Al-Noor University College.

Medical laboratories technics department.

Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Blood and Haemopoietic tissue.

Dr. Ali Ashgar Abd

Blood and Bone Marrow(Haemopoietic tissue)

Blood is a specialized connective tissue consisting of cells and fluid extracellular material called **plasma**. Propelled mainly by rhythmic contractions of the heart, about 5 L of blood in an average adult moves unidirectionally within the closed circulatory system.

The so-called formed elements circulating in the plasma are **erythrocytes** (red blood cells), **leukocytes** (white blood cells [WBCs]), and **platelets**. When blood leaves the circulatory system, either in a test tube or in the extracellular matrix (ECM) surrounding blood vessels, plasma proteins react with one another to produce a clot, which includes formed elements and a pale yellow liquid called **serum**.

Serum contains growth factors and other proteins released from platelets during clot formation, which confer biological properties very different from those of plasma.

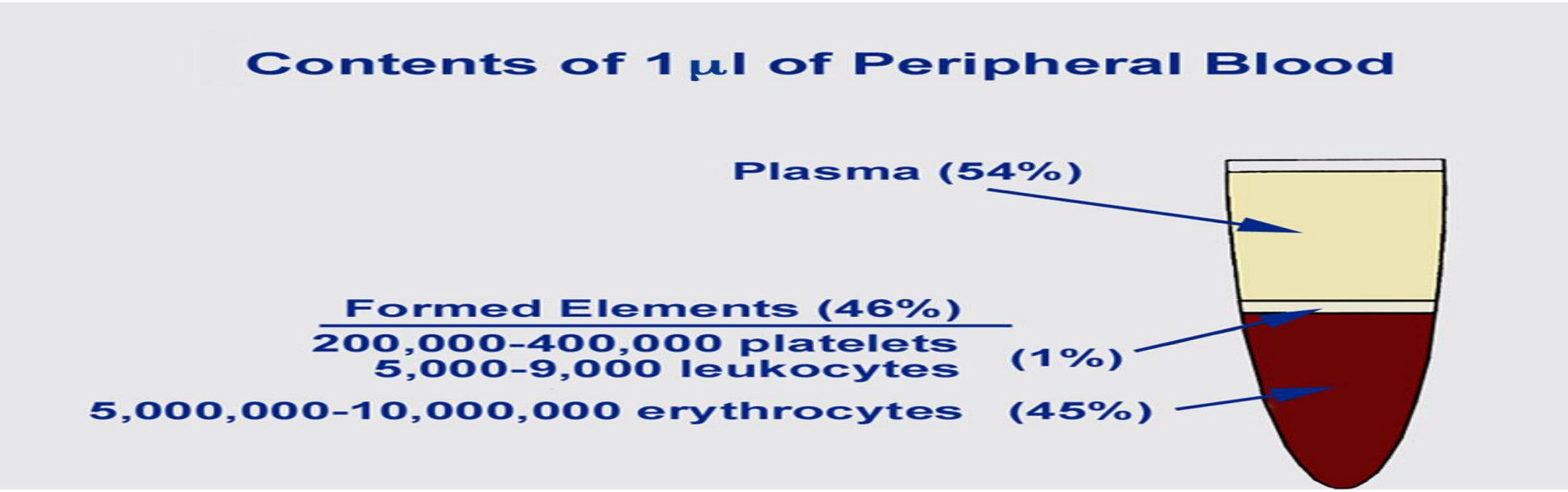
Functions of the Blood

1.To transport nutrients,oxygen,wastes and carbon dioxide to and from the tissue.

2.To convey hormones ,cytokines,chemokines and other soluble regulatory molecules.

3. To transport leukocytes and antibodies through the tissues.

4.To maintain homeostasis



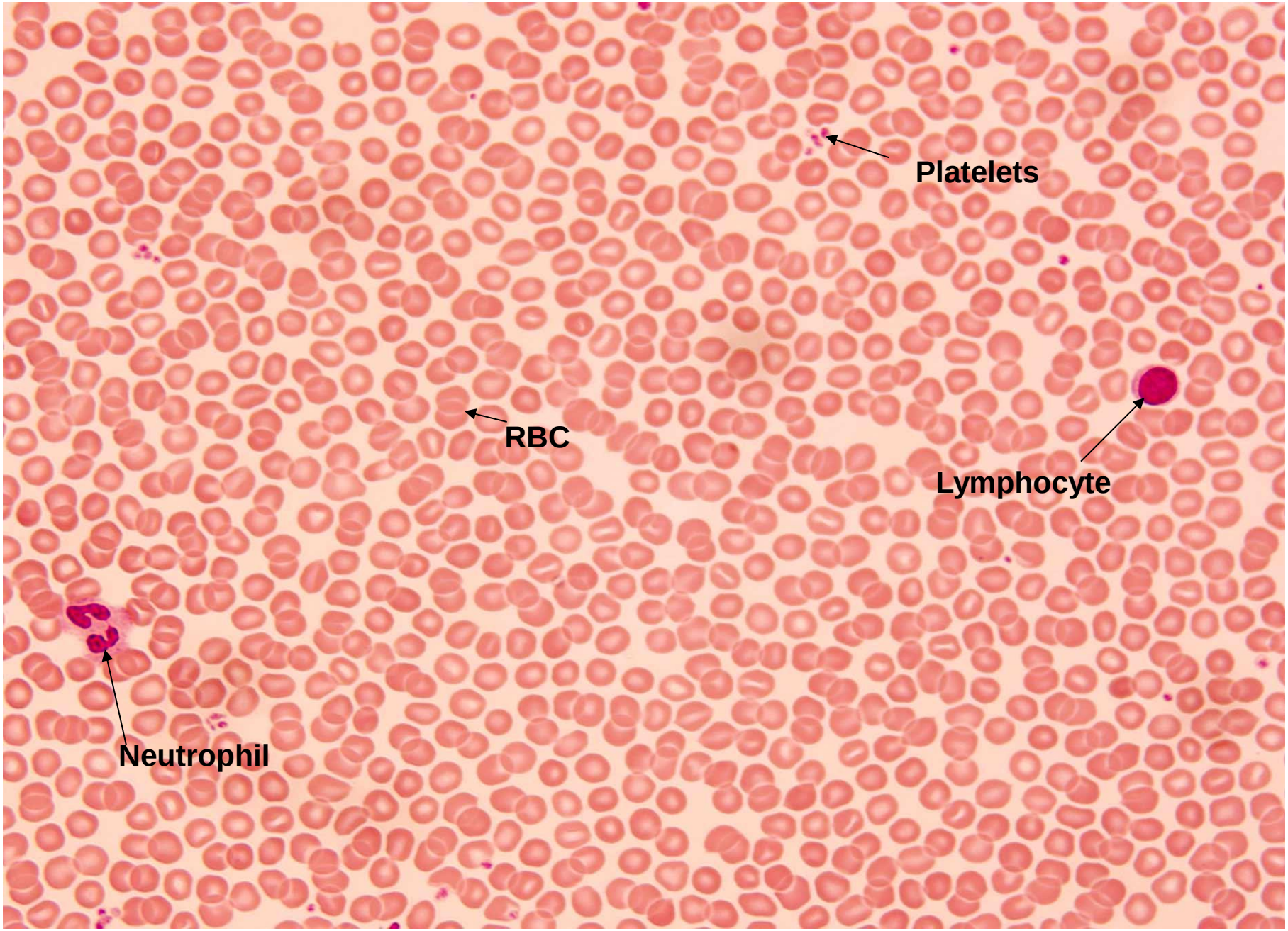
Major Plasma Proteins

Protein	Function
Albumin	**Maintain colloid osmotic pressure; transport insoluble metabolites**
Globulins	
α and β	**Transport metal ions, protein-bound lipids, lipid-soluble vitamins**
γ	**Antibodies for host defense**
Complement proteins	**Destruction of microorganisms**
Clotting factors	**Formation of blood clots**
Plasma lipoproteins	**Transport of triglycerides and cholesterol to/from liver**

Cells of the blood

- **Erythrocytes** (red blood cells, RBC)
- **Platelets** (thrombocytes)
- **Leukocytes** (white blood cells, WBC)
  - **Granulocytes** (with specific granules)
    - **Neutrophil (~60% of WBC)**
    - **Eosinophil (~4% of WBC)**
    - **Basophil (<1% of WBC)**
  - **Agranulocytes** (without specific granules)
    - **Lymphocyte (B-cell, T-cell) (~27% of WBC)**
    - **Monocyte (~8% of WBC)**

Human blood smear, with RBCs, WBCs and platelets



Erythrocyte (red blood cell, RBC)

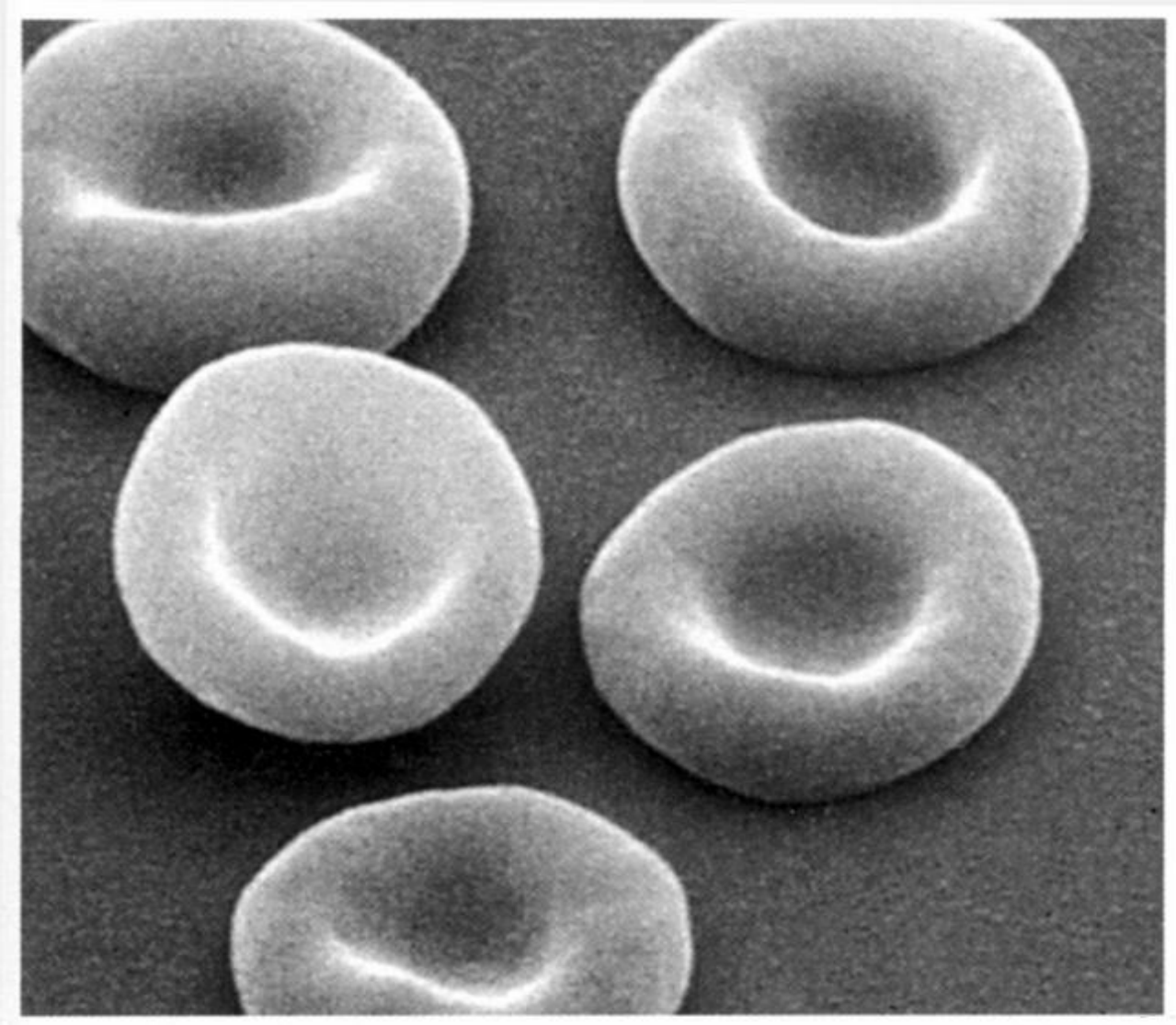
1. **Life span in blood:** **About 120 days.**
2. **Size and shape:**
   - **biconcave disk, 8 μm diameter, 2μm at thickest point, 1 μm at thinnest**
   - **shape maintained by a cytoskeletal complex inside the plasma membrane (involving spectrin, actin and other components)**
   - **flexible: RBC's normally bend to pass through small capillaries**
3. **LM appearance in smear:** **Pink circle with light center (center is thinner because of the biconcave shape). No nucleus.**

4. TEM appearance: **Solid dark gray cytoplasm, because of highly concentrated hemoglobin.**

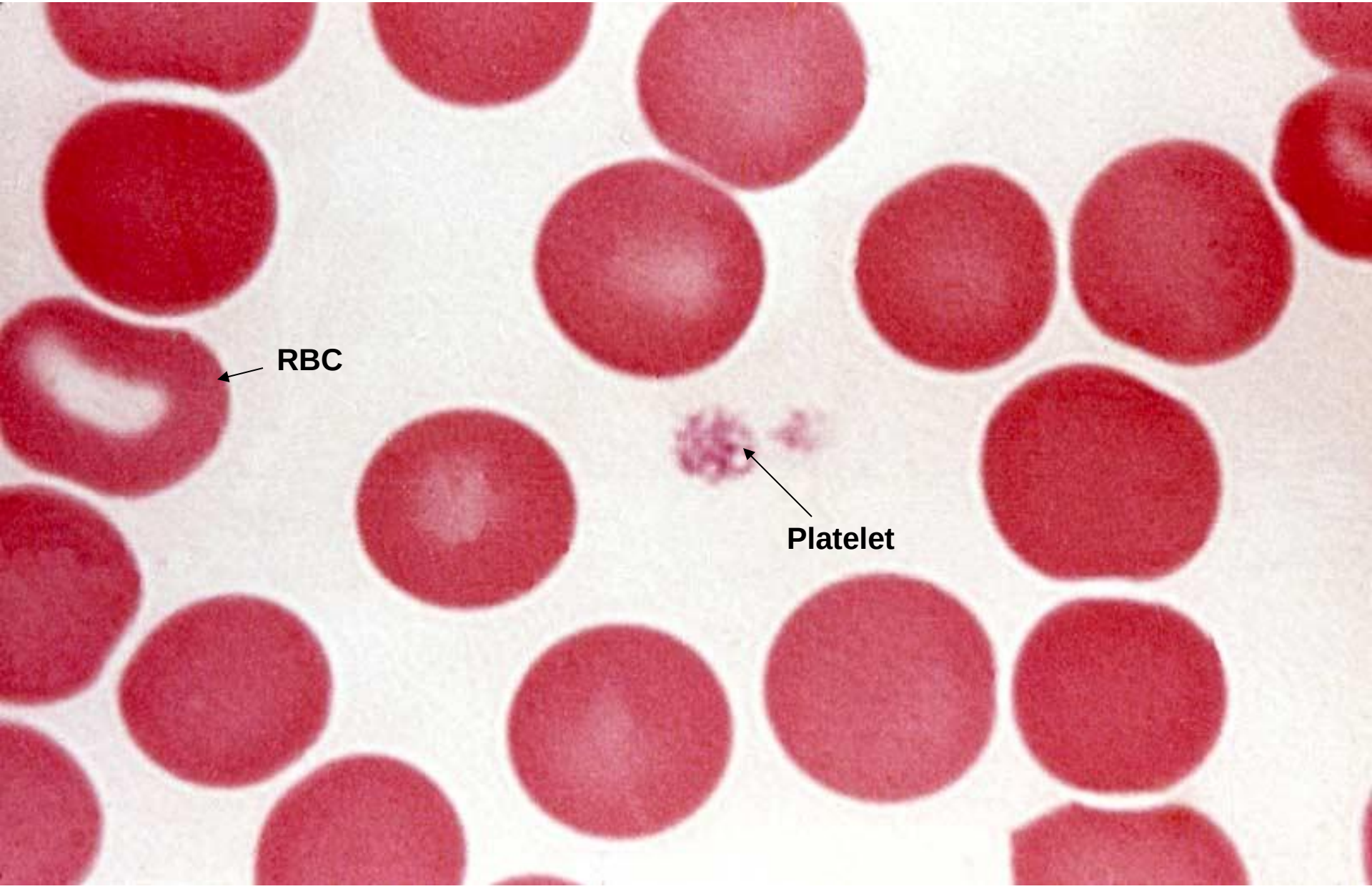
5.Function:

- **Transport of oxygen and carbon dioxide**
  - **bound to hemoglobin (oxyhemoglobin and carboxyhemoglobin)**
  - **majority of CO_2 transported as HCO_3^-**
- **pH homeostasis**
  - **carbonic anhydrase: $CO_2 + H_2O \rightarrow HCO_3^- + H^+$**
  - **band 3 membrane protein: exchanges HCO_3^- for extracellular Cl^-**

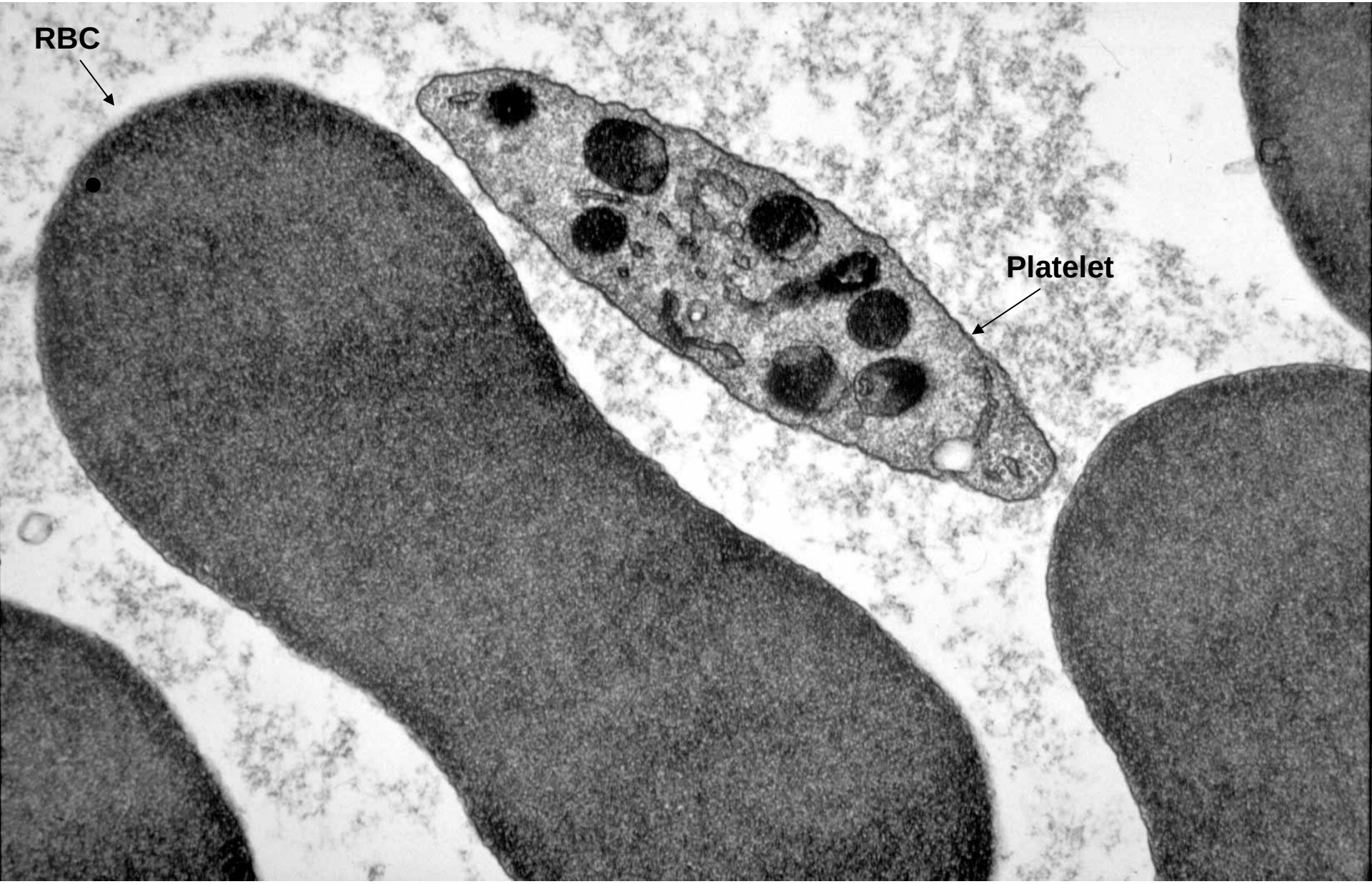
RBCs, scanning electron microscopy



Red blood cells in a blood smear



RBC, transmission electron microscopy



RBC Cytoskeleton and Membrane-Associated Proteins

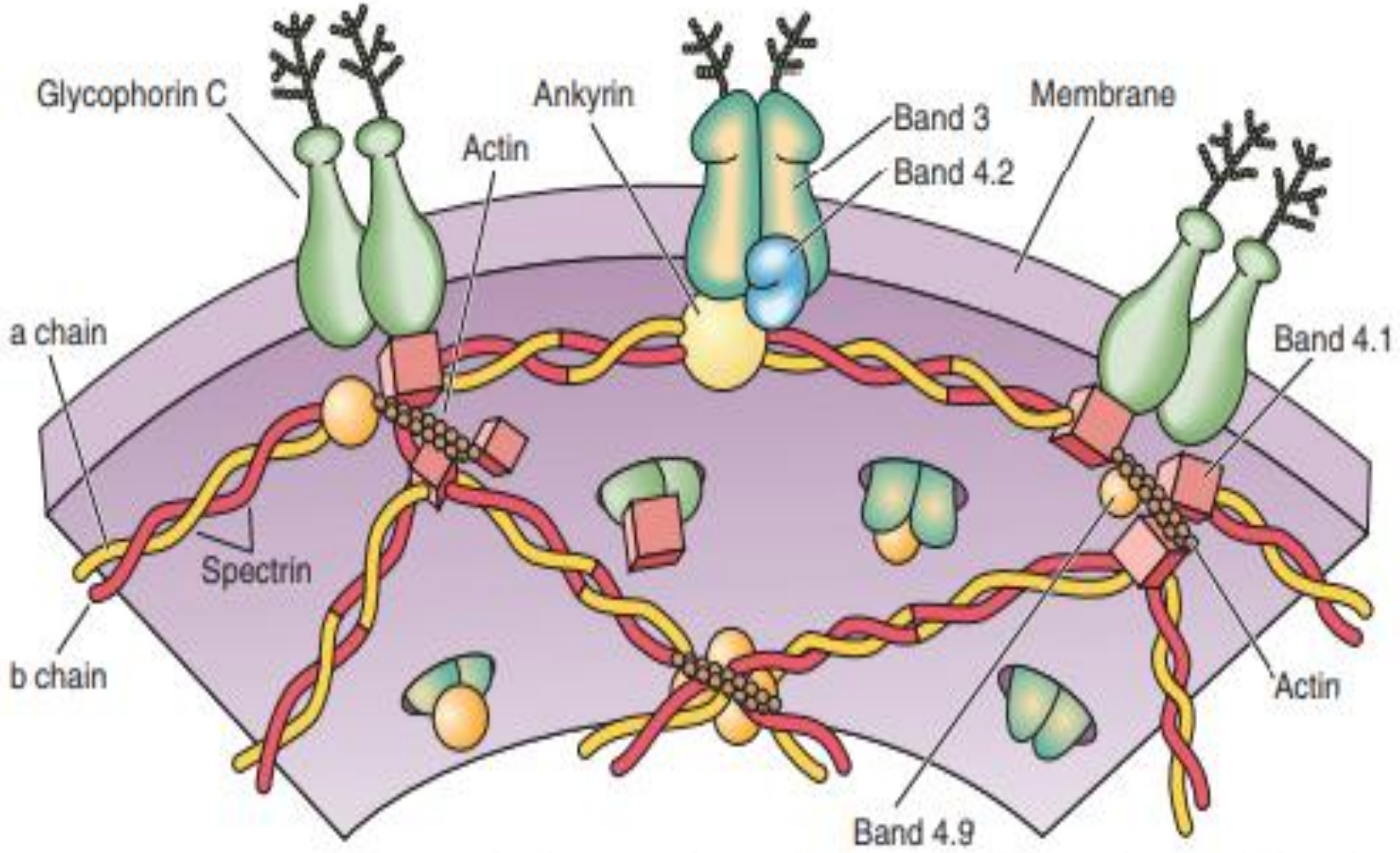
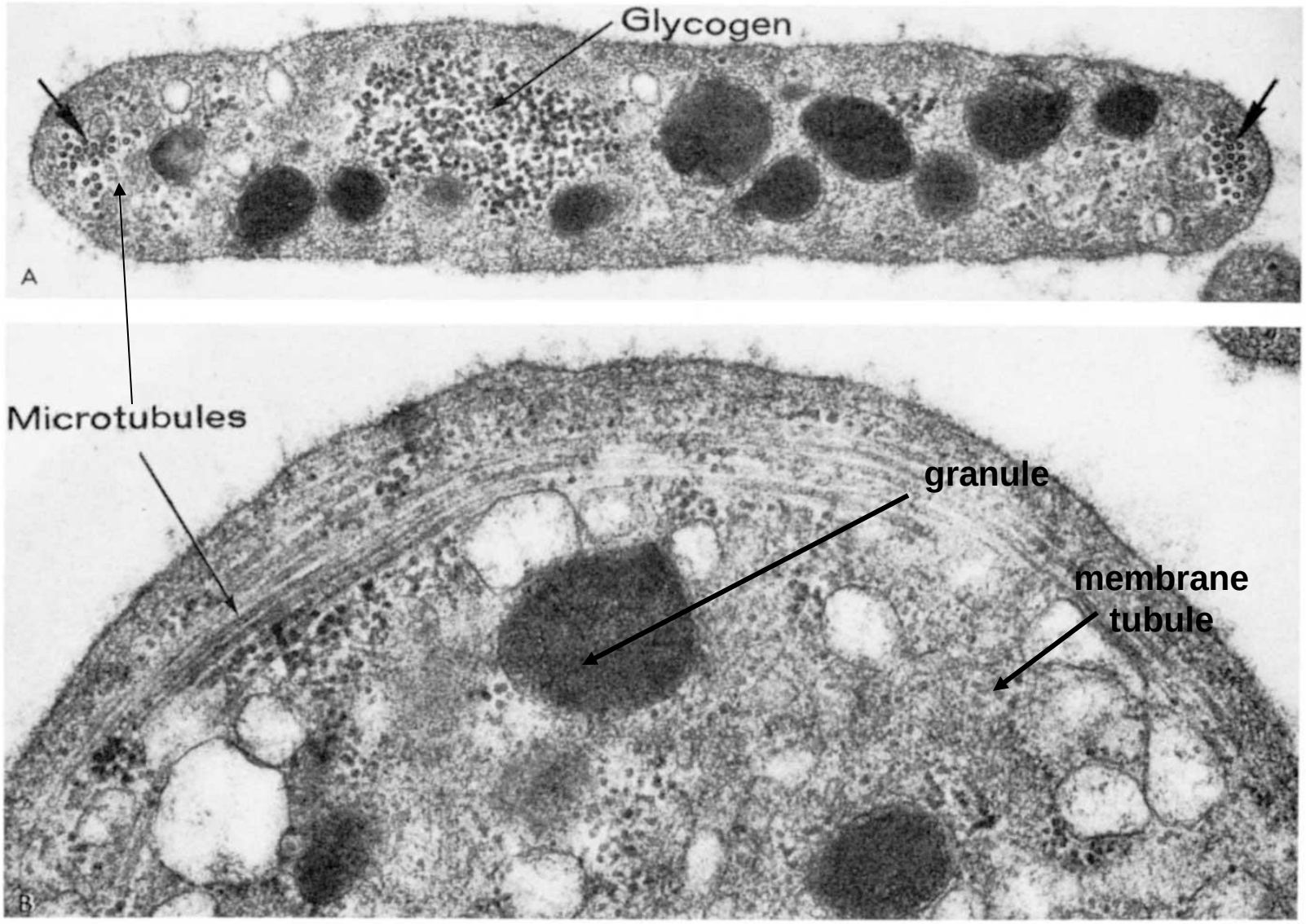


Figure Diagram of the cytoskeleton and integral proteins of the erythrocyte plasmalemma. Spectrin forms a hexagonal lattice-work that is anchored to the erythrocyte plasma membrane by band 4.1 and band 3 proteins as well as by ankyrin.

Platelets (thrombocytes)

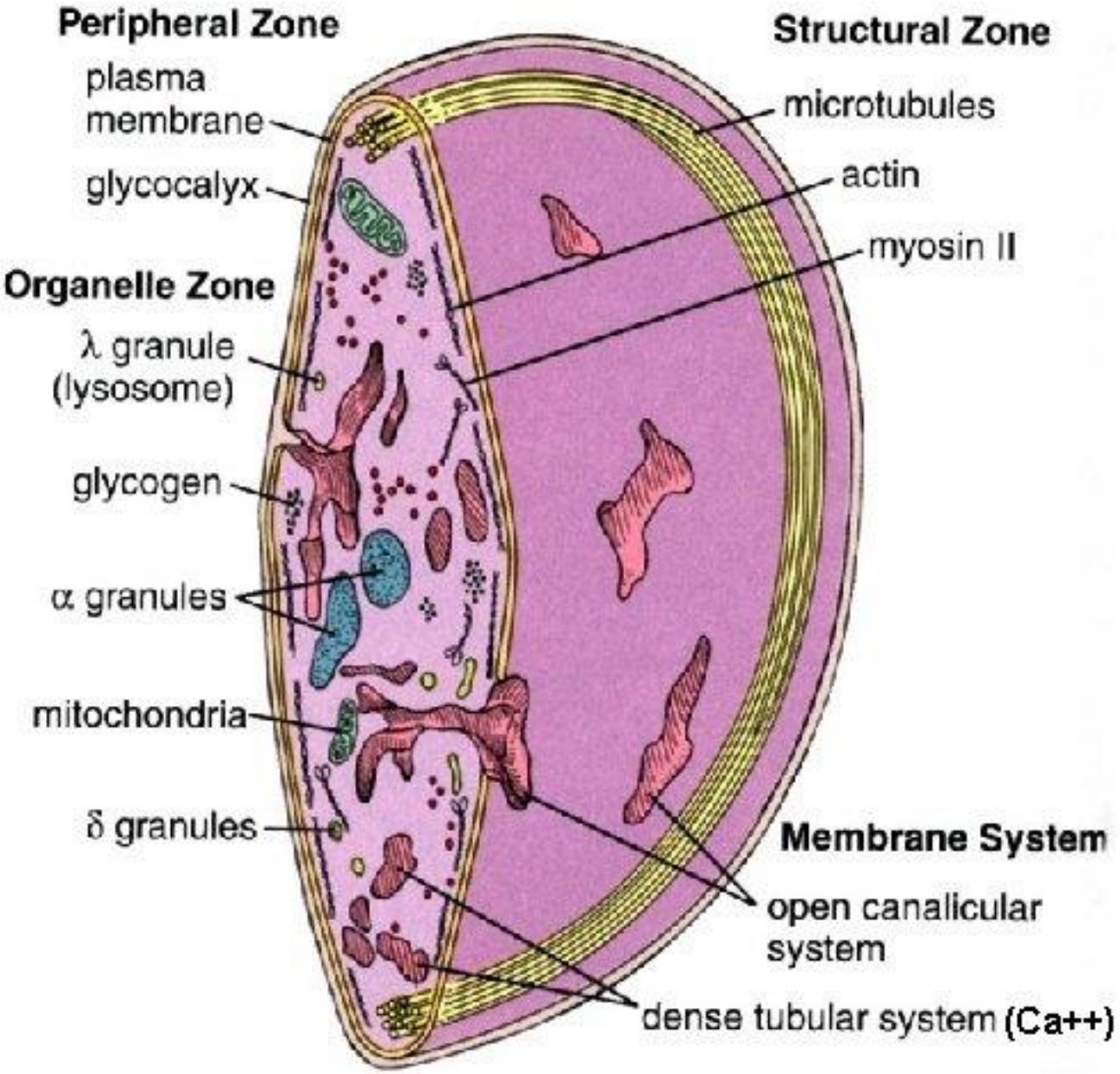
1. **Life Span:** about 10 days
2. **Shape, size, and origin:** Small, biconvex disks, 2-3 µm in diameter. Non-nucleated cell fragments derived from cytoplasm of a very large cell, the megakaryocyte, in bone marrow. Platelets have a life span of about 10 days.
3. **LM appearance in smears:** Small basophilic fragments, often appearing in clusters.
4. **TEM appearance:** The platelet is bounded by a plasma membrane, and has a bundle of microtubules around the margin of the disk (which maintains the disk shape). There are three types of granules, containing fibrinogen, plasminogen, thromboplastin and other factors for clotting. There are also membrane tubules and glycogen.
5. **Function:** Platelets initiate blood clots.

Transmission electron micrographs of a platelet seen in cross section (above) and in a section in the plane of the disk (below)



Cutaway diagram of a platelet

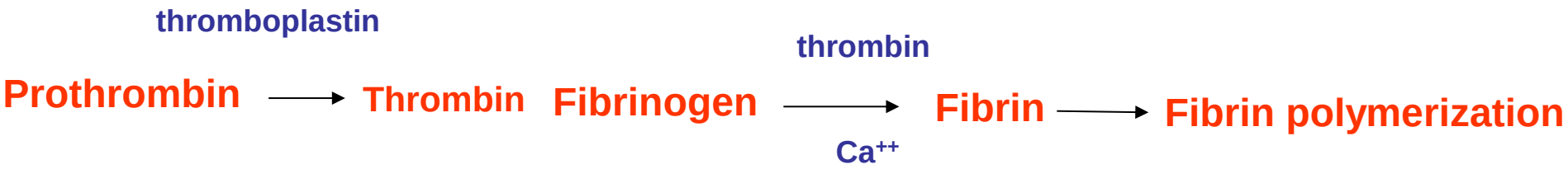
1. Peripheral microtubule bundle (maintains shape)
2. Actin and myosin (clot contraction)
3. Organelles facilitate clotting:
   - Mitochondria for ATP production
   - Granules contain clotting factors
   - Dense tubular system sequesters Ca^{++} for signaling (similar to SR in skeletal muscle)
   - Open canalicular system facilitates signaling and secretion



Platelets and blood clot formation

When a blood vessel wall is damaged, factors from the damaged endothelial cells and the ECM induce the clotting cascade. Platelets aggregate and release proteins for clot formation and resolution:

1. Vasoconstriction –via release of **serotonin**
2. Further platelet aggregation –mediated via **thromboxane A_2** and **ADP**
3. Fibrin polymerization –initiated by **thromboplastin** and free **Ca^{++}**



4.Clot contraction –via **actin**, **myosin**, and **ATP** released into the matrix of the clot

5. Clot resolution –**platelet plasminogen activator** (**pPA**, converts **plasminogen** into active fibrinolytic **plasmin**)

6. Tissue repair –**platelet derived growth factor** (**PDGF**, stimulates smooth muscle and fibroblast proliferation)

Neutrophil (polymorphonuclear leukocyte)

1. **Life Span: < 1 week**
2. **Granulocyte with specific and non-specific granules**

Specific granules

- **Type IV collagenase (aids migration)**
- **Lactoferrin (sequesters iron)**
- **Phospholipase A_2 (leukotriene synthesis)**
- **Lysozyme (digests bacterial cell wall)**

Non-specific granules (lysosomes)

- **Lysozyme**
- **Acid hydrolase**
- **Myeloperoxidase**
- **Elastase**

3. **LM appearance in smear: About 9-12 µm in diameter (thus larger than RBC). Nucleus long and multi-lobed (usually 2-4 lobes).**

4.Cytoplasm has small, neutrally stained specific granules. Non-specific granules are azurophilic.

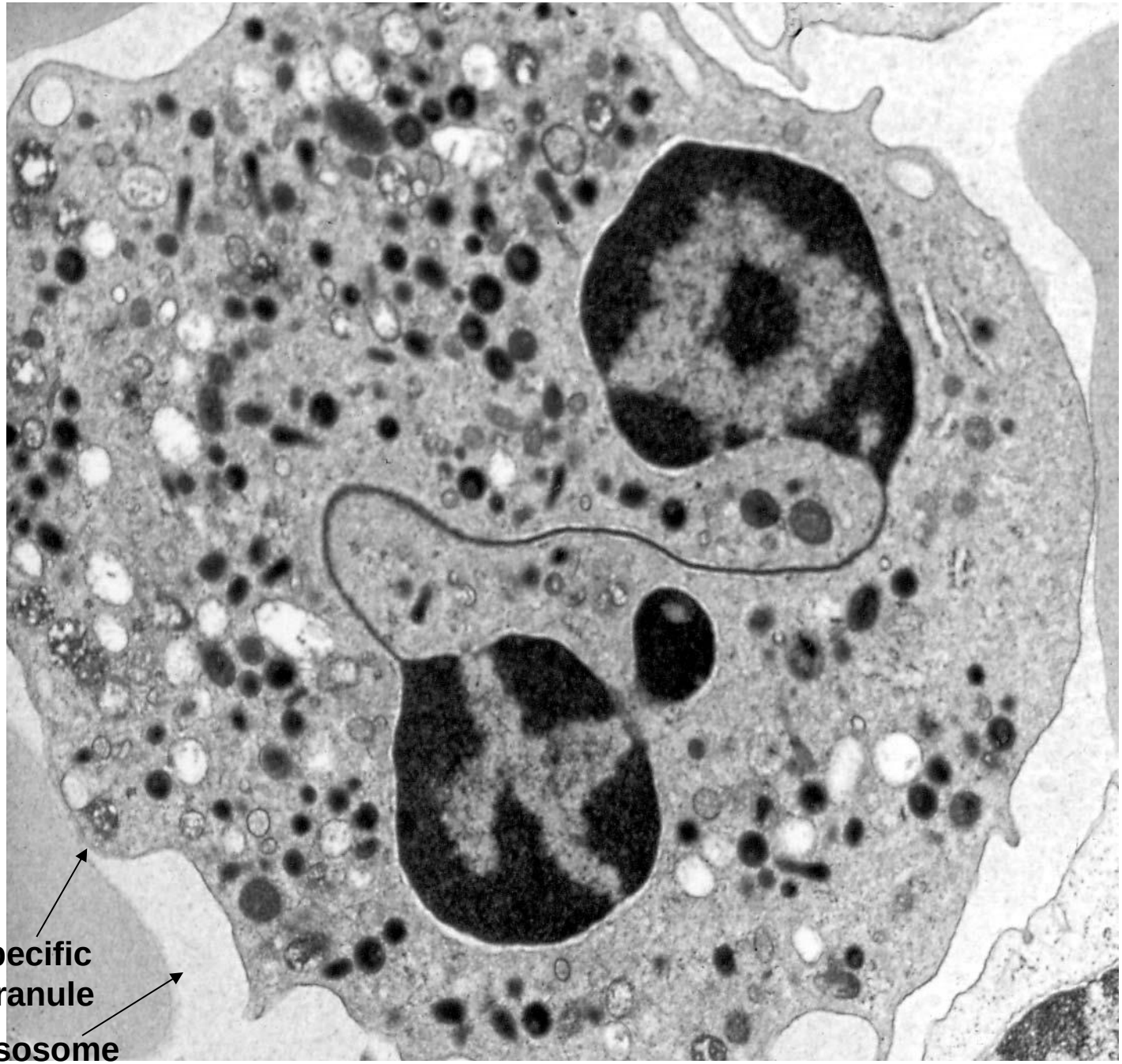
5.TEM appearance: Multi-lobed nucleus and numerous specific granules and lysosomes (=azurophilic granules in LM).

6.Function: Primarily antibacterial

- **Neutrophils leave the blood and follow chemotaxic signals to sites of wounding or other inflammation, and phagocytose foreign agents such as bacteria. Pus is composed largely of dead neutrophils.**

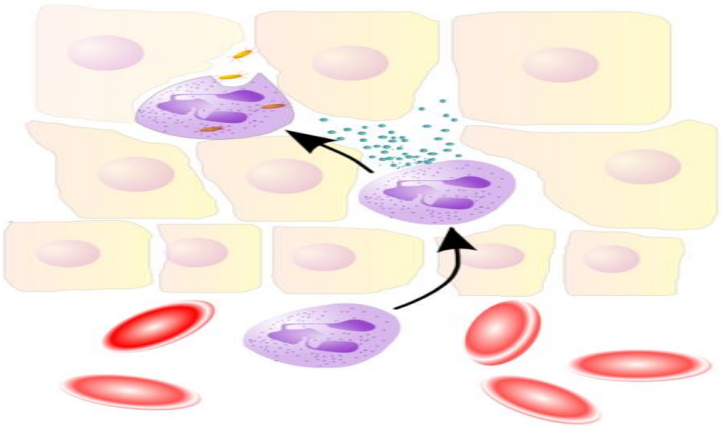
Neutrophil, transmission electron micrograph

TEM appearance: Multi-lobed nucleus and numerous specific granules and lysosomes (=azurophilic granules in LM).



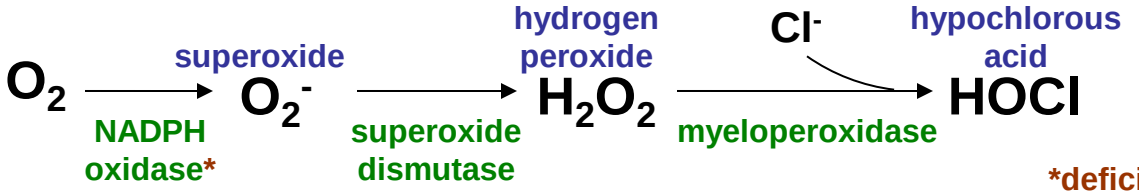
Extravasation via diapedesis

- **Selectin-selectin receptor interaction causes neutrophil to slow & roll along surface.**
- **Chemokines from endothelium leads to expression of integrins & immunoglobulin family adhesion molecules on neutrophil cell membrane.**
- **Neutrophil firmly attached to vessel wall & extends pseudopod into vessel wall.**
- **Vascular permeability mediated by heparin & histamines released by mast cells/basophils.**
- **Once in connective tissue, neutrophils respond to chemoattractants & migrate to injury site.**



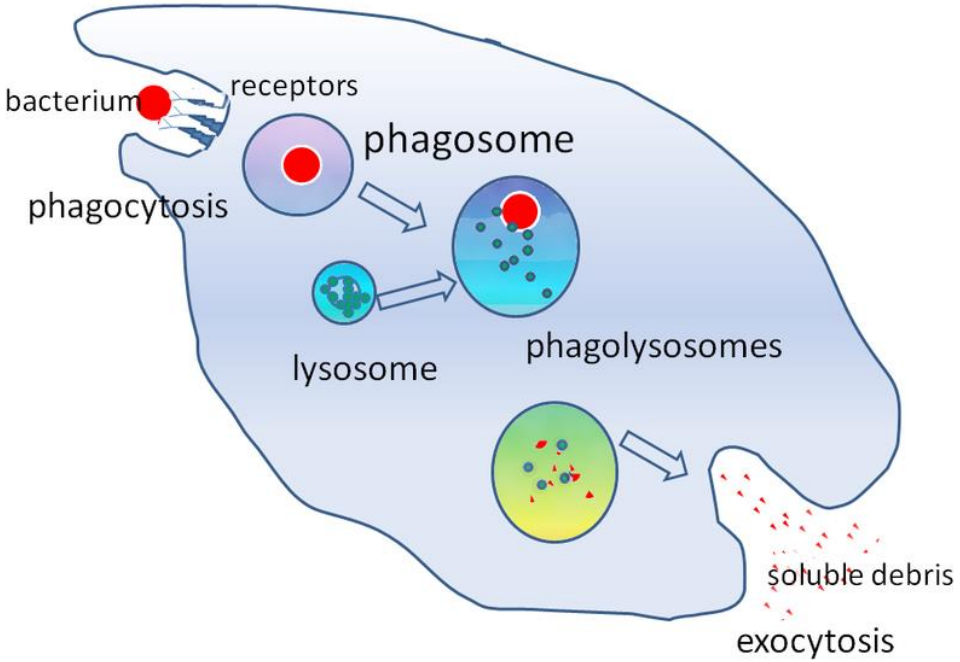
Neutrophil antibacterial activity

1. Chemotaxis and migration (chemokine synthesis and matrix proteolysis)
2. Phagocytosis and bacterial destruction
   - Digestion via lysozymes
   - Production of reactive oxygen compounds (respiratory burst)



*deficiency increases risk of persistent bacterial infections

   - Iron sequestration via lactoferrin
3. Release factors to increase inflammatory response (and increase neutrophil production)



Eosinophil

1. **Life Span: < 2 weeks**
2. **Granulocyte with specific and non-specific granules**

Specific granules

- **Major basic protein**
- **Eosinophilic cationic protein**
- **Neurotoxin**
- **Histaminase**

Non-specific granules (lysosomes)

- **Lysozyme**
- **Acid hydrolase**
- **Myeloperoxidase**
- **Elastase**

3. **LM appearance in smear: About 10-14 µm in diameter. Bilobed nucleus. The cytoplasm has prominent pink/red specific granules (stained with eosin dye). If the smear is not stained properly, the granules may be brownish.**

4. TEM appearance: **The specific granules are ovoid in shape, and contain a dark crystalloid body composed of major basic protein (MBP), effective against parasites. The rest of the granule contains other anti-parasitic substances. The cytoplasm also contains lysosomes (=azurophilic granules).**

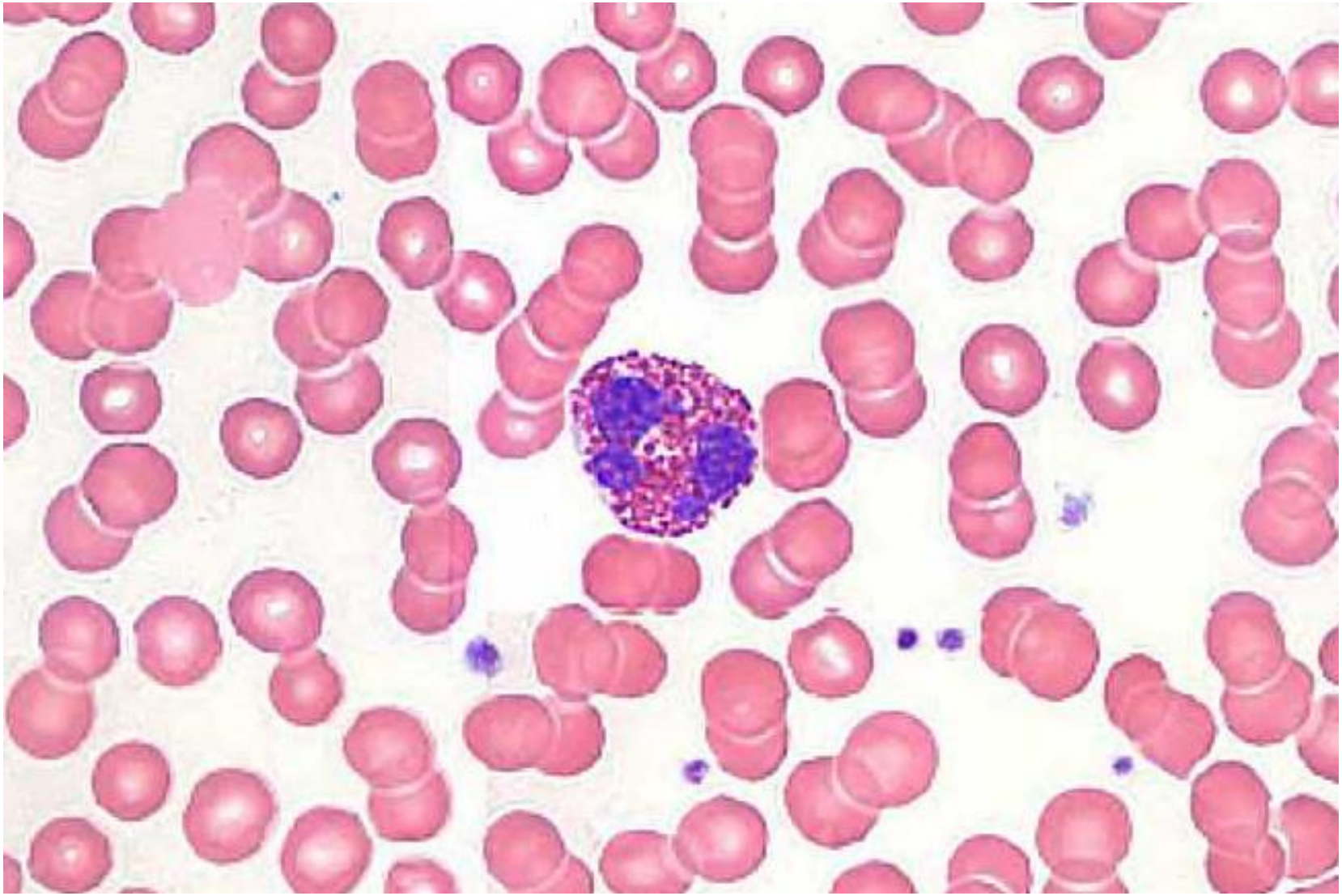
5. Function:

- **Anti-parasitic activity**
- **Mediators of inflammatory/allergic responses in tissues**

Inactivate leukotrienes and histamine secreted by basophils

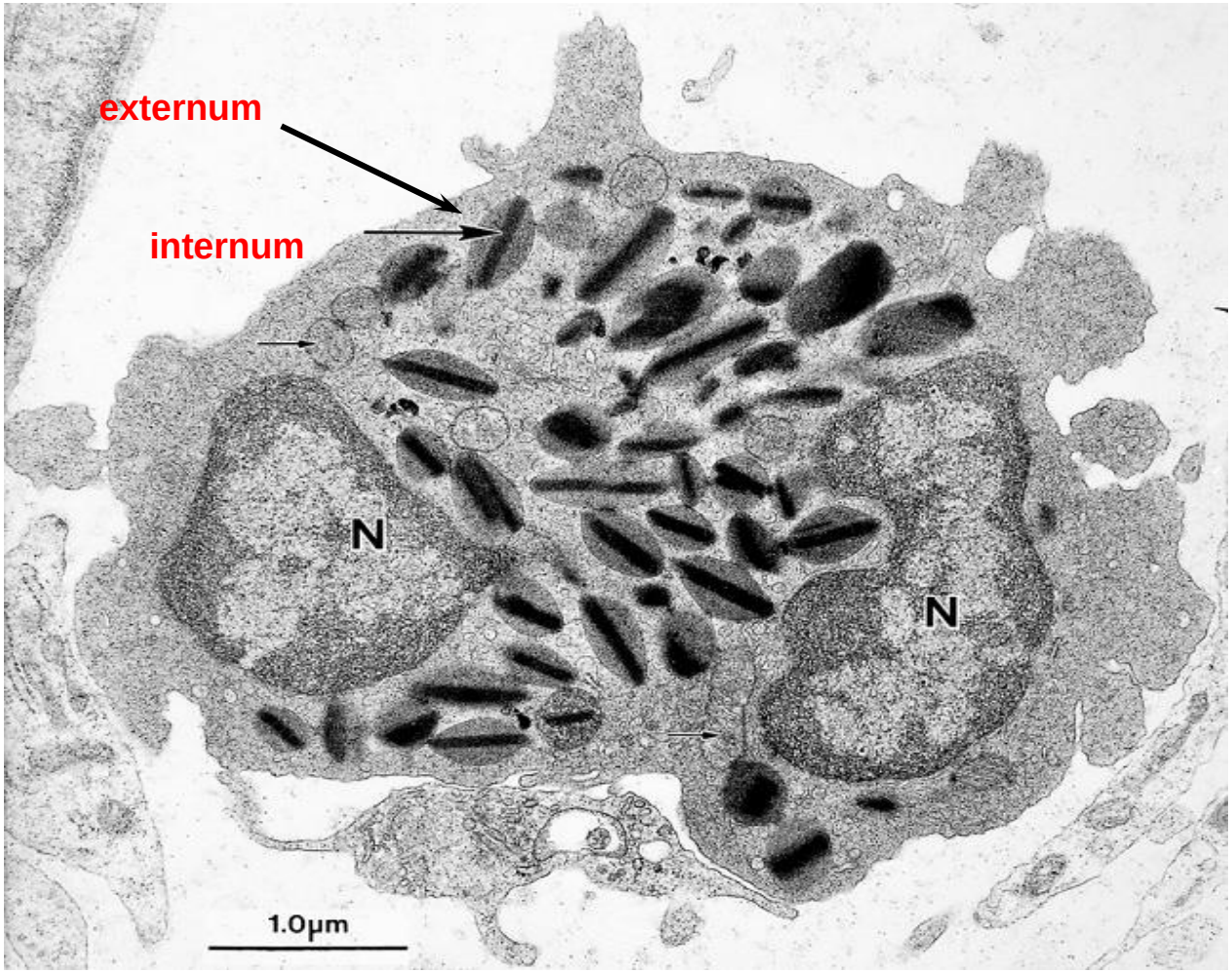
- **Engulf and sequester antigen-antibody complexes**
- **Inflammatory stimulus increases production/release of eosinophils from bone marrow, whereas inflammatory suppression decreases eosinophil numbers in peripheral blood.**
- **But, they also secrete PRO-inflammatory chemokines AND they can degranulate inappropriately to cause tissue damage (as in reactive airway disease)**

Eosinophil in a human blood smear



LM appearance in smear: About 10-14 µm in diameter. Bilobed nucleus. The cytoplasm has prominent pink/red specific granules (stained with eosin dye). If the smear is not stained properly, the granules may be brownish.

Eosinophil, transmission electron microscopy



TEM appearance: **The specific granules are ovoid in shape, and contain a dark crystalloid body composed of major basic protein (MBP), effective against parasites. The rest of the granule contains other anti-parasitic substances and histaminase. The cytoplasm also contains lysosomes (=azurophilic granules).**

Basophil

1. **Life Span: 1-2 years (?)**
2. **Granulocyte with specific and non-specific granules**

Specific granules

- **Histamine**
- **Heparin**
- **Eosinophil chemotactic factor**
- **Phospholipids for synthesis of leukotrienes, e.g. slow-reacting substance of anaphylaxis (SRS-A)**

Non-specific granules (lysosomes)

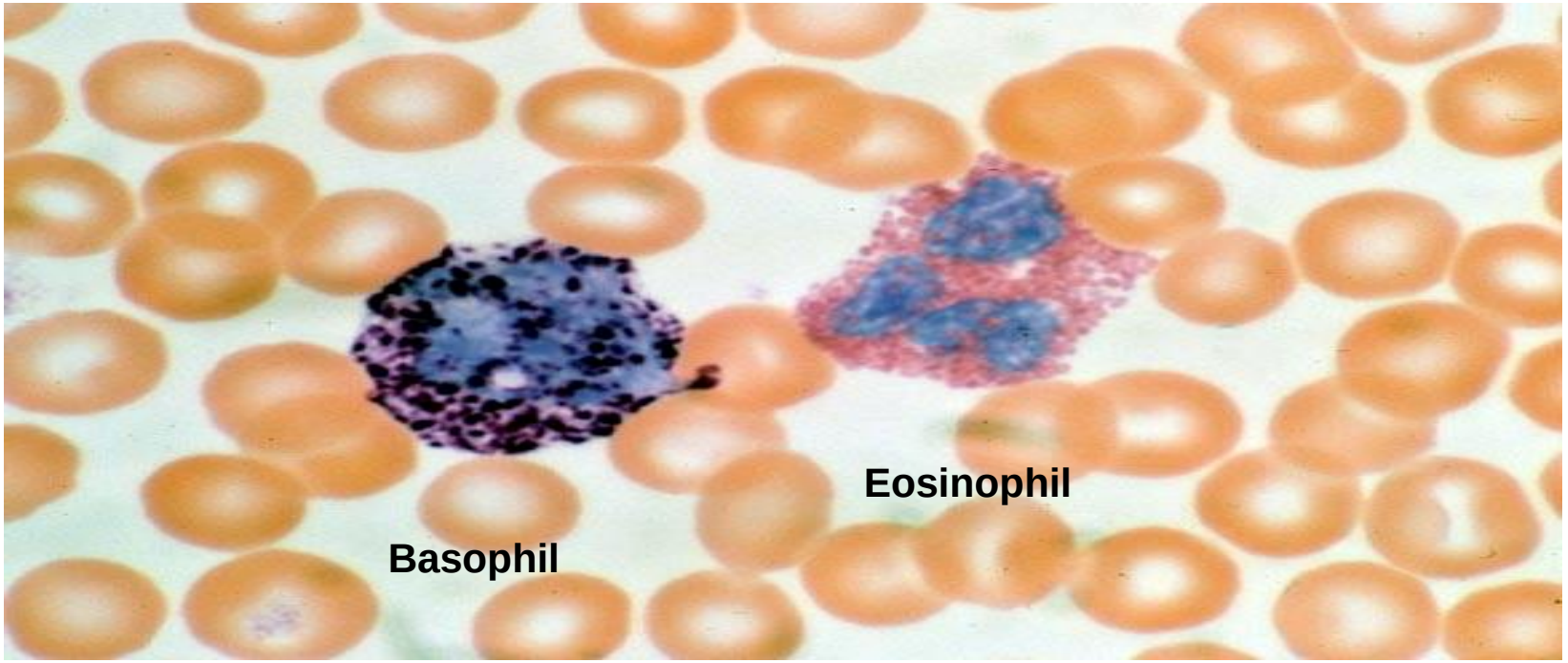
- **Lysozyme**
- **Acid hydrolase**
- **Myeloperoxidase**
- **Elastase**

2. **LM appearance in smear:** **About 8-10 µm in diameter. The cytoplasm contains large, purple/black specific granules (stained with the basic dye) that are larger but not as numerous as those of eosinophils. The nucleus is usually bilobed, but usually is partially obscured by granules, which can lie over it.**

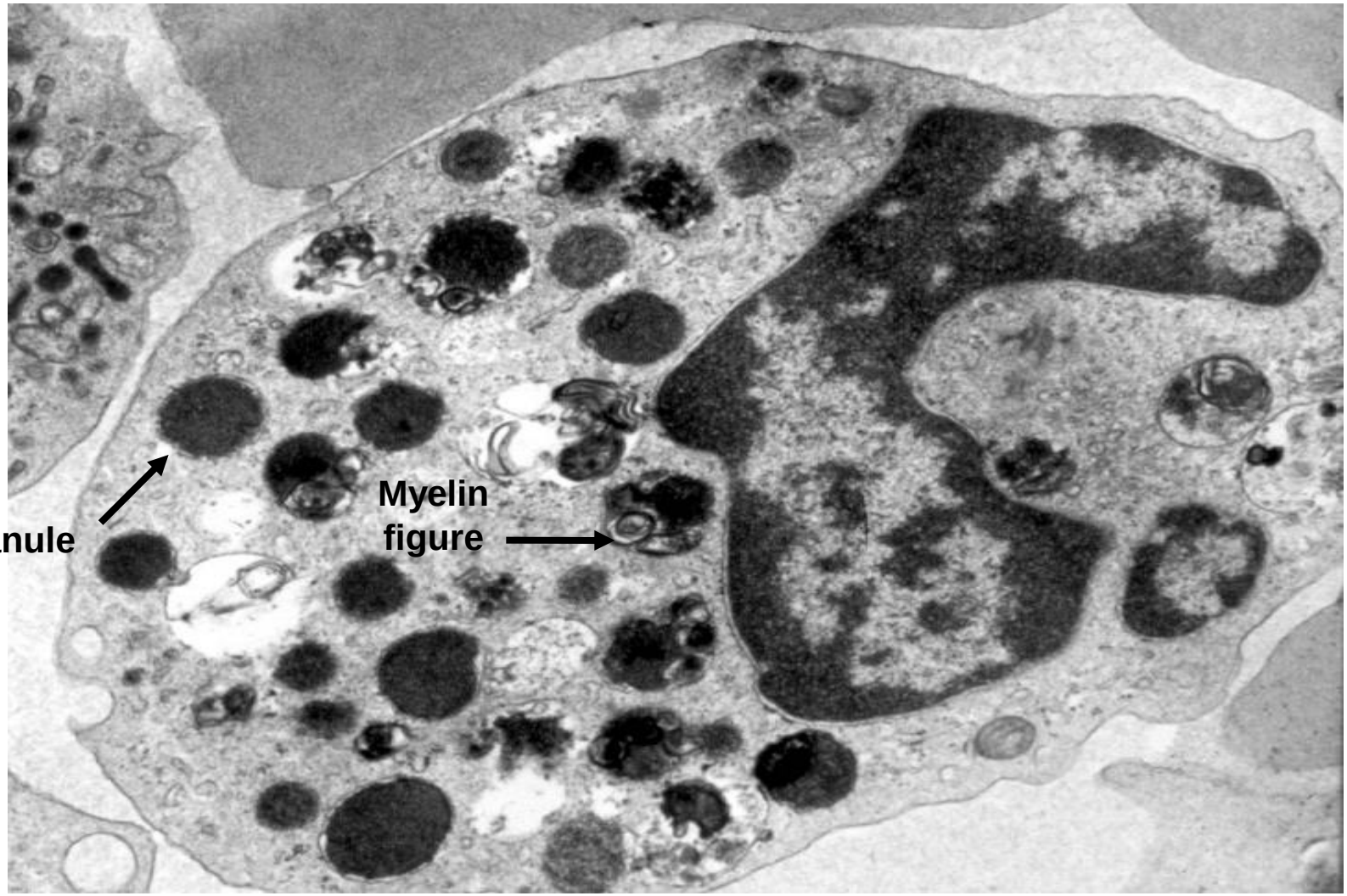
3. **TEM appearance:** **The specific granules vary in size and shape, and have occasional myelin figures (usually formed from phospholipids). The cytoplasm also has some lysosomes (=azurophilic granules).**

4. **Function:** **Allergies and anaphylaxis (hypersensitivity reaction)**
   - **Binding of antigens to membrane-bound IgE antibodies induces degranulation of specific granules, which leads to allergic reaction.**
   - **In hypersensitivity reaction, widespread vasodilation (arteriolar) and vessel leakiness induce circulatory shock. Bronchial spasms cause respiratory insufficiency; combined effect is anaphylactic shock.**
5. **Similarity to tissue mast cells:** **Tissue mast cells also have IgE receptors and similar (though not identical) granule content. Mast cells and basophils have a common precursor in bone marrow.**

Comparison of basophil and eosinophil in a blood smear



Basophil, transmission electron microscopy



TEM appearance: **The specific granules vary in size and shape, and have occasional myelin figures (usually formed from phospholipids). The cytoplasm also has some lysosomes (=azurophilic granules).**

Lymphocytes

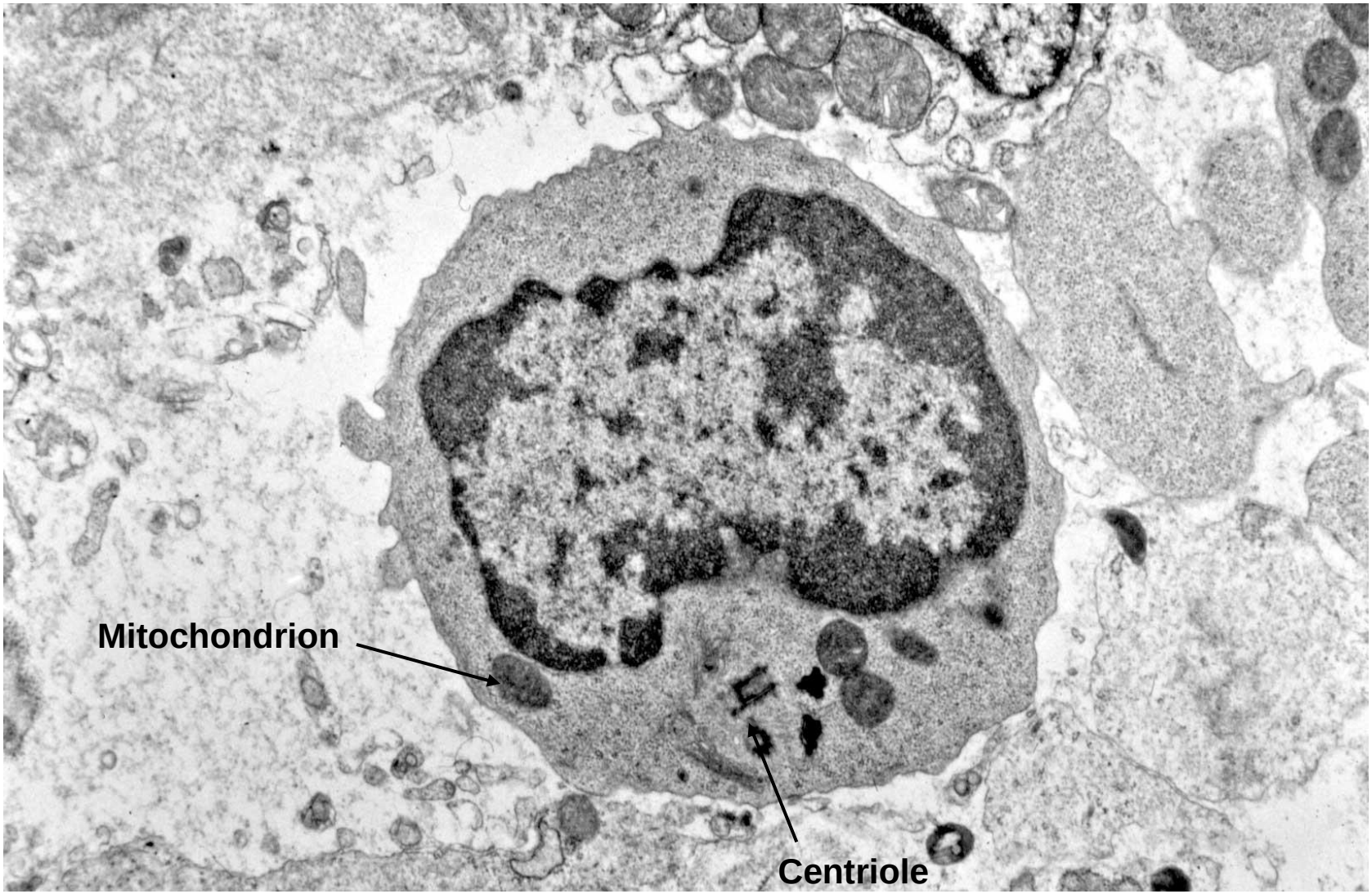
1. **Life Span: variable (few days to several years)**
2. **LM appearance in smear: Small lymphocyte (about 90% of lymphocytes you will see) are ~8 µm in diameter, while large lymphocytes may be up to about 15 µm. Round, dense nucleus (abundant heterochromatin). The cytoplasm of a small lymphocyte is a narrow rim around the nucleus, and when well stained is pale blue. T-lymphocytes and B-lymphocytes cannot be distinguished in a smear.**

