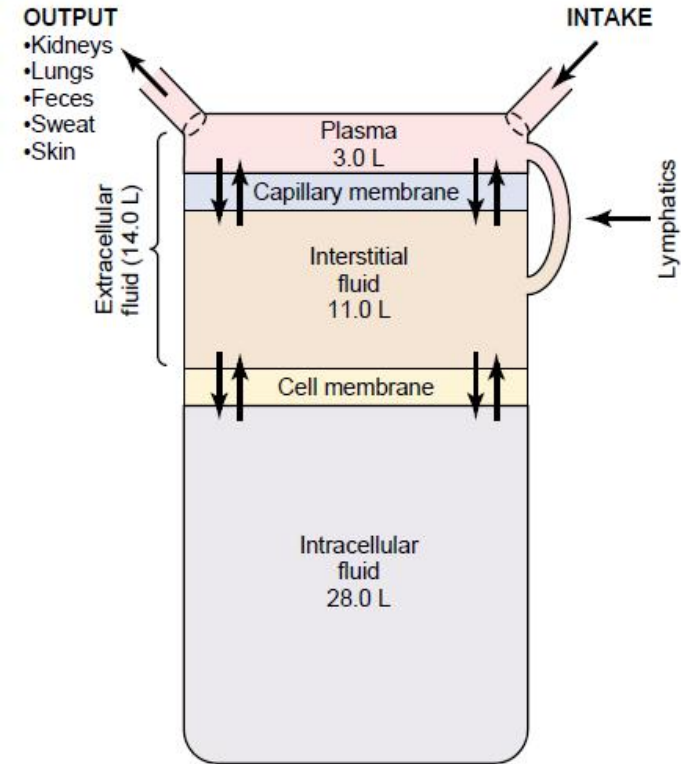
Capillary membrane

Plasma  
3.0 L

## ❖ Intracellular Fluid Compartment:

➤ About 28 liters of the 42 liters (40% of the total body weight ) of fluid in the body are inside the 75 trillion cells and are collectively called the *intracellular fluid*.

➤ The intracellular fluid of all the different cells together is considered to be one large fluid compartment.



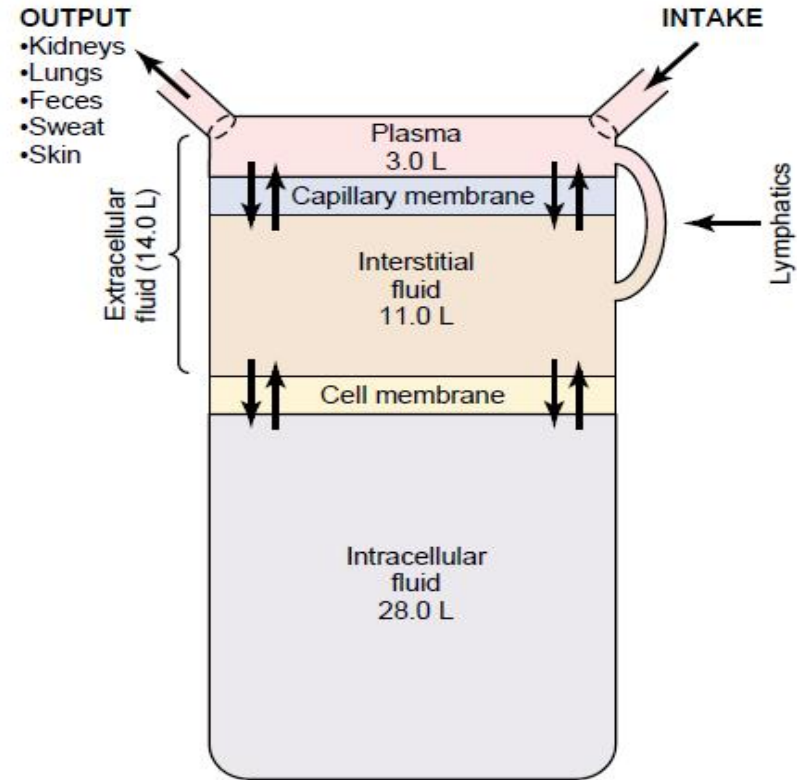
# ❖ Extracellular Fluid Compartment

## Fluid

- All the fluids outside the cells are collectively called the *extracellular fluid*.
- Together these fluids account for about 20 % of the body weight (14 liters).

❑ The two largest compartments of the extracellular fluid are:

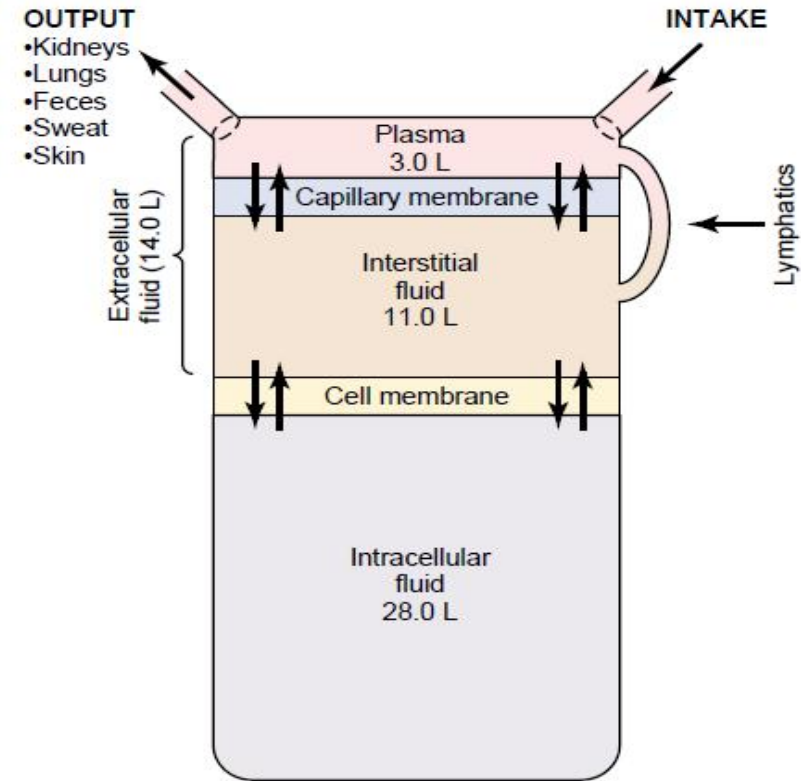
- The *interstitial fluid*, which makes up more than three fourths of the extracellular fluid.
- The *plasma*, which makes up almost one fourth of the extracellular fluid, or about 3 liters.



➤ The plasma is the non cellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes.

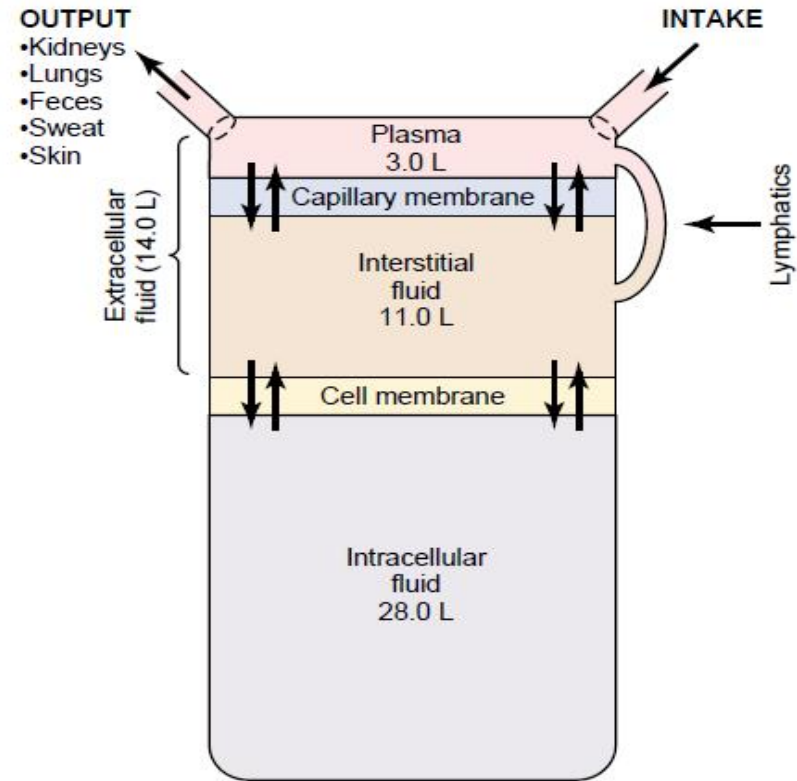
➤ These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins.

➤ Therefore, the extracellular fluids are constantly mixing, so that the plasma and interstitial fluids have about the same composition except for proteins, which have a higher concentration in the plasma.



# ❖ Blood Volume

➤ Blood contains both extracellular fluid (the fluid in plasma) and intracellular fluid (the fluid in the red blood cells). However, blood is considered to be a separate fluid compartment because it is contained in a chamber of its own, the circulatory system.

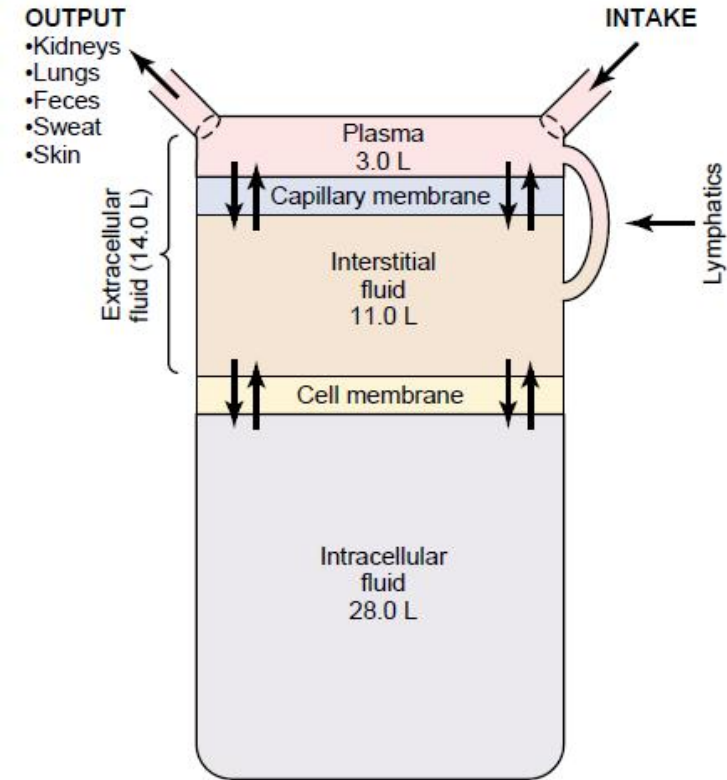




- **The blood volume is especially important in the control of cardiovascular dynamics.**
- **The average blood volume of adults is about 7 per cent of body weight, or about 5 liters.**
- **About 60 per cent of the blood is plasma and 40 per cent is red blood cells, but these percentages can vary considerably in different people, depending on gender, weight, and other factors.**

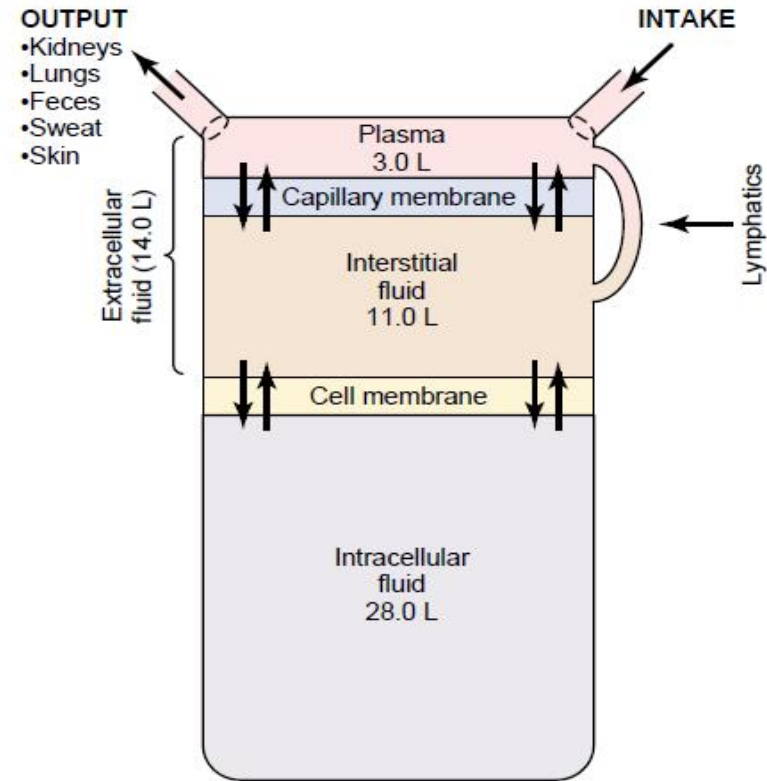
# ❖ Ionic composition of plasma and interstitial fluid is similar

- Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar.
- The most important difference between these two compartments is the higher concentration of **protein** in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues.

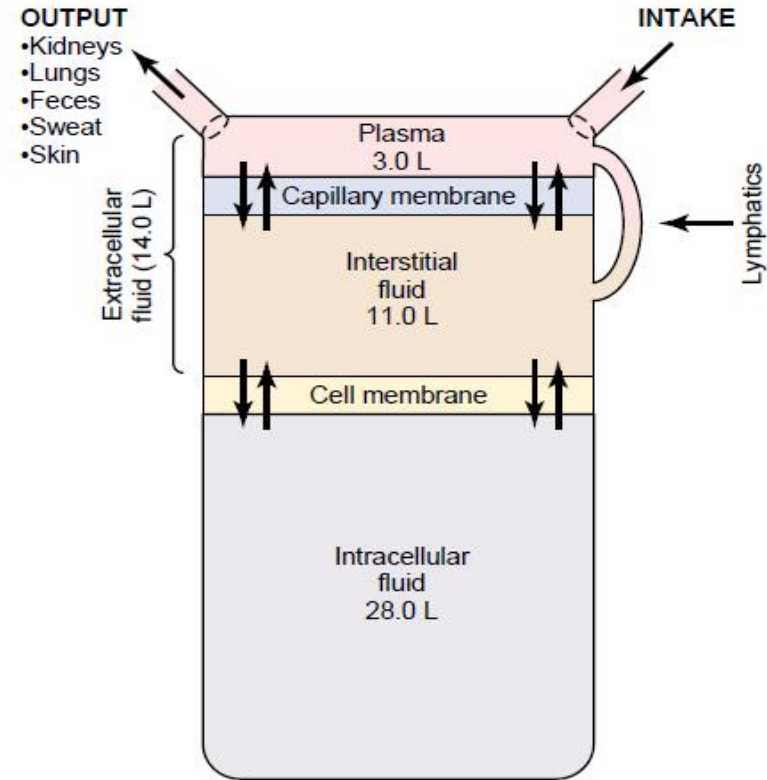


## ❖ *The Donnan effect:*

- The concentration of positively charged ions (cations) is slightly greater (about 2%) in the plasma than in the interstitial fluid.
- The plasma proteins have a net negative charge and, therefore, tend to bind cations, such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins.



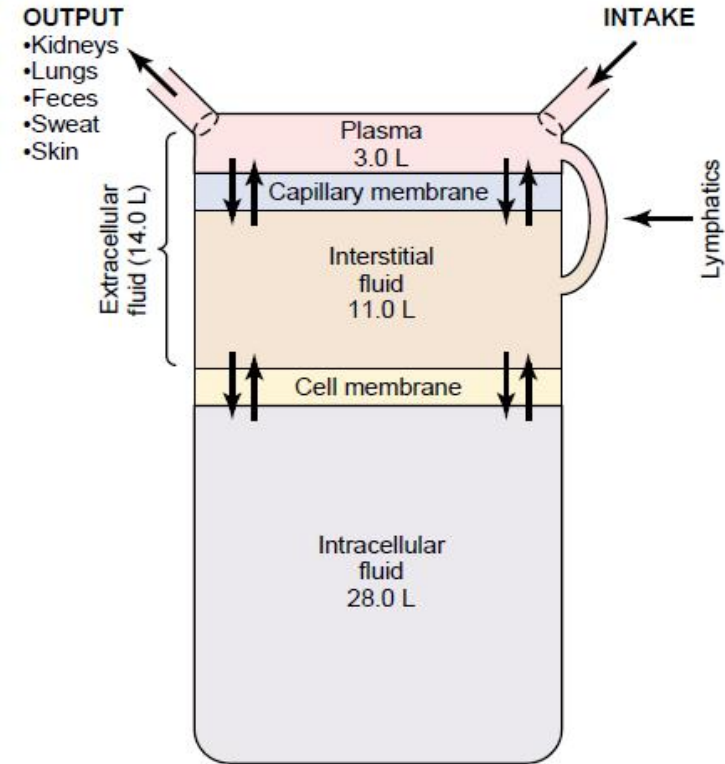
- Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions.



➤ The concentration of ions in interstitial fluid and in the plasma is considered to be about **equal**.

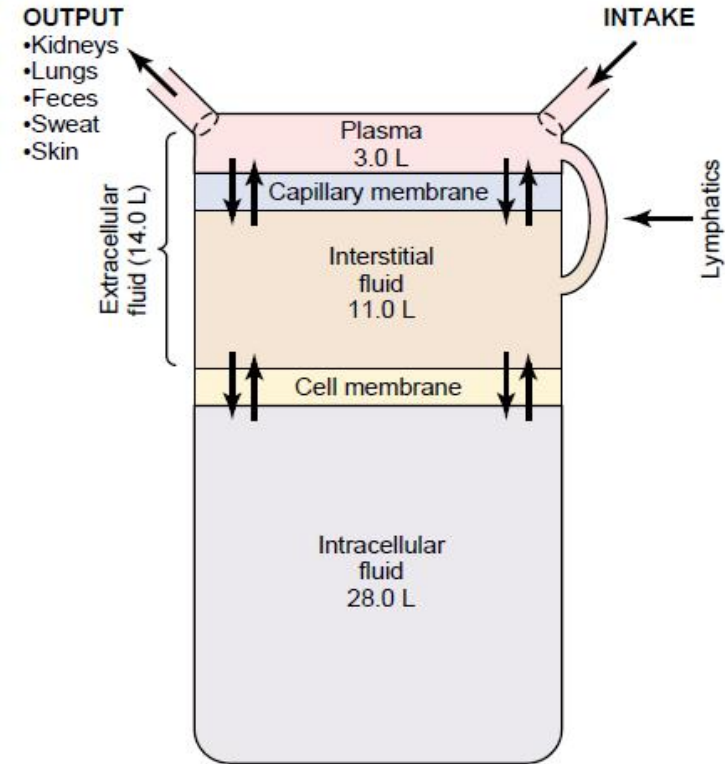
➤ The extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of **sodium** and **chloride** ions, **bicarbonate** ions.

➤ But only small quantities of **potassium**, **calcium**, **magnesium**, **phosphate**, and **organic acid** ions.



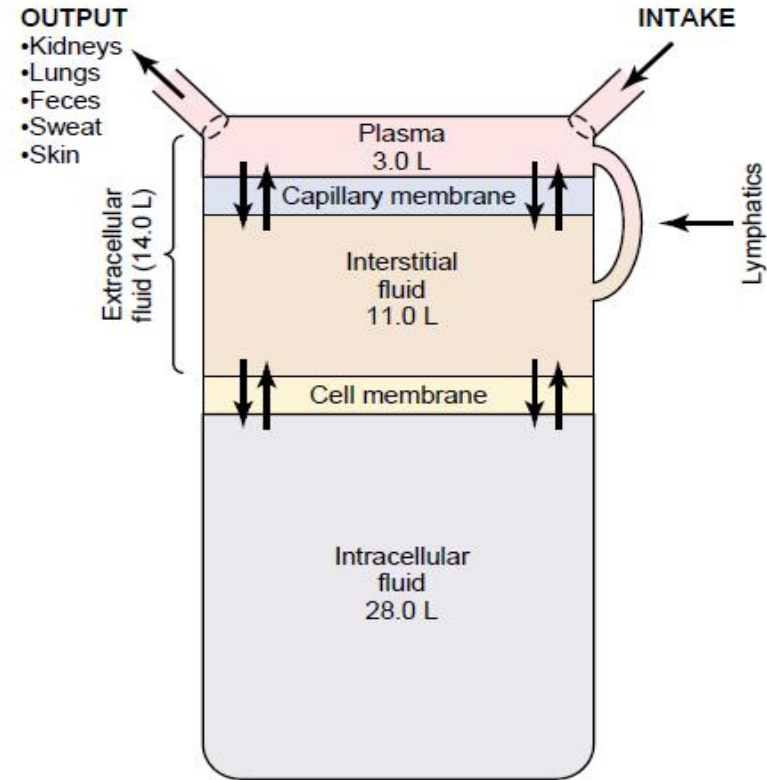
➤ The composition of extracellular fluid is carefully regulated by various mechanisms, especially by the kidneys.

➤ This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.



## ❖ Important constituents of the intracellular fluid:

- The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to **water** but not to most of the **electrolytes** in the body.
- The intracellular fluid contains only small quantities of **sodium** and **chloride** ions and almost **no calcium** ions.
- It contains large amounts of **potassium** and **phosphate**, ions plus moderate quantities of **magnesium** and **sulfate** ions, all of which have low concentrations in the extracellular fluid.
- Also, cells contain large amounts of **protein**, almost four times as much as in the plasma.

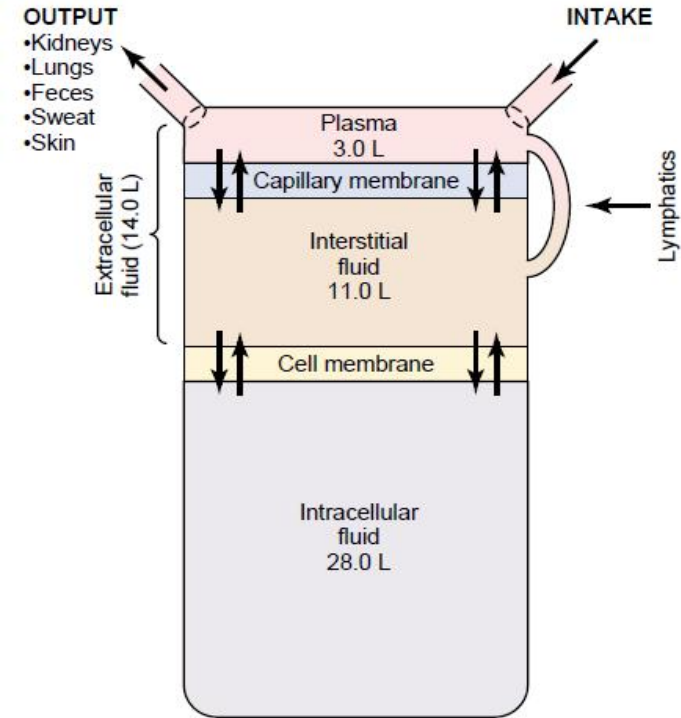




❖ Regulation of fluid exchange and osmotic equilibrium between intracellular and extracellular fluid:

➤ The relative amounts of extracellular fluid distributed between the plasma and interstitial spaces are determined mainly by the balance of hydrostatic and colloid osmotic forces across the capillary membranes.

➤ The distribution of fluid between intracellular and extracellular compartments is determined mainly by the osmotic effect of the smaller solutes—especially sodium, chloride, and other electrolytes—acting across the cell membrane.



➤ The reason for this is that the cell membranes are highly permeable to water but relatively impermeable to even small ions such as sodium and chloride.

➤ Therefore, water moves across the cell membrane rapidly, so that the intracellular fluid remains isotonic with the extracellular fluid.

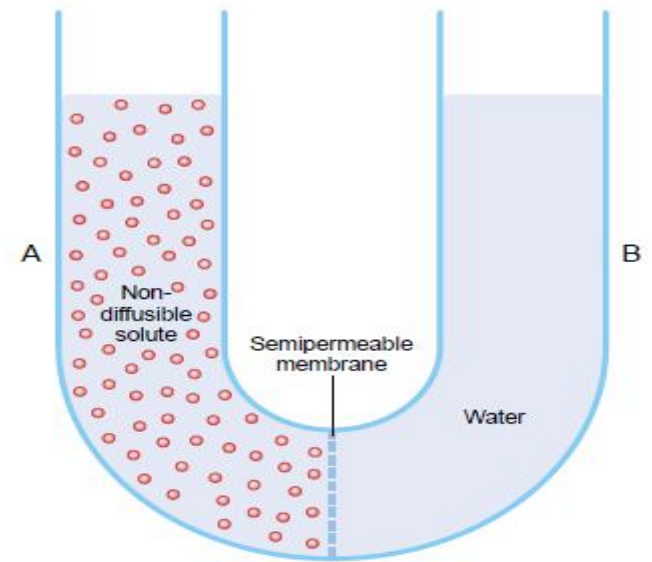


Figure 4-10

Demonstration of osmotic pressure caused by osmosis at a semi-permeable membrane.

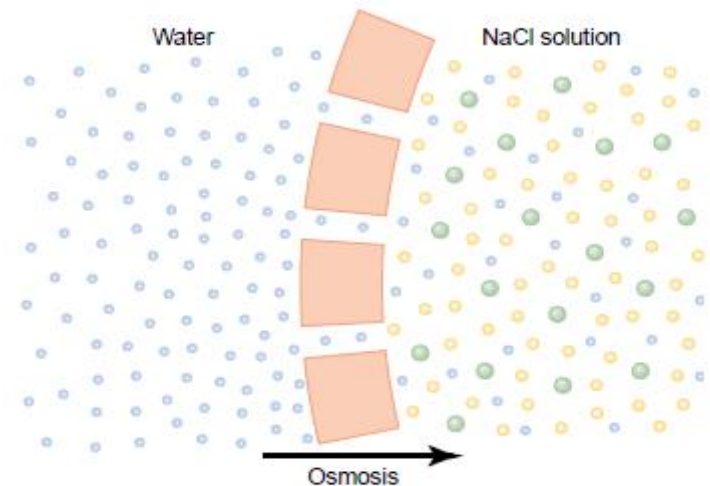


Figure 4-9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

## ❖ Basic principles of osmosis and osmotic pressure:

- Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration.
- When a solute is added to pure water, this reduces the concentration of water in the mixture.
- Thus, the higher the solute concentration in a solution, the lower the water concentration.
- So, water diffuses from a region of low solute concentration (high water concentration) to one with a high solute concentration (low water concentration).

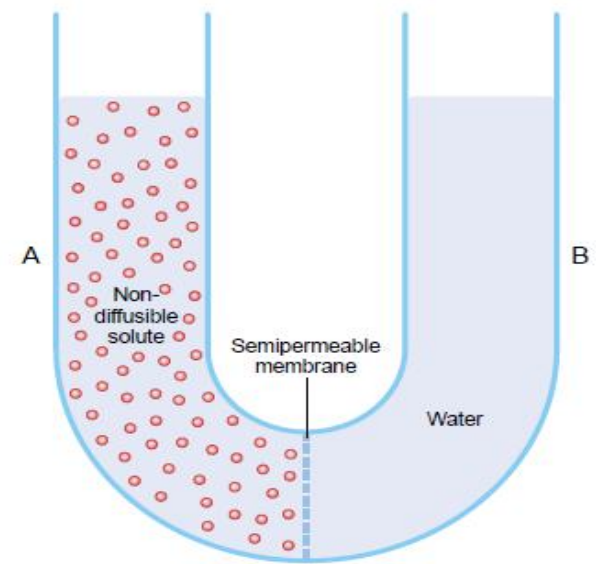


Figure 4-10

Demonstration of osmotic pressure caused by osmosis at a semi-permeable membrane.

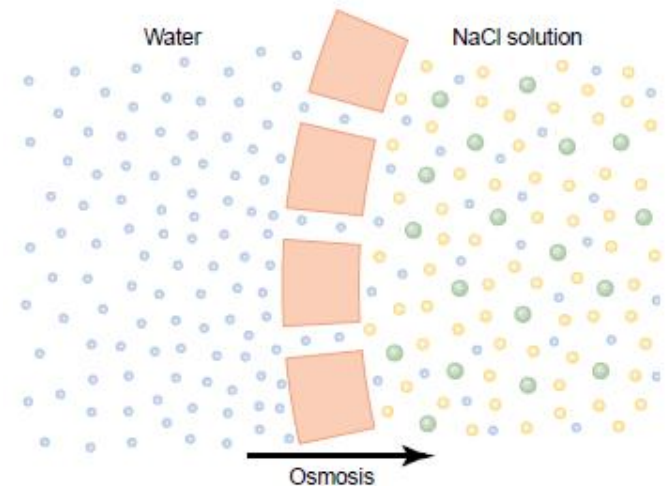


Figure 4-9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

➤ Thus, if a solute such as sodium chloride is added to the extracellular fluid, water rapidly diffuses from the cells through the cell membranes into the extracellular fluid until the water concentration on both sides of the membrane becomes equal.

➤ Conversely, if a solute such as sodium chloride is removed from the extracellular fluid, water diffuses from the extracellular fluid through the cell membranes into the cells.

➤ The rate of diffusion of water is called the *rate of osmosis*.

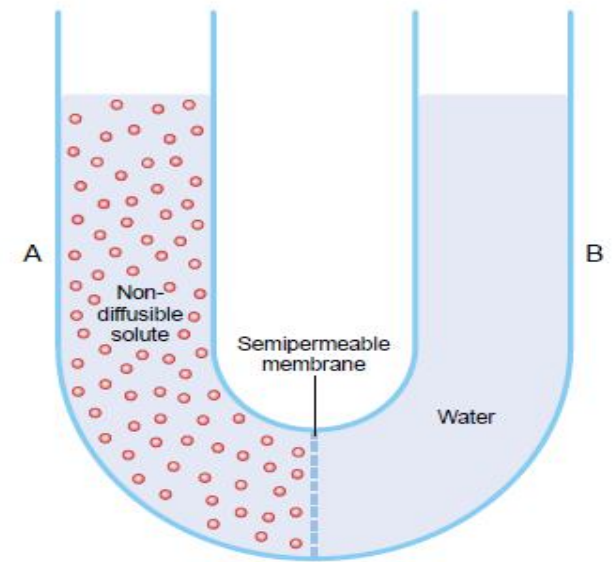


Figure 4-10

Demonstration of osmotic pressure caused by osmosis at a semipermeable membrane.

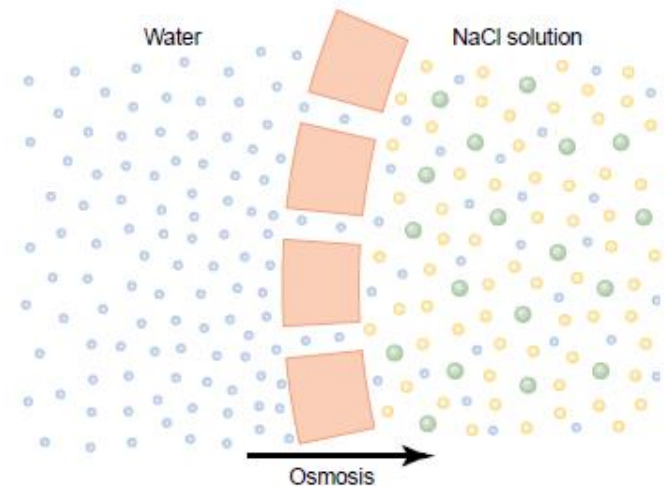


Figure 4-9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

- The osmotic pressure of a solution is directly proportional to the concentration of osmotically active particles in that solution.
- Regardless of whether the solute is a large molecule or a small molecule. (eg. one molecule of **albumin** with a molecular weight of **70,000** has the same osmotic effect as one molecule of **glucose** with a molecular weight of **180**.)
- One molecule of **sodium chloride**, however, has two osmotically active particles, **Na<sup>+</sup>** and **Cl<sup>-</sup>**, and therefore has twice the osmotic effect of either an **albumin** molecule or a **glucose** molecule.

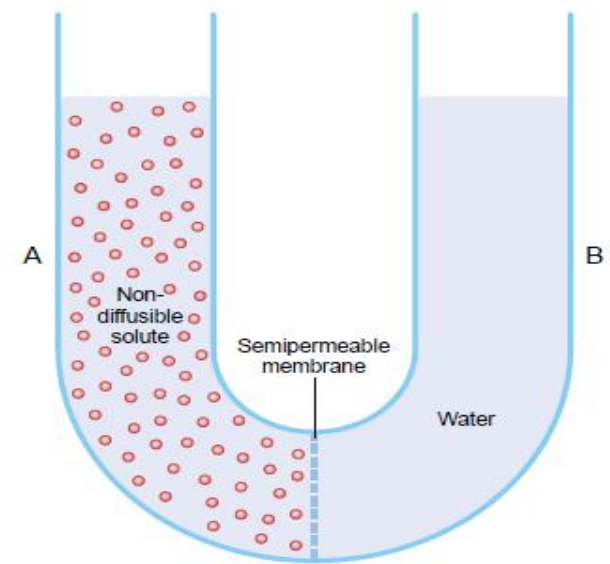


Figure 4-10

Demonstration of osmotic pressure caused by osmosis at a semipermeable membrane.

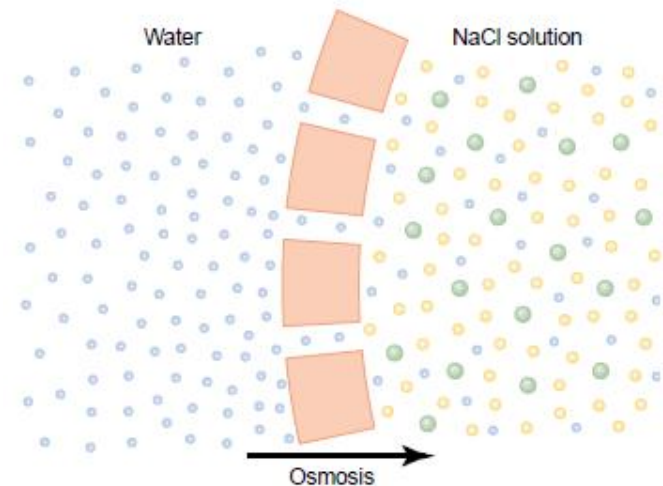


Figure 4-9

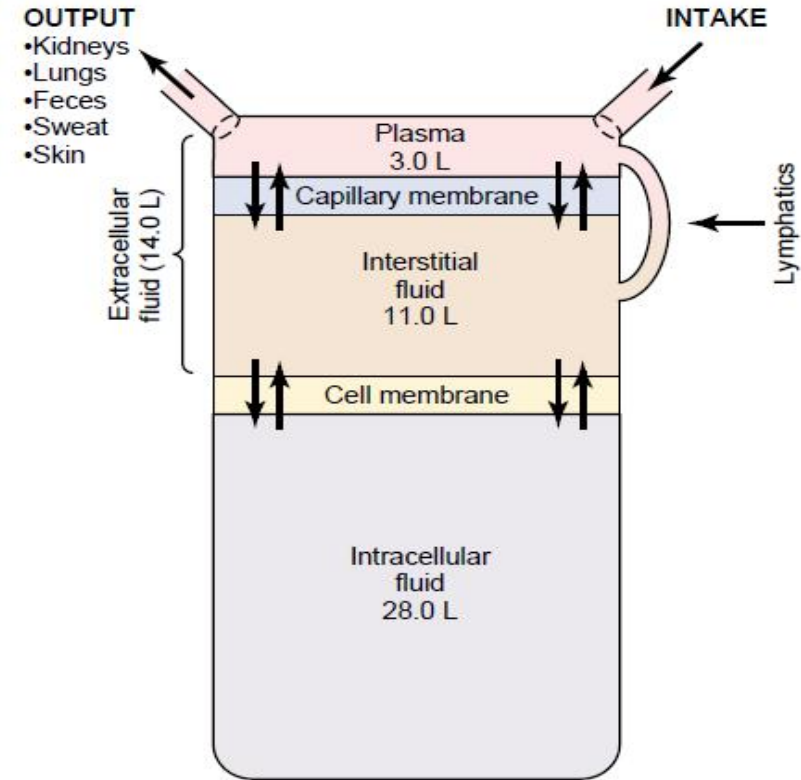
Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.



## ❖❖ Osmolarity of the body fluids:

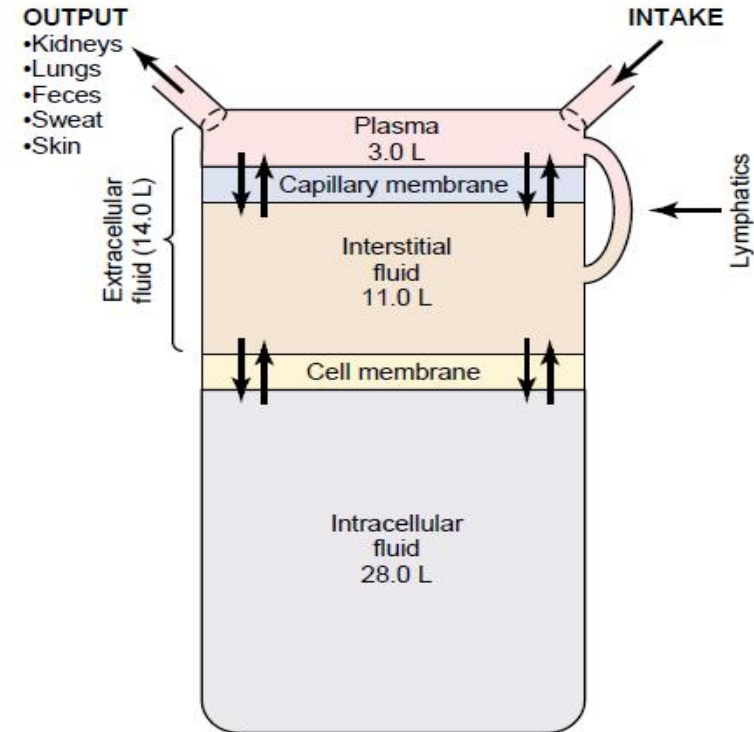
The approximate osmolarity of the various osmotically active substances in plasma, interstitial fluid, and intracellular fluid.

- About 80 % of the total osmolarity of the interstitial fluid and plasma is due to sodium and chloride ions.
- whereas for intracellular fluid. Almost half the osmolarity is due to potassium ions, and the remainder is divided among many other intracellular substances.



➤ The total osmolarity of each of the three compartments is about **300 mOsm/L**, with the plasma being about **1 mOsm/L** greater than that of the interstitial and intracellular fluids.

➤ The slight difference between plasma and interstitial fluid is caused by the osmotic effects of the plasma proteins, which maintain about **20 mm Hg** greater pressure in the capillaries than in the surrounding interstitial spaces.





## ❖ Isotonic, Hypotonic, and Hypertonic fluids.

- If a cell is placed in a solution of impermeant solutes having an osmolarity of **282 mOsm/L**, the cells will not shrink or swell because the water concentration in the intracellular and extracellular fluids is equal and the solutes cannot enter or leave the cell.
- Such a solution is said to be *isotonic* because it neither shrinks nor swells the cells.
- Examples of isotonic solutions include a 0.9 per cent solution of sodium chloride or a 5 per cent glucose solution.
- These solutions are important in clinical medicine because they can be infused into the blood without the danger of upsetting osmotic equilibrium between the intracellular and extracellular fluids.

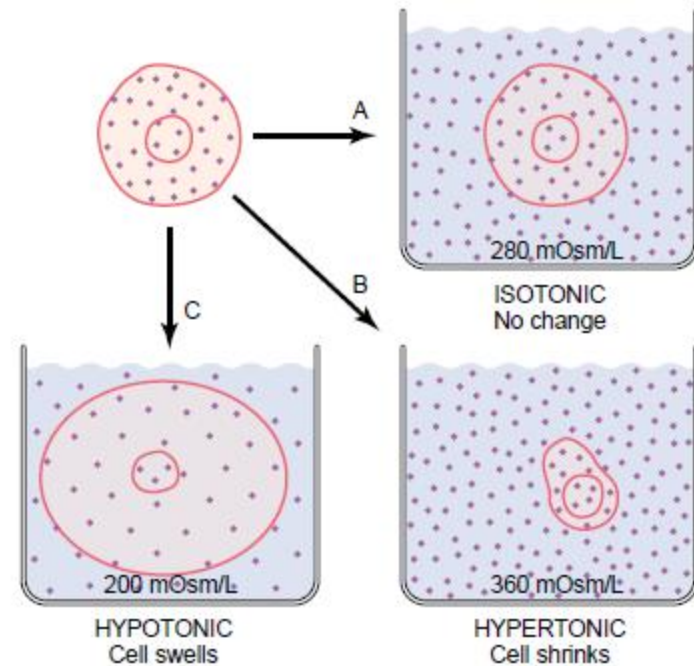
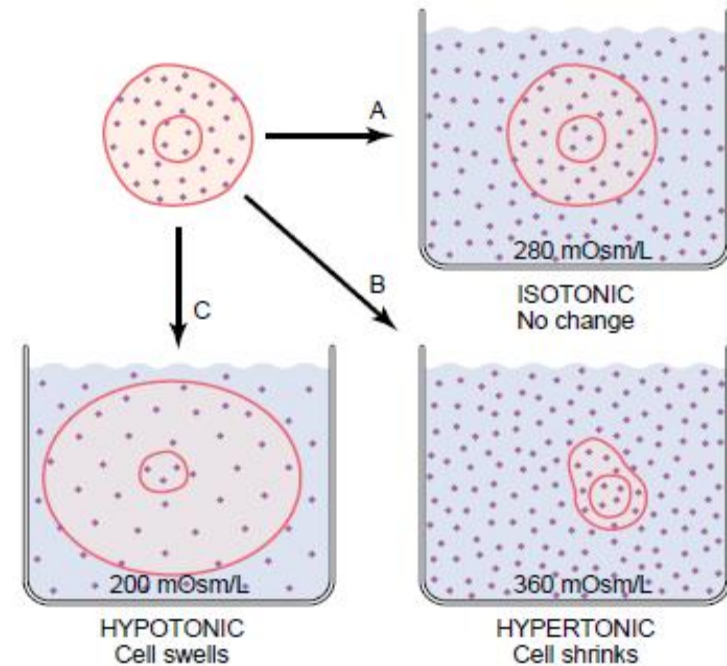


Figure 25-5

Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume.

- **Hypotonic fluid:** If a cell is placed into a *hypotonic* solution that has a lower concentration of impermeant solutes (less than **282 mOsm/L**).
- water will diffuse into the cell, causing it to swell; water will continue to diffuse into the cell, diluting the intracellular fluid while also concentrating the extracellular fluid until both solutions have about the same osmolarity.
- Solutions of sodium chloride with a concentration of less than 0.9 per cent are hypotonic and cause cells to swell.



**Figure 25-5**

Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume.

- **Hypertonic fluid:** If a cell is placed in a *hypertonic* solution having a higher concentration of impermeant solutes, water will flow out of the cell into the extracellular fluid, concentrating the intracellular fluid and diluting the extracellular fluid.
- In this case, the cell will shrink until the two concentrations become equal.
- Sodium chloride solutions of greater than 0.9 per cent are hypertonic.

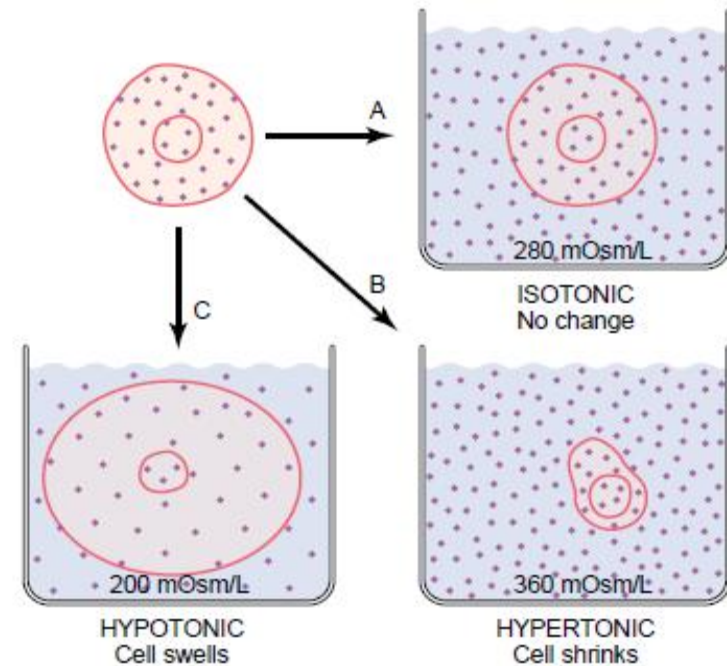


Figure 25-5

Effects of isotonic (A), hypertonic (B), and hypotonic (C) solutions on cell volume.