3.TEM appearance: **The cytoplasm doesn't appear to be very active, containing mainly mitochondria and free ribosomes.**

4. Function: **Cellular and humoral immunity (more detail in the lecture and lab on lymphatic system histology). In general:**

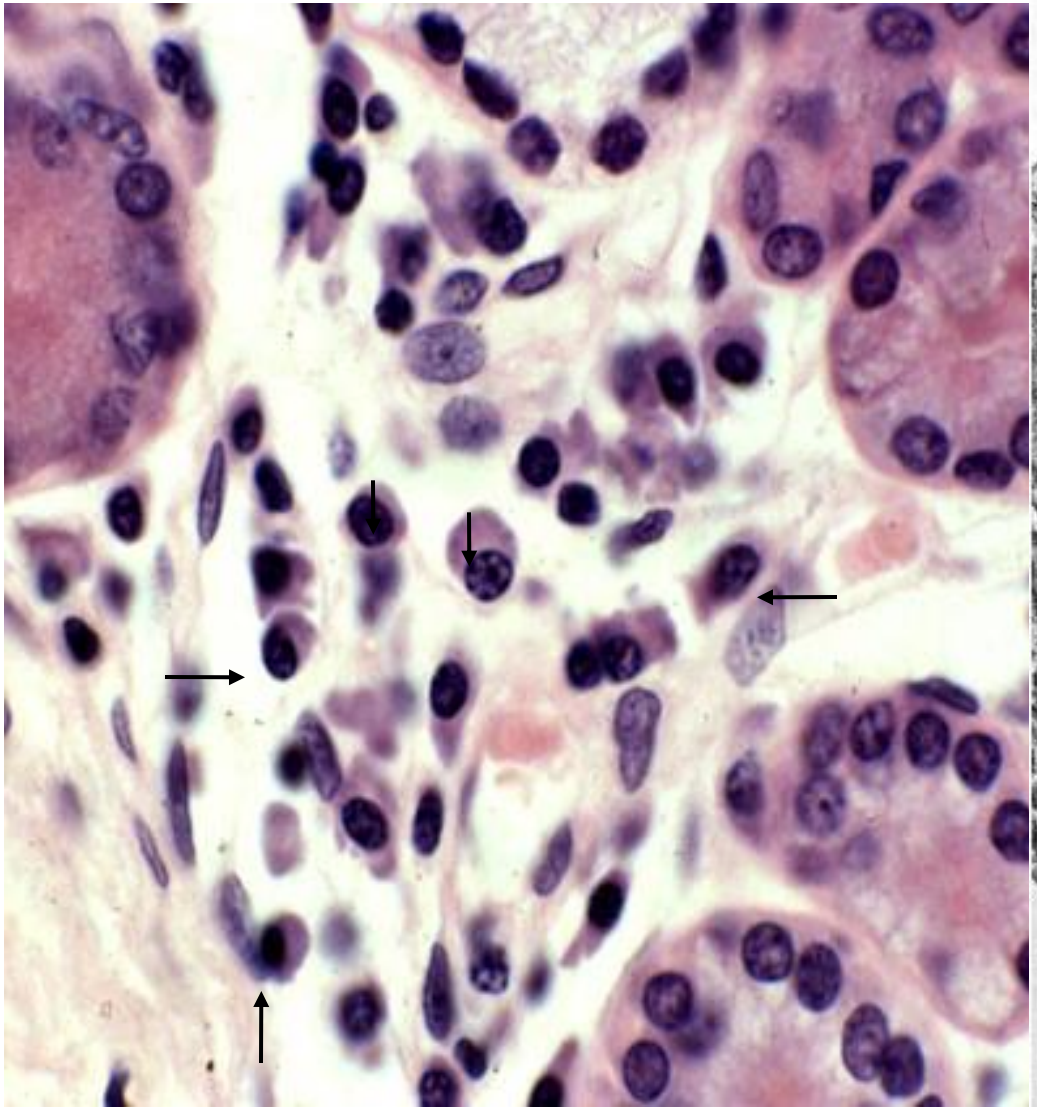
- **B-lymphocytes (B-cells): may differentiate into tissue plasma cells which make antibodies. Some B-cells become memory cells.**
- **T-lymphocytes (T-cells): cytotoxic T cells and helper T cells.**

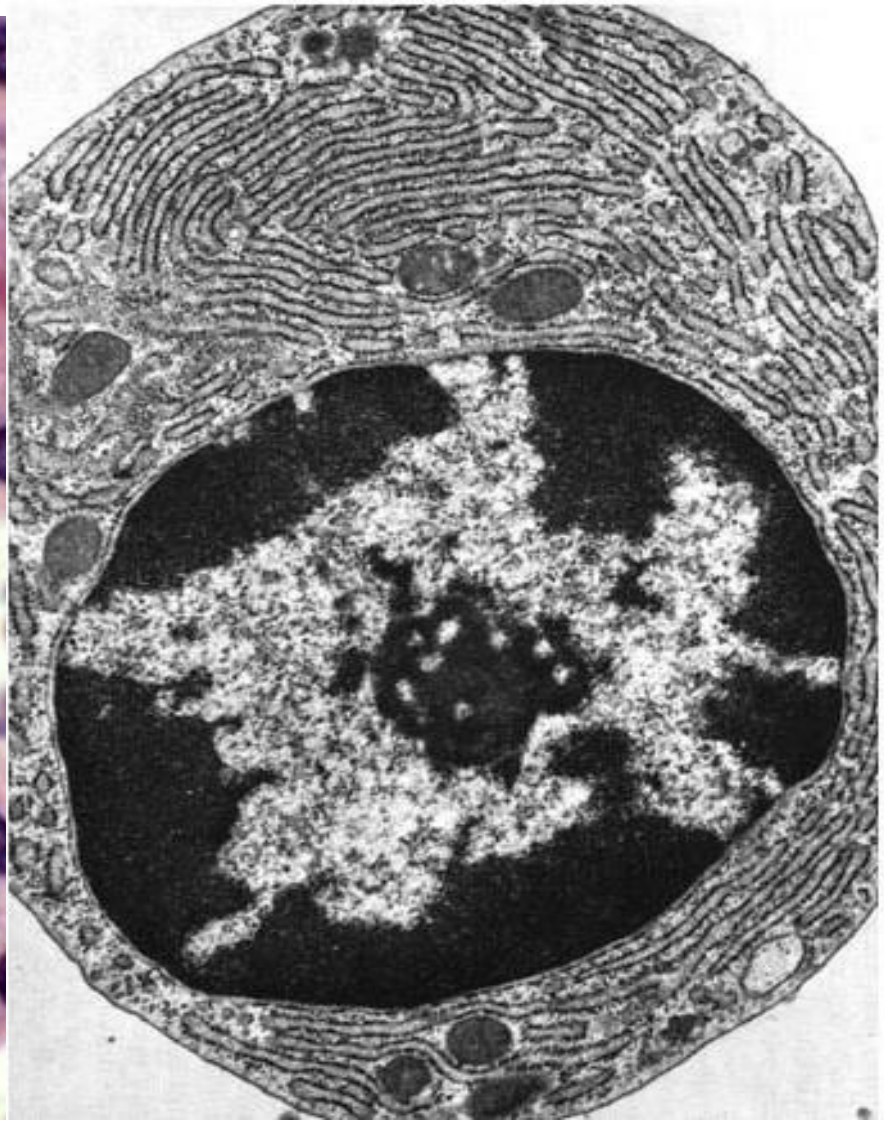
Electron micrograph of a lymphocyte



TEM appearance: **The cytoplasm doesn't appear to be very active, containing mainly mitochondria and free ribosomes.**

Tissue plasma cells (derived from B-lymphocytes)





Monocyte

1. **Life Span:** **few days in blood, several months in connective tissue**
2. **LM appearance in smears:** **About 16 µm in smears, thus the largest leukocyte. Large, eccentric nucleus either oval, kidney-shaped or horseshoe-shaped, with delicate chromatin that is less dense than that of lymphocytes. Pale cytoplasm, often grayish, may contain occasional stained granules (lysosomes = azurophilic granules). Large lymphocytes may resemble monocytes, but the lymphocyte nucleus is usually more dense.**

3. TEM appearance: **Cytoplasm contains mitochondria and some small lysosomes.**

4. Function

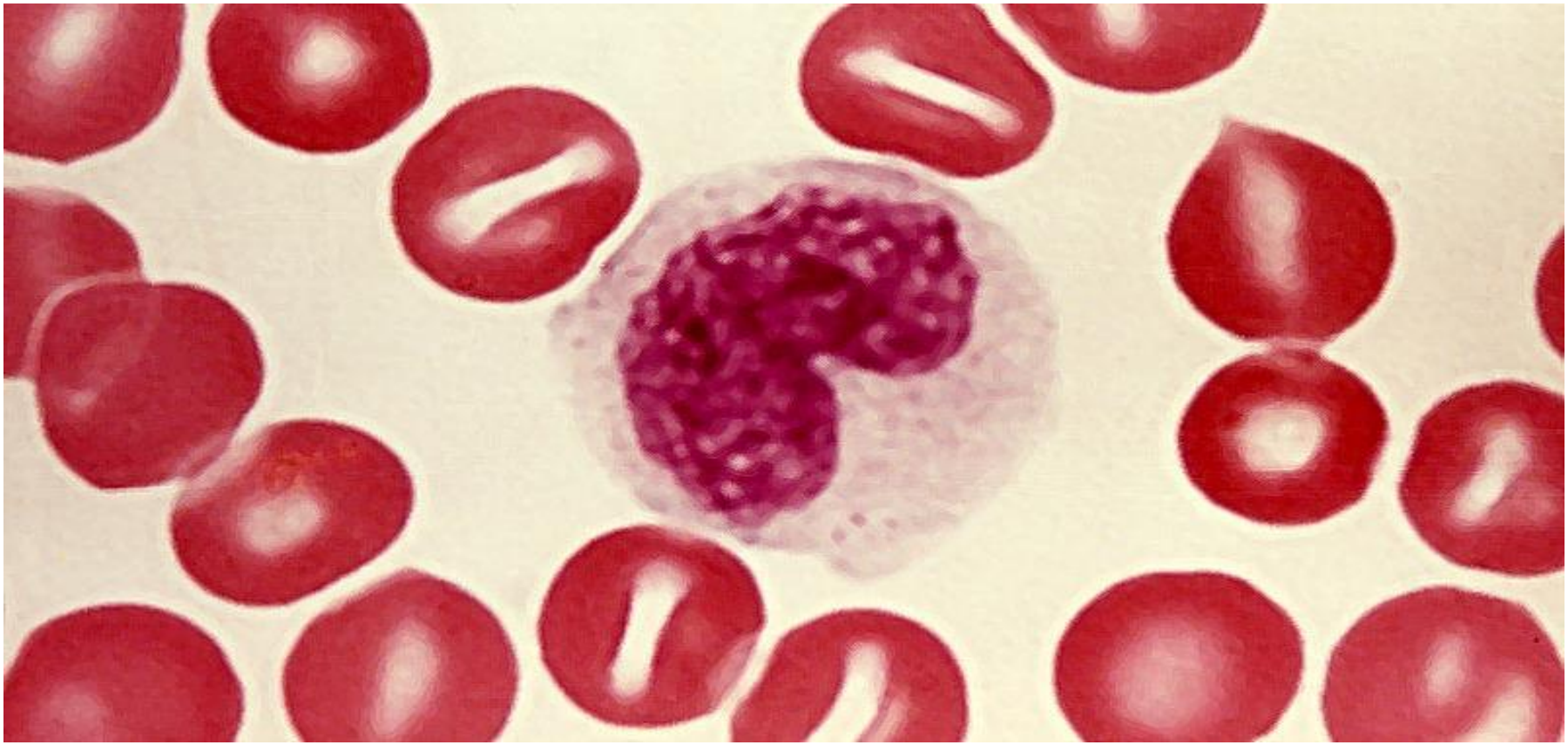
- **Migrate into tissues and constitute mononuclear phagocyte system that help destroy foreign bodies and maintain or remodel tissues**

  Tissue macrophages **Kupfer cells (liver)**

  Osteoclasts (bone) **Dust cells (lungs)**

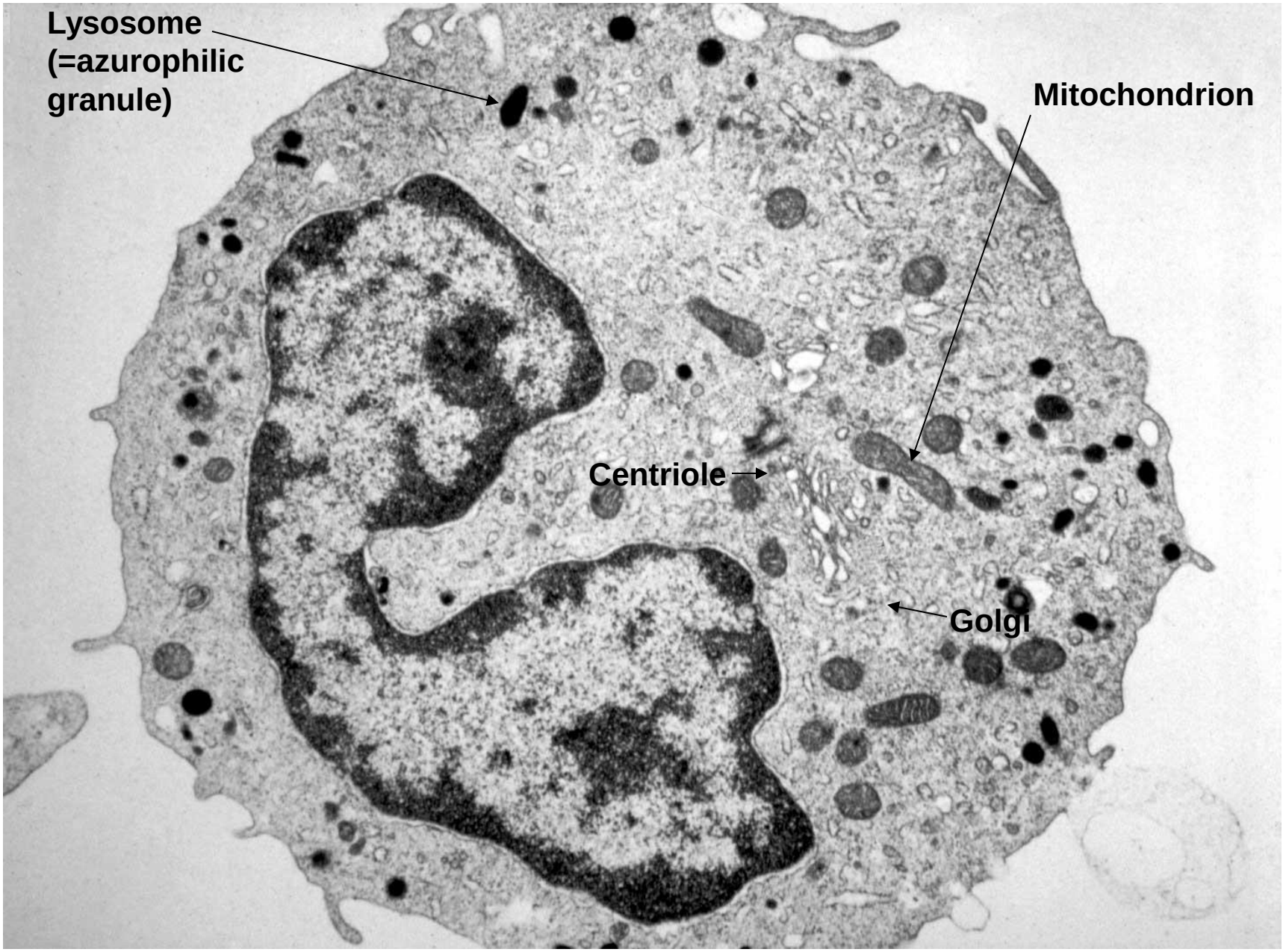
  Microglia (brain)
- **Mediate inflammatory response**
- **Antigen presenting cells: Dendritic Cells, Langerhans cells**

Monocyte in a blood smear



LM appearance in smears: **About 16 µm in smears, thus the largest leukocyte. Large, eccentric nucleus either oval, kidney-shaped or horseshoe-shaped, with delicate chromatin that is less dense than that of lymphocytes. Pale cytoplasm, often grayish, may contain occasional stained granules (lysosomes = azurophilic granules). Large lymphocytes may resemble monocytes, but the lymphocyte nucleus is usually more dense.**

Monocyte, transmission electron microscopy



TEM appearance: Cytoplasm contains mitochondria and some small lysosomes.

Blood cell development (hematopoiesis = hemopoiesis)

1. **Normally occurs in red bone marrow in adult (also spleen & liver, if necessary)**

   *** Erythrocytes still have nuclei; leukocytes do not appear until 8 wks**

   Phases: mesoblastic (yolk sac, 2 wks)* → hepatic (6 wks)* → splenic (12 wks) → myeloid (marrow, 24 wks)

2. **Mitotic stem and progenitor cells undergo increasing lineage restriction to produce committed precursors.**
3. **Precursors undergo cell division and differentiation into mature cells.**

4. Maturation involves (note exceptions for megakaryocytes below):

- **decrease in cell size***
- **shutting down transcription (nucleoli disappear and chromatin condenses)***
- **adoption of morphological characteristics specific to that lineage.**

– **Future granulocytes produce specific and non-specific granules, and then shape their nucleus.**

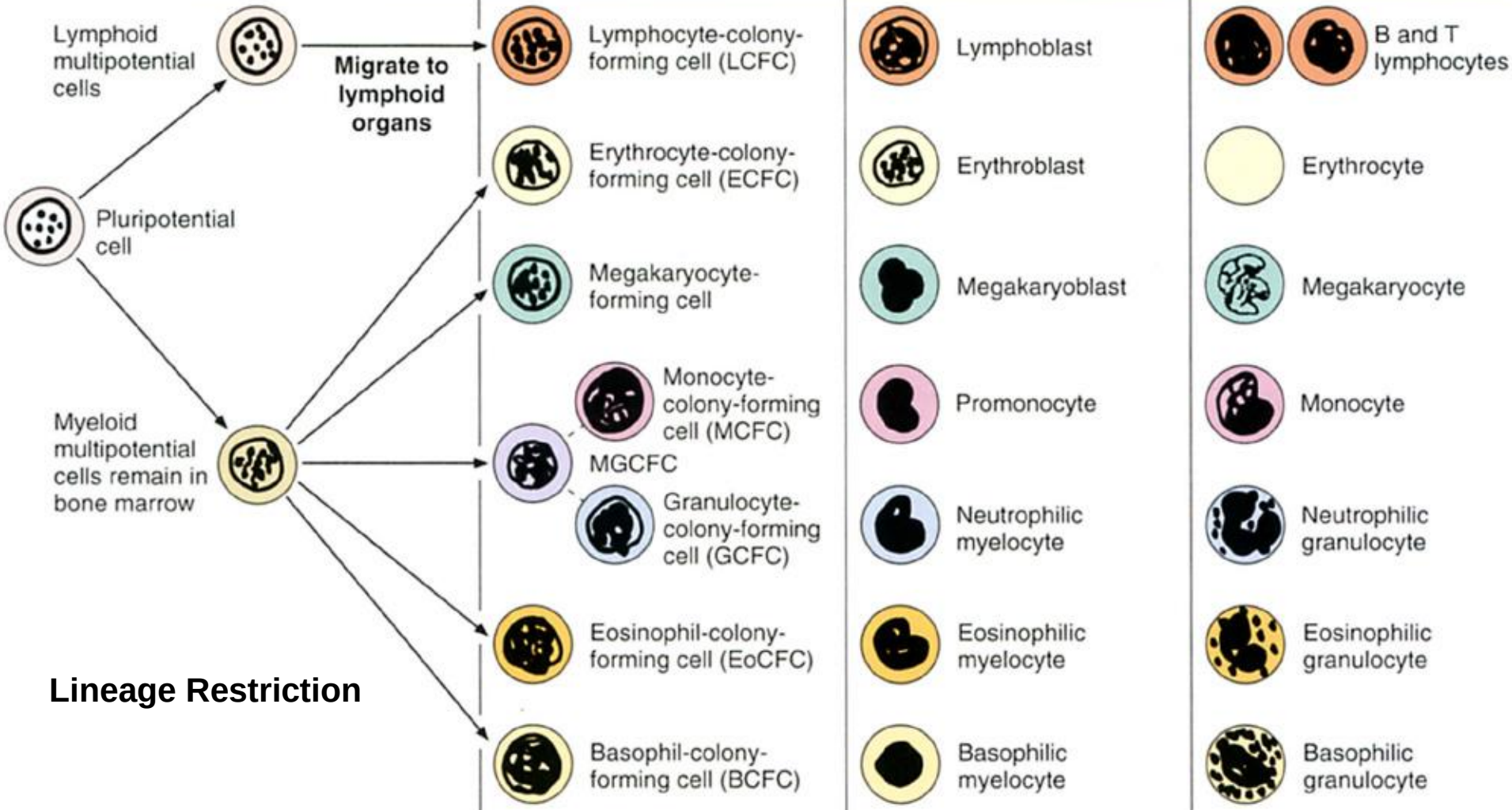
– **Future monocytes produce non-specific granules and shape their nucleus.**

- **Future small lymphocytes decrease their size and enter the blood, but then undergo extensive further maturation at another site (T-cells in the thymus, and B-cells in the "bursa equivalent" –to be discussed in immune system lecture).**
- **Future erythrocytes fill cytoplasm with hemoglobin, synthesized on free polysomes (ribosomes on mRNA), and eventually extrude their nucleus.**

5.Mature cells enter marrow sinus; immature cells in peripheral blood typically indicates disease.

*** Megakaryocytes develop into large polyploid cells that remain transcriptionally active and extrude platelets as cytoplasmic fragments directly into marrow sinus.**

Phase	Stem Cells	Progenitor Cells	Precursor Cells (Blasts)	Mature Cells
Early morphologic	Not morphologically distinguishable; have the general aspect of lymphocytes		Beginning of morphologic differentiation	Clear morphologic differentiation
Mitotic activity	Low mitotic activity; self-renewing; scarce in bone marrow	High mitotic activity; self-renewing; common in marrow and lymphoid organs; mono- or bipotential	High mitotic activity; not self-renewing; common in marrow and lymphoid organs; monopotential	No mitotic activity; abundant in blood and hematopoietic organs



Lineage Restriction

Cellular Changes during Myeloid Differentiation

Mitotic Cell — *Postmitotic Cells*

Myelocyte | Metamyelocyte | Band Cell | Mature Neutrophil

Nuclear Changes-

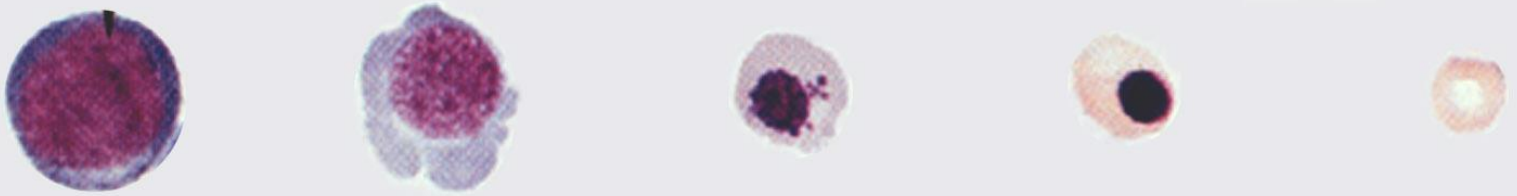
Large, euchromatic, transcriptionally active nucleus → Smaller, euchromatic, less transcriptionally active nucleus → Condensed, heterochromatic, transcriptionally inactive nucleus

Cytoplasmic Changes-

Basophilic cytoplasm, active synthesis of specific and non-specific granules → Reduced basophilia, granule maturation → Pale bluish-pink cytoplasm, mature granules

Changes during Erythroblast Differentiation

Mitotic Cells | *Postmitotic Cells*



Proerythroblast | Early Erythroblast | Middle Erythroblast | Late Erythroblast | Erythrocyte (Reticulocyte)

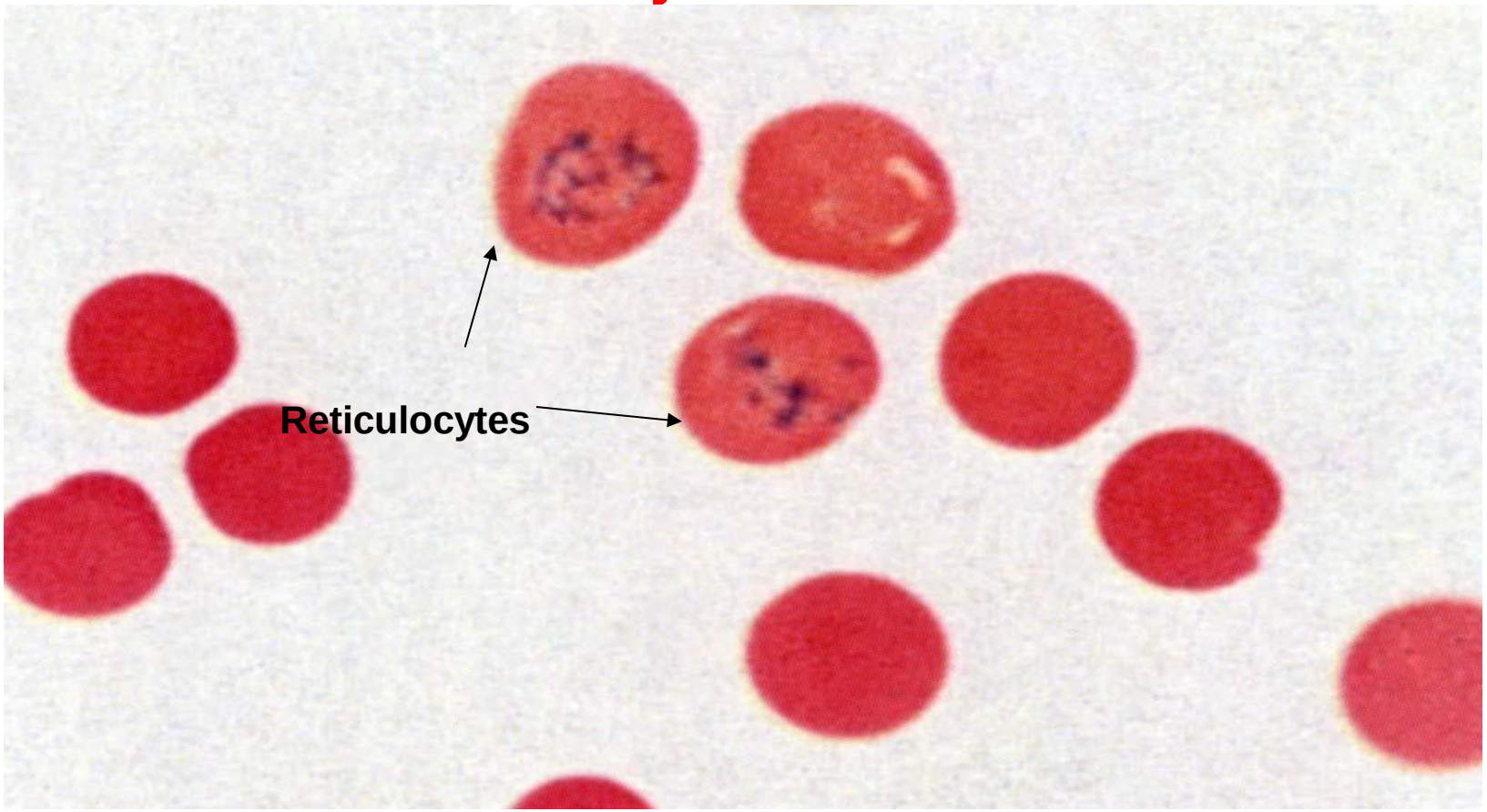
Nuclear Changes-

Large, euchromatic, and transcriptionally active → Smaller, heterochromatic, and transcriptionally inactive → Absent

Cytoplasmic Changes-

Basophilic with abundant RER → Polychromatic (basophilic and acidophilic) with abundant RER and hemoglobin → Acidophilic, with abundant hemoglobin

Reticulocytes (somewhat immature RBCs) in blood smear, cresyl blue stain



Residual ribosomes in cytoplasm are basophilic. Number of reticulocytes in peripheral blood reflects status of erythropoesis –generally increased by anemia and hypoxia.

Section of bone marrow, LM

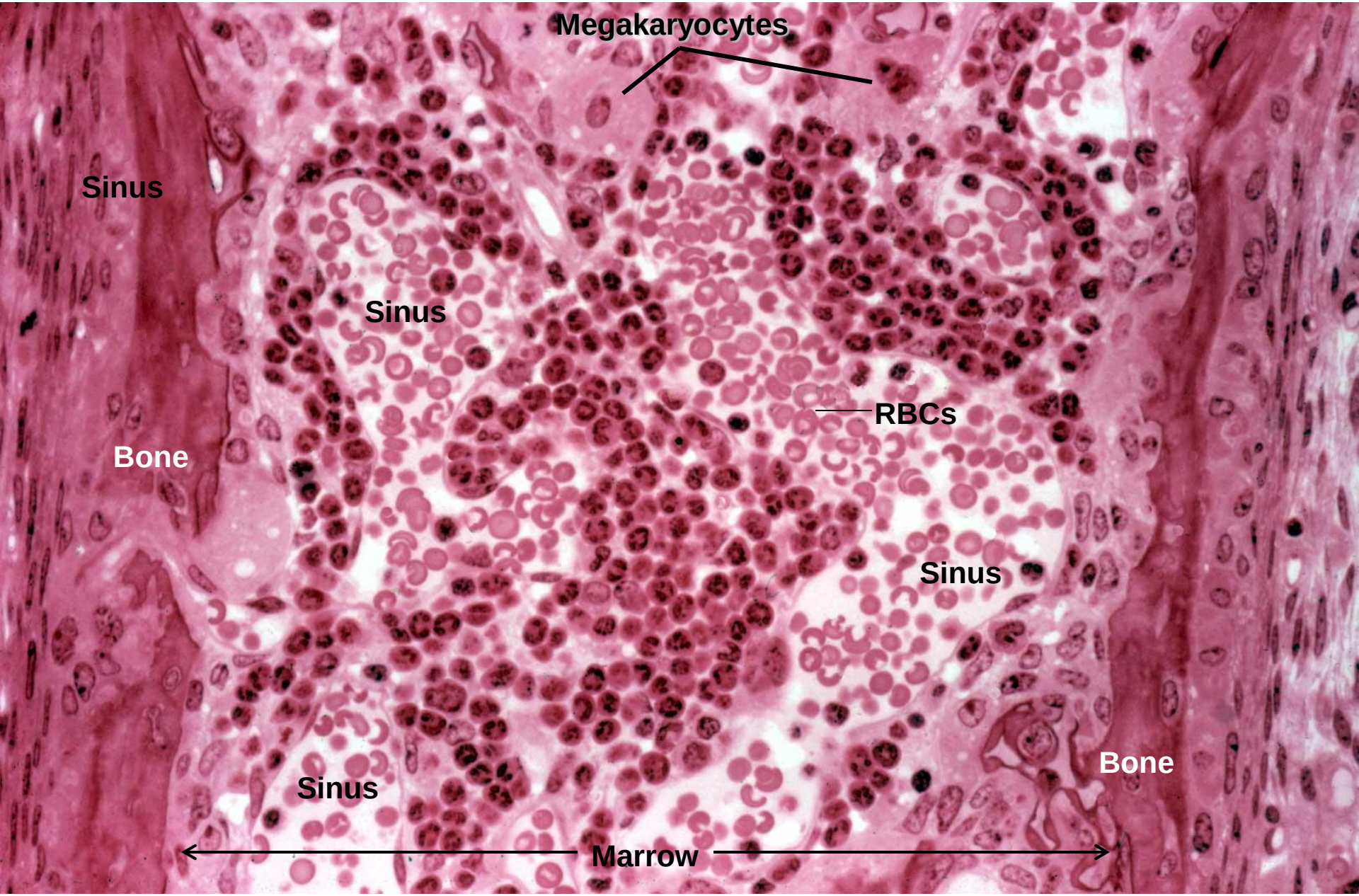
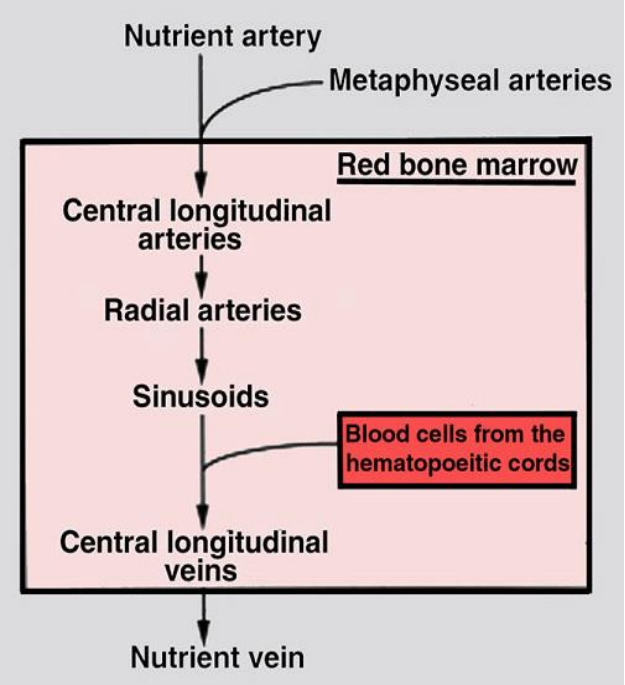
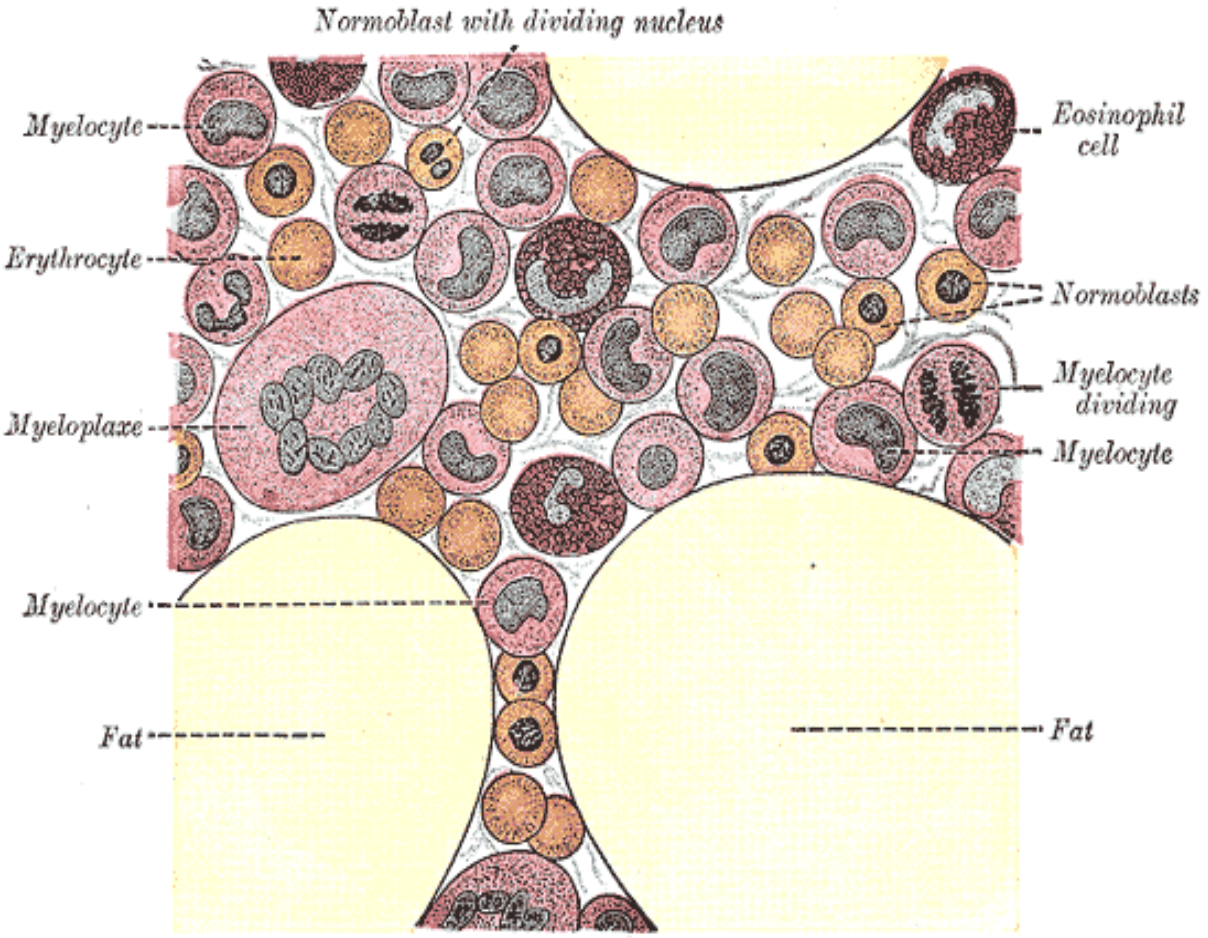


Diagram of bone marrow

Blood flow through marrow:





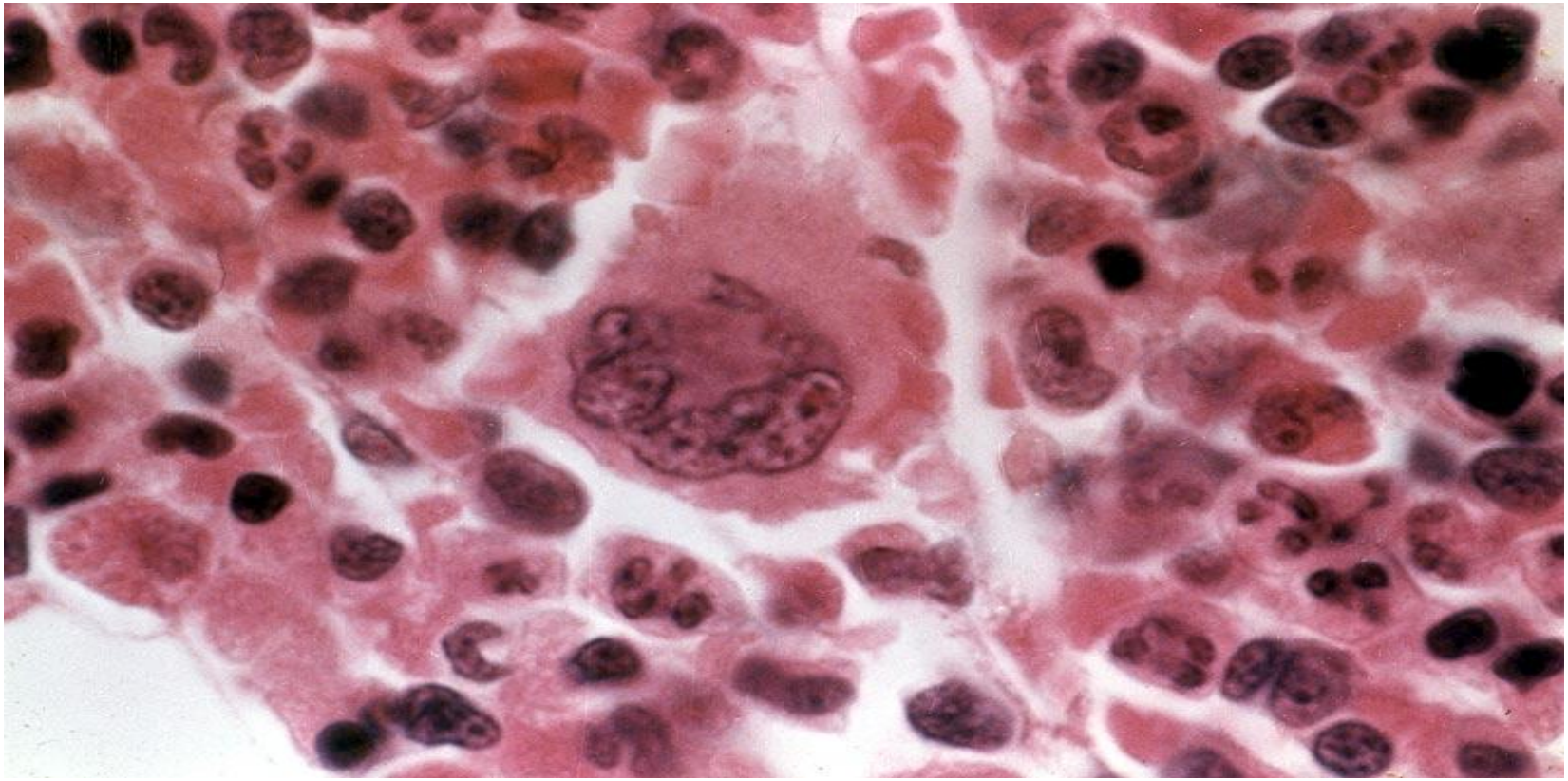
Marrow sinuses are sinusoidal, discontinuous capillaries. Mature cells enter the sinuses and are conveyed to the systemic circulation via nutrient veins.

Megakaryocytes in bone marrow produce blood platelets

- **LM appearance:** **A huge cell, up to 50 µm in diameter. Its long nucleus has several lobes (the nucleus is polyploid and can be up to 64N). The cytoplasm is pale pink/red, without visible granules. In bone marrow, megakaryocytes are situated adjacent to a marrow sinus (large capillary), although this may not be obvious in tissue sections.**

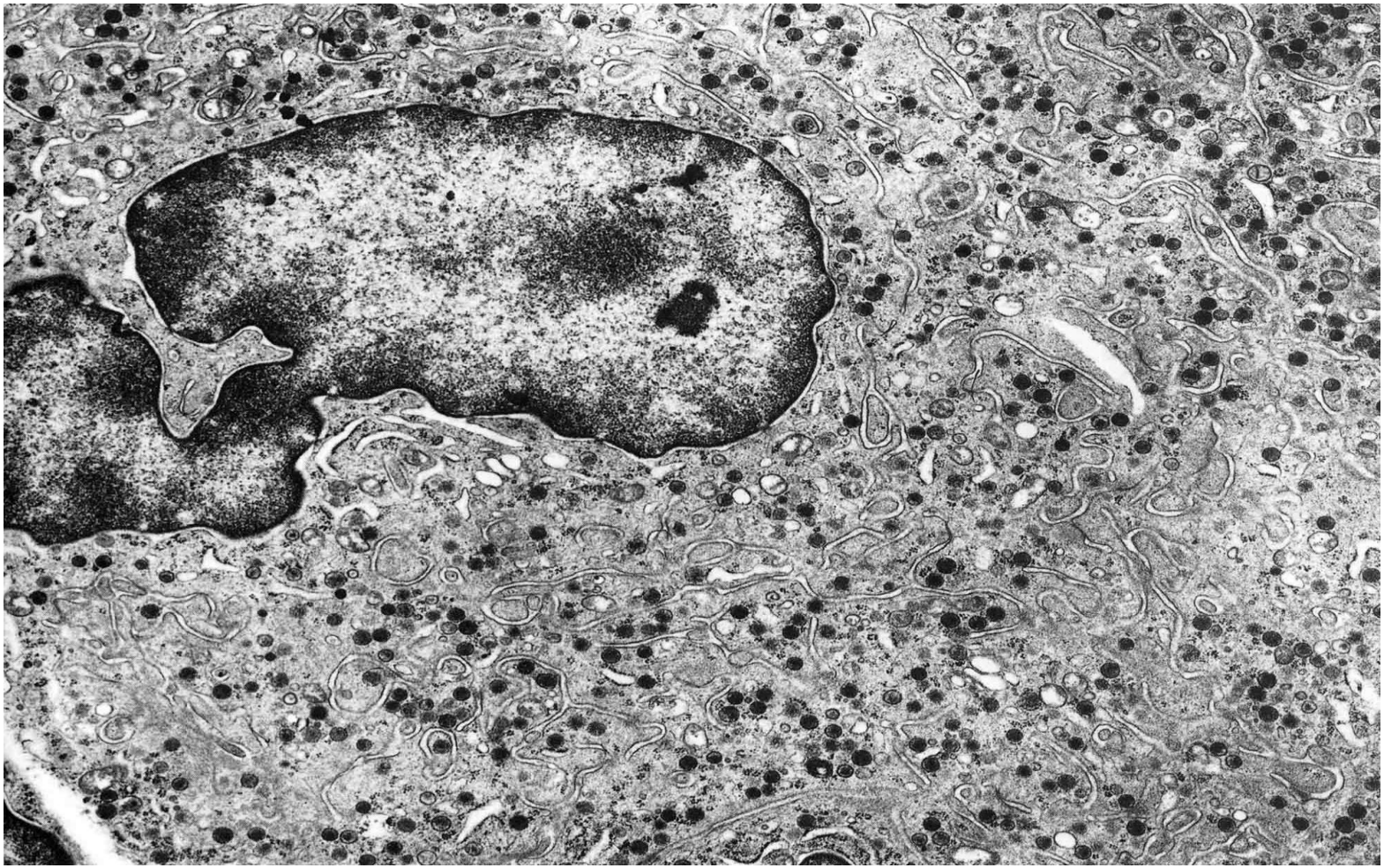
- **TEM appearance:** **Particularly striking in the cytoplasm are many curved white lines that are the platelet demarcation channels, membrane-bound spaces forming the boundaries between future platelets. The cytoplasm also contains granules of various sizes, that will be in the platelets.**
- **Function:** **Megakaryocytes produce blood platelets by fragmentation of their cytoplasm, extending cell processes through the endothelium of a marrow sinus, and releasing clusters of immature platelets into the blood, to become mature platelets.**

Megakaryocyte, LM section



LM appearance: **A huge cell, up to 50 µm in diameter. Its long nucleus has several lobes (the nucleus is polyploid and can be up to 64N). The cytoplasm is pale pink/red, without visible granules. In bone marrow, megakaryocytes are situated adjacent to a marrow sinus (large capillary), although this may not be obvious in tissue sections.**

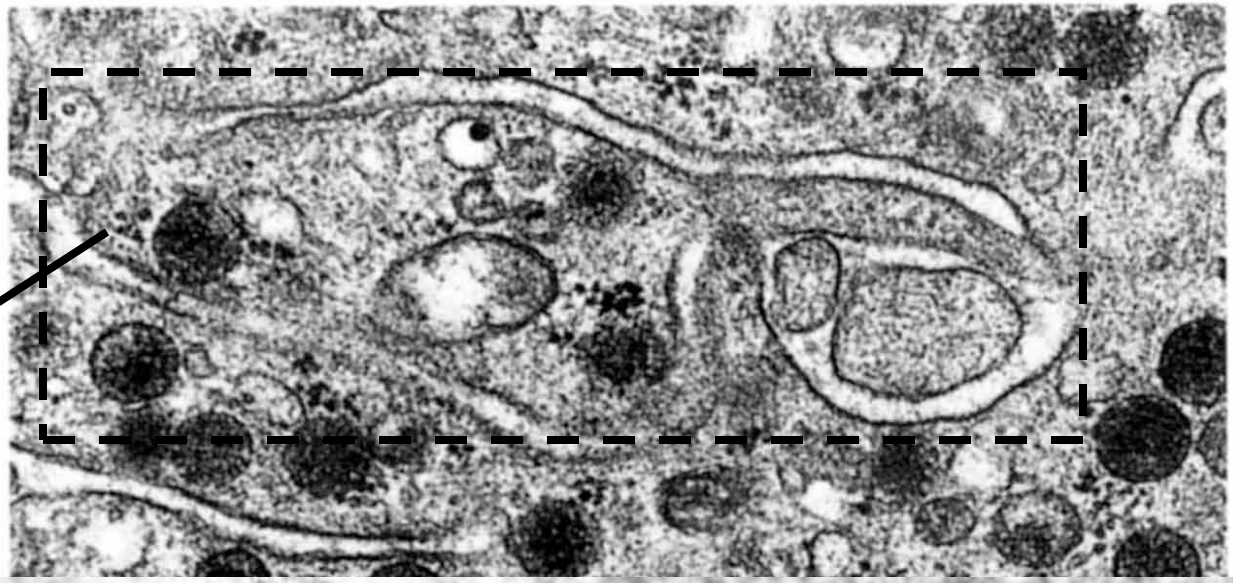
Electron micrograph of megakaryocyte, source of platelets

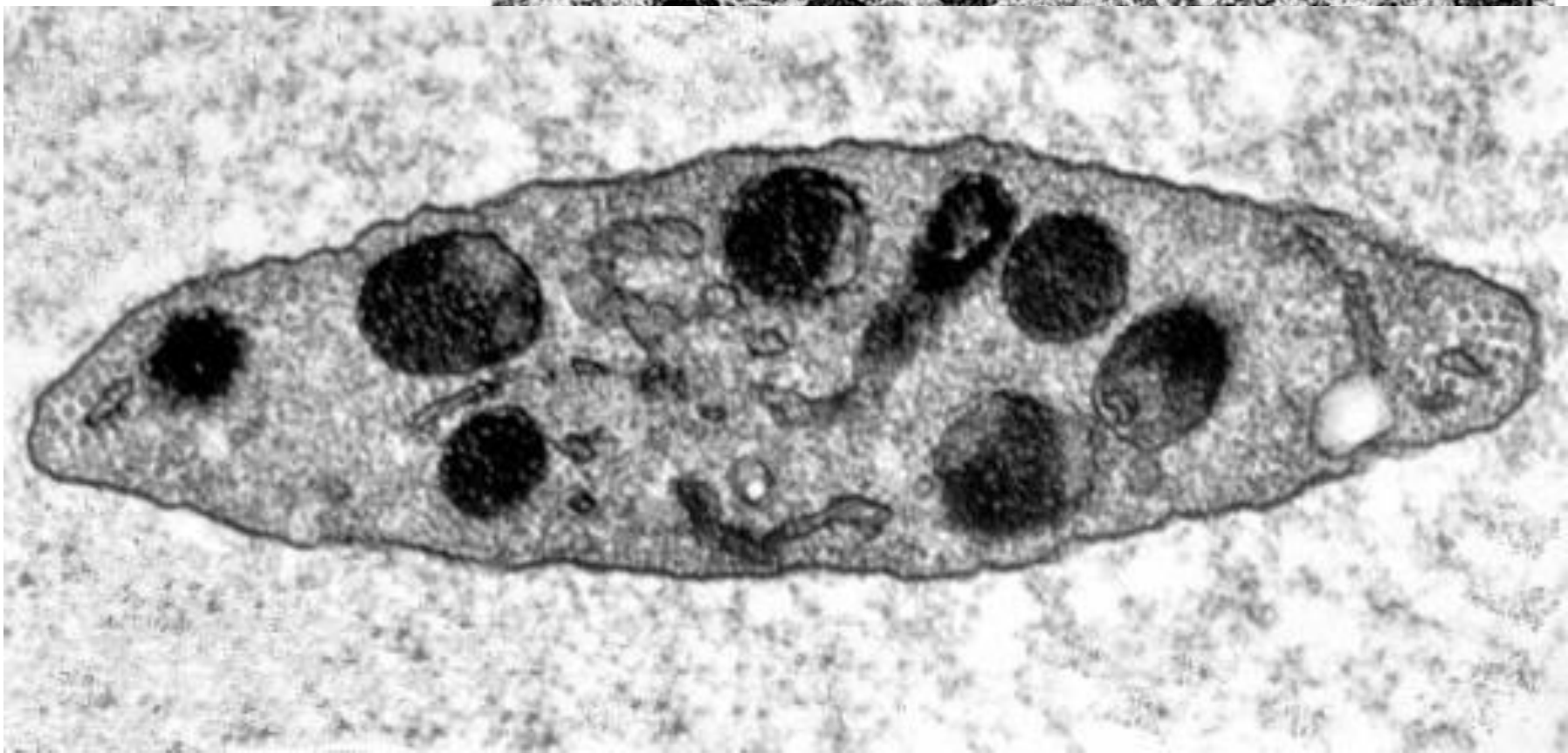


Particularly striking in the cytoplasm are many curved white lines that are the platelet demarcation channels, membrane-bound spaces forming the boundaries between future platelets. The cytoplasm also contains granules of various sizes that will be incorporated into the platelets.

EM detail of megakaryocyte cytoplasm

Will be extruded as a platelet





Al-Noor University College.

Medical laboratories technics department.

Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Bone .

Dr. Ali Ashgar Abd

BONE

- As the main constituent of the adult skeleton, bone tissue :
  1-Provides solid support for the body

  2-Protects vital organs such as those in the cranial and thoracic cavities.

3-Encloses internal (medullary) cavities containing bone marrow where blood cells are formed.

4- Bone (or osseous) tissue also serves as a reservoir of calcium, phosphate, and other ions that can be released or stored in a controlled fashion to maintain constant concentrations in body fluids.

5- Bones form a system of levers that multiply the forces generated during skeletal muscle contraction and transform them into bodily movements.

This mineralized tissue therefore confers mechanical and metabolic functions to the skeleton.

Bone is a specialized connective tissue composed of calcified extracellular material, the bone matrix, and following three major cell types (Figure):

- **Osteocytes** (Gr. osteon, bone + kytos, cell), which are found in cavities (lacunae) between bone matrix layers (lamellae), with cytoplasmic processes in small canaliculi (L. canalis, canal) that extend into the matrix (Figure b)
- **Osteoblasts** (osteon + Gr. blastos, germ), growing cells which synthesize and secrete the organic components of the matrix
- **Osteoclasts** (osteon + Gr. klastos, broken), which are giant, multinucleated cells involved in removing calcified bone matrix and remodeling bone tissue.

Because metabolites are unable to diffuse through the calcified matrix of bone, the exchanges between osteocytes and blood capillaries depend on communication through the very thin, cylindrical spaces of the canaliculi.

All bones are lined on their internal and external surfaces by layers of connective tissue containing osteogenic cells— endosteum on the internal surface surrounding the marrow cavity and periosteum on the external surface.

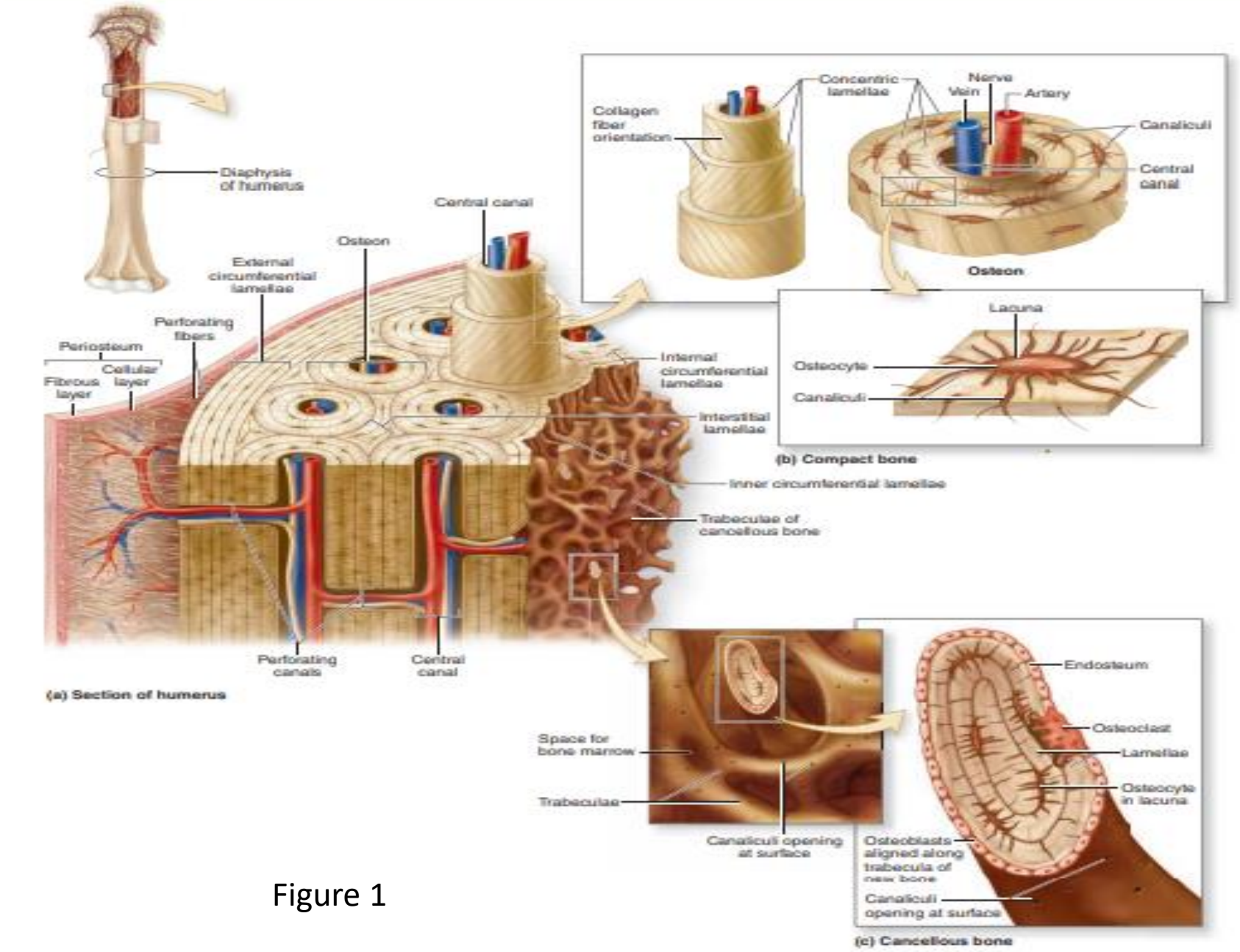

Components of bone.
Diaphysis of humerus
Central canal
Osteon
External circumferential lamellae
Perforating fibers
Periosteum
Cellular layer
Fibrous layer
Internal circumferential lamellae
Interstitial lamellae
Inner circumferential lamellae
Trabeculae of cancellous bone
Perforating canals
Central canal
(a) Section of humerus
Concentric lamellae
Collagen fiber orientation
Nerve
Vein
Artery
Canaliculi
Central canal
Osteon
Lacuna
Osteocyte
Canaliculi
(b) Compact bone
Space for bone marrow
Trabeculae
Canaliculi opening at surface
Endosteum
Osteoclast
Lamellae
Osteocyte in lacuna
Osteoblasts aligned along trabecula of new bone
Canaliculi opening at surface
(c) Cancellous bone

Figure 1

BONE CELLS

Osteoblasts

Originating from mesenchymal stem cells, osteoblasts produce the organic components of bone matrix, including type I collagen fibers, proteoglycans, and matricellular glycoproteins such as osteonectin. Deposition of the inorganic components of bone also depends on osteoblast activity. Active osteoblasts are located exclusively at the surfaces of bone matrix, to which they are bound by integrins, typically forming a single layer of cuboidal cells joined by adherent and gap junctions (Figure 2a). When their synthetic activity is completed, some osteoblasts differentiate as osteocytes entrapped in matrix bound lacunae, some flatten and cover the matrix surface as **bone lining cells**, and the majority undergo apoptosis.

During the processes of matrix synthesis and calcification, osteoblasts are polarized cells with ultrastructural features denoting active protein synthesis and secretion. Matrix components are secreted at the cell surface in contact with existing bone matrix, producing a layer of unique collagen-rich material called **osteoid** between the osteoblast layer and the preexisting bone surface (Figure 2a). This process of bone appositional growth is completed by subsequent deposition of calcium salts into the newly formed matrix.

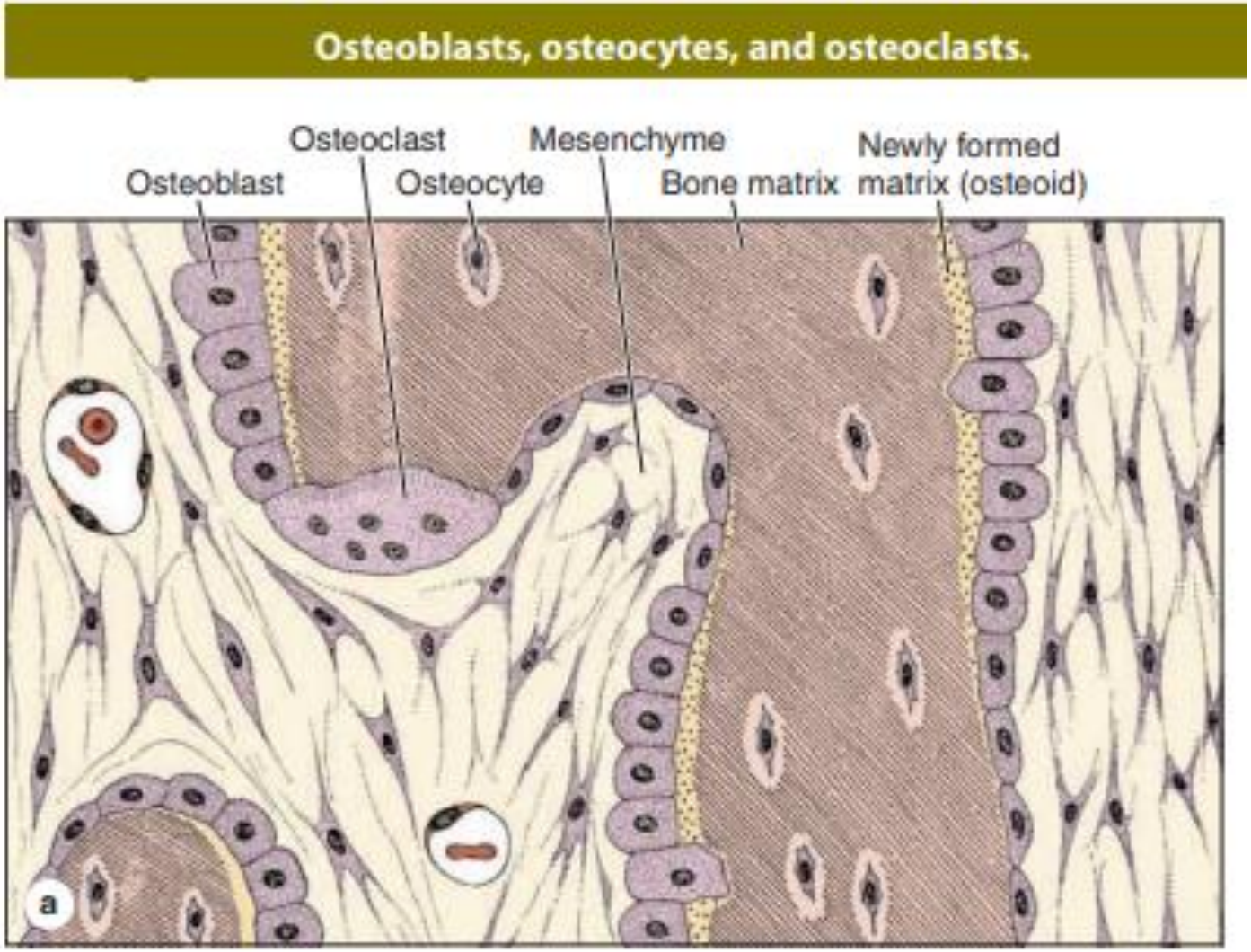

Osteoblasts, osteocytes, and osteoclasts.
Osteoclast
Mesenchyme
Newly formed
Osteoblast
Osteocyte
Bone matrix
matrix (osteoid)
a

Figure 2a

The process of matrix mineralization is not completely understood, but basic aspects of the process are shown in (Figure 2b). Prominent among the noncollagen proteins secreted by osteoblasts is the vitamin K-dependent polypeptide **osteocalcin**, which together with various glycoproteins binds Ca2+ ions and concentrates this mineral locally.