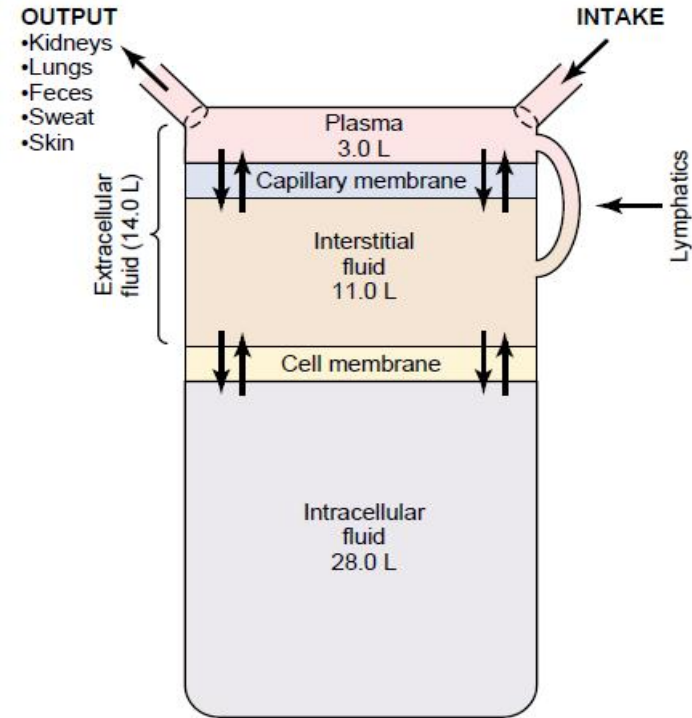
## ❖ Edema: Excess fluid in the tissues

- Edema refers to the presence of excess fluid in the body tissues; edema occurs mainly in the extracellular fluid compartment, but it can involve intracellular fluid as well.

## ❖ Intracellular edema

Two conditions are especially prone to cause intracellular swelling:

- (1) Depression of the metabolic systems of the tissues.
- (2) Lack of adequate nutrition to the cells.



- For example, when blood flow to a tissue is decreased, the delivery of oxygen and nutrients is reduced so the normal tissue metabolism is reduced also, the cell membrane ionic pumps become depressed.
- When this occurs, sodium ions that normally leak into the interior of the cell can no longer be pumped out of the cells, and the excess sodium ions inside the cells cause osmosis of water into the cells.
- Sometimes this can increase intracellular volume of a tissue area—even of an entire ischemic leg, for example—to two to three times normal. When this occurs, it is usually a prelude to death of the tissue.

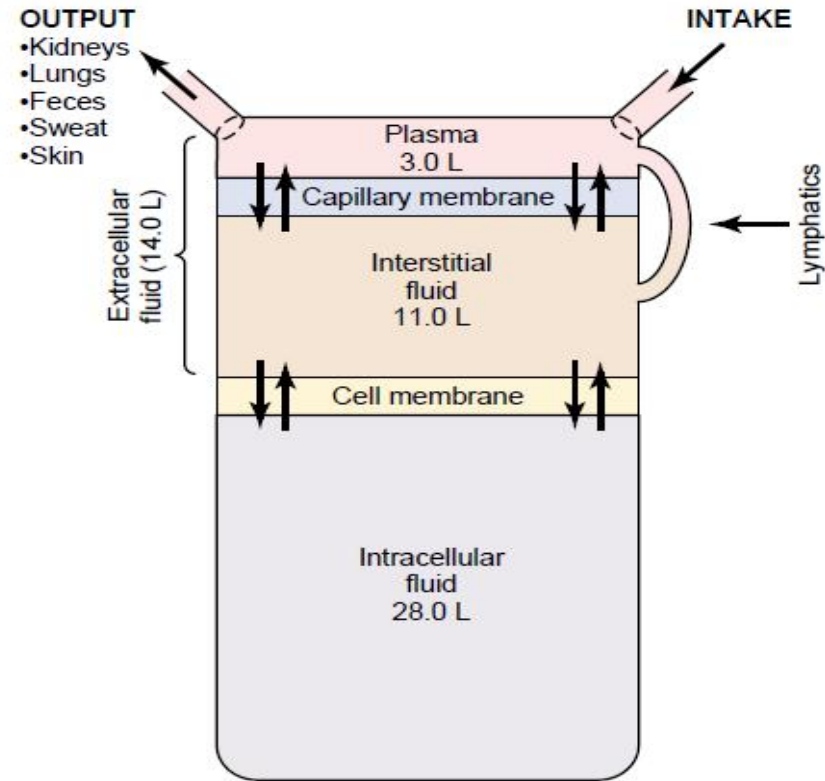
# ❖ Extracellular edema

- Extracellular fluid edema occurs when there is excess fluid accumulation in the extracellular spaces. There are two general causes of extracellular edema:

(1) Abnormal leakage of fluid from the plasma to the interstitial spaces across the capillaries.

(2) Failure of the lymphatic to return fluid from the interstitium back into the blood.

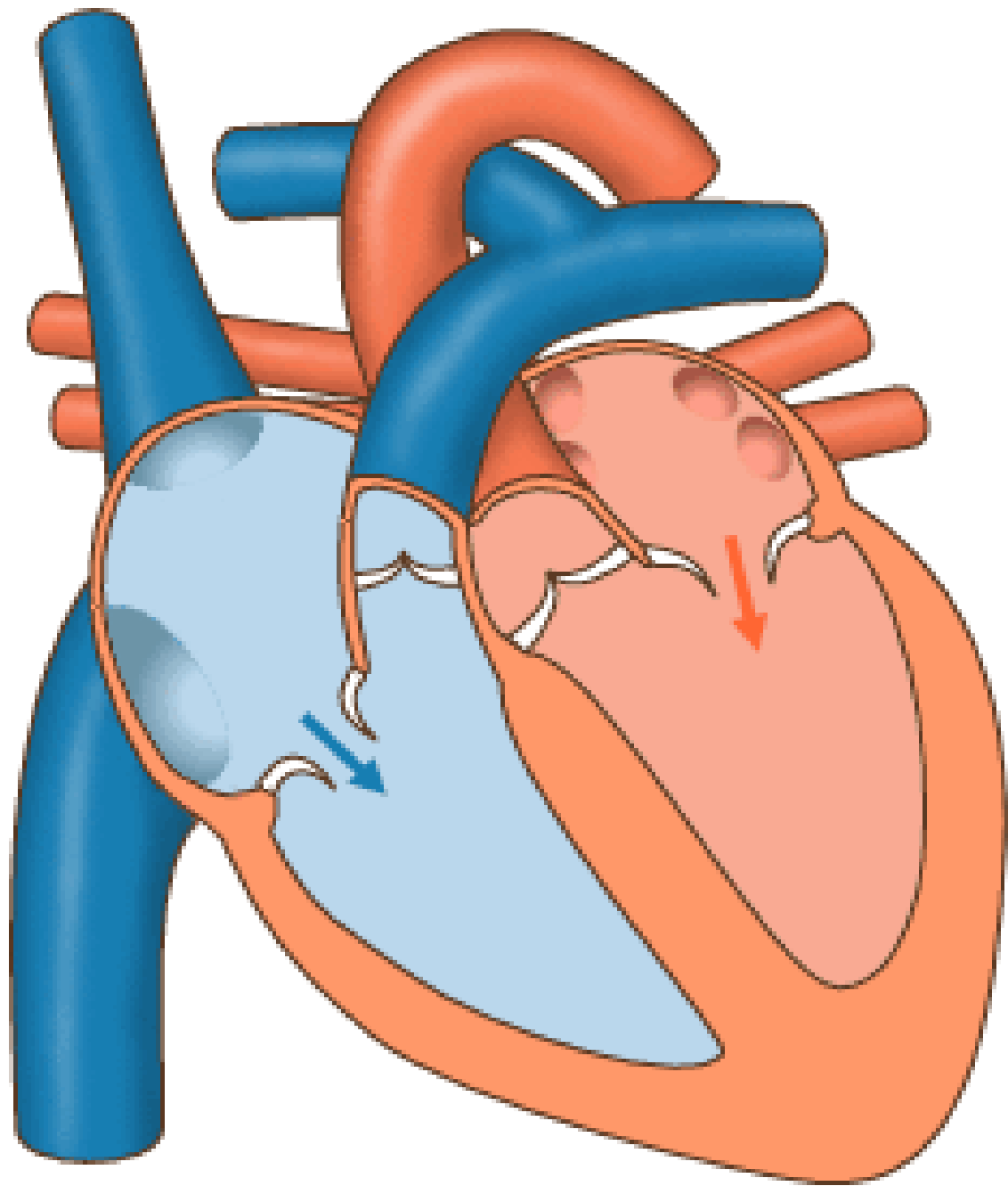
➤ The most common clinical cause of interstitial fluid accumulation is excessive capillary fluid filtration.



# THE CIRCULATION

د . محمد عيسى السبعراوي  
ماجستير فسلجة طبية





# ❖ Systemic circulation (greater circulation or peripheral circulation).

- The systemic circulation supplies blood flow to all the tissues of the body except the lungs.

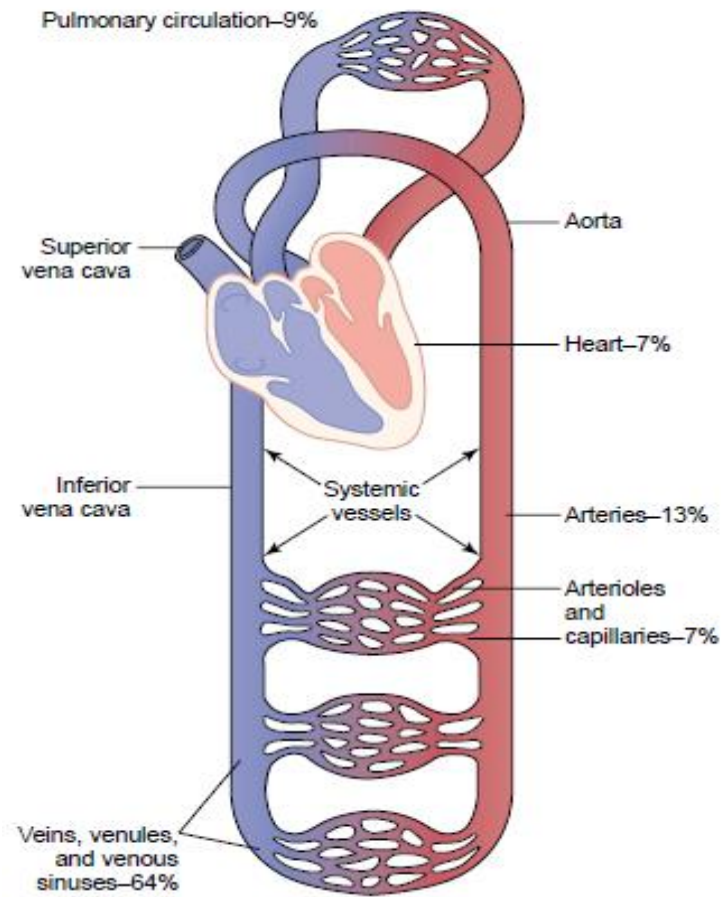


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

## ❖ Pulmonary circulation:

- The pulmonary circulation is the portion of the circulatory system which carries deoxygenated blood away from the right ventricle, to the lungs, and returns oxygenated blood to the left atrium and ventricle of the heart.
- The term pulmonary circulation is readily paired and contrasted with the systemic circulation.
- The vessels of the pulmonary circulation are the pulmonary arteries and the pulmonary veins.

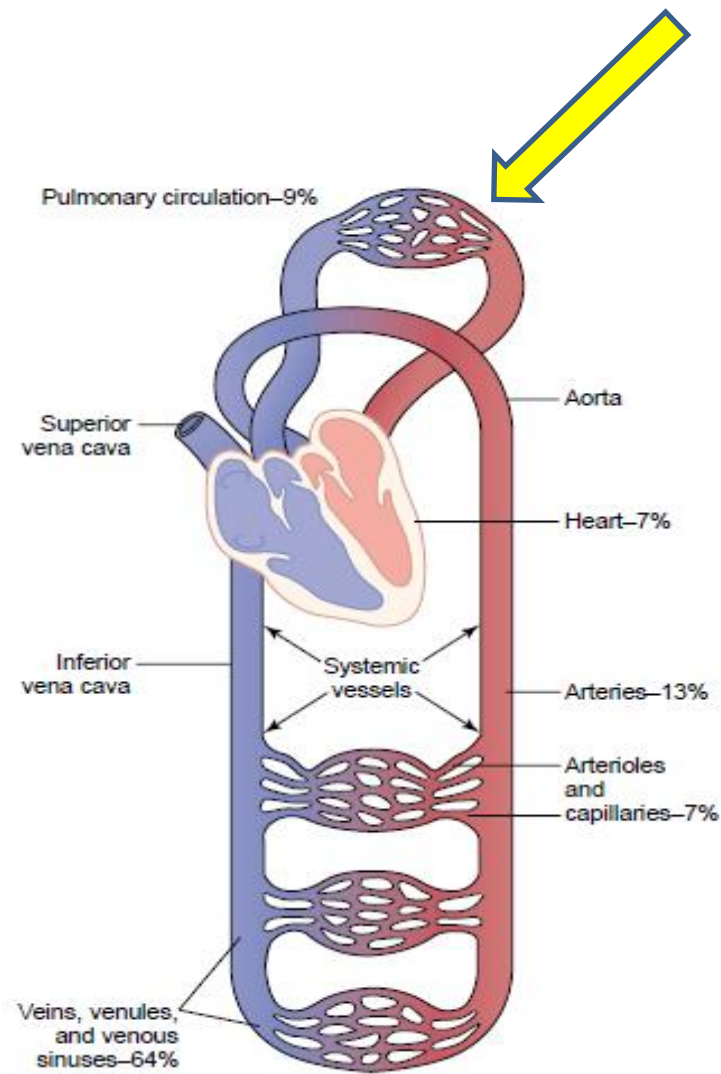


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

❑ The function of the systemic circulation is to service the needs of the body tissues.

➤ To transport nutrients to the body tissues.

➤ To transport waste products away.

➤ To conduct hormones from one part of the body to another.

➤ To maintain an appropriate environment in all the tissue fluids of the body for optimal survival and function of the cells.

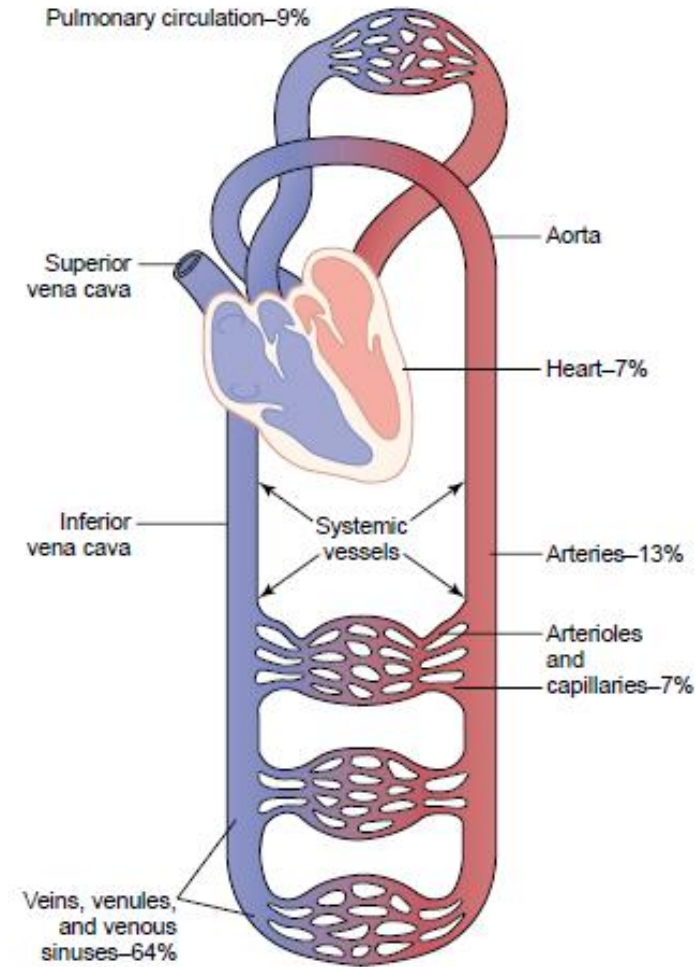


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

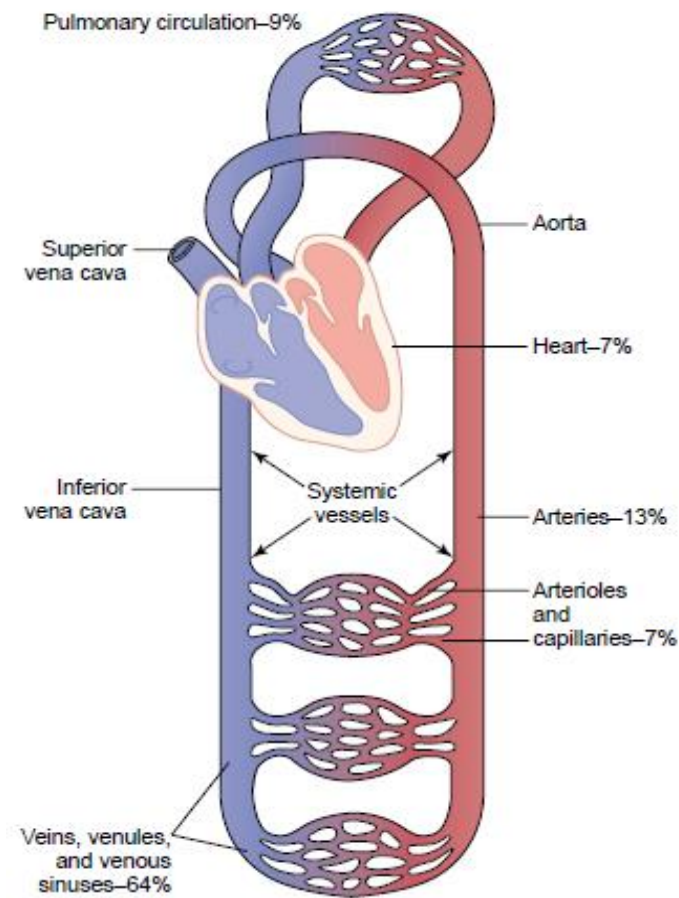
# ❖ Functional Parts of the Circulation:

## ➤ The arteries:

- Transport blood *under high pressure* to the tissues.
- Have a strong vascular walls.
- Blood flows at a high velocity in the arteries.

## ➤ The arterioles:

- The last small branches of the arterial system.
- They act as a *control conduits* through which blood is released into the capillaries.
- Has a strong muscular wall that can close the arteriole completely or can, by relaxing, dilate it several fold.



**Figure 14-1**

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

## ➤ The capillaries:

- Is to exchange fluid, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid.
- The capillary walls are very thin.
- Have numerous minute *capillary pores* permeable to water and other small molecular substances.

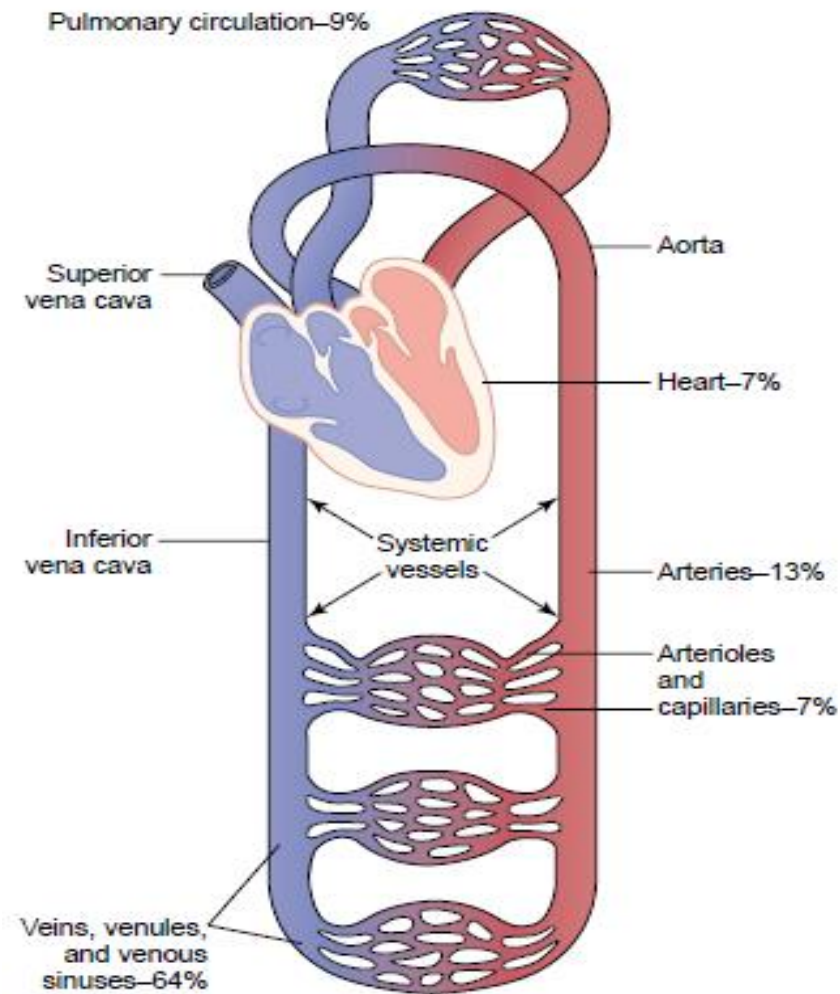


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.



## ➤ The *venules*:

- Collect blood from the capillaries.
- They gradually coalesce into progressively larger veins.

## ➤ The *veins*:

- function as conduits for transport of blood from the venules back to the heart.
- They serve as a major **reservoir** of extra blood; the blood pressure in venous system is very low.
- The venous walls are thin.

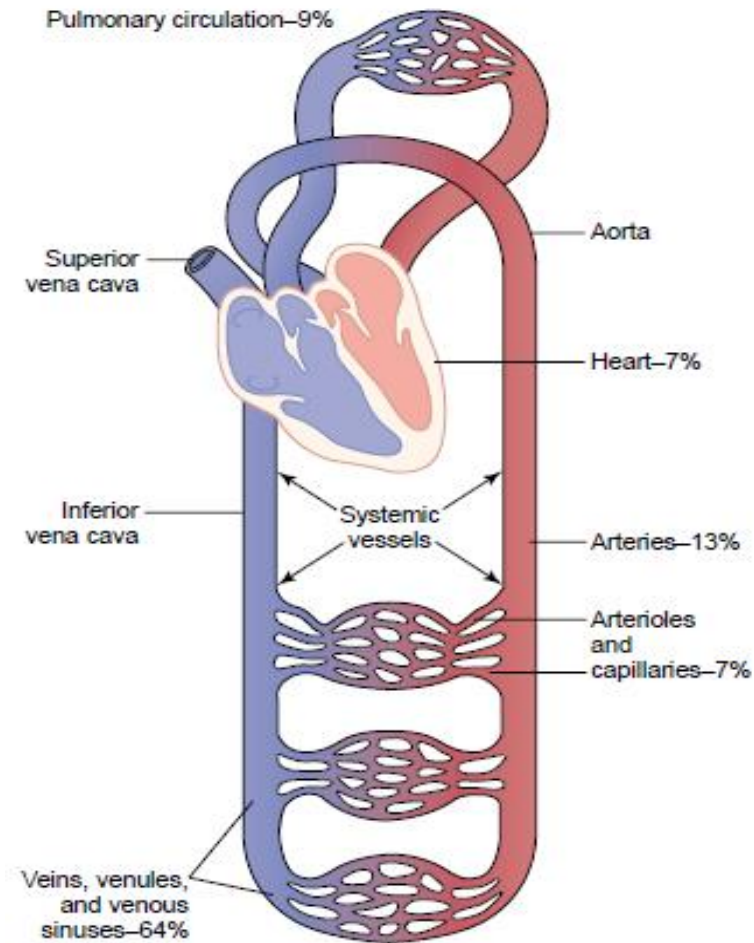


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.



# ❖ Volumes of blood in different parts of the circulation:

- ✓ About 84% of the entire blood volume of the body is in the systemic circulation.
- ✓ 16% in heart and lungs.
- ✓ Of the 84 per cent in the systemic circulation:
  - 64 % is in the veins.
  - 13 % in the arteries.
  - 7 % in the systemic arterioles and capillaries.
- The heart contains 7 % of the blood.
- Pulmonary vessels contain 9 % of the blood.

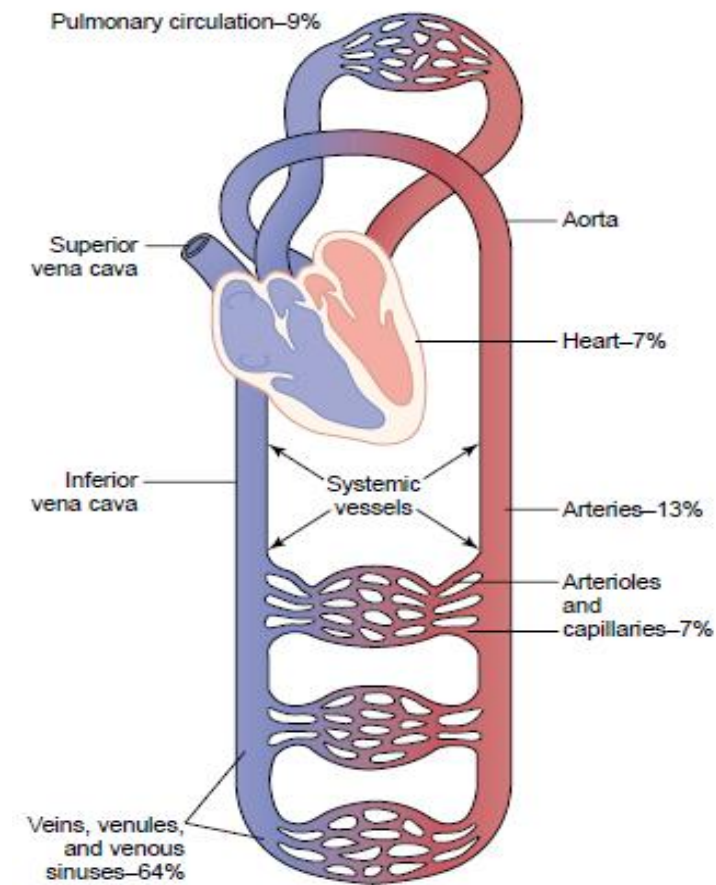


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

## ❖ Cross-Sectional areas and velocities of blood flow:

- If all the *systemic vessels* of each type were put side by side, their approximate total cross-sectional areas for the average human being would be as follows:

Vessel	Cross-Sectional Area (cm <sup>2</sup> )
Aorta	2.5
Small arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small veins	80
Venae cavae	8

- The much larger cross-sectional areas of the veins than of the arteries.
- averaging about four times those of the corresponding arteries.
- This explains the large storage of blood in the venous system in comparison with the arterial system.

Vessel	Cross-Sectional Area (cm <sup>2</sup> )
Aorta	2.5
Small arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small veins	80
Venae cavae	8

- The velocity of blood flow is inversely proportional to vascular cross-sectional area.
- Under resting conditions, the velocity averages about 33 cm/sec in the aorta (1/1000 as rapidly in the capillaries, about 0.3 mm/sec).
- The capillaries have a typical length of only 0.3 to 1 mm, the blood remains in the capillaries for only 1 to 3 seconds.
- All diffusion of nutrient food substances and electrolytes that occurs through the capillary walls must do so in this exceedingly short time.

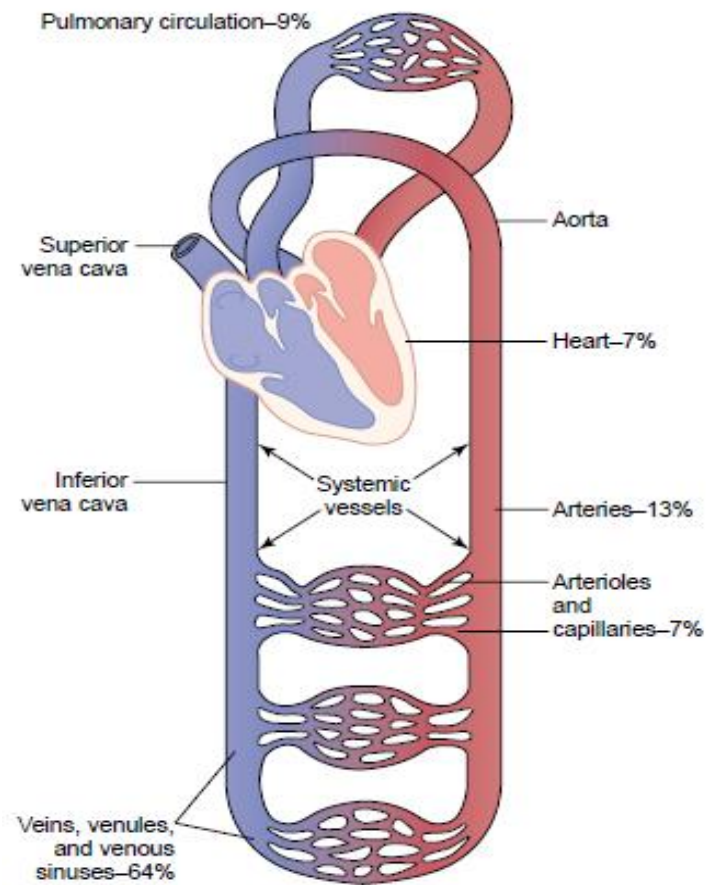


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

## ❖ Blood flow:

- The quantity of blood that passes a given point in the circulation in a given period of time ( *milliliters \minute; liters \minute; milliliters \second* ).
- The overall blood flow in the total circulation of an adult person at rest is about **5000-6000 ml/min**.
- This is called the *cardiac output* because it is the amount of blood pumped into the aorta by the heart each minute.

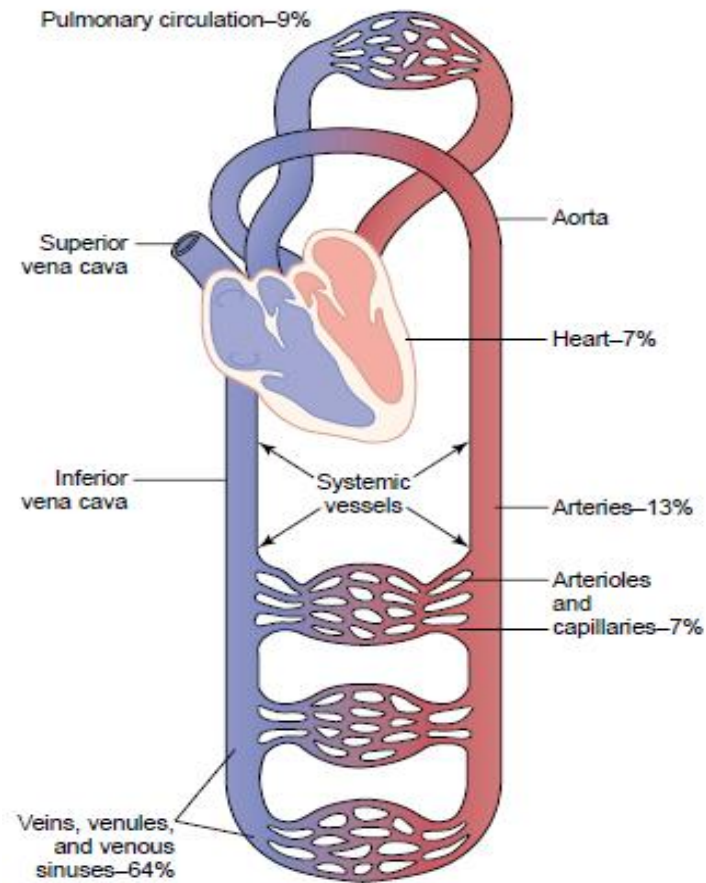
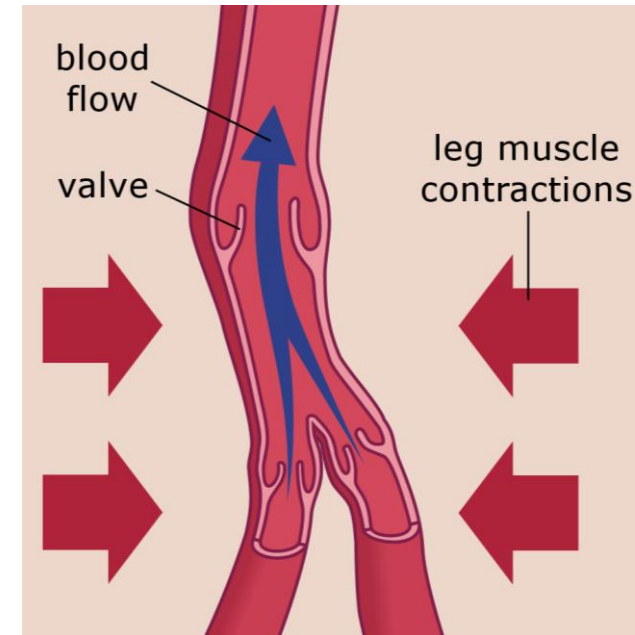
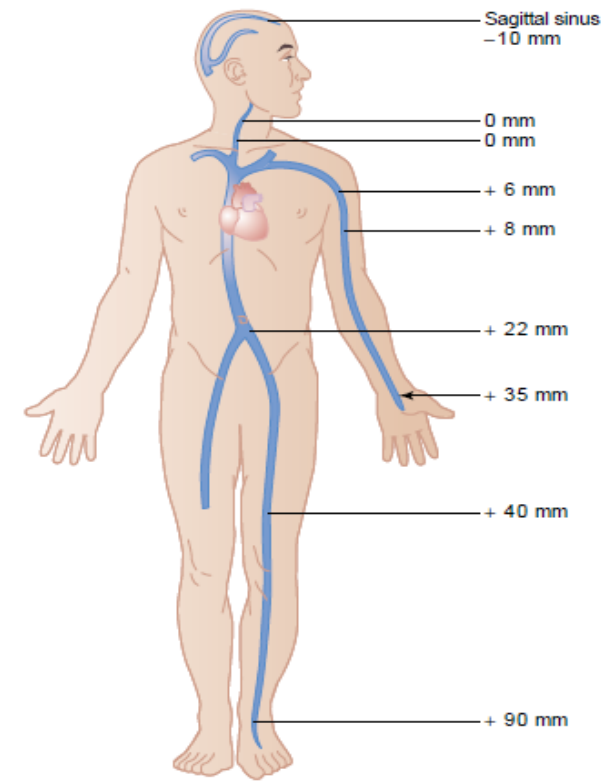


Figure 14-1

Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

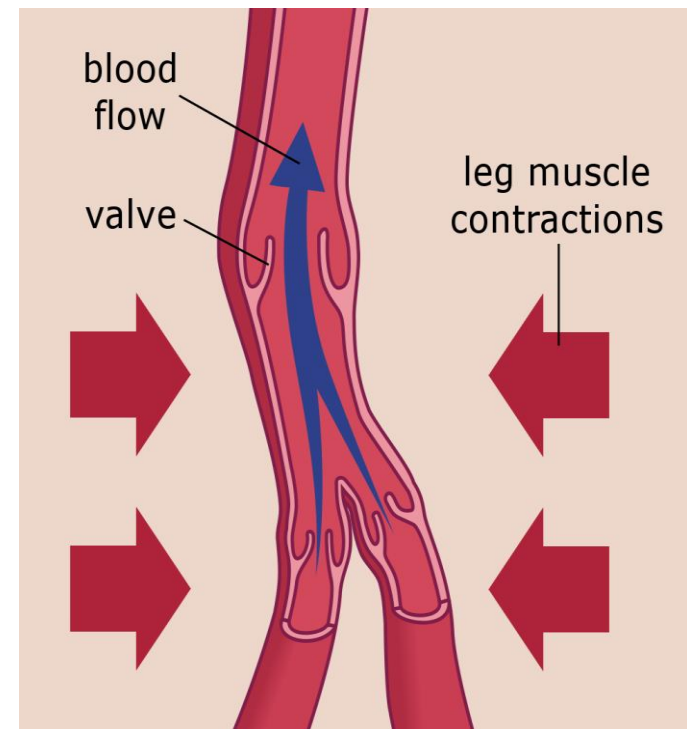
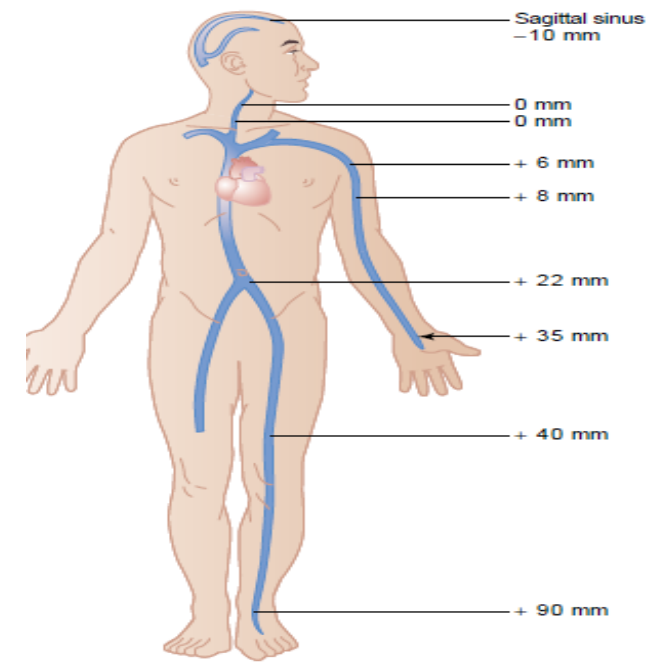
# ❖ Veins and their functions

- 1) Veins are **storing** small or large quantities of blood and making this blood available when it is required by the remainder of the circulation.
- 2) The peripheral veins can also propel blood forward by means of a so-called **venous pump**, and they even help to regulate cardiac output.



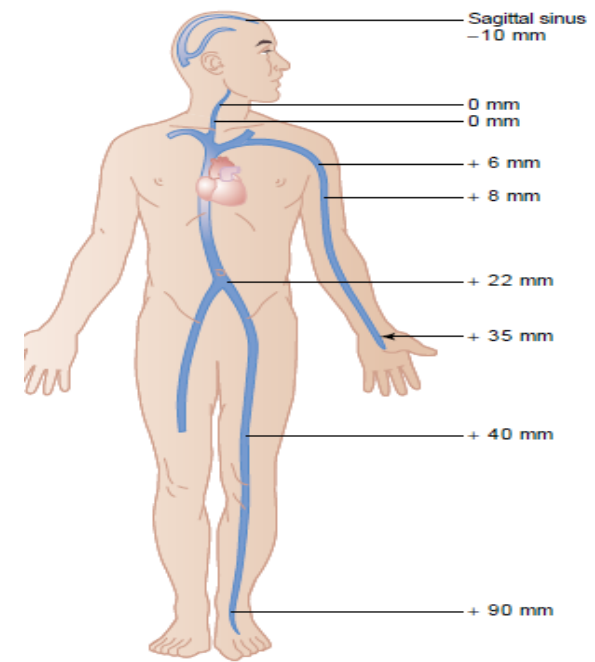
# ❖ Venous Valves and the “Venous Pump”:

- The gravitational pressure effect would cause the venous pressure in the feet always to be about **+90 mm Hg** in a standing adult.
- Every time one should moves the legs, tightens the muscles and compresses the veins in or adjacent to the muscles, and this squeezes the blood out of the veins.

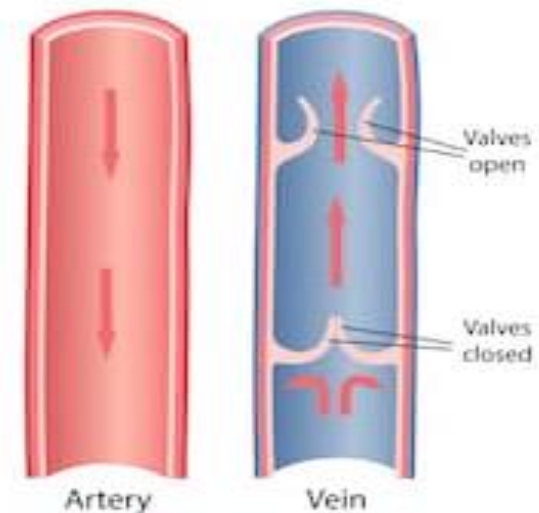




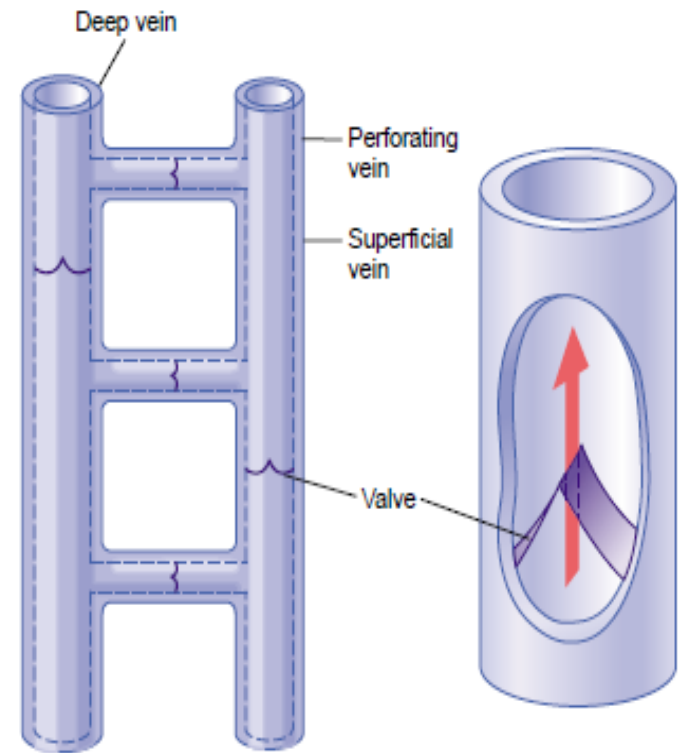
- The valves in the veins are arranged; to keep the direction of venous blood flow only toward the heart.
- So, if a person moves the legs or even tenses the leg muscles, a certain amount of venous blood is propelled toward the heart.
- This pumping system is known as the “venous pump” or “muscle pump,” and it is efficient enough that under ordinary circumstances, the venous pressure in the feet of a walking adult remains less than +20 mm Hg.



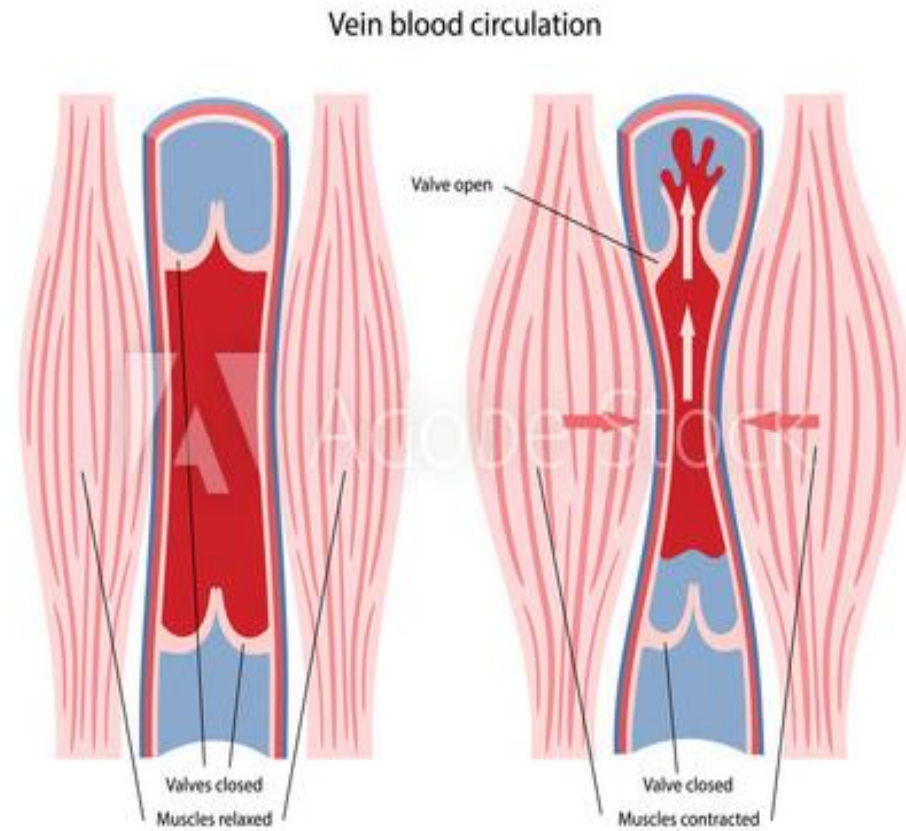
Arterial and vein blood circulation



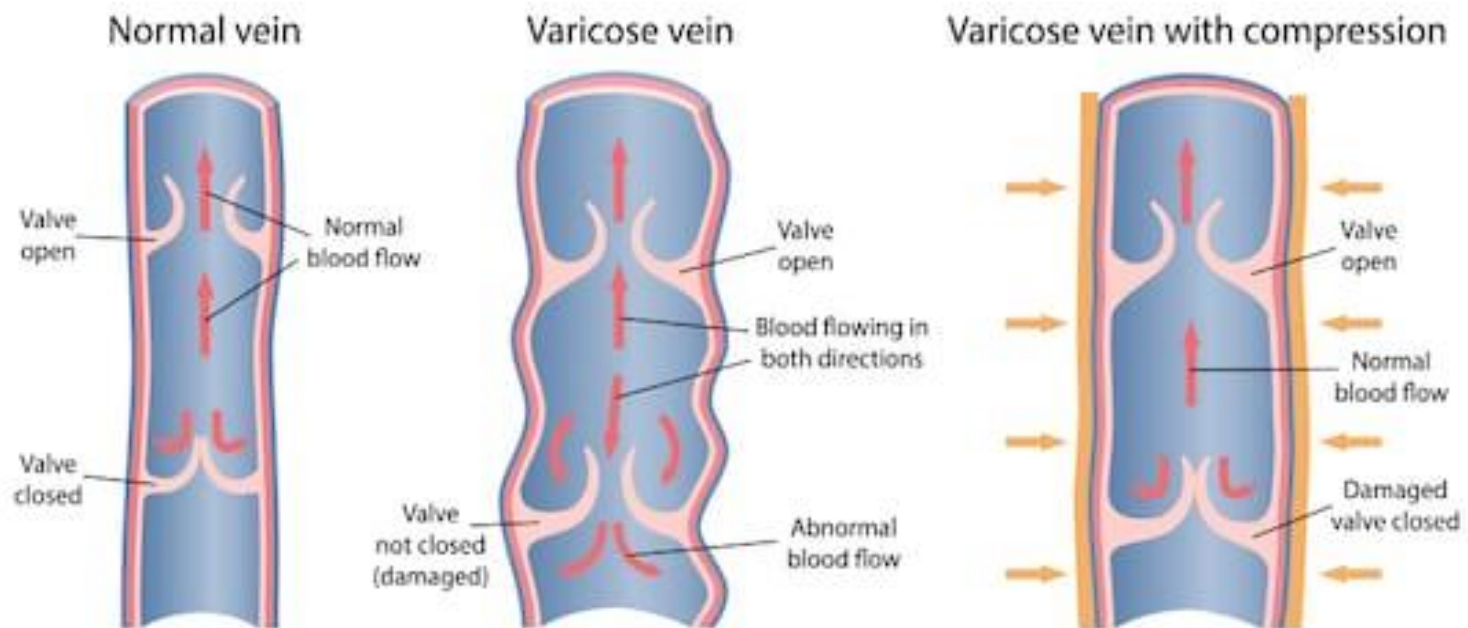
- If a person stands perfectly still, the **venous pump** does not work, and the **venous pressures** in the lower legs increase to the full gravitational value of **90 mmHg** in about **30 seconds**.
- The pressures in the capillaries also increase greatly.



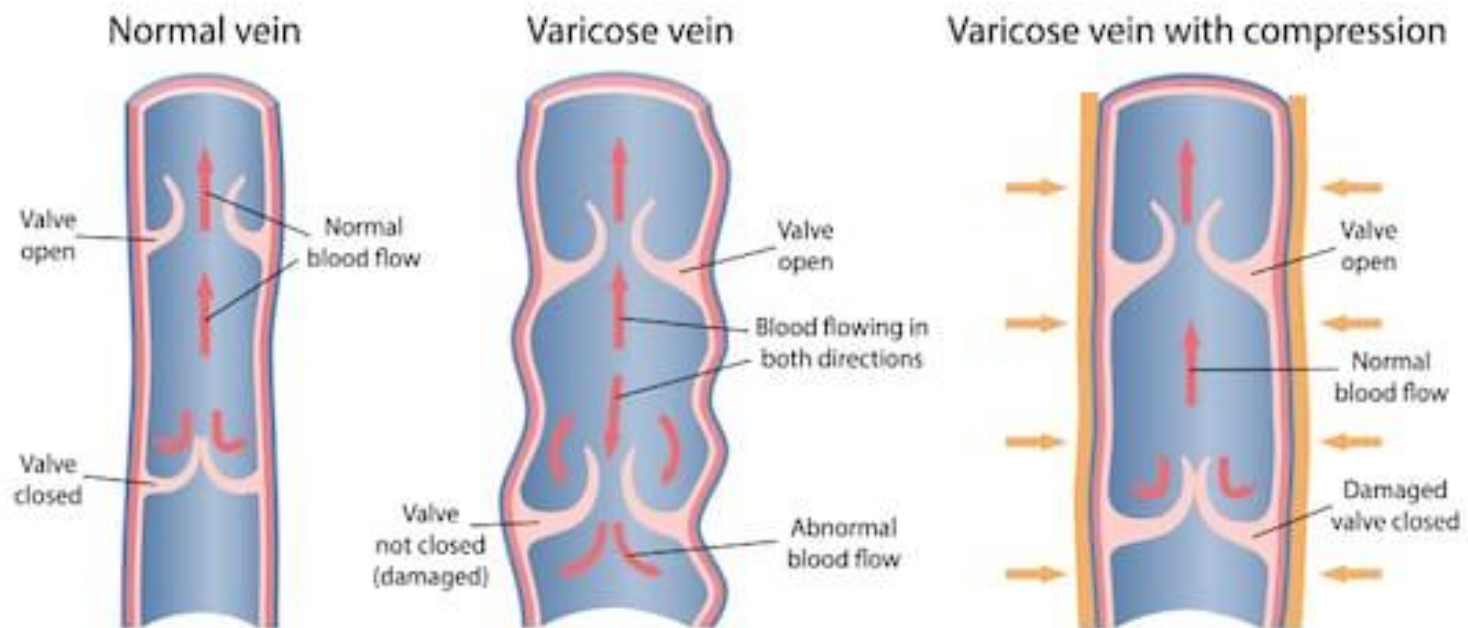
- causing fluid to leak from the circulatory system into the tissue spaces.
- As a result, the legs swell, and the blood volume diminishes.
- 10 - 20% of the blood volume can be lost from the circulatory system within the 15-30 min. of standing, as occurs when a soldier is made to stand at rigid attention.



- **Venous Valve Incompetence Causes “Varicose” Veins.** The valves of the venous system frequently become “incompetent” or sometimes even are destroyed.
- **This is especially true when the veins have been overstretched by excess venous pressure lasting weeks or months, as occurs in pregnancy or when one stands most of the time.**



- Stretching the veins increases their cross-sectional areas, but the leaflets of the valves do not increase in size.
- Therefore, the leaflets of the valves no longer close completely.
- When this develops, the pressure in the veins of the legs increases greatly because of failure of the venous pump; this further increases the sizes of the veins and finally destroys the function of the valves entirely.



- Thus, the person develops “**varicose veins**,” which are characterized by large, bulbous protrusions of the veins beneath the skin of the entire leg, particularly the lower leg.
- Whenever people with varicose veins stand for more than a **few minutes**, the venous and capillary pressures become very high, and leakage of fluid from the capillaries causes constant **edema** in the legs.



➤ The edema in turn prevents adequate diffusion of nutritional materials from the capillaries to the muscle and skin cells.

➤ So that the muscles become painful and weak.

➤ The skin frequently becomes gangrenous and ulcerates.





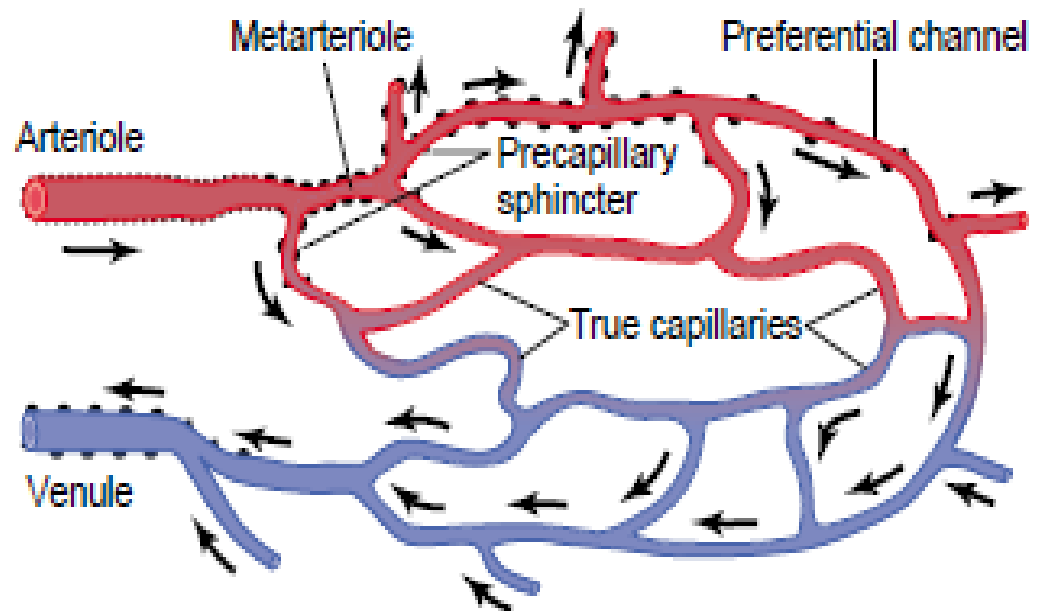
## ❖ Treatment:

- continual elevation of the legs to a level at least as high as the heart.
- Tight binders on the legs also can be of considerable assistance in preventing the edema and its sequelae.
- Surgery.



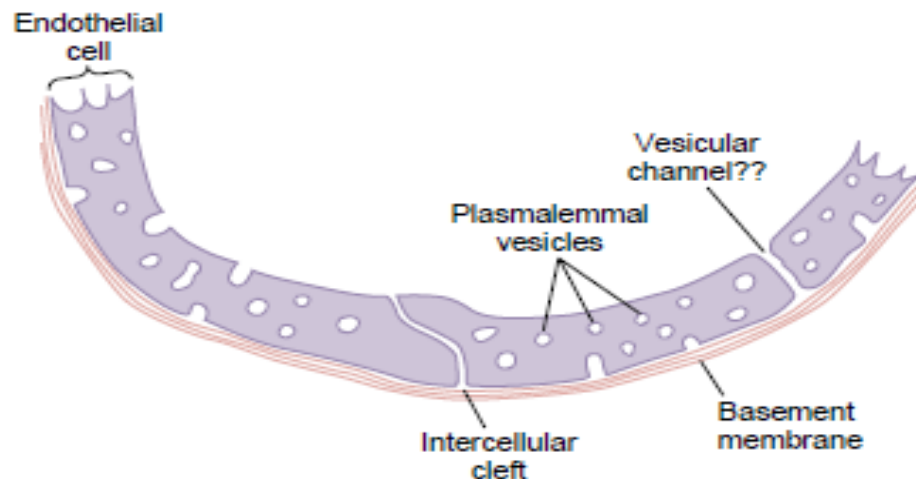
## ❖ Structure of the microcirculation and capillary system:

- Each nutrient artery entering an organ branches 6-8 times before the arteries become small enough to be called *arterioles*, which have internal diameters of only 10 - 15  $\mu\text{m}$ .
- Then the arterioles branched 2-5 times (metaarterioles), reaching diameters of 5 - 9  $\mu\text{m}$  at their ends where they supply blood to the capillaries.

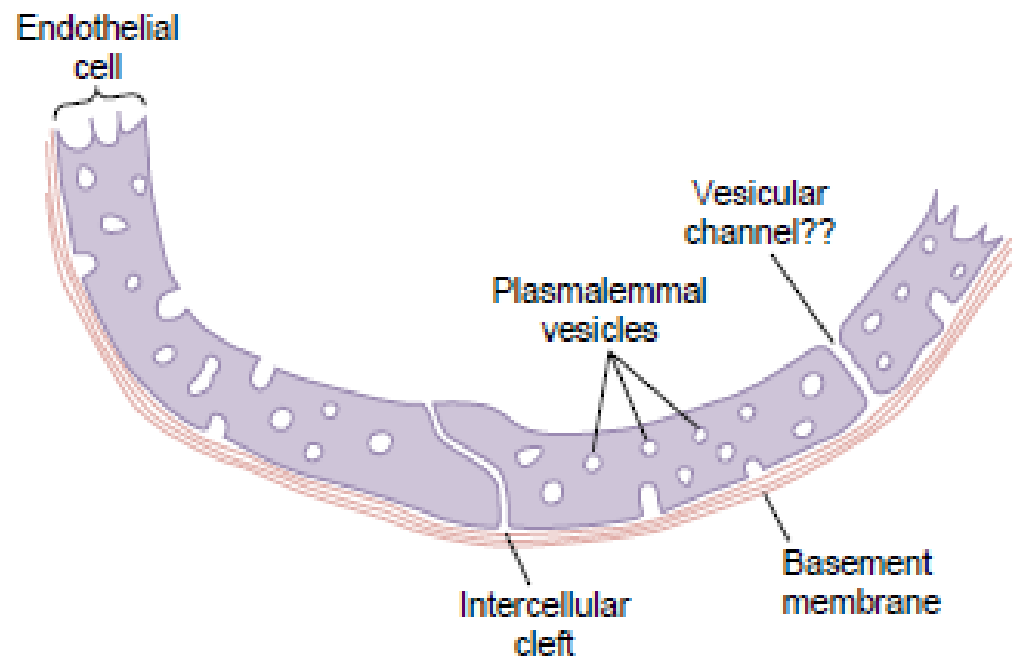


## ❖ The Microcirculation :

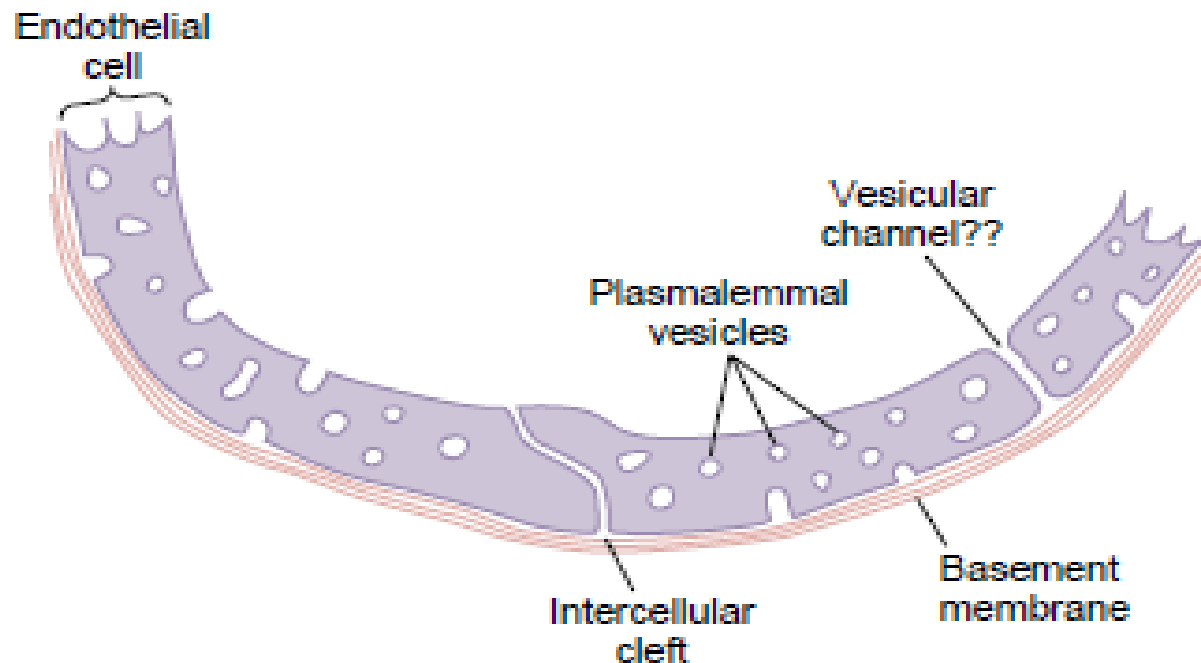
- The walls of the capillaries are extremely thin, constructed of single-layer, surrounded by a very thin basement membrane on the outside of the capillary; highly permeable endothelial cells.
- Therefore, water, nutrients, and waste product can all interchange quickly and easily between the tissues and the circulating blood.



- The peripheral circulation of the whole body has about **10 billion** capillaries with a total surface area estimated to be **500 to 700 m<sup>2</sup>** (about one eighth the surface area of a football field).
- It is rare that any single functional **cell** of the body is more than **20 to 30 μm** away from a **capillary**.

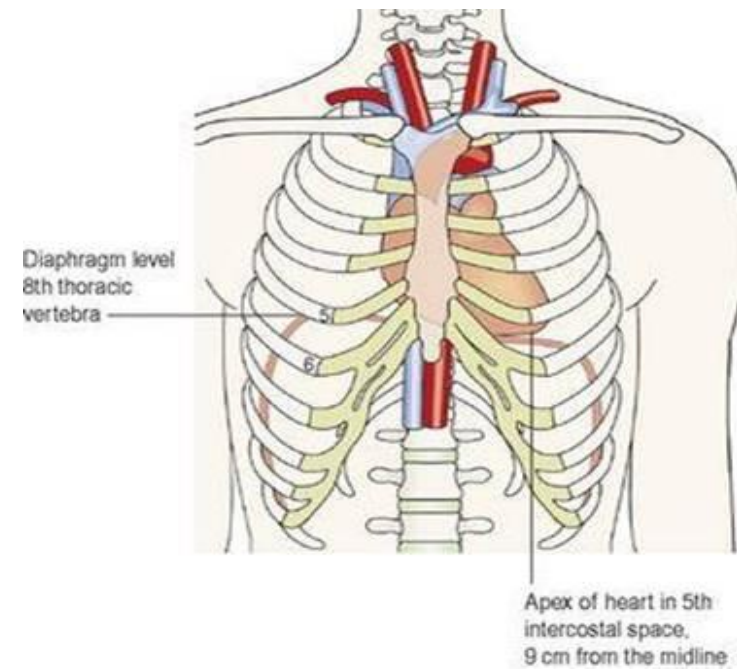
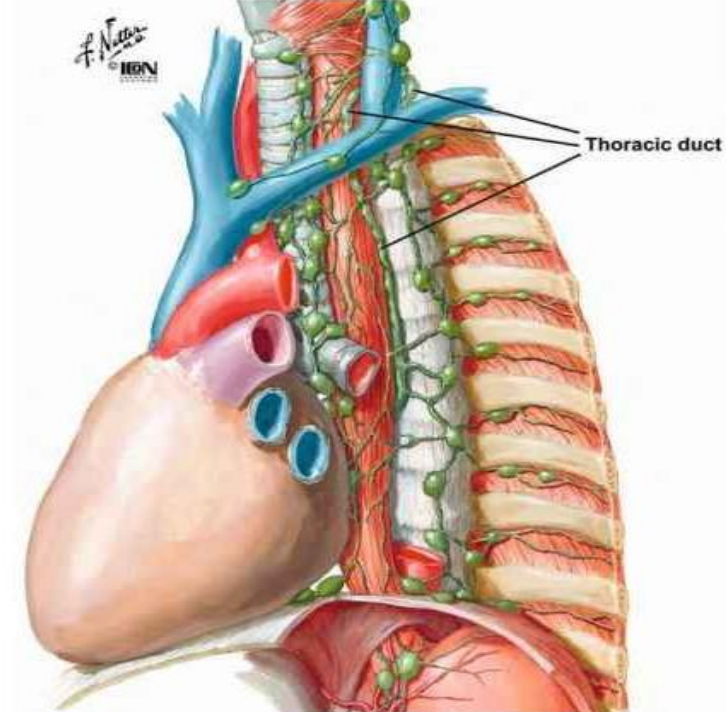


- The total thickness of the capillary wall is only about **0.5  $\mu\text{m}$** .
- The internal diameter of the capillary is **4 - 9  $\mu\text{m}$** , barely large enough for red blood cells and other blood cells to squeeze through.
- Huge number of “Pores” in the capillary membrane.



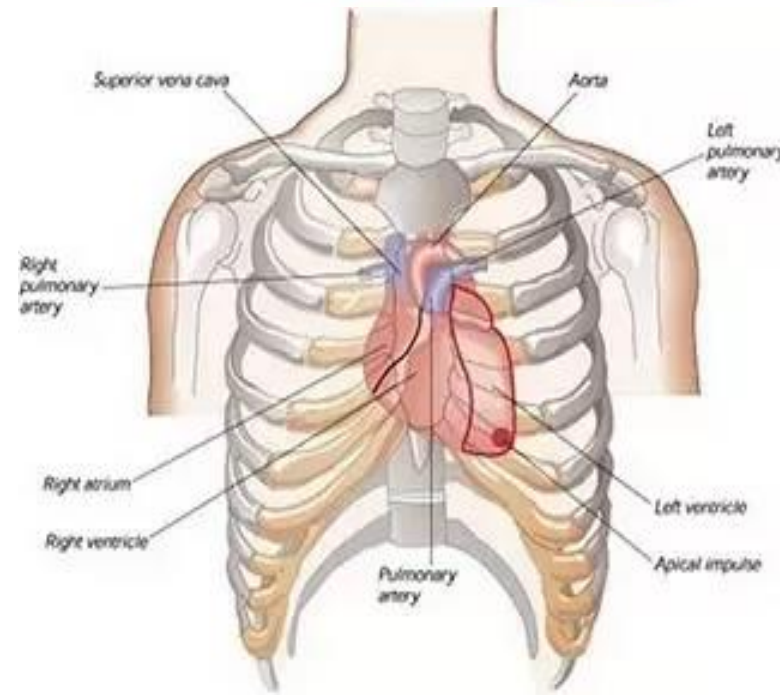
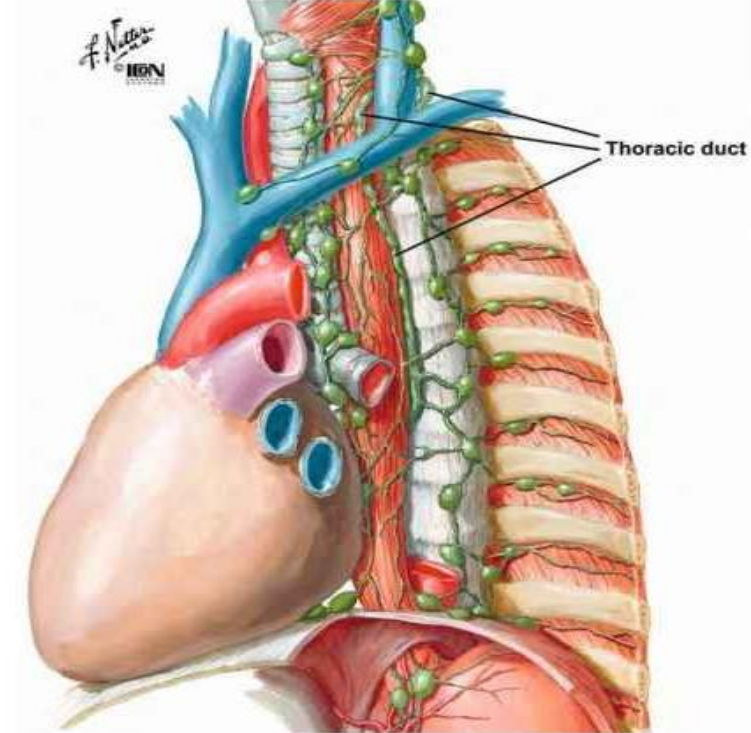
# THE HEART

- The heart is a muscular organ which pumps blood through the blood vessels of the circulatory system.
- The heart is located between the lungs, in the middle compartment of the chest (in the middle mediastinum) at the level of thoracic vertebrae T5-T8.
- The back surface of the heart lies near the vertebral column, and the front surface sits behind the sternum and rib cartilages.

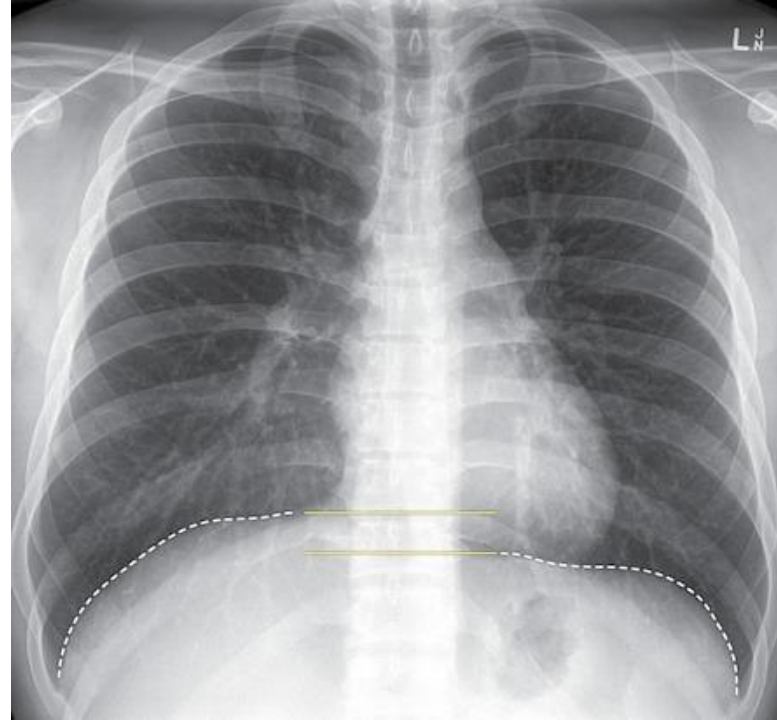




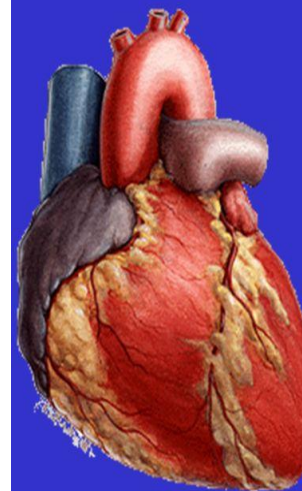
- The upper part of the heart is the attachment point for several large blood vessels (the venae cavae, aorta and pulmonary trunk).
- The upper part of the heart is located at the level of the third costal cartilage.
- The lower tip of the heart, the apex, lies to the left of the sternum (8 to 9 cm from the midsternal line) between the junction of the fourth and fifth ribs near their articulation with the costal cartilages.



- The largest part of the heart is usually slightly offset to the left side of the chest and is felt to be on the left because the left heart is stronger and larger, since it pumps to all body parts.
- Because the heart is between the lungs, the left lung is smaller than the right lung and has a cardiac notch in its border to accommodate the heart.
- The heart is cone-shaped, with its base positioned upwards and tapering down to the apex.



## THE HEART



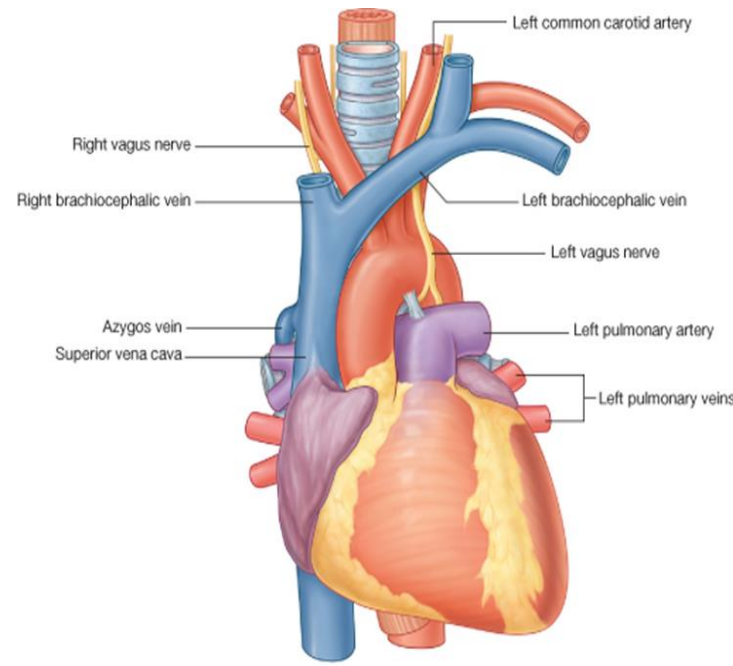
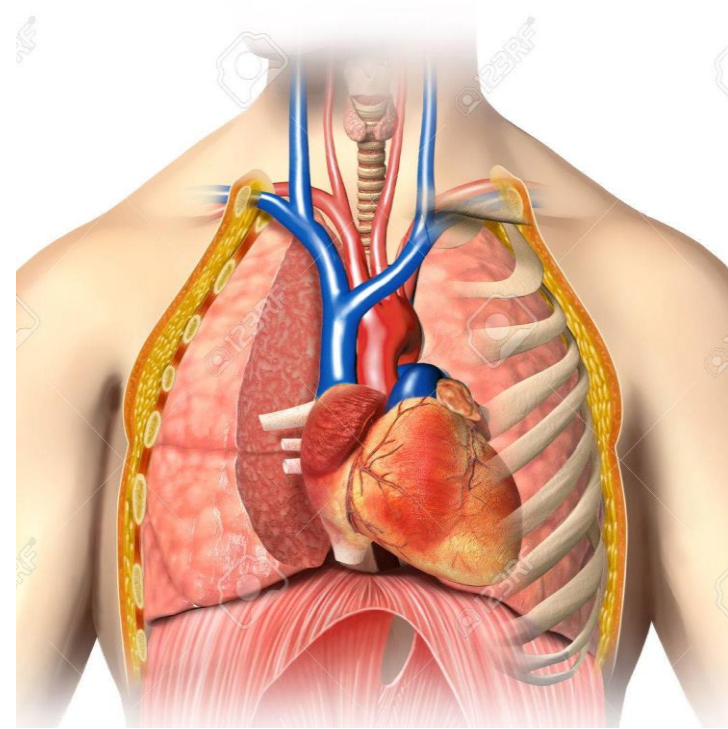
The heart is a cone shaped muscular organ

It is normally placed on the left side of the chest and is of the size of a closed fist

The heart has 4 cavities

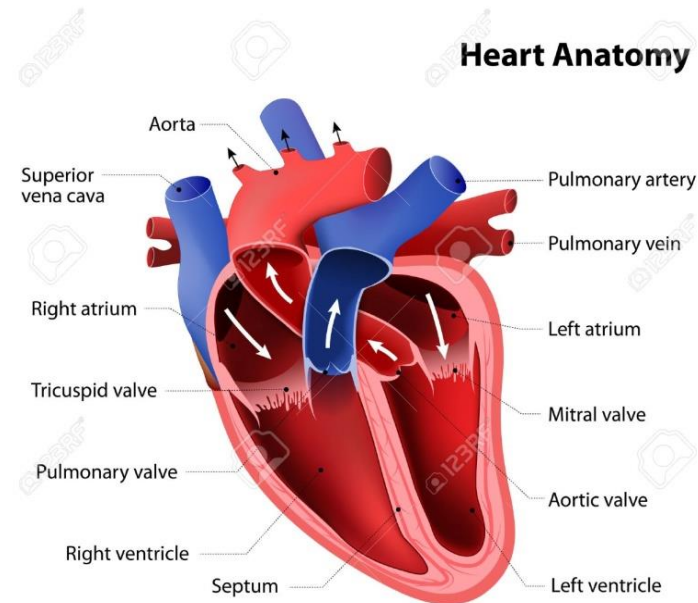
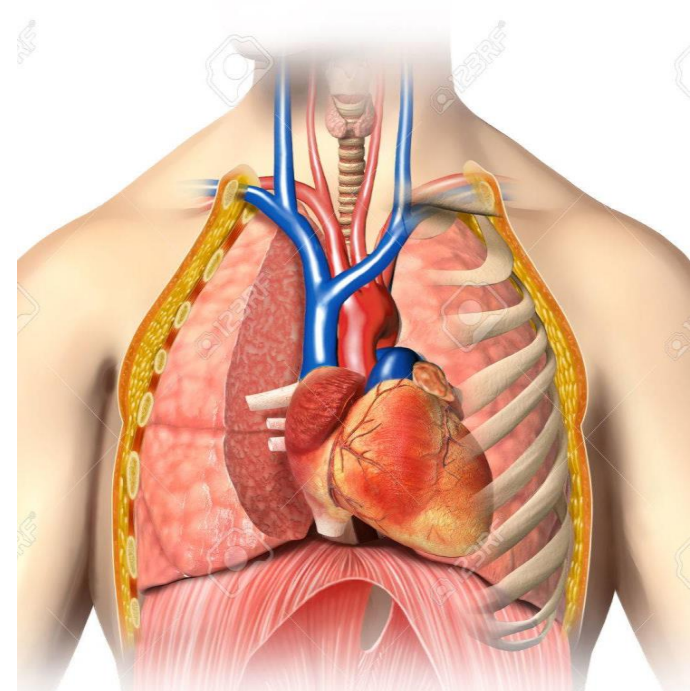
- 2 atria
- 2 ventricles

- An adult heart has a mass of **250–350 grams**.
- The heart is often described as the size of a fist: **12 cm** in length, **8 cm** wide, and **6 cm** in thickness.
- Well-trained athletes can have much larger hearts due to the effects of exercise on the heart muscle, similar to the response of skeletal muscle.

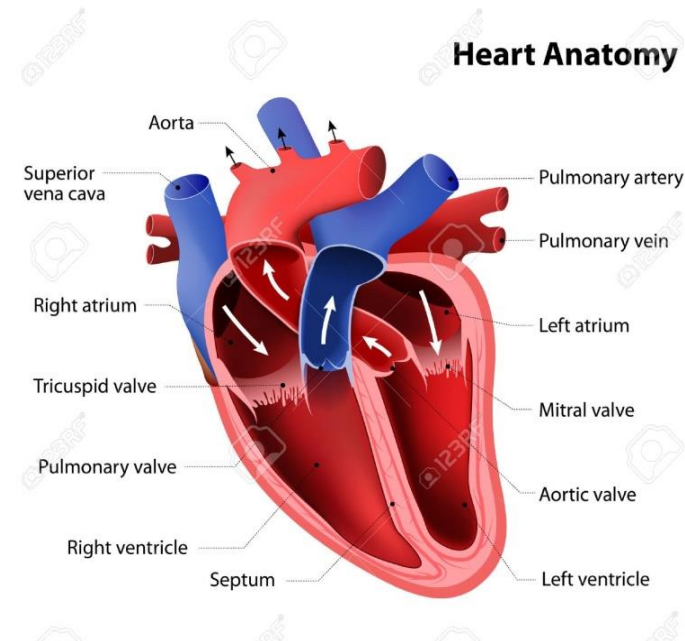
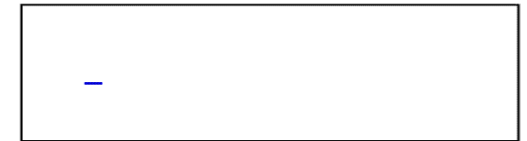
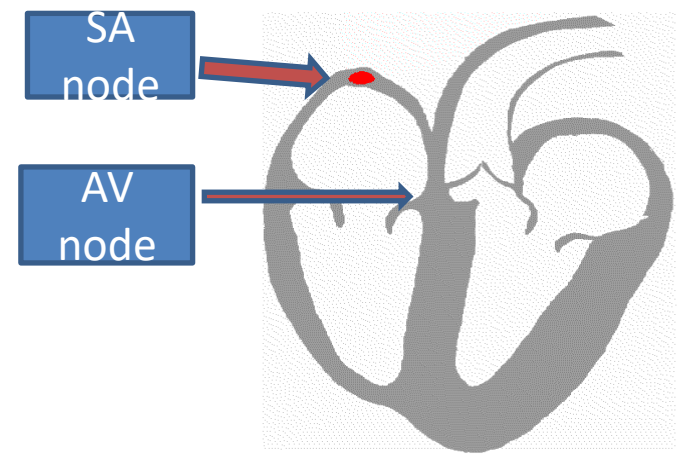




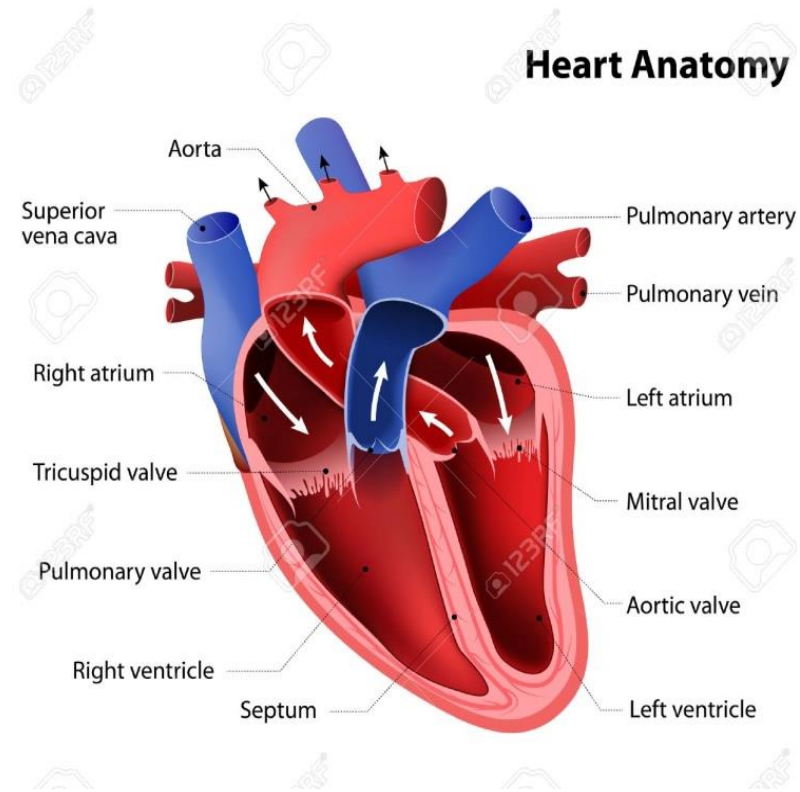
- In a healthy heart blood flows one way through the heart due to heart valves, which prevent backflow.
- The heart is enclosed in a protective sac, the pericardium, which also contains a small amount of fluid.
- The wall of the heart is made up of three layers: epicardium, myocardium, and endocardium.



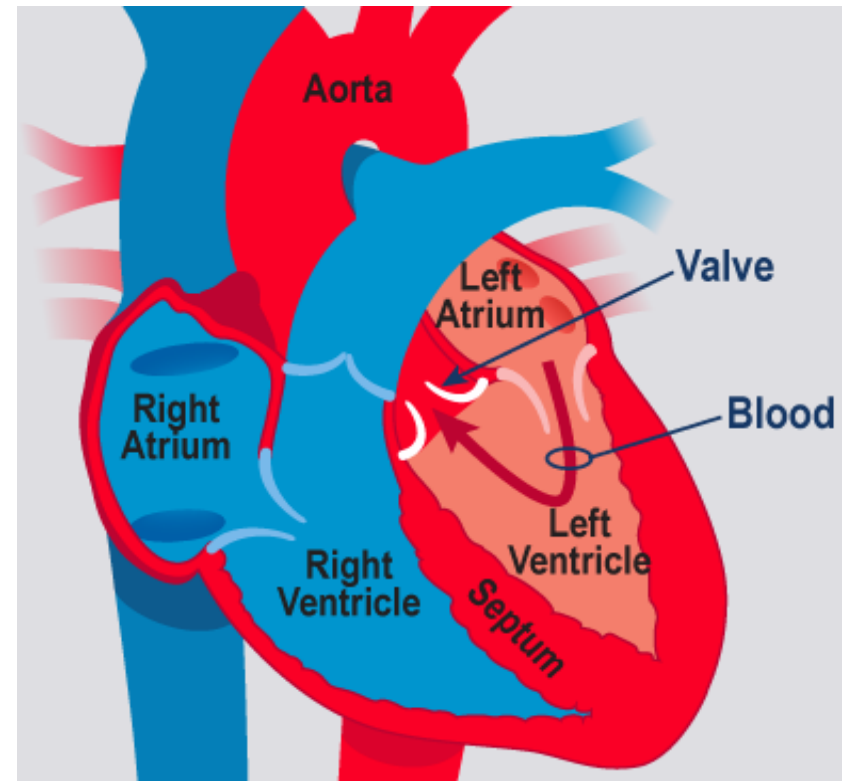
- The heart pumps blood with a rhythm determined by a group of pacemaking cells in the **sinoatrial node (SA node)**.
- These generate a current that causes contraction of the heart, traveling through the **atrioventricular node** and along the **conduction system** of the heart.



- The heart receives blood low in oxygen from the systemic circulation, which enters the right atrium from the superior and inferior venae cavae and passes to the right ventricle.
- From here it is pumped into the pulmonary circulation, through the lungs where it receives oxygen and gives off carbon dioxide.



- Oxygenated blood then returns to the left atrium, passes through the left ventricle and is pumped out through the aorta to the systemic circulation.
- The heart beats at a resting rate close to **72 beats per minute**.
- During exercise the rate can be **150 bpm** with maximum rates reaching from **200 to 220 bpm**.
- Exercise temporarily increases the rate, but lowers resting heart rate in the long term, and is good for heart health.



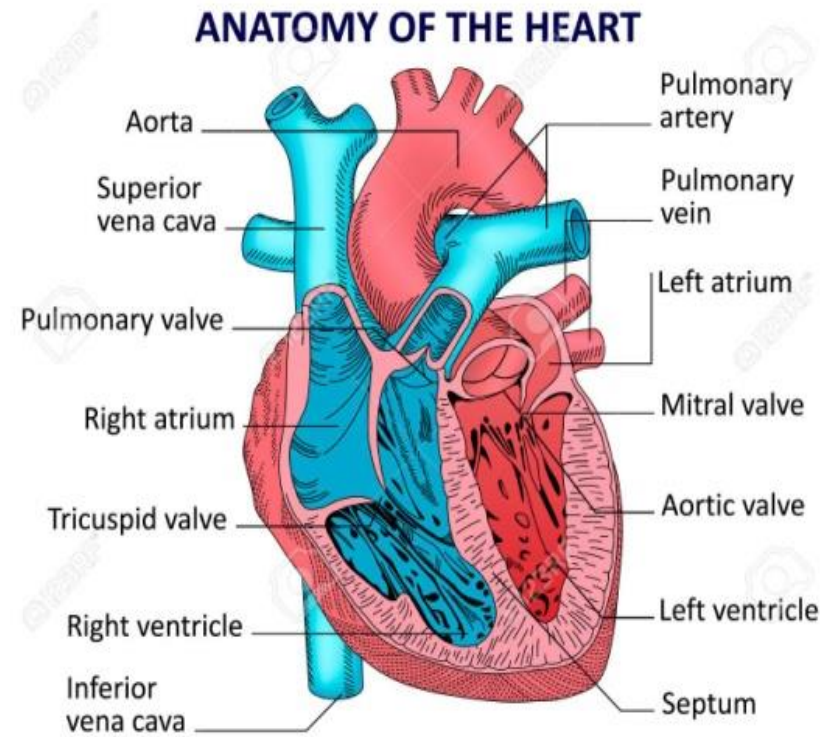


# ❖ Physiology of Cardiac Muscle

- The heart is composed of three major types of cardiac muscle:
  - *Atrial muscle.*
  - *Ventricular muscle.*
  - *Specialized excitatory and conductive muscle fibers.*
- The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer.