Osteoblasts also release membrane-enclosed **matrix vesicles** rich in alkaline phosphatase and other enzymes whose activity raises the local concentration of PO4 3− ions. In the microenvironment with high concentrations of both these ions, matrix vesicles serve as foci for the formation of hydroxyapatite [Ca10(PO4)6 (OH)2] crystals, the first visible step in calcification. These crystals grow rapidly by accretion of more mineral and eventually produce a confluent mass of calcified material embedding the collagen fibers and proteoglycans (Figure 2b).

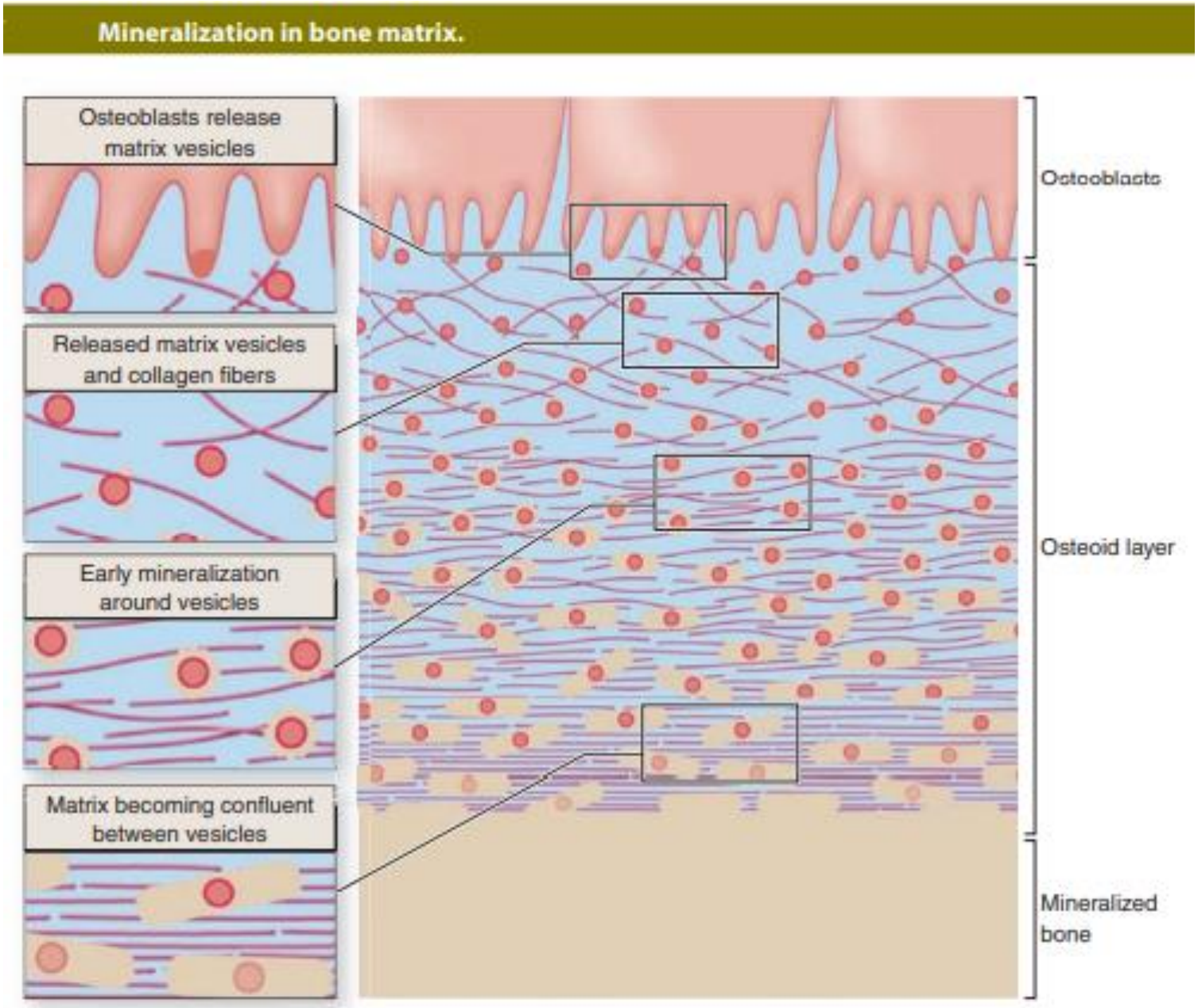

Mineralization in bone matrix.
Osteoblasts release matrix vesicles
Released matrix vesicles and collagen fibers
Early mineralization around vesicles
Matrix becoming confluent between vesicles
Osteoblasts
Osteoid layer
Mineralized bone

Figure 2b

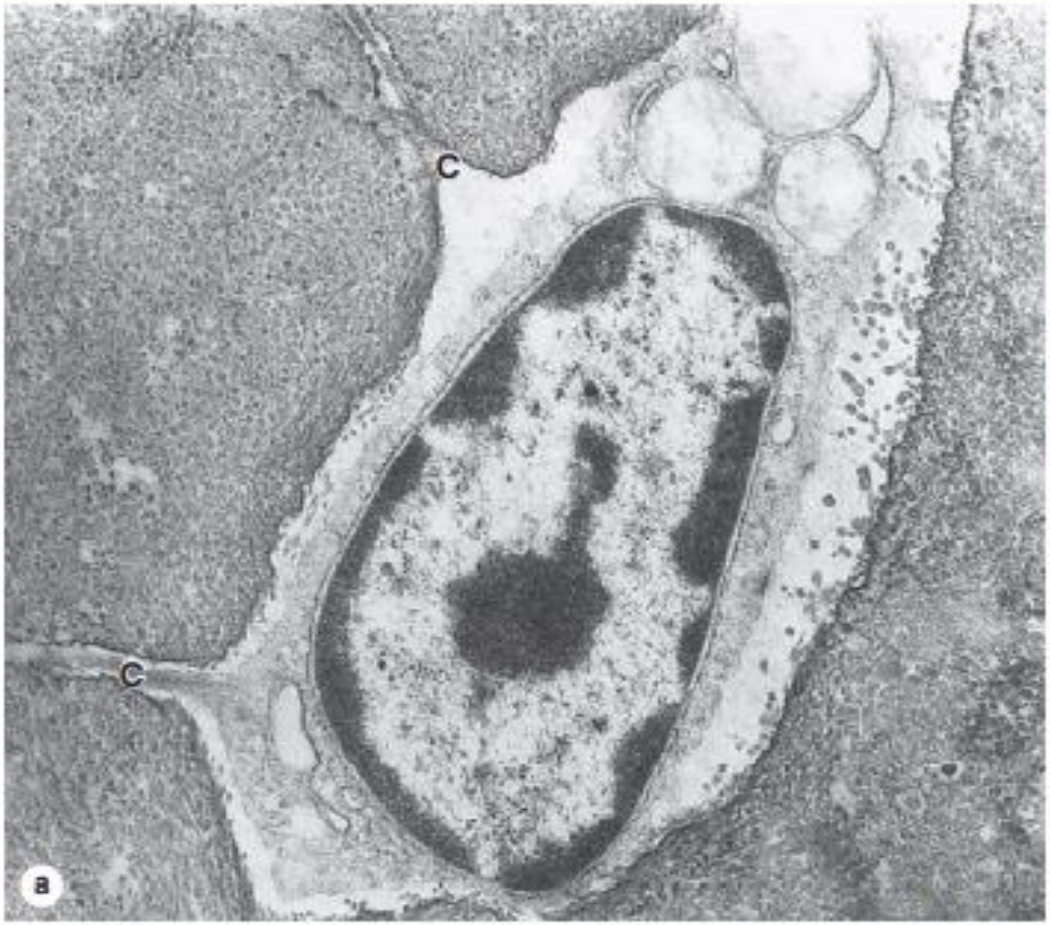
Osteocytes

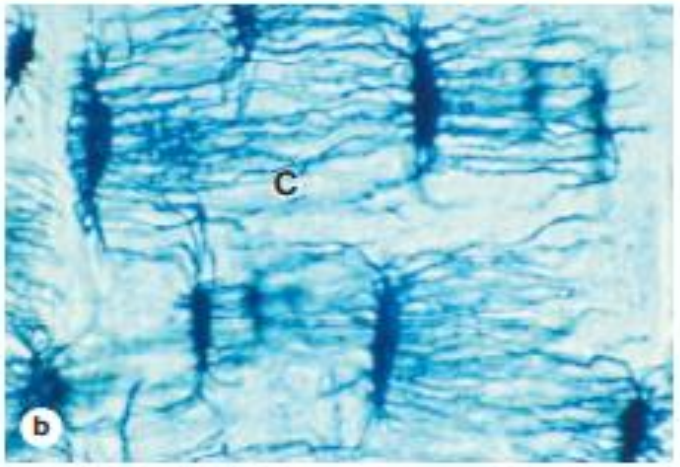
As mentioned some osteoblasts become surrounded by the material they secrete and then differentiate as **osteocytes** enclosed singly within the **lacunae** spaced throughout the mineralized matrix. During the transition from osteoblasts to osteocytes, the cells extend many long dendritic processes, which also become surrounded by calcifying matrix. The processes thus come to occupy the many canaliculi, 250-300 nm in diameter, radiating from each lacuna (Figures 3 and 3b). Diffusion of metabolites between osteocytes and blood vessels occurs through the small amount of interstitial fluid in the canaliculi between the bone matrix and the osteocytes and their processes. Osteocytes also communicate with one another and ultimately with nearby osteoblasts and bone lining cells via gap junctions at the ends of their processes.

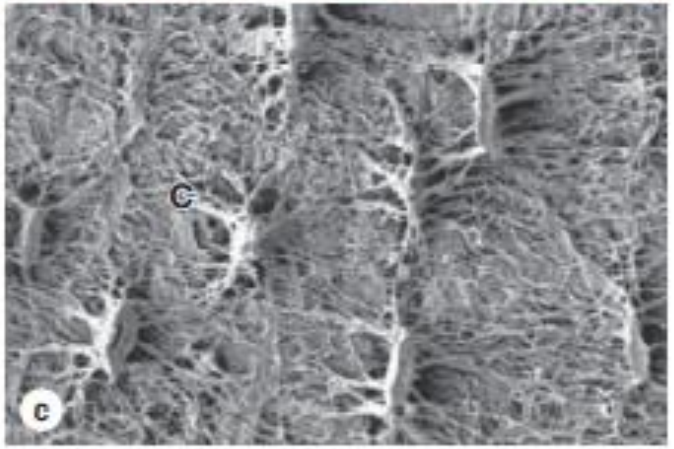
These connections between osteocyte processes and nearly all other bone cells in the extensive lacunar-canalicular network allow osteocytes to serve as mechanosensors detecting the mechanical load on the bone as well as stress- or fatigue-induced microdamage and to trigger remedial activity in osteoblasts and osteoclasts.

Normally the most abundant cells in bone, osteocytes exhibit significantly less RER, smaller Golgi complexes, and more condensed nuclear chromatin than osteoblasts (Figure 3). Osteocytes maintain the calcified matrix and their death is followed by rapid matrix resorption. While sharing most matrix related activities with osteoblasts, osteocytes also express many different proteins, including factors with paracrine and endocrine effects that help regulate bone remodeling

Osteocytes in lacunae.







(a) TEM showing an osteocyte in a lacuna and two dendritic processes in canaliculi (**C**) surrounded by bony matrix. Many such processes are extended from each cell as osteoid is being secreted; this material then undergoes calcification around the processes, giving rise to canaliculi. (X30,000)

(b) Photomicrograph of bone, not decalcified or sectioned, but ground very thin to demonstrate lacunae and canaliculi. The lacunae and canaliculi (**C**) appear dark and show the communication between these structures through which nutrients derived from blood vessels diffuse and are passed from cell to cell in living bone. (X400; Ground bone)

(c) SEM of nondecalcified, sectioned, and acid-etched bone showing lacunae and canaliculi (**C**). (X400)

Osteoclasts

are very large, motile cells with multiple nuclei (Figure 4) that are essential for matrix resorption during bone growth and remodeling. The large size and multinucleated condition of osteoclasts are due to their origin from the fusion of bone marrow-derived monocytes. Osteoclast development requires two polypeptides produced by osteoblasts: macrophage-colony-stimulating factor and the receptor activator of nuclear factor-κB ligand (RANKL). In areas of bone undergoing resorption, osteoclasts on the bone surface lie within enzymatically etched depressions or cavities in the matrix known as **resorption lacunae** (or **Howship lacunae**).

In an active osteoclast, the membrane domain that contacts the bone forms a circular **sealing zone** that binds the cell tightly to the bone matrix and surrounds an area with many surface projections, called the **ruffled border**. This circumferential sealing zone allows the formation of a specialized microenvironment between the osteoclast and the matrix in which bone resorption occurs (Figure 4).

Into this subcellular pocket the osteoclast pumps protons to acidify and promote dissolution of the adjacent hydroxyapatite, and releases matrix metalloproteinases and other hydrolytic enzymes from lysosome-related secretory vesicles for the localized digestion of matrix proteins. Osteoclast activity is controlled by local signaling factors from other bone cells. Osteoblasts activated by parathyroid hormone produce M-CSF, RANKL, and other factors that regulate the formation and activity of osteoclasts

PERIOSTEUM & ENDOSTEUM

External and internal surfaces of all bones are covered by connective tissue of the periosteum and endosteum, respectively (Figures 1). The **periosteum** is organized much like the perichondrium of cartilage, with an outer fibrous layer of dense connective tissue, containing mostly bundled type I collagen, but also fibroblasts and blood vessels. Bundles of periosteal collagen, called **perforating (or Sharpey) fibers**, penetrate the bone matrix and bind the periosteum to the bone. Periosteal blood vessels branch and penetrate the bone, carrying metabolites to and from bone cells.

The periosteum's inner layer is more cellular and includes osteoblasts, bone lining cells, and mesenchymal stem cells referred to as **osteoprogenitor** cells. With the potential to proliferate extensively and produce many new osteoblasts, osteoprogenitor cells play a prominent role in bone growth and repair. Internally the very thin **endosteum** covers small **trabeculae** of bony matrix that project into the marrow cavities (Figure 1). The endosteum also contains osteoprogenitor cells, osteoblasts, and bone lining cells, but within a sparse, delicate matrix of collagen fibers.

osteoclast

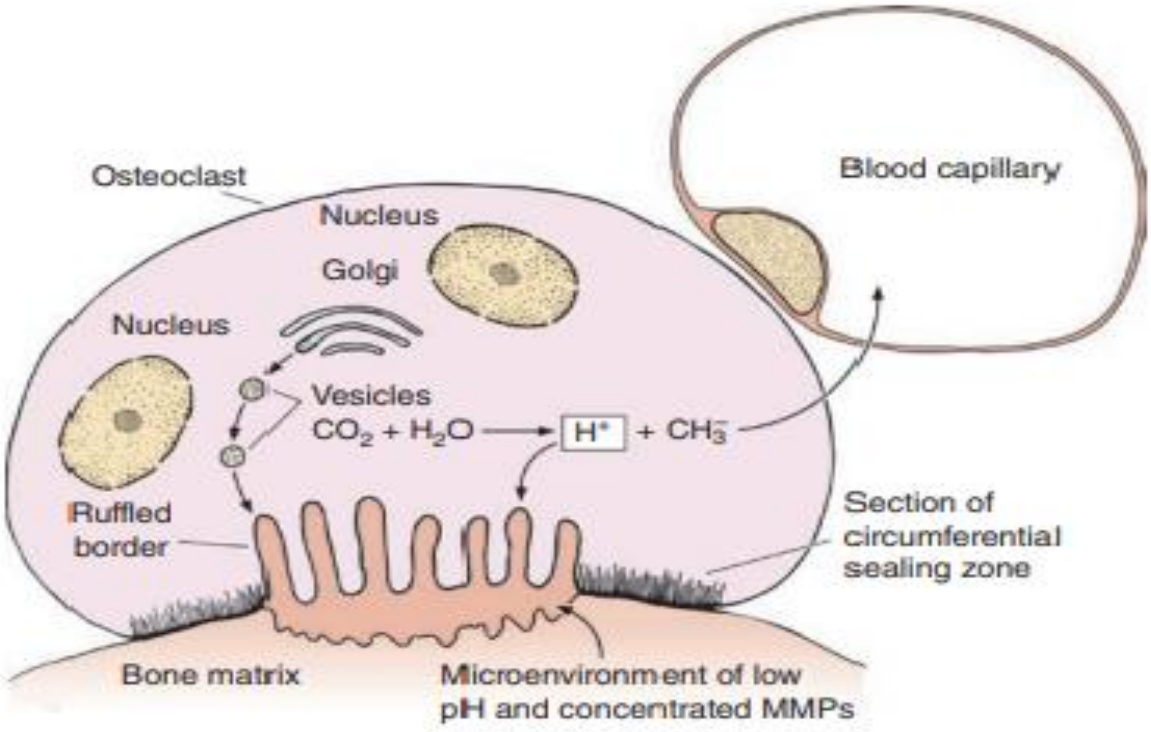


Figure 4

BONE MATRIX

About 50% of the dry weight of bone matrix is inorganic materials. Calcium hydroxyapatite is most abundant, but bicarbonate, citrate, magnesium, potassium, and sodium ions are also found. Significant quantities of noncrystalline calcium phosphate are also present. The surface of hydroxyapatite crystals are hydrated, facilitating the exchange of ions between the mineral and body fluids. The organic matter embedded in the calcified matrix is 90% type I collagen, but also includes mostly small proteoglycans and multiadhesive glycoproteins such as **osteonectin**. Calciumbinding proteins, notably osteocalcin, and the phosphatases

released from cells in matrix vesicles promote calcification of the matrix. Other tissues rich in type I collagen lack osteocalcin and matrix vesicles and therefore do not normally become calcified.

The association of minerals with collagen fibers during calcification provides the hardness and resistance required for bone function. If a bone is decalcified by a histologist, its shape is preserved but it becomes soft and pliable like other connective tissues. Because of its high collagen content, decalcified bone matrix is usually acidophilic.

TYPES OF BONE

dense area near the surface corresponding to **compact (cortical) bone**, which represents 80% of the total bone mass, and deeper areas with numerous interconnecting cavities, called **cancellous (trabecular) bone**, constituting about 20% of total bone mass. Histological features and important locations of the major types of bone are summarized in Table 1.

At the microscopic level both compact and cancellous bones typically show two types of organization: mature **lamellar bone**, with matrix existing as discrete sheets, and **woven bone**, newly formed with randomly arranged components.

TABLE 8–1 Summary of bone types and their organization.

Type of Bone	Histological Features	Major Locations	Synonyms
Woven bone, newly calcified	Irregular and random arrangement of cells and collagen; lightly calcified	Developing and growing bones; hard callus of bone fractures	Immature bone; primary bone; bundle bone
Lamellar bone, remodeled from woven bone	Parallel bundles of collagen in thin layers (lamellae), with regularly spaced cells between; heavily calcified	All normal regions of adult bone	Mature bone; secondary bone
Compact bone, ~80% of all lamellar bone	Parallel lamellae or densely packed osteons, with interstitial lamellae	Thick, outer region (beneath periosteum) of bones	Cortical bone
Cancellous bone, ~20% of all lamellar bone	Interconnected thin spicules or trabeculae covered by endosteum	Inner region of bones, adjacent to marrow cavities	Spongy bone; trabecular bone; medullary bone

In long bones, the bulbous ends—called **epiphyses** (Gr. epiphysis, an excrescence)—are composed of cancellous bone covered by a thin layer of compact cortical bone. The cylindrical part—the **diaphysis** (Gr. diaphysis, a growing between)—is almost totally dense compact bone, with a thin region of cancellous bone on the inner surface around the central **marrow cavity** (Figure 1). Short bones such as those of the wrist and ankle usually have cores of cancellous bone surrounded completely by compact bone. The flat bones that form the calvaria (skullcap) have two layers of compact bone called **plates**, separated by a thicker layer of cancellous bone called the **diploë**

Lamellar Bone Most bone in adults, compact or cancellous, is organized as **lamellar bone**, characterized by multiple layers or **lamellae** of calcified matrix, each 3-7 µm thick. The lamellae are organized as parallel sheets or concentrically around a central canal. In each lamella, type I collagen fibers are aligned, with the pitch of the fibers' orientation shifted orthogonally (by about 90 degrees) in successive lamellae (Figure 1). This highly ordered organization of collagen within lamellar bone causes birefringence with polarizing light microscopy; the alternating bright and dark layers are due to the changing orientation of collagen fibers in the lamellae .

Like the orientation of wood fibers in plywood the highly ordered, alternating organization of collagen fibers in lamellae adds greatly to the strength of lamellar bone.

An **osteon** (or **Haversian system**) refers to the complex of concentric lamellae, typically 100-250 µm in diameter, surrounding a central canal that contains small blood vessels, nerves, and endosteum .Between successive lamellae are lacunae, each with one osteocyte, all interconnected by the canaliculi containing the cells' dendritic processes. Processes of adjacent cells are in contact via gap junctions, and all cells of an osteon receive nutrients and oxygen from vessels in the central canal (Figure 1). The outer boundary of each osteon is a layer called the cement line that includes many more noncollagen proteins in addition to mineral and collagen.

Each osteon is a long, sometimes bifurcated, cylinder generally parallel to the long axis of the diaphysis. Each has 5-20 concentric lamellae around the central canal that communicates with the marrow cavity and the periosteum. Canals also communicate with one another through transverse **perforating canals** (or **Volkmann canals**) that have few, if any, concentric lamellae (Figures1). All central osteon canals and perforating canals form when matrix is laid down around areas with preexisting blood vessels.

Scattered among the intact osteons are numerous irregularly shaped groups of parallel lamellae called interstitial lamellae. These structures are lamellae remaining from osteons partially destroyed by osteoclasts during growth and remodeling of bone.

Compact bone (eg, in the diaphysis of long bones) also includes parallel lamellae organized as multiple **external circumferential lamellae** immediately beneath the periosteum and fewer inner circumferential lamellae around the marrow cavity (Figure 1). The lamellae of these outer and innermost areas of compact bone enclose and strengthen the middle region containing vascularized osteons.

Bone remodeling occurs continuously throughout life. In compact bone, remodeling resorbs parts of old osteons and produces new ones. As shown in (Figure 5) osteoclasts remove old bone and form small, tunnel-like cavities. Such tunnels are quickly invaded by osteoprogenitor cells from the endosteum or periosteum and sprouting loops of capillaries. Osteoblasts develop, line the wall of the tunnels, and begin to secrete osteoid in a cyclic manner, forming a new osteon with concentric lamellae of bone and trapped osteocytes (Figure 5) In healthy adults 5%-10% of the bone turns over annually.

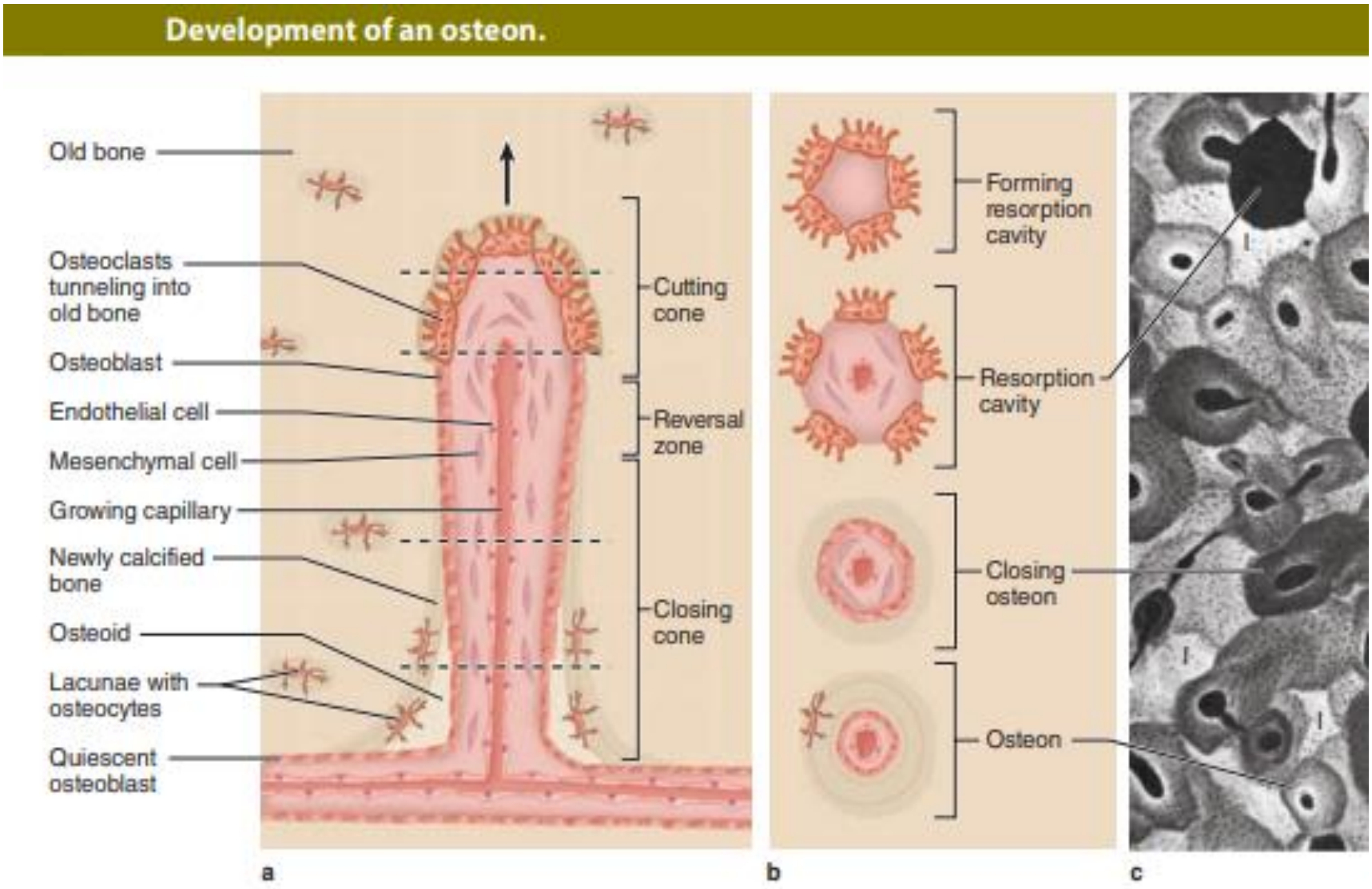

Development of an osteon.
Old bone
Osteoclasts tunneling into old bone
Osteoblast
Endothelial cell
Mesenchymal cell
Growing capillary
Newly calcified bone
Osteoid
Lacunae with osteocytes
Quiescent osteoblast
Cutting cone
Reversal zone
Closing cone
a
Forming resorption cavity
Resorption cavity
Closing osteon
Osteon
b
c

Figure 5

OSTEOGENESIS

Bone development or **osteogenesis** occurs by one of two processes:

1. **Intramembranous ossification**.
2. **Endochondral ossification.**

Intramembranous Ossification:

Intramembranous ossification, by which most flat bones begin to form, takes place within condensed sheets (“membranes”) of embryonic mesenchymal tissue. Most bones of the skull and jaws, as well as the scapula and clavicle, are formed embryonically by intramembranous ossification.

Within the condensed mesenchyme bone formation begins in **ossification centers**, areas in which osteoprogenitor cells arise, proliferate, and form incomplete layers of osteoblasts around a network of developing capillaries. Osteoid secreted by the osteoblasts calcifies as described earlier, forming small irregular areas of woven bone with osteocytes in lacunae and canaliculi .Continued matrix secretion and calcification enlarges these areas and leads to the fusion of neighboring ossification centers. The anatomical bone forms gradually as woven bone matrix is replaced by compact bone that encloses a region of cancellous bone with marrow and larger blood vessels. Mesenchymal regions that do not undergo ossification give rise to the endosteum and the periosteum of the new bone.

In cranial flat bones, lamellar bone formation predominates over bone resorption at both the internal and external surfaces. Internal and external plates of compact bone arise, while the central portion (diploë) maintains its cancellous nature. The fontanelles or “soft spots” on the heads of newborn infants are areas of the skull in which the membranous tissue is not yet ossified.

Endochondral Ossification :

Endochondral (Gr. endon, within + chondros, cartilage) ossification takes place within hyaline cartilage shaped as a small version, or model, of the bone to be formed. This type of ossification forms most bones of the body and is especially well studied in developing long bones, where it consists of the sequence of events shown in (Figure 6).

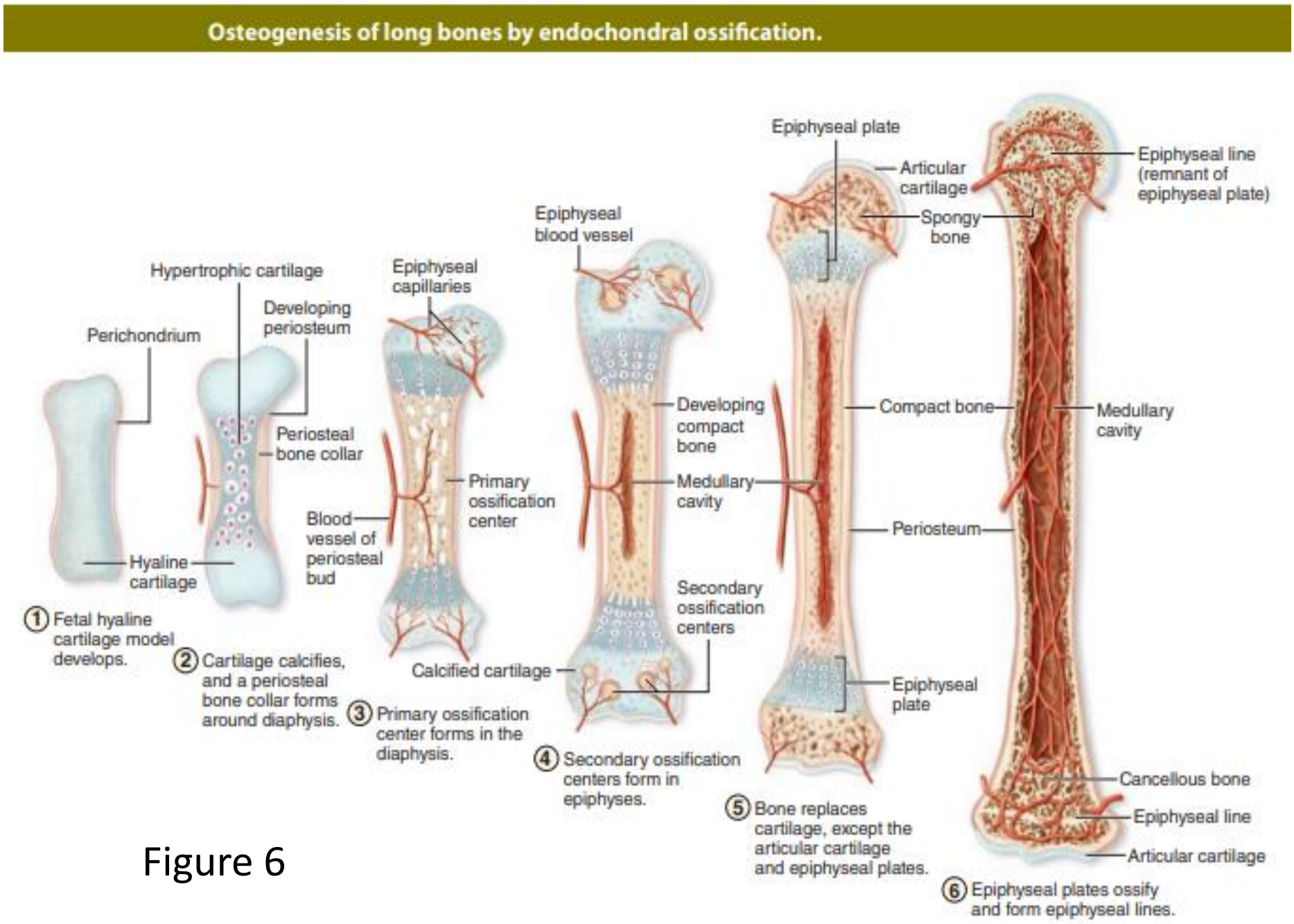

Osteogenesis of long bones by endochondral ossification.
Perichondrium
Hypertrophic cartilage
Developing periosteum
Hyaline cartilage
Periosteal bone collar
Blood vessel of periosteal bud
Epiphyseal capillaries
Primary ossification center
Calcified cartilage
Epiphyseal blood vessel
Developing compact bone
Medullary cavity
Secondary ossification centers
Epiphyseal plate
Articular cartilage
Spongy bone
Compact bone
Periosteum
Epiphyseal plate
Epiphyseal line (remnant of epiphyseal plate)
Medullary cavity
Cancellous bone
Epiphyseal line
Articular cartilage
1 Fetal hyaline cartilage model develops.
2 Cartilage calcifies, and a periosteal bone collar forms around diaphysis.
3 Primary ossification center forms in the diaphysis.
4 Secondary ossification centers form in epiphyses.
5 Bone replaces cartilage, except the articular cartilage and epiphyseal plates.
6 Epiphyseal plates ossify and form epiphyseal lines.

Figure 6

In this process ossification first occurs within a **bone collar** produced by osteoblasts that differentiate within the perichondrium (transitioning to periosteum) around the cartilage model diaphysis. The collar impedes diffusion of oxygen and nutrients into the underlying cartilage, causing local chondrocytes to swell up (hypertrophy), compress the surrounding matrix, and initiate its calcification by releasing osteocalcin and alkaline phosphatase. The hypertrophic chondrocytes eventually die, creating empty spaces within the calcified matrix. One or more blood vessels from the perichondrium (now the periosteum) penetrate the bone collar, bringing osteoprogenitor cells to the porous central region. Along with the vasculature newly formed osteoblasts move into all available spaces and produce woven bone. The remnants of calcified cartilage at this stage are basophilic and the new bone is more acidophilic .

This process in the diaphysis forms the **primary ossification** center (Figure 6), beginning in many embryonic bones as early as the first trimester. **Secondary ossification** centers appear later at the epiphyses of the cartilage model and develop in a similar manner. During their expansion and remodeling both the primary and secondary ossification centers produce cavities that are gradually filled with bone marrow and trabeculae of cancellous bone.

With the primary and secondary ossification centers, two regions of cartilage remain:

- **Articular cartilage** within the joints between long bones (Figure 6), which normally persists through adult life
- The specially organized **epiphyseal cartilage** (also called the **epiphyseal plate** or growth plate), which connects each epiphysis to the diaphysis and allows longitudinal bone growth (Figure 6)

Joints

Joints are regions where adjacent bones are capped and held together firmly by other connective tissues. The type of joint determines the degree of movement between the bones. Joints classified as **synarthroses** (Gr. syn, together + arthrosis, articulation) allow very limited or no movement and are subdivided into fibrous and cartilaginous joints, depending on the type of tissue joining the bones. Major subtypes of synarthroses include the following:

Synostoses involve bones linked to other bones and allow essentially no movement. In older adults synostoses unite the skull bones, which in children and young adults are held together by **sutures**, or thin layers of dense connective tissue with osteogenic cells.

Syndesmoses join bones by dense connective tissue only. Examples include the interosseous ligament of the inferior tibiofibular joint and the posterior region of the sacroiliac joints.

Symphyses have a thick pad of fibrocartilage between the thin articular cartilage covering the ends of the bones. All symphyses, such as the intervertebral discs and pubic symphysis, occur in the midline of the body.

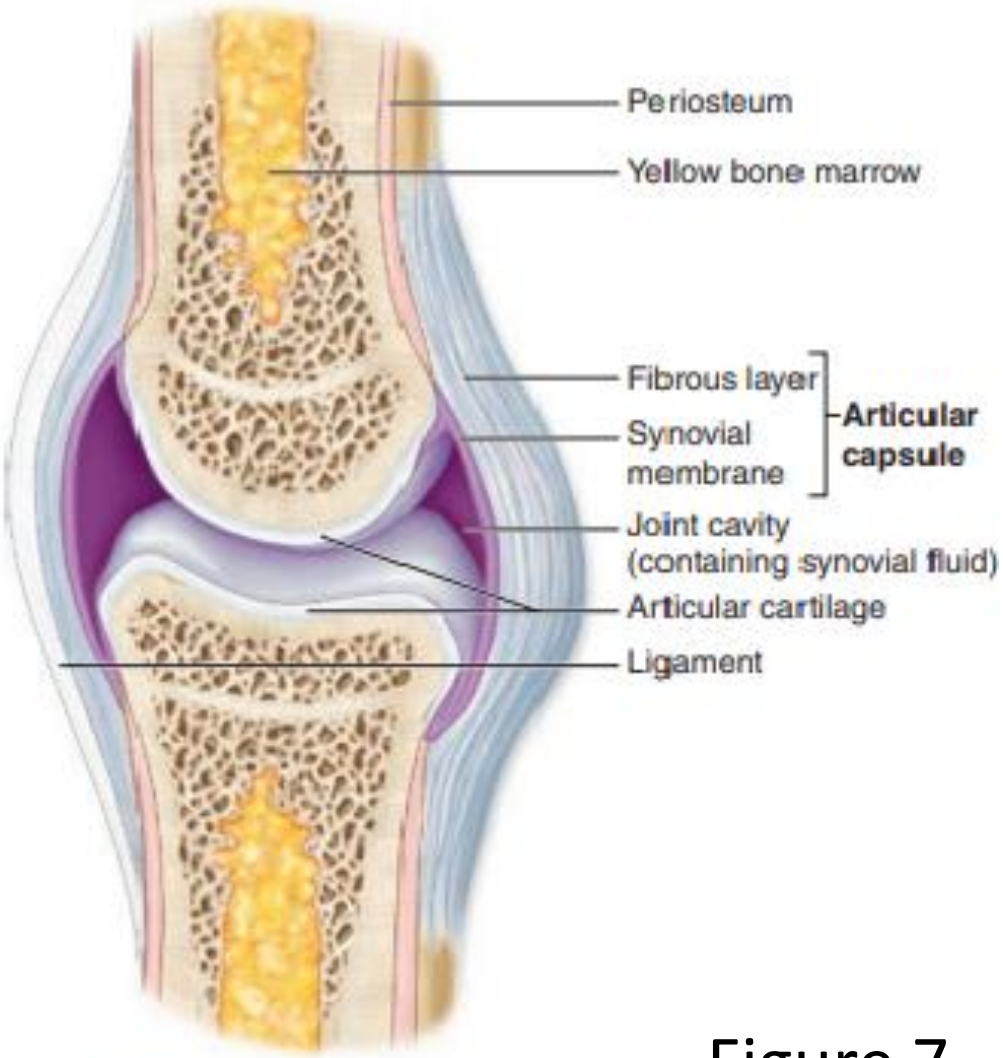
Joints classified as **diarthroses** permit free bone movement. Diarthroses (Figure 7) such as the elbow and knee generally unite long bones and allow great mobility. In a diarthrosis ligaments and a capsule of dense connective tissue

maintain proper alignment of the bones. The capsule encloses a sealed **joint cavity** containing a clear, viscous liquid called **synovial fluid**. The joint cavity is lined, not by epithelium, but by a specialized connective tissue called the **synovial** membrane that extends folds and villi into the joint cavity and produces the lubricant synovial fluid.

In different diarthrotic joints the synovial membrane may have prominent regions with dense connective tissue or fat. The superficial regions of this tissue however are usually well vascularized, with many porous (fenestrated) capillaries. Besides having cells typical of connective tissue proper and a changing population of leukocytes, this area of a synovial membrane is characterized by two specialized cells with distinctly different functions and origins:

- **Macrophage-like synovial cells**, also called **type A** cells, are derived from blood monocytes and remove wear-and-tear debris from the synovial fluid. These modified macrophages, which represent approximately 25% of the cells lining the synovium, are important in regulating inflammatory events within diarthrotic joints.
- **Fibroblastic synovial cells**, **or type B** cells, produce abundant hyaluronan and smaller amounts of proteoglycans. Much of this material is transported by water from the capillaries into the joint cavity to form the synovial fluid, which lubricates the joint, reducing friction on all internal surfaces, and supplies nutrients and oxygen to the articular cartilage.

Diarthroses or synovial joints.



Typical synovial joint

Figure 7

Thank you

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Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Cartilage .

Dr. Ali Ashgar Abd

cartilage

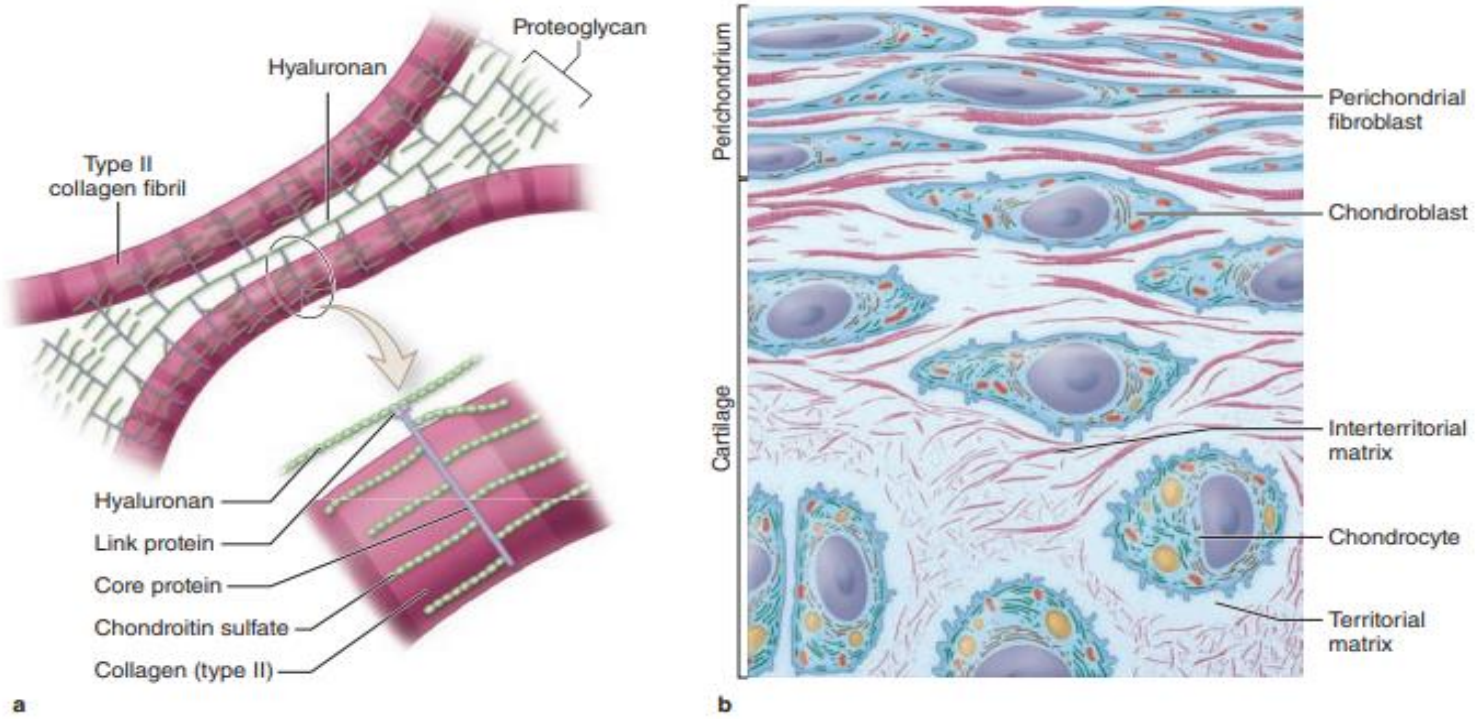
cartilage is a tough, durable form of supporting connective tissue, characterized by **an extracellular matrix (ECM)** with high concentrations of GAGs and proteoglycans, interacting with collagen and elastic fibers. Structural features of its matrix make cartilage ideal for a variety of mechanical and protective roles within the adult skeleton and elsewhere .Cartilage ECM has a firm consistency that allows the tissue to bear mechanical stresses without permanent distortion. In the respiratory tract, ears, and nose, cartilage forms the framework supporting softer tissues. Because of its resiliency and smooth, lubricated surface, cartilage provides cushioning and sliding regions within skeletal joints and facilitates bone movements. cartilage also guides development and growth of long bones, both before and after birth. Cartilage consists of cells called **chondrocytes** (Gr. chondros, cartilage + kytos, cell) embedded in the ECM which unlike connective tissue proper contains no other cell types. Chondrocytes synthesize and maintain all ECM components and are located in matrix cavities called **lacunae**.

The physical properties of cartilage depend on electrostatic bonds between **type II collagen** fibrils**, hyaluronan**, and the sulfated GAGs on densely packed **proteoglycans**. Its semi-rigid consistency is attributable to water bound to the negatively charged hyaluronan and GAG chains extending from proteoglycan core proteins, which in turn are enclosed within a dense meshwork of thin type II collagen fibrils. The high content of bound water allows cartilage to serve as a shock absorber, an important functional role.

All types of cartilage lack vascular supplies and chondrocytes receive nutrients by diffusion from capillaries in surrounding connective tissue (the perichondrium). In some skeletal elements, large blood vessels do traverse cartilage to supply other tissues, but these vessels release few nutrients to the chondrocytes. As might be expected of cells in an avascular tissue, chondrocytes exhibit low metabolic activity. Cartilage also lacks nerves.

The **perichondrium** (Figure 1)is a sheath of dense connective tissue that surrounds cartilage in most places, forming an interface between the cartilage and the tissues supported by the cartilage. The perichondrium harbors the blood supply serving the cartilage and a small neural component. Articular cartilage, which covers the ends of bones in movable joints and which erodes in the course of arthritic degeneration, lacks perichondrium and is sustained by the diffusion of oxygen and nutrients from the synovial fluid. As shown in (Figure 2) , variations in the composition of the matrix characterize three main types of cartilage: hyaline cartilage, elastic cartilage, and fibrocartilage. Important features of these are summarized in Table.

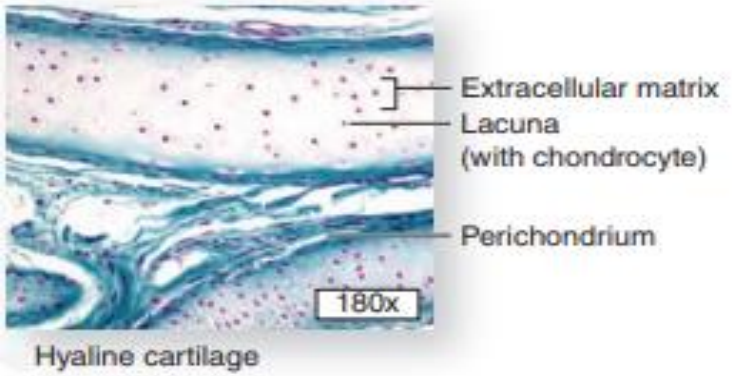
FIGURE 1 The structure of cartilage matrix and cells



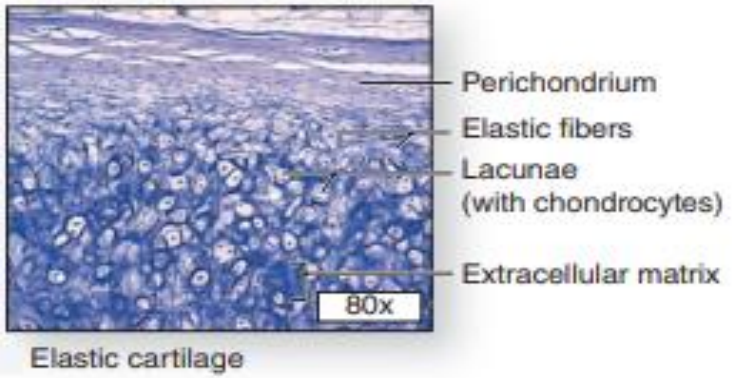
a)Structure of matrix

b)General structure of hyaline cartilage

a



b



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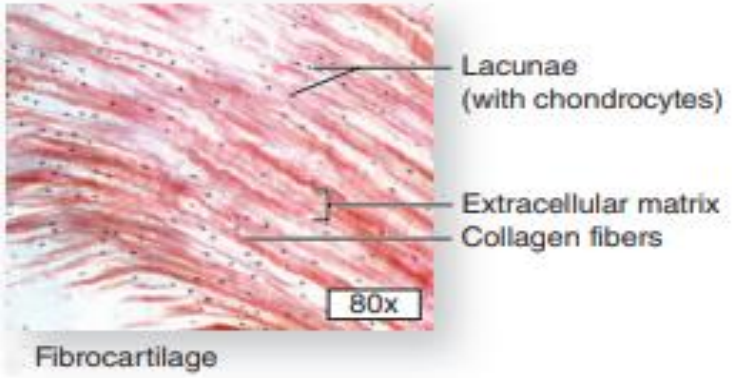


Figure 2

The photomicrographs show the main features of (a) hyaline cartilage, (b) elastic cartilage, and (c) fibrocartilage. Dense connective tissue of perichondrium is shown here with hyaline and elastic cartilage

Types of cartilages

HYALINE CARTILAGE

Hyaline (Gr. hyalos, glass) cartilage, the most common of the three types, is homogeneous and semitransparent in the fresh state. In adults hyaline cartilage is located in the articular surfaces of movable joints, in the walls of larger respiratory passages (nose, larynx, trachea, bronchi), in the ventral ends of ribs, where they articulate with the sternum, and in the epiphyseal plates of long bones, where it makes possible longitudinal bone growth (Figure 2). In the embryo, hyaline cartilage forms the temporary skeleton that is gradually replaced by bone.

Matrix

The dry weight of hyaline cartilage is nearly 40% collagen embedded in a firm, hydrated gel of proteoglycans and structural glycoproteins. In routine histology preparations, the proteoglycans make the matrix generally basophilic and the thin collagen fibrils are barely discernible. Most of the collagen in hyaline cartilage is **type II,** although small amounts of minor collagens are also present. **Aggrecan** ,chondroitin sulfate and keratan sulfate, is the most abundant proteoglycan of hyaline cartilage. Hundreds of these proteoglycans are bound noncovalently by link proteins to long polymers of hyaluronan, as shown schematically in Figure 1a. These proteoglycan complexes bind further to the surface of type II collagen fibrils (Figure 1a). Another important component of cartilage matrix is the structural multiadhesive glycoprotein **chondronectin**. Like fibronectin in other connective tissues, chondronectin binds specifically to GAGs, collagen, and integrins, mediating the adherence of chondrocytes to the ECM.

Staining variations within the matrix reflect local differences in its molecular composition. Immediately surrounding each chondrocyte, the ECM is relatively richer in GAGs than collagen, often causing these areas of **territorial matrix** to stain differently from the intervening areas of interterritorial matrix (Figure 1b).

Chondrocytes

Cells occupy relatively little of the hyaline cartilage mass. At the periphery of the cartilage, young chondrocytes or chondroblasts have an elliptic shape, with the long axes parallel to the surface .Deeper in the cartilage, they are round and may appear in groups of up to eight cells that originate from mitotic divisions of a single chondroblast and are called **isogenous aggregates**. As the chondrocytes become more active in secreting collagens and other ECM components, the aggregated cells are pushed apart and occupy separate lacunae.

Cartilage cells and matrix may shrink slightly during routine histologic preparation, resulting in both the irregular shape of the chondrocytes and their retraction from the matrix. In living tissue chondrocytes fill their lacunae completely. Because cartilage matrix is avascular, chondrocytes respire under low-oxygen tension. Hyaline cartilage cells metabolize glucose mainly by anaerobic glycolysis. Nutrients from the blood diffuse to all the chondrocytes from the cartilage surface, with movements of water and solutes in the cartilage matrix promoted by intermittent tissue compression and decompression during body movements. The limits of such diffusion define the maximum thickness of hyaline cartilage, which usually exists as small, thin plates

Chondrocyte synthesis of sulfated GAGs and secretion of proteoglycans are accelerated by many hormones and growth factors. A major regulator of hyaline cartilage growth is the pituitary-derived protein called growth hormone or somatotropin. This hormone acts indirectly, promoting the endocrine release from the liver of insulin-like growth factors, or somatomedins, which directly stimulate the cells of hyaline cartilage.

Perichondrium

Except in the articular cartilage of joints, all hyaline cartilage is covered by a layer of dense connective tissue, the perichondrium, which is essential for the growth and maintenance of cartilage. The outer region of the perichondrium consists largely of collagen type I fibers and fibroblasts, but an inner layer adjoining the cartilage matrix also contains mesenchymal stem cells which provide a source for new chondroblasts that divide and differentiate into chondrocytes.

ELASTIC CARTILAGE

Elastic cartilage is essentially similar to hyaline cartilage except that it contains an abundant network of elastic fibers in addition to a meshwork of collagen type II fibrils (Figure 2c), which give fresh elastic cartilage a yellowish color. With appropriate staining the elastic fibers usually appear as dark bundles distributed unevenly through the matrix.

More flexible than hyaline cartilage, elastic cartilage is found in the auricle of the ear, the walls of the external auditory canals, the auditory (Eustachian) tubes, the epiglottis, and the upper respiratory tract.

Elastic cartilage in these locations includes a perichondrium similar to that of most hyaline cartilage. Throughout elastic cartilage the cells resemble those of hyaline cartilage both physiologically and structurally

FIBROCARTILAGE

Fibrocartilage takes various forms in different structures but is essentially a mingling of hyaline cartilage and dense connective tissue (Figure 2d). It is found in intervertebral discs, in attachments of certain ligaments, and in the pubic symphysis—all places where it serves as very tough, yet cushioning support tissue for bone.

Chondrocytes of fibrocartilage occur singly and often in aligned isogenous aggregates, producing type II collagen and other ECM components, although the matrix around these chondrocytes is typically sparse. Areas with chondrocytes and hyaline matrix are separated by other regions with fibroblasts and dense bundles of type I collagen which confer extra tensile strength to this tissue. The relative scarcity of proteoglycans overall makes fibrocartilage matrix more acidophilic than that of hyaline or elastic cartilage. There is no distinct surrounding perichondrium in fibrocartilage.

Intervertebral discs of the spinal column are composed primarily of fibrocartilage and act as lubricated cushions and shock absorbers preventing damage to adjacent vertebrae from abrasive forces or impacts. Held in place by ligaments, Important features of the three major types of cartilage are summarized in Table .

TABLE

Important features of the major cartilage types.

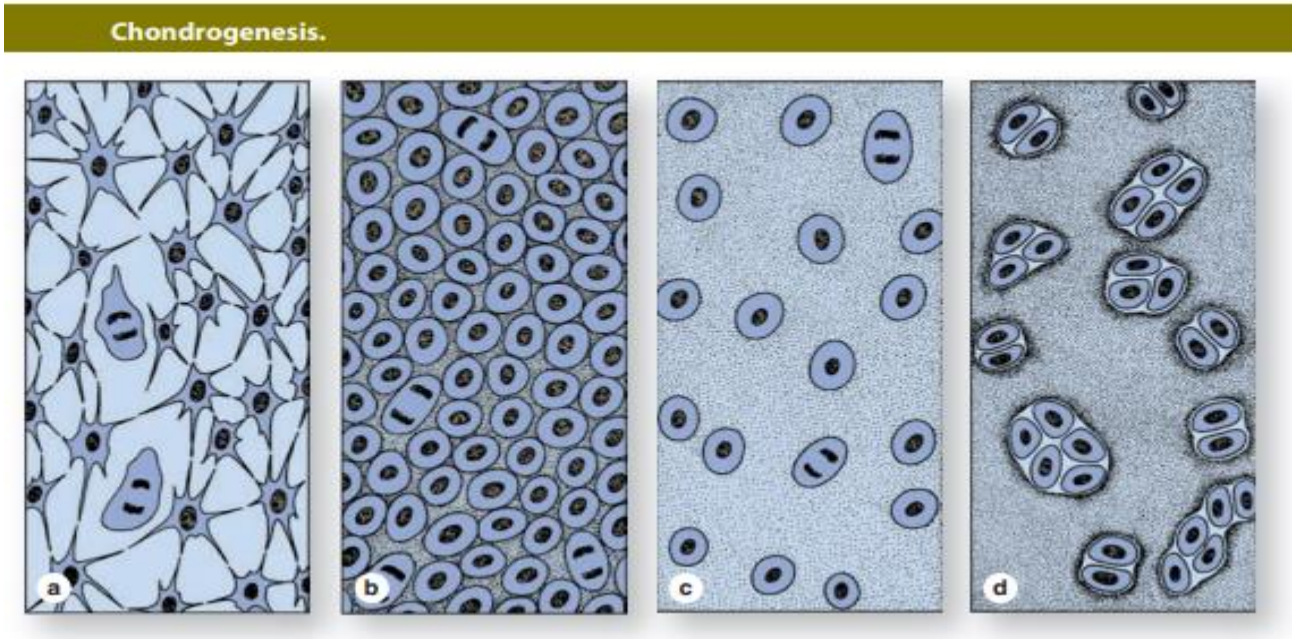
	Hyaline Cartilage	Elastic Cartilage	Fibrocartilage
Main features of the extracellular matrix	Homogeneous, with type II collagen and aggrecan	Type II collagen, aggrecan, and darker elastic fibers	Type II collagen and large areas of dense connective tissue with type I collagen
Major cells	Chondrocytes, chondroblasts	Chondrocytes, chondroblasts	Chondrocytes, fibroblasts
Typical arrangement of chondrocytes	Isolated or in small isogenous groups	Usually in small isogenous groups	Isolated or in isogenous groups arranged axially
Presence of perichondrium	Yes (except at epiphyses and articular cartilage)	Yes	No
Main locations or examples	Many components of upper respiratory tract; articular ends and epiphyseal plates of long bones; fetal skeleton	External ear, external acoustic meatus, auditory tube; epiglottis and certain other laryngeal cartilages	Intervertebral discs, pubic symphysis, meniscus, and certain other joints; insertions of tendons
Main functions	Provides smooth, low-friction surfaces in joints; structural support for respiratory tract	Provides flexible shape and support of soft tissues	Provides cushioning, tensile strength, and resistance to tearing and compression

CARTILAGE FORMATION, GROWTH, & REPAIR

All cartilage forms from embryonic mesenchyme in the process of chondrogenesis (Figure 3). The first indication of cell differentiation is the rounding up of the mesenchymal cells, which retract their extensions, multiply rapidly, and become more densely packed together. In general the terms “chondroblasts” and “chondrocytes” respectively refer to the cartilage cells during and after the period of rapid proliferation. At both stages the cells have basophilic cytoplasm rich in RER for collagen synthesis (Figuer 4) . Production of the ECM encloses the cells in their lacunae and then gradually separates chondroblasts from one another. During embryonic development, the cartilage differentiation takes place primarily from the center outward; therefore the more central cells have the characteristics of chondrocytes, whereas the peripheral cells are typical chondroblasts. The superficial mesenchyme develops as the perichondrium.

Once formed, the cartilage tissue enlarges both by **interstitial growth**, involving mitotic division of preexisting chondrocytes, and by **appositional growth**, which involves chondroblast differentiation from progenitor cells in the perichondrium (Figure 1b). In both cases, the synthesis of matrix contributes greatly to the growth of the cartilage. Appositional growth of cartilage is more important during postnatal development,, interstitial growth in cartilaginous regions within long bones is important in increasing the length of these structures. In articular cartilage, cells and matrix near the articulating surface are gradually worn away and must be replaced from within, because there is no perichondrium to add cells by appositional growth.

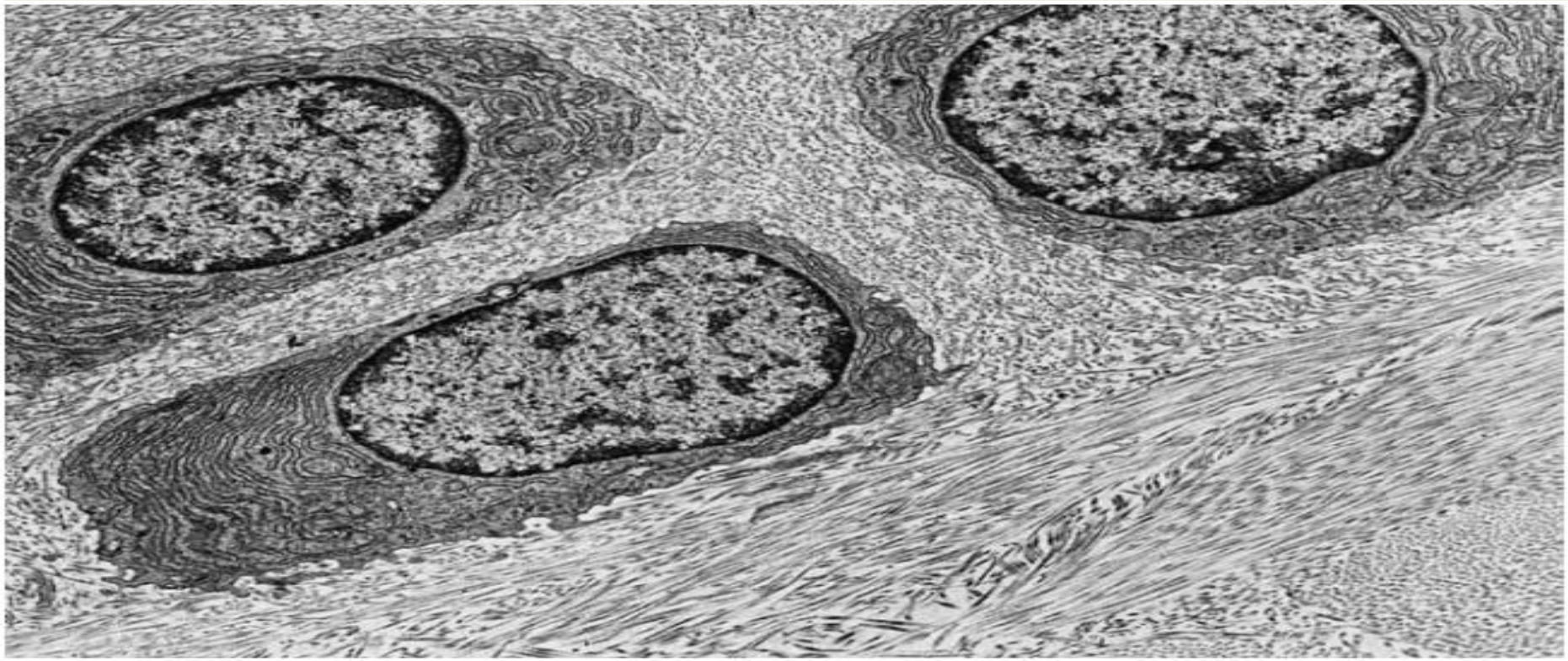
Except in young children, damaged cartilage undergoes slow and often incomplete repair, primarily dependent on cells in the perichondrium which invade the injured area and produce new cartilage. In damaged areas the perichondrium produces a scar of dense connective tissue instead of forming new cartilage. The poor capacity of cartilage for repair or regeneration is due in part to its a vascularity and low metabolic rate



Figur 3

The major stages of embryonic cartilage formation, or chondrogenesis, are shown here. (a) Mesenchyme is the precursor for all types of cartilage. (b) Mitosis and initial cell differentiation produces a tissue with condensations of rounded cells called chondroblasts. (c) Chondroblasts are then separated from one another again by their production of the various matrix components, which collectively swell with water and form the very extensive ECM. (d) Multiplication of chondroblasts within the matrix gives rise to isogenous cell aggregates surrounded by a condensation of territorial matrix. In mature cartilage, this interstitial mitotic activity ceases and all chondrocytes typically become more widely separated by their production of matrix.

Chondrocytes in growing cartilage.



Figuer 4

This TEM of fibrocartilage shows chondrocytes with abundant RER actively secreting the collagen-rich matrix. Bundles of collagen fibrils, sectioned in several orientations, are very prominent around the chondrocytes of fibrocartilage. Collagen types I and II are both present in fibrocartilage. Chondrocytes in growing hyaline and elastic cartilage have more prominent Golgi complexes and synthesize abundant proteoglycans in addition to collagens. (X3750

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Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

The Circulatory system.

Lecture 1

Dr. Ali Ashgar Abd

The Circulatory System

The circulatory system pumps and directs blood cells and substances carried in blood to all tissues of the body. It includes both the blood and lymphatic vascular systems, and in an adult the total length of its vessels is estimated at between 100,000 and 150,000 km. The blood vascular system, or cardiovascular system consists of the following structures : ■ The heart propels blood through the system. ■ Arteries, a series of vessels efferent from the heart that become smaller as they branch into the various organs, carry blood to the tissues.