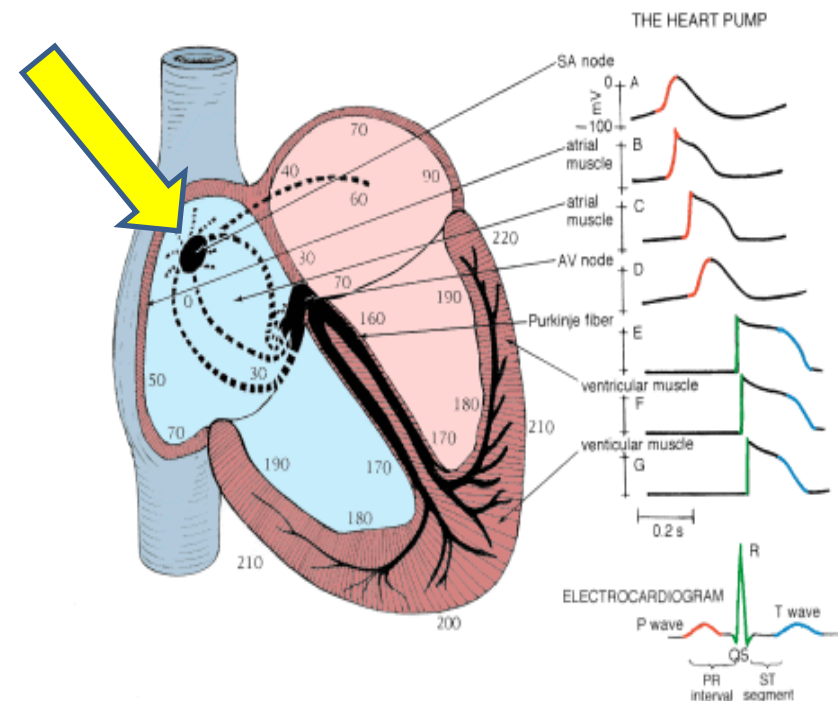
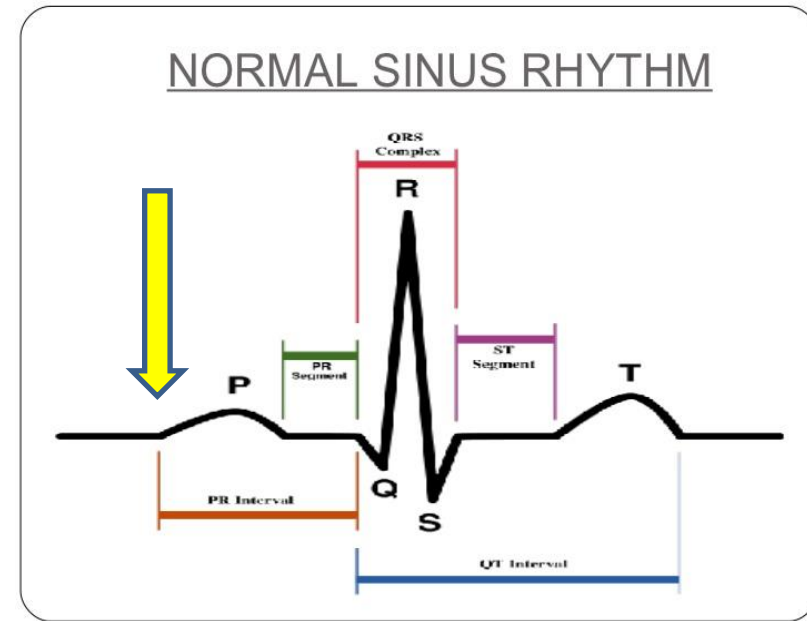


- Conversely, the specialized excitatory and conductive fibers contract only feebly because they contain few contractile fibrils.
- Instead, they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart.

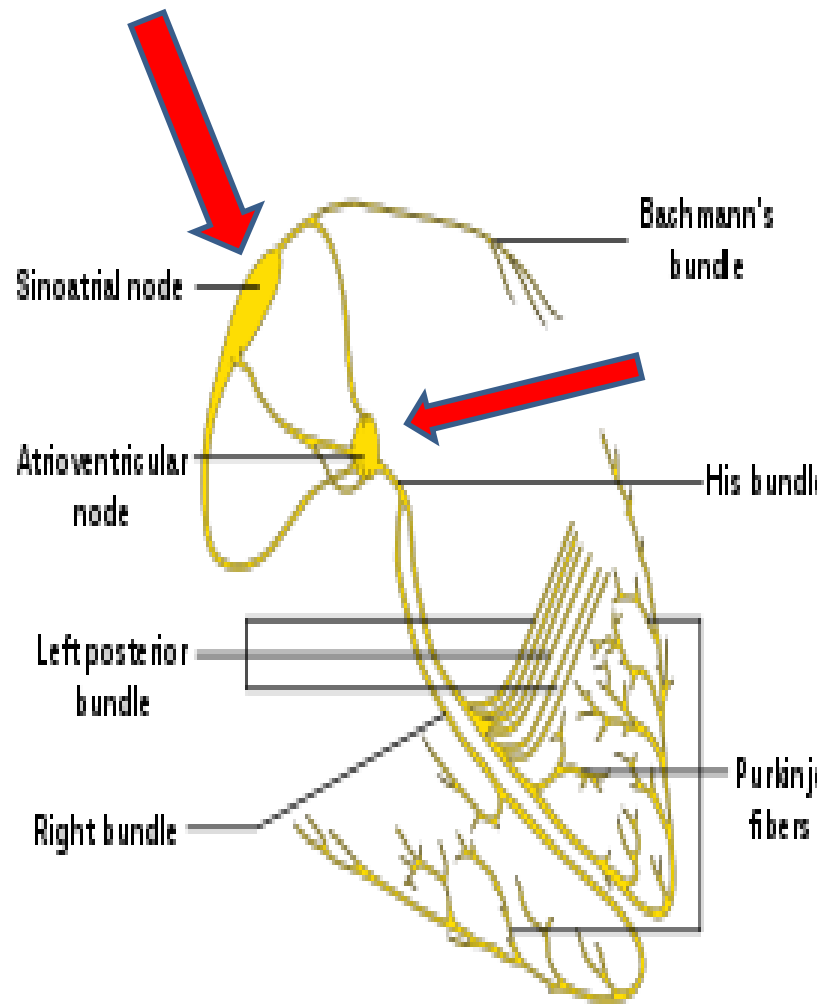


# ❖ The Cardiac Cycle

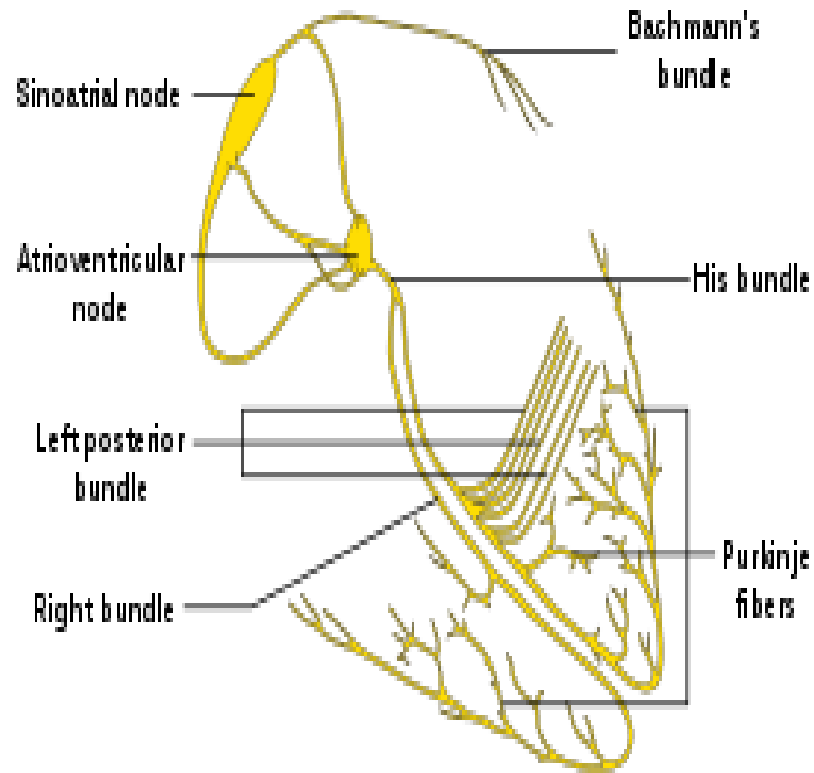
- The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the *cardiac cycle*.
- Each cycle is initiated by spontaneous generation of an action potential in the *sinoatrial node (SA node)*.
- This node is located in the superior lateral wall of the right atrium near the opening of the *superior vena cava*.



- The signal then travels to the atrioventricular node.
- This is found at the bottom of the right atrium in the atrioventricular septum.
- The septum is part of the cardiac skeleton tissue within the heart that the electrical signal cannot pass through, which forces the signal to pass through the atrioventricular node only.



- The signal then travels along the bundle of His to left and right bundle branches through to the ventricles of the heart.
- In the ventricles the signal is carried by specialized tissue called the Purkinje fibers which then transmit the electric charge to the heart muscle.



- Because of this special arrangement of the conducting system from the atria into the ventricles.
- There is a delay of more than 0.1 second during passage of the cardiac impulse from the atria into the ventricles.
- This allows the atria to contract ahead of ventricular contraction.



- Thereby pumping blood into the ventricles before the strong ventricular contraction begins.
- Thus, the atria act as *primer pumps* for the ventricles.
- The ventricles in turn provide the major source of power for moving blood through the body's vascular system.





# ❖ Diastole and Systole

- The cardiac cycle consists of a period of relaxation called *diastole*, during which the heart fills with blood, followed by a period of contraction called *systole*.
- During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves.



- Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values.
- The moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles.



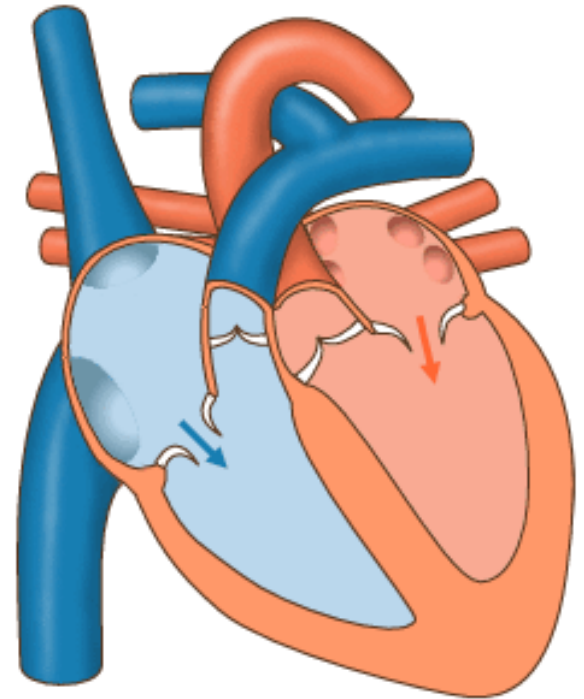
## ❖ Emptying of the ventricles during systole.

- Immediately after ventricular contraction begins, the ventricular pressure rises abruptly, causing the A-V valves to close.
- Then an additional **0.02 to 0.03 second** is required for the ventricle to build up sufficient pressure to push the semilunar (aortic and pulmonary) valves open.
- Therefore during this period, contraction is occurring in the ventricles.

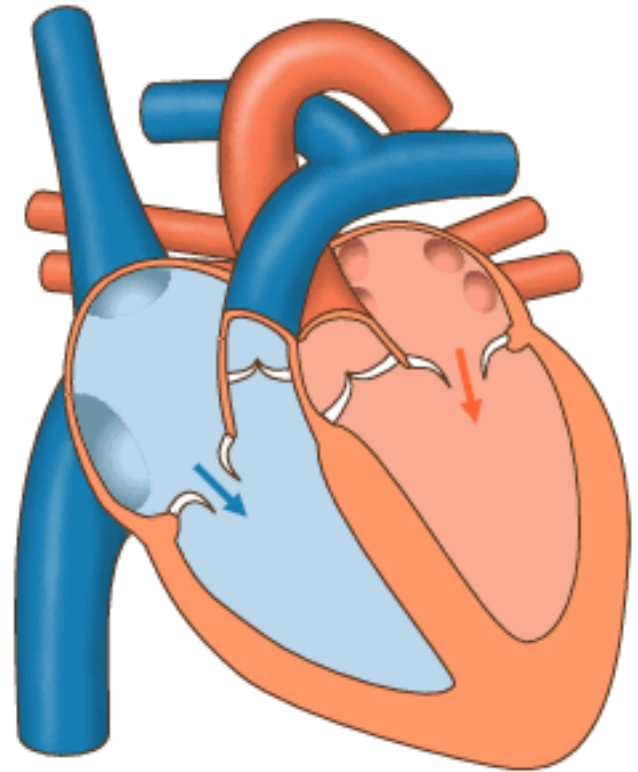


## ❖ Cardiac output (CO):

- Is a measurement of the amount of blood pumped by each ventricle (stroke volume) in one minute.
- This is calculated by multiplying the stroke volume (SV) by the beats per minute of the heart rate (HR).
- So that:  $CO = SV \times HR$ .



- The average cardiac output, using an average stroke volume of about **70mL**, is **5.25 L/min** (with a normal range of **4.0–8.0 L/min.**).
- The stroke volume is normally measured using an echocardiogram and can be influenced by the:
  - size of the heart.
  - physical condition.
  - mental condition of the individual.
  - Sex.
  - Contractility.
  - Duration of contraction.
  - preload and afterload.

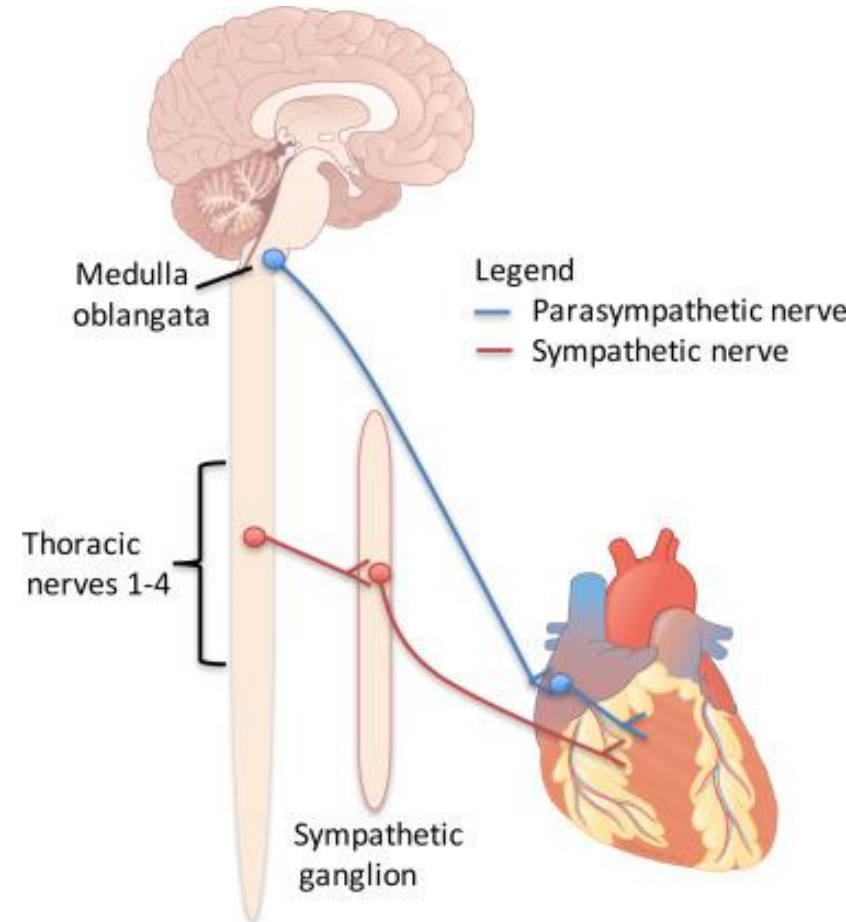


## ❖ The heart rate is affected by the following factors:

- Exercise.
- Age.
- body temperature.
- basal metabolic rate.
- Emotional state.
- High levels of the hormones epinephrine, norepinephrine, and thyroid hormones can increase the heart rate.
- low blood oxygen.
- low blood pressure.
- Dehydration may increase it.

# ❖ Regulation of Heart Pumping:

- When a person is at rest, the heart pumps only **4 to 6** liters of blood each minute.
- During severe exercise, the heart may be required to pump **four to seven times** this amount.

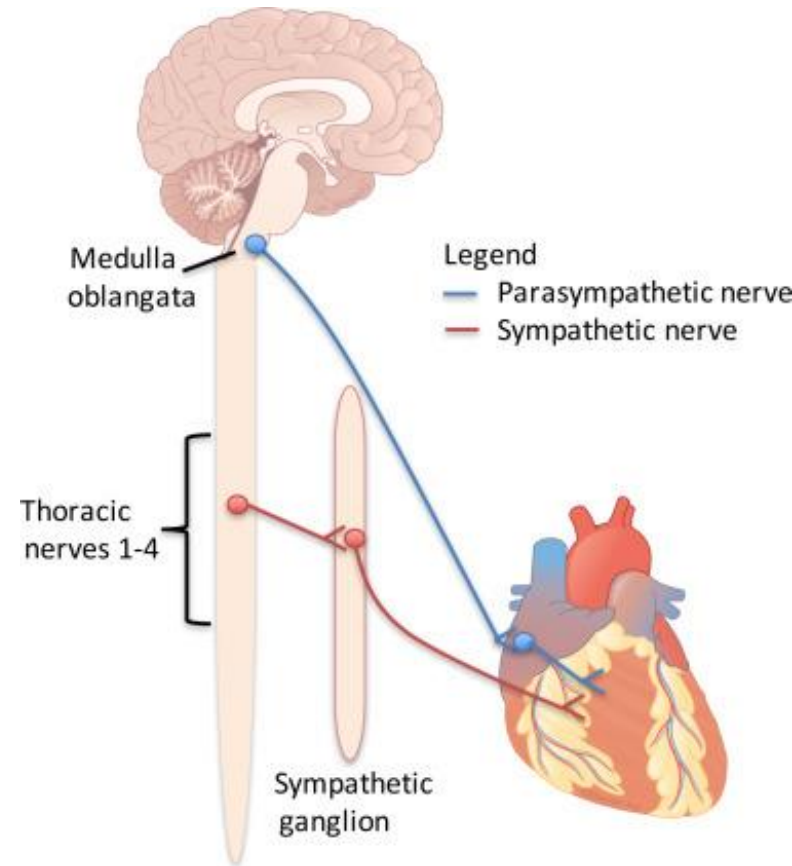




❑ The basic means by which the volume pumped by the heart is regulated are:

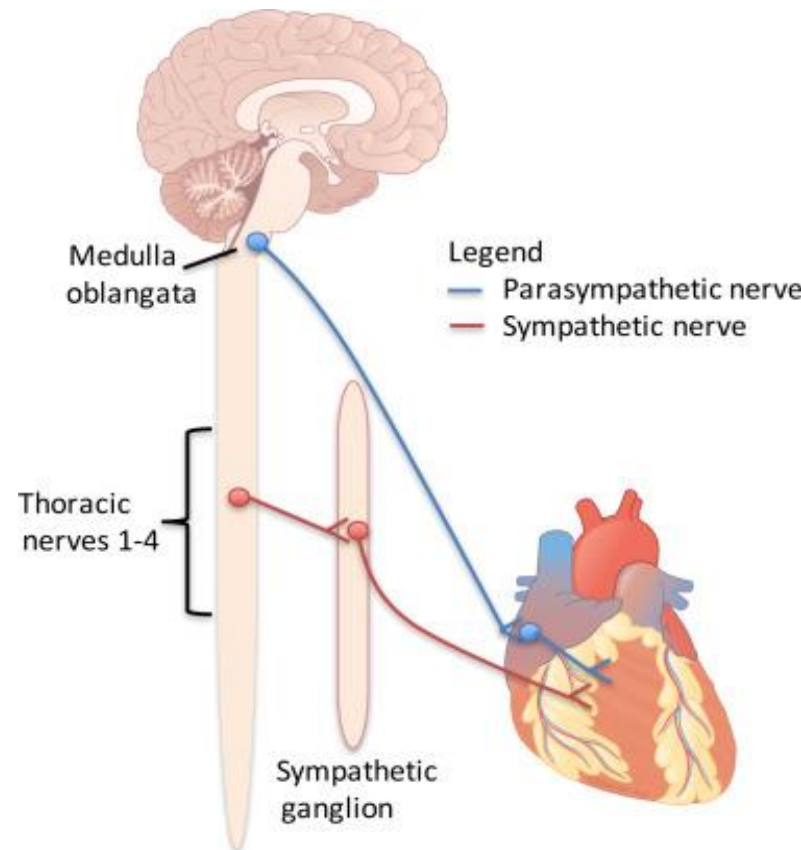
(1) Intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart.

(2) Control of heart rate and strength of heart pumping by the autonomic nervous system.



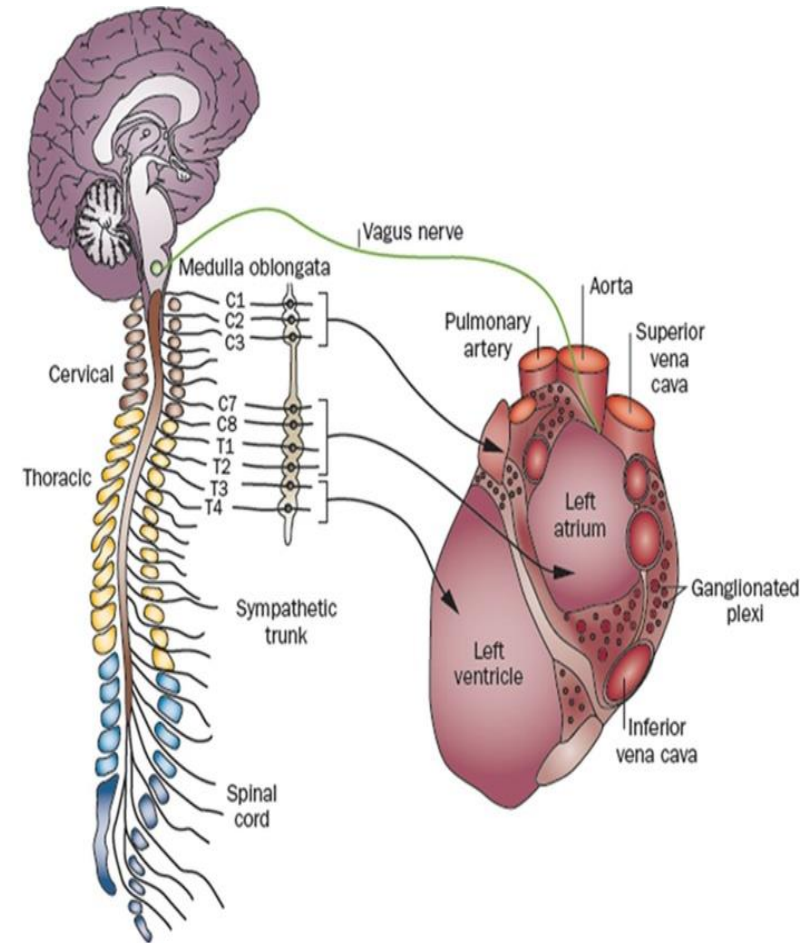
# ❖ Control of the Heart by the Sympathetic and Parasympathetic Nerves

- The pumping effectiveness of the heart also is controlled by the *sympathetic* and *parasympathetic* (*vagus*) nerves, which abundantly supply the heart.
- The amount of blood pumped each minute (*cardiac output*) often can be increased more than 100 per cent by sympathetic stimulation.
- By contrast, the output can be decreased to as low as zero (or almost zero) by vagal (parasympathetic) stimulation.



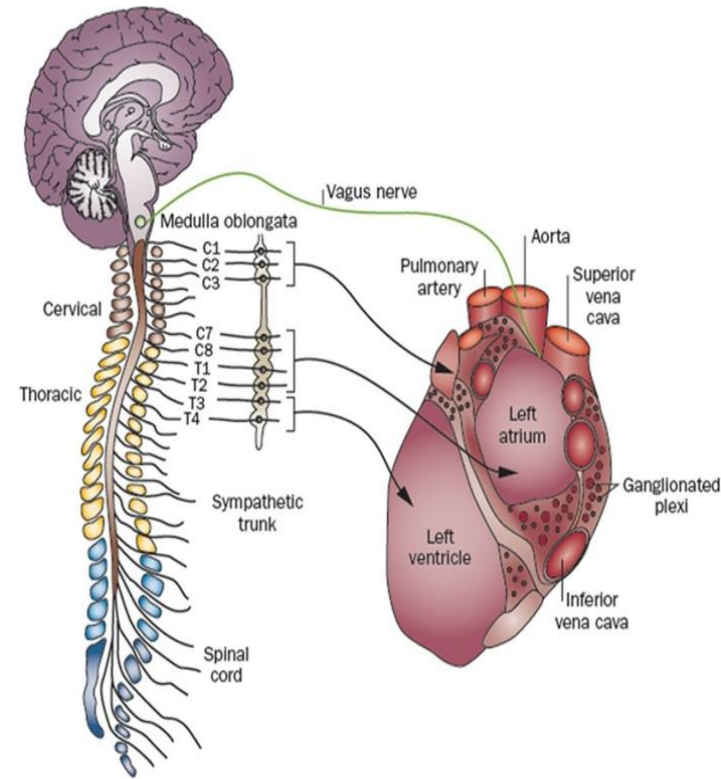
## ❖ Mechanisms of Excitation of the Heart by the Sympathetic Nerves.

- Strong sympathetic stimulation can increase the heart rate in young adult humans from the normal rate of **70 beats per minute** up to **180 to 200** and, rarely, even **250 beats per minute**.
- Also, sympathetic stimulation increases the force of heart contraction to as much as **double normal**.
- Thereby increasing the volume of blood pumped and increasing the ejection pressure.
- Thus, sympathetic stimulation can increase cardiac output as much as **twofold to threefold**.

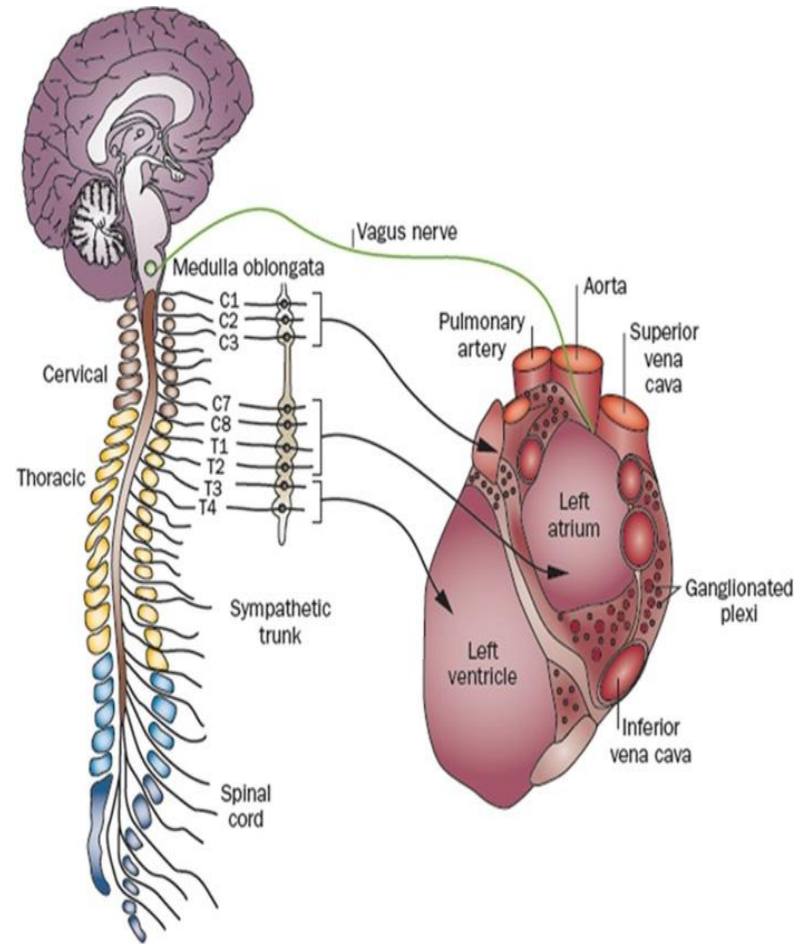


## ❖ Parasympathetic (Vagal) Stimulation of the Heart:

- Strong stimulation of the parasympathetic nerve fibers in the vagus nerves to the heart can **stop the heartbeat for a few seconds**.
- But then the heart usually **“escapes”** and beats at a rate of **20 to 40 beats per minute** as long as the parasympathetic stimulation continues.
- In addition, strong vagal stimulation can decrease the strength of heart muscle contraction by **20 to 30 %**
- The vagal fibers are distributed mainly to the atria and not much to the ventricles, where the power contraction of the heart occurs.



- This explains the effect of vagal stimulation mainly to decrease heart rate rather than to decrease greatly the strength of heart contraction.
- Nevertheless, the great decrease in heart rate combined with a slight decrease in heart contraction strength can decrease ventricular pumping 50 % or more.

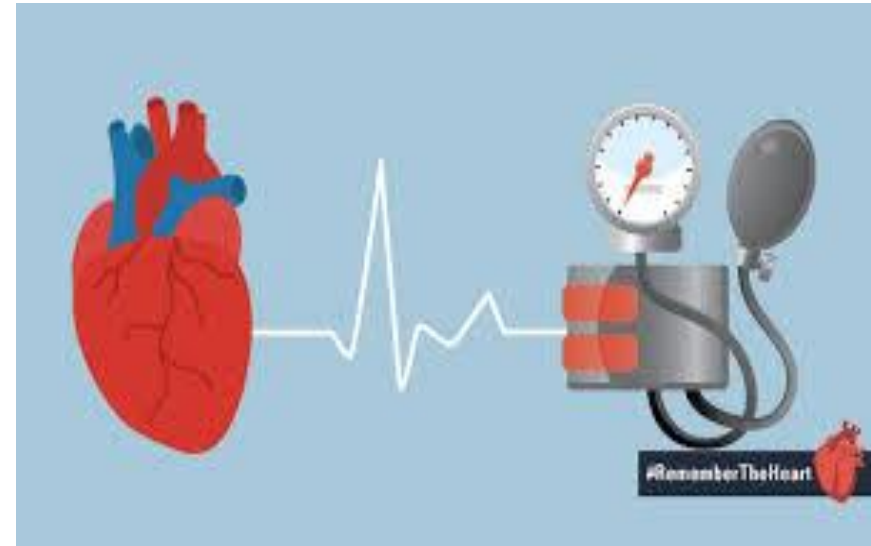


**BLOOD PRESSURE**

**PHYSIOLOGY**

## ❖ **Blood pressure (BP):**

- Is the pressure of circulating blood against the walls of blood vessels.
- Most of this pressure results from the heart pumping blood through the circulatory system.
- Blood pressure is usually expressed in terms of the **systolic pressure** (maximum pressure during one heartbeat) over **diastolic pressure** (minimum pressure between two heartbeats) in the cardiac cycle.
- It is measured in millimeters of mercury (mmHg) above the surrounding atmospheric pressure.





❑ **Blood pressure is one of the vital signs —together with:**

- **Respiratory rate.**
- **Heart rate.**
- **Oxygen saturation.**
- **body temperature.**
- **that healthcare professionals use in evaluating a patient's health.**
- **Normal resting blood pressure, in an adult is approximately 120 millimetres of mercury systolic over 80 millimetres of mercury diastolic, denoted as "120/80 mmHg".**



➤ **Blood pressure is influenced by:**

- **Cardiac output.**
- **Systemic vascular resistance.**
- **Arterial stiffness.**

➤ **Blood pressure varies depending on:**

- **Physical activity.**
- **Relative health.**
- **Temperature.**
- **Noise.**
- **Emotional stress.**

- **Consumption of food or liquid.**
- **Dietary factors.**
- **Changes in posture (such as standing-up).**
- **Drugs.**
- **Disease.**

- **Blood pressure that is too low is called hypotension, pressure that is consistently too high is called hypertension, and normal pressure is called normotension.**
- **Both hypertension and hypotension have many causes and may be of sudden onset or of long duration.**
- **Long-term hypertension is a risk factor for many diseases, including heart disease, stroke and kidney failure.**
- **Long-term hypertension is more common than long - term hypotension.**



Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Pre hypertension	120 – 139	or	80 – 89
High Blood Pressure (Hypertension) Stage 1	140 – 159	or	90 – 99
High Blood Pressure (Hypertension) Stage 2	160 or higher	or	100 or higher
<u>Hypertensive Crisis</u> (Emergency care needed)	Higher than 180	or	Higher than 110

- The people who maintain arterial pressures at the low end of these pressure ranges have much better long - term cardiovascular health.
- Blood pressure fluctuates from minute to minute and normally shows a circadian rhythm over a 24-hour period, with highest readings in the early morning and evenings and lowest readings at night.
- Loss of the normal fall in blood pressure at night is associated with a greater future risk of cardiovascular disease.



- There is no accepted diagnostic standard for hypotension, although pressures less than 90/60 are commonly regarded as hypotensive.
- In practice blood pressure is considered too **low** only if **symptoms** are present.
- In the past, most attention was paid to diastolic pressure; but nowadays it is recognized that both **high systolic pressure** and **high pulse pressure** (the numerical difference between systolic and diastolic pressures) are also **risk factors**.





- In some cases, it appears that is; excessive decrease in diastolic pressure can actually increase risk, due probably to the increased difference between systolic and diastolic pressures.
- If systolic blood pressure is elevated ( $>140$  mmHg) with a normal diastolic blood pressure ( $<90$  mmHg), it is called "isolated systolic hypertension" and may present a health concern.





- A large fall in blood pressure upon standing (persistent systolic/diastolic blood pressure decrease of  $>20/10$  mm Hg) is termed **orthostatic hypotension** (postural hypotension) and represents a failure of the body to compensate for the effect of gravity on the circulation.
- Standing results in an increased hydrostatic pressure in the blood vessels of the lower limbs.

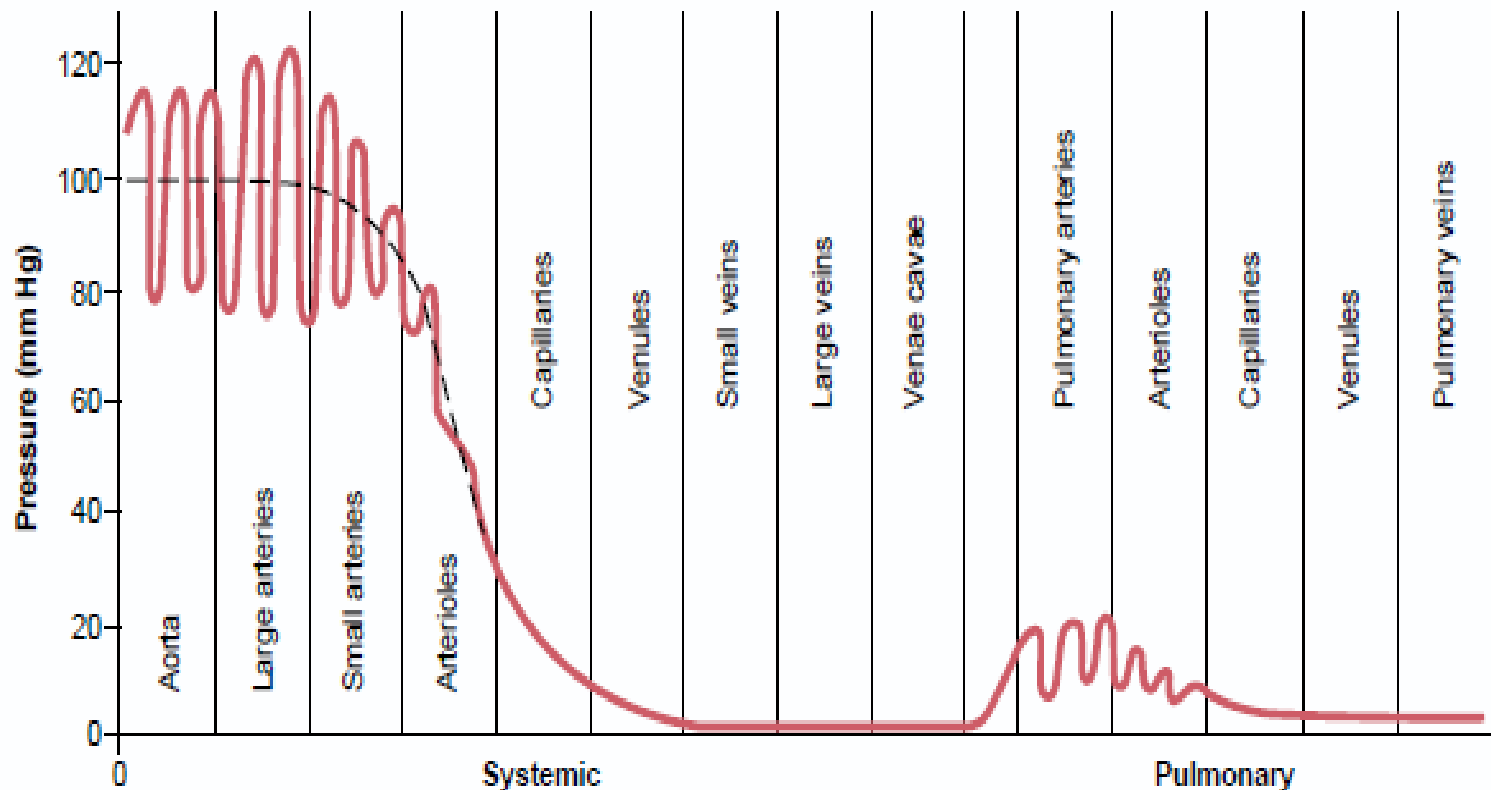


- The consequent distension of the veins below the diaphragm (venous pooling) causes ~500 ml of blood to be relocated from the chest and upper body.
- This results in a rapid decrease in central blood volume and a reduction of ventricular preload which in turn reduces stroke volume, and mean arterial pressure.

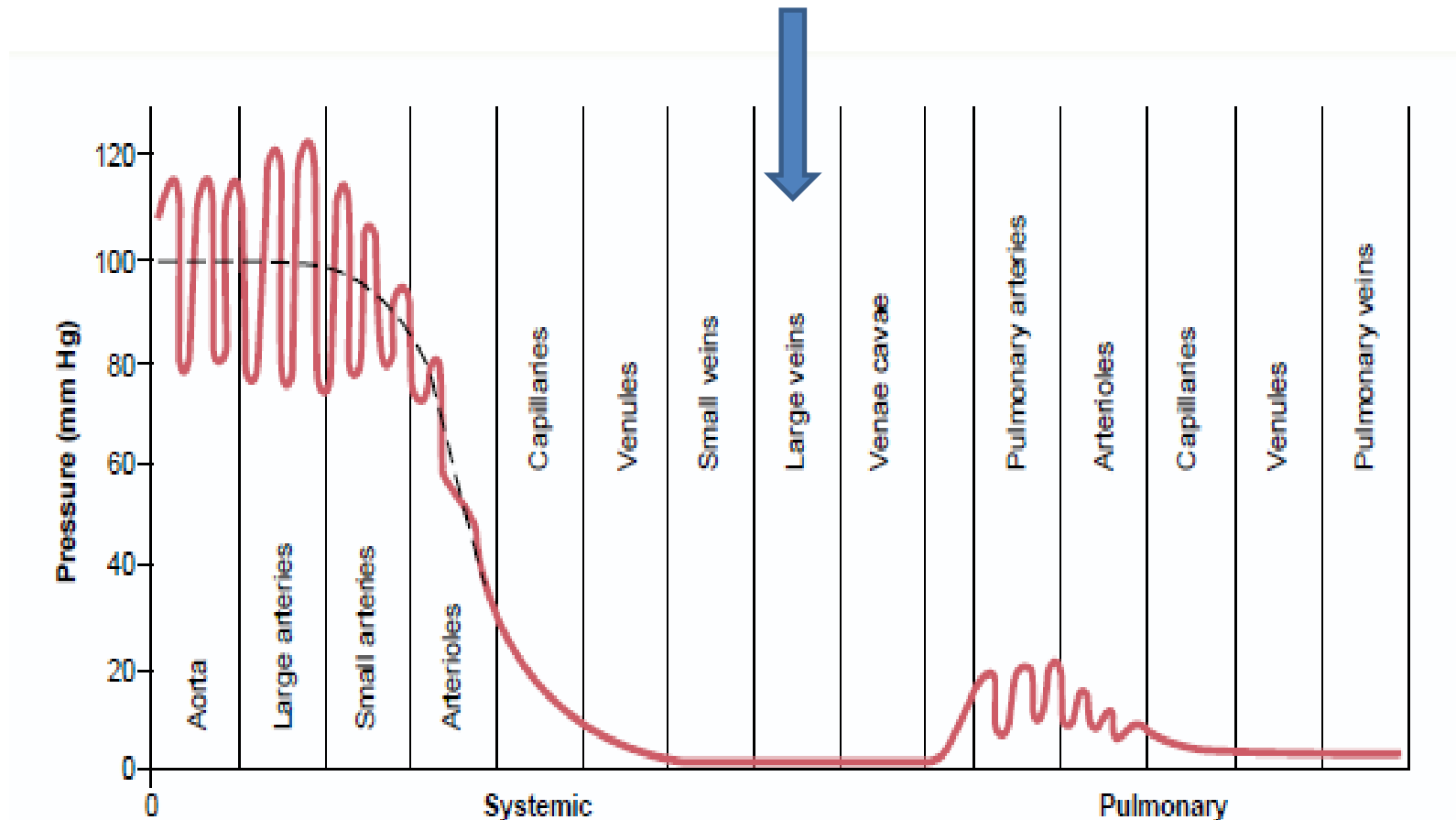


## ❖ Pressures in the various portions of the circulation:

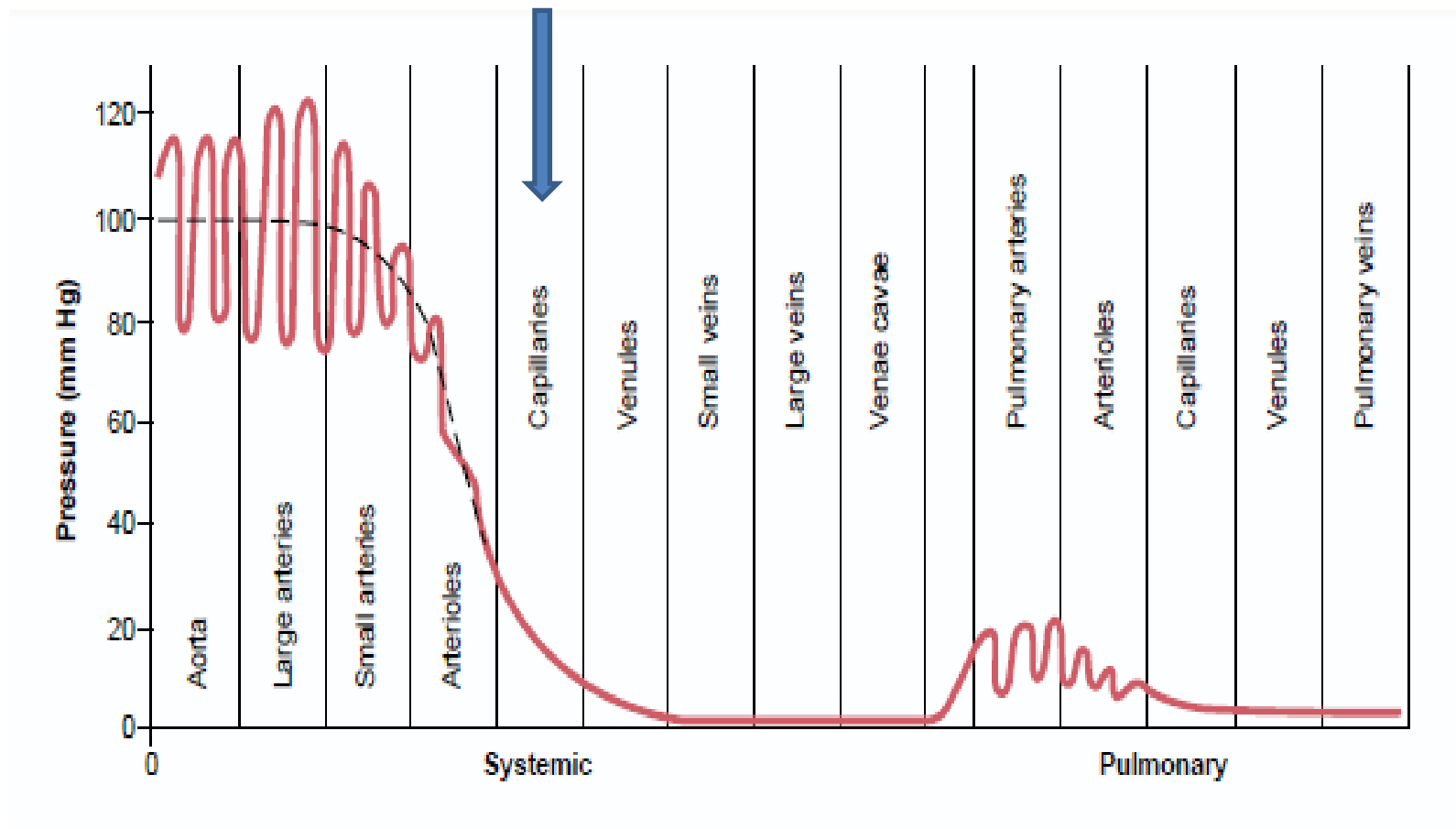
- The mean pressure in the aorta is high, averaging about **100 mm Hg**.
- Heart pumping is pulsatile, so the arterial pressure alternates between a *systolic pressure level of 120 mm Hg* and a *diastolic pressure level of 80 mm Hg*.



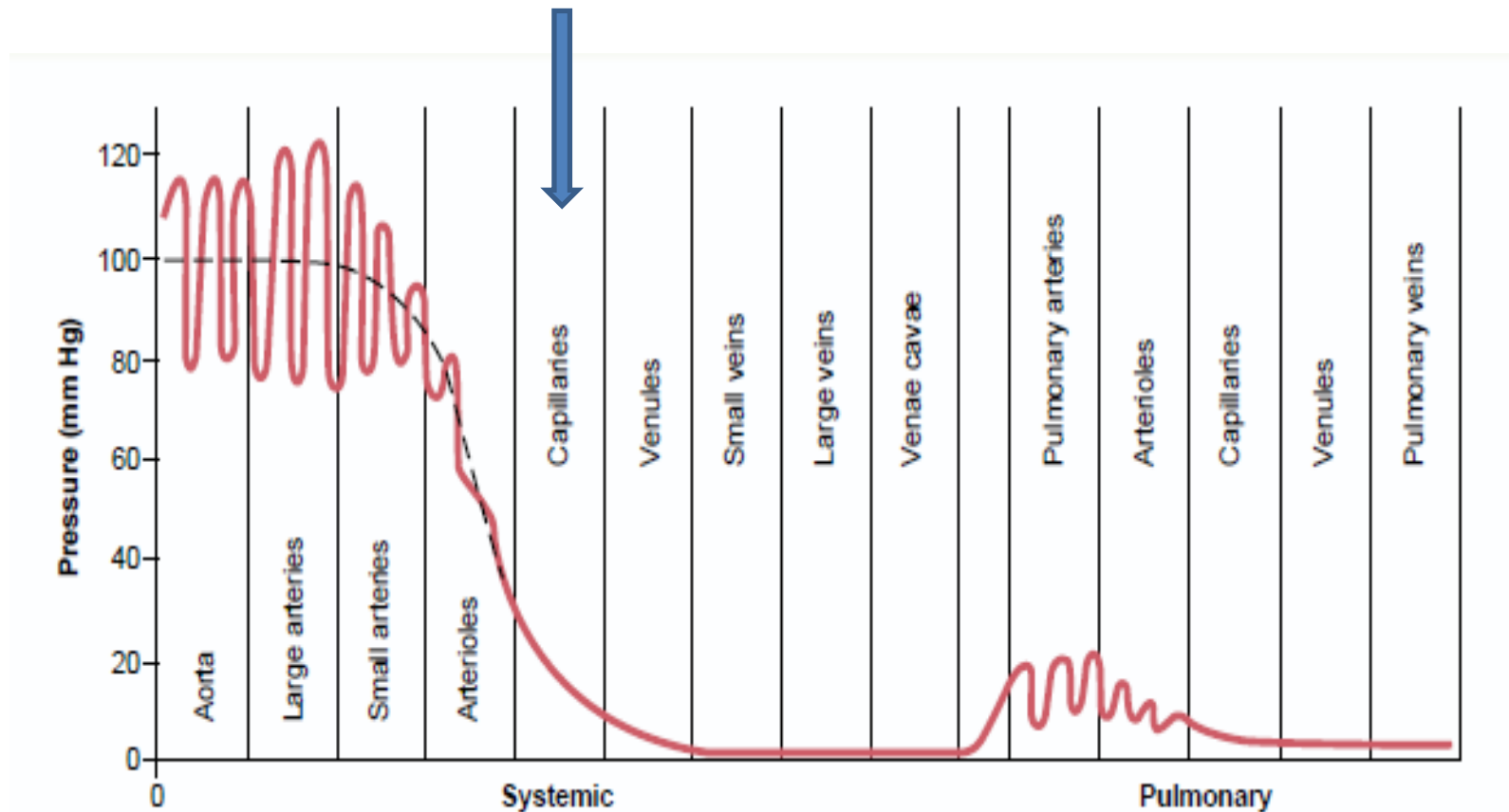
- As the blood flows through the *systemic circulation*, its mean pressure falls progressively to about **0 mm Hg** by the time it reaches the termination of the venae cavae where they empty into the right atrium of the heart.



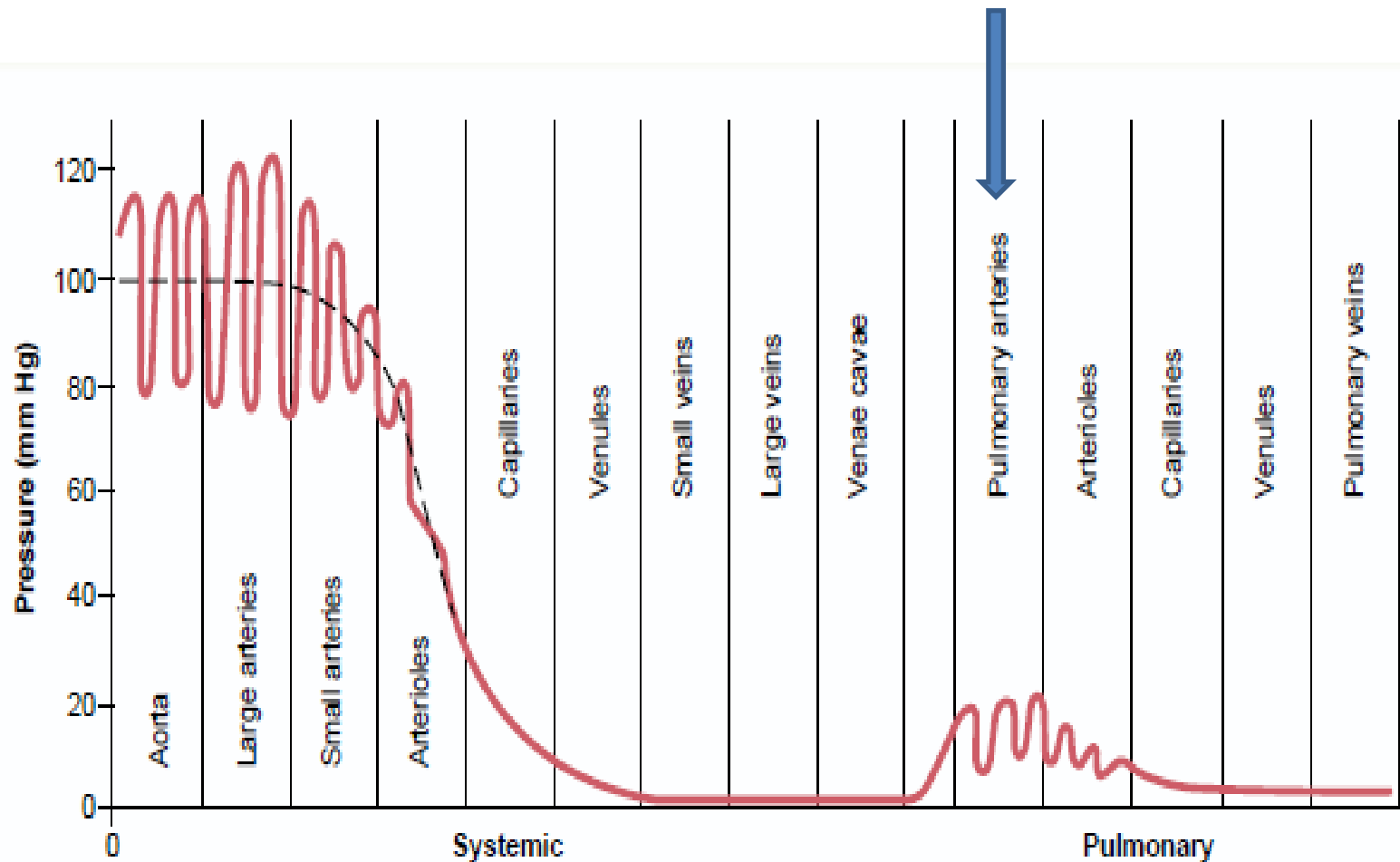
- The pressure in the systemic capillaries varies from as high as **35 mm Hg** near the arteriolar ends to as low as **10 mm Hg** near the venous ends.



- Their average “functional” pressure in most vascular beds is about **17 mm Hg**, a pressure low enough that little of the plasma leaks through the minute *pores* of the capillary walls, even though nutrients can *diffuse* easily through these same pores to the outlying tissue cells.

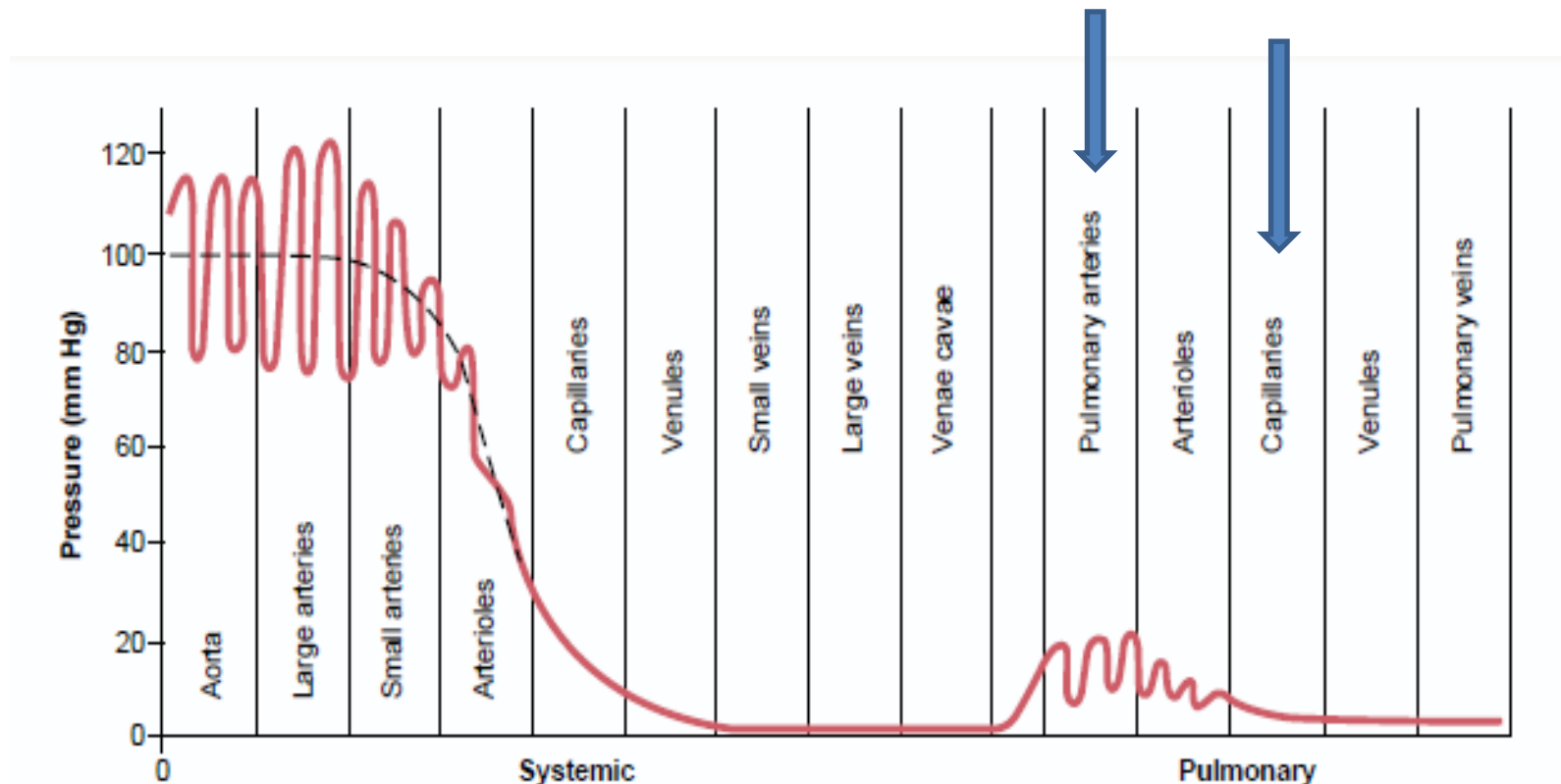


- The low pressures of the pulmonary system are in accord with the needs of the lungs, because all that is required is to expose the blood in the pulmonary capillaries to oxygen and other gases in the pulmonary alveoli.





- pulmonary artery systolic pressure about **25 mm Hg** and diastolic pressure **8 mm Hg**, (mean pulmonary arterial pressure of only **16 mm Hg**).
- The mean pulmonary capillary pressure averages only **7 mm Hg**. Yet the total blood flow through the lungs each minute is the same as through the systemic circulation.



# ❖ Regulation of blood pressure:

## 1) Baroreceptor reflex:

- In the high pressure receptor zones detect changes in arterial pressure.
- These baroreceptors send signals ultimately to the medulla of the brain stem.
- The medulla (by way of the autonomic nervous system) will adjust the mean arterial pressure by altering both the force and speed of the heart's contractions, as well as the systemic vascular resistance.
- The most important arterial baroreceptors are located in the left and right carotid sinuses and in the aortic arch.

**2) Renin–angiotensin system (RAS): This system is generally known for its long-term adjustment of arterial pressure.**

- This system allows the kidney to compensate for loss in blood volume or drops in arterial pressure by activating an endogenous vasoconstrictor known as **angiotensin II**.**

3) Aldosterone: This steroid hormone is released from the adrenal cortex in response to **angiotensin II** or high serum potassium levels.

- Aldosterone stimulates **sodium** retention and **potassium** excretion by the kidneys.
- Since sodium is the main ion that determines the amount of fluid in the blood vessels by osmosis, **aldosterone** will increase fluid retention, and indirectly, **arterial pressure**.

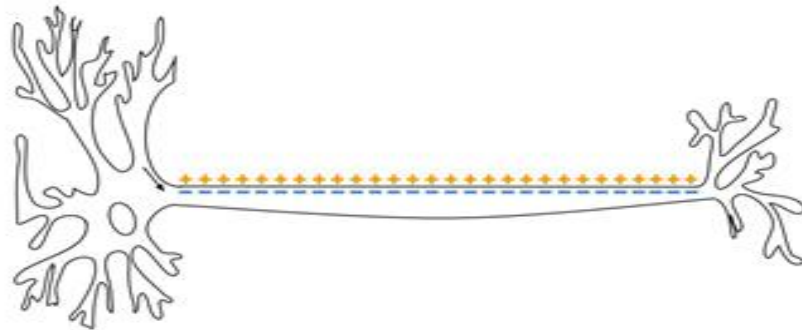


**THANK  
YOU**

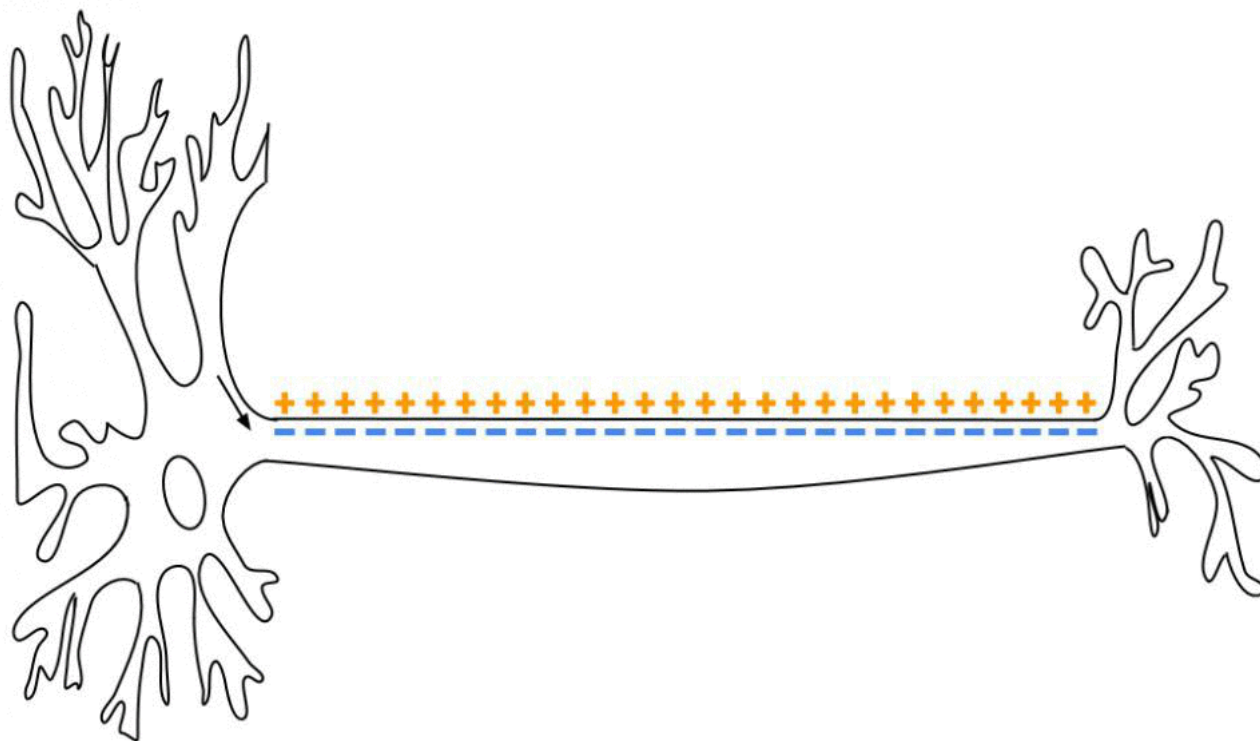
# Physiology of the nerve and muscle

د. محمد عيسى السبعراوي  
ماجستير فسلجة طبية

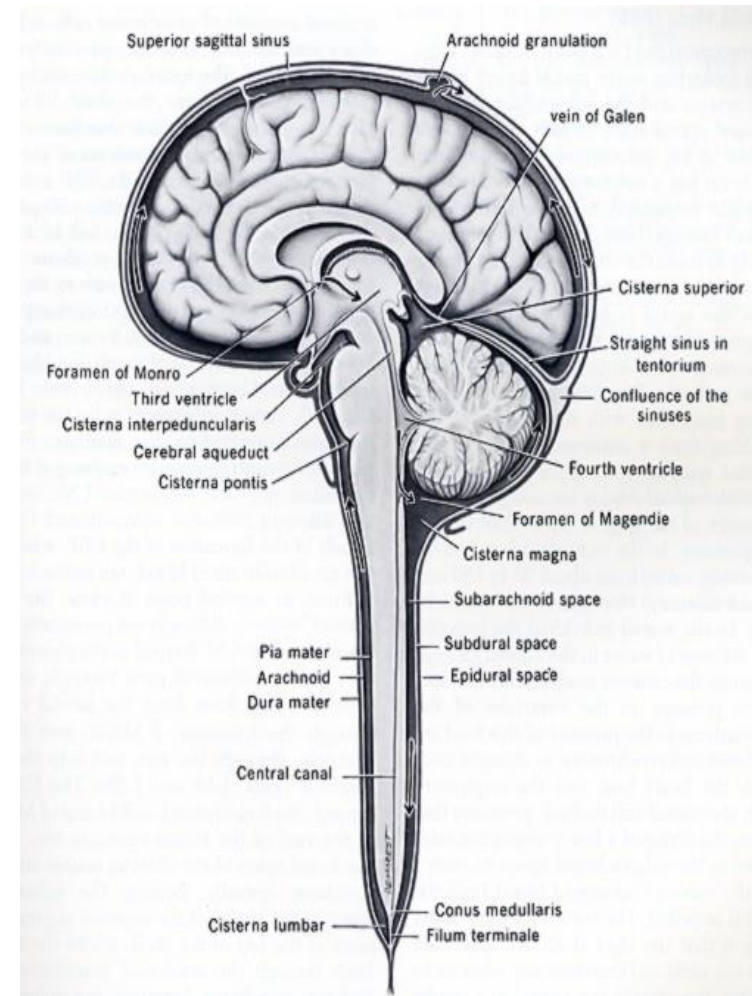
- **Electrical potentials exist across the membranes of virtually all cells of the body.**
- **Nerve and muscle cells, are capable of generating rapidly changing electrochemical impulses at their membranes.**
- **These impulses are used to transmit signals along the nerve or muscle membranes.**





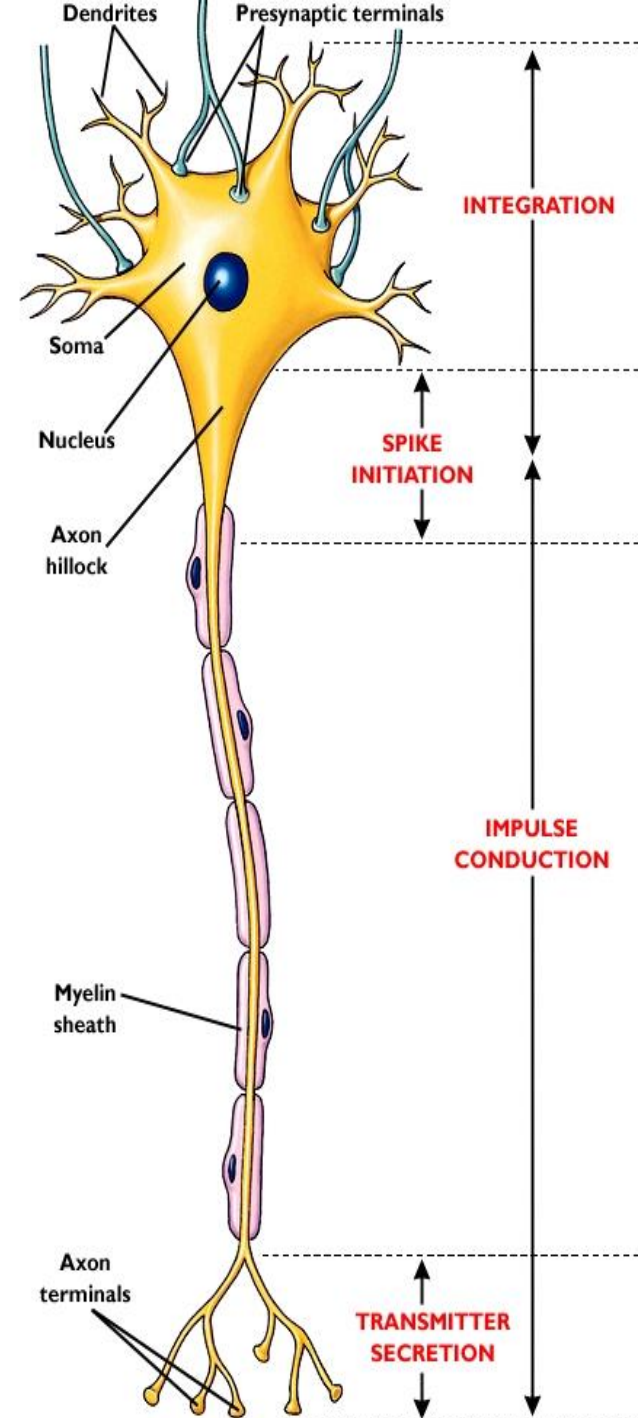


➤ **Nervous tissues**  
**found in the:**  
**brain.**  
**spinal cord.**  
**peripheral nerves.**  
**The basic cells are**  
**called nerve cells or**  
**neurons**

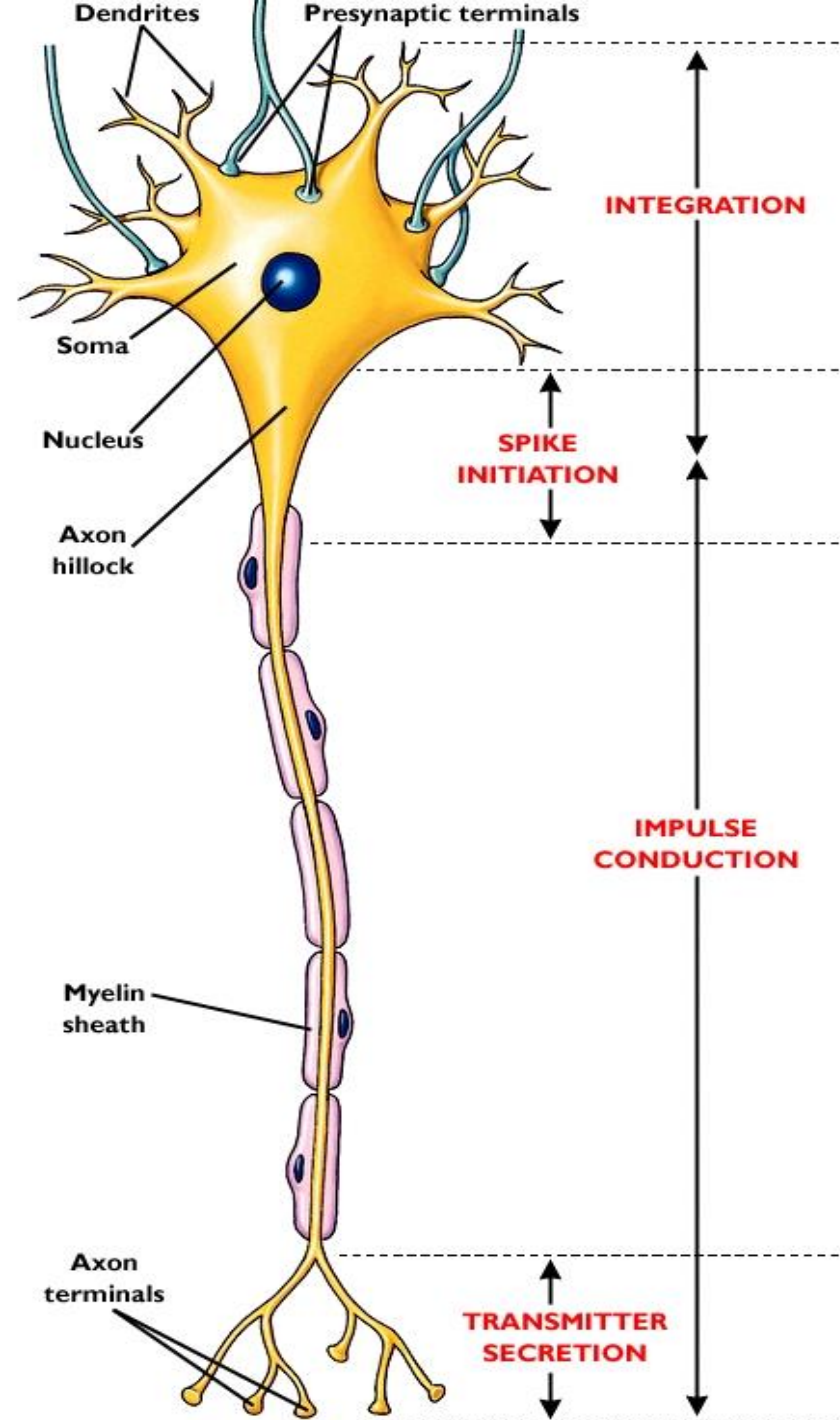


## ❖ Nerve cell:

- Represent the building block of the nervous system.
- specialized function of impulse transmission .
- The nerve cell composed of cell body –soma- with 5-7 short projections –dendrites- and a longer fibrous- axon.



➤ The axon of some nerve fiber have a myelin sheath, it is a lipid insulator led down by Schwann cell which wrapping around the axon, the sheath envelops the axon except at it's end and there are periodic constriction of 1 mm distance called **node of Ranvier**.

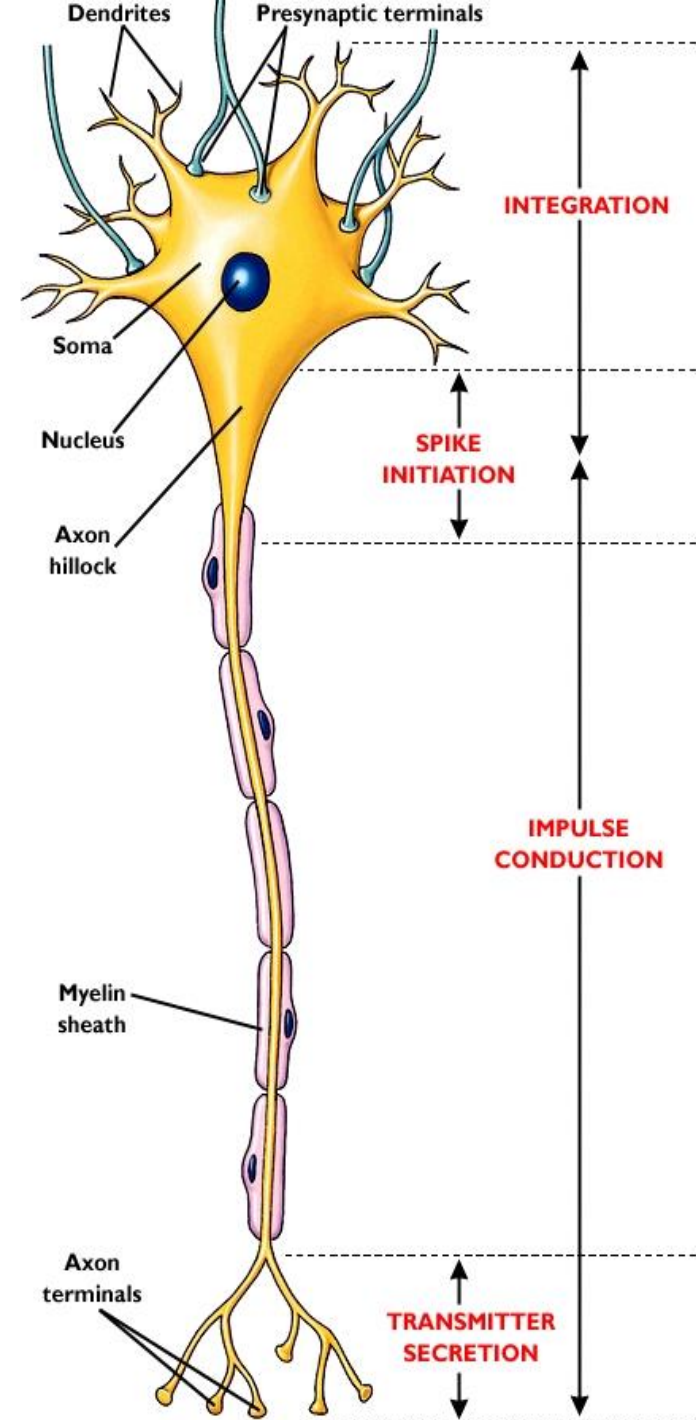


■ according to the present or absent of this sheath the nerve fiber can be :

\*myelinated nerve fiber .

\*Unmyelinated nerve fiber.

the axon ends in number of synaptic knobs (terminal buttons) which store the neurotransmitter synthesized by the cell body.



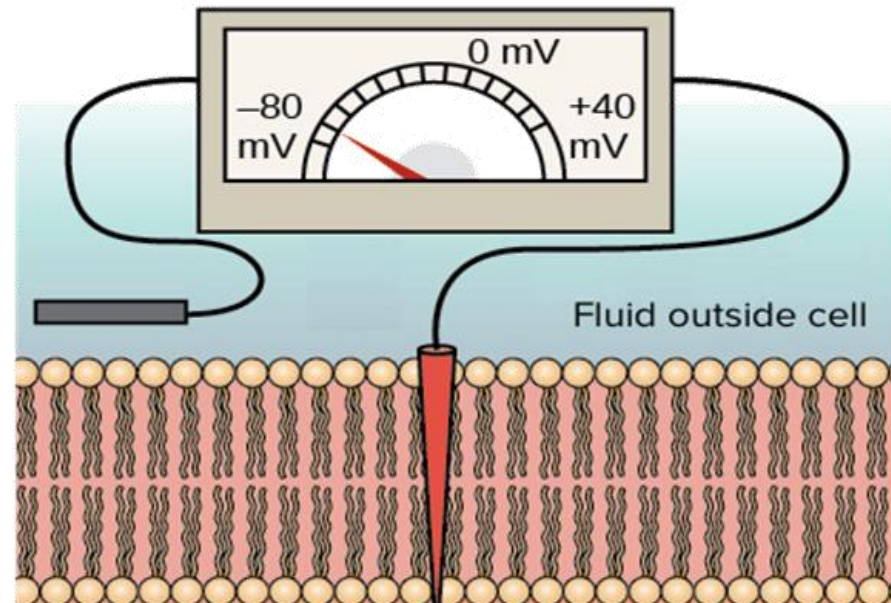
## ❖ Membrane potentials.

The concentration difference of ions (high  $\text{Na}^+$  in ECF, high  $\text{K}^+$  in ICF) across a selectively permeable membrane can under appropriate conditions create a membrane potential.



# ❖ Resting membrane potential (RMP):

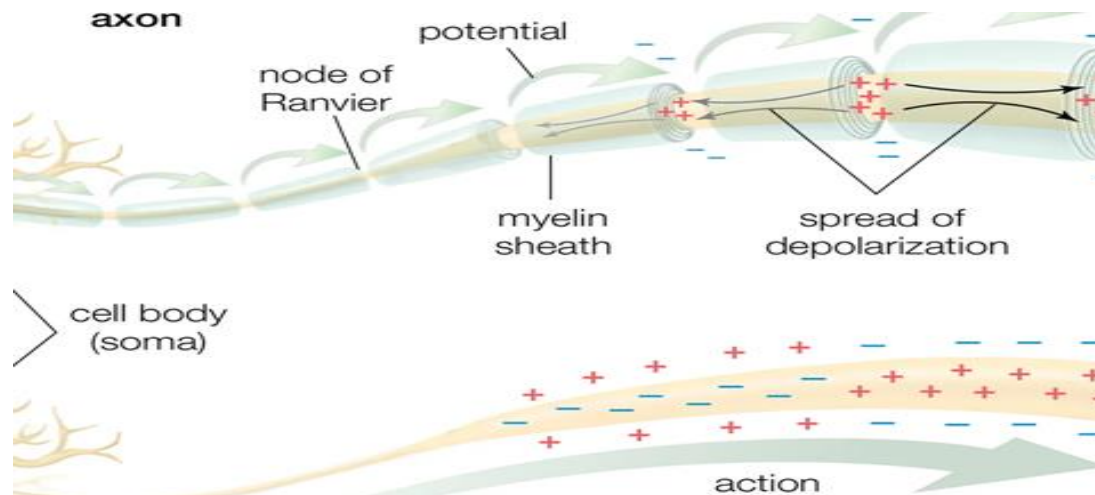
- Electrical potential exists across the membrane of all body cells with a negative charge inside the cell .
- The resting membrane potential of large nerve fiber ,when not transmitting nerve signals is about **-90 millivolts**.





# ❖ Nerve action potential

- Nerve signals are transmitted by action potentials which are rapidly changes in the membrane potential that spread rapidly along the nerve fiber membrane .
- Each action potential begins with a sudden change from the normal negative resting potential inside to a positive membrane potential and then ends with rapid return back to the negative resting potential .
- Action potential moves along the nerve fiber to it is end in a constant rate and amplitude .

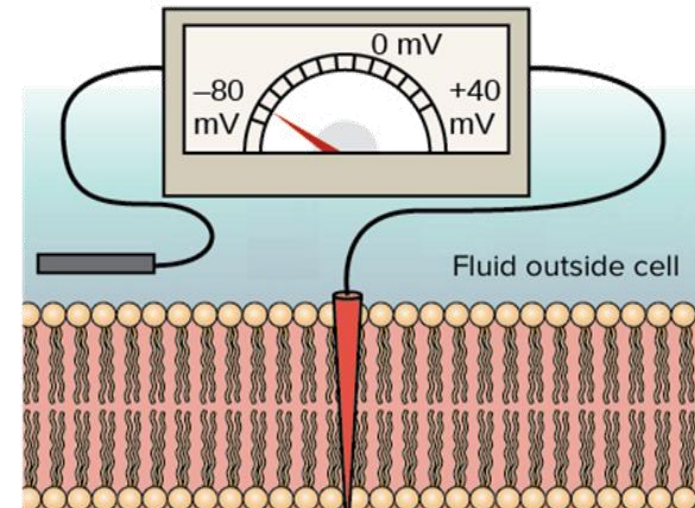
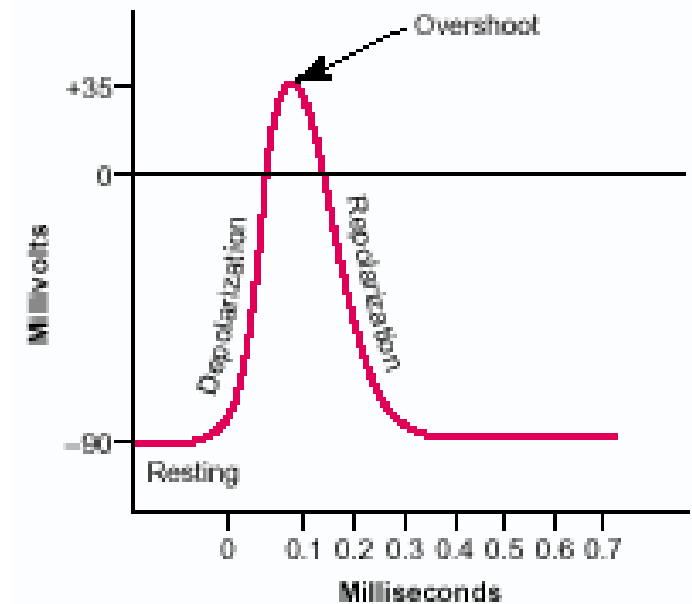


# ❖ Stage of action potential

## □ Resting Stage:

This is the resting membrane potential before the action potential begins.

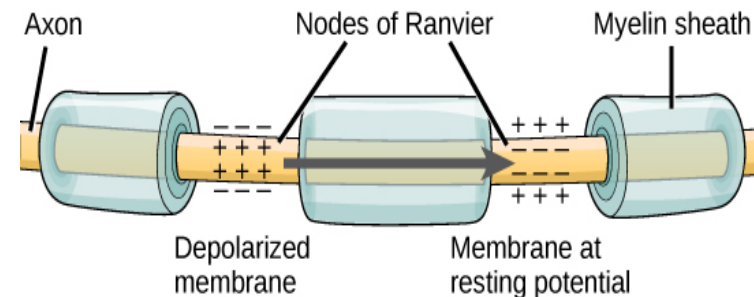
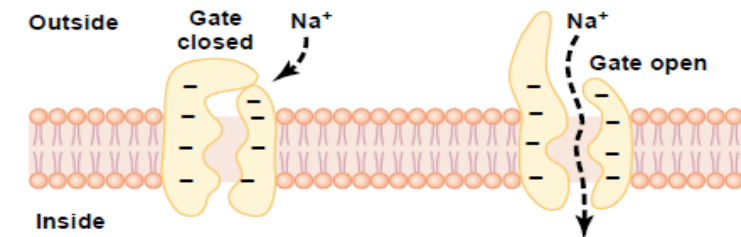
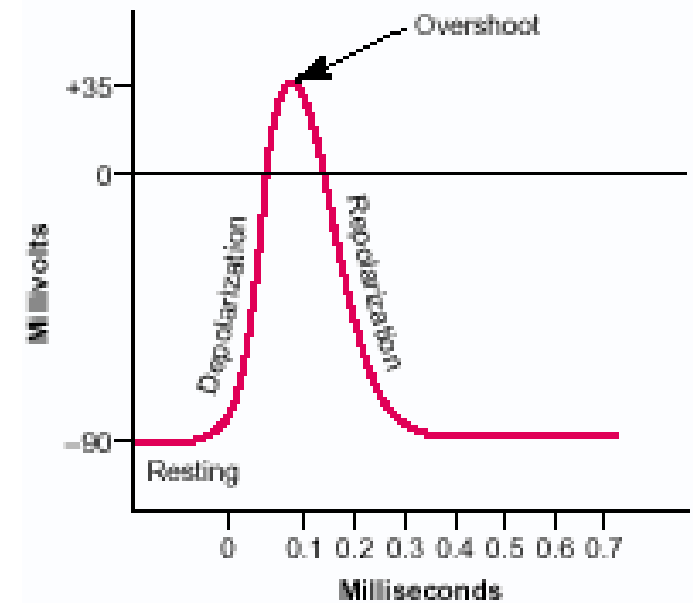
The membrane is said to be “polarized” during this stage because of the  $-90$  mv. negative membrane potential that is present.



## ❖ Depolarization Stage.

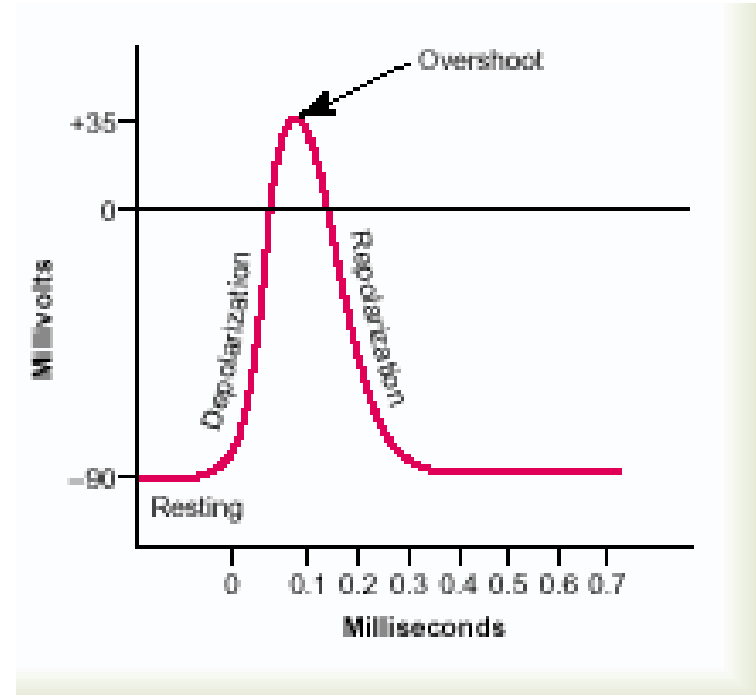
The membrane becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon.

The normal “polarized” state of  $-90$  mv is neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called “*Depolarization*”.



● In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually “overshoot” beyond the zero level and to become somewhat positive.

● In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not over-shoot to the positive state.

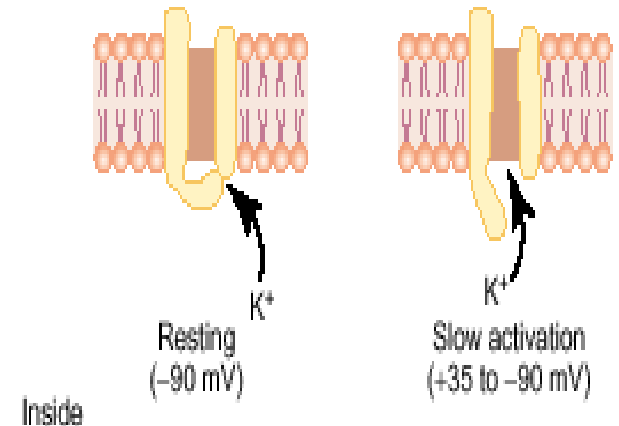
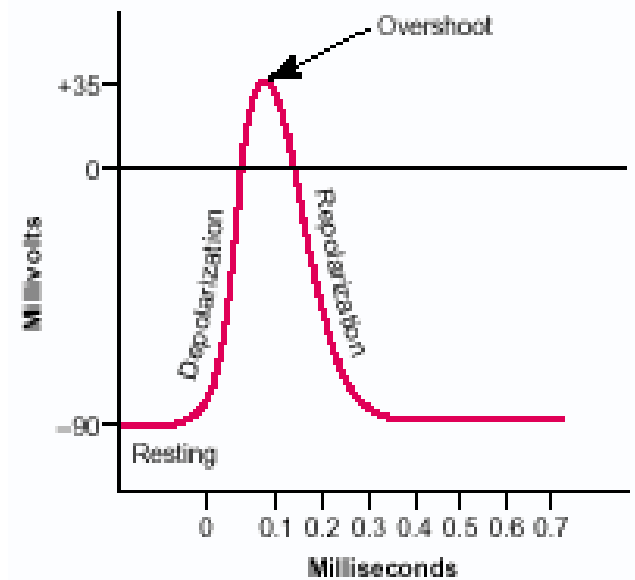


## ❖ Repolarization Stage

- The sodium channels begin to closed.
- The potassium channels opened.

Then, rapid diffusion of potassium ions to the exterior to re-establishes the normal negative resting membrane potential. This is called *Repolarization*.

Action potential lasts for **1 ms** in large myelinated nerve fiber.



## ❖ Voltage –gated Na<sup>+</sup> and K<sup>+</sup> channels

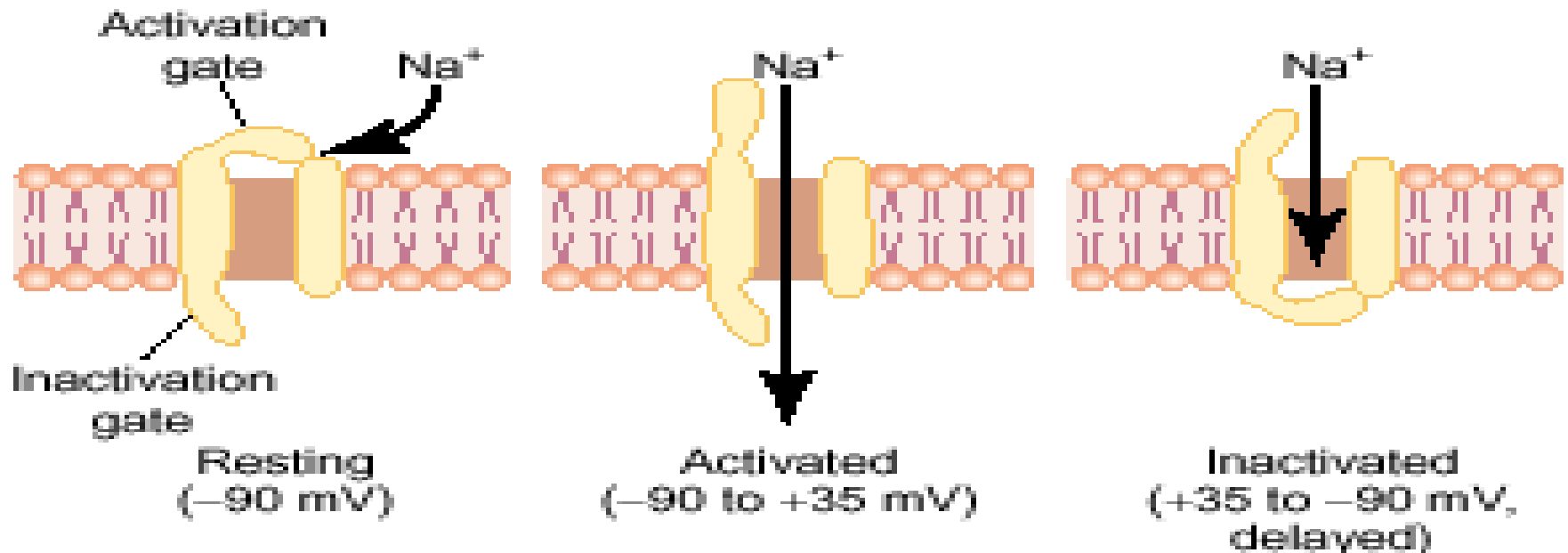
The important factors which causing depolarization and repolarization of the nerve membrane during the action potential is the:

- voltage gated Na<sup>+</sup> channel.
- voltage gated K<sup>+</sup> channel.