■ Capillaries, the smallest vessels, are the sites of O2 , CO2 , nutrient, and waste product exchange between blood and tissues. Together with the smallest arterial and venous branches carrying blood to and from them, capillaries in almost every organ form a complex network of thin, anastomosing tubules called the microvasculature or microvascular bed. ■ Veins result from the convergence of venules into a system of larger channels which continue enlarging as they approach the heart, toward which they carry the blood to be pumped again .

Two major divisions of arteries, microvasculature, and veins make up the pulmonary circulation, where blood is oxygenated in the lungs, and the systemic circulation, where blood brings nutrients and removes wastes in tissues throughout the body. vascular .

The lymphatic system, begins with the lymphatic capillaries, which are thin-walled, closed-ended tubules carrying lymph which merge to form vessels of steadily increasing size. The largest lymph vessels connect with the blood vascular system and empty into the large veins near the heart. This returns fluid from tissue spaces all over the body to the blood.

The internal surface of all components of the blood and lymphatic systems is lined by a simple squamous epithelium called endothelium. As the interface between blood and the organs, cardiovascular endothelial cells have crucial physiologic and medical importance. Not only must endothelial cells maintain a selectively permeable, antithrombogenic (inhibitory to clot formation) barrier, they also determine when and where white blood cells leave the circulation for the interstitial space of tissues and secrete a variety of paracrine factors for vessel dilation, constriction, and growth of adjacent cells.

TISSUES OF THE VASCULAR WALL

Walls of all blood vessels except capillaries contain smooth muscle and connective tissue in addition to the endothelial lining. The amount and arrangement of these tissues in vessels are influenced by mechanical factors, primarily blood pressure, and metabolic factors reflecting the local needs of tissues. The endothelium is a specialized epithelium that acts as a semipermeable barrier between two major internal compartments: the blood and the interstitial tissue fluid. Vascular endothelial cells are squamous, polygonal, and elongated with the long axis in the direction of blood flow. Endothelium with its basal lamina is highly differentiated to mediate and actively monitor the bidirectional exchange of molecules by simple and active diffusion, receptor-mediated endocytosis, transcytosis, and other mechanisms Besides their key role in metabolite exchanges between blood and tissues, endothelial cells have several other functions:

Smooth muscle

Smooth muscle fibers occur in the walls of all vessels larger than capillaries and are arranged helically in layers. In arterioles and small arteries, the smooth muscle cells are connected by many more gap junctions and permit vasoconstriction and vasodilation that are of key

the overall blood pressure. importance in regulating

Connective tissue

Connective tissue components are present in vascular walls in variable amounts and proportions based on local functional requirements. Collagen fibers are found in the subendothelial layer, between the smooth muscle layers.

and in the outer covering. Elastic fibers provide the resiliency required for the vascular wall to expand under pressure. Elastin is a major component in large arteries where it forms parallel lamellae, regularly distributed between the muscle layers. Variations in the amount and composition of ground substance components such as proteoglycans and hyaluronate also contribute to the physical and metabolic properties of the wall in different vessels, especially affecting their permeability. The walls of all blood vessels larger than the microvasculature have many components in common and similar organization.

Branching of the vessels helps produce reductions in their size that are accompanied by gradual changes in the composition of the vascular wall. Transitions such as those from “small arteries” to “arterioles” are not clear-cut. However, all of these larger vessels have walls with three concentric layers, or tunics (L. tunica, coat) ■ The innermost tunica intima consists of the endothelium and a thin subendothelial layer of loose connective tissue sometimes containing smooth muscle fibers. In arteries the intima includes a thin layer, the internal elastic lamina, composed of elastin, with holes allowing better diffusion of substances from blood deeper into the wall.

■ The tunica media, the middle layer, consists chiefly of concentric layers of helically arranged smooth muscle cells Interposed among the muscle fibers are variable amounts of elastic fibers and elastic lamellae, reticular fibers, and proteoglycans, all of which are produced by the smooth muscle cells. In arteries the media may also have an external elastic lamina separating it from the outermost tunic.

■ The outer adventitia, or tunica externa, is connective tissue consisting principally of type I collagen and elastic fibers. The adventitia is continuous with and bound to the stroma of the organ through which the blood vessel runs.

Just as the heart wall is supplied with its own coronary vasculature for nutrients and O2 , large vessels usually have vasa vasorum ("vessels of the vessel"): arterioles, capillaries, and venules in the adventitia and outer part of the media. The vasa vasorum are required to provide metabolites to cells in those tunics in larger vessels because the wall is too thick to be nourished solely by diffusion from the blood in the lumen. Luminal blood alone does provide the needs of cells in the intima. Because they carry deoxygenated blood, large veins commonly have more vasa vasorum than arteries. The adventitia of larger vessels also contains a network of unmyelinated autonomic nerve fibers, the vasomotor nerves, which release the vasoconstrictor norepinephrine. The density of this innervation is greater in arteries than in veins.

VASCULATURE

Large blood vessels and those of the microvasculature branch frequently and undergo gradual transitions into structures with different histologic features and functions. For didactic purposes vessels can be classified arbitrarily as the types discussed here and listed in Table

Elastic Arteries

Elastic arteries are the aorta, the pulmonary artery, and their largest branches; these large vessels are also called conducting arteries because their major role is to carry blood to smaller arteries. As shown in Figure 1a, the most prominent feature of elastic arteries is the thick tunica media in which elastic lamellae alternate with layers of smooth muscle fibers. The adult aorta has about 50 elastic lamellae (more if the individual is hypertensive).

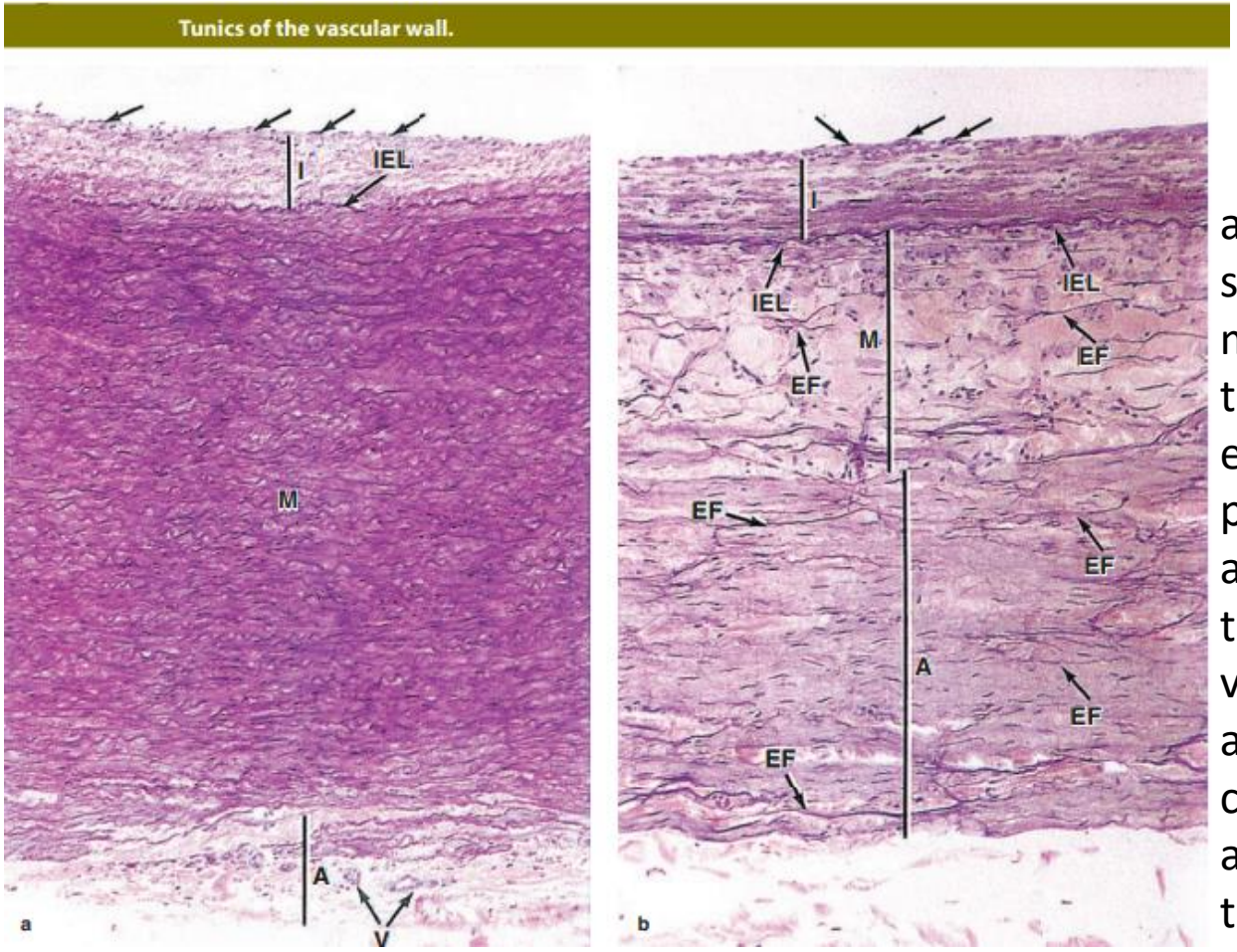
The tunica intima is well developed, with many smooth muscle cells in the subendothelial connective tissue, and often shows folds in cross section as a result of the loss of blood pressure and contraction of the vessel at death .

Between the intima and the media is the internal elastic lamina, which is more well-defined than the elastic laminae of the media .

The adventitia is much thinner than the media.

The numerous elastic laminae of these arteries contribute to their important function of making the blood flow more uniform.

During ventricular contraction (systole) blood is moved through the arteries forcefully and the elastin is stretched, distending the wall within the limit set by the wall's collagen. When the ventricles relax (diastole) ventricular pressure drops to a low level, but the elastin rebounds passively, helping to maintain arterial pressure. The aortic and pulmonary valves prevent backflow of blood into the heart, so the rebound continues the blood flow away from the heart. Arterial blood pressure and blood velocity decrease and become less variable as the distance from the heart increases.



Comparison of the three major layers or tunics in the largest artery and vein. (a) Aorta, (b) vena cava. Simple squamous endothelial cells (arrows) line the intima (I) that also has subendothelial connective tissue and in arteries is separated from the media by an internal elastic lamina (IEL), a structure absent in all but the largest veins. The media (M) contains many elastic lamellae and elastic fibers (EF)

alternating with layers of smooth muscle. The media is much thicker in large arteries than veins, with relatively more elastin. Elastic fibers are also present in the outer tunica adventitia (A), which is relatively thicker in large veins. Vasa vasorum (V) are seen in the adventitia of the aorta. The connective tissue of the adventitia always merges with the less dense connective tissue around it. (Both X122; Elastic stain)

Arterial Sensory Structures

Carotid sinuses are slight dilations of the bilateral internal carotid arteries where they branch from the (elastic) common carotid arteries; they act as important baroreceptors monitoring arterial blood pressure. At these sinuses the tunica media is thinner, allowing greater distension when blood pressure rises, and the adventitia contains many sensory nerve endings from cranial nerve IX, the glossopharyngeal nerve. The brain's vasomotor centers process these afferent impulses and adjust vasoconstriction, maintaining normal blood pressure. Functionally similar baroreceptors present in the aortic arch transmit signals pertaining to blood pressure via cranial nerve X, the vagus nerve.

Histologically more complex chemoreceptors which monitor blood CO2 and O2 levels, as well as its pH, are found in the carotid bodies and in the aortic bodies, located in the walls of the carotid sinuses and aortic arch, respectively. These structures are parts of the autonomic nervous system called para ganglia with rich capillary networks. The capillaries are closely surrounded by large, neural crest-derived glomus cells filled with dense-core vesicles containing dopamine, acetylcholine, and other neurotransmitters, which are supported by smaller satellite cells .

Ion channels in the glomus cell membranes respond to stimuli in the arterial blood, primarily hypoxia (low O2), hypercapnia (excess CO2), or acidosis, by activating release of neurotransmitters.

Muscular Arteries

The muscular arteries, also called distributing arteries, distribute blood to the organs and help regulate blood pressure by contracting or relaxing the smooth muscle in the media.

The intima has a thin subendothelial layer and a prominent internal elastic lamina .The media may contain up to 40 layers of large smooth muscle cells interspersed with a variable number of elastic lamellae (depending on the size of the vessel). An external elastic lamina is present only in the larger muscular arteries. The adventitial connective tissue contains lymphatic capillaries, vasa vasorum, and nerves, all of which may penetrate to the outer part of the media.

Arterioles

Muscular arteries branch repeatedly into smaller and smaller arteries, until reaching a size with three or four layers of medial smooth muscle. The smallest arteries branch as arterioles, which have only one or two smooth muscle layers; these indicate the beginning of an organ's microvasculature (Figures 2 and 3) where exchanges between blood and tissue fluid occur. Arterioles are generally less than 0.1 mm in diameter, with lumens approximately as wide as the wall is thick .

The subendothelial layer is very thin, elastic laminae are absent, and the media consists of the circularly arranged smooth muscle cells. In both small arteries and arterioles the adventitia is very thin and inconspicuous.

Arterioles almost always branch to form anastomosing networks of capillaries that surround the parenchymal cells of the organ. At the ends of arterioles the smooth muscle fibers act as sphincters and produce periodic blood flow into capillaries (Figure 3). Muscle tone normally keeps arterioles partially closed, resisting blood flow, which makes these vessels the major determinants of systemic blood pressure.

In certain tissues and organs, arterioles deviate from this simple path to accommodate various specialized functions .For example, thermoregulation by the skin involves arterioles that can bypass capillary networks and connect directly to venules. The media and adventitia are thicker in these arteriovenous shunts (or arteriovenous anastomoses) and richly innervated by sympathetic and parasympathetic nerve fibers. The autonomic fibers control the degree of vasoconstriction at the shunts, regulating blood flow through the capillary beds. High capillary blood flow in the skin allows more heat dissipation from the body, while reduced capillary blood flow conserves heat—important functions when the environmental temperature is hot or cold, respectively.

Another important alternative microvascular pathway is a venous portal system ,in which blood flows through two successive capillary beds separated by a portal vein. This arrangement allows for hormones or nutrients picked up by the blood in the first capillary network to be delivered most efficiently to cells around the second capillary bed before the blood is returned to the heart for general distribution. The best examples are the hepatic portal system of the liver and the hypothalamic hypophyseal portal system in the anterior pituitary gland, both of which have major physiologic importance.

Capillary Beds

Capillaries permit and regulate metabolic exchange between blood and surrounding tissues. These smallest blood vessels always function in networks called capillary beds, whose size and overall shape conforms to that of the structure supplied. The density of the capillary bed is related to the metabolic activity of the tissues. Tissues with high metabolic rates, such as the kidney, liver, and cardiac and skeletal muscle, have abundant capillaries; the opposite is true of tissues with low metabolic rates, such as smooth muscle and dense connective tissue.

Capillary beds are supplied preferentially by one or more terminal arteriole branches called metarterioles, which are continuous with thoroughfare channels connected with the postcapillary venules (Figure 3). Capillaries branch from the metarterioles, which are encircled by scattered smooth muscle cells, and converge into the thoroughfare channels, which lack muscle. The metarteriole muscle cells act as precapillary sphincters that control blood flow into the capillaries. These sphincters contract and relax cyclically, with 5-10 cycles per minute, causing blood to pass through

capillaries in a pulsatile manner. When the sphincters are closed, blood flows directly from the metarterioles and thoroughfare channels into postcapillary venules.

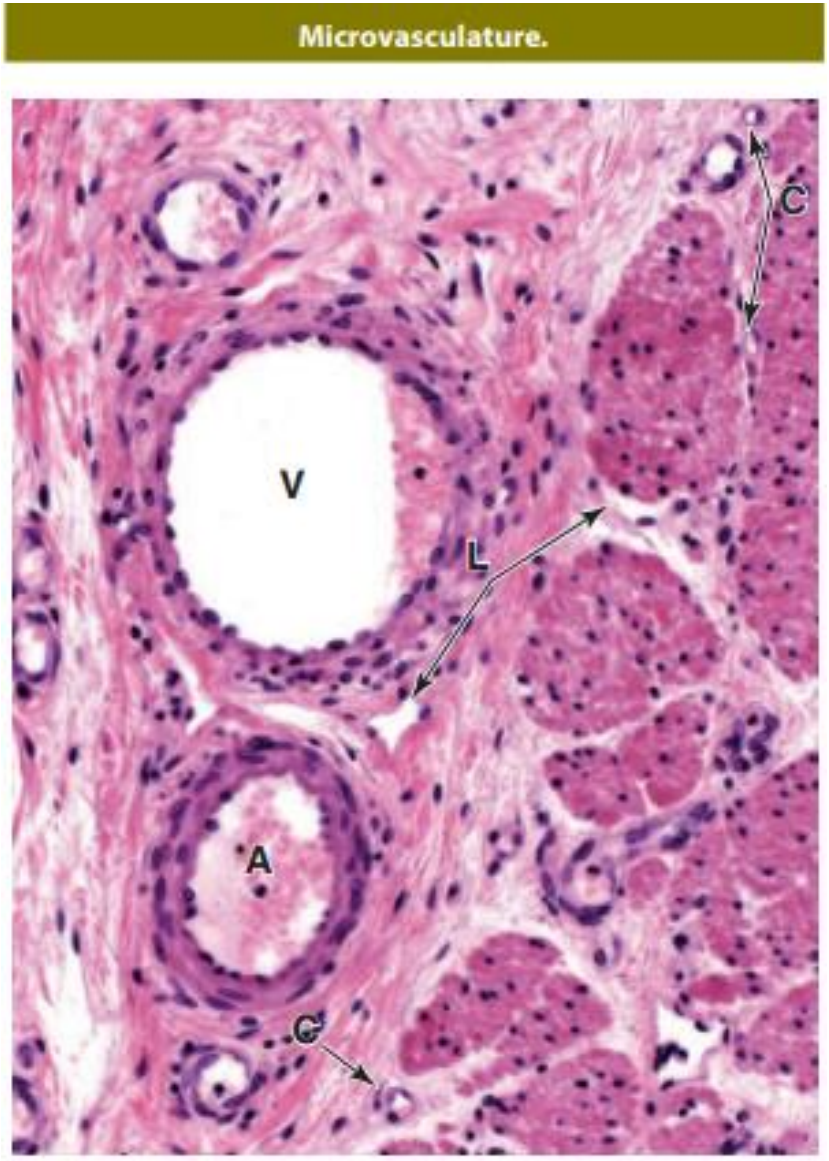


Figure 2

Arterioles (A), capillaries (C), and venules (V) comprise the microvasculature where, in almost every organ, molecular exchange takes place between blood and the interstitial fluid of the surrounding tissues. Lacking media and adventitia tunics and with diameters of only 4-10 µm, capillaries (C) in paraffin sections can be recognized by nuclei adjacent to small lumens or by highly eosinophilic red blood cells in the lumen. As described in Figure 5–20, not all interstitial fluid formed at capillary beds is drained into venules; the excess is called lymph and collects in thinwalled, irregularly shaped lymphatic vessels (L), such as those seen in connective tissue and smooth muscle here. (200X; H&E)

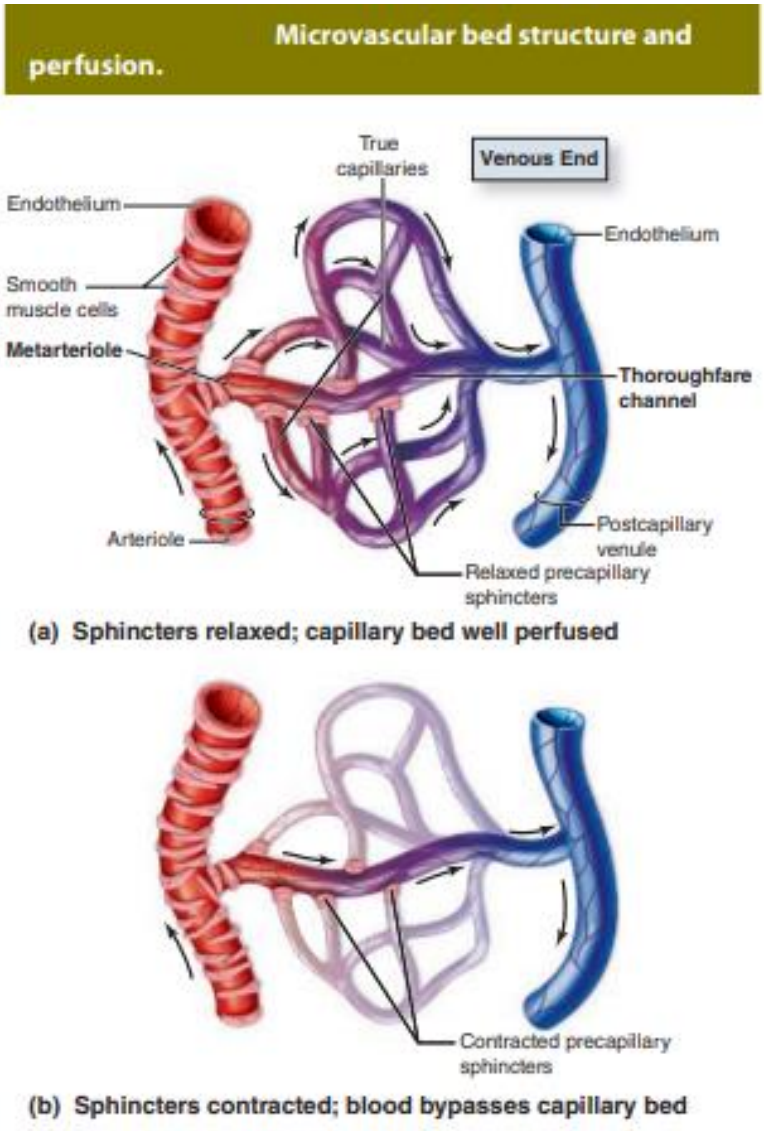


Figure3

Arterioles supplying a capillary bed typically form smaller branches called metarterioles in which the smooth muscle cells are dispersed as bands which act as precapillary sphincters. The distal portion of the metarteriole, sometimes called a thoroughfare channel, lacks smooth muscle cells and merges with the postcapillary venule. Branching from the metarteriole and thoroughfare channel are the smallest vessels, true capillaries, which lack smooth muscle cells (although pericytes may be present). The precapillary sphincters regulate blood flow into the true capillaries. Part a shows a well-perfused capillary bed with all the sphincters relaxed and open; part b shows a capillary bed with the blood shunted away by contracted sphincters. At any given moment, most sphincters are at least partially closed and blood enters the capillary bed in a pulsatile manner for maximally efficient exchange of nutrients, wastes, O2 , and CO2 across the endothelium. Except in the pulmonary circulation, blood enters the microvasculature well oxygenated and leaves poorly oxygenated.

TABLE **Size ranges, major features, and important roles of major blood vessel types.**

Type of Artery	Outer Diameter (Approx. Range)	Intima	Media	Adventitia	Roles in Circulatory System
Elastic arteries	> 10 mm	Endothelium; connective tissue with smooth muscle	Many elastic lamellae alternating with smooth muscle	Connective tissue, thinner than media, with vasa vasorum	Conduct blood from heart and with elastic recoil help move blood forward under steady pressure
Muscular arteries	10-1 mm	Endothelium; connective tissue with smooth muscle, internal elastic lamina prominent	Many smooth muscle layers, with much less elastic material	Connective tissue, thinner than media; vasa vasorum maybe present	Distribute blood to all organs and maintain steady blood pressure and flow with vasodilation and constriction
Small arteries	1-0.1 mm	Endothelium; connective tissue less smooth muscle	3-10 layers of smooth muscle	Connective tissue, thinner than media; no vasa vasorum	Distribute blood to arterioles, adjusting flow with vasodilation and constriction
Arterioles	100-10 µm	Endothelium; no connective tissue or smooth muscle	1-3 layers of smooth muscle	Very thin connective tissue layer	Resist and control blood flow to capillaries; major determinant of systemic blood pressure

Type of Artery	Outer Diameter (Approx. Range)	Intima	Media	Adventitia	Roles in Circulatory System
Capillaries	10-4 µm	Endothelium only	A few pericytes only	None	Exchange metabolites by diffusion to and from cells
Venules (postcapillary, collecting, and muscular)	10-100 µm	Endothelium; no valves	Pericytes and scattered smooth muscle cells	None	Drain capillary beds; site of leukocyte exit from vasculature
Small veins	0.1-1 mm	Endothelium; connective tissue with scattered smooth muscle fibers	Thin, 2-3 loose layers of smooth muscle cells	Connective tissue, thicker than media	Collect blood from venules
Medium veins	1-10 mm	Endothelium; connective tissue, with valves	3-5 more distinct layers of smooth muscle	Thicker than media; longitudinal smooth muscle may be present	Carry blood to larger veins, with no backflow
Large veins	> 10 mm	Endothelium; connective tissue, smooth muscle cells; prominent valves	> 5 layers of smooth muscle, with much collagen	Thickest layer, with bundled longitudinal smooth muscle	Return blood to heart

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Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Nervous system .

Dr. Ali Ashgar Abd

CENTRAL NERVOUS SYSTEM(CNS)

The major structures comprising the CNS are the brain (mainly: **cerebrum, cerebellum**) and **spinal cord** .

The CNS is completely covered by connective tissue layers, the meninges, but CNS tissue contains very little collagen or similar material, making it relatively soft and easily damaged by injuries affecting the protective skull or vertebral bones.

Many structural features of CNS tissues can be seen in unstained, freshly dissected specimens. Many regions show organized areas of **white matter** and **gray matter**, differences caused by the differential distribution of lipid-rich myelin. The main components of **white matter are myelinated axons** ,often grouped together as tracts, and the myelin-producing oligodendrocytes. Astrocytes and microglia are also present, but very few neuronal cell bodies. Gray matter contains abundant neuronal cell bodies, dendrites, astrocytes, and microglial cells, and is where most synapses occur. Gray matter makes up the thick cortex or surface layer of both the cerebrum and the cerebellum; most white matter is found in deeper regions.

Deep within the brain are localized, variously shaped darker areas called the **cerebral nuclei**, each containing large numbers of aggregated neuronal cell bodies.

In the folded cerebral cortex, neuroscientists recognize six layers of neurons with different sizes and shapes. The most conspicuous of these cells are the efferent pyramidal neurons .

Neurons of the cerebral cortex function in the integration of sensory information and the initiation of voluntary motor responses.

The sharply folded cerebellar cortex coordinates muscular activity throughout the body and is organized with three layers :

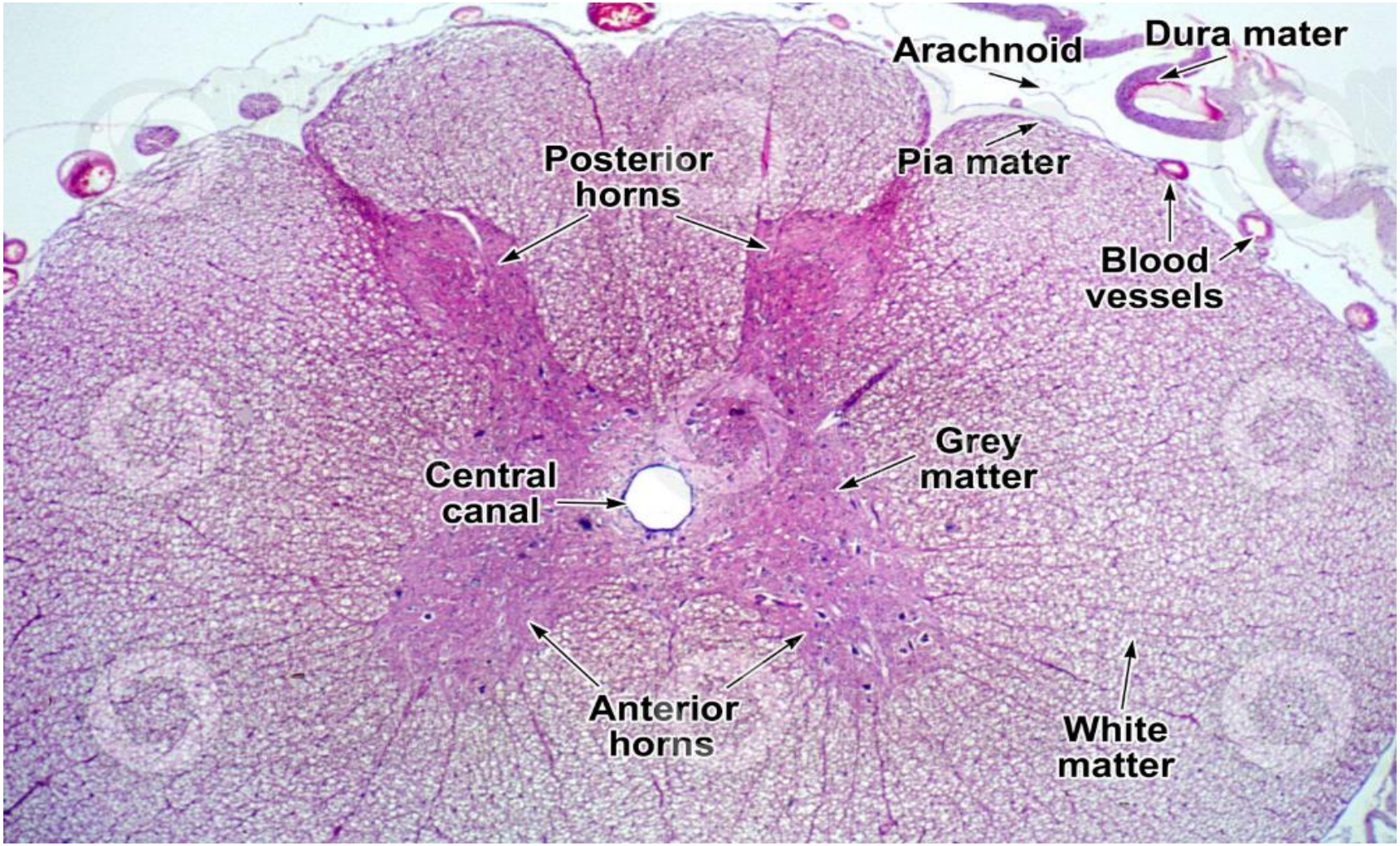
■ A thick outer **molecular layer** has much neuropil and scattered neuronal cell bodies

■ A thin middle layer consists only of very large neurons called **Purkinje cells** (named for the 19th century Czech histologist Jan Purkinje). These are conspicuous even in H&E-stained sections, and their dendrites extend throughout the molecular layer as a branching basket of nerve fibers .

■ A thick inner **granular layer** contains various very small, densely packed neurons (including granule cells, with diameters of only 4-5 µm) and little neuropil.

In cross sections of the **spinal cord**, the white matter is peripheral and the gray matter forms a deeper, H-shaped mass (Figure). The two anterior projections of this gray matter, the **anterior horns,** contain cell bodies of very large motor neurons whose axons make up the ventral roots of spinal nerves. The two **posterior horns** contain interneurons which receive sensory fibers from neurons in the spinal (dorsal root) ganglia. Near the middle of the cord the gray matter surrounds a small **central canal**, which develops from the lumen of the neural tube, is continuous with the ventricles of the brain, is lined by ependymal cells, and contains CSF.

Figure:Cross section through the spinal cord



Meninges

The skull and the vertebral column protect the CNS, but between the bone and nervous tissue are membranes of connective tissue called the meninges. Three meningeal layers are distinguished: the dura, arachnoid, and pia maters (Figure)

Dura Mater

The thick external **dura mater** (L. dura mater, tough mother) consists of dense irregular connective tissue organized as an outer periosteal layer continuous with the periosteum of the skull and an inner meningeal layer. These two layers are usually fused, but along the superior sagittal surface and other specific areas around the brain they separate to form the blood-filled **dural venous sinuses** (Figure). Around the spinal cord the dura mater is separated from the periosteum of the vertebrae by the **epidural space**, which contains a plexus of thin-walled veins and loose connective tissue (Figure). The dura mater may be separated from the arachnoid by formation of a thin subdural space.

Arachnoid The arachnoid (Gr. arachnoeides, spider web-like) has two components: (1) a sheet of connective tissue in contact with the dura mater and (2) a system of loosely arranged trabeculae composed of collagen and fibroblasts, continuous with the underlying pia mater layer. Surrounding these trabeculae is a large, sponge-like cavity, the subarachnoid space, filled with cerebrospinal fluid (CSF). This fluid-filled space helps cushion and protect the CNS from minor trauma. The **subarachnoid space** communicates with the ventricles of the brain where the CSF is produced. The connective tissue of the arachnoid is said to be avascular because it lacks nutritive capillaries, but larger blood vessels run through it. Because the arachnoid has fewer trabeculae in the spinal cord, it can be more clearly distinguished from the pia mater in that area. The arachnoid and the pia mater are intimately associated and are often considered a single membrane called the pia-arachnoid.

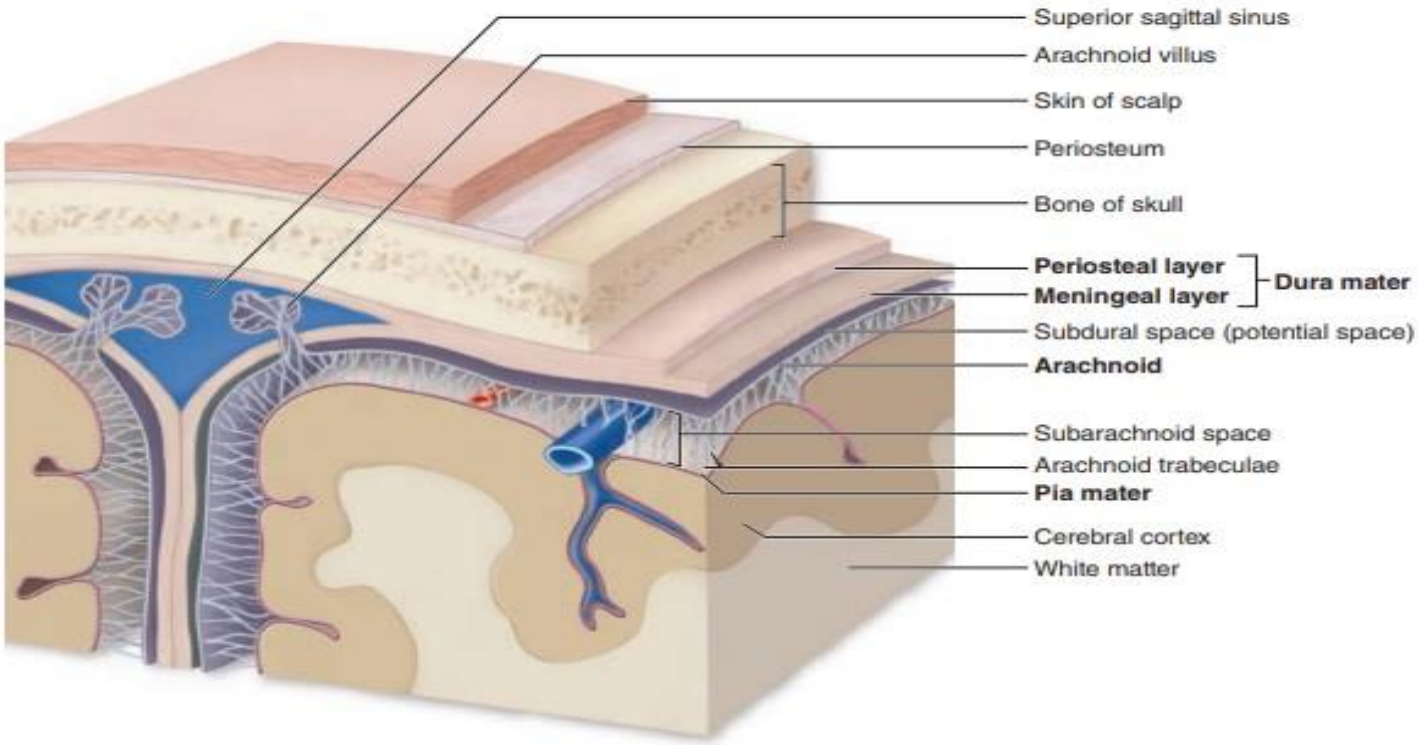
Pia Mater

The innermost pia mater (L. pia mater, tender mother) consists of flattened, mesenchymally derived cells closely applied to the entire surface of the CNS tissue. The pia does not directly contact nerve cells or fibers, being separated from the neural elements by the very thin superficial layer of astrocytic processes (the glial limiting membrane, or glia limitans), which adheres firmly to the pia mater. Together, the pia mater and the layer of astrocytic end feet form a physical barrier separating CNS tissue from CSF in the subarachnoid space (Figure).

Blood vessels penetrate CNS tissue through long **perivascular spaces** covered by pia mater, although the pia disappears when the blood vessels branch to form the small capillaries. However, these capillaries remain completely covered by the perivascular layer of astrocytic processes (Figures).

The **dura**, **arachnoid,** and **pia maters** also surround the brain and as shown here the relationships among the cranial meninges are similar to those of the spinal cord. The diagram includes **arachnoid villi,** which are outpocketings of arachnoid away from the brain, which penetrate the dura mater and enter blood-filled **venous sinuses** located within that layer. The arachnoid villi function in releasing excess CSF into the blood. Blood vessels from the arachnoid branch into smaller arteries and veins that enter brain tissue carrying oxygen and nutrients. These small vessels are initially covered with pia mater, but as capillaries they are covered only by the perivascular feet of astrocytes.

FIGURE **Meninges around the brain.**



Ganglia

Ganglia are typically ovoid structures containing neuronal cell bodies and their surrounding glial satellite cells supported by delicate connective tissue and surrounded by a denser capsule. Because they serve as relay stations to transmit nerve impulses, at least one nerve enters and another exits from each ganglion. The direction of the nerve impulse determines whether the ganglion will be a **sensory** and **autonomic** ganglion.

Sensory Ganglia

Sensory ganglia receive afferent impulses that go to the CNS. Sensory ganglia are associated with both cranial nerves (cranial ganglia) and the dorsal roots of the spinal nerves (spinal ganglia). The large neuronal cell bodies of ganglia are associated with thin, sheetlike extensions of small glial **satellite cells**.

Sensory ganglia are supported by a distinct connective tissue capsule and an internal framework continuous with the connective tissue layers of the nerves. The neurons of these ganglia are pseudounipolar and relay information from the ganglion's nerve endings to the gray matter of the spinal cord via synapses with local neurons.

Autonomic Ganglia

Autonomic ganglia appear as bulbous dilatations in

autonomic nerve .Some are located within certain organs ,especially in the walls of digestive tract ,where they constitute the intramural ganglia .

These ganglia are devoid of connective tissue capsules ,and their cells are supported by the stroma of the organ in which they are found .

Autonomic ganglia usually have multipolar neurons.

As with craniospinal ganglia ,autonomic ganglia have neuronal perikaryons with fine Nissl bodies .

A layer of satellite cells frequently envelops the neuurons of autonomic ganglia .in intramural ganglia ,only few satellite cells are seen around each neuron.

Autonomic nervous system

The autonomic (Gr. autos, self, + nomos, law) nervous system is related to the control of smooth muscle, the secretion of some glands, and the modulation of cardiac rhythm. Its function is to

make adjustments in certain activities of the body to maintain a constant internal environment **(homeostasis).**

Although the autonomic nervous system is by definition a motor system, fibers that receive sensation originating in the interior of the organism

accompany the motor fibers of the autonomic system.

The concept of the autonomic nervous system is mainly functional. Anatomically, It is composed of collections of nerve cells located in the central nervous system, fibers that leave the central nervous system through cranial or spinal nerves, and nerve ganglia situated in the paths of these fibers.

The term autonomic covers all the neural elements concerned with visceral function. In fact, the so-called autonomic functions are as dependent on the central nervous system as are the moto neurons that trigger muscle contractions.

The autonomic nervous system is a two-neuron network. The first neuron of the autonomic chain is located in the central nervous system.

Its axon forms a synapse with the seconed multipolar neuron in the chain, located in a ganglion of the peripheral nervous system.

The nerve fibers (axons) of the first neuron are called **preganglionic fibers**; the axons of the second neuron to the effectors -muscle or gland -are called **postganglionic fibers**.

The chemical mediator present in the synaptic vesicles of all preganglionic endings and at anatomically parasympathetic postganglionic endings is **acetylcholine**, which is release from the terminals by nerve impulses.

The adrenal medulla is the only organ that receives preganglionic fibers,, because the majority of the cells, after migration Into the gland, differentiate into secretory cells rather than ganglion cells.

The autonomic nervous system is composed of two parts that differ both anatomically and functionally:

the sympathetic system and the parasympathetic system.

Nerve fibers that release acetylcholine are called cholinergic. Cholinergic fibers include all the preganglionic autonomic fibers (sympathetic as well as parasympathetic) and postganglionic parasympathetic fibers to smooth muscles, heart, and exocrine glands.

sympathetic system

The nuclei (formed by a collection of nerve cell bodies) of the Sympathetic System are located in the thoracic and lumbar segments of the spinal cord. Therefore, the sympathetic system is also called the **thoracolumbar division** of the autonomic nervous system. The axons of these neurons-preganglionic fibers-leave the central nervous system by way of the ventral roots and white communicating rami of the thoracic and lumbar nerves.

The chemical mediator of the postganglionic fibers of the sympathetic system is **norepinephrine**, which is also produced by the adrenal medulla.

Nerve fibers that release norepinephrine are called **adrenergic** (a word derived from noradrenalin, another term for norepinephrine). Adrenergic fibers innervate sweat glands and blood vessels of skeletal

muscle. Cells of the adrenal medulla release epinephrine and norepinephrine in response to preganglionic sympathetic stimulation.

Parasympathetic System

The parasympathetic system has its nuclei in the medulla and midbrain and in the sacral portion of the spinal cord. The preganglionic fibers of these neurons leave through four of the cranial nerves (III, VII, LX, and X) and also through the second ,third, and fourth sacral spinal nerves. The parasympathetic system is therefore also called the craniosacral division of the autonomic system.

The second neuron of the parasympathetic series is found in ganglia smaller than those of the sympathetic system; it is always located near or within the effector organs. These neurons are usually located in the walls of organs (eg, stomach, intestines),in which case the preganglionic fibers enter the organs and form a synapse there with the second neuron in the chain.

The chemical mediator released by the pre- and postganglionic nerve endings of the parasympathetic system, **acetylcholine**, is readily inactivated by acetylcholinesterase- one of the reasons parasympathetic stimulation has both a more discrete and a more localized action than does sympathetic stimulation.

Thank you

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Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Connective Tissues.

Dr. Ali Ashgar Abd

Connective tissues

- Connective tissue, as the name implies, forms a continuum with epithelial tissue, muscle, and nervous tissue as well as with other components of connective tissues to maintain a functionally integrated body.

- Structurally, connective tissue is formed by three classes of components: cells, fibers, and ground substance. Unlike the other tissue types (epithelium, muscle, and nerve), which consist mainly of cells, the major constituent of connective tissue is the **extracellular matrix (ECM)** **.**

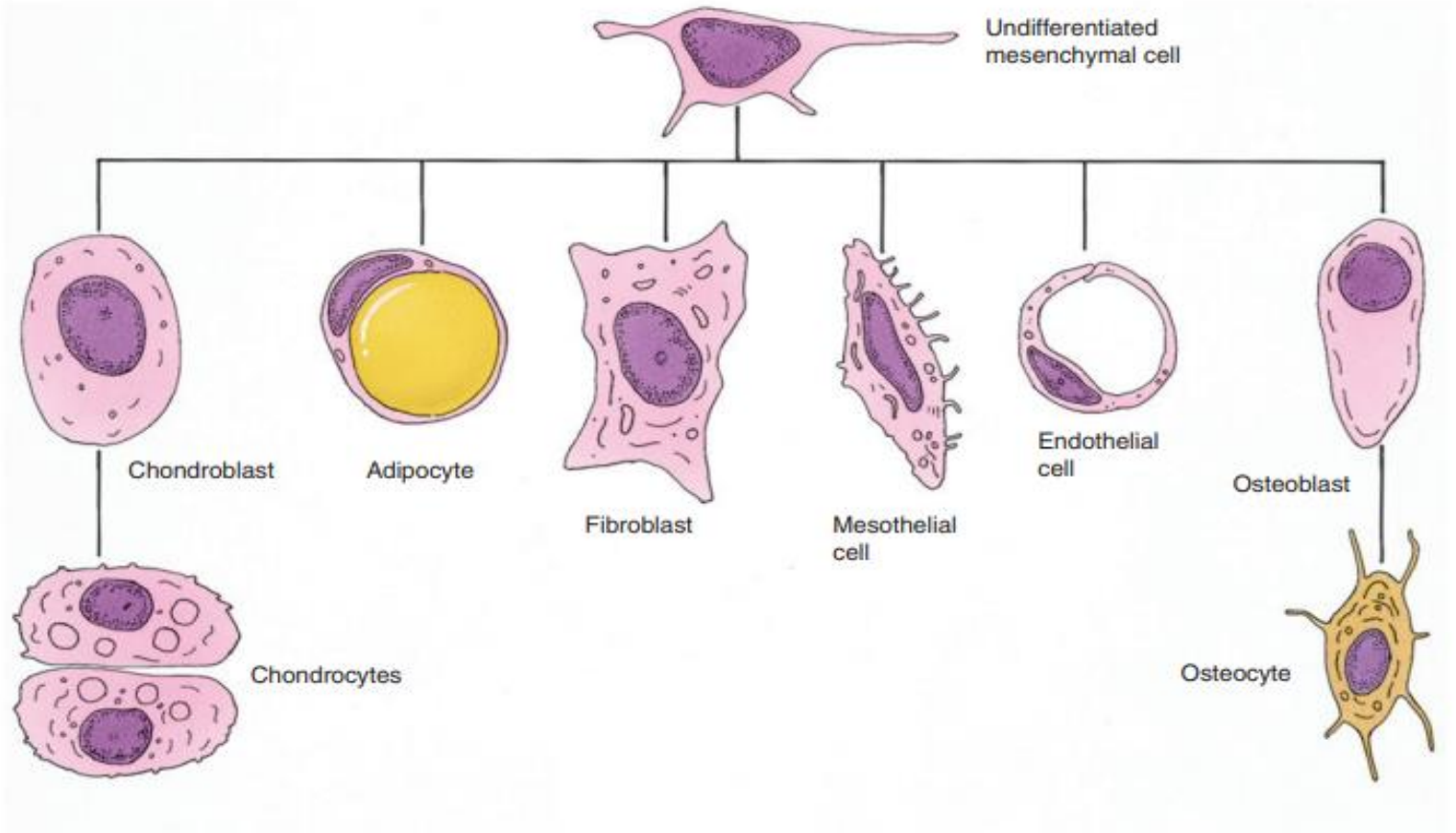
- *origin*
- All connective tissue cells are derived from mesenchymal cells. **Mesenchyme cells** are found in embryos and are for the most part derived fro the middle germ layer of the embryo (mesoderm).
- Several of the connective tissues of the head region are derived from the neural crest (ectodermal origin), in addition the melanocytes also derived from neural crest (ectoderm).

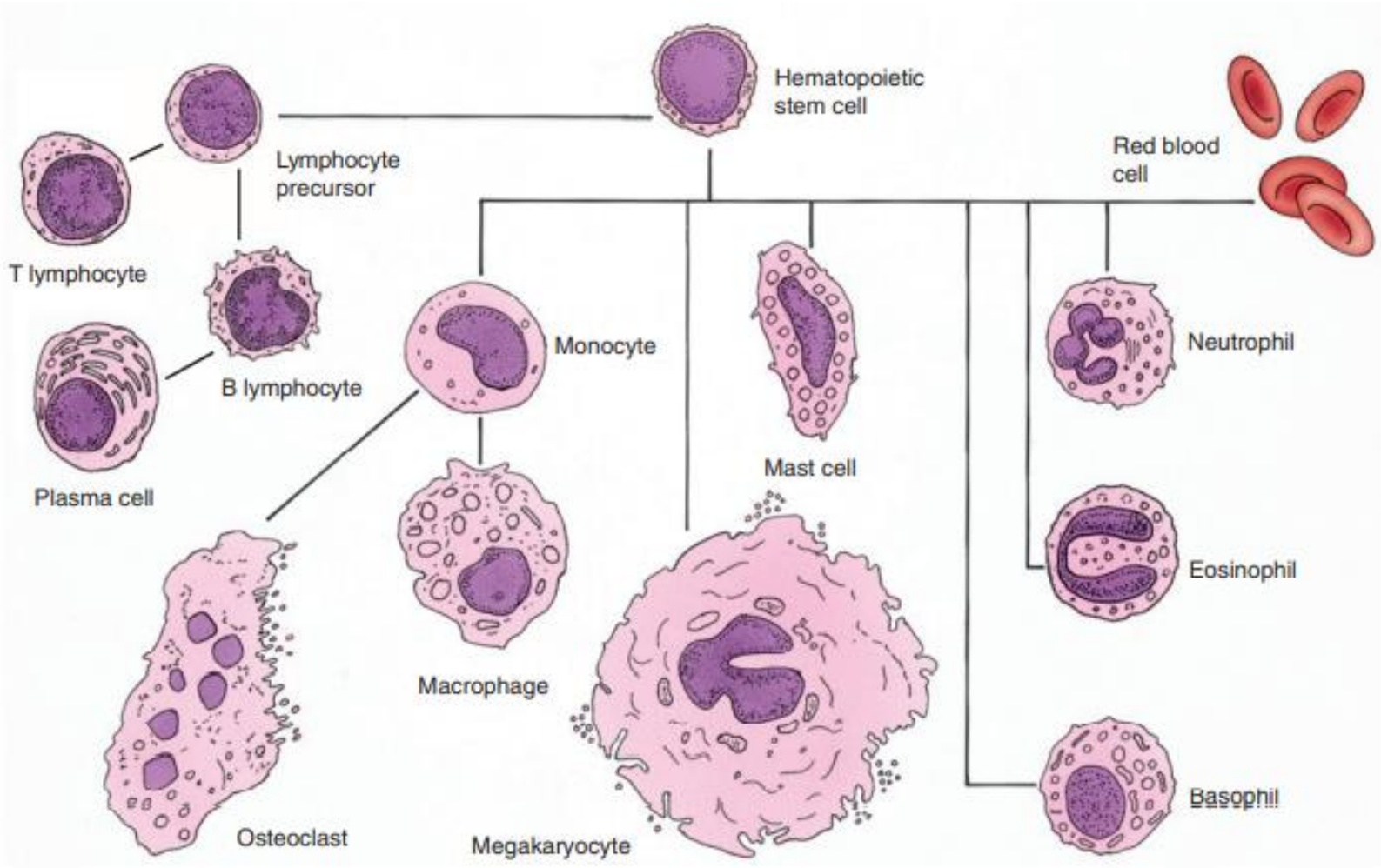
Connective Tissue

Extracellular matrices consist of different combinations of **protein fibers** (collagen, reticular, and elastic fibers) and **ground substance.** Ground substance is a highly hydrophilic, viscous complex of anionic macromolecules. The hydrated nature of much connective tissue provides the medium through which nutrients and metabolic wastes are exchanged between cells and their blood supply.

The connective tissues originate from the **mesenchyme,** an embryonic tissue formed by elongated undifferentiated cells, the **mesenchymal cells.** These cells are characterized by oval nuclei with prominent nucleoli and fine chromatin.

Schematic diagram of the origins of the cells of connective tissue.




Hematopoietic stem cell
Lymphocyte precursor
T lymphocyte
B lymphocyte
Plasma cell
Monocyte
Macrophage
Osteoclast
Mast cell
Megakaryocyte
Red blood cell
Neutrophil
Eosinophil
Basophil

Functions of connective Tissues

1. mechanical function :
   a. providing support with mobility
   b. increasing elasticity in tissues and organs
   c. providing pathways for blood vessels and nerves
   d. packing unused spaces in the body

- 2. Transport - It allows the movement of food, oxygen and wastes between capillaries and tissue cells.
- 3. Defense
- 4. Repair - The fibroblasts of areolar tissue produce new fiber and ground substance to repair damage.

Functions of connective tissue cells

Cell Type	Representative Product or Activity	Representative Function
Fibroblast, chondroblast, osteoblast, odontoblast	Production of fibers and ground substance	Structural
Plasma cell	Production of antibodies	Immunologic (defense)
Lymphocyte (several types)	Production of immunocompetent cells	Immunologic (defense)
Eosinophilic leukocyte	Participation in allergic and vasoactive reactions, modulation of mast cell activities and the inflammatory process	Immunologic (defense)
Neutrophilic leukocyte	Phagocytosis of foreign substances, bacteria	Defense
Macrophage	Secretion of cytokines and other molecules, phagocytosis of foreign substances and bacteria, antigen processing and presentation to other cells	Defense
Mast cell and basophilic leukocyte	Liberation of pharmacologically active molecules (eg, histamine)	Defense (participate in allergic reactions)
Adipocyte	Storage of neutral fats	Energy reservoir, heat production

- The cells in connective tissues are grouped into two categories: **fixed cells** and **transient cells** .
- **Fixed cells** are a resident population of cells that have developed and remain in place within the connective tissue, where they perform their functions. The fixed cells are a stable and long-lived population that include
- **Fibroblasts**
- **Adipose cells (Adipocyte)**
- **Reticular cells**
- **Pericytes**
- **Mast cells**
- **Macrophages**
- **Osteocytes**
- **Chondrocytes**
- **Hemocytoblasts**
- **Melanocyts**
- **Transient cells** (free or wandering cells) originate mainly in the bone marrow and circulate in the bloodstream. Upon receiving the proper stimulus or signal, these cells leave the bloodstream and migrate into the connective tissue to perform their specific functions

Transient cells include

• Plasma cells • Lymphocytes • Neutrophils • Eosinophils • Basophils • Monocytes • Macrophage

Macrophages localized in certain regions of the body were given specific names before their origin was completely understood. Thus**, Kupffer cells** of the liver ,**dust cells** of the lung, **Langerhans cells** of the skin, **monocytes** of the blood, and **macrophages** of the connective tissue, spleen, lymph nodes, thymus, and bone marrow are all members of the mononuclear phagocyte system and possess similar morphology and functions. Additionally, **osteoclasts** of bone and **microglia** of the brain, although morphologically different, belong to the mononuclear phagocyte system.

TABLE **Distribution and main functions of the cells of the mononuclear phagocyte system.**

Cell Type	Major Location	Main Function
Monocyte	Blood	Precursor of macrophages
Macrophage	Connective tissue, lymphoid organs, lungs, bone marrow, pleural and peritoneal cavities	Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing, and presentation
Kupffer cell	Liver (perisinusoidal)	Same as macrophages
Microglial cell	Central nervous system	Same as macrophages
Langerhans cell	Epidermis of skin	Antigen processing and presentation
Dendritic cell	Lymph nodes, spleen	Antigen processing and presentation
Osteoclast (from fusion of several macrophages)	Bone	Localized digestion of bone matrix
Multinuclear giant cell (several fused macrophages)	In connective tissue under various pathological conditions	Segregation and digestion of foreign bodies

Fixed Connective Tissue Cells

Fibroblast: The most abundent and most widely distributed resident cells of connective tissue synthesize extracellular matrix components (Graound substance :glycosaminoglycans, proteoglycans and multiadhesive glycoproteins) ,collagen, elastin.

The active fibroblast has an abundant and irregularly branched cytoplasm. Its nucleus is ovoid, large, and pale-staining, with fine chromatin and a prominent nucleolus. The cytoplasm is rich in rough ER, and the Golgi apparatus is well developed. The quiescent fibroblast or fibrocyte is smaller than the active fibroblast and is usually spindle-shaped.

In adults, fibroblasts in connective tissue rarely undergo division; mitosis can resume when the organ requires additional fibroblasts as in wound healing.

- Fibroblasts may occur in either an active state or a quiescent state. Some histologists differentiate between them, calling the quiescent cells fibrocytes; however, because the two states are transitory, the term fibroblast is used in this text.
- Active fibroblasts often reside in close association with collagen bundles, where they lie parallel to the long axis of the fiber .Such fibroblasts are elongated, fusiform cells possessing pale-staining cytoplasm, which is often difficult to distinguish from collagen when stained with hematoxylin and eosin. The most obvious portion of the cell is the darker-stained, large, granular, ovoid nucleus containing a well-defined nucleolus. Electron microscopy reveals a prominent Golgi apparatus and abundant rough endoplasmic reticulum (RER) in the fibroblast, especially when the cell is actively manufacturing matrix, as in wound healing. Actin and α-actinin are localized at the periphery of the cell,whereas myosin is present throughout the cytoplasm.

- Inactive fibroblasts are smaller and more ovoid and possess an acidophilic cytoplasm. Their nucleus is smaller, elongated, and more deeply stained. Electron microscopy reveals sparse amounts of RER but an abundance of free ribosomes.
- Histologically, fibroblasts and **myofibroblasts** are not easily distinguished by routine light microscopy. Electron microscopy, however, reveals that myofibroblasts have bundles of actin filaments and myosin and dense bodies similar to those of smooth muscle cells. Additionally, the surface profile of the nucleus resembles that of a smooth muscle cell. Myofibroblasts differ from smooth muscle cells in that an external lamina (basal lamina) is absent. Myofibroblasts represent transitional modifications of fibroblasts as a result of being contacted by signaling molecules within the regional intercellular matrix. Myofibroblasts are abundant in areas undergoing wound healing where they function in wound contraction.

Adipocytes

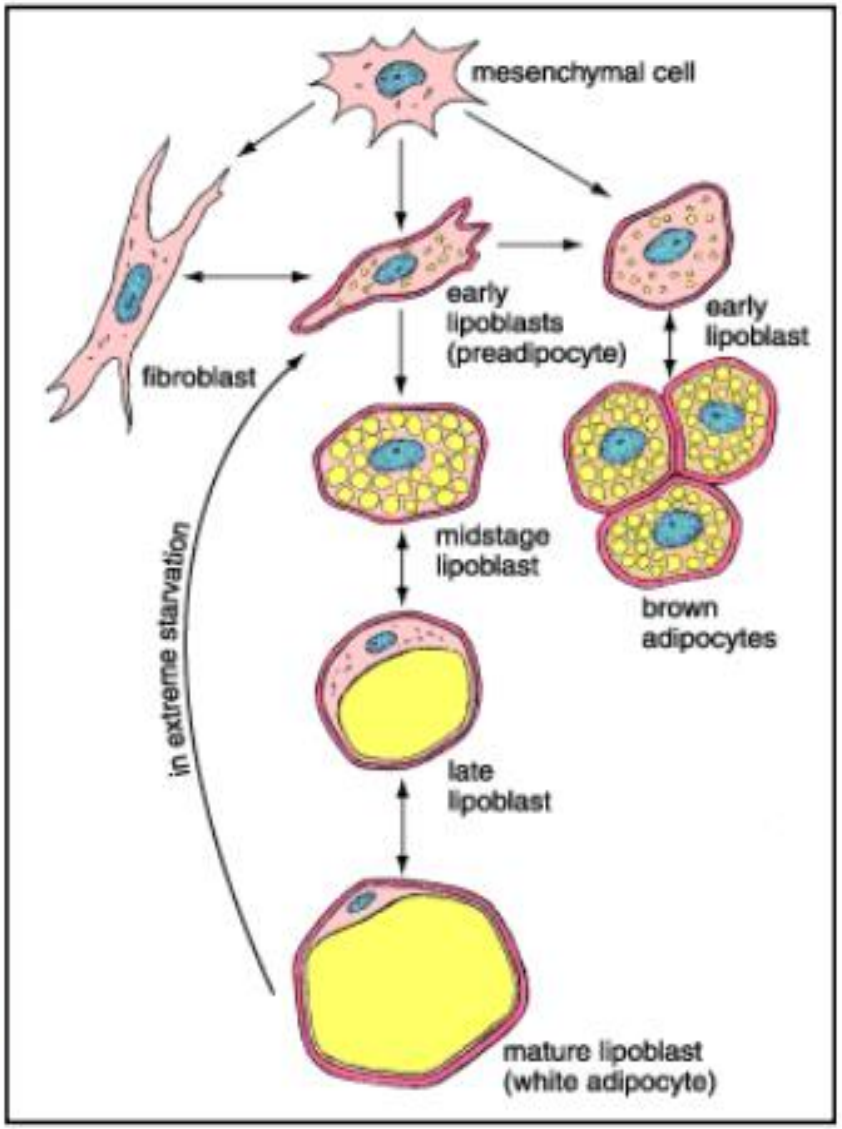
- Adipocytes (Fat cells)
- Adipocytes are connective tissue (C.T.) cell store neutral fat, and produce a variety of hormones.
- They are differentiated from undifferentiated mesenchymal cells, and accumulate fat in their cytoplasm.
- There are two types of fat cells:-
- Unilocular fat cells as in white adipose tissue.
- Multilocular fat cells as in brown adipose tissue.

-Unilocular fat cells are large, spherical cells (120um), store fat gradually making the cytoplasm and the nucleus displaced peripherally giving the cell a signet ring appearance.

- Also, there are a small Golgi apparatus, few mitochondria, sparse rER, and abundant free ribosomes.

Histogenesis:

- Unilocular adipocytes derive from mesenchymal precursor cells that resemble fibroblasts. The appearance of numerous small lipid droplets in the cytoplasm signals the transformation of these cells into lipoblasts. As lipid accumulation continues, the small droplets fuse until a single lipid droplet forms.



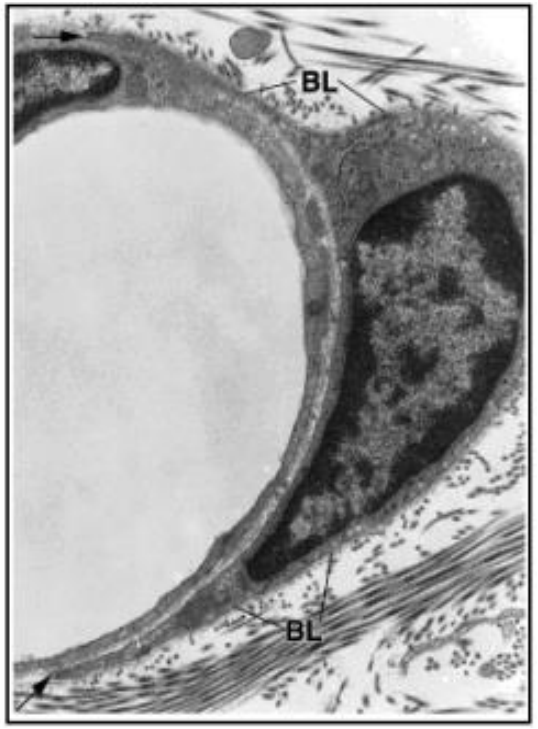
- The multilocular adipocytes of brown fat derive from mesenchymal precursors that assume an epithelial shape and arrangement. The multiple small fat droplets that appear during development do not coalesce during maturation.

Reticular cells

- Reticular cells are typically stellate with long, thin cytoplasmic processes. Each has a central, pale, irregularly rounded nucleus and a prominent nucleolus. In the cytoplasm, the number of mitochondria and the degree of development of the Golgi complex and RER are variable. They produce the reticular fibers that form the network stroma of hematopoietic and lymphoid tissues. Some can phagocytose antigenic material and cellular debris.
- Others (antigen-presenting cells) collect antigens on their surfaces and help activate immunocompetent cells to mount an immune response.

Pericytes (Perivascular cells)

- They are branched cells with flattened nuclei.
- Derived from undifferentiated mesenchymal cells.
- Surround endothelial cells of blood capillaries and venules.
- They have the characters of both smooth muscle cells and endothelial cells
- They can differentiate into fibroblasts and smooth muscle cells (myo-epithelial cells).