# ❖ Voltage –gated $\text{Na}^+$ channel .

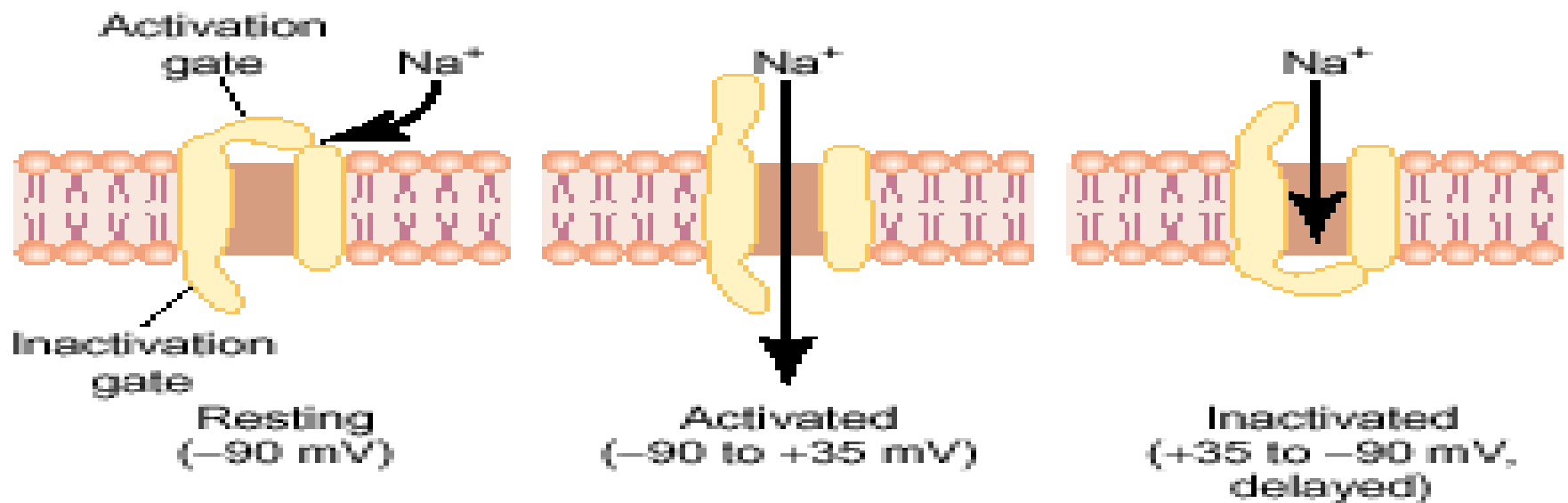
This channel has two gates ,one called

- The activation gate: near the outside of the channel
- The inactivation gate: near the inside of the channel.
- It also called fast channels.



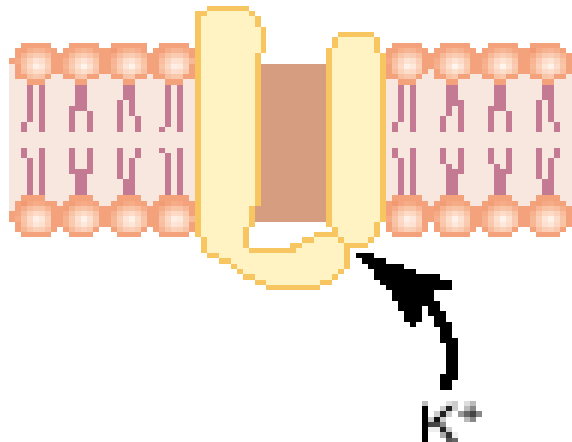


- At rest they are closed preventing  $\text{Na}^+$  entry into cell.
- After stimulation  $\text{Na}^+$  channels opened for very short time allowing large amount of  $\text{Na}^+$  ions entering the cell resulting in depolarization .
- At the end of depolarization they closed and remains so until membrane potential returns again to resting level.

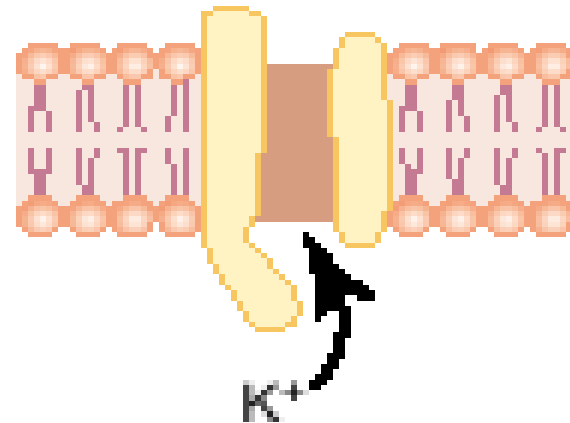


## ❖ Voltage – gated $K^+$ channel:

Closed at rest but opened near the end of depolarization allowing large amount of  $K^+$  to move out resulting in membrane **Repolarization**.



Resting  
( $-90$  mV)



Slow activation  
( $+35$  to  $-90$  mV)

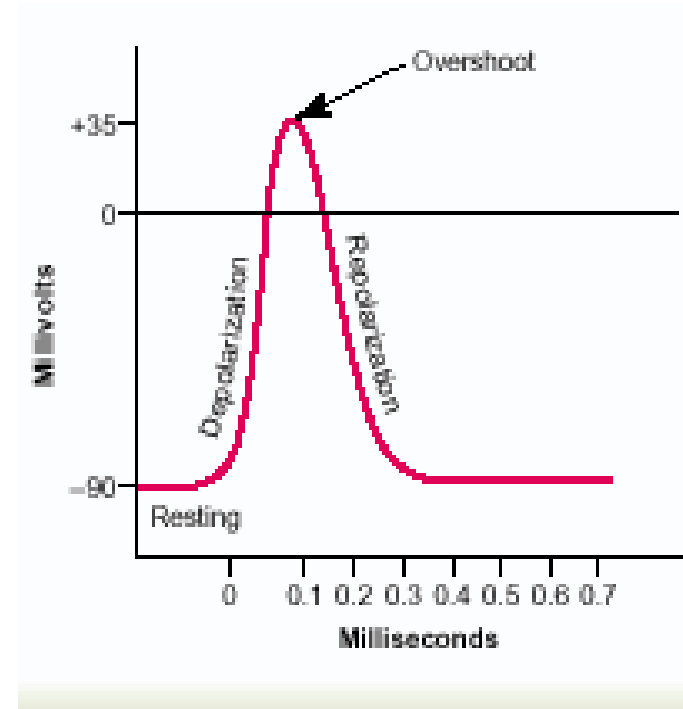
Inside

## ❖ Initiation of the action potential

As long as the membrane of the nerve fiber remains undisturbed, no action potential occurs.

If any event causes enough initial rise in the membrane potential from  $-90$  mv. toward the zero level, the rising voltage itself causes many voltage-gated sodium channels to begin opening.

This allows rapid inflow of sodium ions, which causes a further rise in the membrane potential.



- Thus opening still more voltage-gated sodium channels and allowing more streaming of sodium ions to the interior of the fiber.
- This process is a **positive-feedback vicious cycle** that, once the feedback is strong enough, continues until all the voltage-gated sodium channels have become activated (opened).
- Then, within another fraction of a millisecond, the rising membrane potential causes closure of the sodium channels as well as opening of potassium channels, and the action potential soon terminates.

# ❖ Stimulus for nerve excitation:

1.chemical

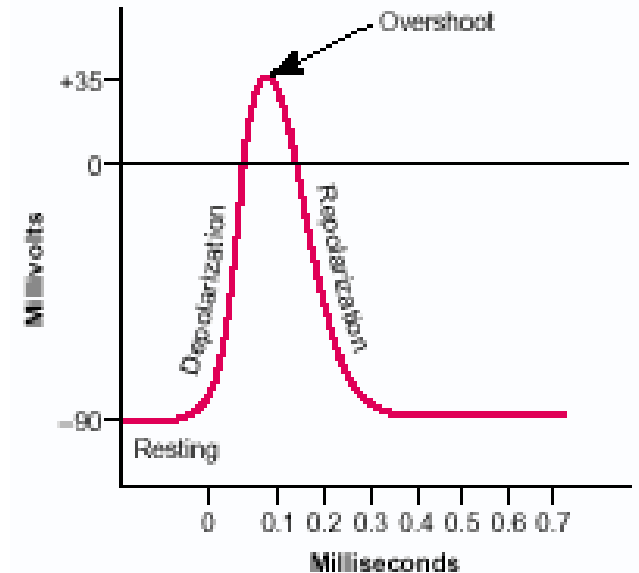
2. mechanical

3.electrical.

- The above factors increase **Na<sup>+</sup>** permeability shifting the membrane potential toward the firing level causing an action potential.

## ❖ Threshold stimulus

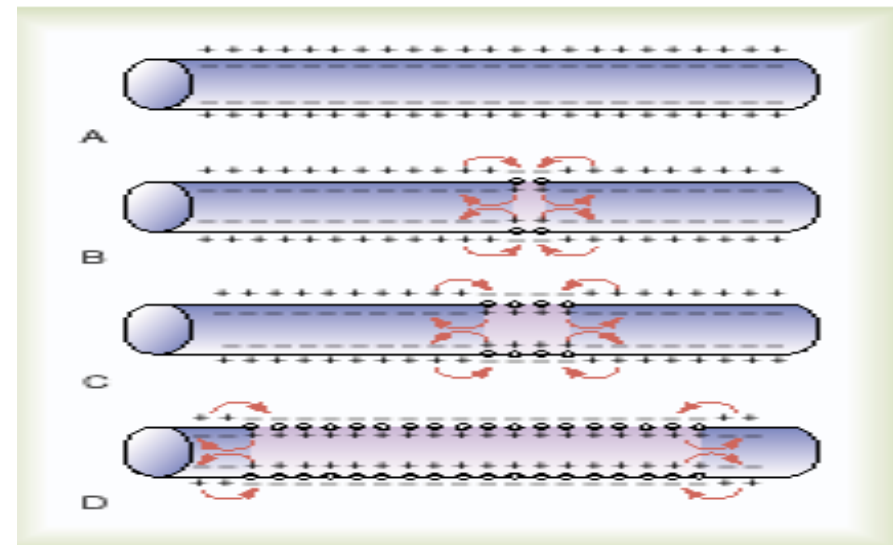
- The minimum intensity of stimulus that will just produce a response (A P) is called **threshold stimulus**, it varies according to the type of axon; therefore different axon within the same nerve trunk has different thresholds, at the level of single axon any stimulus with **sub threshold** intensity will not produce AP.
- Increasing stimulation intensity above threshold level will produce no change in response so the AP of single nerve axon is said to obey the all or none law, action potential always run in same duration and amplitude.



# ❖ Propagation of the Action Potential:

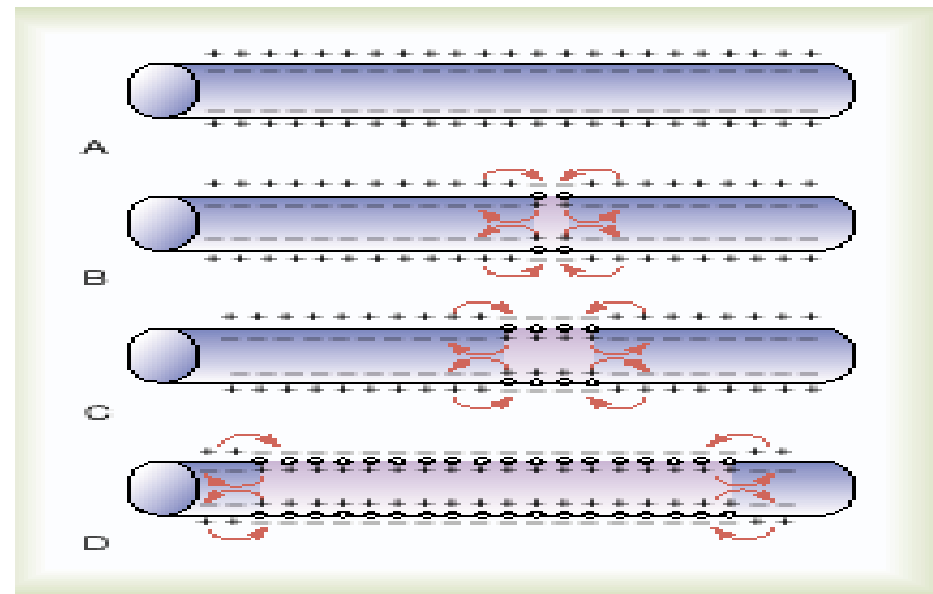
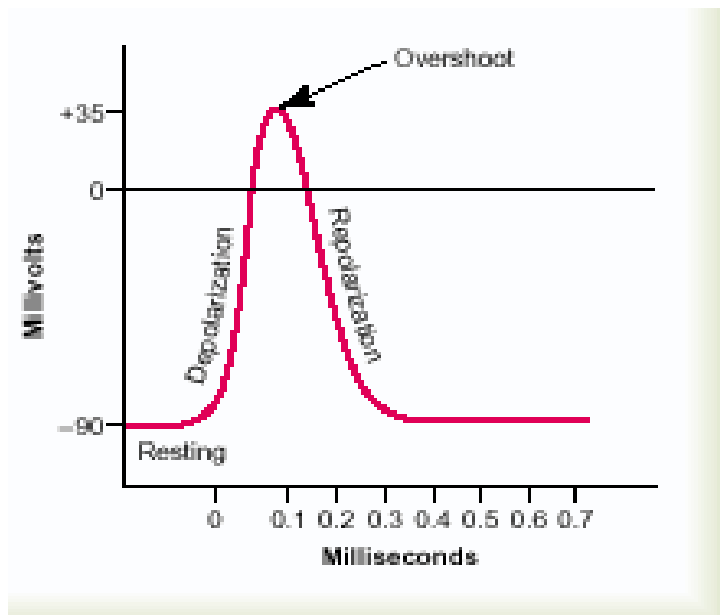
An action potential elicited at any one point on an excitable membrane usually excites adjacent portions of the membrane, resulting in propagation of the action potential along the membrane.

When normal resting nerve fiber that has been excited in its mid-portion that is, suddenly develops increased permeability to sodium; Leading to “local circuit” of current flow from the depolarized areas of the membrane to the adjacent resting membrane areas.



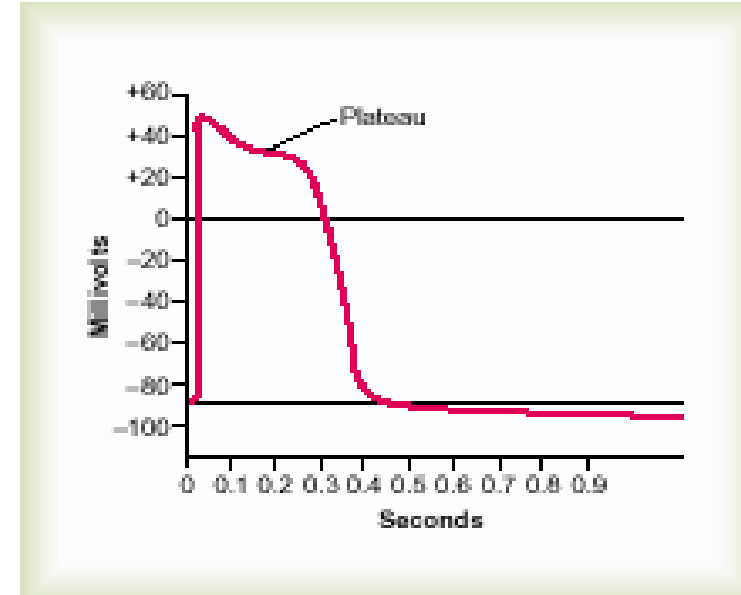
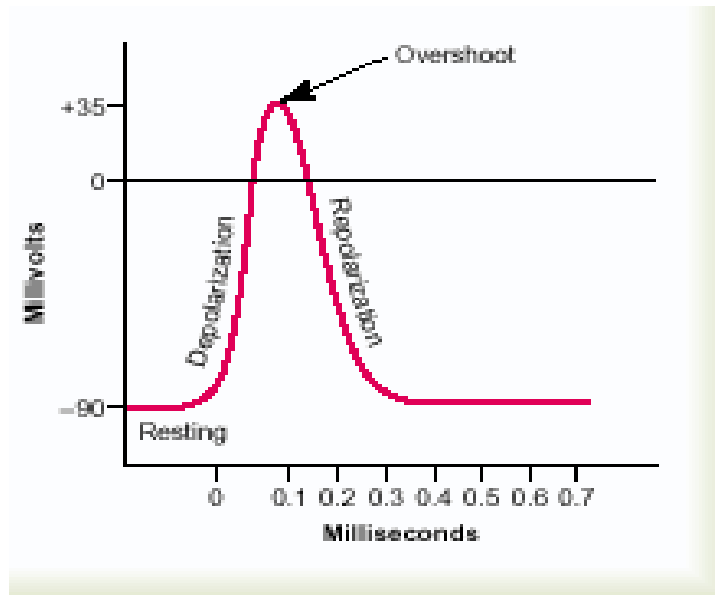


- Occasionally, the action potential reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. So the spread of depolarization stops.
- Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than (1). This “greater than 1” requirement is called the *safety factor for propagation*.

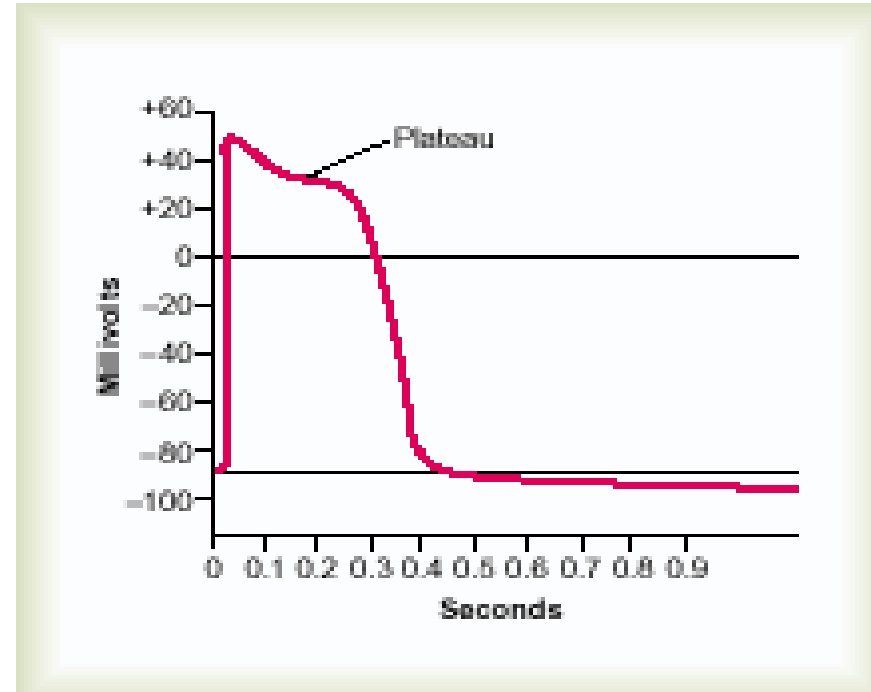


## ❖ Plateau in Some Action Potentials:

□ In some instances, the excited membrane does not repolarize immediately after depolarization; instead, the potential remains on a **plateau** near the peak of the spike potential for many **milliseconds**, and then does repolarization begin.



□ Type of action potential occurs in heart muscle fibers, where the plateau lasts for as long as **0.2 to 0.3 second** and causes contraction of heart muscle to last for this same long period.

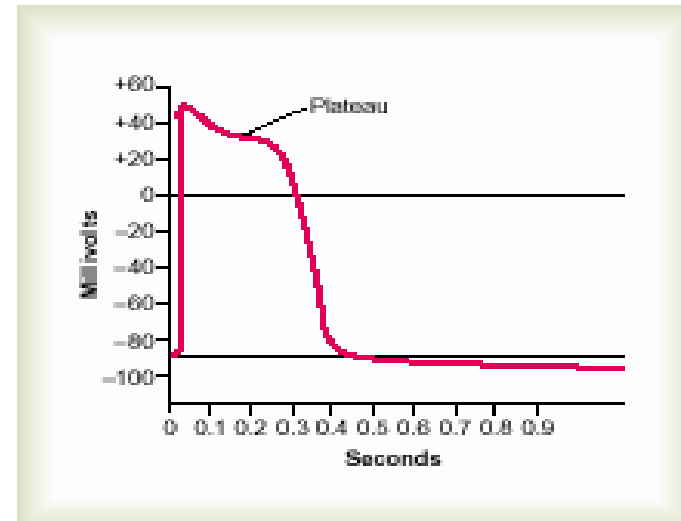


# ❖ The cause of the plateau is a combination of several factors.

**First;** in heart muscle, two types of channels enter into the depolarization process:

- 1- The usual voltage-activated sodium channels, called *fast channels*.
- 2- Voltage-activated calcium-sodium channels, which are slow to open and therefore are called *slow channels*.

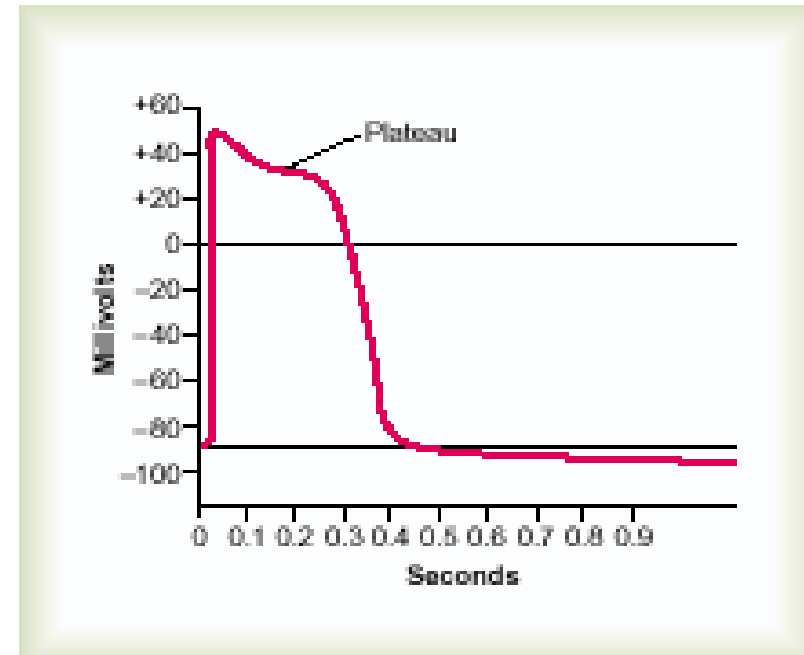
Opening of fast channels causes the spike portion of the action potential, whereas the slow, prolonged opening of the slow calcium-sodium channels mainly allows calcium ions to enter the fiber, which is largely responsible for the plateau portion of the action potential.



**Second factor;** that may be partly responsible for the plateau :

● The voltage - gated potassium channels are slower than usual to open, often not opening very much until the end of the plateau.

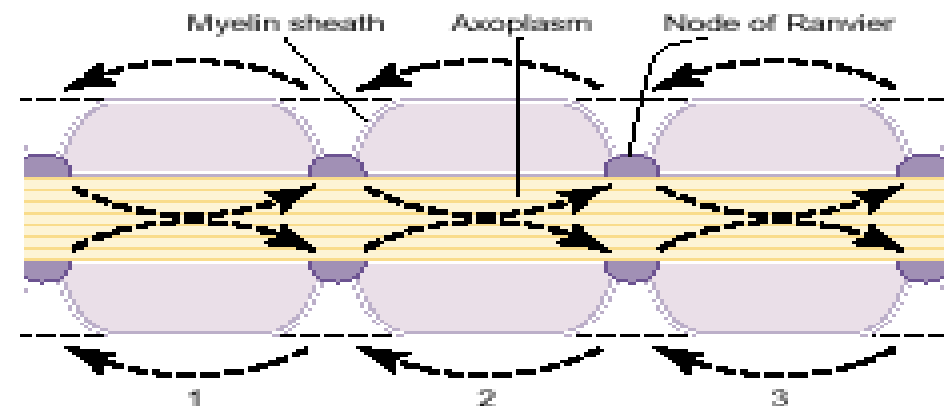
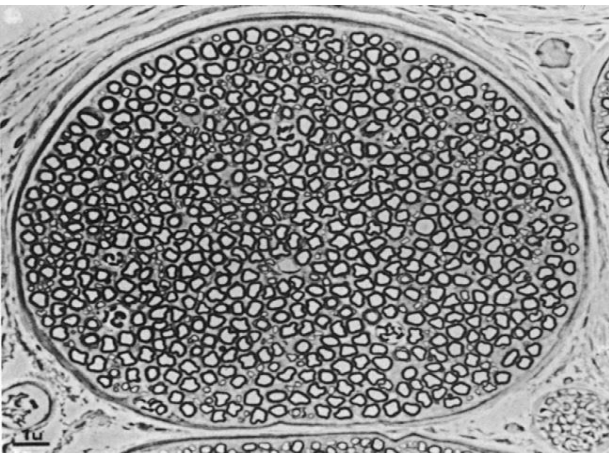
This delays the return of the membrane potential toward its normal negative value of **-90 mv.**



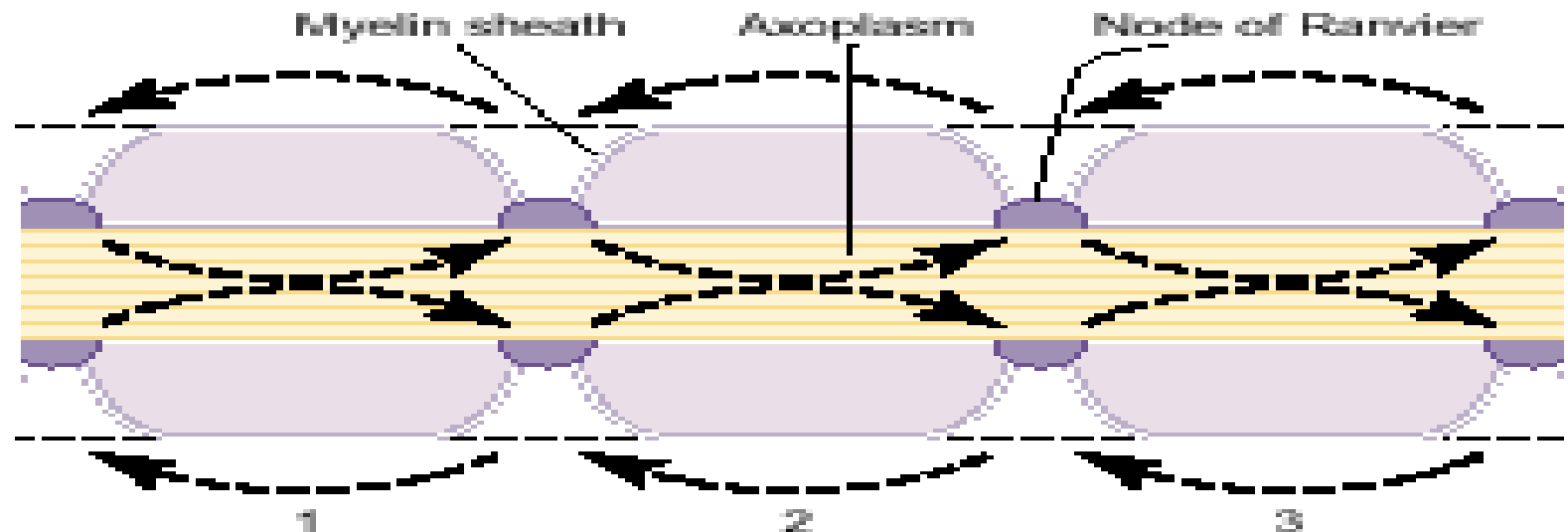
## ❖ Special characteristics of signal transmission in nerve trunks:

🌐 The large fibers are *myelinated*, and the small ones are *unmyelinated*. The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers.

🌐 “Saltatory” Conduction in Myelinated Fibers from Node to Node, no ions can flow through the thick myelin sheaths of myelinated nerves, they can flow through the nodes of Ranvier. Therefore, action potentials occur *only at the nodes*.



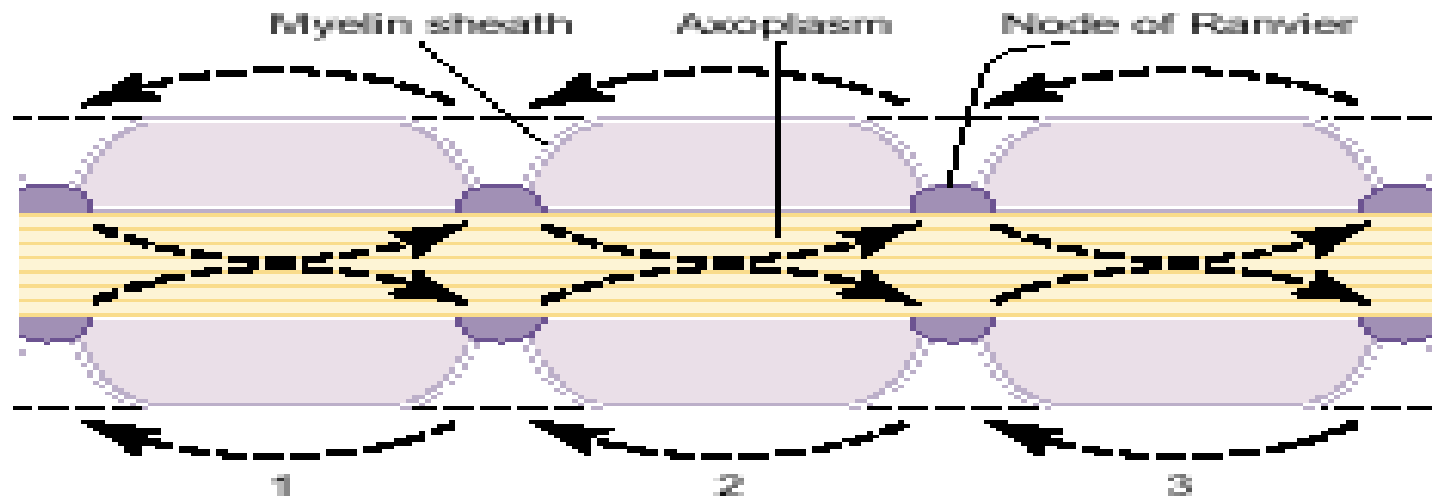
■ Yet the action potentials are conducted from node to node; this is called ***"Saltatory conduction"***. That is electrical current flows through the surrounding extra-cellular fluid outside the myelin sheath as well as through the axoplasm inside the axon from node to node, exciting successive nodes one after another.





## ❖ Saltatory conduction is of value for two reasons:




1. By causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the velocity of nerve transmission in myelinated fibers as much as **5- to 50-fold**.
2. **Saltatory conduction conserves energy for the axon:** because only the nodes depolarize, allowing perhaps **100 times** less loss of ions than would otherwise be necessary, and therefore requiring little metabolism for re-establishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses.



# Factors which affect the conduction velocity:

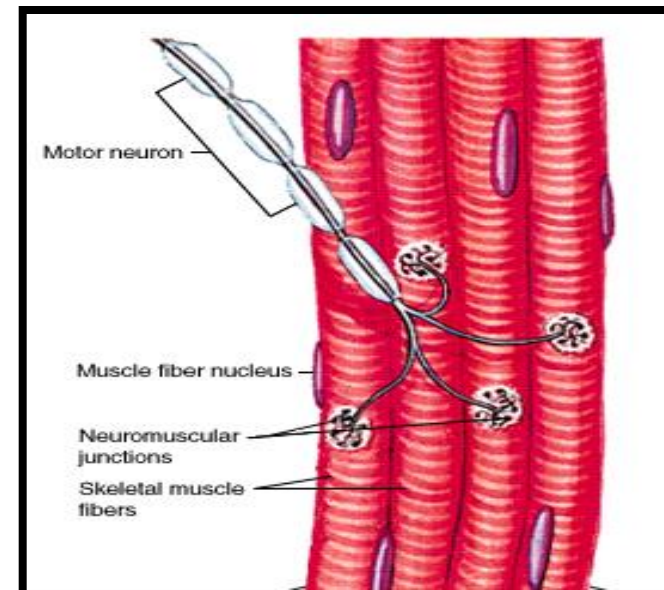
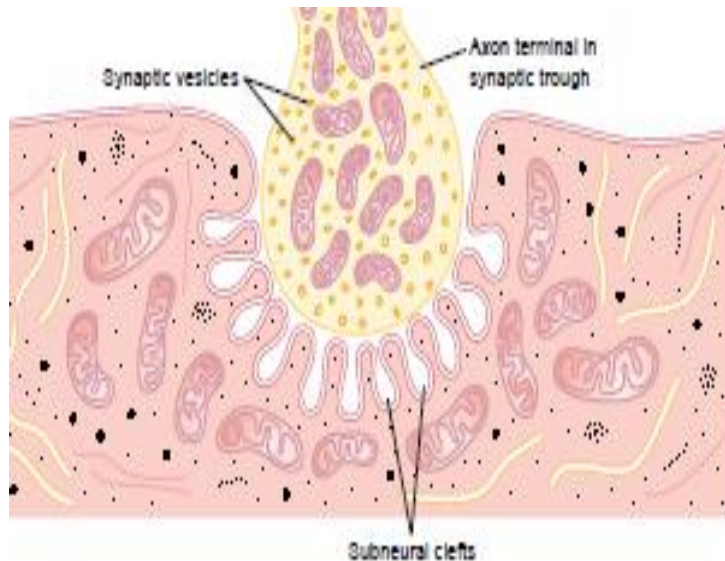
1. Myelination : myelinated nerve is about 50 times faster.
2. Axon diameter: in unmyelinated axon the conduction velocity is directly proportional to the square root of axon diameter; in small unmyelinated nerve axon the velocity is about  $0.5 \text{ m/s}$  while in large myelinated axon is about  $100 \text{ m/s}$ .

# Factors which inhibit nerve excitability:

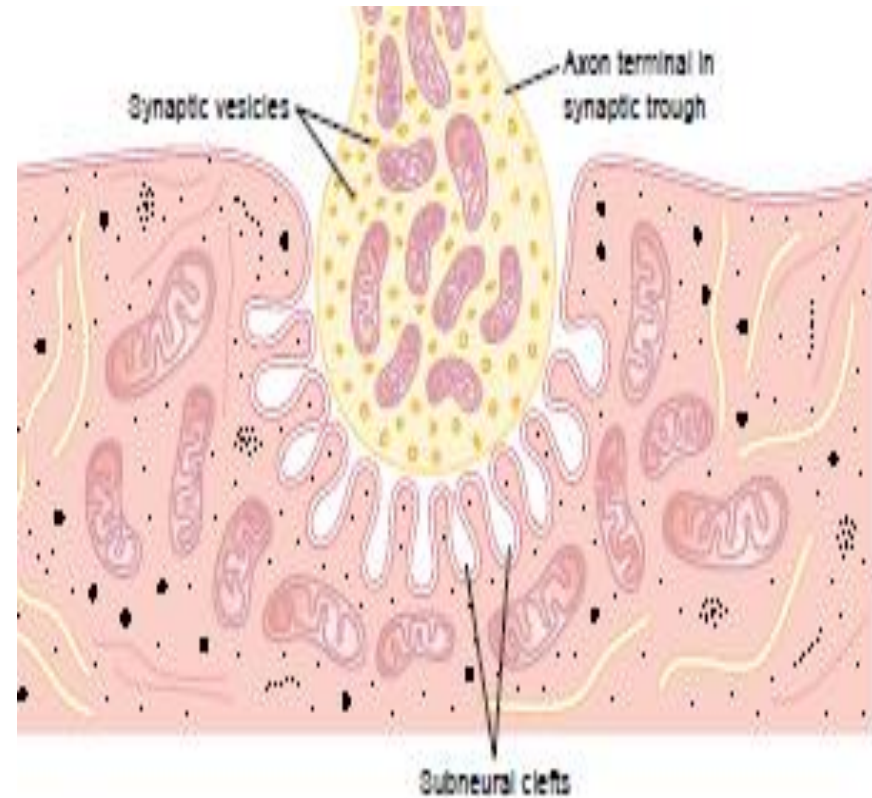
-  **hyper  $\text{Ca}^{+}$  :** excess  $\text{Ca}^{+}$  bind to sodium channels  
so higher voltage is required to open them.
-  **hypo  $\text{K}^{+}$  :** This decrease membrane potential to  
level which favors closure of most  $\text{Na}^{+}$  channels.
-  **local anesthetics:** it decrease  $\text{Na}^{+}$  permeability.

**PHYSIOLOGIC ANATOMY OF  
THE NEUROMUSCULAR  
JUNCTION—THE MOTOR END  
PLATE:**

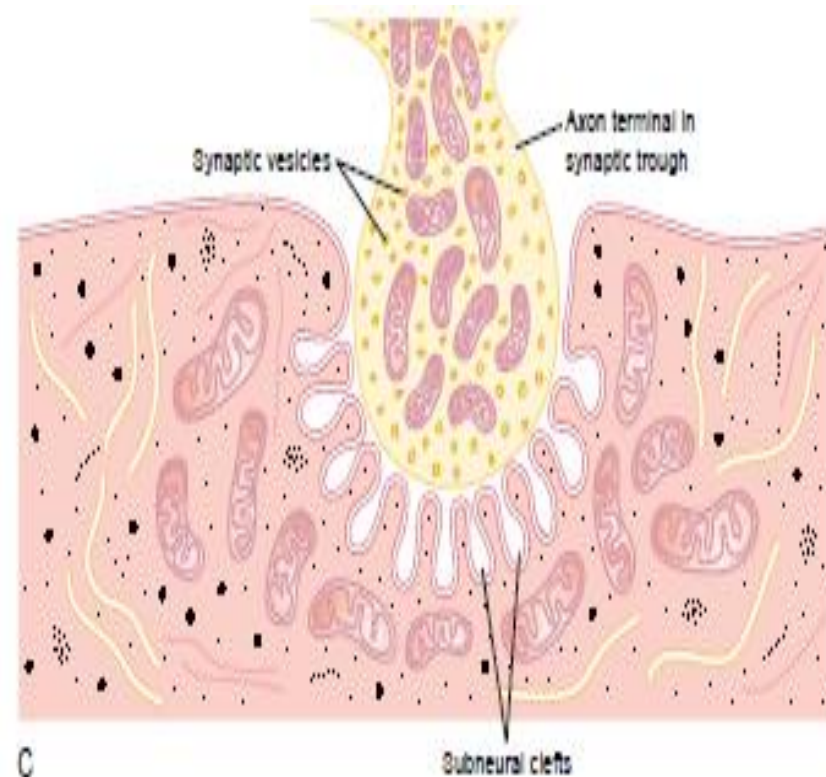
- The nerve fiber forms a complex of *branching nerve terminals* that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane.
- The entire structure is called the *motor endplate*.



● The invaginated membrane is called the *synaptic gutter* or *synaptic trough*, and the space between the terminal and the fiber membrane is called the *synaptic space* or *synaptic cleft*. At the bottom of the gutter are numerous smaller *folds* of the muscle membrane called *subneural clefts*, which greatly increase the surface area.

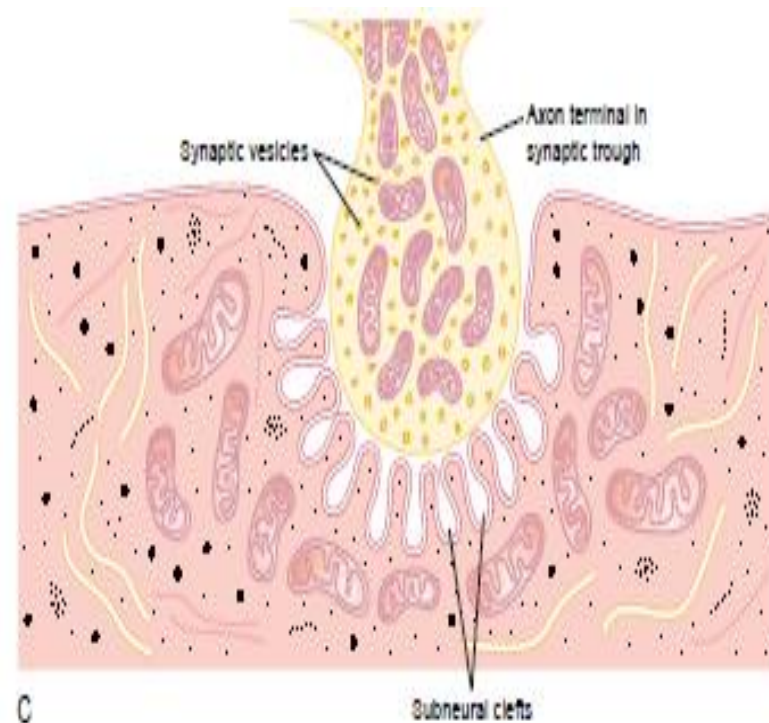


● At the nerve terminals there are many mitochondria that supply adenosine triphosphate (ATP), the energy source that used for synthesis of an excitatory transmitter *acetylcholine*.

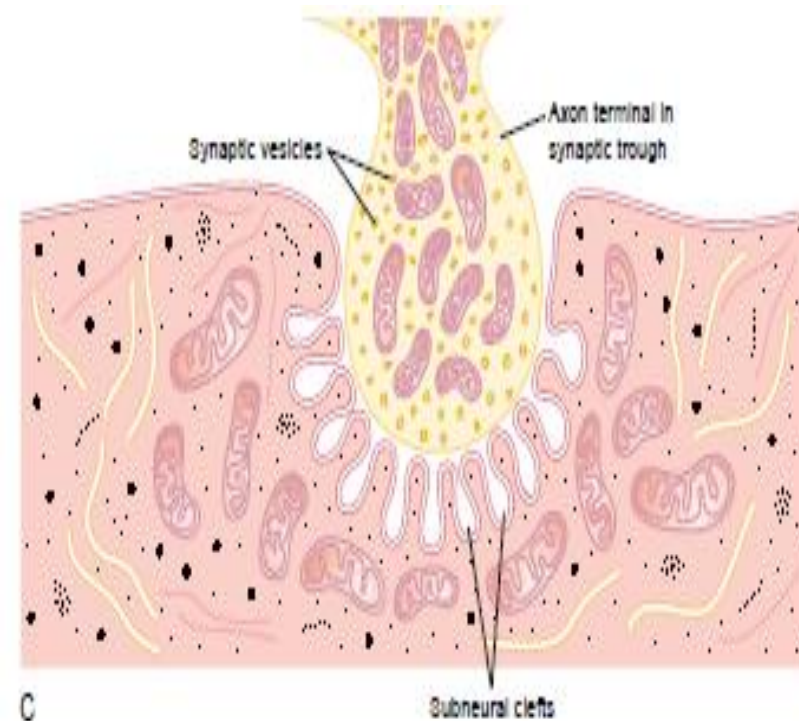




● **Acetylcholine (Ach)** is synthesized in the cytoplasm of the terminal (about 300,000 of which are normally in the terminals of a single end plate). When a nerve impulse reaches the neuromuscular junction, about 125 vesicles of (Ach) are released from the terminals into the synaptic space,

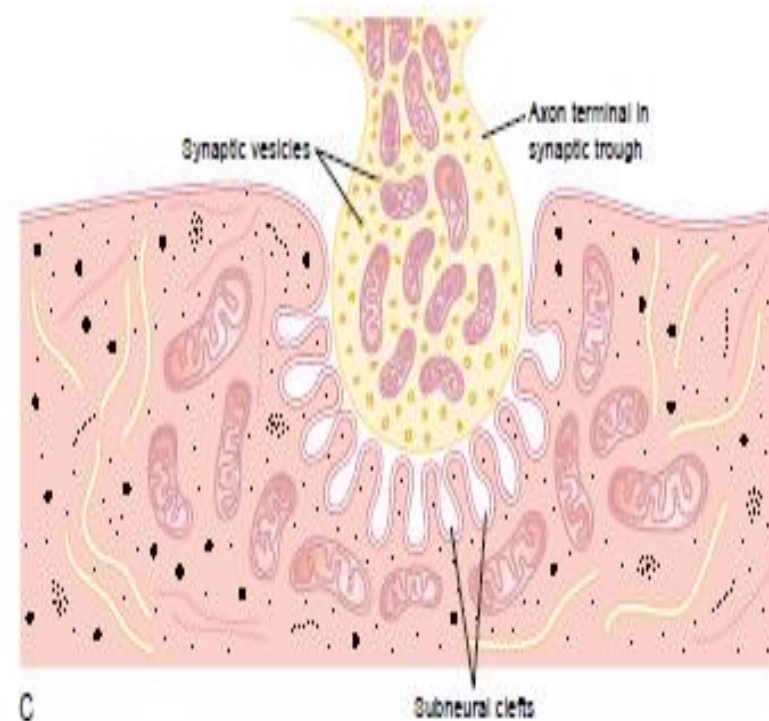


- In the synaptic space are large quantities of the enzyme *acetylcholinesterase*, which destroys Ach a few milliseconds after it has been released from the synaptic vesicles.



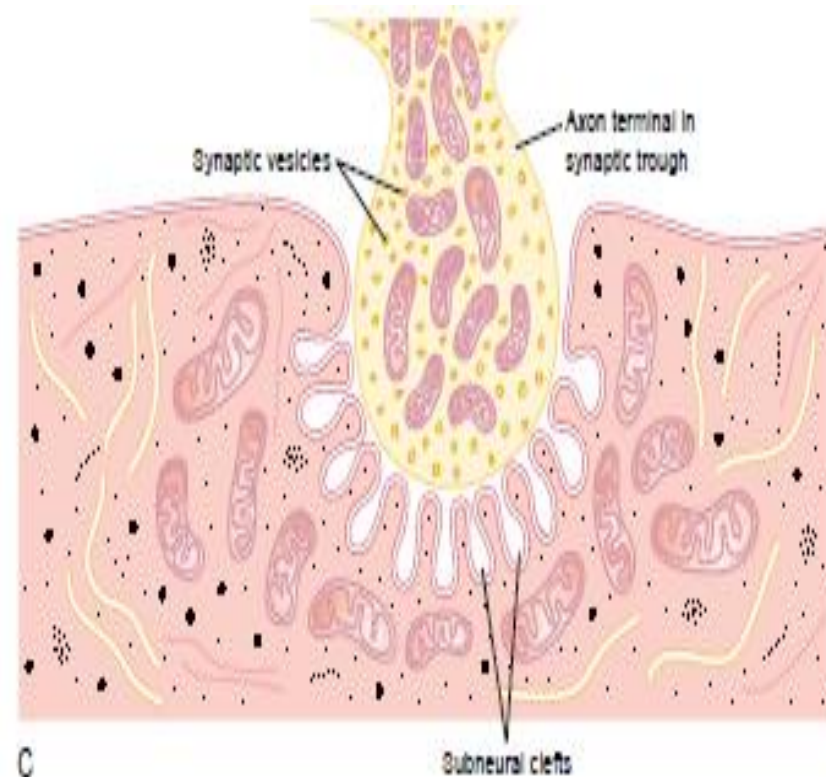
● Ach stimulate calcium ions to diffuse from the synaptic space to the interior of the nerve terminal, calcium in turn stimulate more Ach vesicle release.

● Ach also stimulate the opening of acetylcholine-gated channels to allow large numbers of sodium ions to pour inside the muscle fiber, carrying with them large numbers of positive charges.



● This creates a local positive potential change inside the muscle fiber membrane, called the *end plate potential*.

● Which initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.



**SKELETAL MUSCLE**

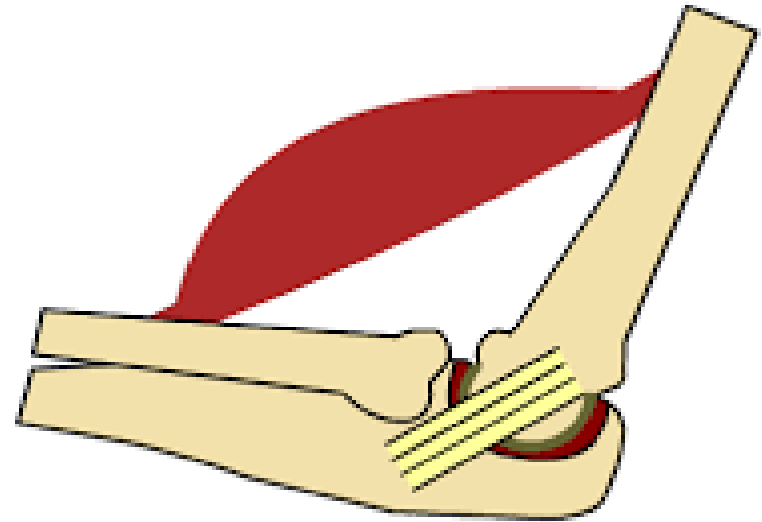
**CONTRACTION**

## ❖ Skeletal Muscle:

- 40 per cent of the body is skeletal muscle
- 10 percent is smooth and cardiac muscle.

### □ Physiologic and anatomy of skeletal muscle:

- Skeletal muscles are composed of numerous fibers (10-80  $\mu\text{m}$  in diameter).
- Each fiber is usually innervated by only one nerve ending, located near the middle of the fiber.



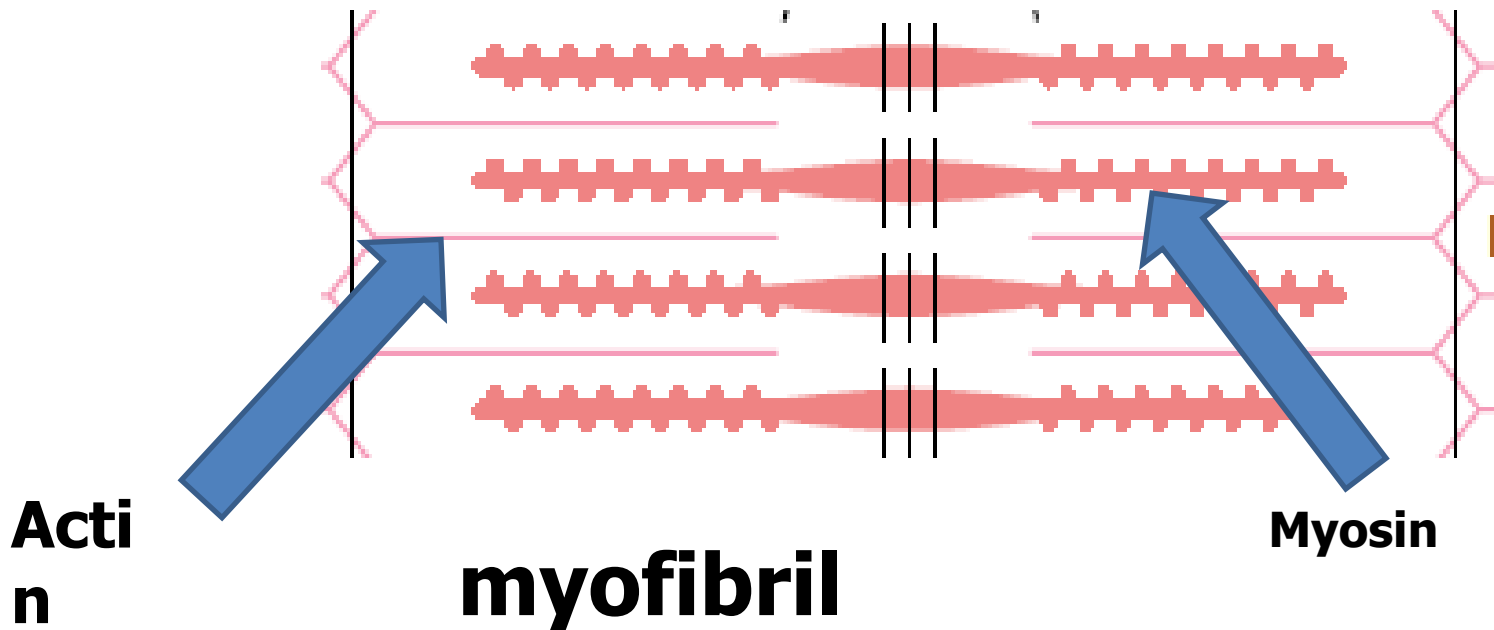
## ❑ Sarcolemma:

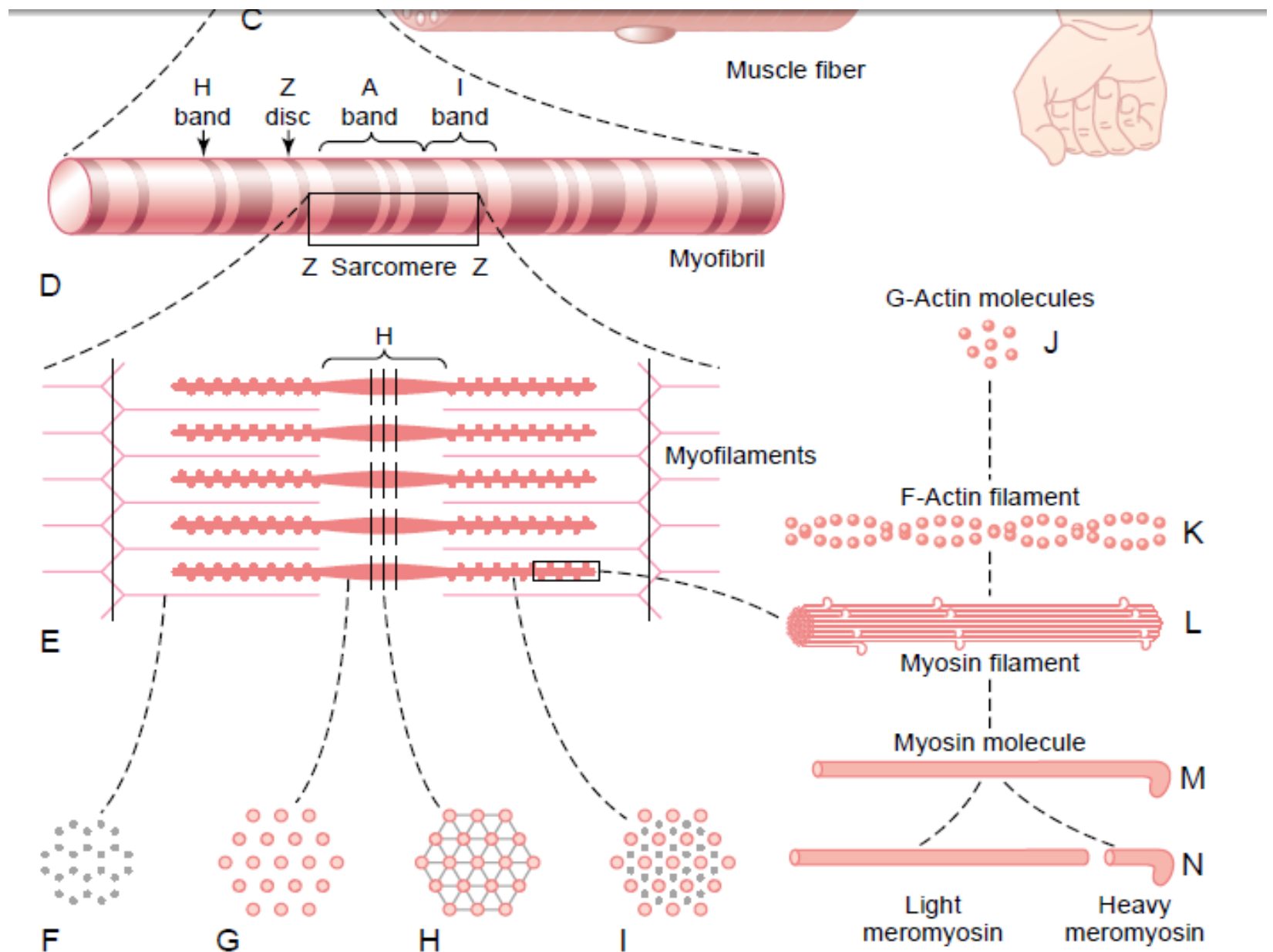
- Is the cell membrane of the muscle fiber;  
It consists of a true cell membrane, called the *plasma membrane*.
- It fuses with a tendon fiber, and the tendon fibers in turn collect into bundles to form the muscle tendons that then insert into the bones.



## ❖ Myofibrils; Actin and Myosin Filaments:

- Each m. f. contain several hundred - several thousand of myofibril.
- Myofibril composed of about **1500 myosin filaments and 3000 actin filaments.**
- Actin and myosin are large polymerized protein molecules that are responsible for the actual muscle contraction.



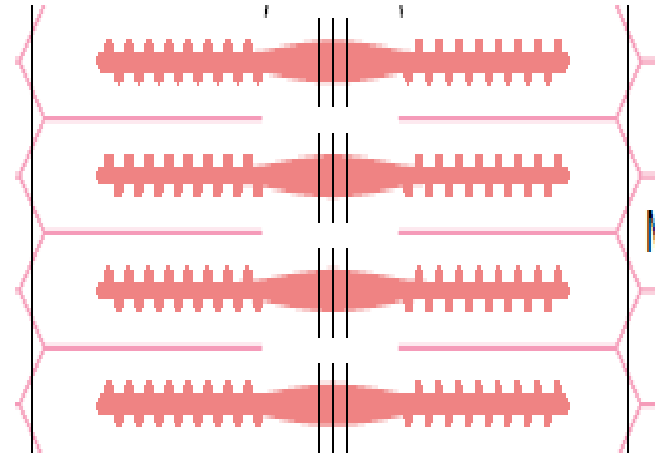


# □ The sarcoplasm:

- Is the intracellular fluid that fill the spaces between the myofibrils, containing large quantities of  $K^+$ ,  $Mg^+$ , and  $Ph^+$ , plus multiple protein enzymes.
- The mitochondria that lie parallel to the myofibrils are supply the contracting myofibrils with large amounts of energy.

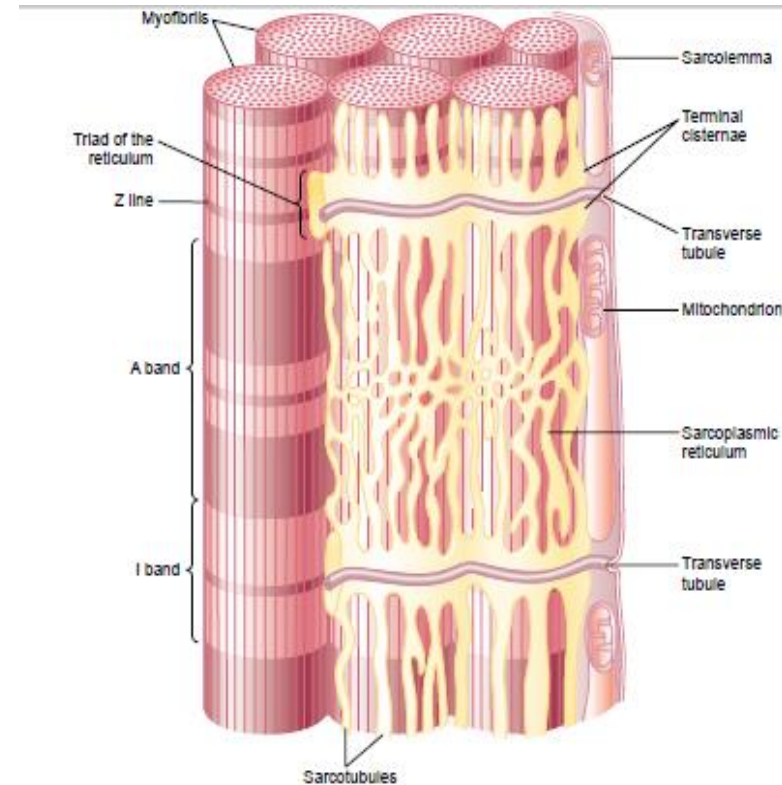
## ❖ Titin Filamentous Molecules.

- It Keeps the Myosin and Actin Filaments in Place .
- it's *very springy*.
- It act as a frame work that holds the myosin and actin filaments in place so that the contractile machinery of the sarcomere will work.



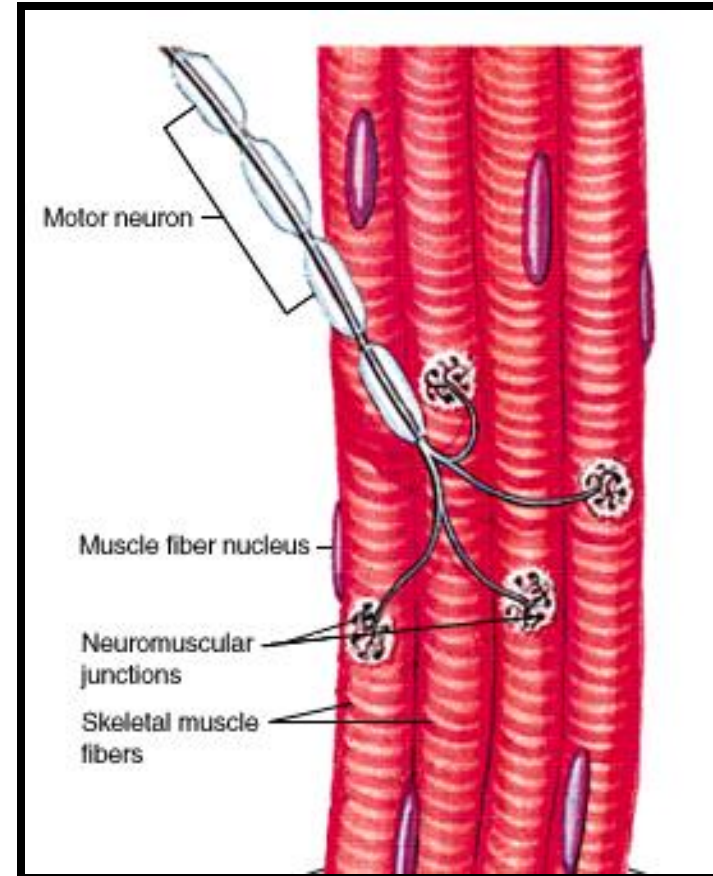
## ❖ Sarcoplasmic Reticulum:

- Present in the sarcoplasm surrounding the myofibrils, it's important in controlling muscle contraction, the very rapidly contracting types of muscle fibers have especially extensive sarcoplasmic reticulum.



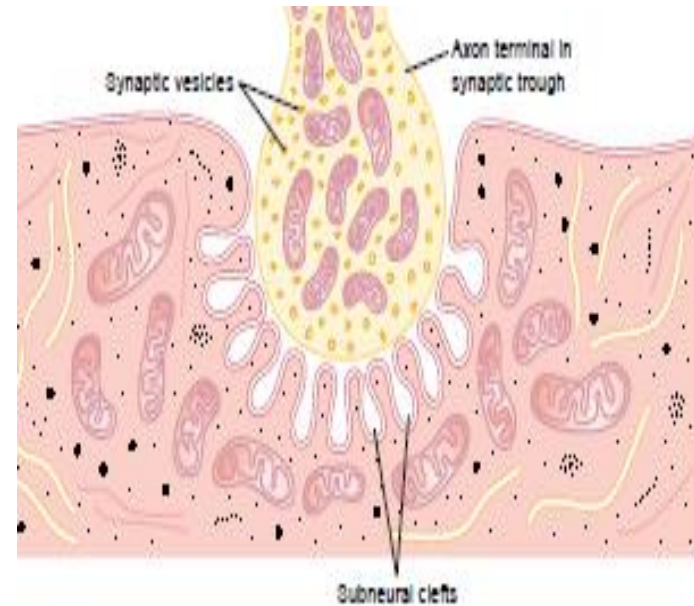
## ❖ Motor unit:

- ❑ Each motor neuron innervates multiple muscle.
- ❑ All muscle fibers that innervated by a single nerve fiber are called motor unit.
- ❑ Small muscle that reacts rapidly; have more nerve fiber for fewer muscle fiber as few as 2-3 muscle fiber per motor unit in some of laryngeal muscle.
- ❑ Large muscle that does not require fine contraction such as soleus muscle have several hundred muscle fiber in a motor unit. In general 80-100 muscle fiber is provided by to a motor unit.



# ❖ General mechanism of muscle contraction:

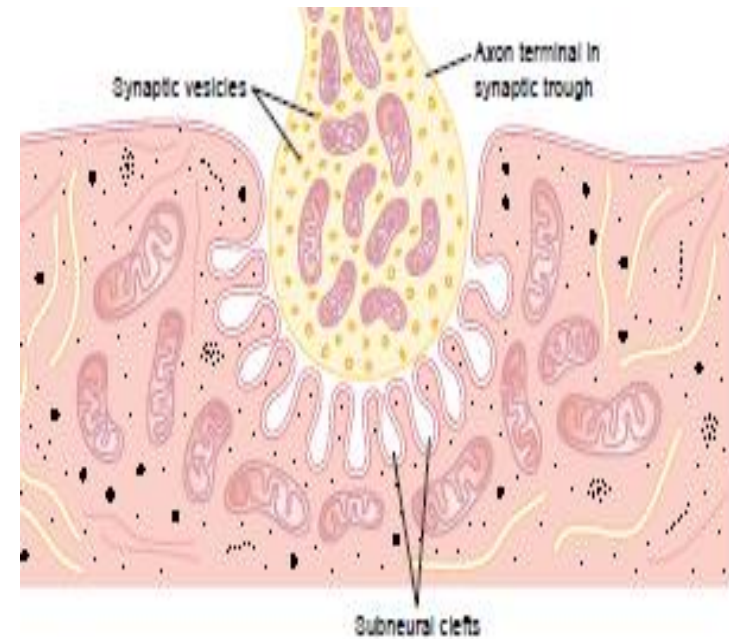
- An action potential travels along a motor nerve to its endings on muscle fibers.
- At each ending, the nerve secretes a small amount of the neurotransmitter substance Ach.





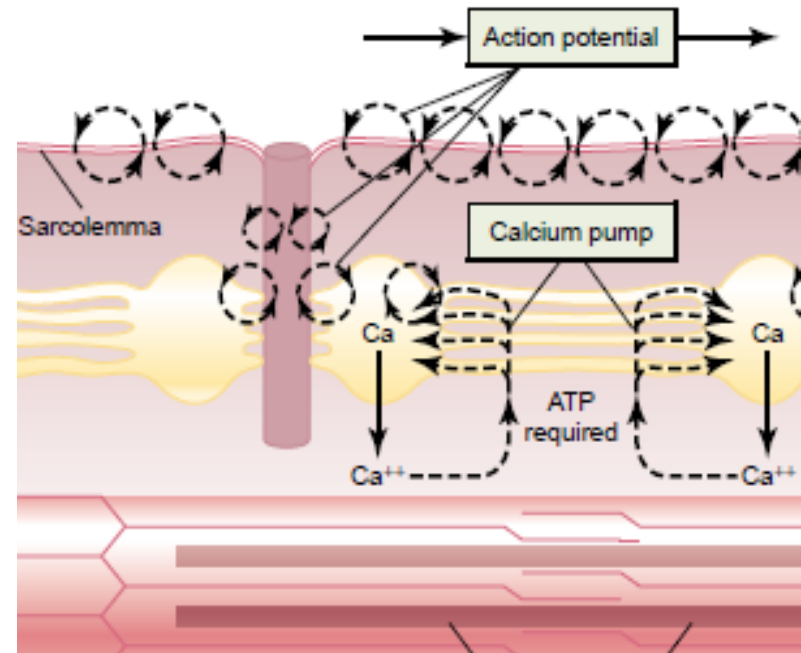
- The Ach acts on a local area of the muscle fiber membrane to open multiple acetylcholine-gated channels through protein molecules floating in the membrane.

- Opening of the acetylcholine-gated channels allows a large quantities of sodium ions to diffuse to the interior of the muscle fiber membrane, this initiates an action potential at the membrane.

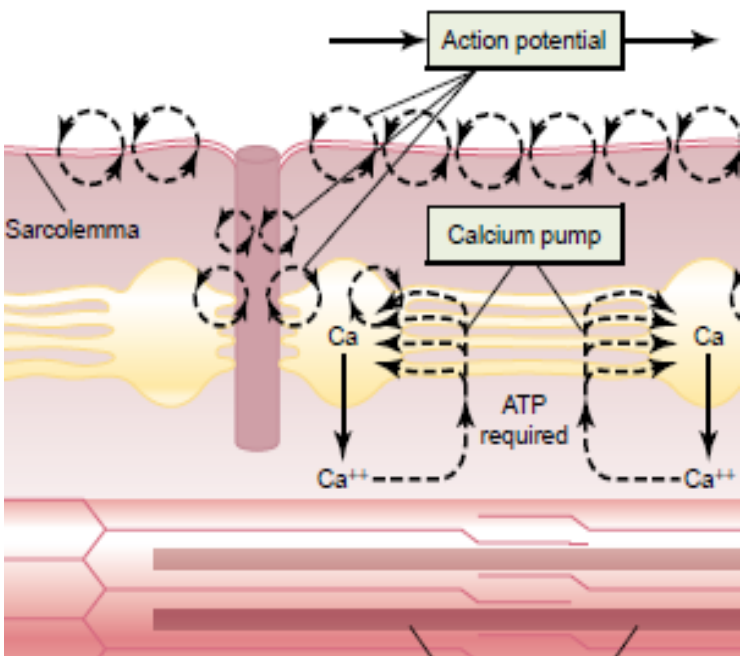


- The action potential travels along the muscle fiber membrane (and deeply) in the same way that action potentials travel along nerve fiber membranes.

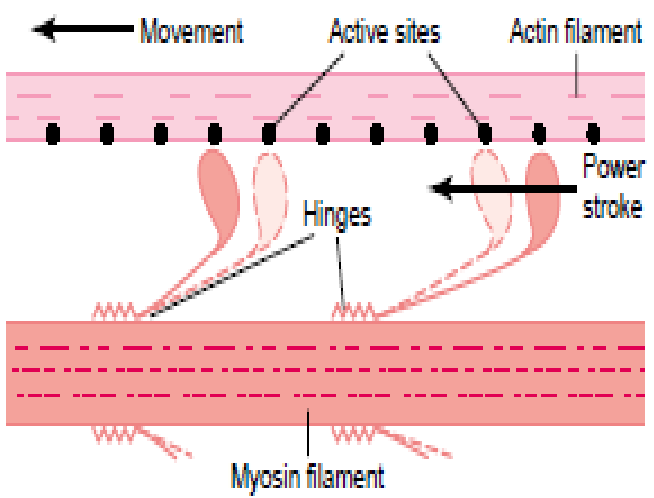
- The action potential depolarizes the muscle membrane, and much of the action potential electricity flows through the center of the muscle fiber; here it activates the sarcoplasmic reticulum to release large quantities of calcium ions that have been stored.



● The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide alongside each other(walking-along mechanism), which is the contractile process.



● After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by calcium membrane pump, this removal of calcium ions from the myofibrils causes the muscle contraction to cease.



## ❖ Fast versus slow muscle fibers.

- every muscle of the body is composed of a mixture of *fast* and *slow muscle fiber*.
- The muscles that react rapidly are composed mainly of “fast” fibers with only small numbers of the slow variety.
- Conversely, the muscles that respond slowly but with prolonged contraction are composed mainly of “slow” fibers.

## ❖ Skeletal Muscle Tone.

Even when muscles are at rest, a certain amount of tautness usually remains, called *muscle tone*.

This results from :

- A low rate of nerve impulses coming from the spinal cord.
- Signals transmitted from the brain to the appropriate spinal cord anterior motor neurons.
- Partly by signals that originate in *muscle spindles* located in the muscle itself.

# **CONTRACTION AND EXCITATION OF SMOOTH MUSCLE**

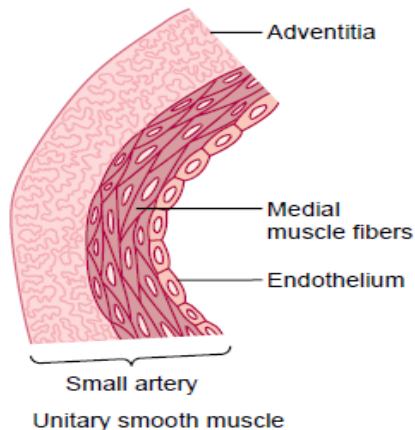
## ❖ Contraction of Smooth Muscle:

- The smooth muscle composed of small fibers, 1 to 5  $\mu\text{m}$  in diameter and only 20 to 500  $\mu\text{m}$  in length.

## ❖ Types of Smooth Muscle

smooth muscle can generally be divided into two major types :

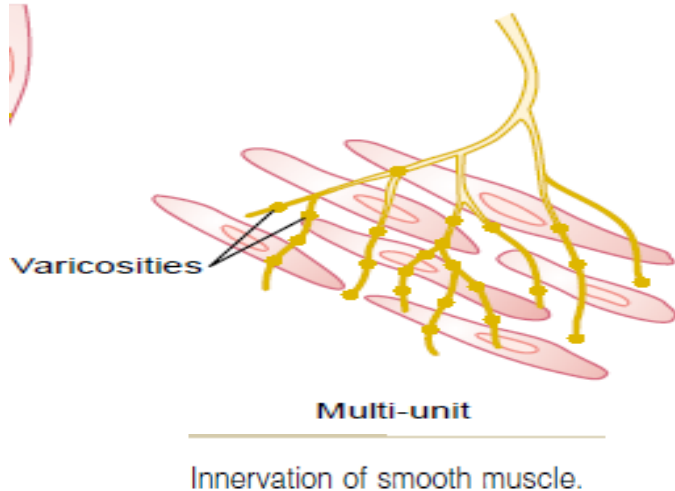
- (1) multi-unit smooth muscle .
- (2) unitary (or single-unit) smooth muscle.





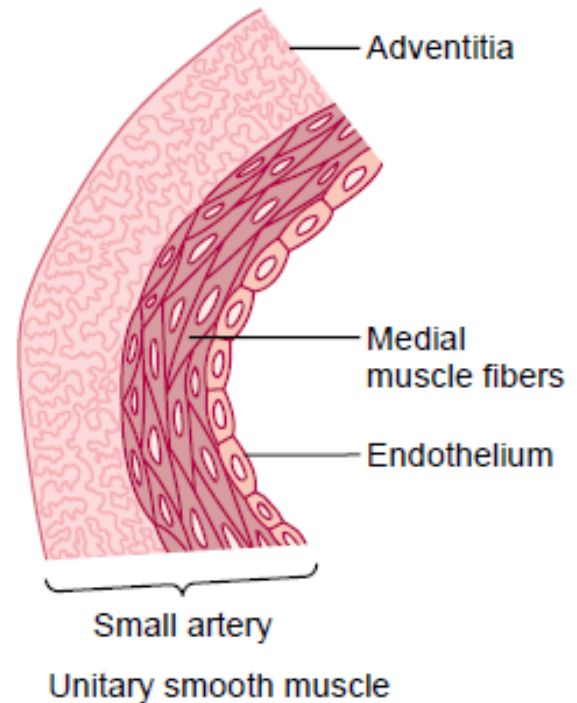
## ❖ Multi-Unit Smooth Muscle.

- It composed of discrete, separate s. m. f.
- it innervated by a single nerve ending.
- The outer surfaces of these fibers are covered by a thin layer of basement membrane.
- Each fiber can contract independently of the others, and their control is exerted mainly by nerve signals.
- Examples: ciliary muscle, iris muscle and the pilo erector muscles.



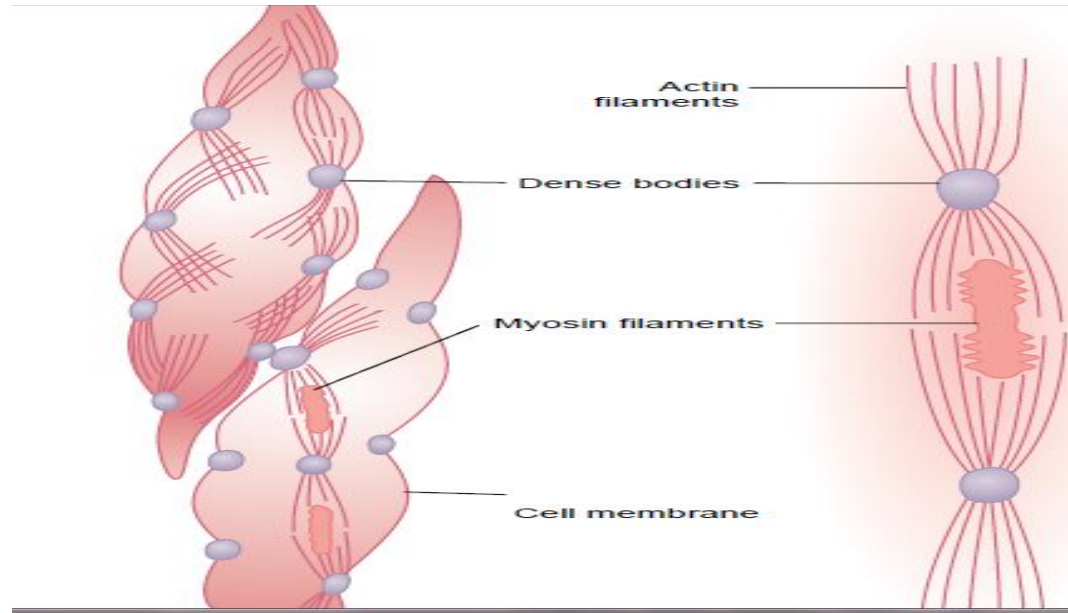
## ❖ Unitary Smooth Muscle.

- It means a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit.
- The fibers are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points (*gap junctions*) through which ions can flow freely from one muscle cell to the next so that action potentials or simple ion flow.



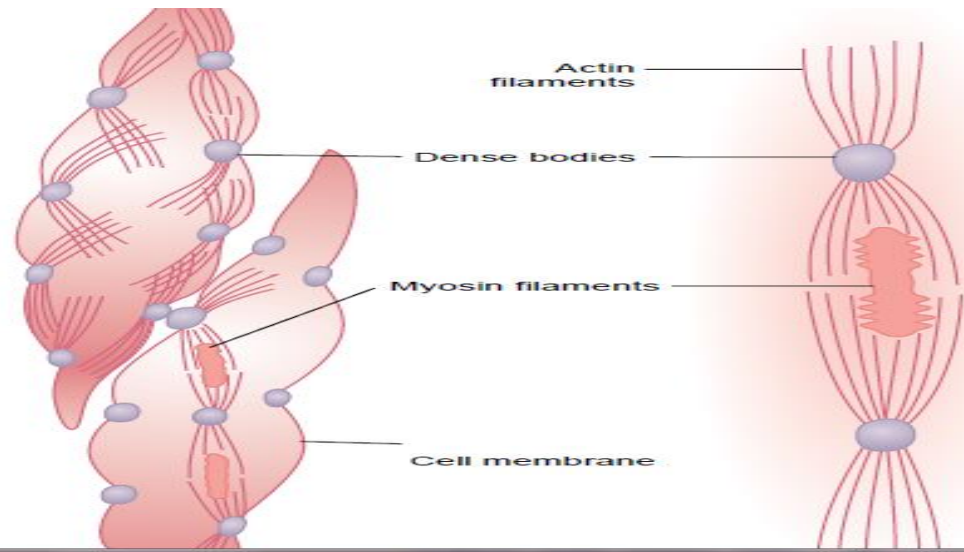
## ❖ Contractile Mechanism in Smooth Muscle:

- Smooth muscle contains both *actin* and *myosin filaments*, having chemical characteristics. They interact with each other.
- The contractile process is activated by:  
**calcium ions.**  
**adenosine triphosphate (ATP);** which is degraded to adenosine diphosphate (ADP) to provide the energy for contraction.

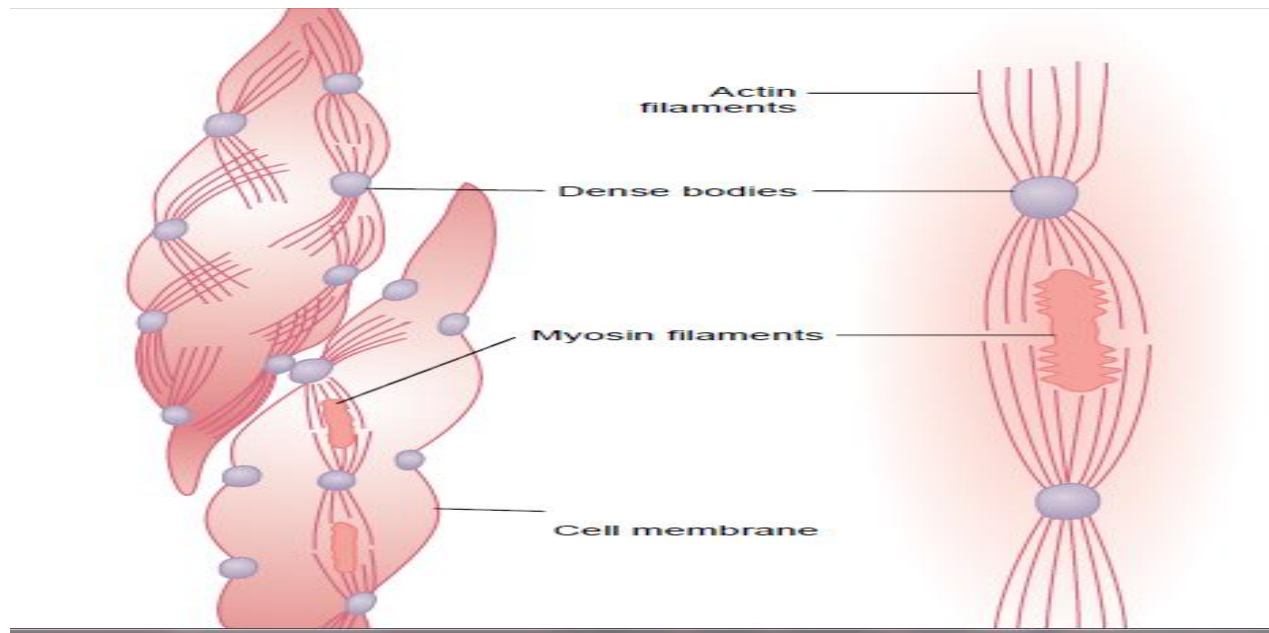


## ❖ Physical Basis for Smooth Muscle Contraction:

- Actin filaments attached to so-called dense bodies. Some of these bodies are attached to the cell membrane. Others are dispersed inside the cell.
- Interspersed among the actin filaments are myosin filaments. These have a diameter more than twice that of the actin filaments. Actin filaments are **5 to 10 times** as many as myosin filaments.



- Actin are radiating from two dense bodies; the ends of these filaments overlap a myosin filament located midway between the dense bodies.
- Most of the myosin filaments have “side polar” cross-bridges ,hinge in one direction and those on the other side hinge in the opposite direction. The value of this organization is that it allows smooth muscle cells to contract as much as **80 per cent** of their length.



## ❖ **Comparison of Smooth Muscle Contraction and Skeletal Muscle Contraction**

- 1) Slow Cycling of the Myosin Cross-Bridges.** The rapidity of cycling of the myosin cross-bridges in smooth muscle is much, much slower in smooth muscle than in skeletal muscle.
- 2) Energy Required to Sustain Smooth Muscle Contraction.**  
Only **1/10 to 1/300** as much energy is required to sustain the same tension of contraction in smooth muscle as in skeletal muscles.

### 3) Slowness of onset of contraction and relaxation of the total smooth muscle tissue.

- A typical smooth muscle tissue begins to contract **50-100 ms** after it is excited, reaches full contraction about **0.5 second** later, and then declines in contractile force in another **1 to 2 seconds**.
- This is about **30 times** as long as a single contraction of an average skeletal muscle fiber. It is due to slowness of attachment and detachment of the **cross-bridges** with the actin filaments; and slow response to calcium ions.



## 4) Force of Muscle Contraction.

- ✓ The maximum force of contraction of smooth muscle is often greater than that of skeletal muscle.
  - 4 to 6 kg/cm<sup>2</sup> for smooth muscle.
  - 3 to 4 kg/cm<sup>2</sup> for skeletal muscle.
- ✓ This great force of smooth muscle contraction results from the prolonged period of attachment of the myosin cross bridges to the actin filaments.

# ❖ Nervous and Hormonal Control of Smooth Muscle Contraction:

- Smooth muscle can be stimulated to contract by multiple types of signals:

1. Nervous signals.
2. Hormonal stimulation.
3. Stretch of the muscle.
4. Several other ways.

- The principal reason for the difference is that the smooth muscle membrane contains many types of **receptor** proteins that can **initiate** the contractile process. Still other receptor proteins **inhibit** smooth muscle contraction, which is another difference from skeletal muscle.

## ❖ Neuromuscular Junctions of Smooth Muscle:

- The *autonomic nerve fibers* that innervate smooth muscle generally branch diffusely on top of a sheet of muscle fibers.
- These fibers do not make direct contact with the smooth muscle fiber cell membranes but instead form so-called *diffuse junctions*.
- They secrete their transmitter substance into the matrix coating of the smooth muscle often a few **nanometers** to a few **micrometers** away from the muscle cells.

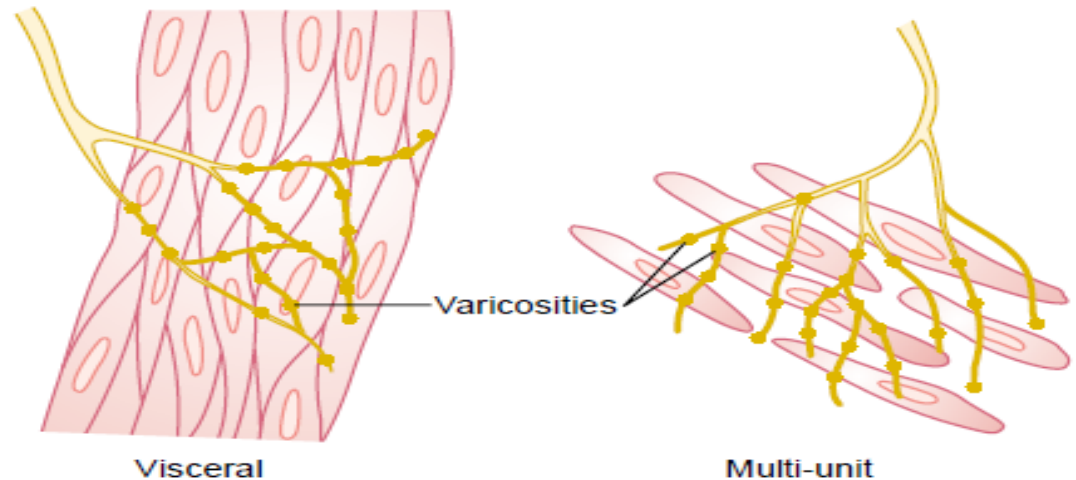
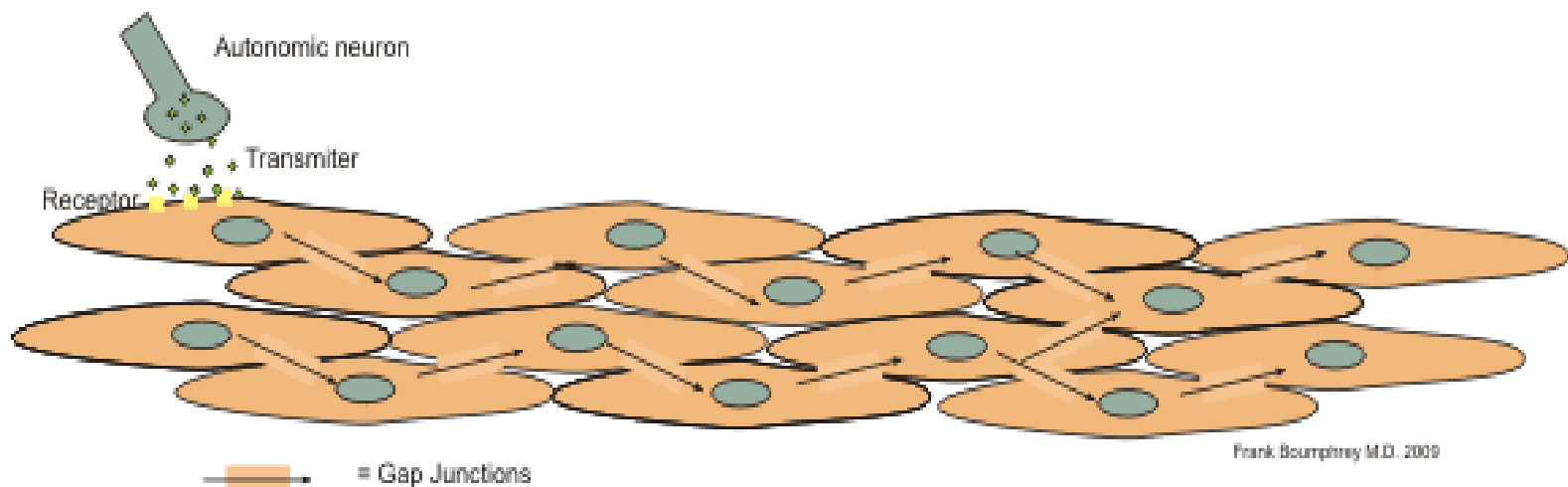


Figure 8-3

Innervation of smooth muscle.