Mast cell

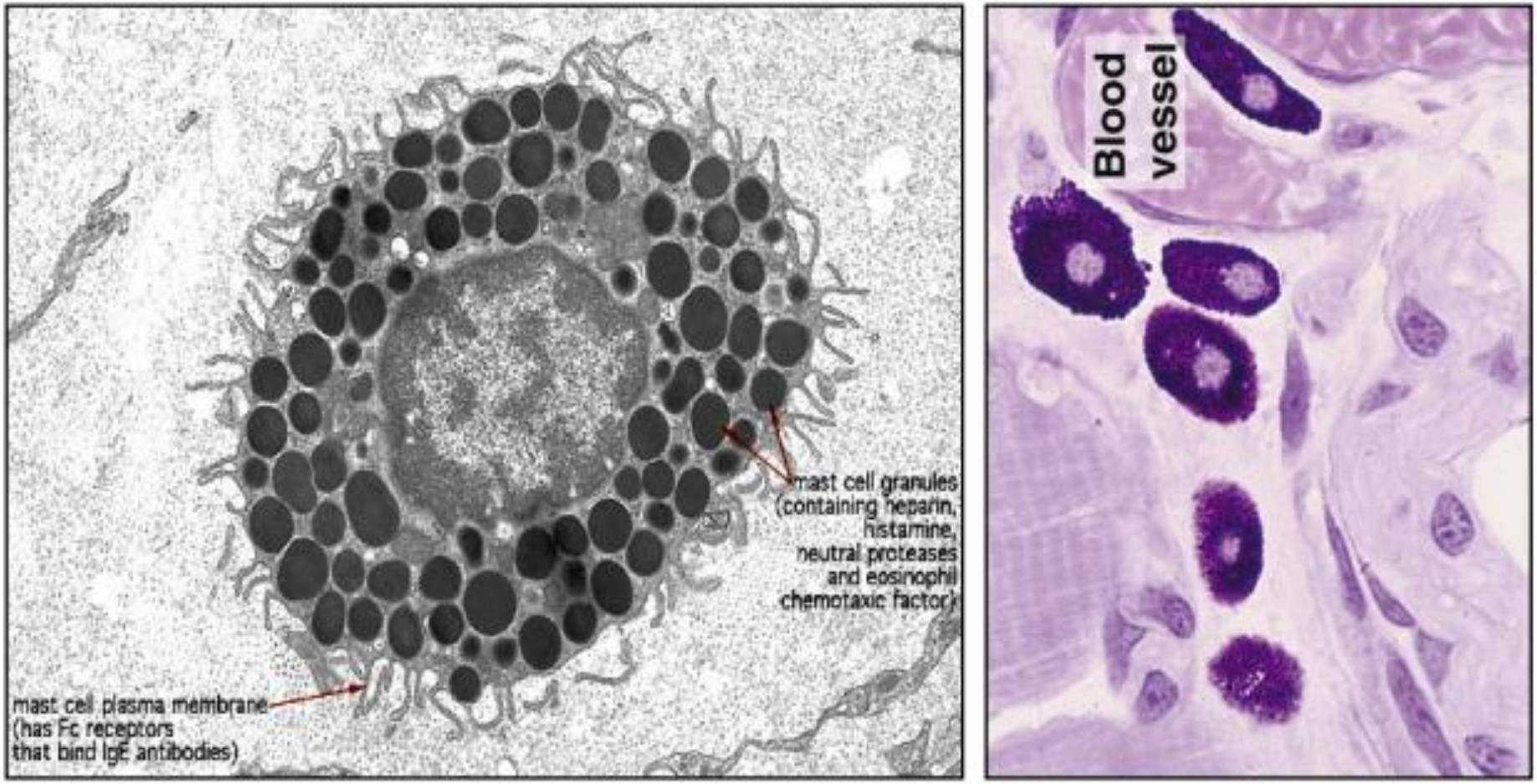
- Mast cells are derived from bone marrow, and differentiate in C.T., and present along B.Vs.
- They are large, ovoid cells (20 – 30um), with spherical nucleus and granulated cytoplasm.
- These granules are membrane-bound (0.3-0.8 um), contain sulfated glycosaminoglycan and other inflammatory mediators, giving them metachromatic stainability with toluidine blue stain.
- The cell surface contains numerous microvilli and folds.
- The cytoplasm contains small amount of rER, mitochondria, and a Golgi apparatus.
- There are two types of human mast cells has been identified based on the morphology and biochemical properties:-

  - C.T. mast cells have cytoplasmic granules with lattice-

like internal structure, and they contain granule-associated tryptase and chymase (MCTC).

  - Mucosal mast cells have granules with a scroll-like internal structure, and produce tryptase only (MCT).

- The granules contain some pharmacological substances called primary mediators, such as heparin, histamine (chondroitin sulfate), neutral proteases (tryptase, chymase), eosinophil chemotactic factor (ECF), slow reacting substance of anaphylactic, neutrophil chemotactic factor (NCF), and secondary mediators such as bradykinins, interleukins, tumor necrosis factor-alpha, platelet activating factor (PAV).
- Secretion of mast cell granules can result in immediate hypersensitivity reaction, and anaphylaxis.
- Mast cells have high affinity cell surface receptors for Ig E, initiating an inflammatory response known as immediate hypersensitivity reaction.



EM and light microscopic picture of mast cell showing the cytoplasmic granules

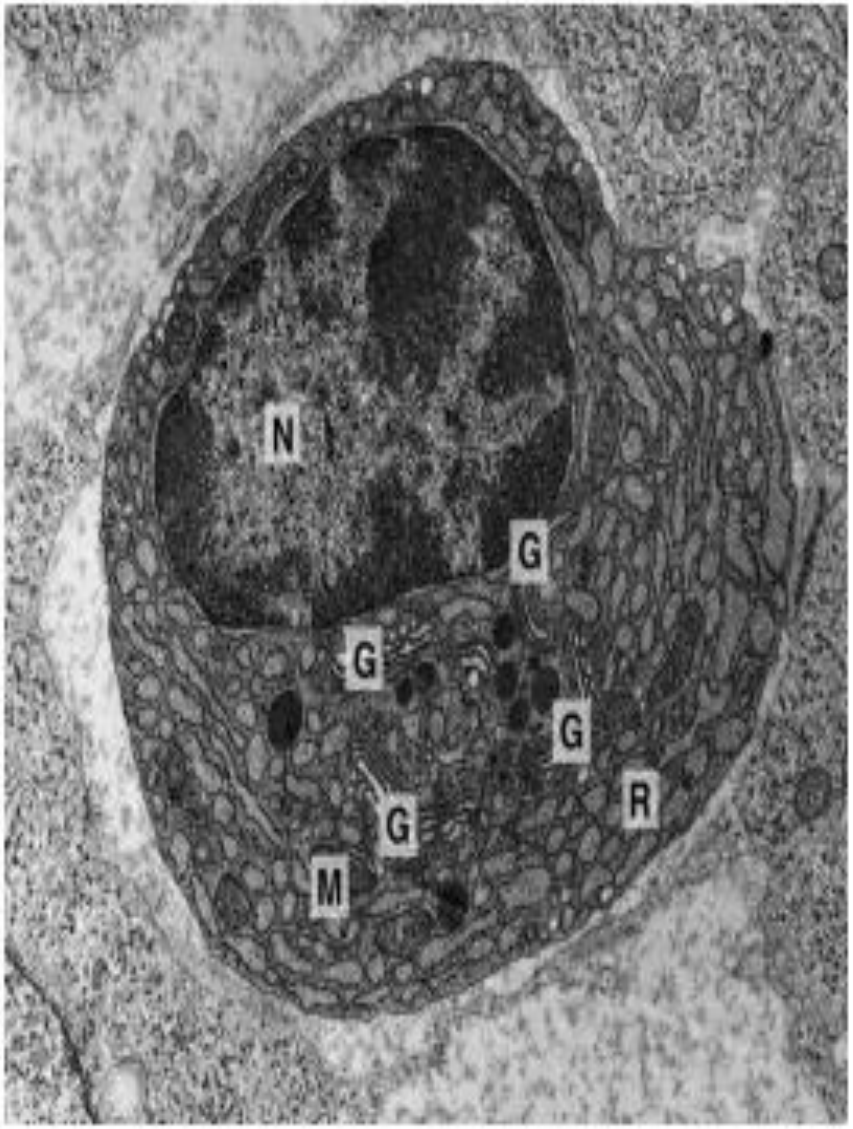
Macrophage

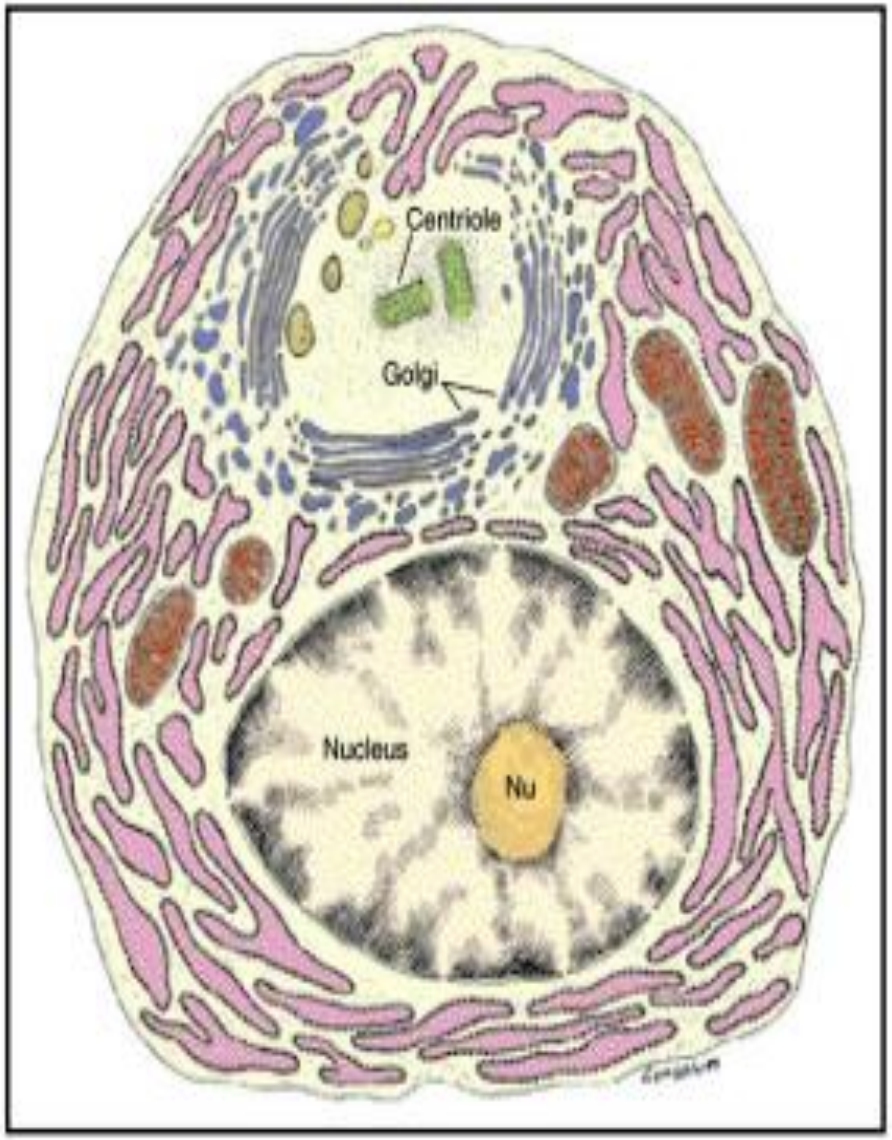
- Macrophages (Histiocytes) are phagocytic cells and are derived from monocytes.
- The surface shows numerous folds and finger like projections.
- Macrophages contain large Golgi apparatus, rER, sER, mitochondria, indented or kidney shaped nucleus, secretory vesicles and many lysosomes.
- Their function is phagocytosis, either as a defense activity (phagocytosis of bacteria), or as a clean up operation (phagocytosis of cell debris), and acting as antigen presenting cells
- When encounter large foreign bodies they fuse to form multinucleated cells that engulf the foreign bodies (foreign body giant cells).
- Under chronic inflammatory conditions, macrophages congregate, greatly enlarge, and become polygonal epithelioid cells. When the particulate matter to be disposed of is excessively large, several to many macrophages may fuse to form a foreign-body giant cell, a giant multinucleated macrophage

- **Hemocytoblasts** **:**occur in the bone marrow and produce erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (formerly called thrombocytes).
- **Melanocytes** :are pigment cells found in the connective tissues of the skin and choroid coat of the eye. The melanin produced by these cells is known to absorb ultra violet light

Transient Connective tissue cells

- **Plasma cells**
- They are derived from B-lymphocytes that have interacted with antigen to produce and secret antibodies.
- Plasma cells are scattered throughout C.T., particularly in areas of inflammation and where microorganisms enter the tissues.
- Once they are differentiated, they have limited migratory capacity, and a short lifespan (2 – 3 weeks).
- Plasma cells are large, ovoid cells (20um) with an eccentric nucleus, where hetero-chromatin radiating from the center giving it a clock face or cartwheel appearance.
- Their cytoplasm is intensely basophilic with well developed rER with closely spaced cisternae, few mitochondria scattered between rER, acidophilic inclusion (Russel Bodies), pale area close to the nucleus contain Golgi bodies and centrioles (Negative Golgi image).





EM and diagrammatic illustration of plasma cell

Leukocytes

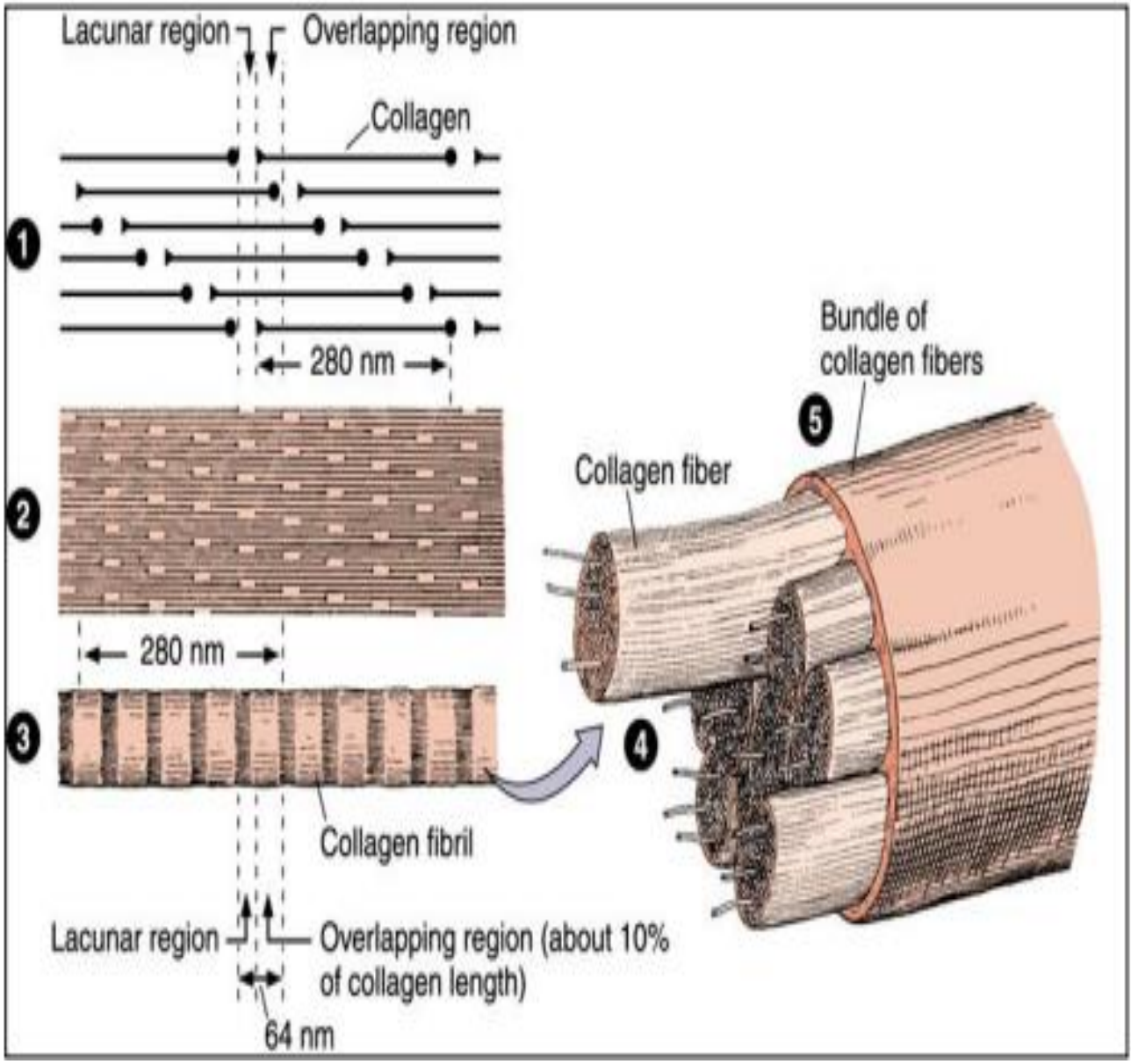
- **Leukocytes** are white blood cells that circulate in the bloodstream. However, they frequently migrate through the capillary walls to enter the connective tissues, especially during inflammation, when they carry out various functions.
- **Monocytes** develop in the bone marrow and circulate in the blood. At the proper signal, they leave the blood stream by migrating through the endothelium of capillaries or venules. In the connective tissue compartment, they mature into macrophages, which normally have a life span of about 2 months..
- **Neutrophils** phagocytose and digest bacteria in areas of acute inflammation, resulting in formation of pus, an accumulation of dead neutrophils and debris.
- **Eosinophils**, similar to neutrophils, are attracted to areas of inflammation by leukocyte chemotactic factors. Eosinophils combat parasites by releasing cytotoxins. They also are attracted to sites of allergic inflammation, where they moderate the allergic reaction and phagocytose antibody-antigen complexes..
- **Basophils** (similar to mast cells) release preformed and newly synthesized pharmacological agents that initiate, maintain, and control the inflammatory process Lymphocytes (T lymphocytes, B lymphocytes, natural killer cells) are present only in small numbers in most connective tissue, except at sites of chronic inflammation, where they are abundant.

Connective Tissue Fibers

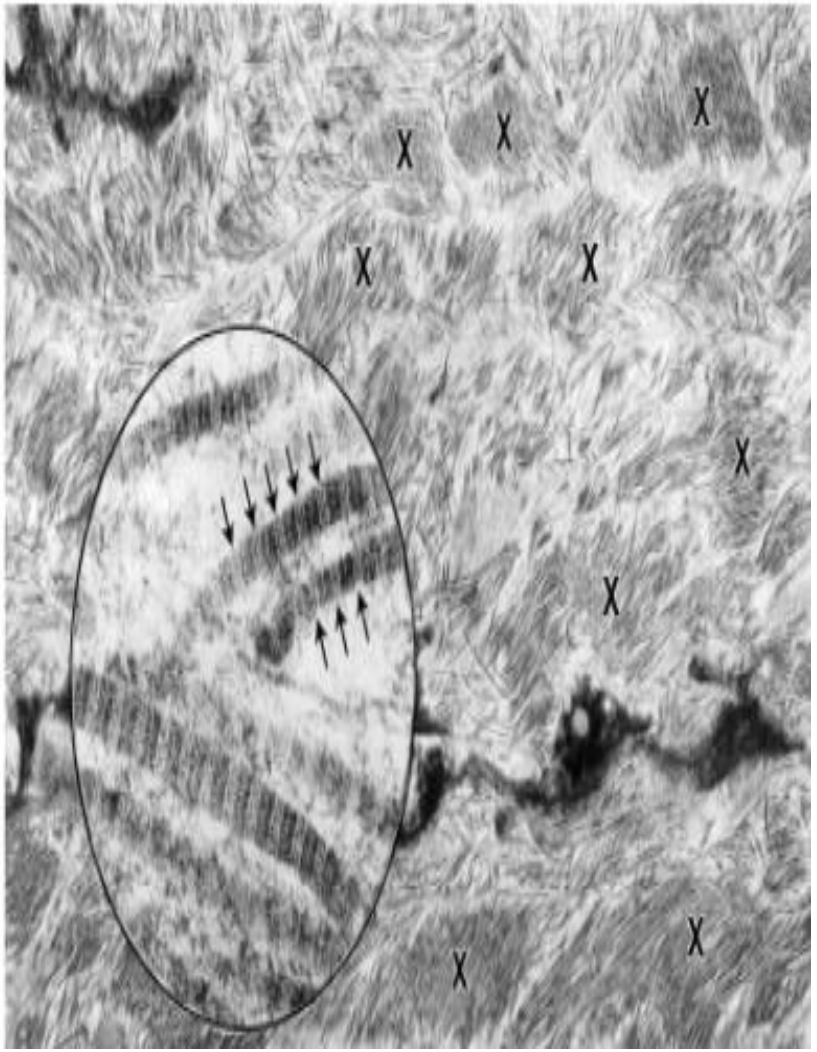
1- Collagen Fibers

- They are found in all connective tissues and in the reticular laminae of certain basement membranes.
- They are flexible and have high tensile strength.
- With L/M. the fibers are wavy with variable width and length.
- They are stained pink with Eosin, blue with Mallory, and green with Masson's trichrome.
- With E/M. appears as bundles of fine fibrils, uniform in diameter, the surface show transverse bands at equal distances (68 nm).
- This regular banding pattern reflects the fibrils sub-unit structure; their size, shape and the arrangement of molecules that form the collagen.
- The collagen molecule (Tropocollagen) measures about 300 nm long and 1.5 nm thick, with a head and tail.
- Within each fibril, the molecules align head to tail in overlapping rows, with equal gaps between the molecules in each row.

Diagrammatic illustration of collagen fiber structure

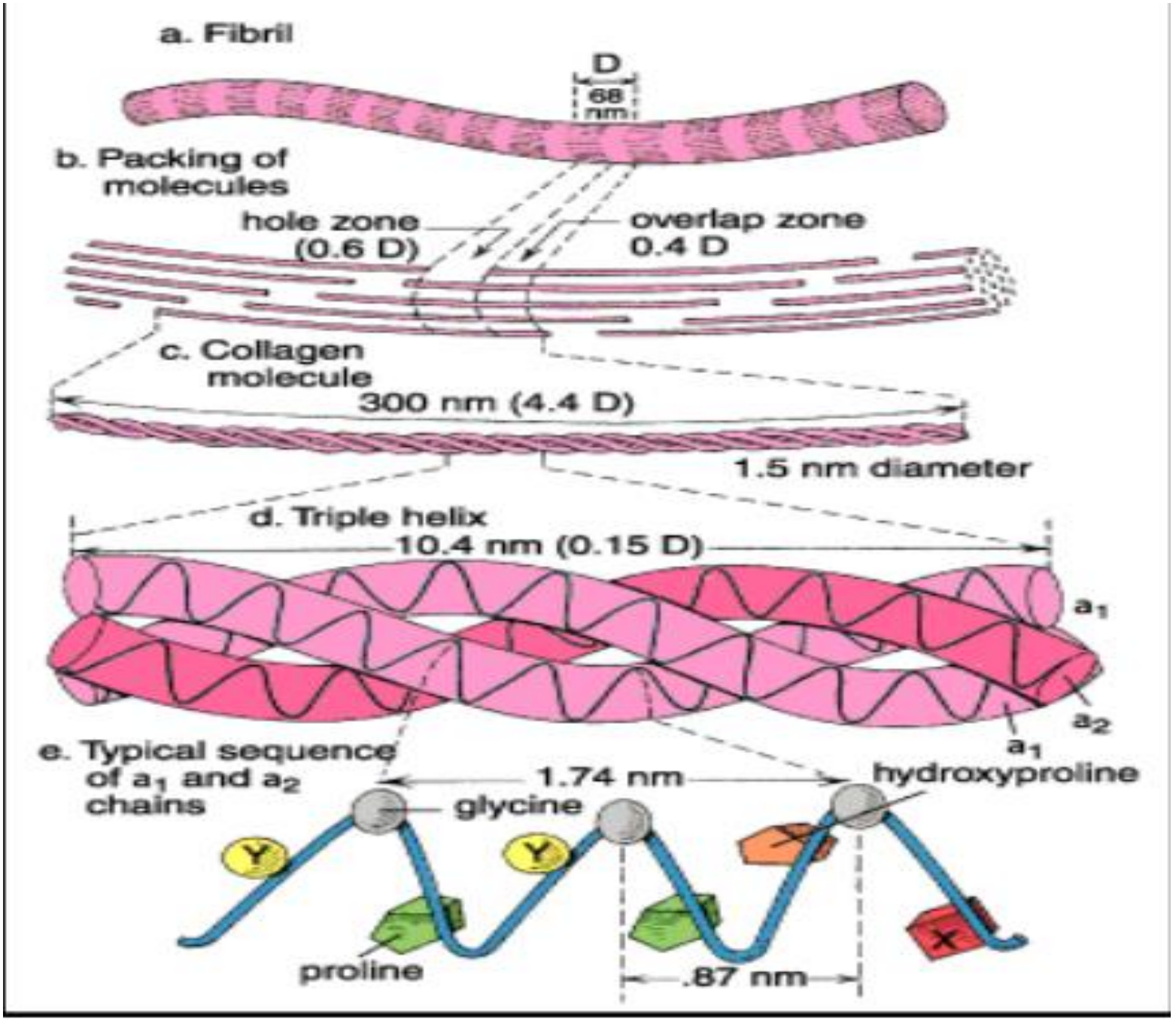


EM picture of collagen fibers showing the striation (arrows within the circle)



Collagen Structure

- A single collagen molecule is formed of three polypeptide chains (α-chains) i.e. a triple helix.
- Every third amino acid in the chain is a glycine molecule, except at the end of the α-chains.
- A hydroxyproline or hydroxylysine precedes each glycine, and a proline follows each glycine in the chain.
- There are sugar groups joined to hydroxylysine given the description of collagen as glycoprotein.
- The α-chains that constitute the helix are not the same, they are vary in size from 600 to 3000 amino acids.
- There are at least 42 types of α-chains encoded by different genes.
- There are about 27 different types of collagens based on combinations of different α-chains.
- Depending on the type of collagen molecules, it may be homotrimeric or heterotrimeric collagen.


a. Fibril
D
68 nm
b. Packing of molecules
hole zone (0.6 D)
overlap zone 0.4 D
c. Collagen molecule
300 nm (4.4 D)
1.5 nm diameter
d. Triple helix
10.4 nm (0.15 D)
a1
a2
a1
e. Typical sequence of a1 and a2 chains
1.74 nm
glycine
hydroxyproline
Y
Y
X
proline
.87 nm
X

Collagen Biosynthesis

- The production of fibrillar collagen involves a series of events within the fibroblast to produce procollagen (precursor of collagen).
- Production of actual fibril occurs outside the cell, involving enzymatic activity at the cell membrane (procollagen peptidase enzyme) to produce the mature collagen molecules.
- The aggregated collagen molecules align together to form collagen fibrils in the extracellular matrix (a process called Fibrillogenesis).
- Collagen fibrils often consist of more than one type of collagen, i.e. different types of collagen molecules assembled into the fibrils.

- For example type I collagen fibrils contain small amounts of type II, III, and XI.
- Collagen molecules are formed by various types of CT cells including fibroblasts, chondrocytes in cartilage, osteoblasts in bone, and pericytes in blood vessels.
- Also, collagen molecules of the basement membrane are produced by the epithelial cells.
- Collagen synthesis is regulated by complex interaction between growth factors, hormones and cytokines.

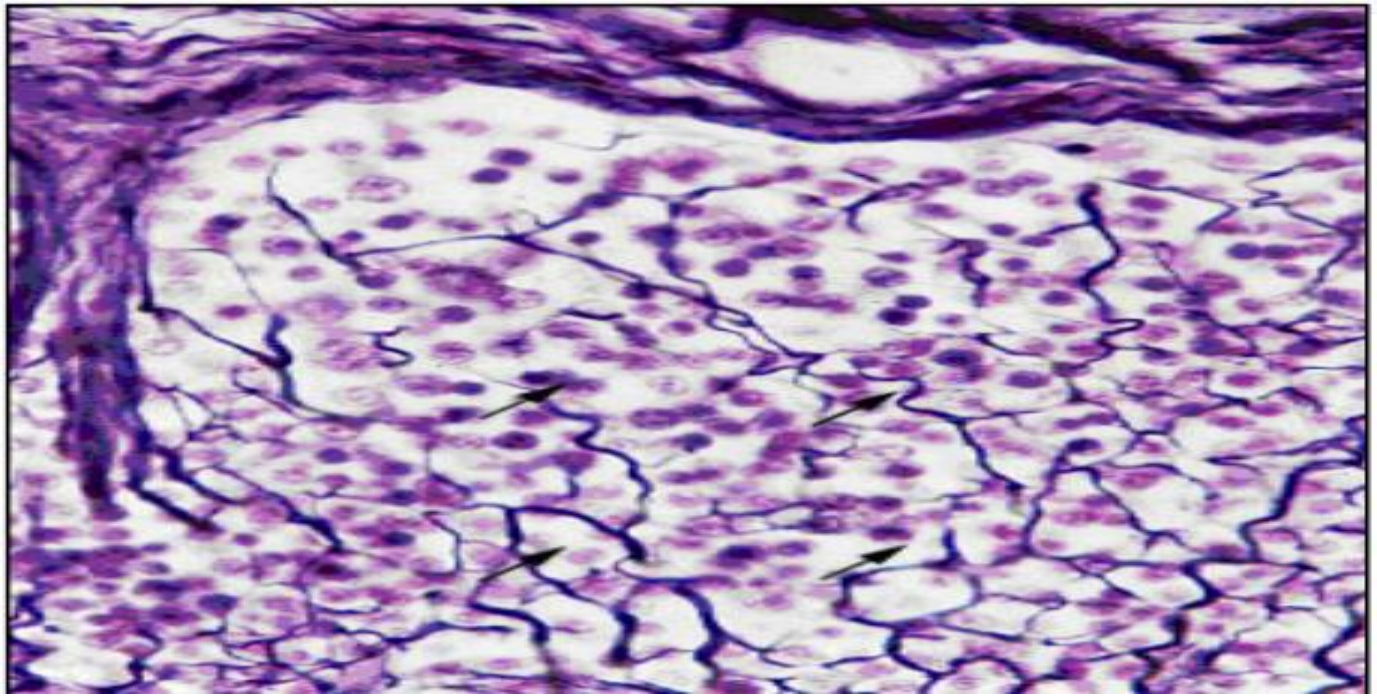
Collagen types

- **Type I collagen,** the most abundant type, forms large fibers and fiber bundles. It occurs in tendons, ligaments, bone, dermis, organ capsules, and loose connective tissue.
- **Type II collagen** is found in adults only in the cartilage matrix and forms thin fibrils.
- **Type III collagen** is similar to type I, but is more heavily glycosylated and stains with silver. Often found in association with type I, type III forms networks of thin fibrils that surround and support soft flexible tissues. It is the major fiber component of hematopoietic tissues (eg, bone marrow, spleen) and of the reticular lamina underlying epithelial basal lamina.
- **Type IV collagen** is the major collagen type in basal lamina. It does not form fibers or fibrils.
- **Type V collagen** is present in placental basement membranes and blood vessels.

2- Reticular Fibers

- Reticular fibers are composed of type III collagen.
- The fibrils are branched, with a narrow diameter, and do not bundle to form thick fibers.
- Reticular fibers provide a supporting framework for cellular constitutes of various organs.
- They are not stained by routine H&E stain, stained with Silver technique, and they are PAS positive (contain sugar group) fibers.
- Reticular cells produce the collagen of reticular fibers in hemopoietic and lymphatic tissues.
- Fibroblasts produced reticular fibers in other locations

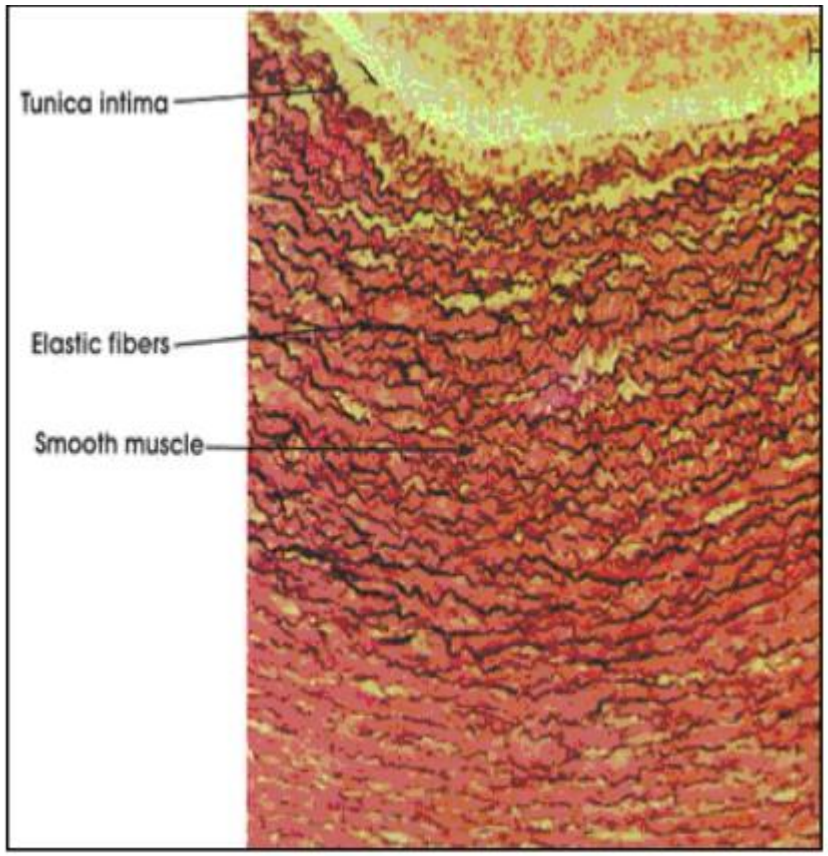
- Schwann cells secret reticular fibers in endoneurium (Nervous system).
- Smooth muscles in the wall of blood vessels and of the alimentary canal secret reticular fibers and other collagen.



3- Elastic Fibers

- Elastic fibers are thin and branched fibers.
- They allow tissue to respond to stretch and distension.
- Elastic fibers are interwoven with collagen fibers to limit the distensibility of tissue and prevent excessive stretching.
- We cannot identify elastic fibers from collagen fibers with routine H&E stain, but we can do with special **ORCEIN** stain as shown in the next figure.
- Elastic fibers are produced as collagen by fibroblast and smooth muscle cells.

- Elastic fibers are composed of a central **elastin** core and a surrounding network of **fibrillin** microfibrils.
- Elastic fibers present in arterial walls, interalveolar septa, bronchi and bronchioles of the lungs, vocal ligaments, and ligamenta flava of the vertebral column



- **ELASTIN** is a protein rich in proline and glycine, but it is poor in hydroxyproline with absence of hydroxylysine.
- Glycines are randomly distributed allowing random coiling of the fibers, sliding the fibers over one another, or stretching the fibers and then recoiling to their original size.
- Elastin forms fibers of variable thicknesses, or lamellar layers as those in elastic arteries (aorta).
- **Fibrillin-1** is a glycoprotein forming fine microfibrils.
- During elastogenesis, the fibrillin microfibrils are formed first, then elastin material deposited on the surface of the microfibrils.
- Absence of fibrillin microfibrils results in the formation of elastin sheet or lamella, as in BV.

Connective Tissue Ground Substance

- The ground substance is a viscous, clear with high water content.
- With the light microscope, it appears amorphous in sections of frozen tissues stained with PAS.
- But it lost during tissue fixation and dehydration in routine H&E stain for the paraffin sections.
- The extracellular matrix is a complex structure that surrounds and supports cells within tissue.
- ground substance that occupies the spaces between the cells and fibers.

- The ground substance contains a variety of molecules secreted by CT cells such as :-
- **Proteoglycans** (aggrecan, syndecan) –
- **Multiadhesive** glycoproteins (fibronectin, laminin).
- **Glycosaminoglycans** (dermatan sulfate, keratan sulfate, hyalronic acid).
- The matrix provides mechanical and structural support as well as tensile strength for the tissues.
- It also provides pathways for cell migration, and cell differentiation.
- It functions as a biochemical barrier and has a role in regulating the metabolic activity.
- The matrix has the ability to bind growth factors which in turn enhance cell growth.
- It facilitates cell communication (transmission of molecules and information across the plasma membranes).

- **Glycosaminoglycans (GAG)**
- Hyalonan: synovial fluid, vitreous humor, matrix of loose CT.
- Chondroitin 4- & 6- sulfate: cartilage, bone, valves of the heart.
- Dermatan sulfate: skin, blood vessels, valves.
- Keratan sulfate: Bone, cartilage, cornea.
- Heparan sulfate: Basal lamina, cell surface.
- Heparin: in granules of mast cells & basophiles.

- **Proteoglycans**
- **Agrecan**: Cartilage & bone .
- **Decorin**: CT, fibroblasts, cartilage & bone .
- **Versican**: Fibroblasts, skin, smooth muscles, brain, mesangial cells of kidney.
- **Syndecan**: Embryonic epithelia, lymphocytes mesenchymal cells, plasma cells.
- **Multiadhesive Glycoproteins**
- **Fibronectin**: Matrix of many tissues.
- **Laminin**: Basal laminae of all epithelial cells, adipocytes, Schwann cells
- **Tenascin**: Embryonic mesenchyme, periosteum, perichondrium, wounds, tumors
- **Osteopontin**: Bone
- **Entactin/Nidogen**: Basal lamina specific protein

Classification of Connective Tissues

A. Embryonic connective tissues

1. Mesenchymal connective tissue
2. Mucous connective tissue

B. Connective tissue proper

1. Loose (areolar) connective tissue
2. Dense connective tissue
   a. Dense irregular connective tissue
   b. Dense regular connective tissue
      - Collagenous
      - Elastic
3. Reticular tissue
4. Adipose tissue

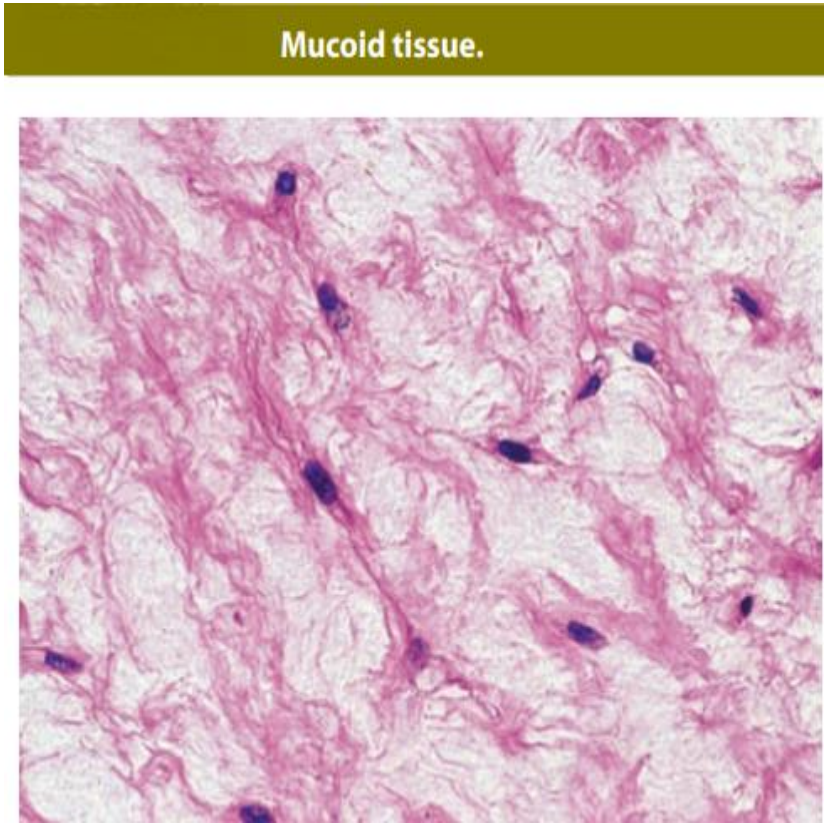
C. Specialized connective tissue

1. Cartilage
2. Bone
3. Blood
4. Hemapoietic tissue

Embryonic Connective Tissue

1.Mesenchymal connective tissue is present only in the embryo and consists of mesenchymal cells in a gel-like, amorphous ground substance containing scattered reticular fibers. **Mesenchymal cells** possess an oval nucleus exhibiting a fine chromatin network and prominent nucleoli. The sparse, pale-staining cytoplasm extends small processes in several directions. Mitotic figures are frequently observed in mesenchymal cells because they give rise to most of the cells of loose connective tissue. It is generally believed that most, if not all, of the mesenchymal cells, once scattered throughout the embryo, are eventually depleted and do not exist as such in the adult, except in the pulp of teeth. In adults, however, pluripotential pericytes, which reside along capillaries, can differentiate into certain other cells of connective tissue.

2.Mucous tissue is a loose, amorphous connective tissue exhibiting a jelly-like matrix primarily composed of hyaluronic acid and sparsely populated with type I and type III collagen fibers and fibroblasts. This tissue, also known as **Wharton jelly**, is found only in the umbilical cord and subdermal connective tissue of embryos.



A section of umbilical cord shows large fibroblasts surrounded by a large amount of very loose ECM containing mainly ground substances very rich in hyaluronan, with wisps of collagen. Histologically mucoid (or mucous) connective tissue resembles embryonic mesenchyme in many respects and is rarely found in adult organs. (X200; H&E)

Connective Tissue Proper

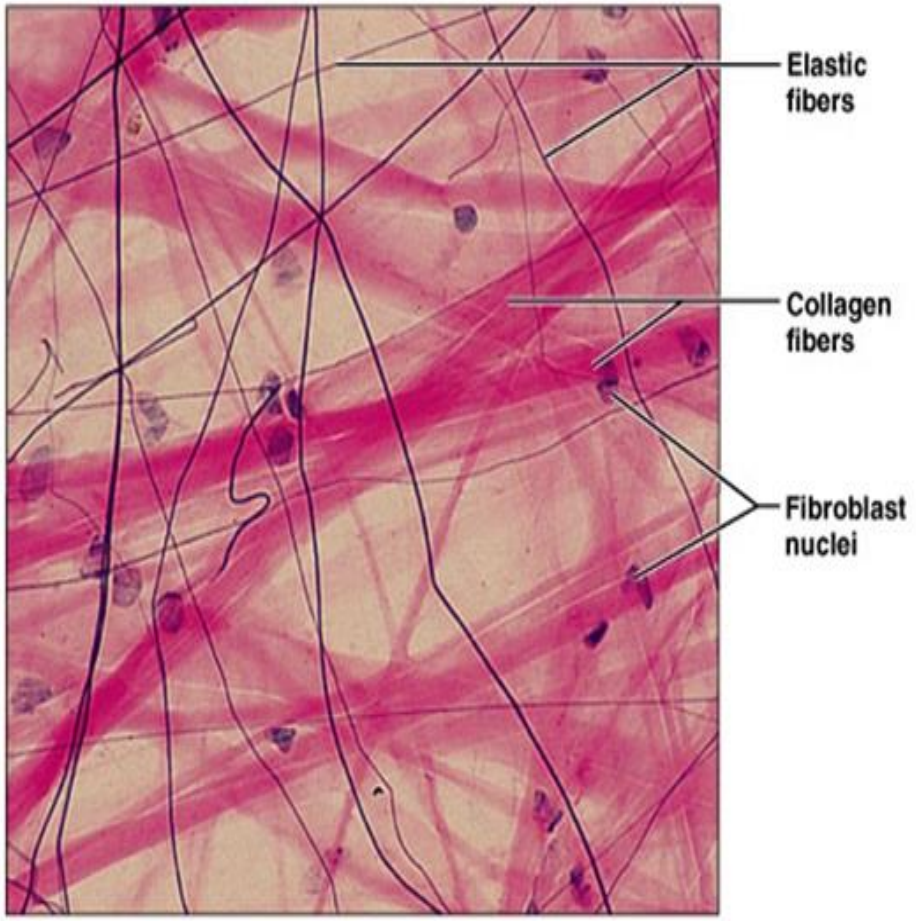
1.Loose (Areolar) Connective Tissue

Loose connective tissue, also known as areolar connective tissue, fills in the spaces of the body just deep to the skin, lies below the mesothelial lining of the internal body cavities, is associated with the adventitia of blood vessels, and surrounds the parenchyma of glands. The loose connective tissue of mucous membranes (as in the alimentary canal) is called the lamina propria.

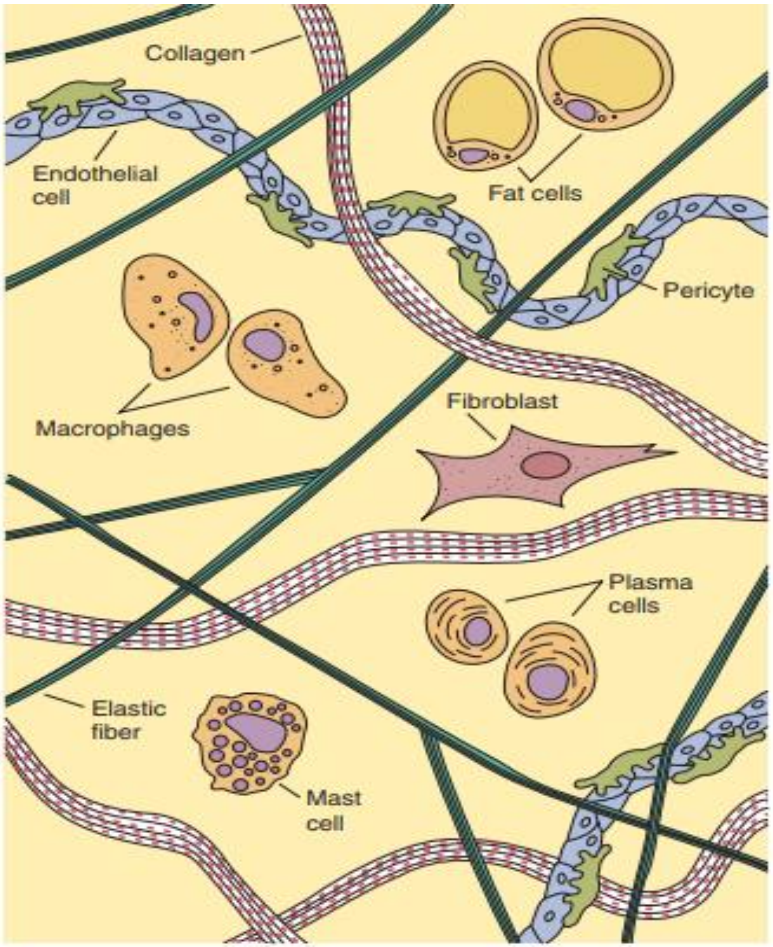
- Loose connective tissue is characterized by abundant **ground substance** and extracellular fluid (tissue fluid) housing the fixed connective tissue cells: **fibroblasts**, **adipose cells**, **macrophages**, and **mast cells** as well as some **undifferentiated cells**. Also scattered throughout the ground substance are loosely woven **collagen, reticular**, and **elastic fibers**. Coursing in this amorphous tissue are small nerve fibers as well as blood vessels, which supply the cells with oxygen and nutrients.

Because this tissue lies immediately beneath the thin epithelia of the digestive and respiratory tracts, it is here that the body first attacks antigens, bacteria, and other foreign invaders.

- therefore, loose connective tissue contains many transient cells responsible for inflammation, allergic reactions, and the immune response. These cells, which originally circulate in the bloodstream, are released from blood vesselsin response to an inflammatory stimulus. Pharmacological agents released by mast cells increase the permeability of small vessels so that excess plasma enters the loose connective tissue spaces, causing it to become swollen.



Areolar connective tissue, a soft packaging tissue of the body



Schematic diagram illustrating the cell types and fiber types in loose connective tissue.

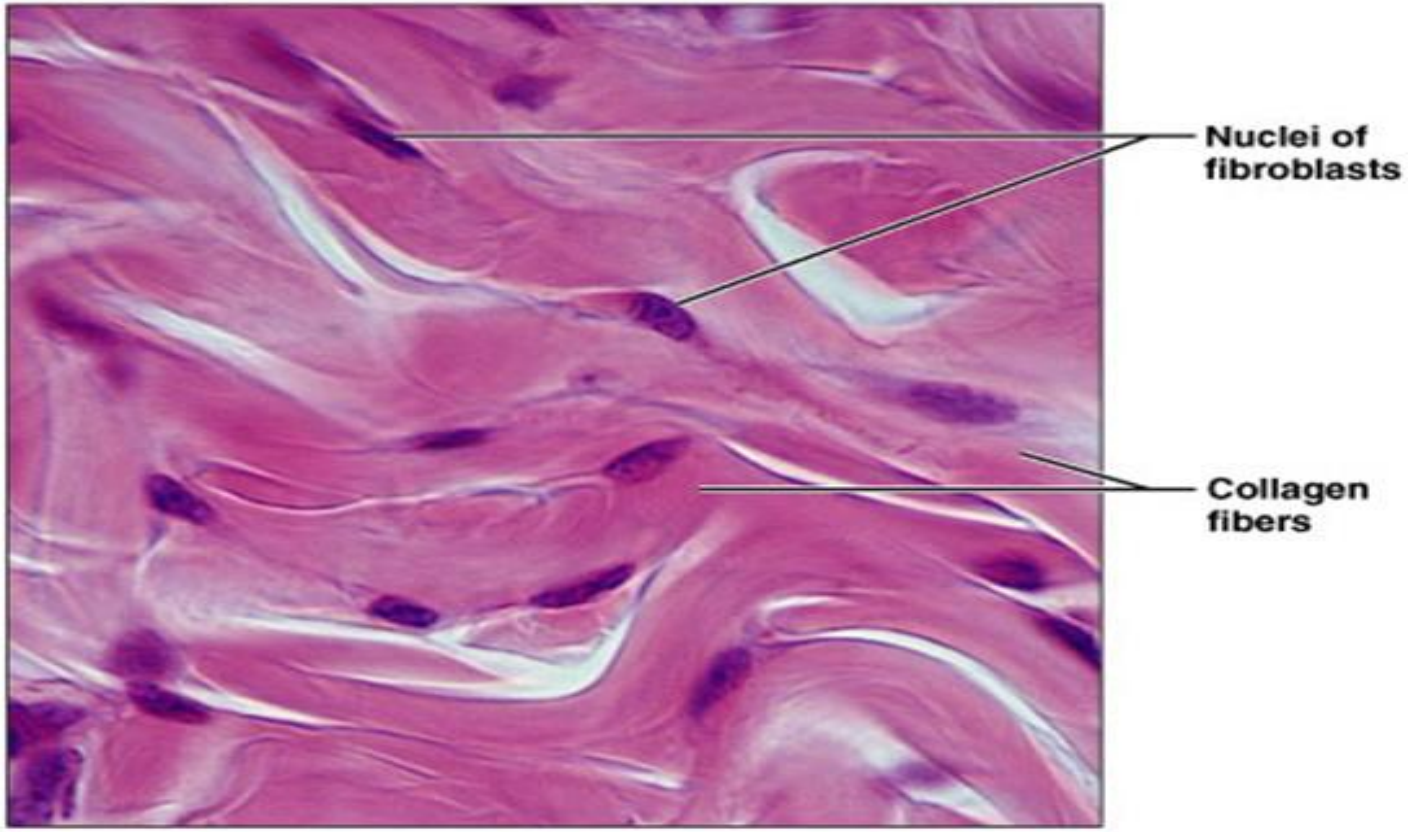
2. Dense Connective Tissue

Dense connective tissue contains most of the same components found in loose connective tissue, except that it has many more fibers and fewer cells. The orientation and the arrangements of the bundles of collagen fibers in this tissue make it resistant to stress. When the collagen fiber bundles are arranged randomly, the tissue is called **dense irregular connective tissue.**

When fiber bundles of the tissue are arranged in parallel or organized fashion, the tissue is called **dense regular connective tissue**, which is divided into **collagenous** and **elastic** types

*Dense irregular connective tissue

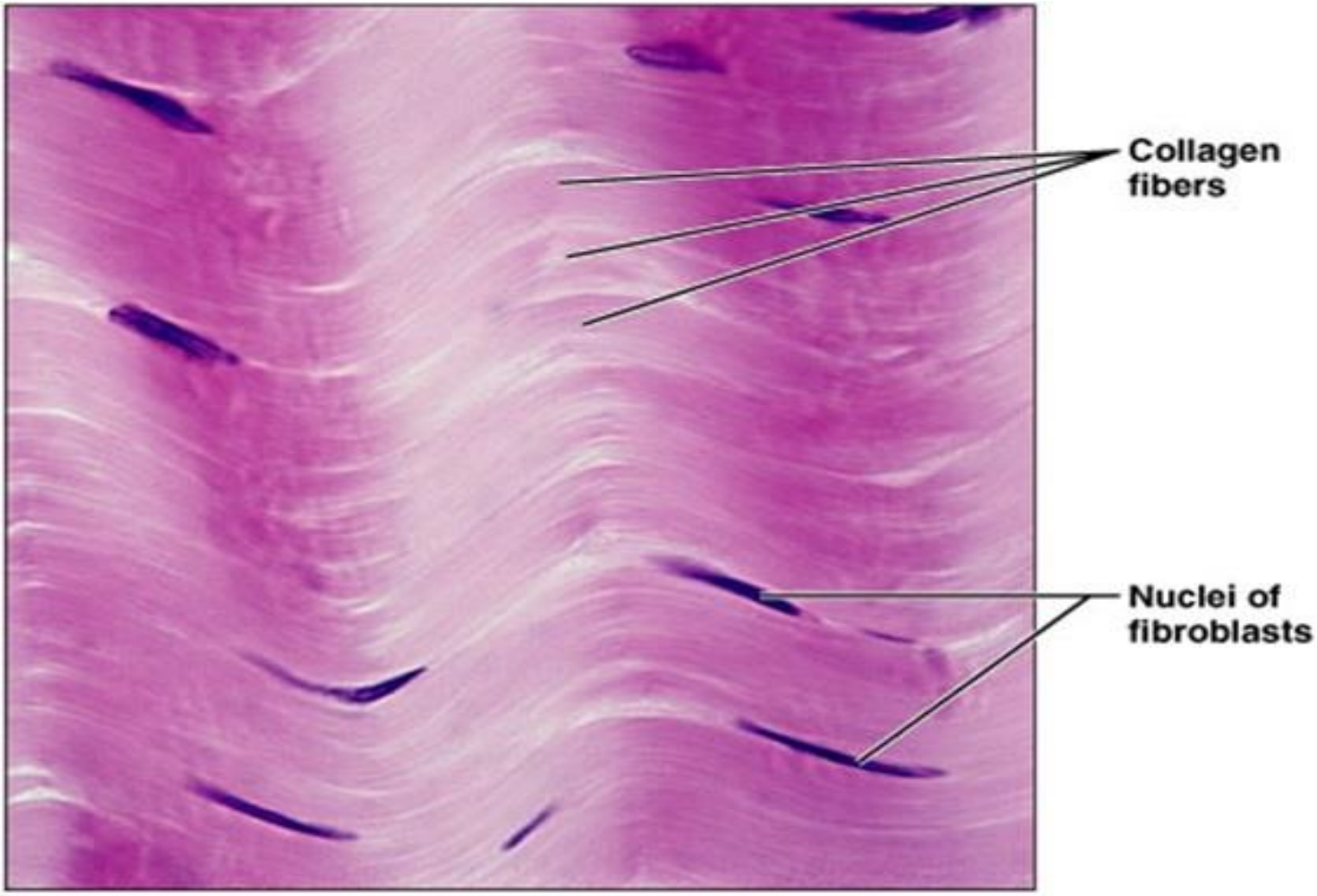
- Dense irregular connective tissue contains mostly coarse collagen fibers interwoven into a meshwork that resists stress from all directions The collagen bundles are packed so tightly that space is limited for ground substance and cells. Fine networks of elastic fibers are often scattered about the collagen bundles. Fibroblasts, the most abundant cells of this tissue, are located in the interstices between collagen bundles. Dense irregular connective tissue constitutes the dermis of skin; the sheaths of nerves; and the capsules of spleen, testes, ovary, kidney, and lymph nodes.



Dense irregular connective tissue from the dermis of the skin

*Dense regular collagenous connective tissue

- Dense regular collagenous connective tissue is composed of coarse collagen bundles densely packed and oriented into parallel cylinders or sheets that resist tensile forces Because of the tight packing of the collagen fibers, little space can be occupied by ground substance and cells. Thin, sheet-like fibroblasts are located between bundles of collagen with their long axes parallel to the bundles. Tendons ligaments, and aponeuroses are examples of dense regular collagenous connective tissue.

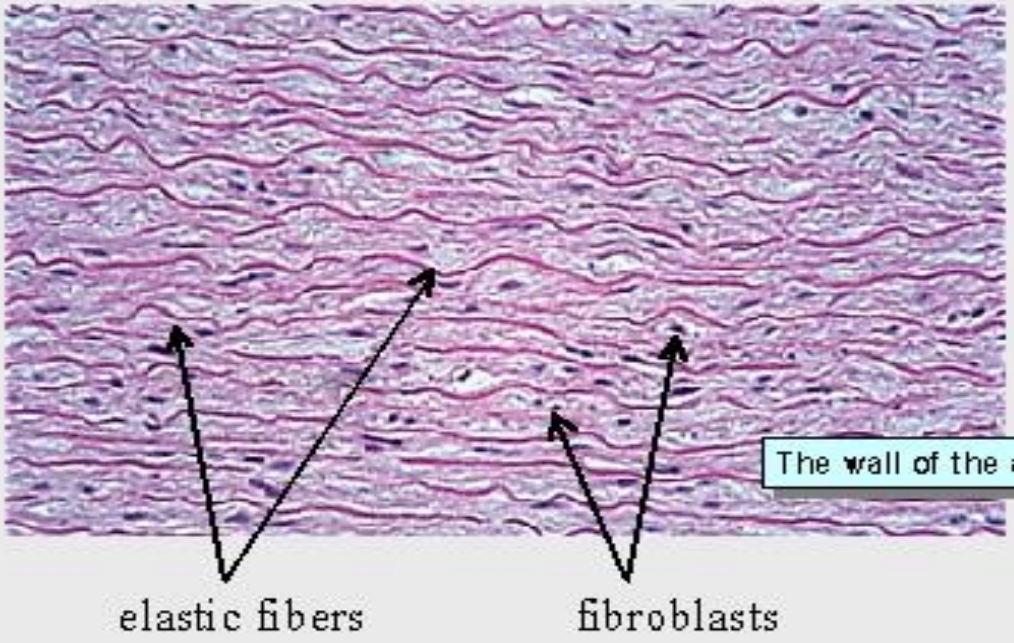


Dense regular connective tissue from a tendon

*Dense regular elastic connective tissue

- Dense regular elastic connective tissue possesses coarse branching elastic fibers with only a few collagen fibers forming networks. Scattered throughout the interstitial spaces are fibroblasts. The elastic fibers are arranged parallel to one another and form either thin sheets or fenestrated membranes. The latter are present in large blood vessels, ligamenta flava of the vertebral column, and the suspensory ligament of the penis.

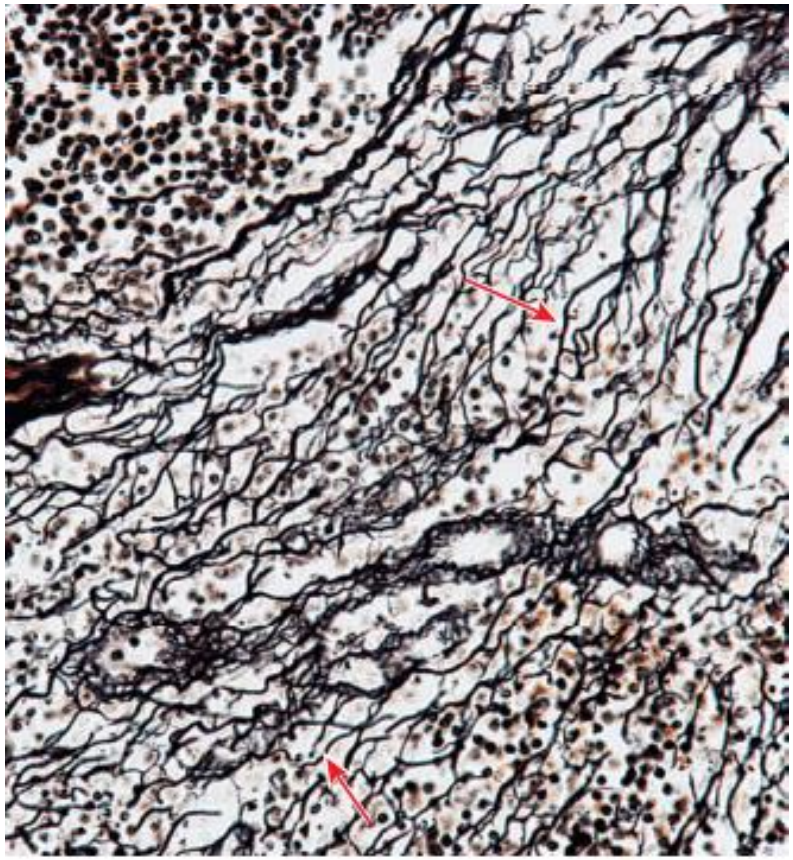
Elastic Connective Tissue



Found in the stroma of the lungs and in the walls of the large arteries.

Reticular Tissue

Type III collagen is the major fiber component of reticular tissue. The collagen fibers form mesh-like networks interspersed with fibroblasts and macrophages It is the fibroblasts that synthesize the type III collagen. Reticular tissue forms the architectural framework of liver sinusoids, adipose tissue, bone marrow, lymph nodes, spleen, smooth muscle, and the islets of Langerhans



Light micrograph of reticular tissue (stained with silver) displaying the networks of reticular fibers (×270). Many lymphoid cells are interspersed between the reticular fibers (arrows)

Adipose Tissue

- **General features**

Adipose tissue, or fat, is a connective tissue specialized to store fuel. The cytoplasm of fat cells contains large triglyceride deposits in the form of one or more lipid droplets without limiting membranes. The clusters of adipocytes scattered throughout the body constitute an important metabolic organ that varies in size and distribution, depending on age, sex, and nutritional status. This clusters of adipocytes are divided into lobes and lobules by septa of collagenous connective tissue of variable density. There are 2 types of adipose tissue, named as white adipose tissue (white fat) and brown adipose tissue (brown fat).

I. WHITE ADIPOSE TISSUE

- It is more abundant than brown adipose tissue, and is termed unilocular adipose tissue; a reference to the single fat droplet in each cell. Sometimes it is named yellow adipose tissue or yellow fat; because the dietary carotenoids accumulate in the lipid droplets, making the tissue yellow. In mature adipocytes, the droplet is so large that it displaces the nucleus and remaining cytoplasm to the cell periphery. Cell diameter varies from 50 to 150µm. Adipocytes in histologic sections have a signet-ring appearance because most of the lipid is dissolved during preparation, leaving only a flattened nucleus and a thin rim of cytoplasm. The cytoplasm near the nucleus contains a Golgi complex, mitochondria, a small amount of RER, and free ribosomes. The cytoplasm in the thin rim contains SER and pinocytotic vesicles.

Distribution of white adipose tissue

1.Subcutaneous fat

(hypodermis) is the layer of white adipose tissue found just beneath the skin except in the eyelids, penis, scrotum, and most of the external ear. In infants it forms a thermal insulating layer of uniform thickness covering the entire body. In adults it becomes thicker or thinner in selected areas, depending upon the person's age, sex, and dietary habits.

2.Intra-abdominal fat

deposits of variable size surround blood and lymphatic vessels in the omentum and mesenteries suspended in the abdominal cavity. Additional accumulations occur in retroperitoneal areas, such as around the kidneys.

Functional Characteristics:

- Adipocytes store fatty acids in triglycerides (esters of glycerol and 3 fatty acids). The triglycerides stored in both white and brown fat undergo continuous turnover. Released fatty acids serve as a source of chemical energy for cells (the predominant source in resting muscle) and as raw materials for making phospholipids (the predominant component of biologic membranes). Turnover is regulated by several histophysiologic factors, which shift the equilibrium toward fat uptake or mobilization, depending on the body's level of, and need for, circulating fatty acids.

II. BROWN ADIPOSE TISSUE

General Features:

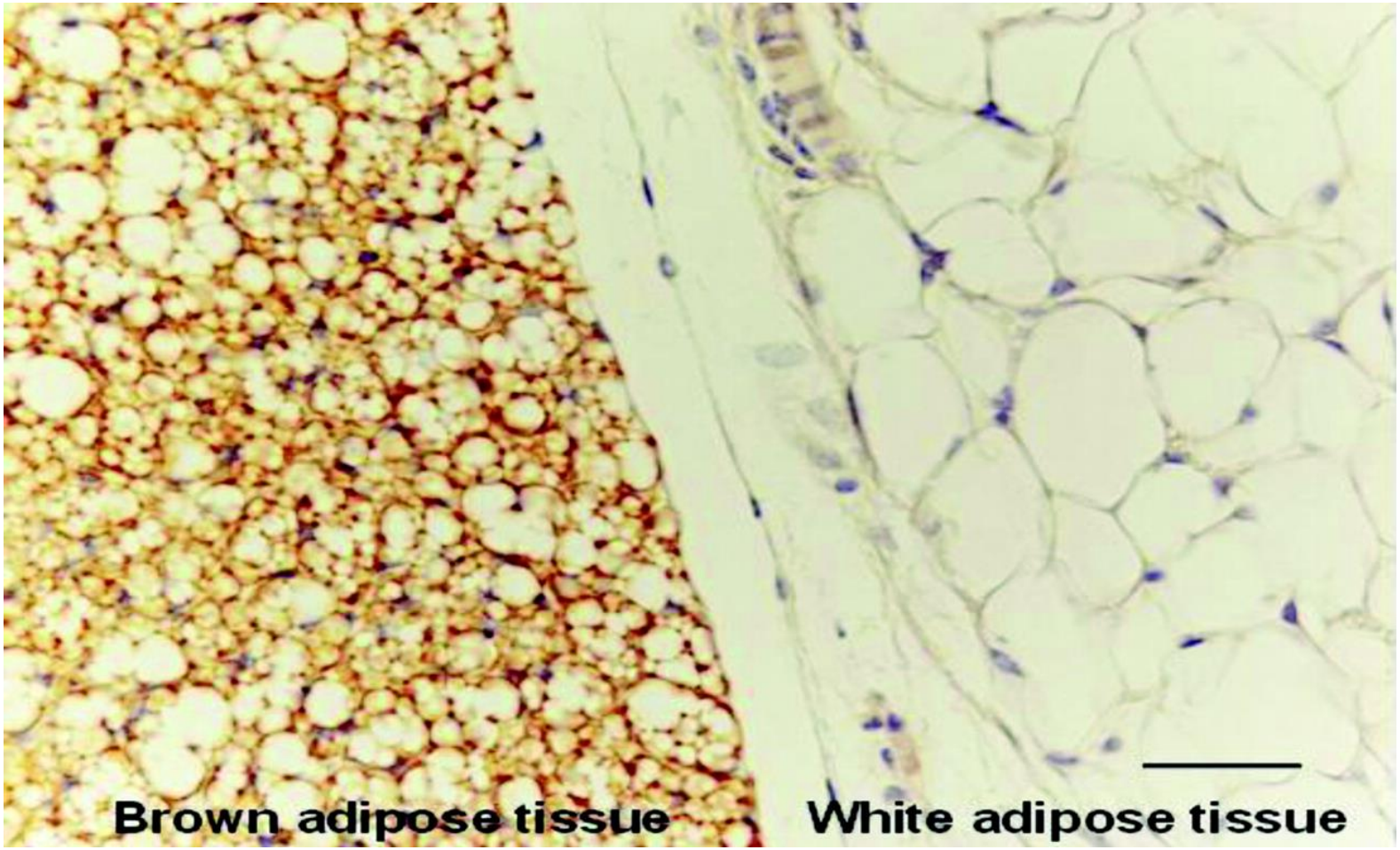
Brown fat is called multilocular adipose tissue because of the multiple small lipid droplets in its adipocytes. Brown adipocytes are smaller than white adipocytes and have a spheric, centrally located nucleus. They contain many mitochondria (the tan to reddish-brown tissue color is due chiefly to mitochondrial cytochromes). Loose connective tissue septa give brown adipose tissue a lobular appearance like that of glands. It is very rich of vascular supply (partly responsible for the color).

Distribution of brown adipose tissue

- Brown fat is less abundant than white at all ages. Young and middle-aged adults have little or none, but fetuses, newborns, and the elderly have accumulations in the axilla, in the posterior triangle of the neck, and around the kidney.

Functional Characteristics:

- Brown fat has many of the same functional capabilities as white, but its metabolic activity is more intense and can lead to generation of heat. Under conditions of excessive cold, autonomic stimulation can cause oxidative phosphorylation in the numerous mitochondria to uncouple from adenosine triphosphate (ATP) synthesis, and the released energy dissipates as heat. The numerous vessels supplying this tissue carry the heat to the body. Brown fat is important in hibernating animals and in human infants before other thermoregulatory mechanisms are well developed.


Brown adipose tissue
White adipose tissue

Thank you

Al-Noor University College.
Medical laboratories technics department.
Second Stage / 2022 – 2023.
Lectures of General Histology (Theory).

Associated glands of digestive system. (3)

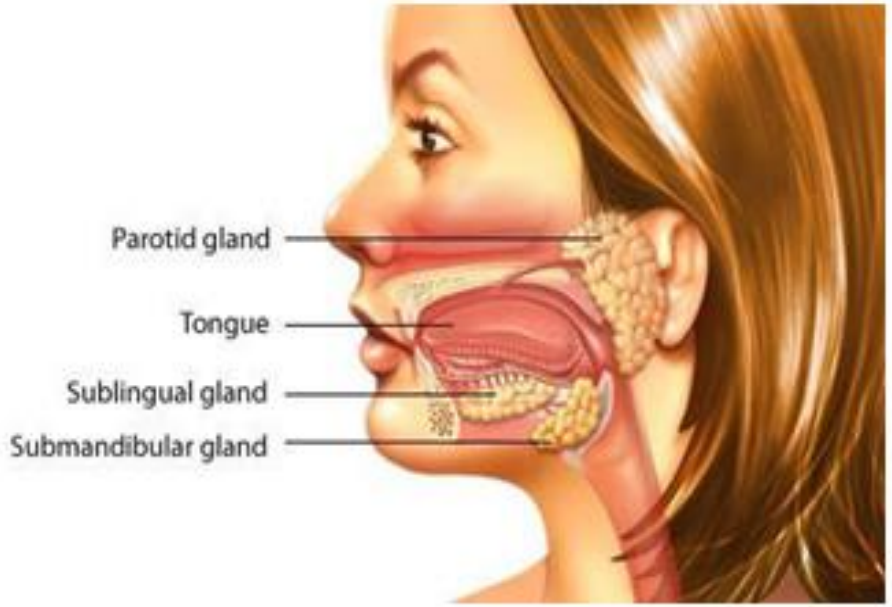
Dr. Ali Ashgar Abd

Glands associated with digestive tract
Salivary Glands

I. Accessory salivary glands are simple tubulo-alvoelar small glands present in the oral cavity.

II. Major salivary glands are paired compound tubulo-alvoelar exocrine glands:

- Parotid glands
- Submandibular glands
- Sublingual glands.



General structure:

A) Connective tissue capsule and septa

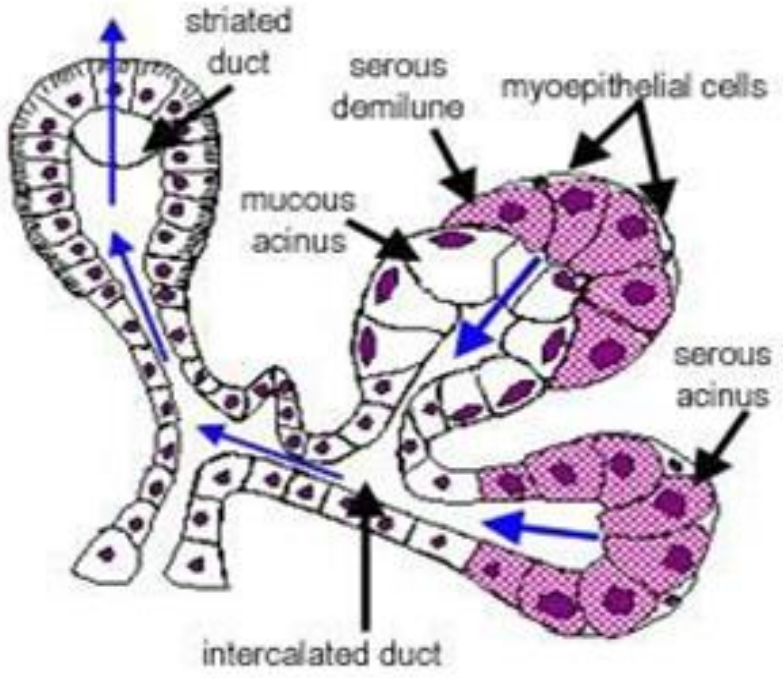
a) **Capsule**: Each gland is surrounded by C. T. capsule rich in collagen fibers.

b) **C. T. septa** arise from the capsule dividing the gland into lobules.

c) **Reticular network**

B) **Parenchyma** It is formed of

- ❑ secretory part (acinus(
- ❑ excretory part (duct(



I- The acini:

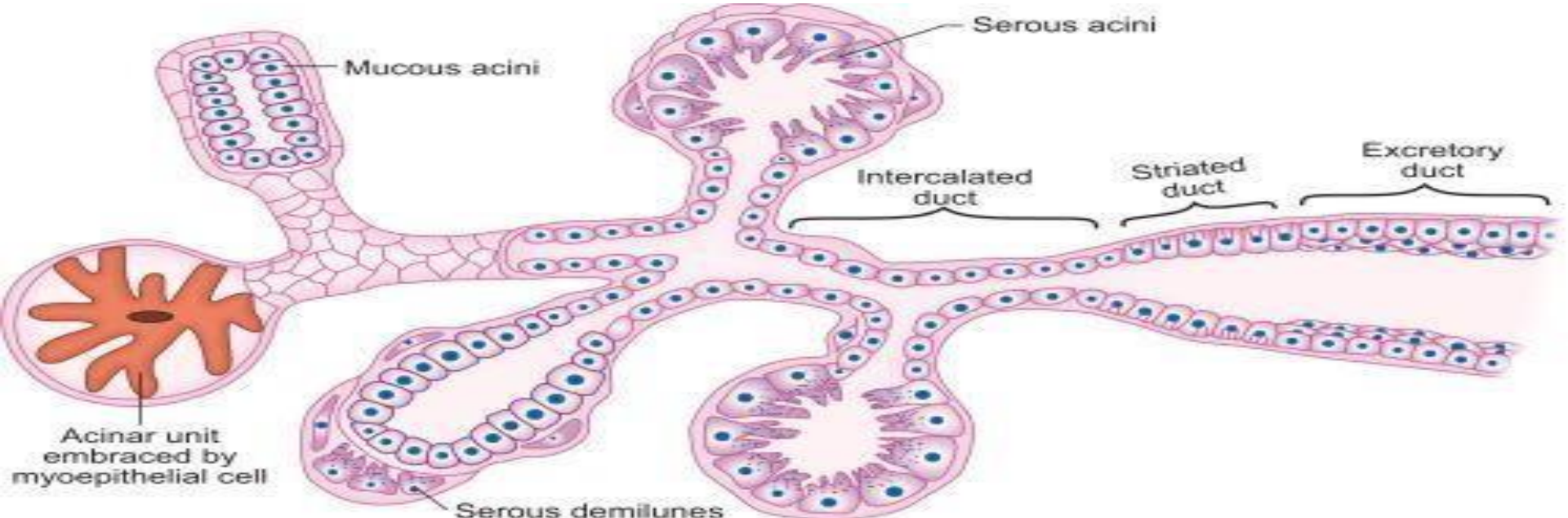
The acinus has a lumen & is lined by glandular epithelial cells . They are of 3 types:

A- Serous acini: They have narrow lumen. The cells are pyramidal, with central rounded nuclei, basal basophilia and apical acidophilic cytoplasm. They secrete watery secretion containing enzymes.

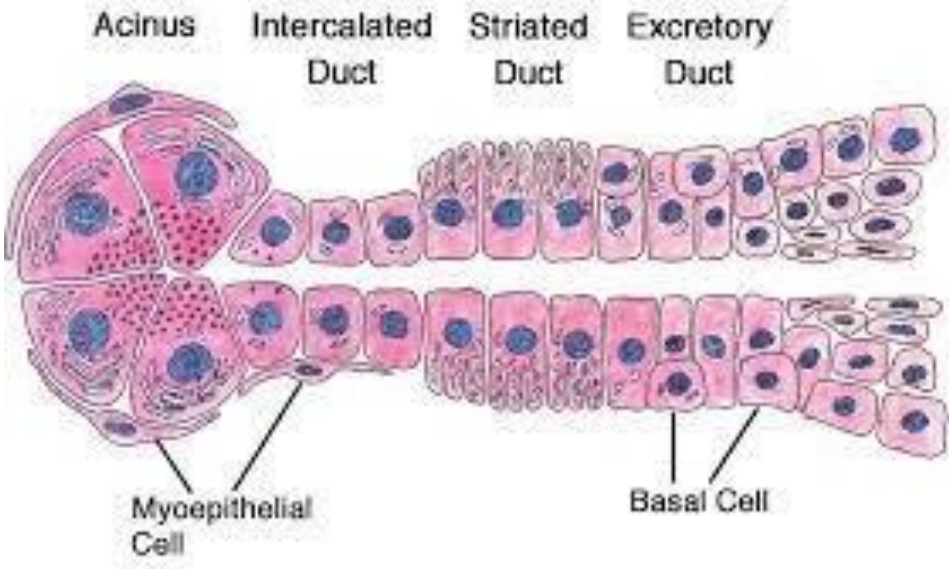
B- Mucous acini: They have wide lumen. The cells are cuboidal, with peripheral flat nuclei and apical foamy pale cytoplasm. They secrete mucus.

C-Mixed acini: They are mucous acini that have a crescent of serous cells.

Myoepithelial cells are present between the cells and the basement membrane. They have



The ducts:



Salivary ducts are classified into:

1- **Intralobular ducts** include;

Intercalated ducts started from the lumen of the acinus. Lined with simple cubical epithelium.

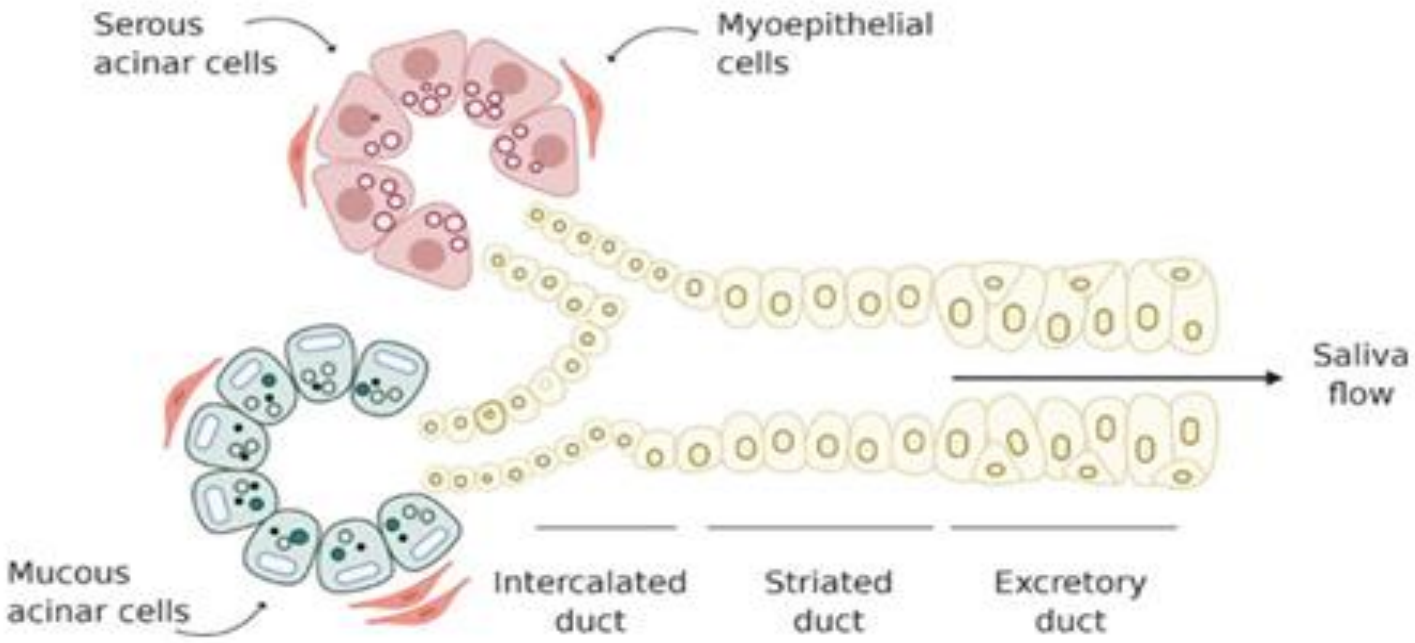
Striated ducts are lined with simple columnar cell and share in the secretion of the gland.

2- **Extralobular ducts** include; interlobular, interlobar and main ducts which open in the oral cavity.

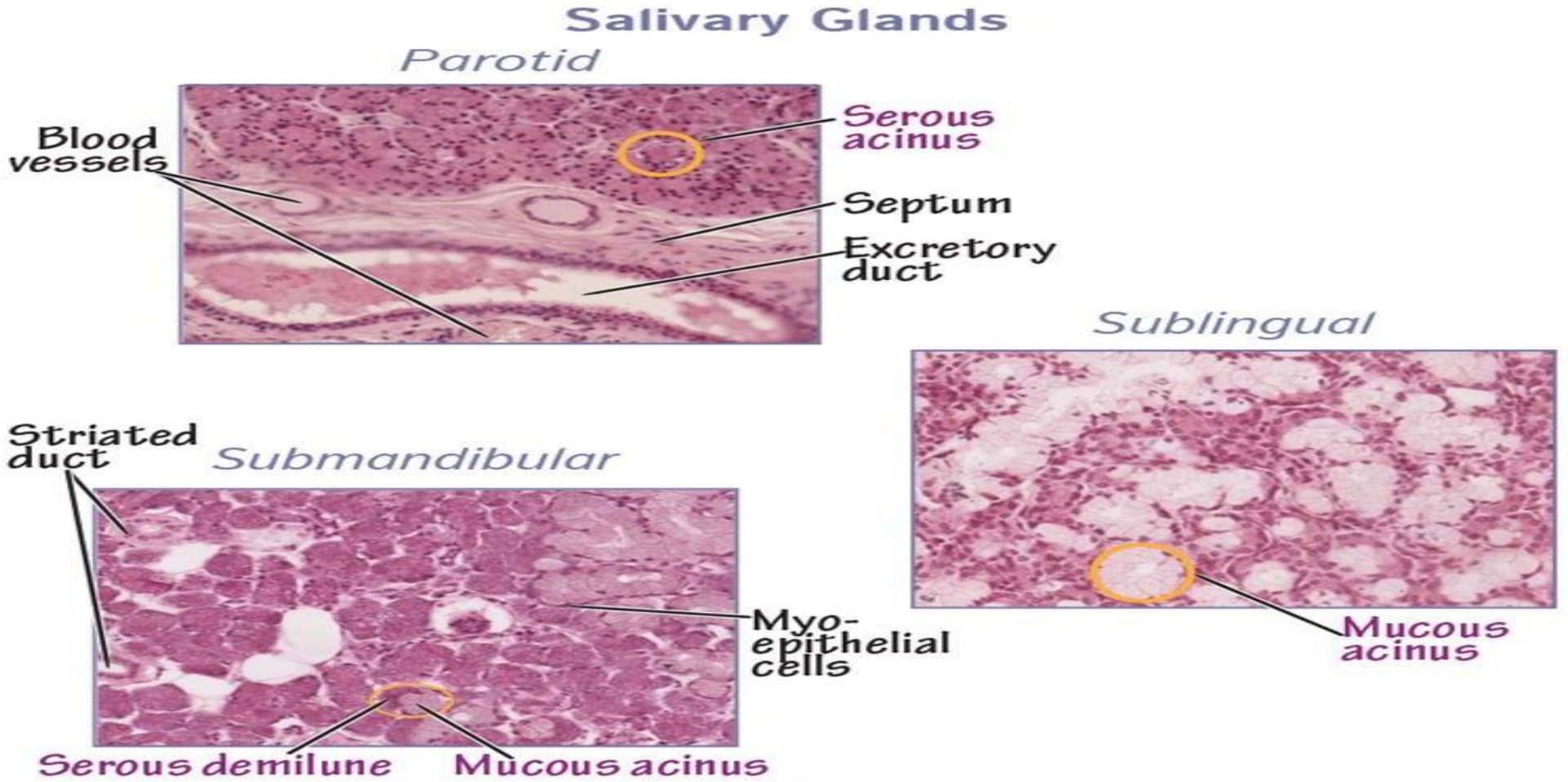
Salivary Glands

General structure of the large salivary glands

- Parenchyma
  - acinus
    - serous acinus
    - mucous acinus
    - seromucous / mixed acinus
  - duct
    - intercalated duct
    - striated/secretory duct
    - interlobular duct
    - excretory duct



1-The parotid glands: Have serous acini only (three main structures transverse this gland – facial nerve, external carotid artery, and retromandibular vein. The parotid duct opens near the upper 2nd molar tooth.



2- The submandibular glands: Have serous and mucous acini, (mainly serous).

Sitting in the submandibular triangle, it is supplied by the facial artery& vein. Submandibular

ducts, which cross the lingual nerves, open on both sides of the tongue frenulum.

3- The sublingual glands: Have mucous and serous acini, (mainly mucous).

The smallest salivary gland sits beneath the oral mucosa in the floor of

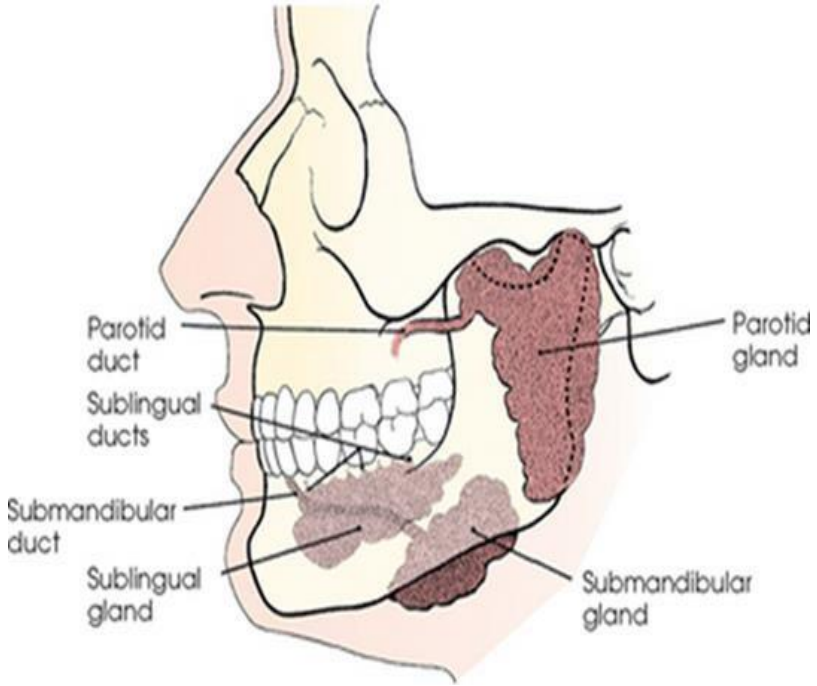
the mouth. It has multiple small openings

Functions:

Lubrication of the food and oral cavity.

Secretion of certain enzymes

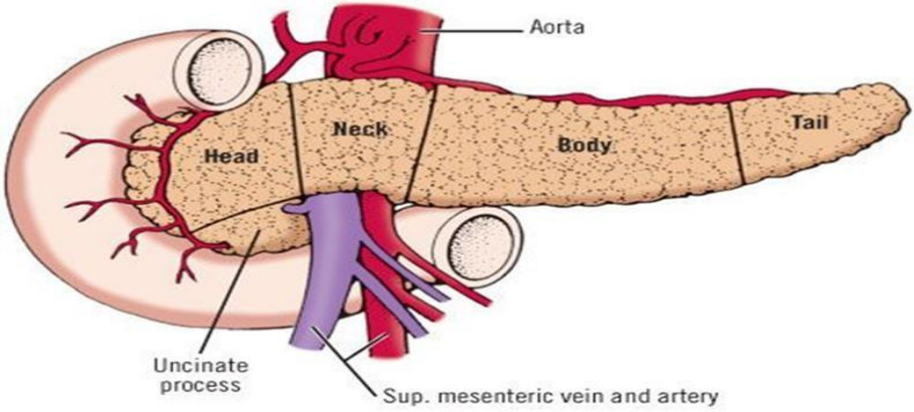
(amylase, maltase, lysosyme)



The pancreas

It is an intra-abdominal mixed exocrine and endocrine gland.

It is formed of head, body and tail.



A) The exocrine portion:

It is similar in structure to the parotid gland, but in the pancreas:

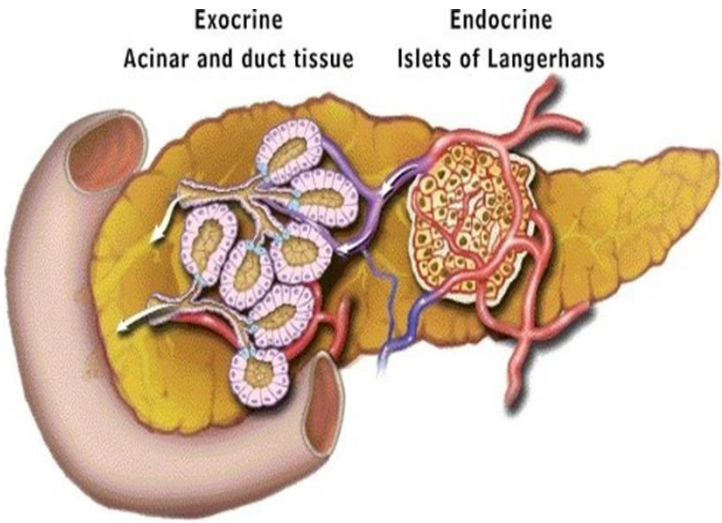
The islets of Langerhans (endocrine portion) are present.

The striated ducts are absent.

The serous cells show:

endoplamicrough(morebasophiliabasalProminent reticulum).

Prominent apical acidophilic zymogenic granules.



The function of exocrine pancreas is secretion of many digestive enzymes as trypsin, chymotrypsin, lipase, & amylase.

B-The endocrine portion:

It is called islets of Langerhans. The islets are more numerous in the tail and less in the head. They appear in H & E section as pale rounded groups of cells in between the serous acini.

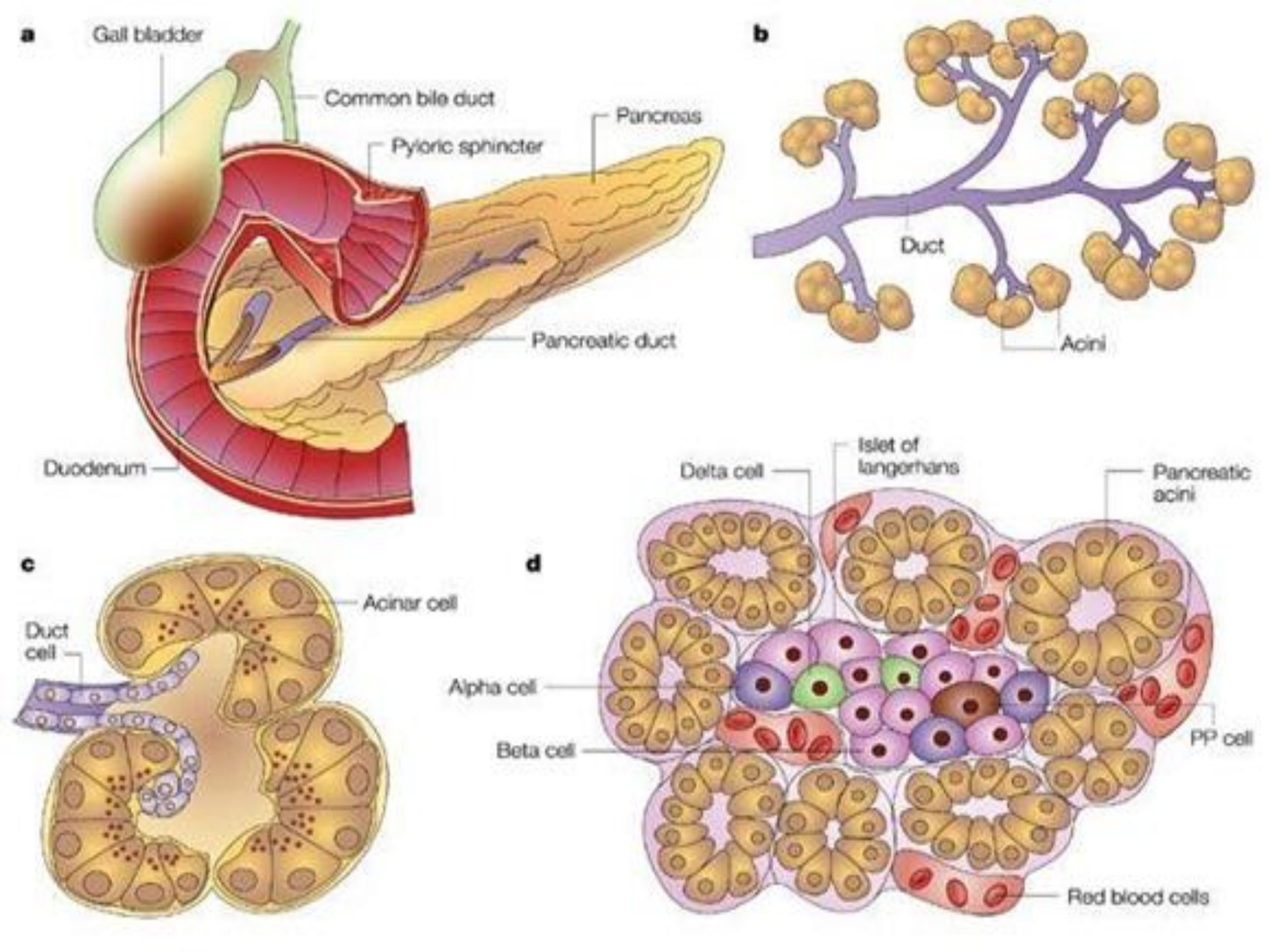
Each islet consists of four main types of cells separated by fenestrated blood capillaries:

A- cells: 20% of cells. They are large cells which secrete glucagon (increases blood sugar).

B- cells: 60-80% of cells. They are small cells which secrete insulin (decreases blood sugar level).

D- cells: They are small cells that secrete somatostatin (inhibits the release of growth hormone).

F- cells: They are small cells which secrete pancreatic polypeptide.


a
Gall bladder
Common bile duct
Pancreas
Pyloric sphincter
Pancreatic duct
Duodenum
b
Duct
Acini
c
Acinar cell
Duct cell
d
Islet of langerhans
Delta cell
Pancreatic acini
Alpha cell
Beta cell
PP cell
Red blood cells

The liver

The liver is the largest gland in the body.

It is formed of two main lobes and two small ones.

Structure: The liver is composed of stroma and parenchyma.

1- Stroma:

Capsule of connective tissue covered with peritoneum.

C.T. septa: The capsule sends C.T septa in between lobes and lobules.

Reticular network formed of reticular fibers and cells for supporting.

2-Parenchyma

It is formed of liver cells (hepatocytes). They are polyhedral 20-30 um in diameter. They are rich in mitochondria (about 1000-2000) and smooth endoplasmic reticulum (acidophilic cytoplasm) and contain all the other organelles and inclusions. They have one or two nuclei with fine chromatin granules.

The hepatocytes are arranged in cords or plates of one or two cells thick. Bile canaliculi are enclosed between the cells. Blood sinusoids are present between the cords or plates. They are irregularly dilated blood capillaries composed of discontinuous layer of endothelial cells associated with marophages (Von Kupffer cells) separated from the liver cells by space of Disse, which contain microvilli of hepatocytes and reticular fibers.

Lobulation of the liver:

1- Classic hepatic lobule:

Hepatic lobule is a polygonal mass of liver cells which drain into a vein in its center called central vein running along its longitudinal axis.

Lobulation of the liver is not obvious in human due to lack of C. T. septa

The cords of liver cells are directed from the periphery of hepatic lobule to its central vein.

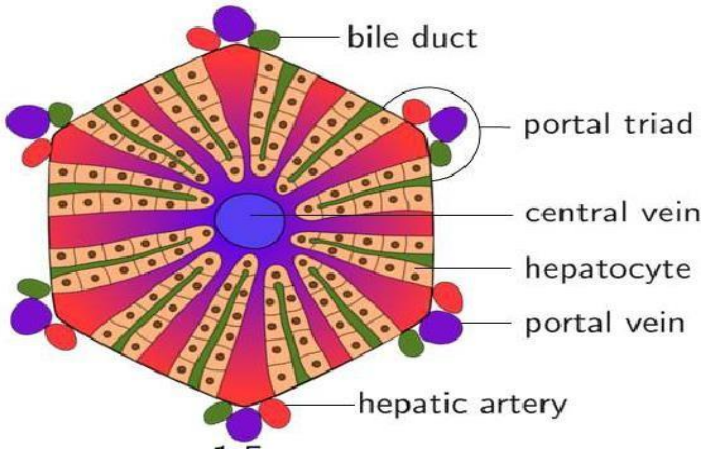
At the corners of each hepatic lobule there are portal areas or spaces, which are formed of C.T containing four structures.

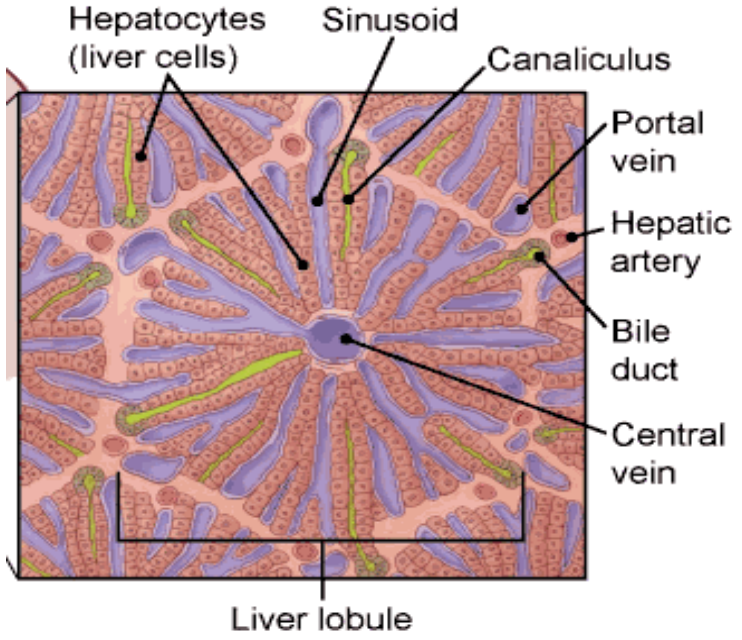
1.Branch of portal vein.

2.Branch of hepatic artery.

3.Bile duct.

4.A lymph vessel.





2-Portal lobules

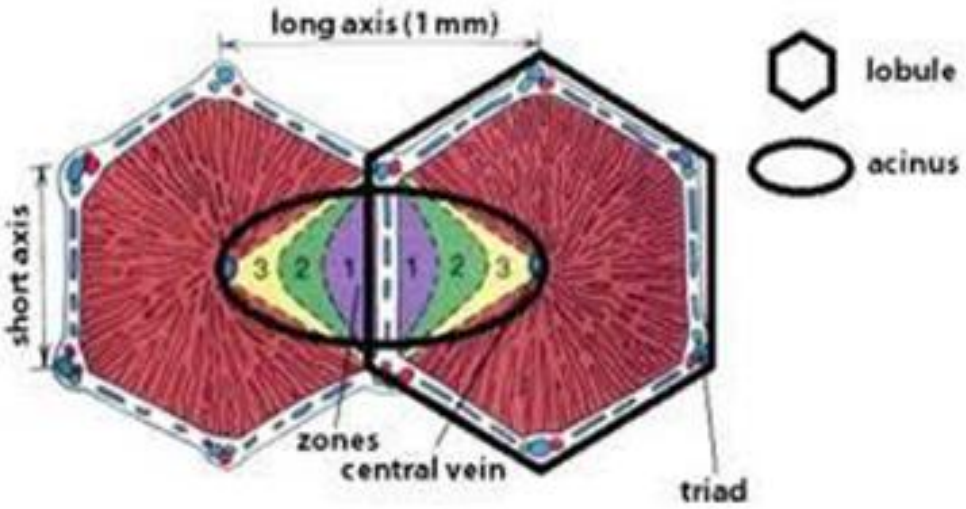
It is the mass of liver cells that drains bile into one bile duct.

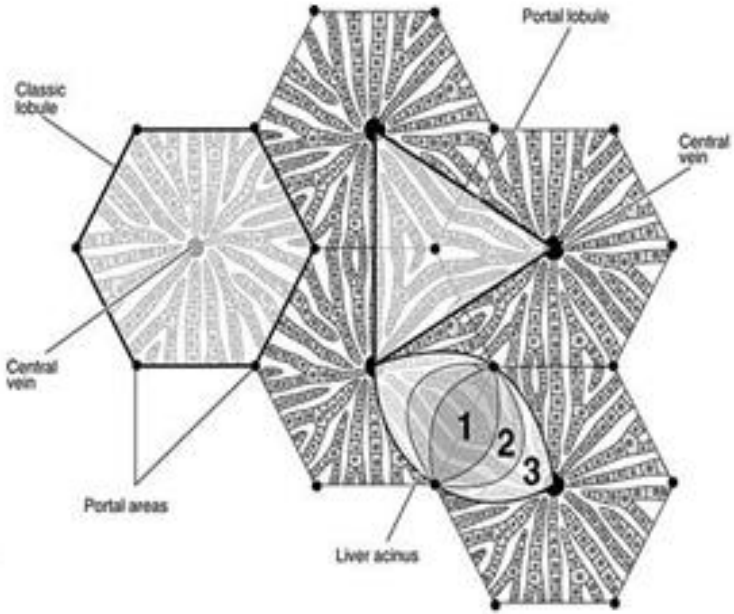
It is formed of parts of three adjacent classical hepatic lobules having a portal area or space in the center. It is triangular in shape.

3-The liver acinus:

It is the mass of liver cells that are supplied by the same terminal branch of portal vein and hepatic artery.

The liver cells of an acinus are present in adjacent areas of 2 (two) adjacent hepatic lobules. It is diamond in shape with each end converging on a central vein.





Functions of the liver

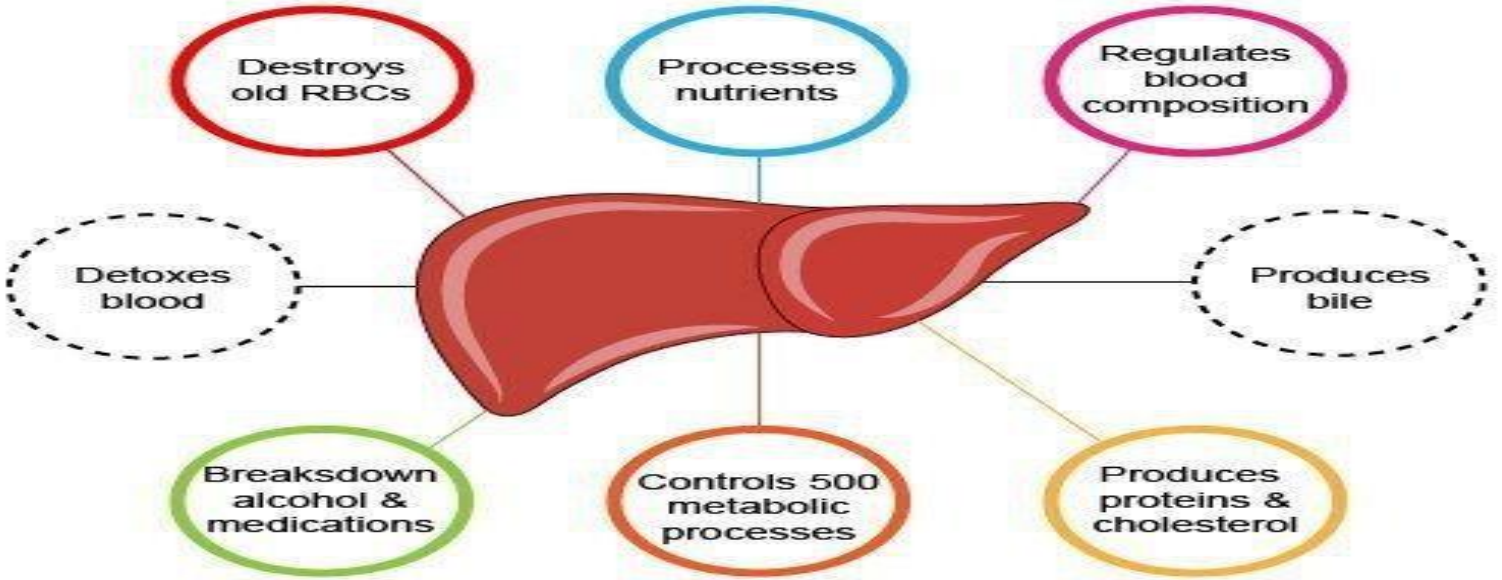
All the liver functions are performed by the hepatocytes:

1- Exocrine function: bile secretion.

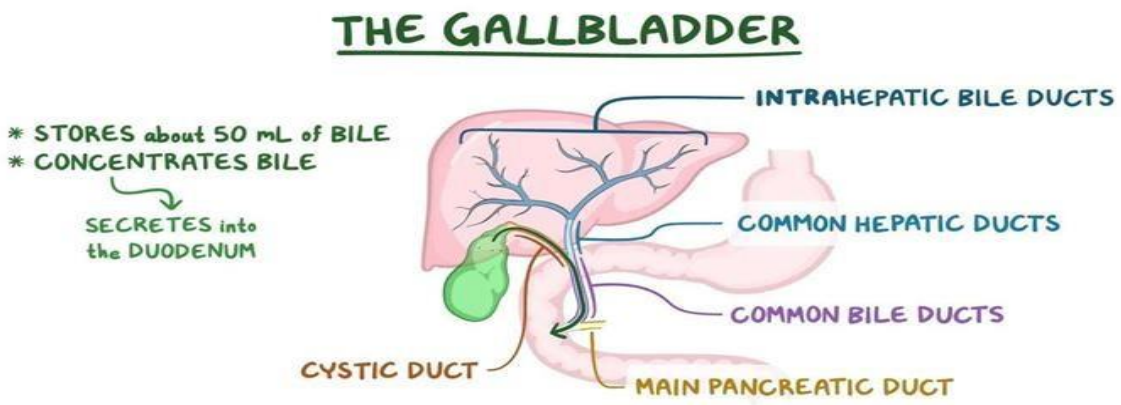
2- Endocrine function: secretion of glucose, blood proteins (e. g. albumin, globulin, fibrinogen, lipoproteins).

3- Detoxification and inactivation of various drugs and substances.

Storage of metabolites (glycogen, lipids, vitamins)



The Gall bladder



It is a cyst (sac-like) organ present on the lower surface of the liver.

The bile is stored and concentrated in the gall bladder.

It's wall consists of:

1- Mucosa: Epithelium: Simple columnar epithelium.

Lamina propria: of loose C. T.

2- Muscle layer: of smooth muscle.

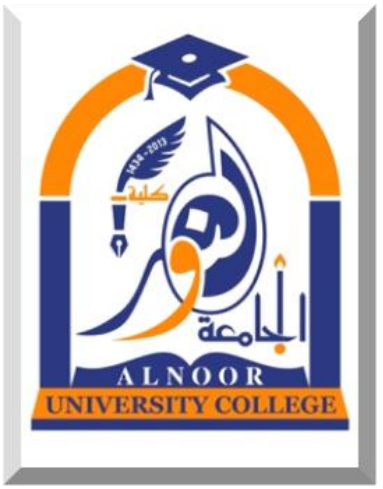
3- Perimuscular C.T: it is formed of dense C.T lined partially by peritoneum

The gall bladder has no villi, no Goblet cells, no glands and no muscularis

mucosa.

Functions: storage and concentration of bile

Al-Noor University College.
Medical laboratories technics department.
Second Stage / 2022 – 2023.
Lectures of General Histology (Theory).

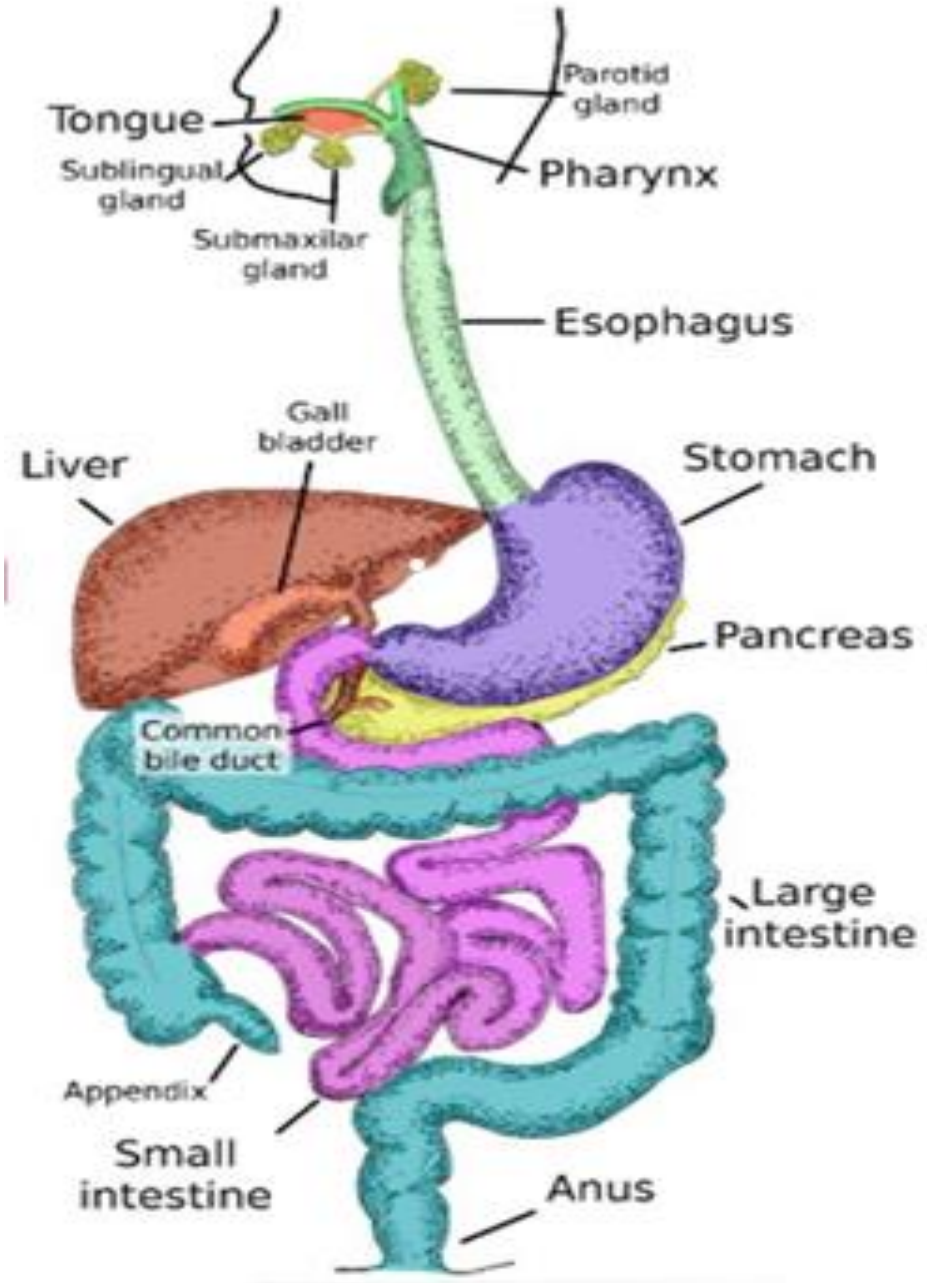


Digestive system. (المحاضرتين 1و2)

Dr. Ali Ashgar Abd

The digestive system consists of the digestive tract— oral cavity, esophagus, stomach, small and large intestines, and anus—and its associated glands—salivary glands, liver, and pancreas. Also called the gastrointestinal (GI) tract or alimentary canal, its function is to obtain molecules from the ingested food that are necessary for the maintenance, growth, and energy needs of the body. During digestion proteins, complex carbohydrates, nucleic acids, and fats are broken down into their small molecule subunits that are easily absorbed through the small intestine lining. Most water and electrolytes are absorbed in the large intestine. In addition, the inner layer of the entire digestive tract forms an important protective barrier between the content of the tract's lumen and the internal milieu of the body's connective tissue and vasculature.

Digestive system



Structures within the digestive tract allow the following:

1-Ingestion, or introduction of food and liquid into the oral cavity;

2-Mastication, or chewing, which divides solid food into digestible pieces;

3-Motility, muscular movements of materials through the tract;

4-Secretion of lubricating and protective mucus, digestive enzymes, acidic and alkaline fluids, and bile;

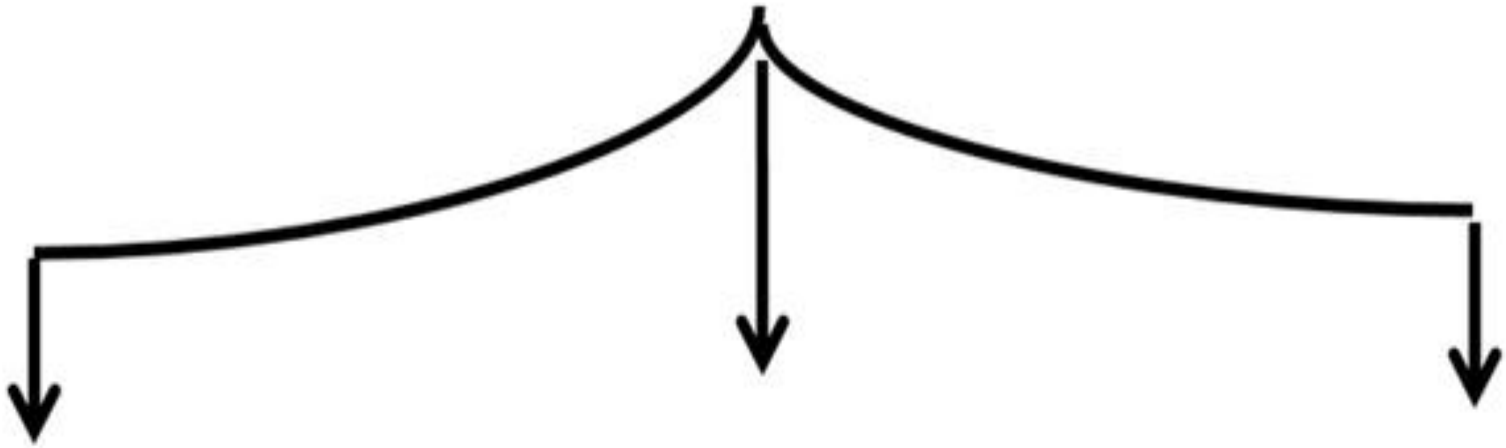
5-Hormone release for local control of motility and secretion;

6-Chemical digestion or enzymatic degradation of large macromolecules in food to smaller molecules and their subunits;

7-Absorption of the small molecules and water into the blood and lymph; and

8-Elimination of indigestible, unabsorbed components of food.

Digestive system



Oral cavity

- Lip
- Tongue
- Cheek
- Palate
- Tooth

Gastrointestinal tract
G I T

- Esophagus
- Stomach
- Small intestine
- Large intestine

Glands

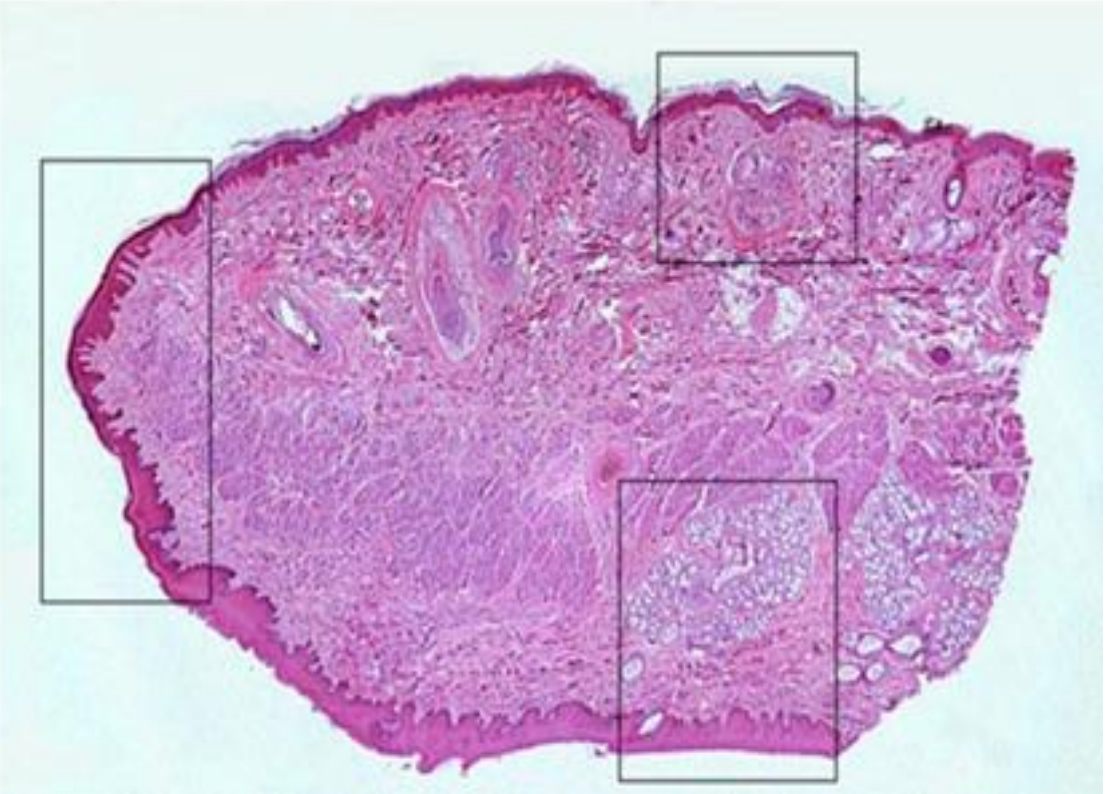
- Salivary glands
- Liver
- Pancreas

I- oral cavity

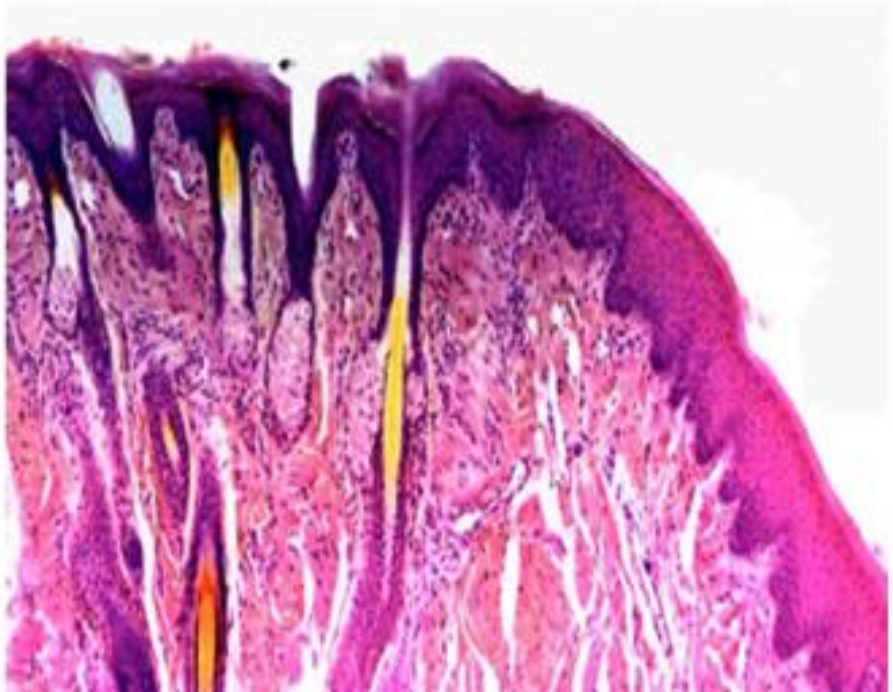
- All parts of the oral cavity and gastrointestinal tract (GIT) are lined by a **mucous membrane**
- This membrane is formed of an **epithelium** with a C.T. layer called **lamina propria.**
- The epithelial lining of the oral cavity is **stratified squamous epithelium:**
  - **Non-keratinized** on the ventral surface of the tongue, the floor of the mouth, the mucosal surface of the lips and cheeks
  - **Keratinized or partially keratinized** over the gingiva, hard palate, most of the dorsum of the tongue, those need more **protection** during eating.

Lips

- Formed of striated muscle (**orbicularis oris**).
- Have three surfaces:
- ***Outer surface.***
- ***Inner surface***.
- ***Red margin***.



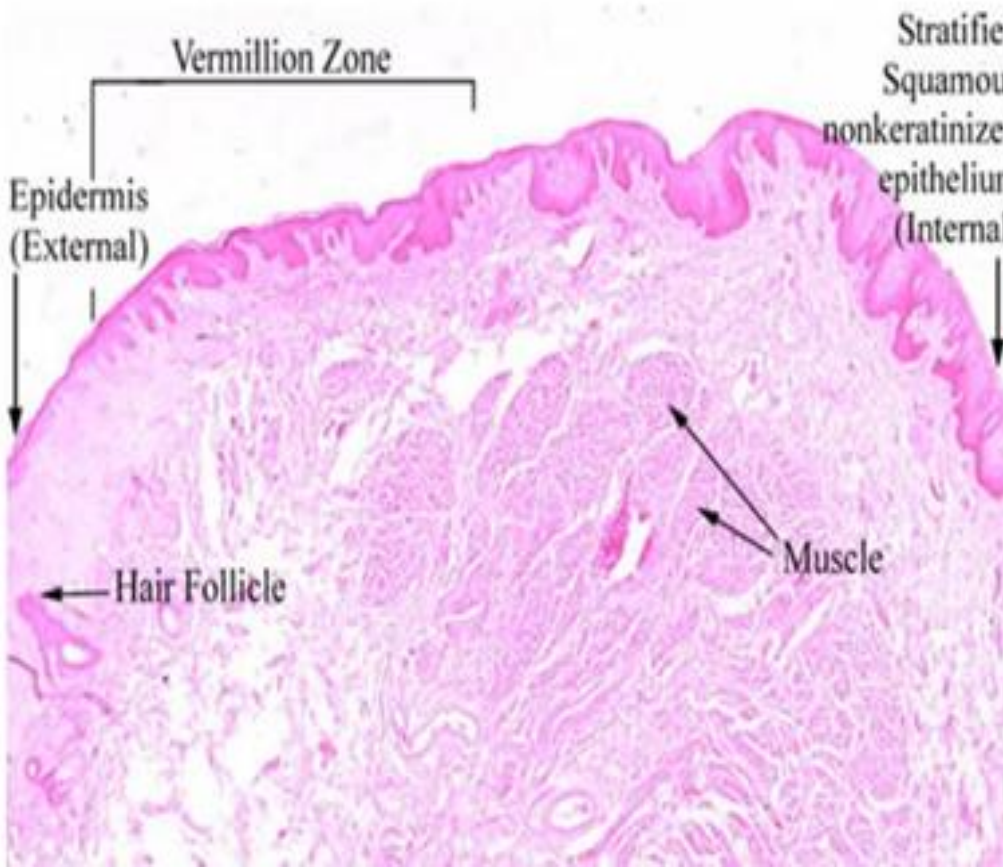
- ***Outer surface*** is **skin**
  - stratified squamous keratinized epithelium with hair follicles, sweat & sebaceous glands.



- ***Inner surface*** is **mucus membrane**
  - covered with stratified squamous nonkeratinized epithelium with mucous secreting glands (labial glands) in the lamina propria.

- ***Red margin***

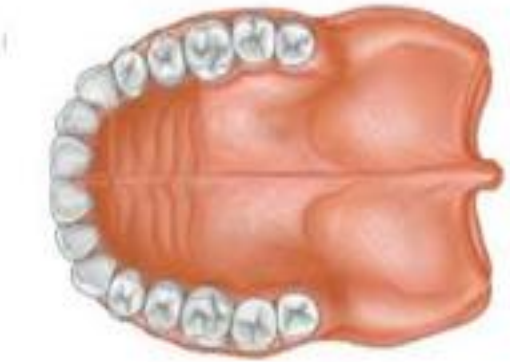
- is a **transition zone** between keratinized and non-keratinized epithelium.
  - rich in **blood vessels** that cause redness of the lip margin.



CHEEKS

- Formed of skeletal muscle (buccinator).
- Covered by skin and subcutaneous C.T.
- Lined by a mucous membrane.
- Small minor salivary glands.

PALATE



- The roof of the mouth.
- Consists of two parts:

a) Hard palate (the anterior two thirds).

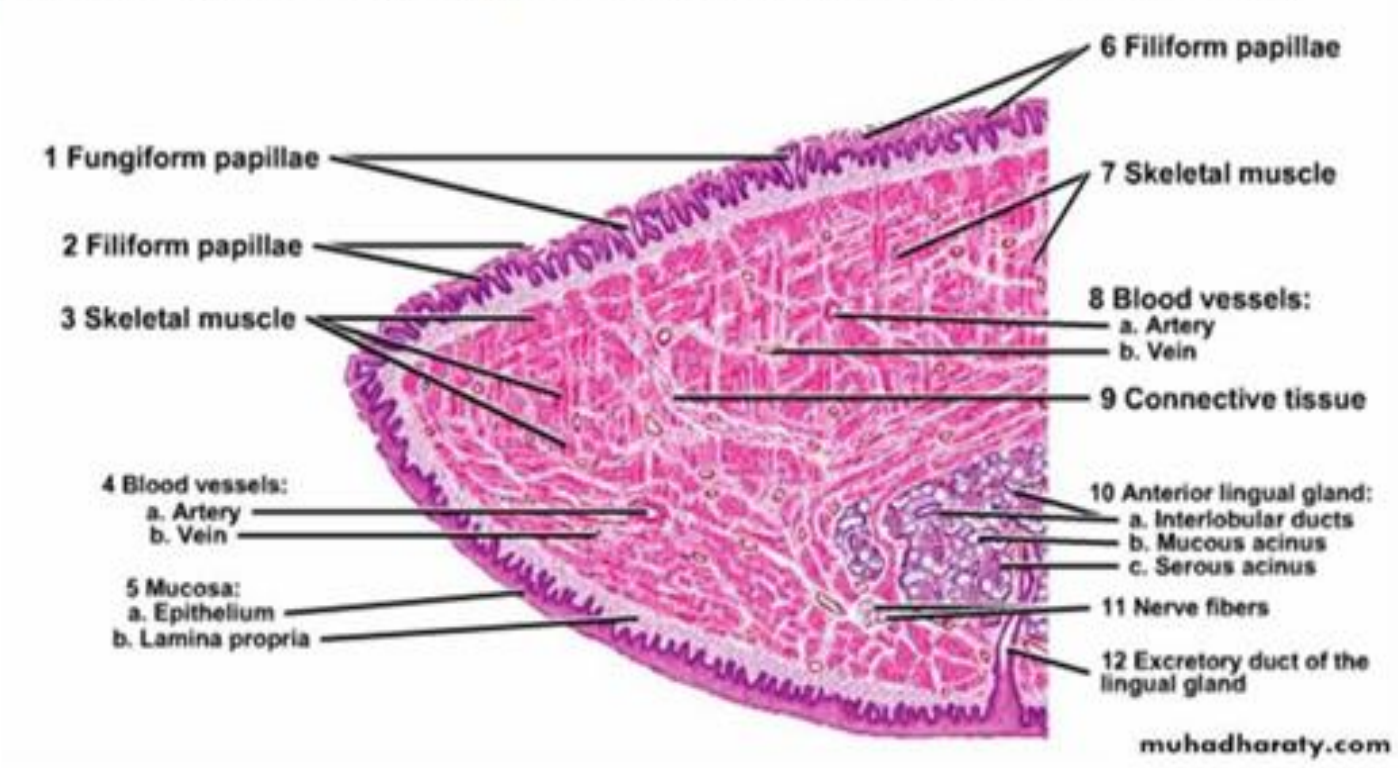
b) Soft palate (the posterior third).

The uvula

- downward extension of soft palate
- conical in shape
- formed of a core of skeletal muscle
- covered by mucous membrane

Tongue

- Mass of striated (skeletal) muscle.
- Covered by mucous membrane.
- Contains some mucous & serous glands.
- Muscle fibers are grouped in bundles.
- Arranged in 3 planes (longitudinal, transverse &vertical).

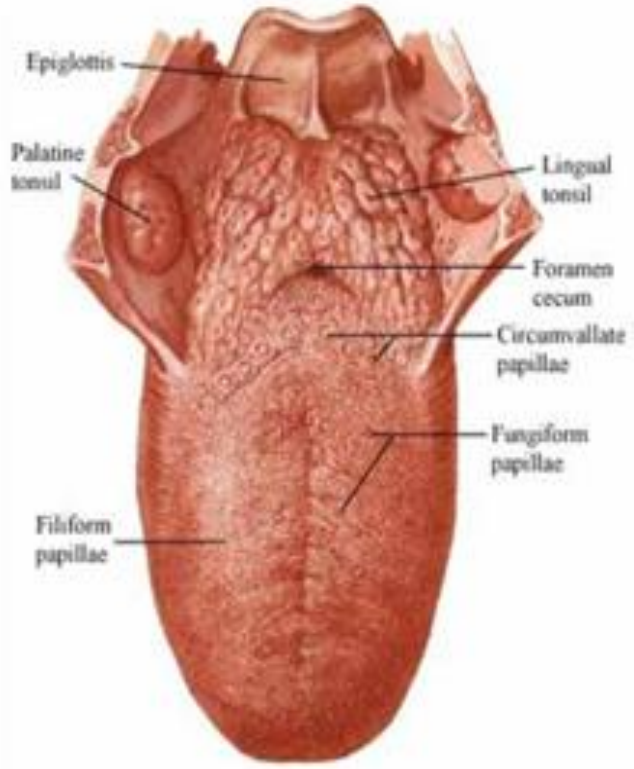


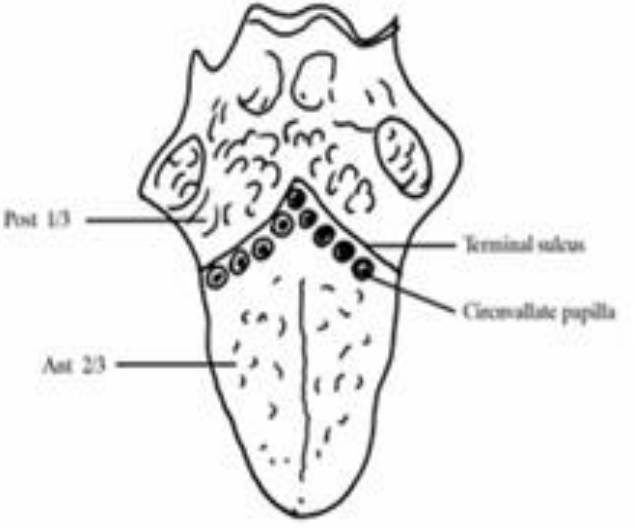
- **On the lower surface**, the mucous membrane is smooth and loosely attached.