- The transmitter substance then diffuses to the cells.
- The nerve fibers often innervate only the outer layer, and muscle excitation travels from this outer layer to the inner layers by action potential or by neurotransmitter.

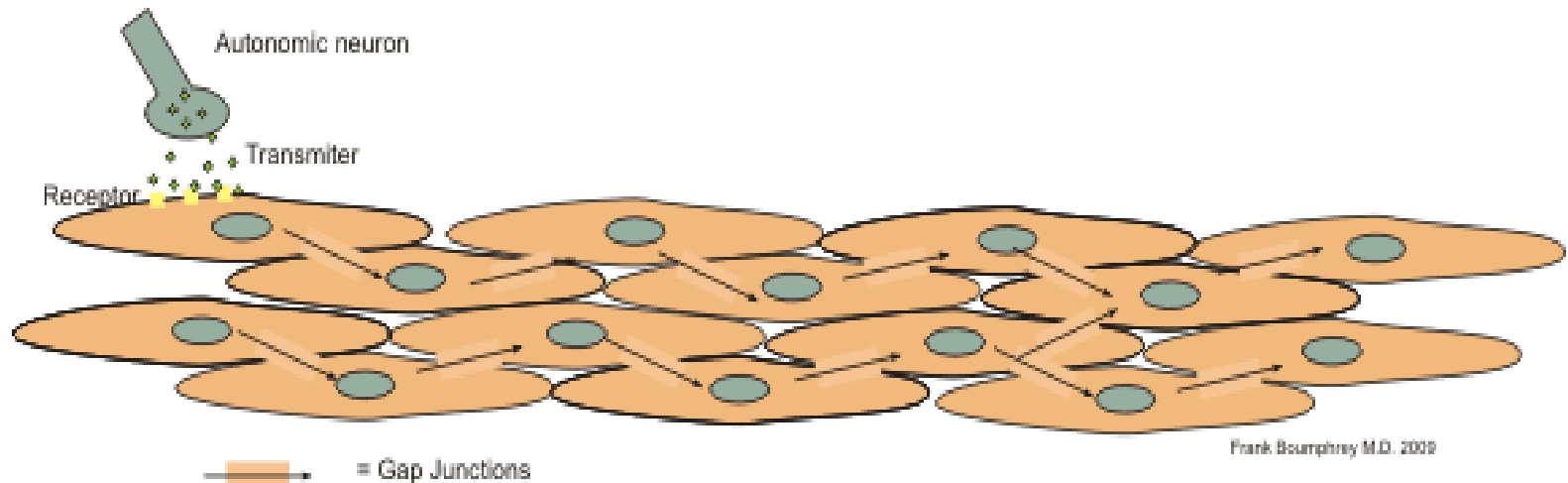


Frank Bourque M.D. 2009

Propagation of Action Potentials through Gap Junctions

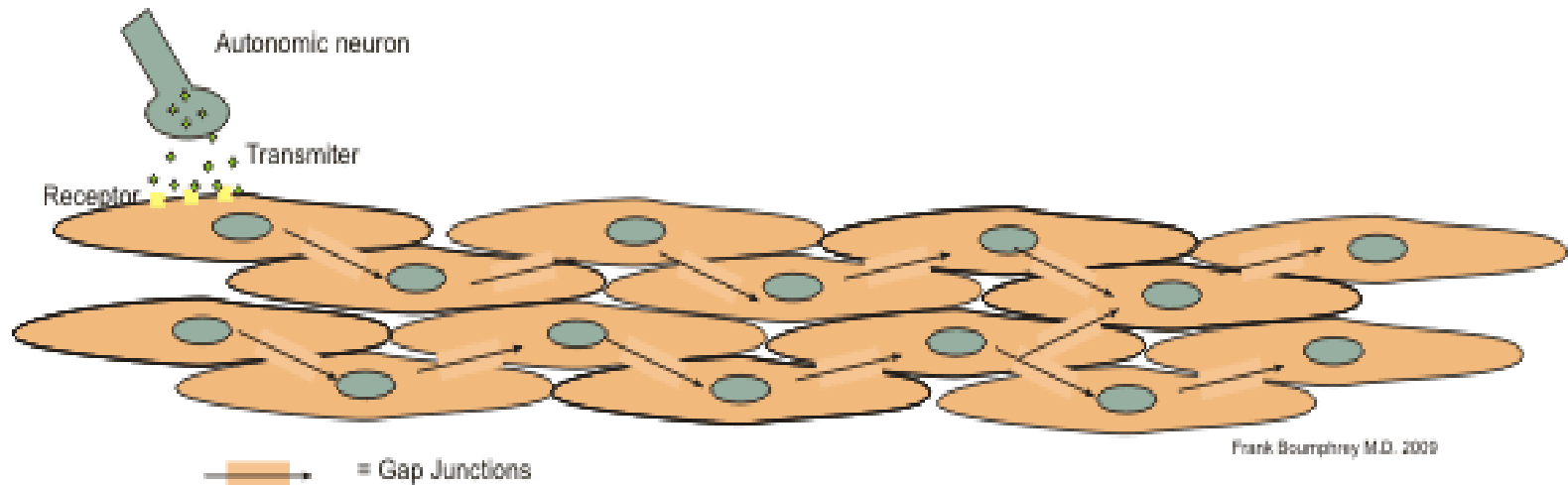
## ❖ Excitatory and Inhibitory Transmitter Substances Secreted at the Smooth Muscle Neuromuscular Junction.

- The most important transmitter substances secreted by the autonomic nerves innervating smooth muscle are **acetylcholine** and **nor epinephrine**, but they are never secreted by the same nerve fibers.
- Acetylcholine is an excitatory transmitter substance for smooth muscle fibers in some organs but an inhibitory transmitter for smooth muscle in other organs.
- When acetylcholine excites a muscle fiber, nor epinephrine ordinarily inhibits it.
- Conversely, when acetylcholine inhibits a fiber, norepinephrine usually excites it.



Propagation of Action Potentials through Gap Junctions

- acetylcholine and nor epinephrine excite or inhibit smooth muscle by first binding with a *receptor protein* on the surface of the muscle cell membrane.
- Some of the receptor proteins are *excitatory receptors*, others are *inhibitory receptors*.
- Thus, the type of **receptor** determines whether the smooth muscle is inhibited or excited and also determines which of the two transmitters, acetylcholine or norepinephrine, is effective in causing the excitation or inhibition.



Frank Bourghney M.D. 2009

Propagation of Action Potentials through Gap Junctions

## ❖ Membrane Potentials and Action Potentials in Smooth Muscle:

### □ Membrane Potentials in Smooth Muscle.

- In the normal resting state, the intracellular potential is usually about **(-50 to -60 mv.)**, which is about **30 mv.** less negative than in skeletal muscle.

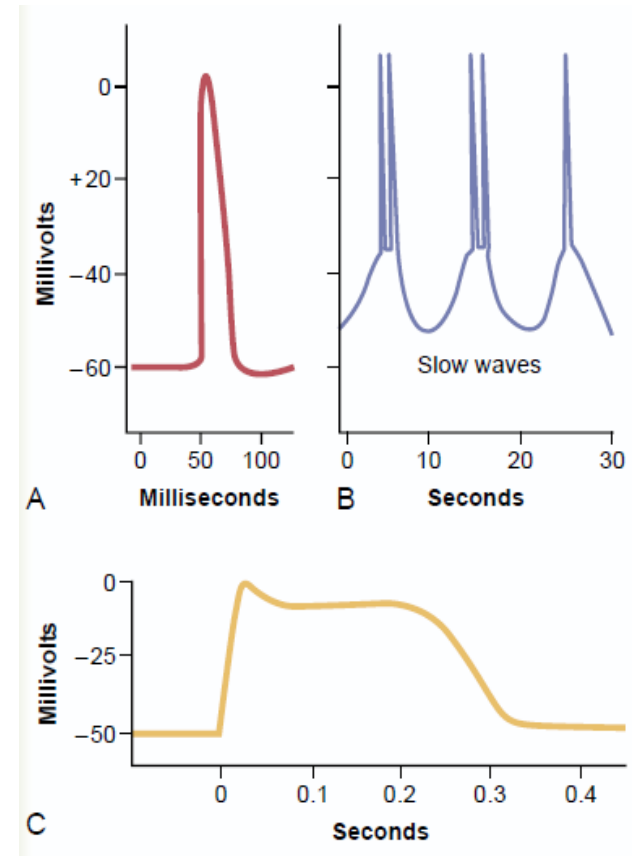


# ❖ Action Potentials in Unitary Smooth Muscle.

- Action potentials occur in unitary smooth muscle (visceral muscle) in one of two forms:

(1) spike potentials.

(2) action potentials with plateaus.

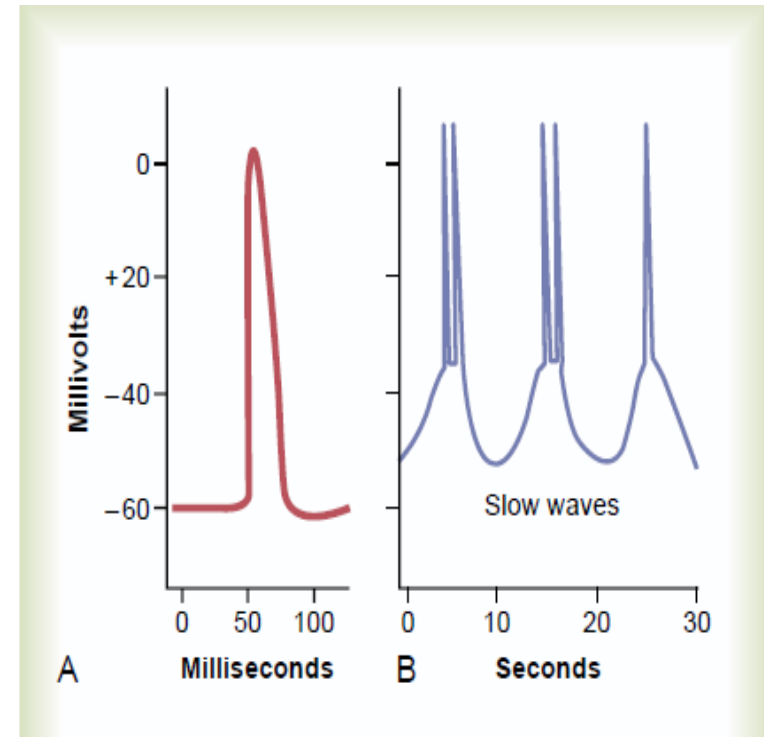


# □ Spike Potentials.

➤ The duration is 10 - 50 ms .

➤ It elicited by:

- 1) Electrical stimulation.
- 2) Hormones stimulation.
- 3) Transmitter substances from nerve fibers.
- 4) Stretch stimulation.

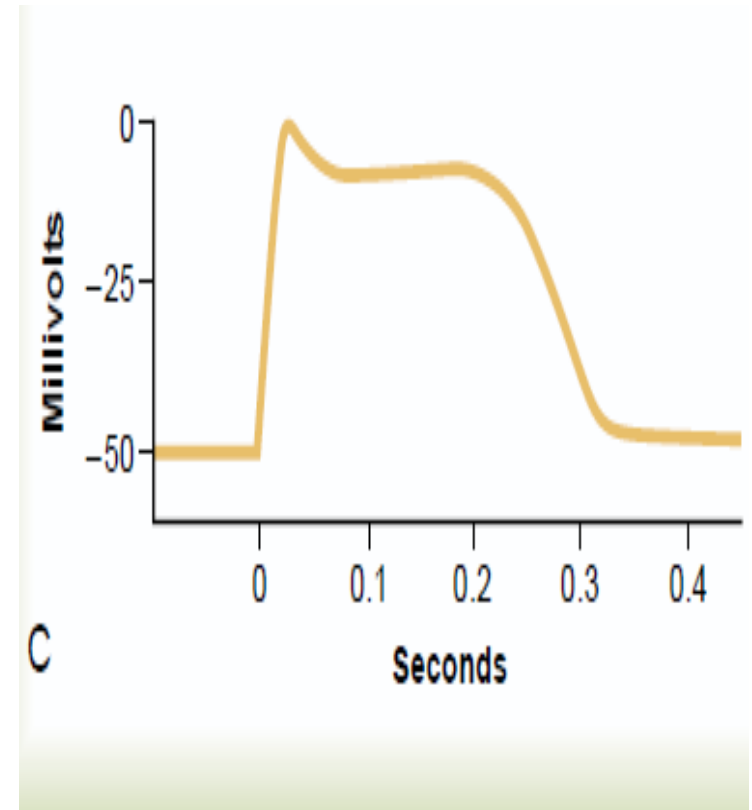


***A, Typical smooth muscle action potential (spike potential) elicited by an external stimulus.***

***B, Repetitive spike potentials, elicited by slow rhythmic electrical waves that occur spontaneously in the smooth muscle of the intestinal wall..***

## ❖ Action Potentials with Plateaus:

- The repolarization is delayed for several hundred to as much as 1000 milliseconds (1 second).
- The importance of the plateau is that it can account for the prolonged contraction that occurs in some types of smooth muscle, such as the **ureter**, **uterus**, **vascular smooth muscle**, **cardiac muscle fibers**.



***C, Action potential with a plateau, recorded from a smooth muscle fiber of the uterus.***

## ❖ Importance of Calcium Channels in Generating the Smooth Muscle Action Potential.

- The smooth muscle cell membrane has far more voltage-gated calcium channels .
- Flow of calcium ions to the interior of the fiber is mainly responsible for the action potential.

- The calcium channels open many times more slowly than do sodium channels, and they also remain open much longer.
- Prolonged plateau action potentials of some smooth muscle fibers.
- The calcium ions act directly on the smooth muscle contractile mechanism to cause contraction. Thus, the calcium performs two tasks at once.

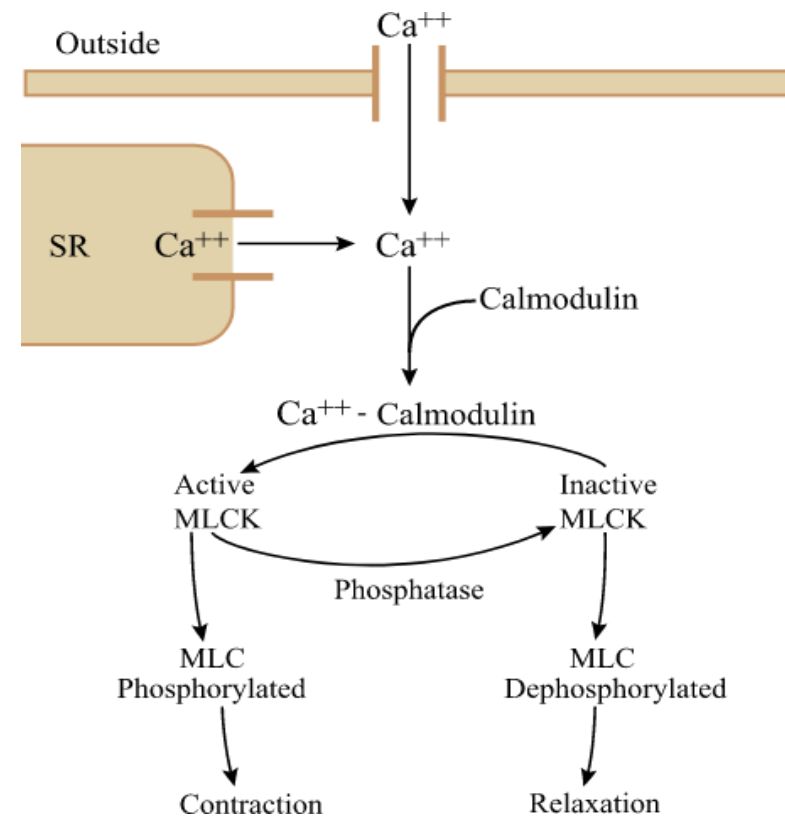
# □ Source of Calcium Ions that cause s. m. contraction.

(1) Through the Cell Membrane .

(2) From the Sarcoplasmic Reticulum.

■ Although the contractile process in smooth muscle, is activated by calcium ions, the source of the calcium ions differs; the sarcoplasmic reticulum, provides less  $Ca^{++}$  needed for contraction of smooth muscle.

■ Almost all the calcium ions that cause contraction enter the muscle cell from the extracellular fluid at the time of the action potential or other stimulus.



## ❖ Effect on Smooth Muscle Contraction Caused by Changing of Extracellular Calcium Ion Concentration.

- Although changing the extracellular fluid calcium ion concentration from normal has little effect on the force of contraction of skeletal muscle, this is not true for most smooth muscle.
- When the extracellular fluid calcium ion concentration falls to about  $\frac{1}{3}$  to  $\frac{1}{10}$  normal, smooth muscle contraction usually ceases.
- Therefore, the force of contraction of smooth muscle usually is highly dependent on extracellular fluid calcium ion concentration.



# ❖ A Calcium Pump Is Required to Cause Smooth Muscle Relaxation.

- The calcium ions must be removed from the intracellular fluids.
- pumps calcium ions out of the smooth muscle fiber back into the extracellular fluid, or into a sarcoplasmic reticulum.
- This pump is slow-acting .
- Therefore, a single smooth muscle contraction often lasts for seconds rather than hundredths to tenths of a second, as occurs for skeletal muscle.

# HEART MUSCLE

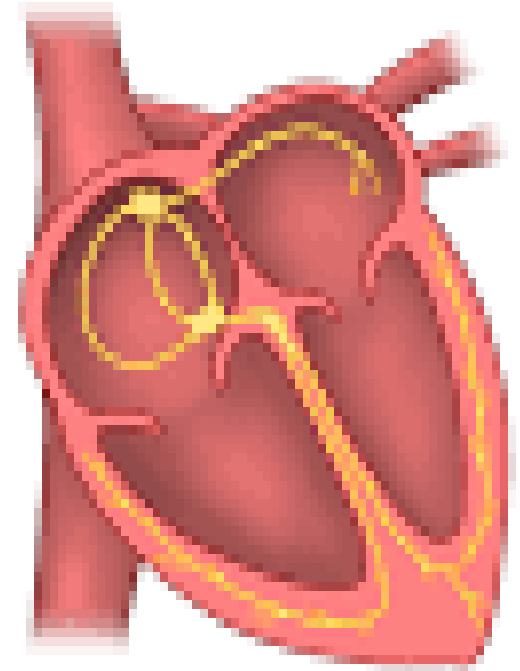
# ❖ Physiology of Cardiac Muscle

The heart is composed of three major types of cardiac muscles:

- *Atrial muscle.*
- *Ventricular muscle.*
- *Specialized excitatory and conductive muscle fibers.*

The atrial and ventricular muscle are contract as the skeletal muscle, except that the duration of contraction is much longer.

- The specialized excitatory and conductive fibers contract only feebly because they contain few contractile fibrils.



# ❖ Physiologic Anatomy of Cardiac Muscle

- Cardiac muscle fibers arranged in a latticework, with the fibers dividing, recombining, and then spreading again.
- Cardiac muscle is *striated*.
- Cardiac muscle has typical myofibrils that contain *actin* and *myosin filaments*; these filaments lie side by side and slide along one another during contraction.

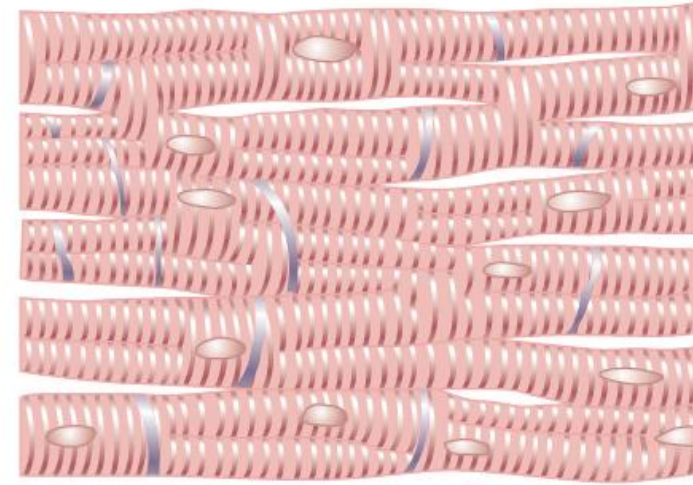


Figure 9-2

"Syncytial," interconnecting nature of cardiac muscle fibers.

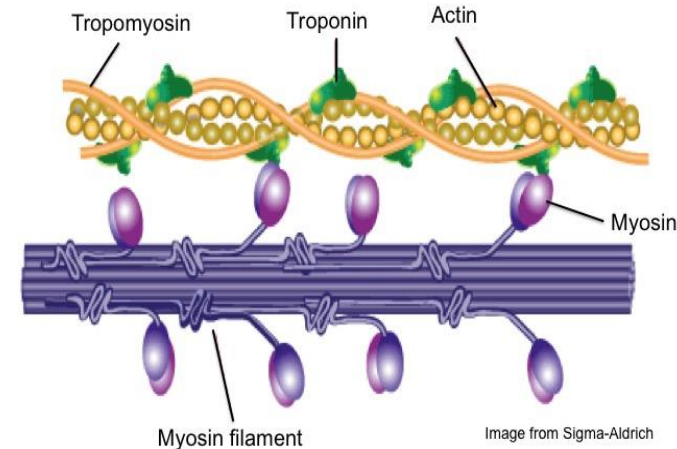
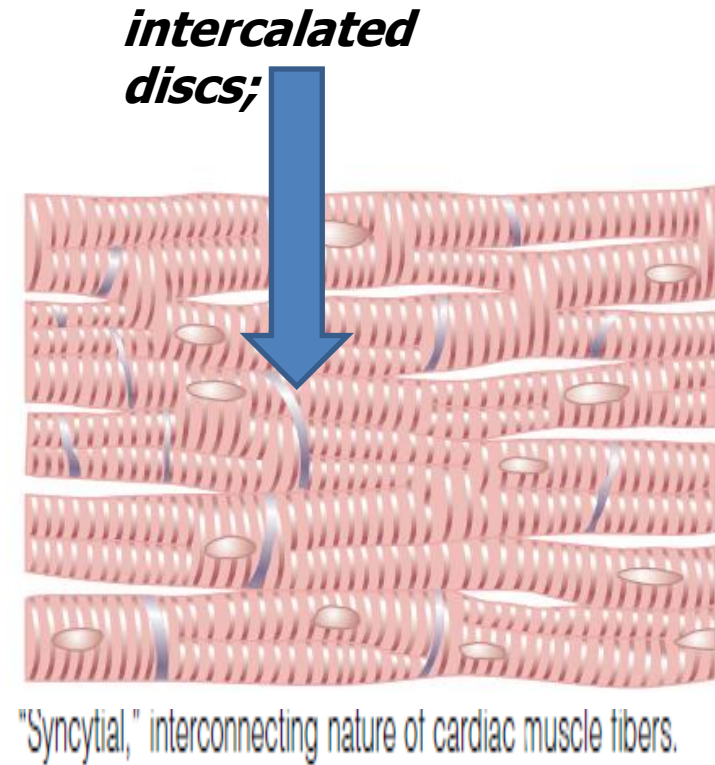


Image from Sigma-Aldrich

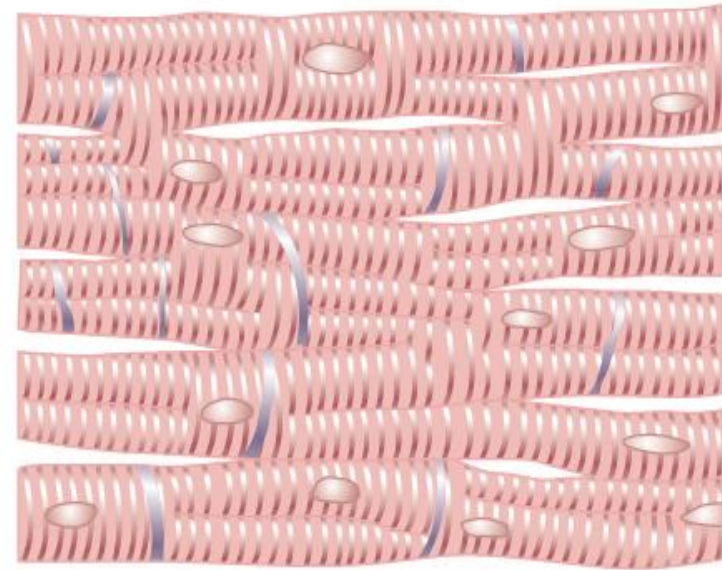
## ❖ Cardiac Muscle as a Syncytium.

- The dark areas crossing the cardiac muscle fibers are called *intercalated discs*; they are actually cell membranes that separate individual cardiac muscle cells from one another.
- Cardiac muscle fibers are made up of many individual cells connected in series and in parallel with one another.



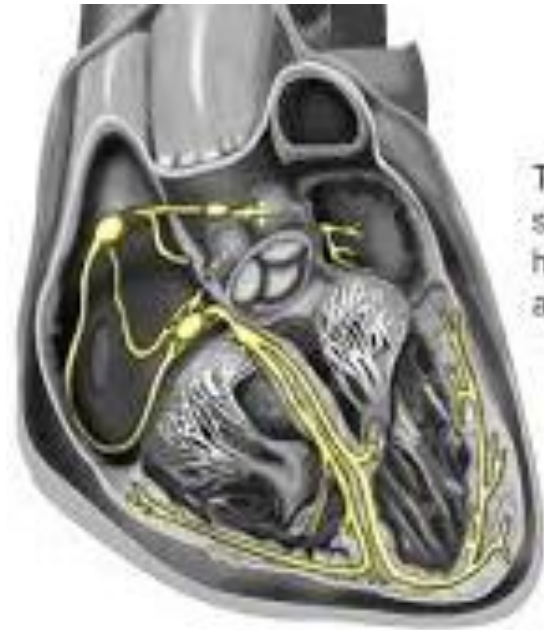
➤ At each intercalated disc the cell membranes fuse with one another, so it form permeable “communicating” junctions (gap junctions) that allow diffusion of ions.

➤ So action potentials travel easily from one cardiac muscle cell to the next, past the intercalated discs.



"Syncytial," interconnecting nature of cardiac muscle fibers.

- The heart actually composed of two syncytiums:
- *Atrial syncytium*.
- *Ventricular syncytium*.
- The atria are separated from the ventricles by fibrous tissue.
- They are conducted only by way of a specialized conductive system called the *A-V bundle*.

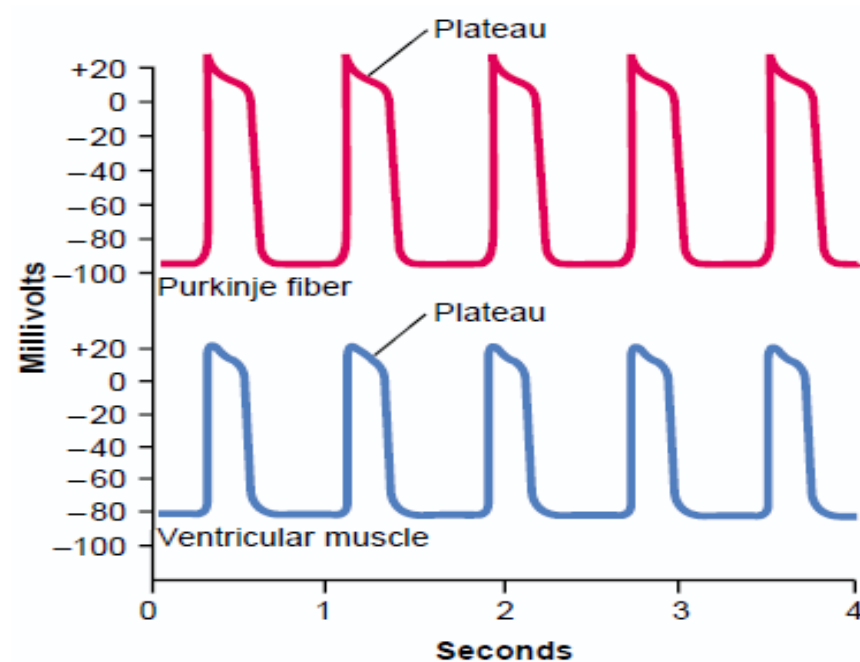


The cells send signals to the heart and cause a contraction.



## ❖ Action potentials in cardiac muscle

- The intracellular potential rises from a very negative value **-85 mv.** to about **+20 mv.** during each beat.
- After the initial *spike*, the membrane remains depolarized for about **0.2 second**, exhibiting a *plateau*, followed by abrupt repolarization.
- This plateau causes ventricular contraction to last as much as **15 times** as long in cardiac muscle as in skeletal muscle.



## ❖ What Causes the Long Action Potential and the Plateau?

- The action potential is caused by opening of two types of channels:

(1) Fast sodium channels.

(2) Slow calcium channels (calcium-sodium channels). they are slower to open and remain open for **several tenths of a second** and this maintains a prolonged period of depolarization, causing the plateau in the action potential.

- Calcium ions that enter during this plateau phase activate the muscle contractile process.

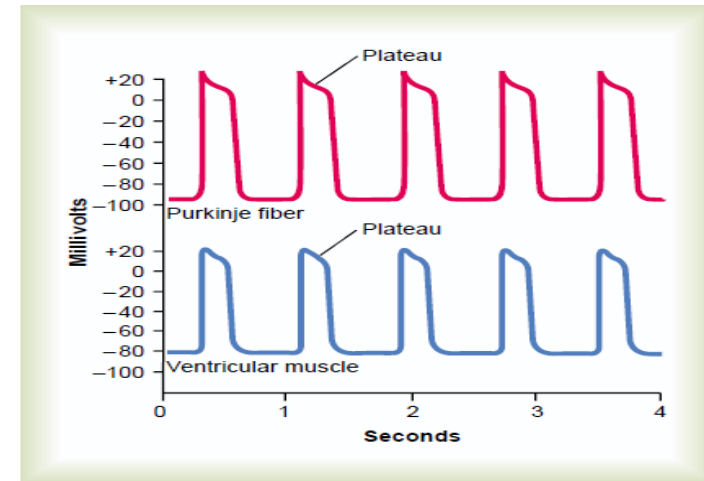


Figure 9-3

Rhythmic action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

- Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions *decreases* about **fivefold**, an effect that **does not occur in skeletal muscle**.
- This decreased potassium permeability may result from the excess calcium influx through the calcium channels; the decreased potassium permeability greatly decreases the out flux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level.

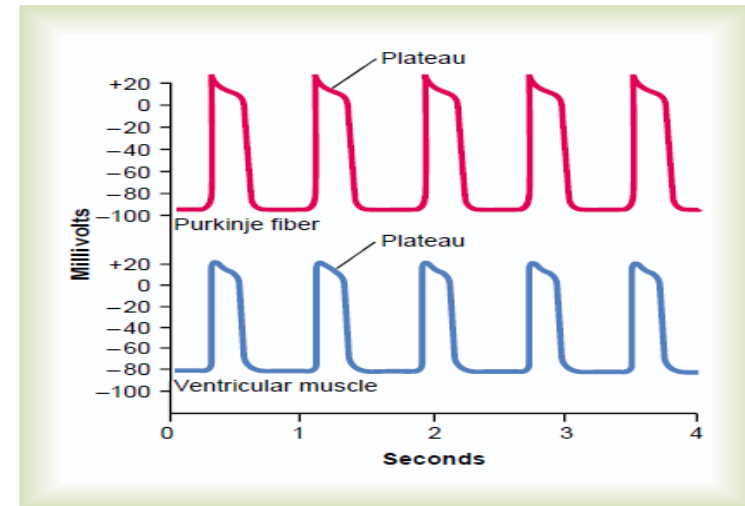
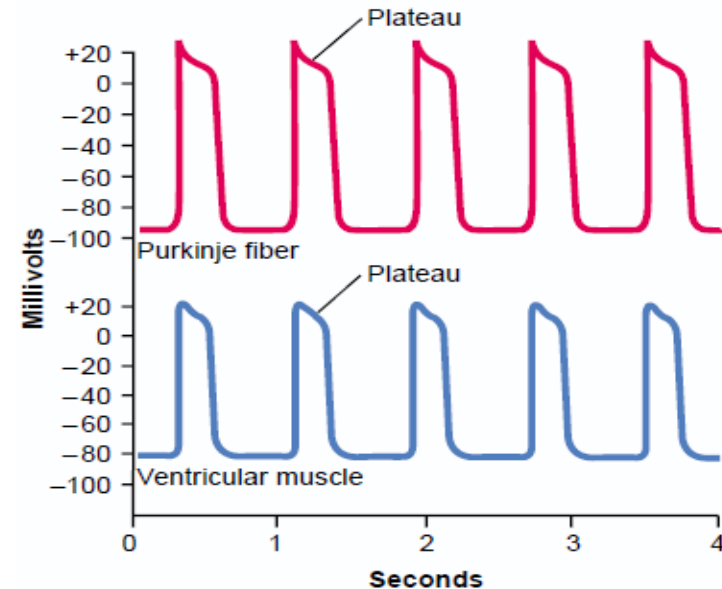


Figure 9-3

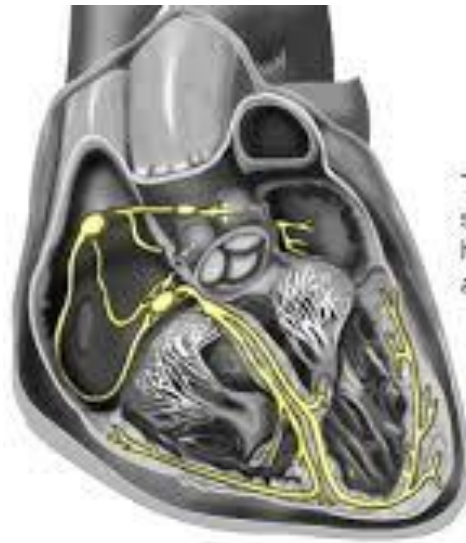
Rhythmical action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

□ When the slow calcium-sodium channels do close at the end of **0.2 to 0.3 second** and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions also increases rapidly; this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.



## ❖ Velocity of signal conduction in cardiac muscle.

- The velocity of conduction of the excitatory action potential signal along both *atrial and ventricular muscle fibers* is about **0.3 to 0.5 m/sec**, or about **1/250** the velocity in very large nerve fibers and about **1/10** the velocity in skeletal muscle fibers.
- The velocity of conduction in the specialized heart conductive system—in the *Purkinje fibers*—is as great as **4 m/sec** in most parts of the system, which allows reasonably rapid conduction of the excitatory signal to the different parts of the heart.

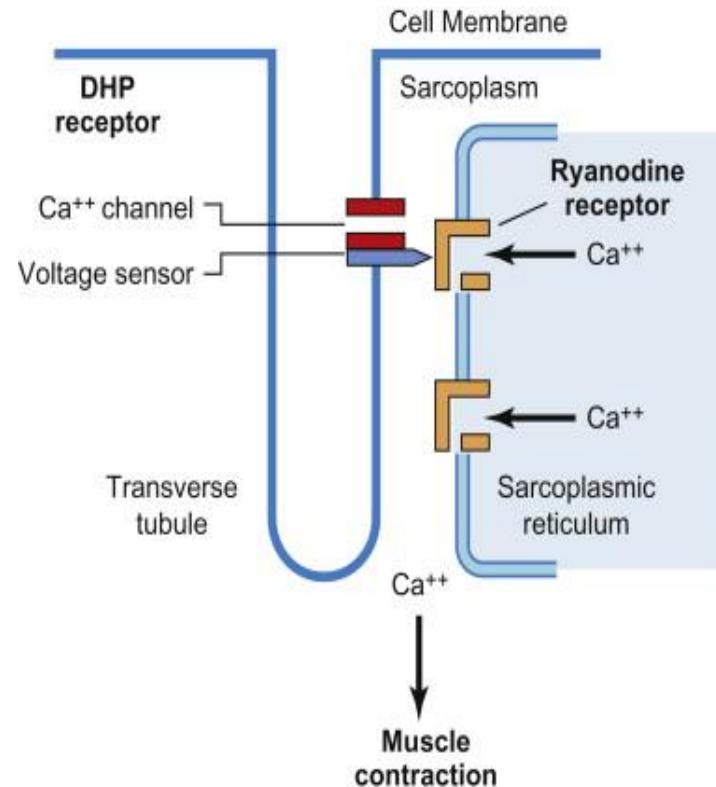


The cells send signals to the heart and cause a contraction.

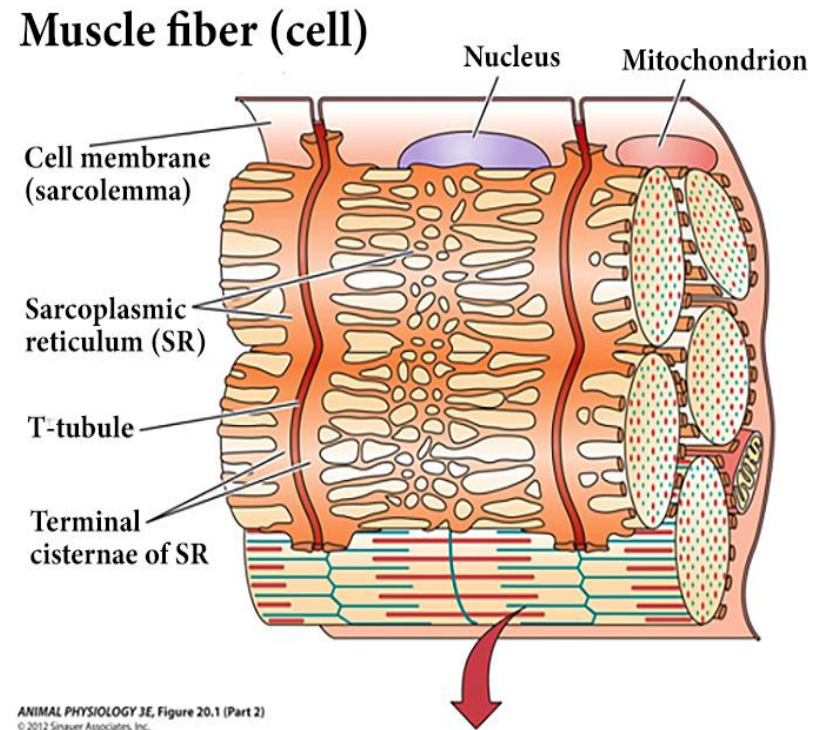
## ❖ Excitation-Contraction Coupling— Function of Calcium Ions and the *Transverse Tubules*.

➤ The term “excitation-contraction coupling” refers to the mechanism by which the action potential causes the myofibrils of muscle to contract.

➤ when an action potential passes over the cardiac muscle membrane, the action potential spreads to the interior of the cardiac muscle fiber along the membranes of the transverse (T) tubules.



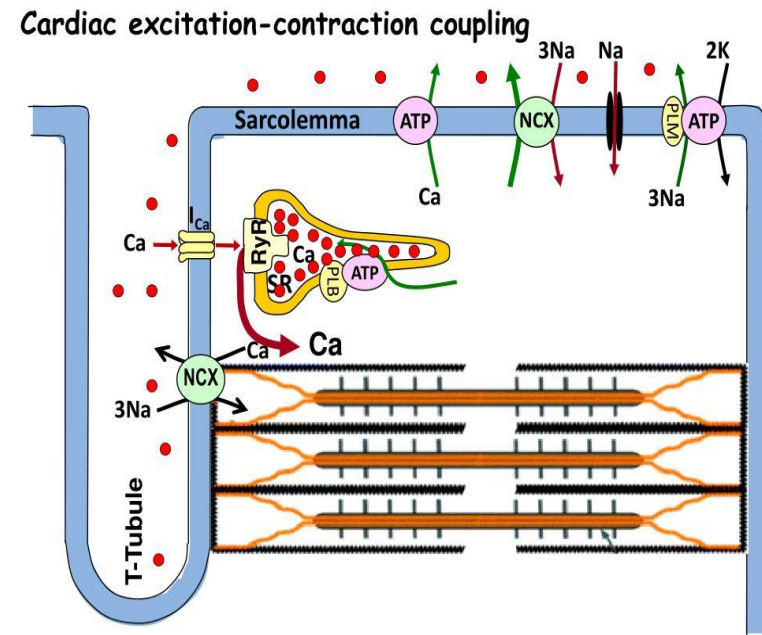
- The **T tubule** action potentials in turn act on the sarcoplasmic tubules to cause release of calcium ions into the muscle sarcoplasm from the sarcoplasmic reticulum.
- These calcium ions promote sliding of the actin and myosin filaments along one another; causing muscle contraction.





➤ Also a large quantity of extra calcium ions also diffuses into the sarcoplasm from the T tubules themselves( extra cellular calicum) at the time of the action potential.

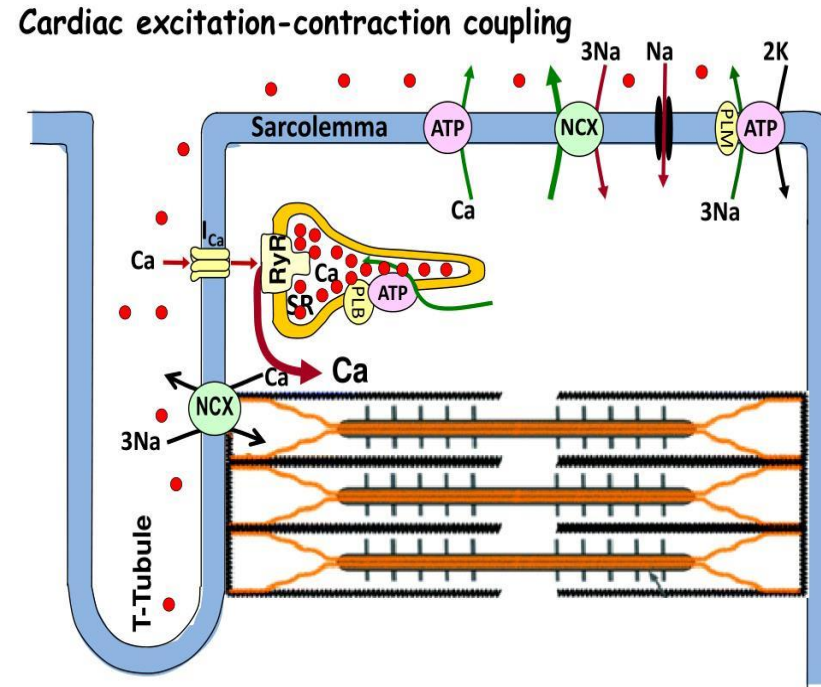
➤ Without this extra calcium from the T tubules, the strength of cardiac muscle contraction would be reduced, because the sarcoplasmic reticulum of cardiac muscle does not store enough calcium to provide full contraction (like sk.m.).



➤ The T tubules of cardiac muscle have a diameter 5 times as great as that of the skeletal muscle tubules (which means a volume 25 times as great).

➤ Also, inside the T tubules is a large quantity of **muco-polysaccharides** that are electro-negatively charged and bind an abundant store of calcium ions, keeping these always available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

➤ The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids.



- The openings of the T tubules pass directly through the cardiac muscle cell membrane into the extracellular spaces surrounding the cells, allowing the same extracellular fluid that is in the cardiac muscle interstitium to percolate through the T tubules as well.
- the quantity of calcium ions in the T tubule depends on the extracellular fluid calcium ion concentration.

- At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off.
- The calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into both the sarcoplasmic reticulum and the T tubule–extracellular fluid space.
- As a result, the contraction ceases until a new action potential comes along.

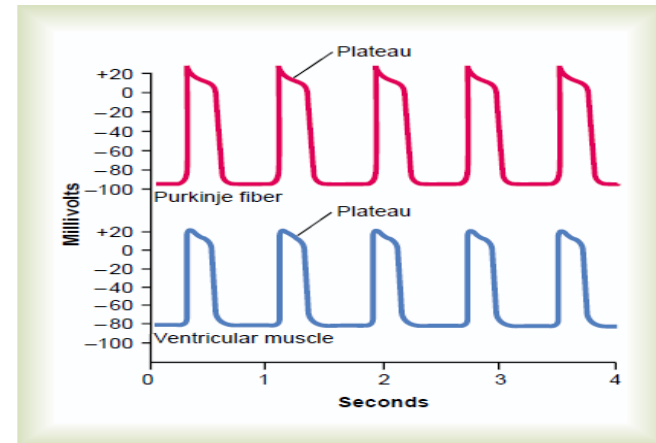


Figure 9-3

Rhythmic action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