- **On the dorsal surface**, the mucous membrane is rough and firmly adherent to the muscle. It shows two regions separated by a V- shaped shallow groove called terminal sulcus.

a) **The anterior two thirds** are covered by a great number of small mucosal projections called lingual papillae.

b) **The posterior one third** is irregular due to presence of lymphoid nodules (lingual tonsils) in the lamina propria.





Palate

Lingual papillae

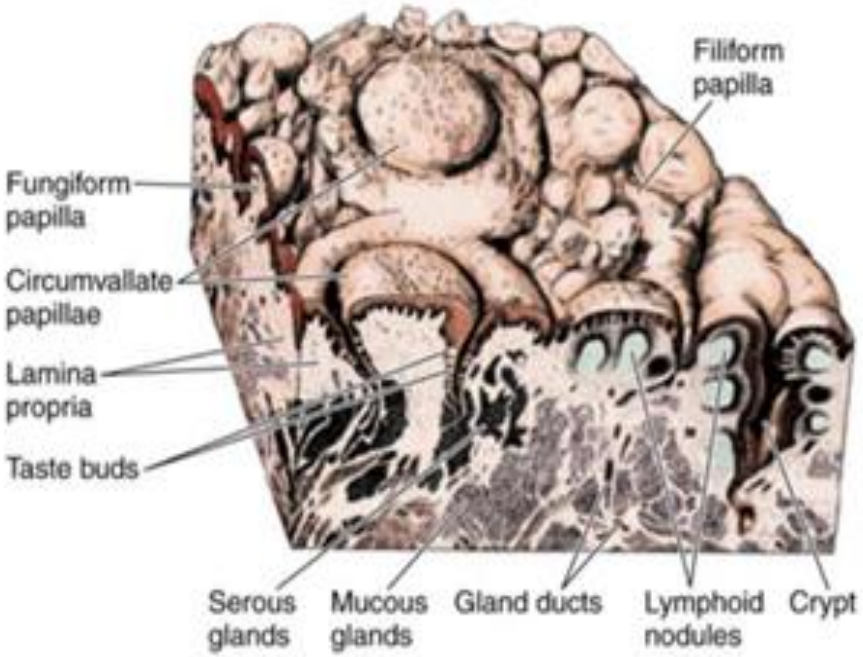
- There are four types:

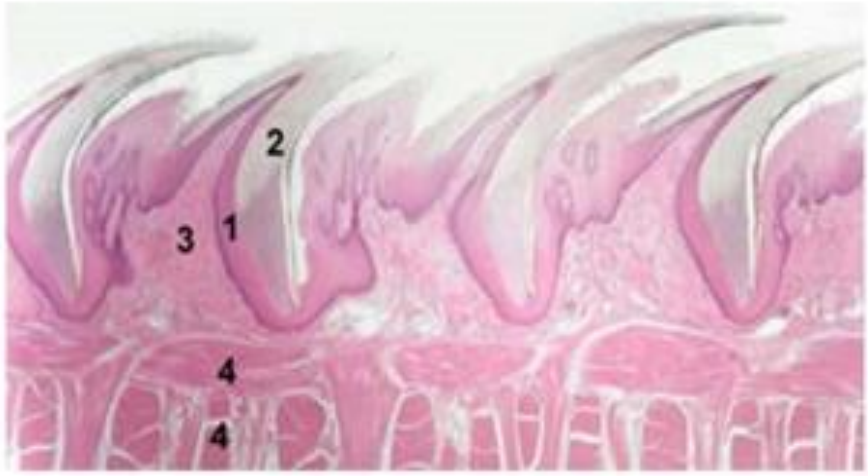
a) Filiform

b) Fungiform

c) Circumvallate

d) Foliate





a) Filiform papillae

- **Conical** in shape
- **Most numerous**
- **No taste buds**
- Epithelium (stratified squamous **partly** keratinized).

b) Fungiform papillae

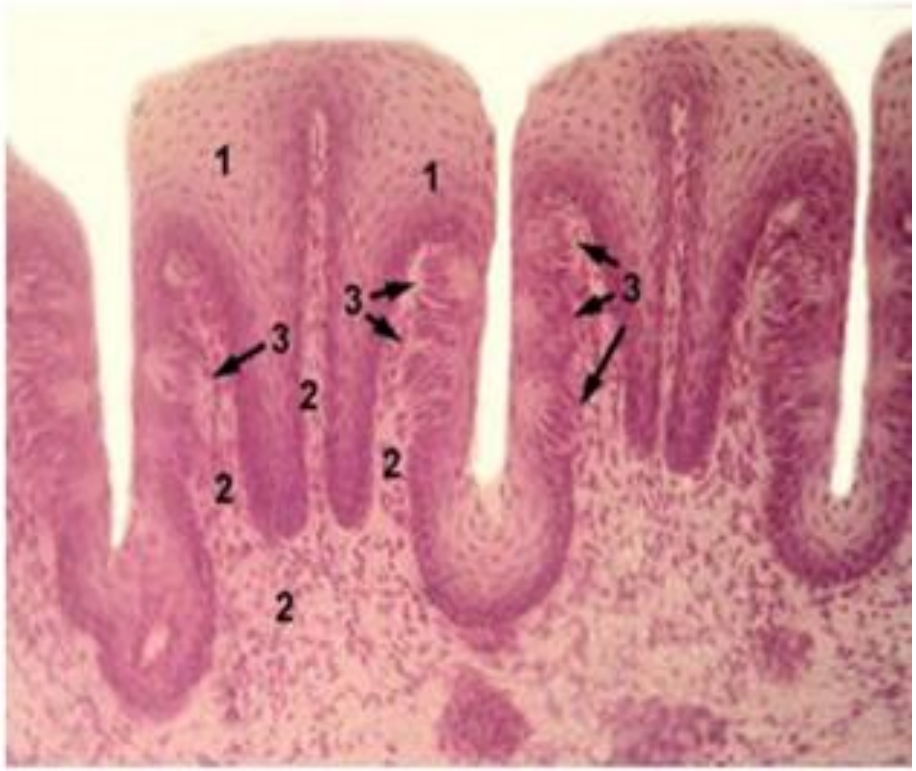
- **Mushroom** shaped with narrow stalk & wide apex.
- **Less** number, scattered between filiform papillae
- Have **few taste buds** on its upper surface
- Epithelium (stratified squamous **non**keratinized).

c) Circumvallate papillae

- **7-12** along the **V-shaped** terminal sulcus
- Resemble large fungiform papilla and surrounded by a deep groove
- **Numerous taste buds** on the lateral surfaces
- Serous secreting (**von Ebner**) glands open into the groove in order to dissolve substances to be tasted and remove food particles to allow reception of new taste stimuli.

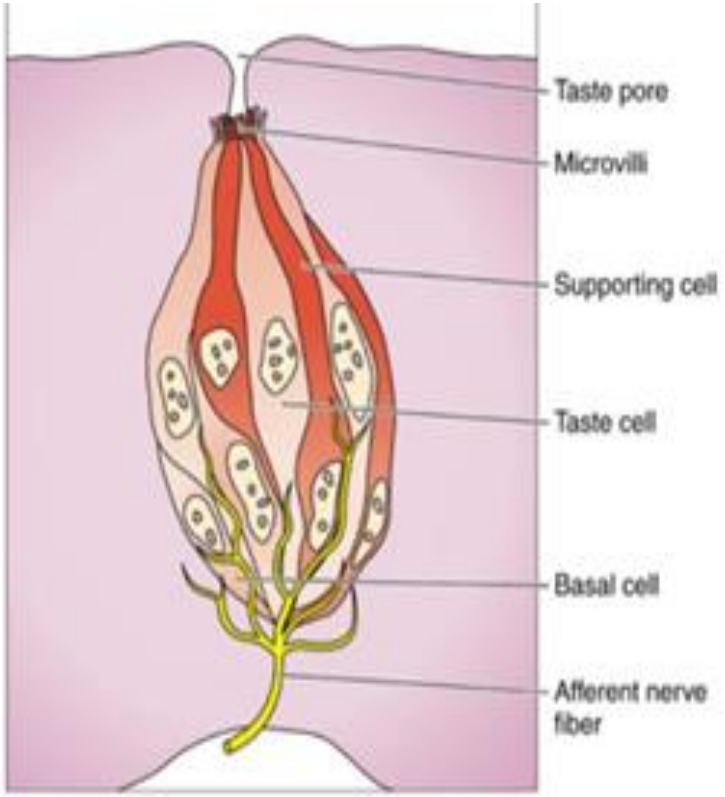
d) Foliate papillae

- Poorly developed in humans, but are well developed in **rabbit.**
- Have **parallel ridges** separated by furrows.
- **Rich in taste buds** that open in the furrows on lateral surfaces.



Taste buds

- Neuroepithelial **bud-like** structures to perceive taste.
- Present in tongue, embedded within the stratified epithelium of the circumvallate, foliate and fungiform papillae.
- Also present on soft palate, epiglottis and posterior wall of pharynx.
- Has a small opening at the epithelial surface called **taste pore** through which chemicals enter the bud.



- Taste buds are composed of 4 types of cells:
  - Type I and type II are tall supporting cells with microvilli.
  - Type III is the sensory cell with close proximity to sensory nerves at its basal surface. It is long, pale stained, with euchromatic nucleus. It also has microvilli on the surface.
  - Type IV is undifferentiated and short basal cell.

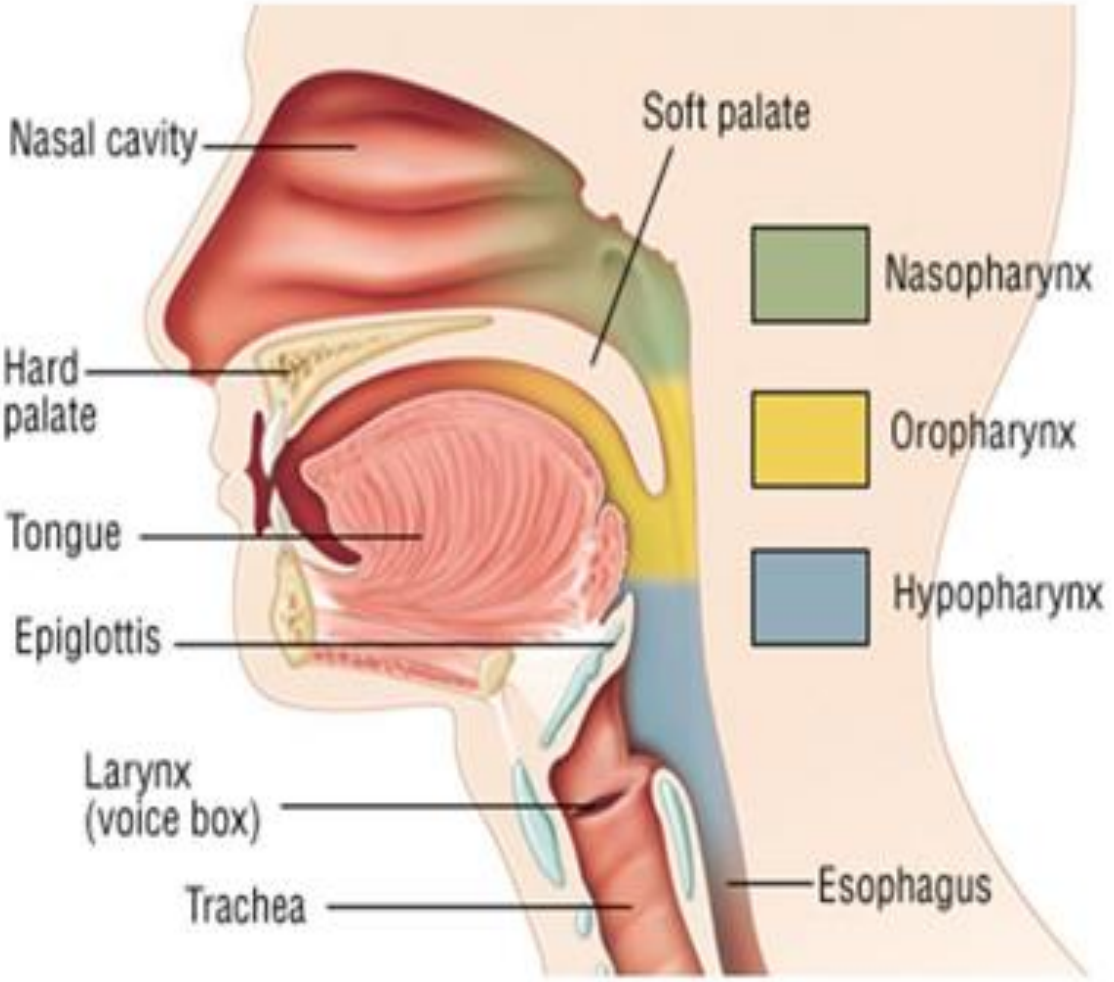
PHARYNX

- Represents a transitional space between oral cavity & respiratory & digestive tracts.
- Divided into 3 regions:

1- Nasopharynx

2- Oropharynx

3- Laryngopharynx.



- Its **mucous membrane** consists of:
  - *Epithelium*
  - *Lamina propria*

Epithelium:

- *In nasopharynx* it is ***pseudostrdified columnar ciliated with goblet cells***
- *In oropharynx and laryngopharynx*, it is ***stratified squamous non-keratinized.***

- *Lamina propria:*

- Separates epithelium from striated muscle of the pharynx.
- Contains mucous glands, blood vessels, lymphatics and nerves.
- In the posterior wall of the nasopharynx it also contains lymphoid aggregation known as ***adenoids (pharyngeal tonsil).***

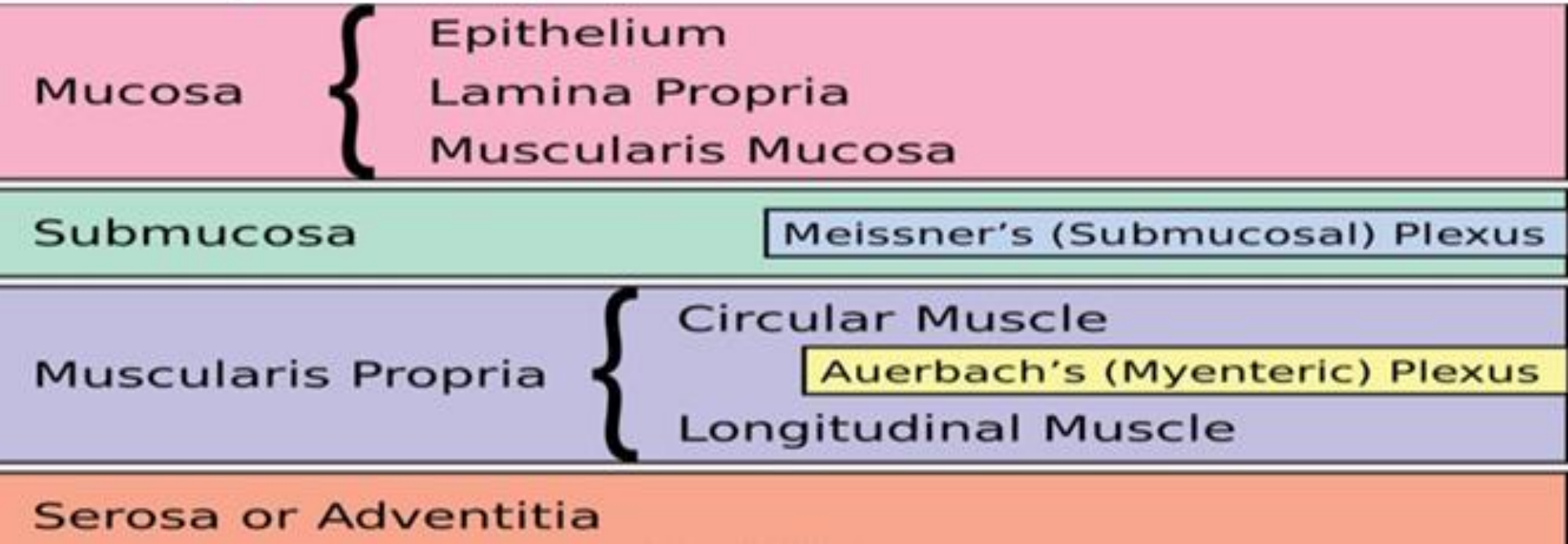
II- GASTRO-INTESTINAL (GIT)

General structure of the GIT

From esophagus to rectum, the digestive tube is a hollow structure with common histologic characteristics.

The wall of the tube is composed of **four major layers**, concentrically arranged enclosing a lumen.

These four layers are ***mucosa, submucosa, muscularis externa and serosa (or adventitia).***



I - Mucosa (mucous membrane):

- It consists of:

1 - Epithelium:

- It differs according to the function of the part it lines. It may be:

Protective, e.g. stratified squamous epithelium of esophagus

Secretory, e.g. simple columnar mucous secreting epithelium of stomach

Absorptive, e.g. simple columnar epithelium of intestine

2 - Lamina propria:

A layer of loose CT underlying the epithelium

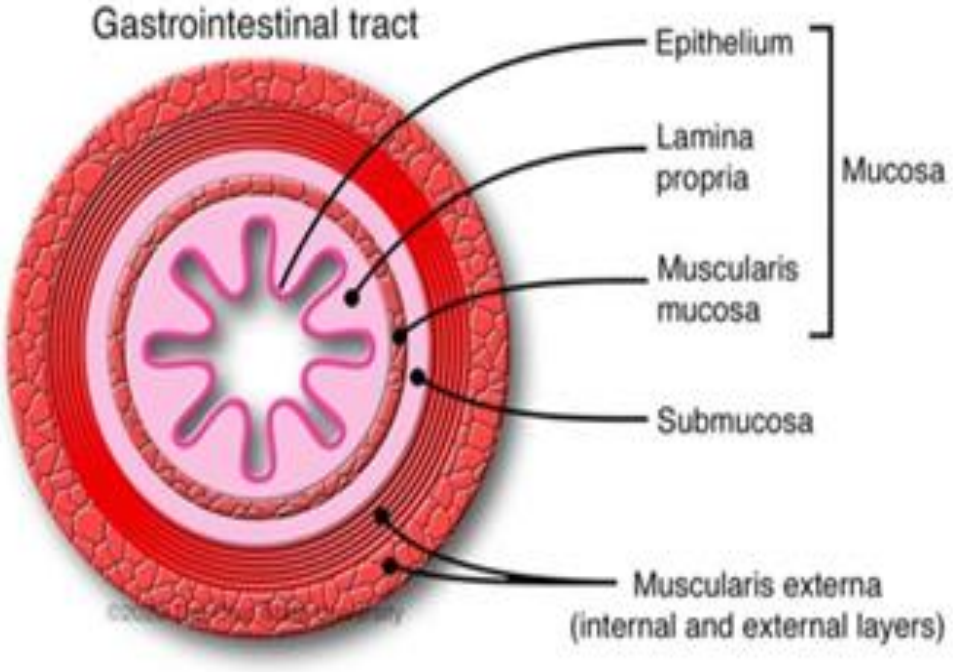
Un-encapsulated lymphatic follicles are commonly found in lamina propria

3 - Muscularis mucosa:

It is formed of two layers of smooth muscle fibers arranged as inner circular & outer longitudinal.

II - *Submucosa:*

- A dense Ct layer between mucosa & muscularis externa. It contains large blood vessels &lymphatics.
- Between submucosa and muscularis externa, there is a plexus of autonomic ganglion cells and nerve fibers called **submucosal (or Meissner's) plexus.**



III - Muscularis externa (Musculosa):

It is the muscle coat of the GIT that supports the wall and is responsible for moving luminal contents along the tract.

It consists of two layers of smooth muscle, inner circular and outer longitudinal.

Between the two layers, there is another autonomic plexus (myenteric or Auerbach's plexus) which is responsible for the rhythmic waves of contraction (peristaltic waves).

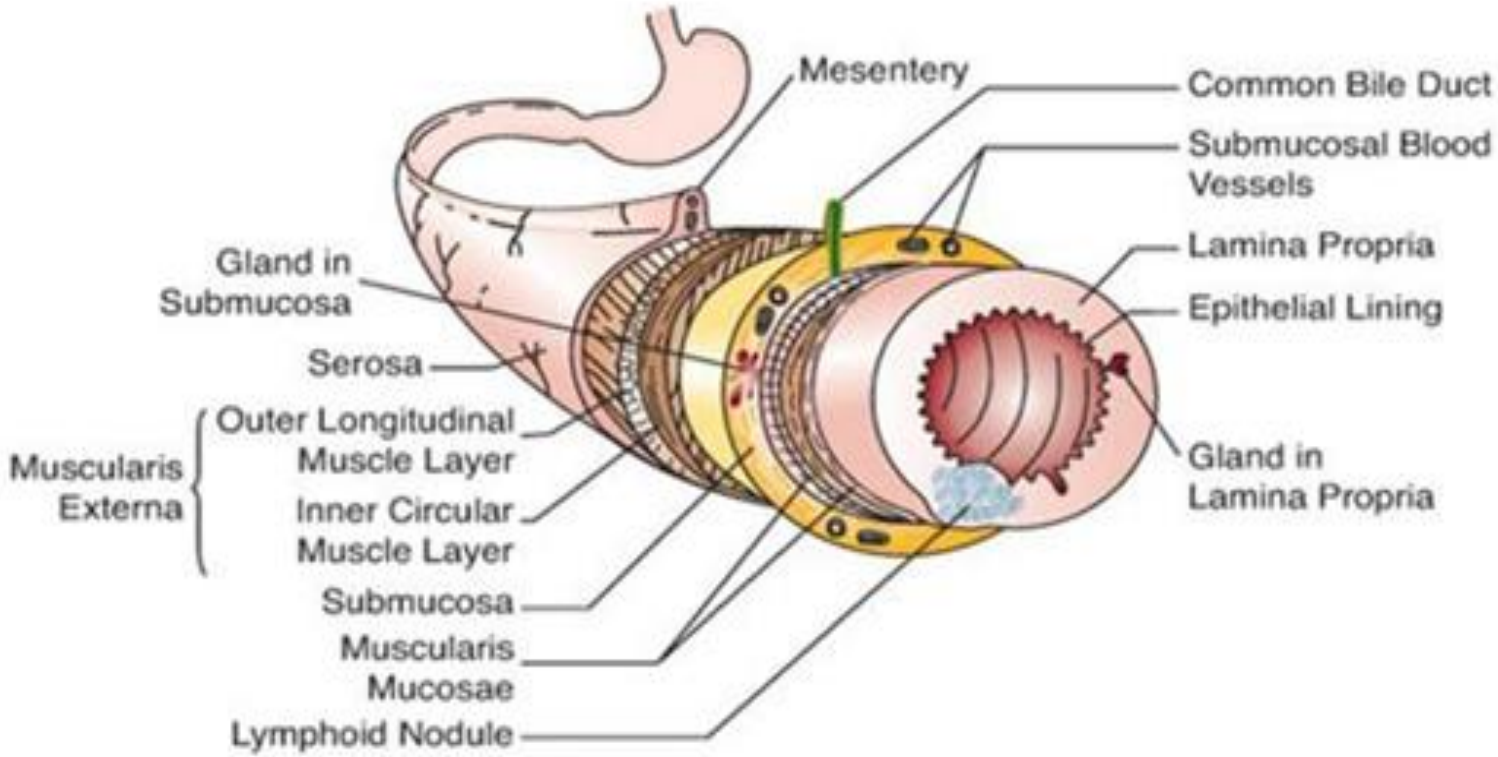
IV - Serosa or adventitia:

It is the outer most **loose CT** coat of the gut wall

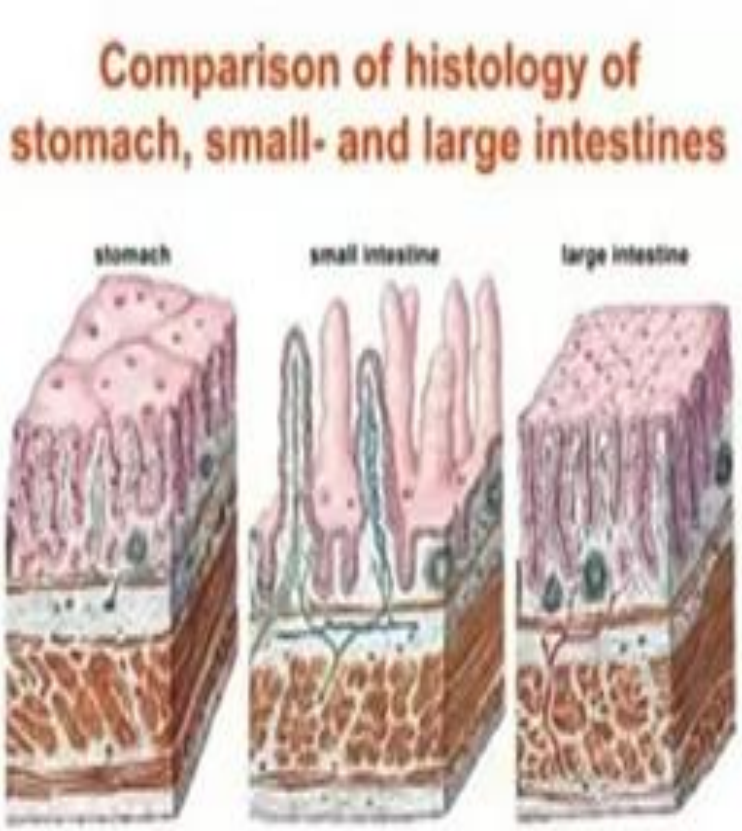
It is known as **serosa** in regions where it is covered by visceral peritoneum (single layer of squamous mesothelial cells).

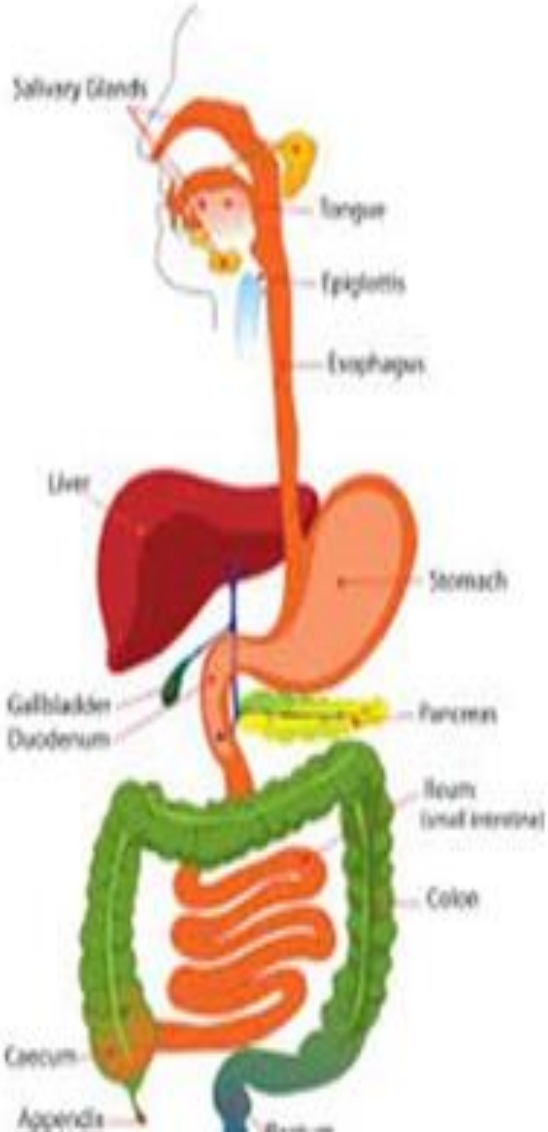
In regions where this mesothelial coat is lacking, it is **called adventitia.**

It contains many blood vessels, lymphatics & nerves.



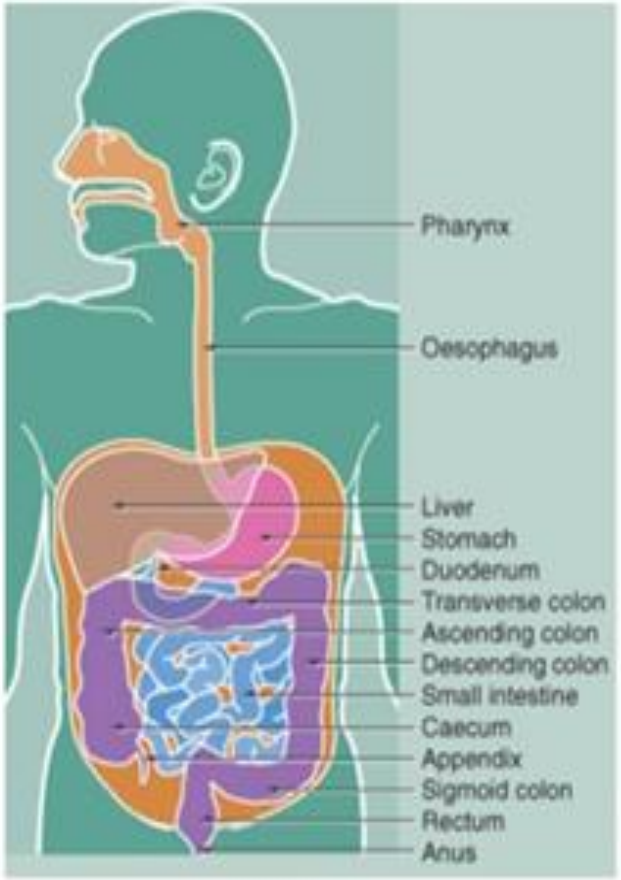
The Gastrointestinal tract





The Gastrintestinal tract

-The digestive tract is essentially a long tube that begins from the oral cavity and continues on to the esophagus, the stomach, the small and large intestines, and finally the anus.



The Esophagus

- The **esophagus** is posterior to the larynx and trachea in the neck region and upper thorax. It travels on the right side of the descending aorta, passes through the diaphragm, and connects with the stomach.

- Transport food quickly from mouth to stomach.

Structure

I- Mucosa:

- Epithelium: stratified squamous non keratinized (protective)

- Lamina propria: loose C.T., may contain simple tubular glands at the lower part and near the stomach (oesophageal cardiac glands).

Muscularis mucosa: inner circular and outer longitudinal smooth muscle layers

II-Submucosa:

Dense C. T. containing mucous secreting esophageal glands.

III- Musculosa:

- Inner circular and outer longitudinal layers of muscle fibers:

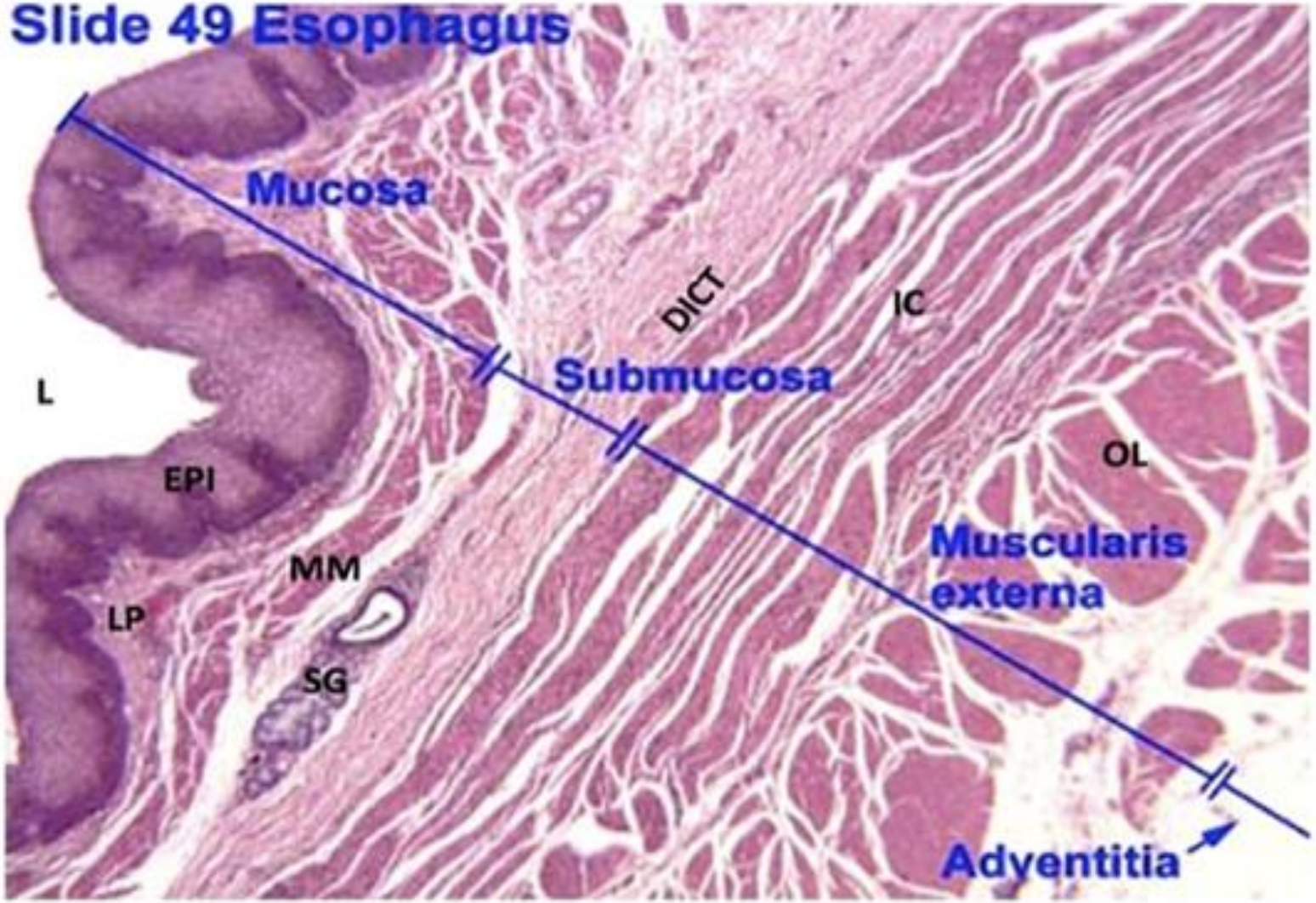
I- In the upper 1/3, it is formed striated muscle.

II- In the middle third, it is formed of both smooth and striated muscle fibers.

III- In the lower 1/3, it is formed of smooth muscle.

IV-Adventitia:

- The intra abdominal lower part of the esophagus has a serosa.



EPI - epithelial layer
LP - lamina propria
MM - muscularis mucosae

IC - inner circular
OL – outer longitudinal
SG – glands within submucosa

L - lumen
A - adventitia

Gastro-oesophageal junction

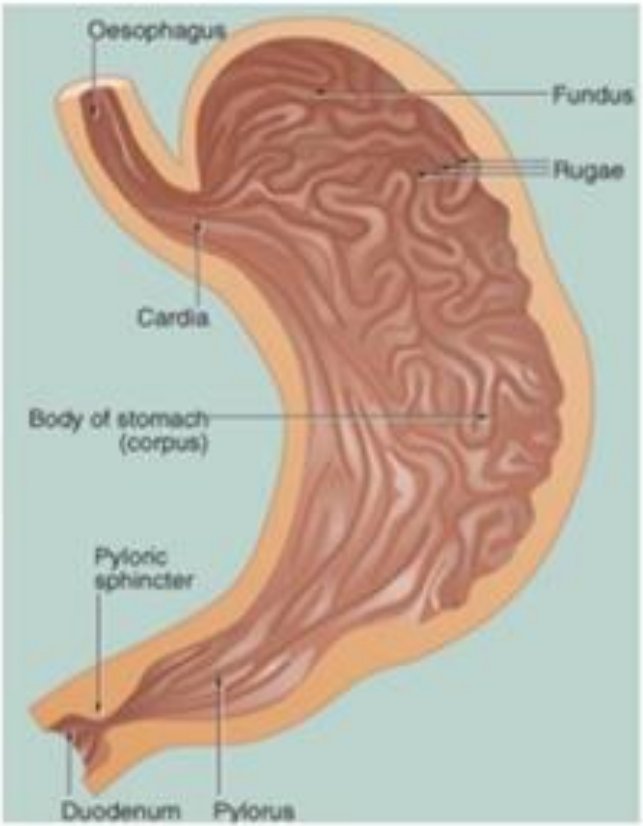
The esophagogastric junction is located approximately at the level of the diaphragm. Contractions of the diaphragm create sphincter-like effects, preventing reflux of stomach acids and content.

The transition of epithelium at the esophagogastric junction, from the non-keratinized stratified squamous epithelium of the esophagus to the columnar gastric surface epithelium.

The stomach

Functions:

- Transform food into semi fluid viscous mass (chyme).
- Digestion of carbohydrate that has started in the mouth.
- Begins absorption of water, drugs and salts.
- Secretion of HCl, mucus, pepsin, rennin and some endocrine hormone (serotonin).



Histologically:

3 regions are described.

- Cardiac region that surrounds the orifice.
- Fundus and body region.
- Pyloric region.

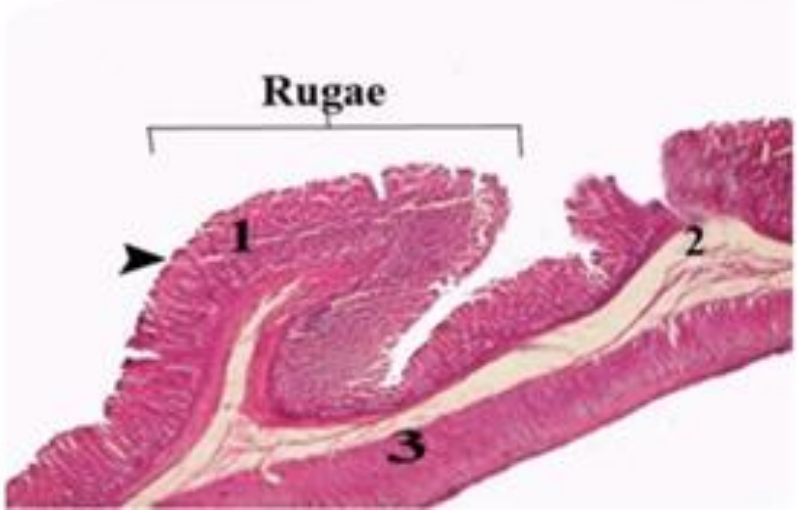
The wall of the stomach is formed of:

1- Mucosa:

- It is folded forming rugae.
- *I)Epithelium*: simple columnar mucous secreting cells lining the surface and is invaginated forming the pits (ducts) of gastric glands.
- *II) Lamina propria*: contains gastric glands.
- *III) Muscularis* mucosa: inner circular and outer longitudinal smooth muscle layers.

2- Submucosa:

- It is formed of C.T rich in blood vessels.



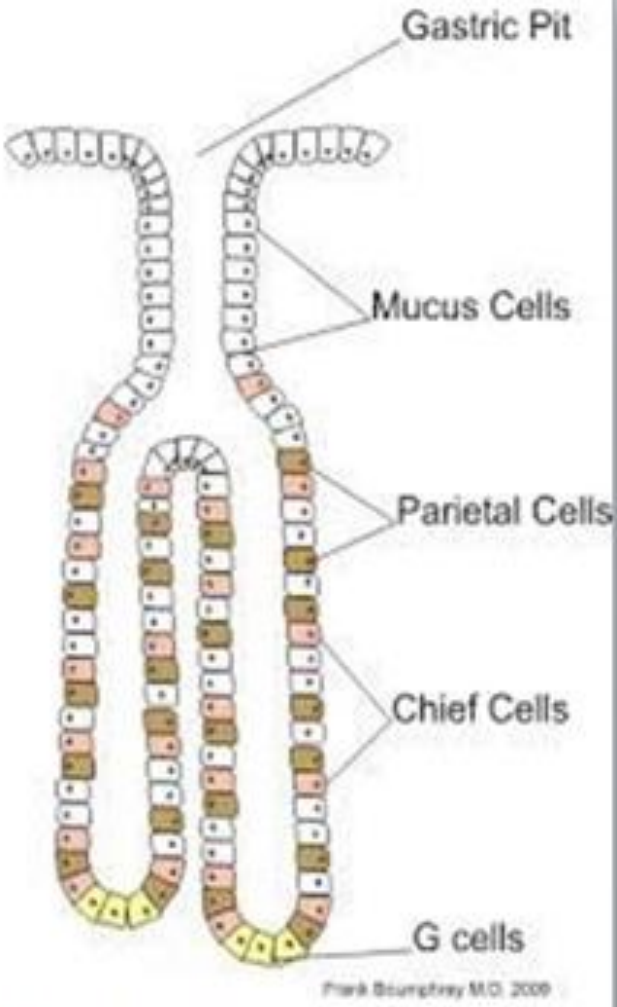
3- Musculosa:

- It is formed of smooth muscle fibers.
- In the fundus it consists of 3 layers of smooth muscle arranges as inner oblique, middle circular and an outer longitudinal layers.
- In the pylorus the muscles are arranged into two layers; thick inner circular forming pyloric sphincter and an outer longitudinal layer.

4- Serosa:

- Loose C. T. covered by a serous membrane (peritoneum).

The Gastric glands



- They are simple branched tubular glands.
- They are present in the lamina propria.
- They extend from gastric pits to muscularis mucosa.
- They are divided into:

1- Neck, the region following the pit.

2- Base the main part of the gland.

- **The cells lining the glands are:**

a- **Zymogenic cells** has basal basophilic cytoplasm and apical acidophilia.

They secrete enzymes (pepsinogen, renin).

b- **Parietal cells** have acidophilic cytoplasm,

secrete Hcl & interinsic factor for absorption of vitamin B_{12}.

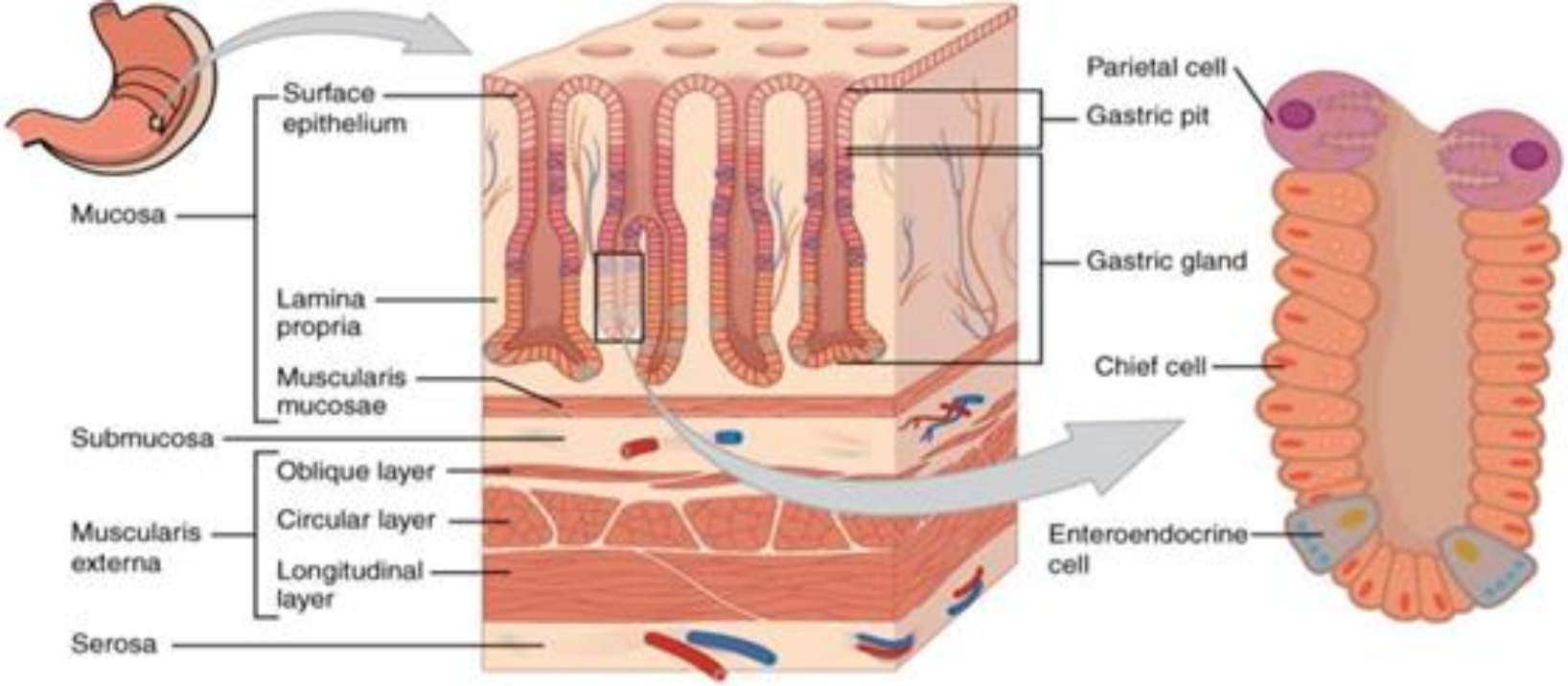
The Gastric glands

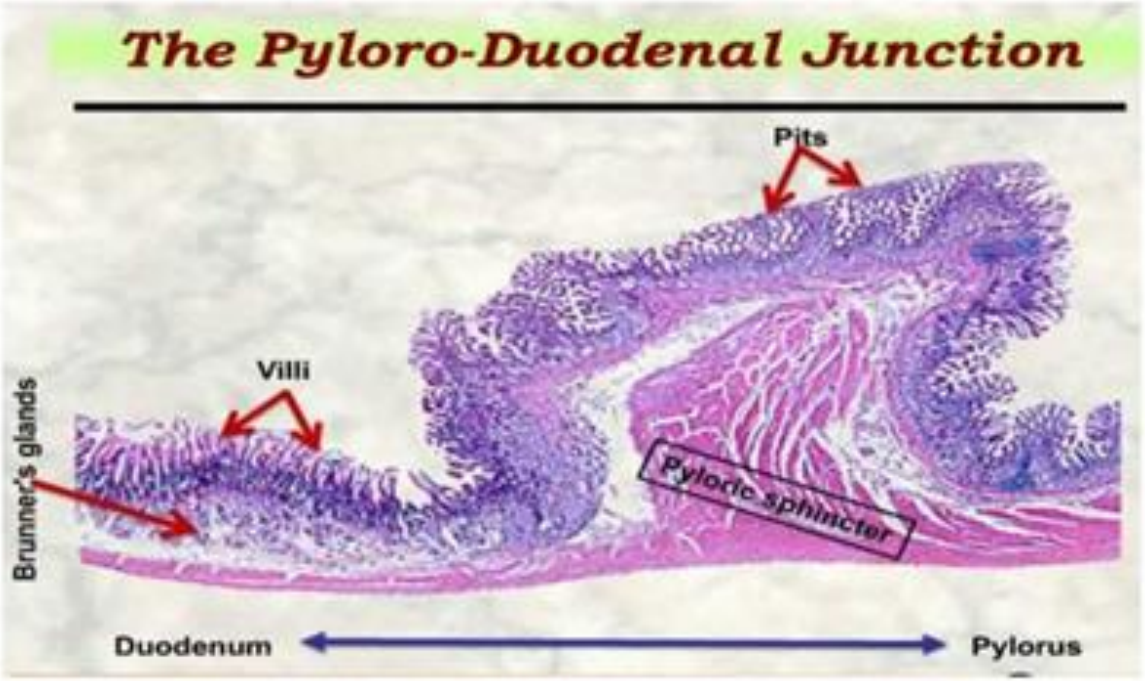
c- ***Mucous neck cells*** secrete mucous. They have pale vacuolated cytoplasm and flattened basal nuclei

d- ***Entero–endocrine cells,*** small, pyramidal, secrete some intestinal hormones.

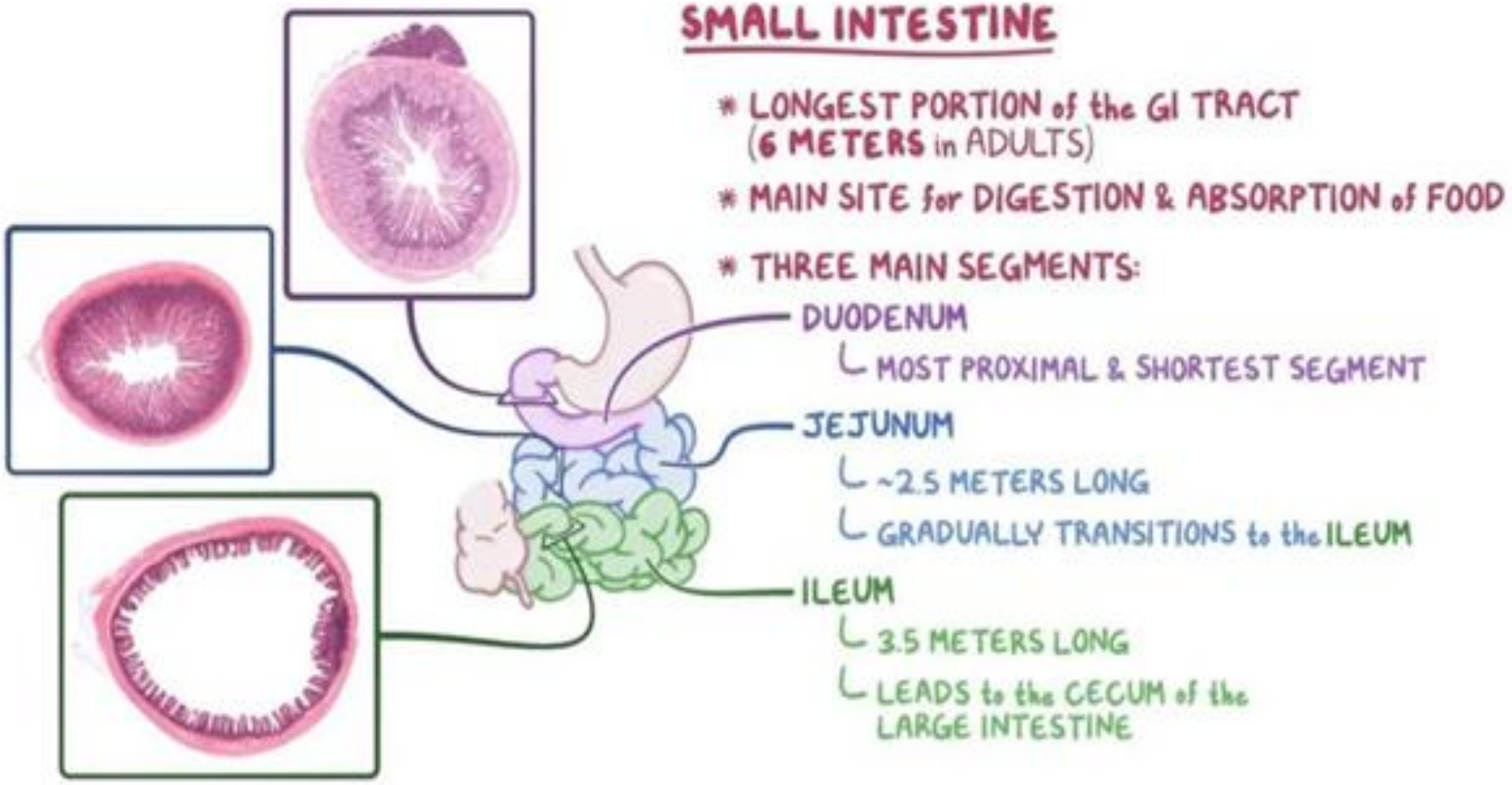
e- ***Undifferentiated stem cells***, they are present in the neck. They show mitotic figure and give all other types.

- The glands in the fundus and body contain all the types of cells.
- The glands in the cardiac and pyloric regions have deeper pits and more branched glands. They have no zymogenic cells and few parietal cells.


Surface epithelium
Mucosa
Lamina propria
Muscularis mucosae
Submucosa
Oblique layer
Circular layer
Muscularis externa
Longitudinal layer
Serosa
Parietal cell
Gastric pit
Gastric gland
Chief cell
Enteroendocrine cell


The Pyloro-Duodenal Junction
Pits
Villi
Brunner's glands
Pyloric sphincter
Duodenum
Pylorus

The Small Intestine



Function

1. Selective absorption of useful substances
2. Completing digestion
3. Secretion of some intestinal enzymes and endocrine hormones

The Small Intestine
General characteristics:

The wall of the small intestine is formed of: Mucosa, submucosa, Musculosa & serosa.

I- Mucosa:

The mucosa of the small intestine is covered by simple columnar absorptive epithelium with goblet cells. It shows:

1-Villi: Epithelial finger like projections

2-Crypts: These are epithelial invaginations in between the villi into the lamina propria forming intestinal glands (Crypt of Lieberkuhn).

3-Lamina propria: Loose connective tissue containing intestinal glands. In the **ileum**, it contains large lymphoid follicles (Peyer's patches).

4-Musclaris Mucosa: It is formed of smooth muscle fibers arranged as inner circular & outer longitudinal.

The epithelium covering the villi

90% are simple columnar absorptive cells with brush border due to the presence of large number of microvilli.

- Goblet cells: secrete mucous.
- Entero-endocrine cells: secrete intestinal hormones (e.g. secretin)

The epithelium lining the intestinal glands (Crypts of Lieberkuhn)

- Simple columnar cells with striated (brush) border.
- Goblet cells.
- Endocrine cells
- Paneth cells are present in the bases of the glands. They secrete digestive enzymes and lysozyme.
- Undifferentiated (stem) cells that have no striated border. They undergo mitosis to replace cells of villi and crypts.

II-Submucosa:

It is formed of loose connective tissue rich in blood vessels, nerves and lymphatics, in the **duodenum**; it contains Brunner's glands that secrete mucous.

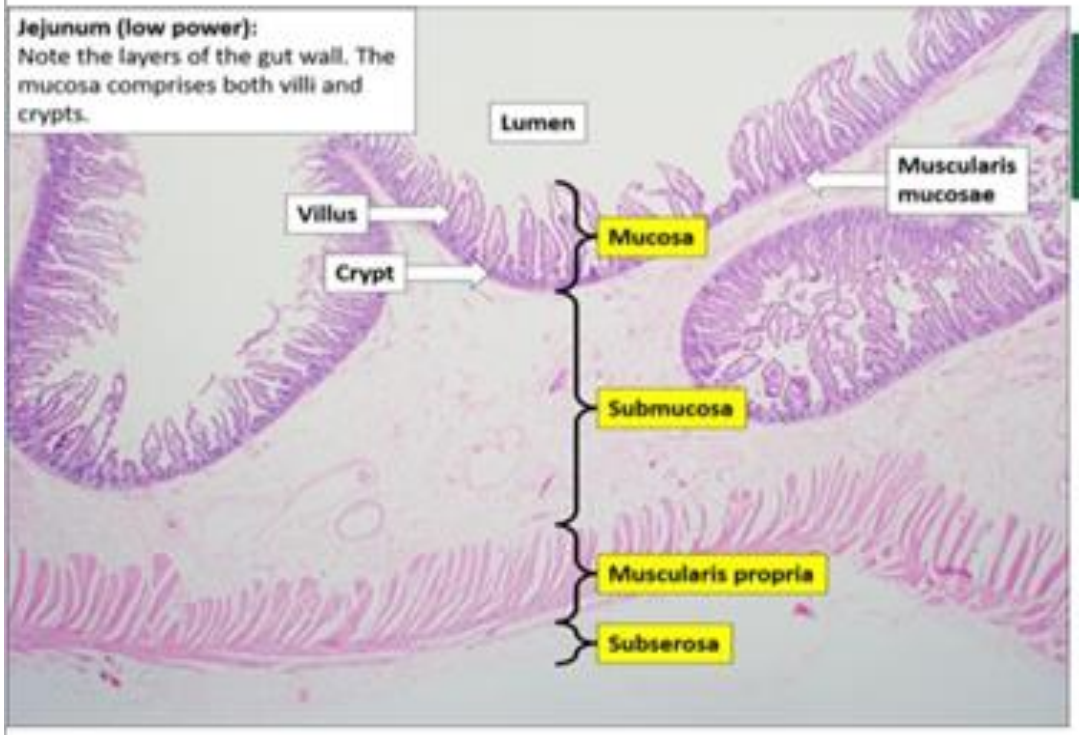
N. B. The jejunum has no Brunner's glands or Peyer's patches.

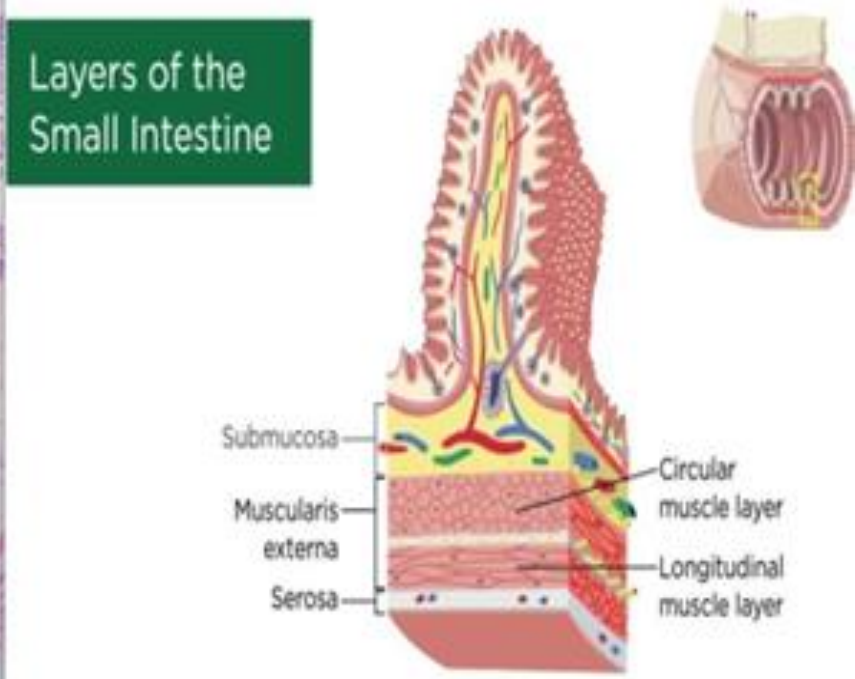
III-Musculosa:

It is formed of 2 layers of smooth muscle, inner circular & outer longitudinal layers.

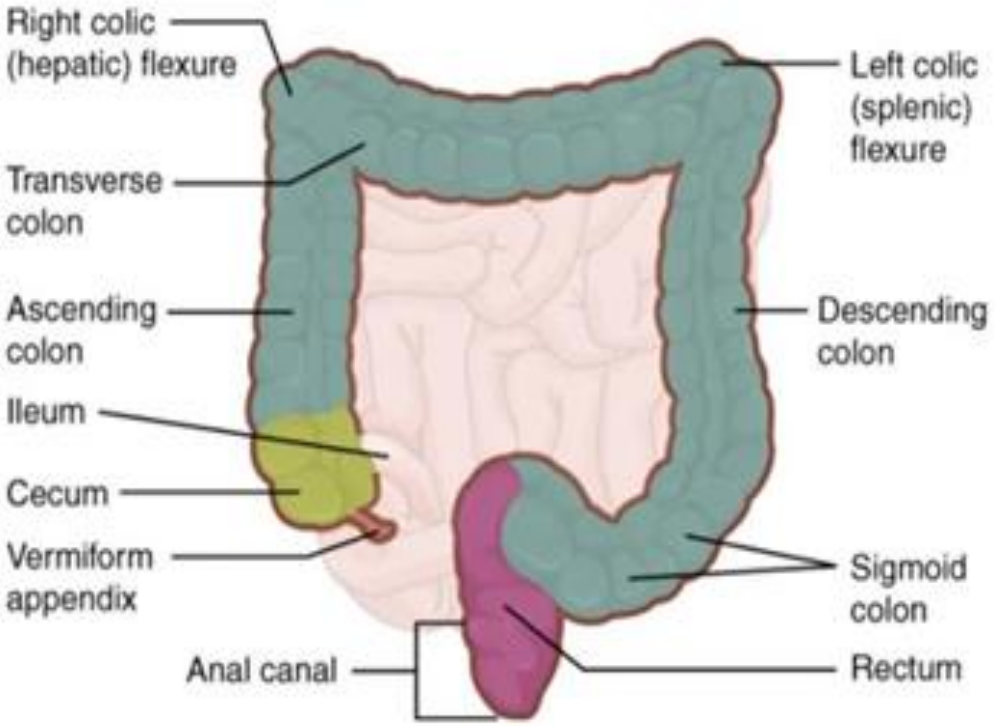
IV-Serosa:

It consists of loose C. T. covered by mesothelium.





The Large Intestine



Functions:

1. Absorption of water.
2. Secretion of protective mucous
3. Formation of faecal mass.

- It consists of
- caecum,
- appendix,
- ascending, transverse, descending and pelvic colons, and rectum.

The Large Intestine - Microscopic structure

I- Mucosa: It has no villi, only crypts are present.

a) Epithelium is simple columnar absorptive cells with numerous Goblet cells. The crypts (glands) are lined by simple columnar cells, large numbers of goblet cells, entero-endocrine cells (few) &undifferentiated stem cells.

b) Lamina propria is rich in lymphocytes and lymphatic nodules.

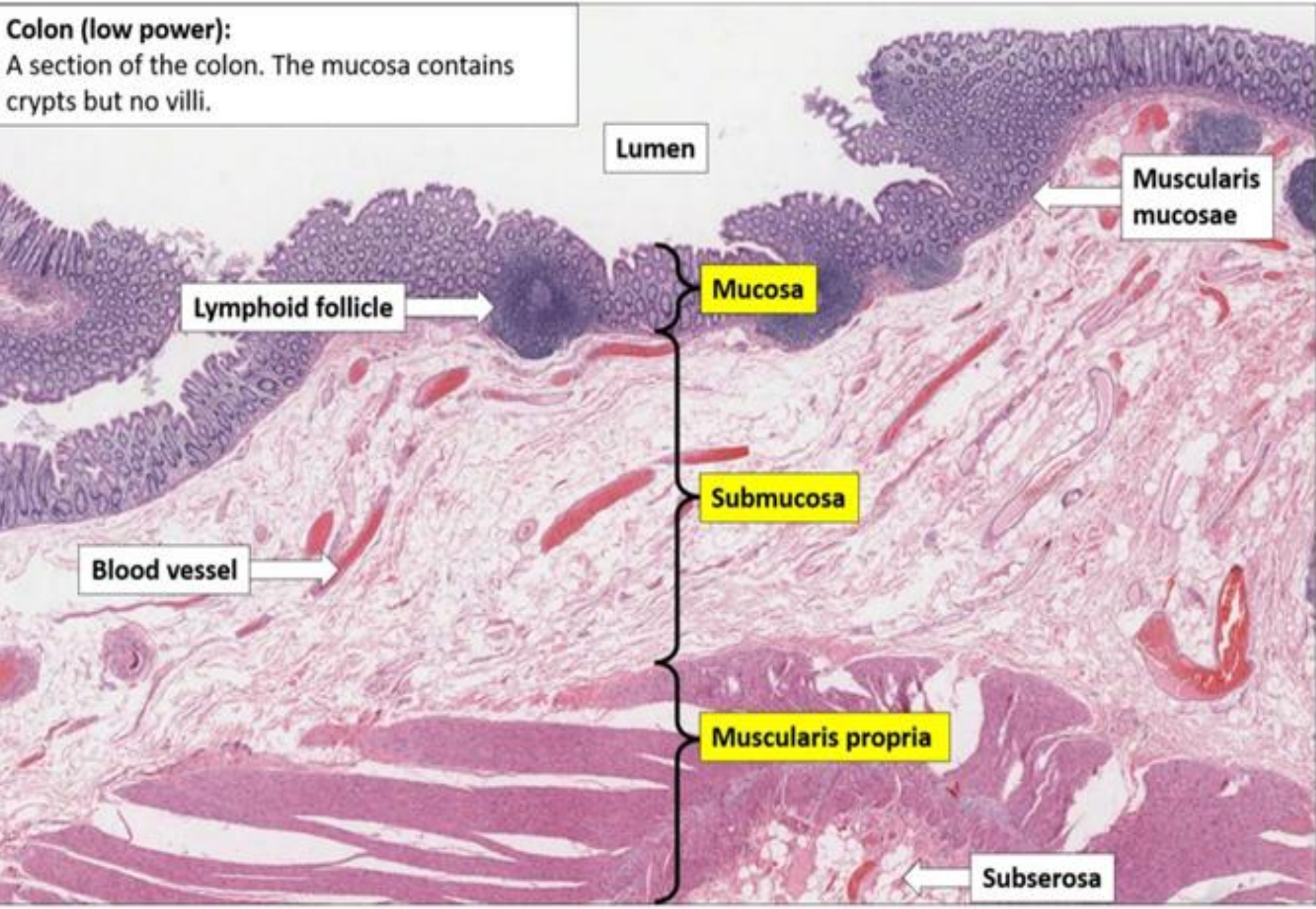
c) Muscularis mucosa is formed of two layers of smooth muscle; Inner circular and outer longitudinal.

II-Submucosa: Loose CT , lymph nodules may extend to it mucosa. It has no glands.

III-Musculosa: It is formed of continuous inner circular, while the outer longitudinal are collected into 3 bands called taenia coli.

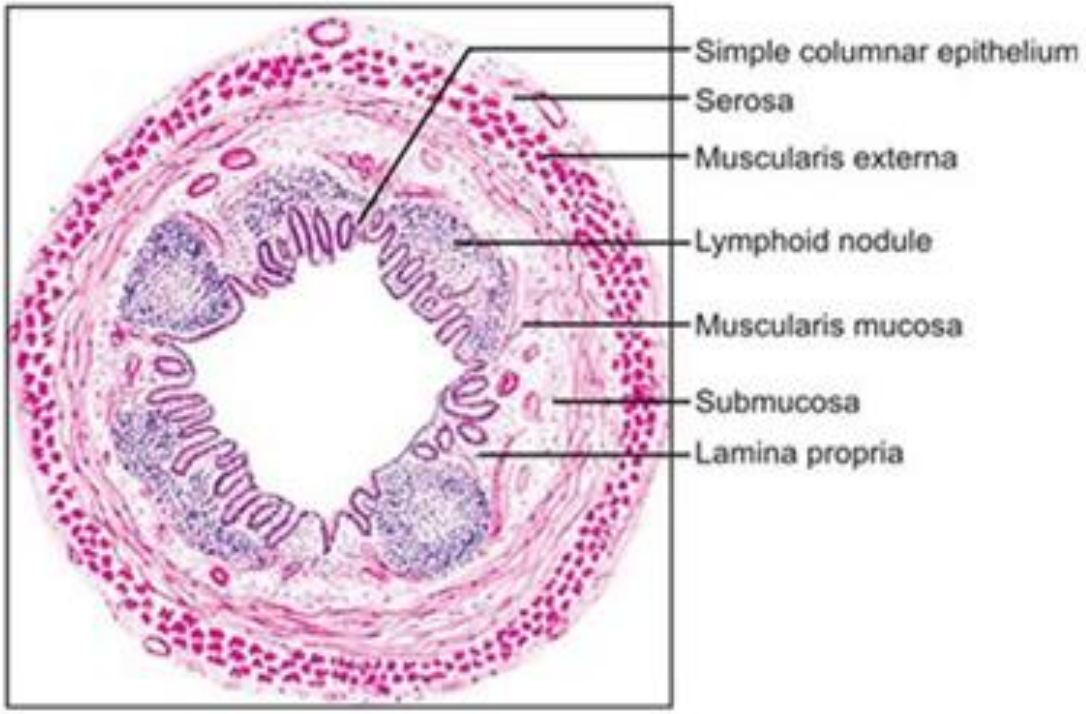
IV-Serosa:

The serous membrane enclose adipose tissue in sac like structure called appendices epiploicae.

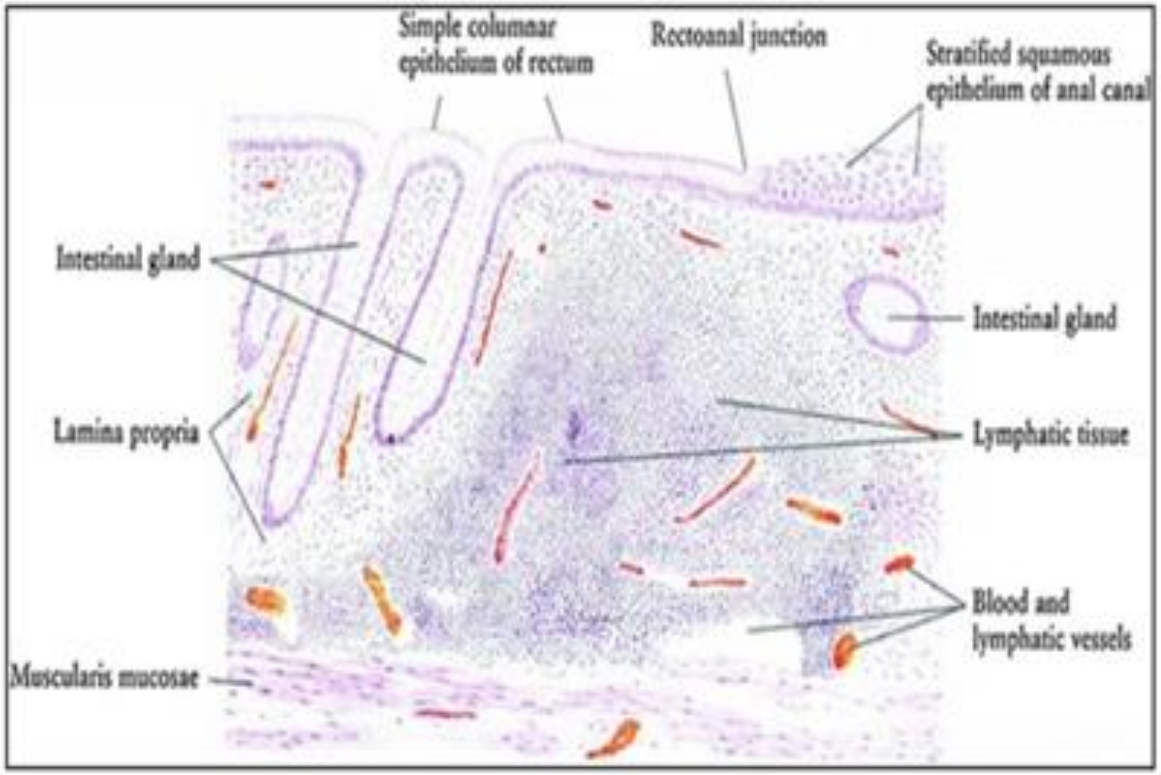

Colon (low power):
A section of the colon. The mucosa contains crypts but no villi.
Lumen
Muscularis mucosae
Mucosa
Lymphoid follicle
Submucosa
Blood vessel
Muscularis propria
Subserosa

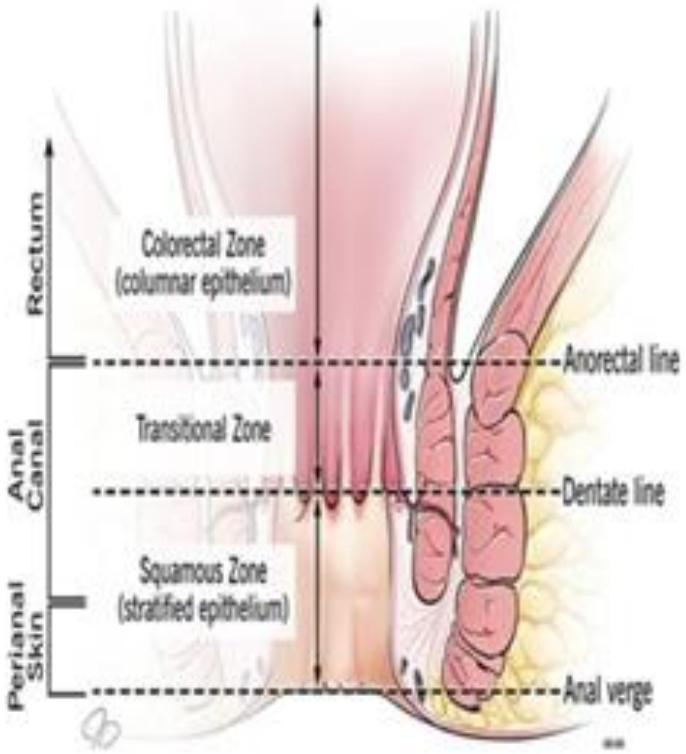
Vermiform Appendix:

- The lumen is small and irregular.
- Abundant lymphoid follicles in the wall.
- Few and short crypts.
- Muscularis mucosa is not well developed.
- No taeniae coli.

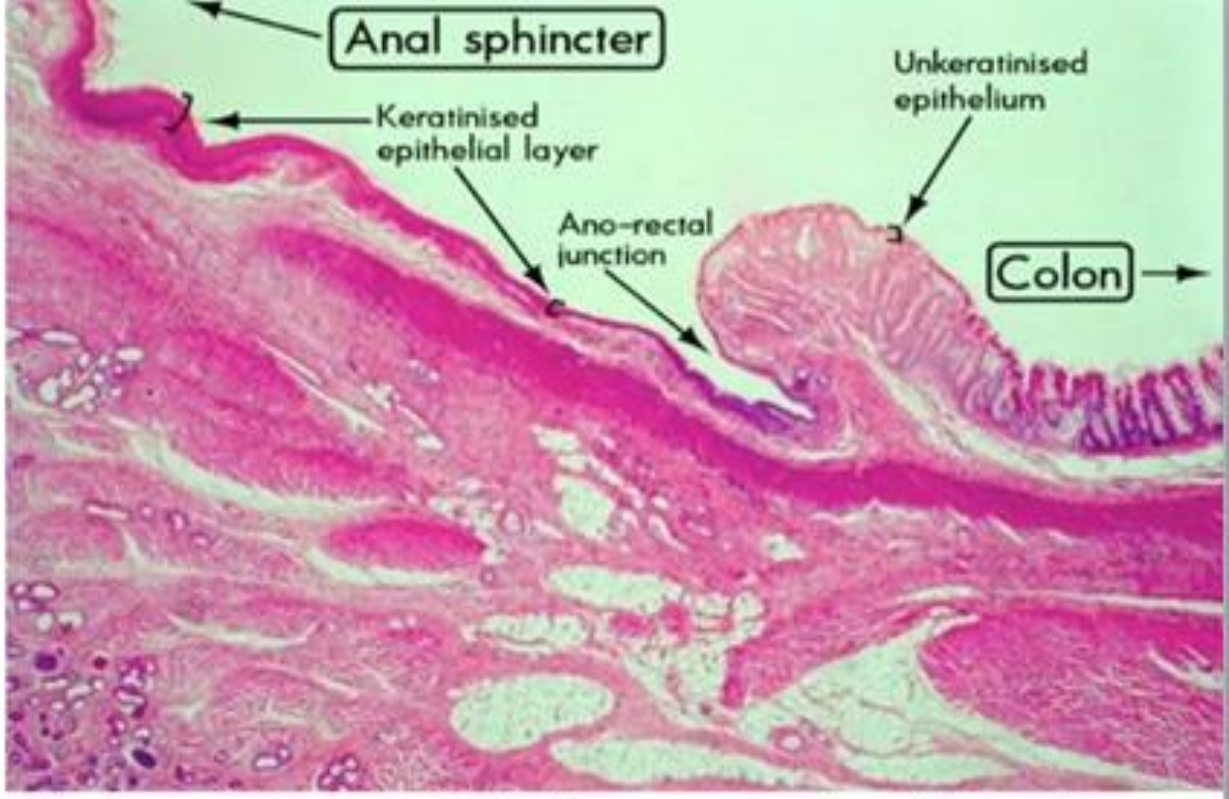


Recto-anal junction

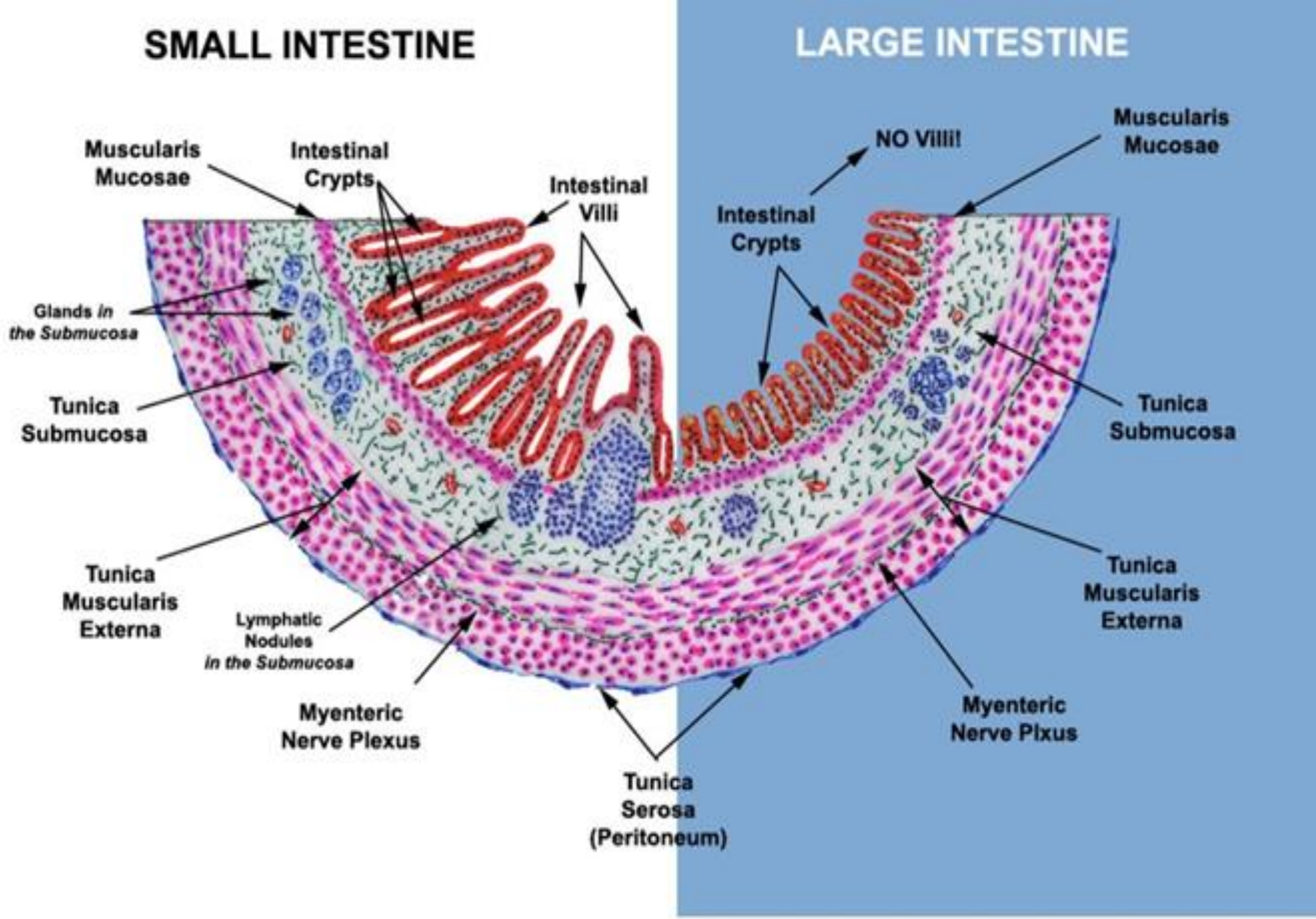




Anal Canal



- The epithelium is stratified squamous epithelium non –keratinized. It becomes keratinized at the anus.
- It has no crypts.
- No muscularis mucosa.
- Lamina propria is continuous with the submucosa and contains plexus of large veins whose dilatation causes haemorroids.
- The inner circular layer of muscularis externa thickens to form external anal sphincter.


SMALL INTESTINE
LARGE INTESTINE
Muscularis Mucosae
Intestinal Crypts
Intestinal Villi
Glands in the Submucosa
Tunica Submucosa
Tunica Muscularis Externa
Lymphatic Nodules in the Submucosa
Myenteric Nerve Plexus
Tunica Serosa (Peritoneum)
NO Villi!
Intestinal Crypts
Muscularis Mucosae
Tunica Submucosa
Tunica Muscularis Externa
Myenteric Nerve Plxus

Histology

Dr. Ali Ashgar

The cell

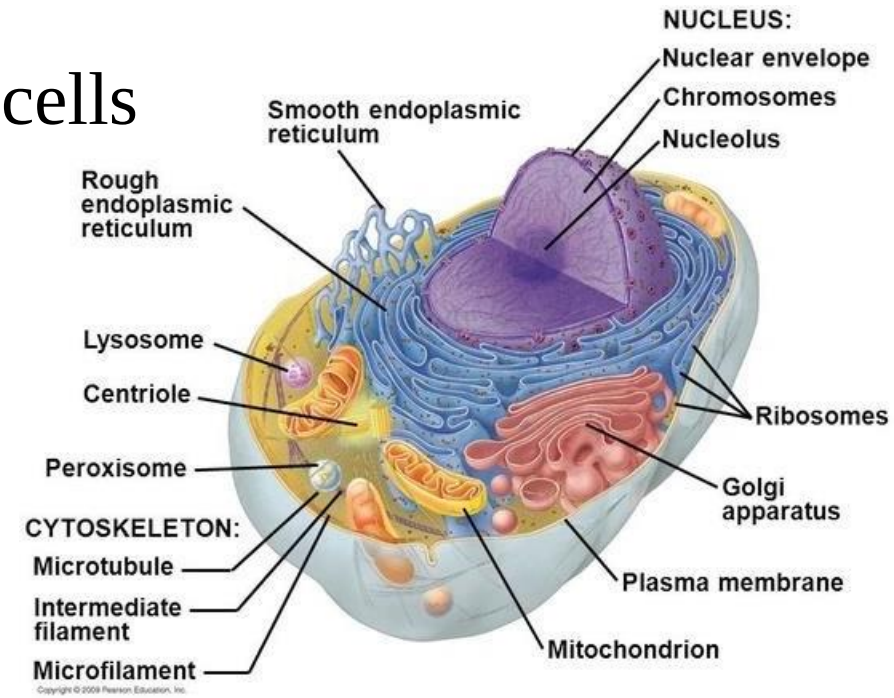
Lec .1

17/9/2023

COMPONENTS OF THE HUMAN BODY

Body, systems, organs, tissues, cells

The cell



- The smallest living part of the body.
- Functional & structural unit of the body.
- Animal cells are eukaryotic

(eu = good, + karyon = nucleus).

STRUCTURE OF THE CELL

I. **Nucleus,** stained dark blue.with hematoxylin.

II. **Cytoplasm, composed of:**

- Matrix (cytosol), a fluid contains hundreds of enzymes.
- Organelles , cytoskeleton and inclusions.

III- Plasma membrane

The cell

- The human organism presents about 200 different cell types
- The shape and motility of cells are determined by the cytoskeleton
- All cells derived from the **zygote,** the single cell formed by fertilization of an oocyte with a spermatozoon.
- Zygot enter cell division give: **blastomeres(stem cells)**
- **Blastomeres** give rise to all tissue types of the adult.

Table. Cellular functions in some specialized cells.

Function	Specialized Cell(S)
Movement	*Muscle and other contractile cells*
Covering and lining	*Epithelial cells*
Synthesize and secrete components of the extracellular matrix	*Fibroblasts, cells of bone and cartilage*
Convert physical and chemical stimuli into action potentials	*Neurons and sensory cells*
Synthesis and secretion of enzymes	*Cells of digestive glands*
Synthesis and secretion of mucous substances	*Mucous-gland cells*
Synthesis and secretion of steroids	*Some adrenal gland, testis, and ovary*
Ion transport	*Cells of the kidney and salivary gland*
Intracellular digestion	*Macrophages and some white blood cells*
Lipid storage	*Fat cells*
Metabolite absorption	*Cells lining the intestine*

Cytoplasmic Organelles

1. **M*embranous*** such as:

1. Mitochondria.
2. ER (Endoplasmic reticulum).
3. Golgi complex.
4. Lysosome.
5. Coated vesicle.

2 .**Non-*membranous*** such as

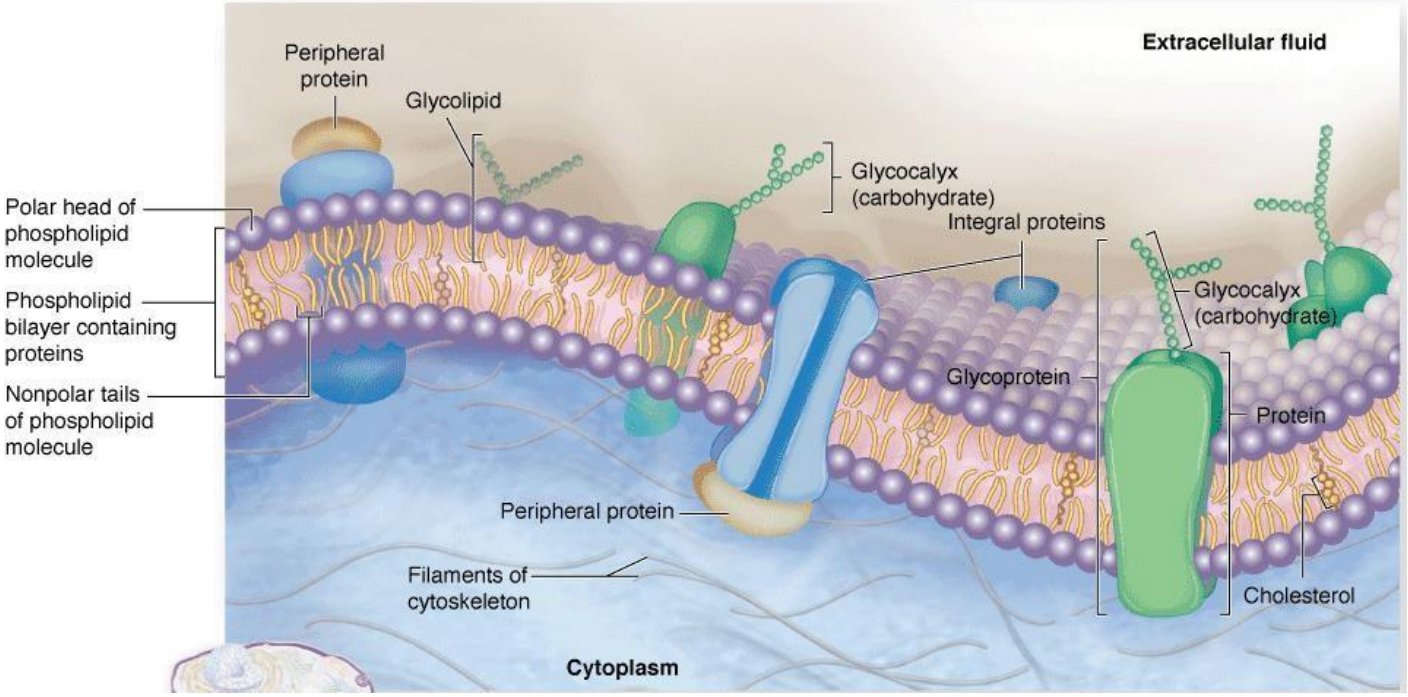
1) Ribosomes.
2) Microtubules.
3) Centeriole.
4) Microvilli.
5) Cilia..

Plasma Membrane

* Outer of the cell, the cytoplasm separated from extracellular environment, by plasma membrane (plasma lemma)

Structure: principal components:

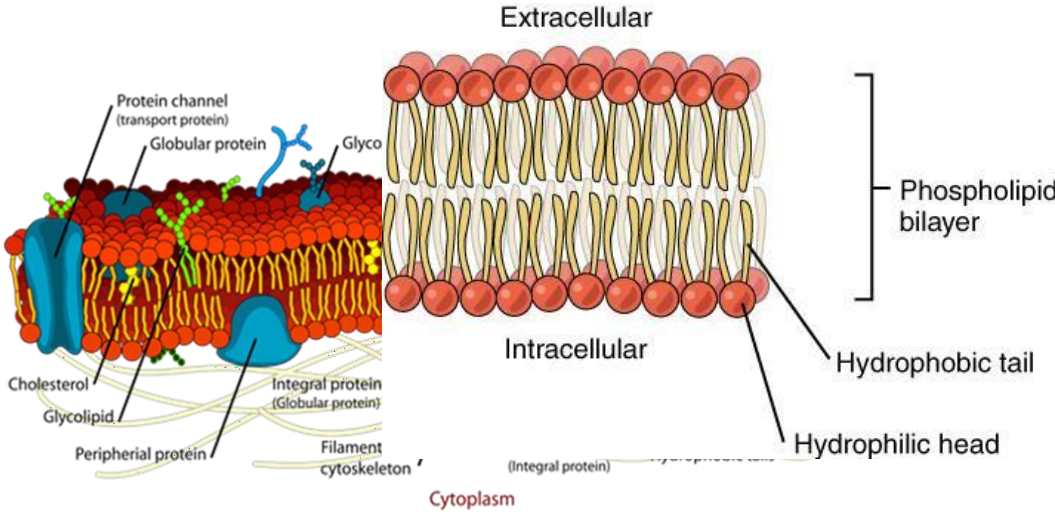
1. **A phospholipid bilayer.**
2. **Cholesterol** molecules interspersed within the bilayer.
3. **Proteins** that are embedded in or on the bilayer.
4. **Glycocalyx**, carbohydrate chains.



Plasma Membrane

CHARACTERS: *

- Is a permeable ,it controls the movement of substances in and out of cells.
- Range from 7.5 to 10 nm in thickness.
- visible only by electron microscope, sometimes seen as a dark line with the light microscope

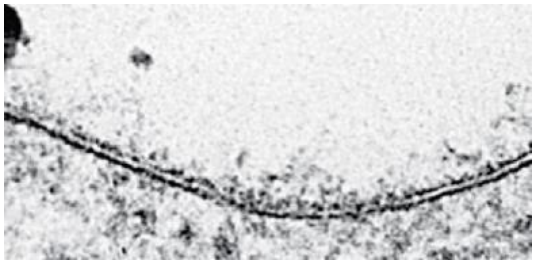


Phospholipid molecule composed of:

1. Head, two fatty acid chains (hydrophobic) .
2. Tail, one phosphate group (.hydrophilic) .

- The **trilaminar structure** composed of:
  Head of the inner layer + fusion of lipid tails of each layer+ Head of outer layer.
- **Fluid mosaic model** , named for the membrane:
  - because Proteins and substances such as cholesterol become embedded in the bilayer, giving the membrane the look of a mosaic.

- A TEM of a cell surface shows the trilaminar unit membrane with glycocalyx



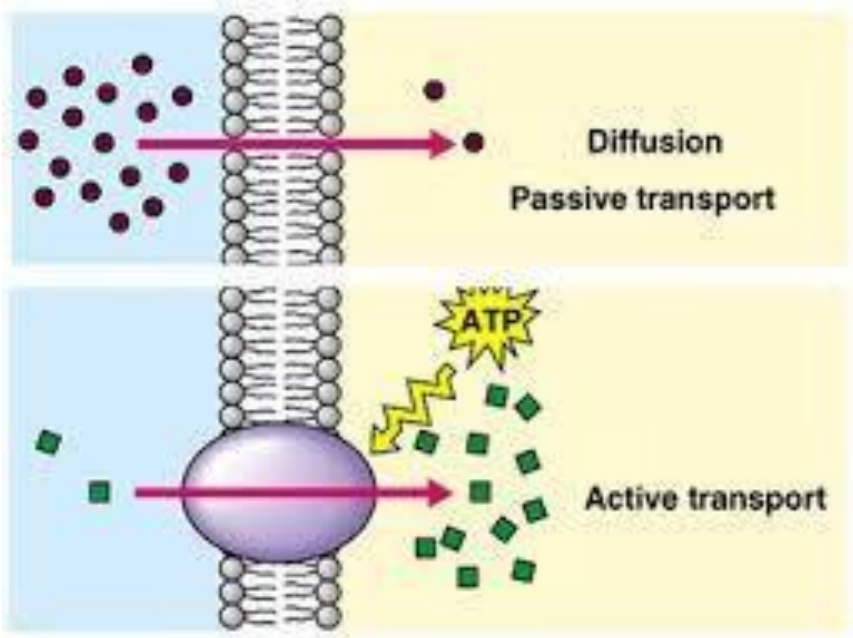
Transport Through the Plasma Membrane

- **Active transport:**

  is any movement of molecules or ions that requires energy (ATP) such as some ions, Na+, K+,Ca2+, and uptake of glucose in the intestines cross the cell membrane

- **Passive transport: (Diffusion)**

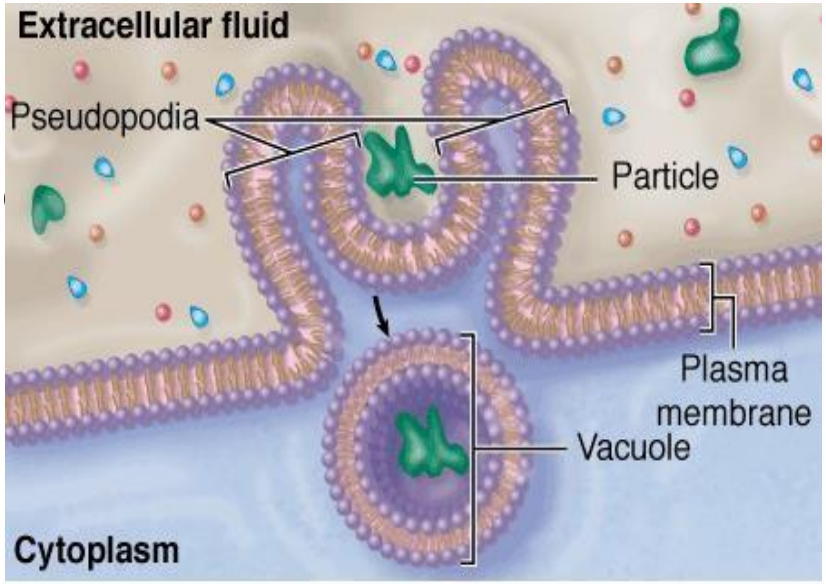
  is any movement of molecules or ions does not require energy.



Transport Through the Plasma Membrane

- Larger materials e.g.(IgA and insulin) move into the cell through **endocytosis** and moved out through **exocytosis. (transcytosis)**

- **Endocytosis** The cell takes in macromolecules by folding and fusion of the plasma membrane to form vesicles which enclose the material transported,



a Phagocytosis

Three types of endocytosis

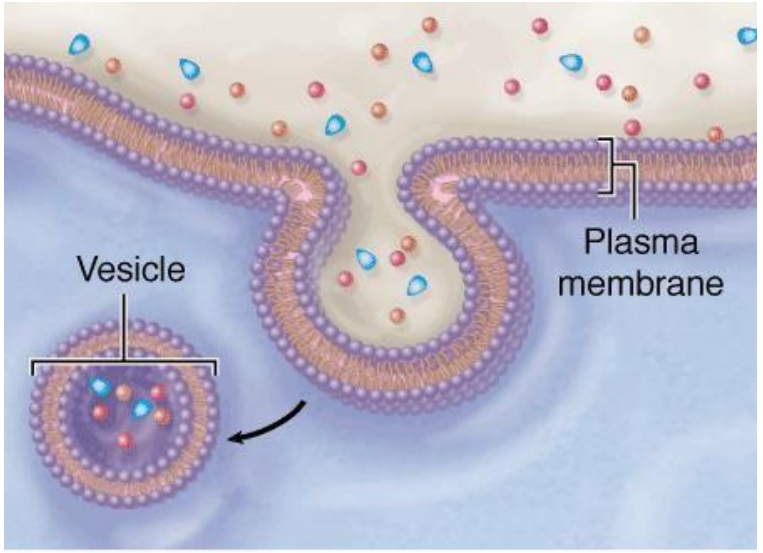
1. **Phagocytosis.** means "cell eating".

- macrophages and neutrophils, are specialized for engulfing bacteria, protozoa, dead cells.
- the cytoplasmic folds called **pseudopodia**.
- Particle inter into cytoplasmic vacuole or **phagosome**.

Transport Through the Plasma Membrane

2.Fluid-phase endocytosis. means "cell drinking“ (**Pinocytosis).**

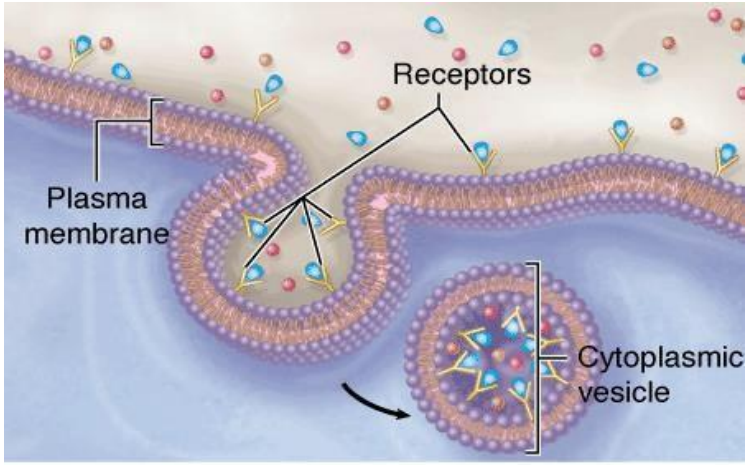
- the cell membrane invaginates to form a pit, forms a **pinocytotic vesicle** containing the fluid



b Pinocytosis

3.Receptor-mediated Endocytosis

- Presence of membrane proteins called **receptors** which bind specific molecules (**ligands**) such as hormones and growth factors.
- receptors aggregate in membrane regions called **coated pits**
- Invaginations of cytoplasm forms vesicle **(Endosome).**
- Vesicles containing both the receptors and the bound ligands.



c Receptor-mediated endocytosis

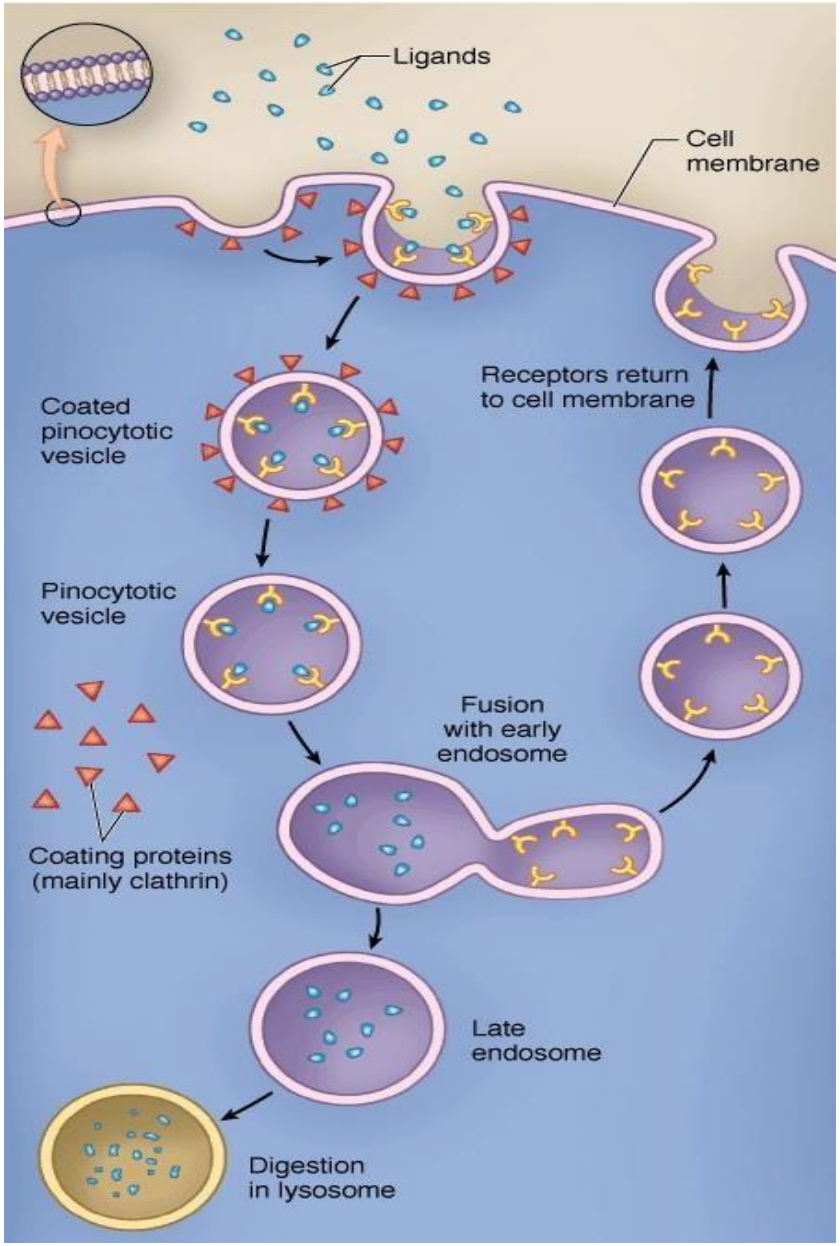
Transport Through the Plasma Membrane (transcytosis(

Membrane trafficking

- Is the movement of macromolecules using membrane bound transport vesicles.
- Membrane trafficking divided into two pathways based on the direction of travel, **exocytosis** and **endocytosis**

Exocytosis

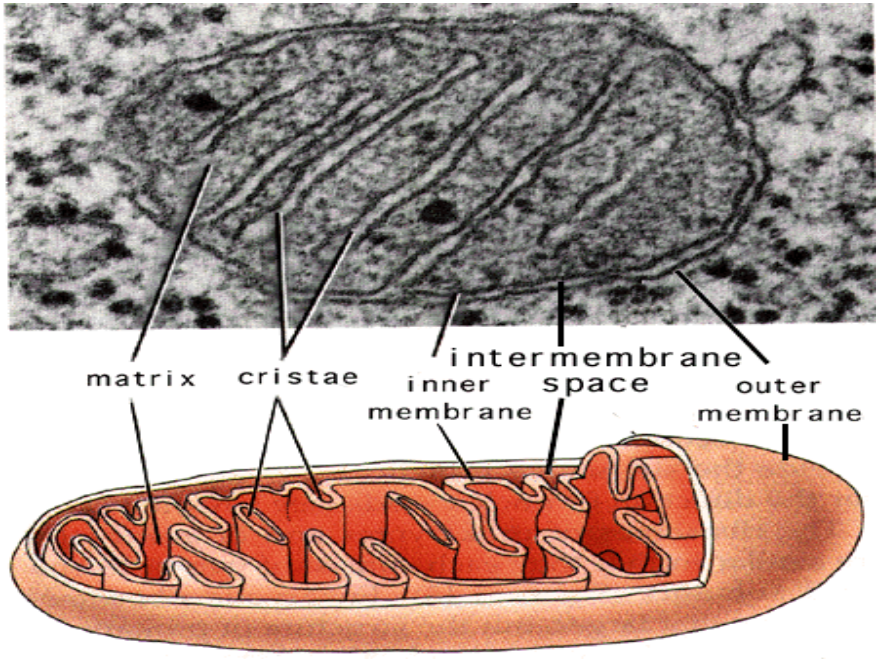
- As part of the secretory pathway,
- newly synthesized proteins, lipids or carbohydrates move from the (ER) via the Golgi throw the cell membrane to extracellular space



Cytoplasmic Organelles

Mitochondria

- Are membranous organelles
- specialized for aerobic respiration and production of adenosine triphosphate (ATP) which contain energy.
- Contain oxidative phosphorylation enzymes
- Mitochondrial enzymes yield 15 times more ATP than is produced by glycolysis.
- Some of the energy is not stored in ATPbut is spread as heat for maintains body temperature.



Glycolysis converts glucose anaerobically to pyruvate

- Number of mitochondria increase in cells of high metabolic activity (eg, cardiac muscle, liver cells & kidney tubules) .
- Stained: blue by haematoxyline.

Mitochondria

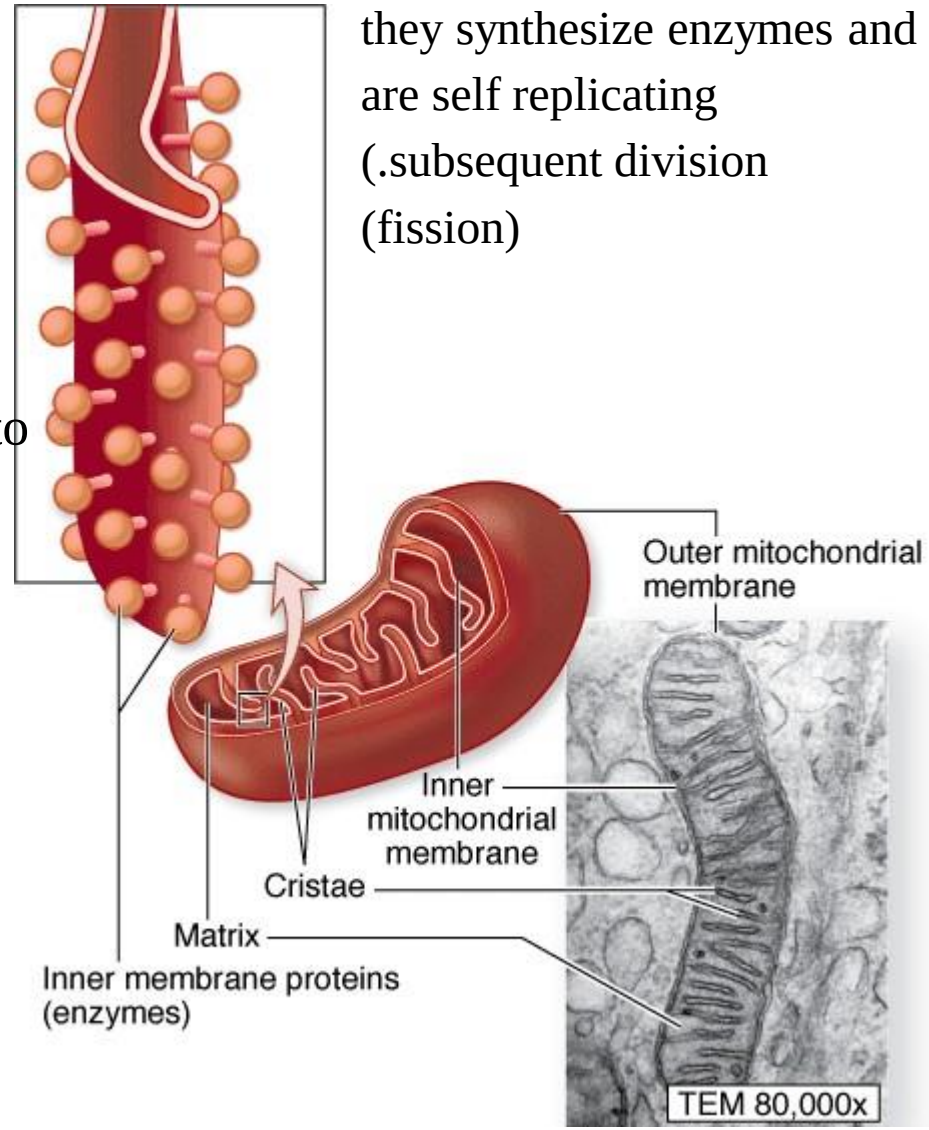
Structure:

- Elongated, 0.5–1 um in diameter and lengths up to ten times greater.
- highly plastic, rapidly changing shape, fusing with one another and dividing.
- **With 2 membranes:**
- Smooth outer membrane.
- Folded inner membranes forming cristae to increase surface area.
- **With 2 spaces**:
- Intermembrane space: narrow space between inner and outer membranes.
- Matrix space: large space enclosed by the inner membrane,

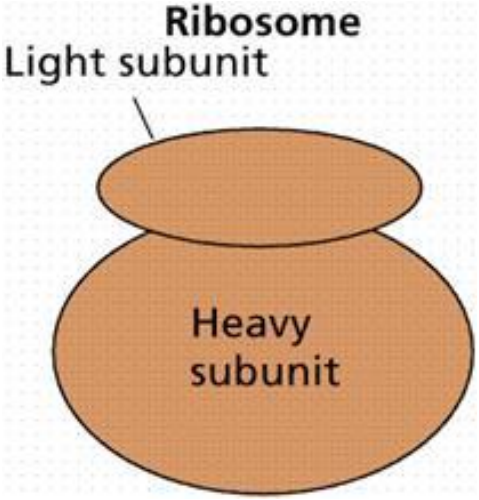
  contains: DNA, RNA, Ribosomes, Enzymes, Calcium (electron dense Granules)

Functions:

- Power house (produce ATP)
- Concentrate calcium.
- Contains DNA & RNA, so they synthesize enzymes and are self replicating (.subsequent division (fission)



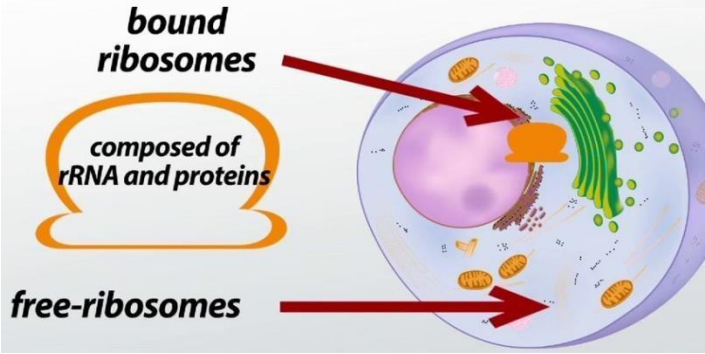
Ribosomes



- Non-membranous cell organelles.
- are small electron-dense particles, about 20 x 30 nm in size.

Types:

- **Free ribosomes**: scattered in the cytoplasm.
- **Attached ribosomes:** attached to ER membranes forming the rough endoplasmic reticulum (RER)



Structure:

- Composed of four segments of rRNA and approximately 80 different proteins.
- Composed of two different-sized **subunits**:
- **Small (light)**, has a binding site for mRNA.
- **Large (heavy),** has two binding sites for tRNA:

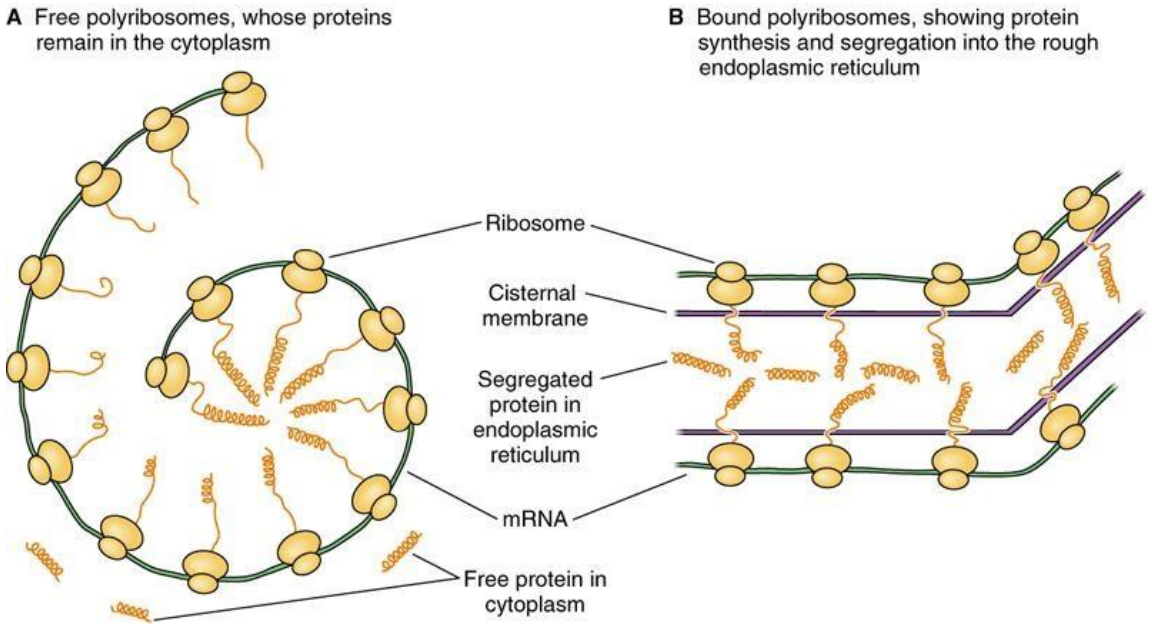
P [peptide] site. And **A** [Amino] site.

- cause basophilia in secretory cells.
- numerous ribosomes are present on an mRNA as polyribosomes (or polysomes).

Ribosomes

Functions:

- Protein synthesis with aid of m-RNA and t-RNA.
- Free ribosomes for synthesis of ***structural proteins*** as cytoskeleton, glycolytic enzymes.
- Attached ribosomes for synthesis of ***secretory proteins,*** as lysosomal enzymes and plasmalemmal proteins.



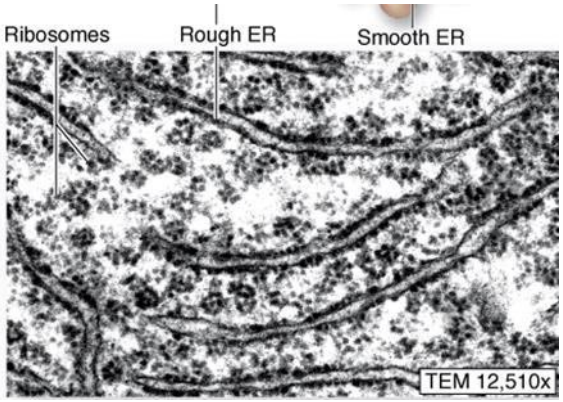
Endoplasmic Reticulum (ER)

- Network of interconnected membranes (cisternae) .

Two types

1. **Rough endoplasmic reticulum** (RER), with ribosomes.

   Basophilic due to presence of ribosomes.



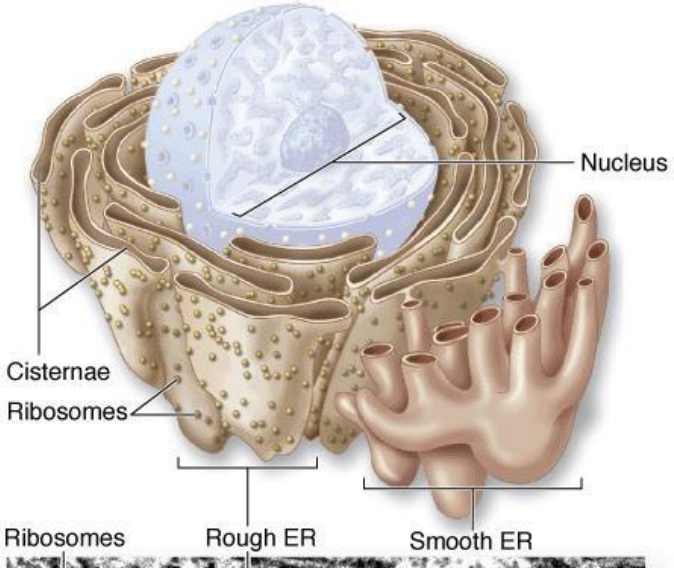
Functions of RER:

- **Synthesis of proteins,** by ribosomes on its outer surface.
- **Transfer vesicles,** transfer the formed protein to Golgi.

2. **Smooth endoplasmic reticulum** (SER), no ribosomes, synthesis of phospholipid molecules

Functions of SER:

- Synthesis of **lipids** & **cholesterol**.
- Synthesis of **steroid** hormones, e.g. cortisone.
- Helps **muscle contraction**, (sarcoplasmic reticulum.(
- **Detoxification** of drugs & toxins.
- abundant in liver cells.



Golgi Apparatus or Golgi complex

- Named for histologist Camillo Golgi who discovered it in .1898
- Is a highly plastic, the secretory organelle of the cell.

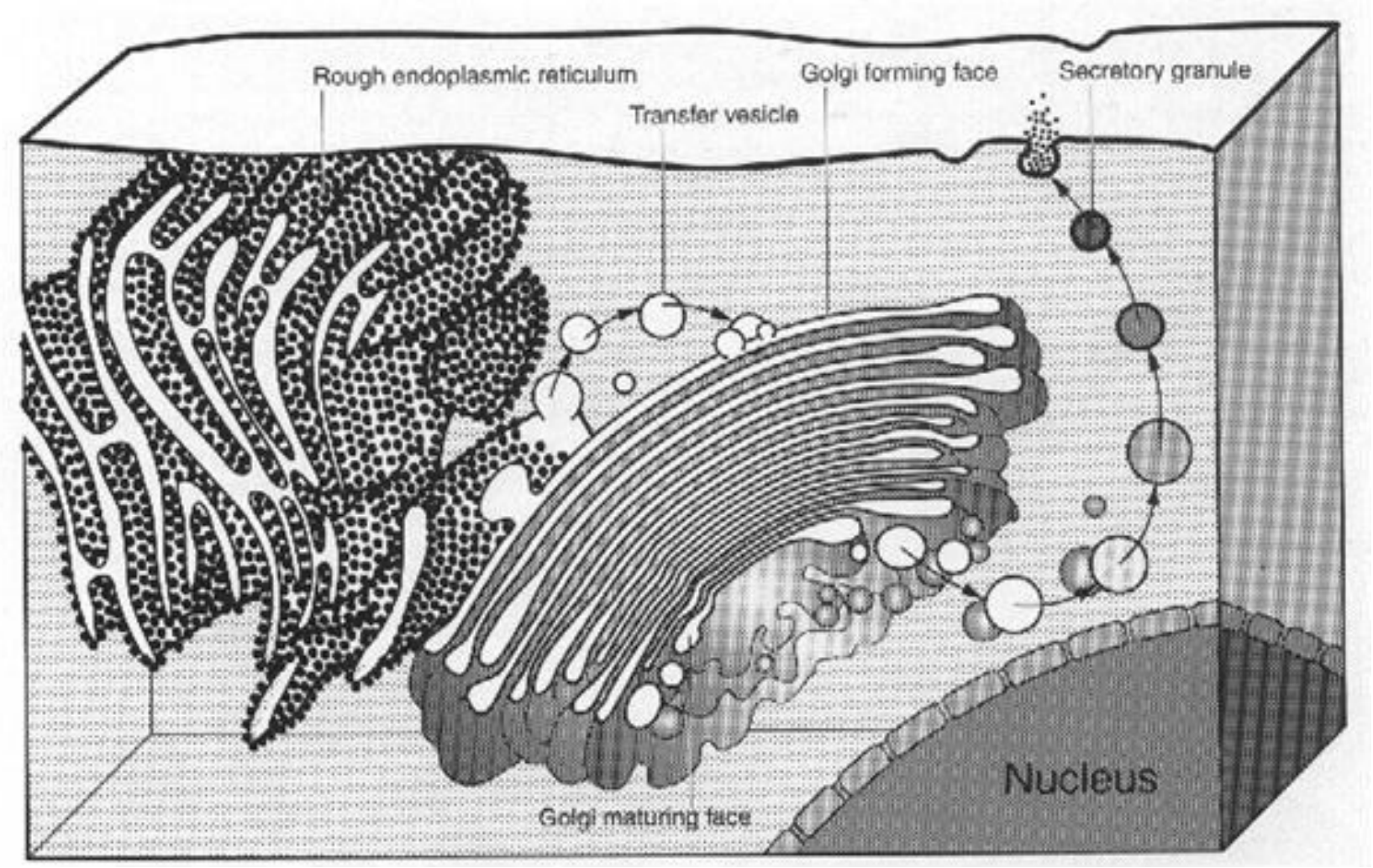
Structure:

- Are membranous organelle.
- Complex traffic of vesicles, each vesicle has two faces: **Convex (forming) face (***cis* face), receives **transfer vesicles. Concave (mature) face (**exit or *trans* face), also named (condensing vacuoles), forms **secretory vesicles.**
- **Inset:**: a small region of a Golgi apparatus with abundance of glycoproteins within some cisternae.

Functions:

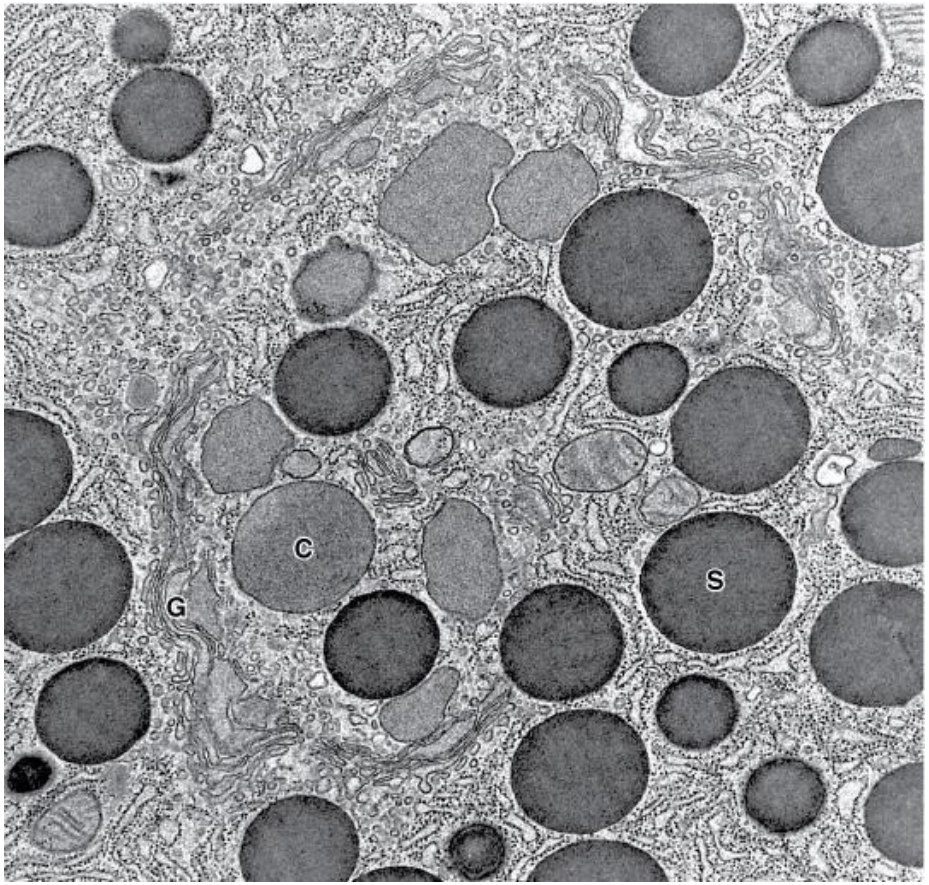
- **Sorting, modification & packaging** of proteins.
- **Secretory vesicles** formation.
- **Formation of lysosomes**.
- Transport vesicles from RER move toward and fuse at the forming face of the Golgi.

Golgi Apparatus or Golgi complex



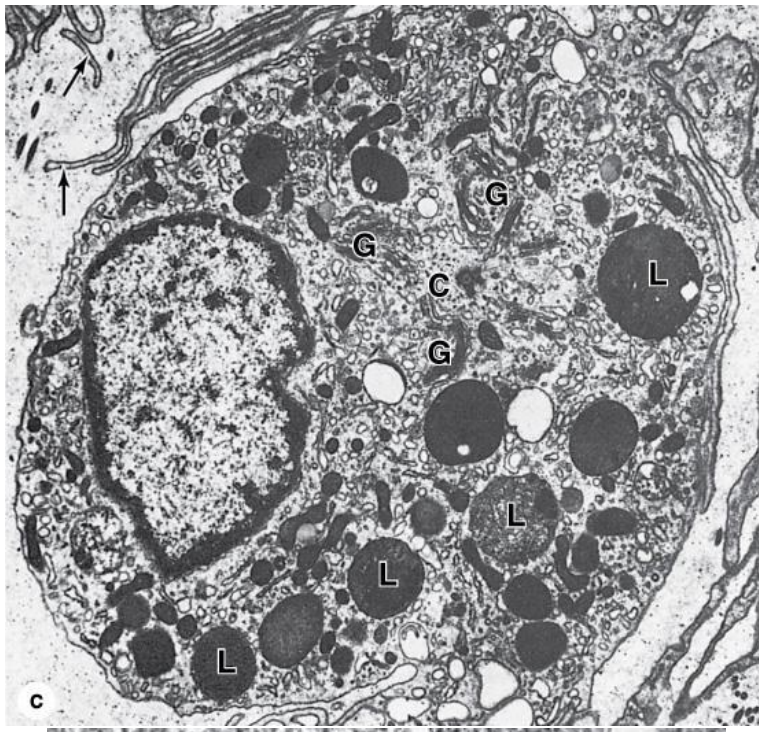
Secretory Vesicles or Granules

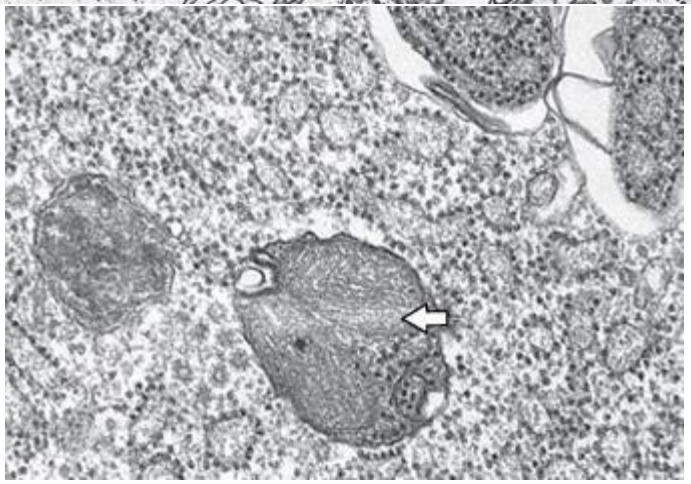
- Originating from Golgi apparatus.
- found in those cells that store a product until its release by exocytosis.
- zymogen granules , with dense contents of inactive digestive enzymes.
- intensely eosinophilic structures.



Lysosomes

- Are sites of intracellular digestion and turnover of cellular components.
- Spherical, diameter from 0.05 to 0.5 um.
- Electron-dense in EM.
- In macrophages and neutrophils, are larger and visible with L⁄M.
- Contain 40 different hydrolytic enzymes which formed in the RER.
- Originate from mature surface of the Golgi apparatus.



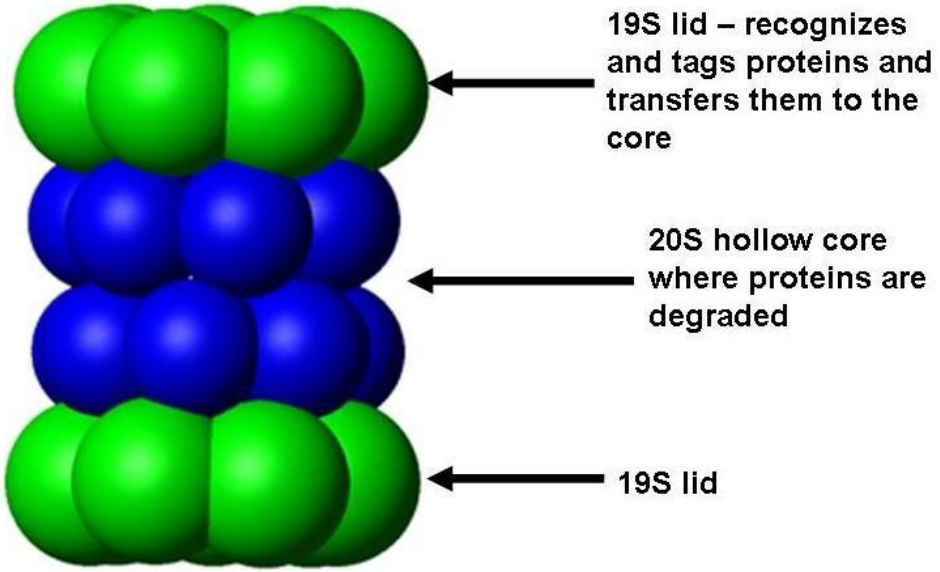


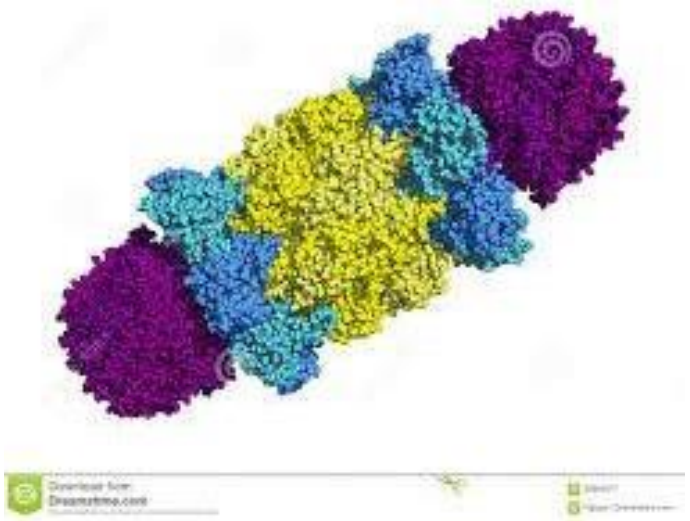
Functions:

- Intracellular digestion of ingested material or old organelles (called **autophagy**).
- turnover of cellular components

Proteasomes

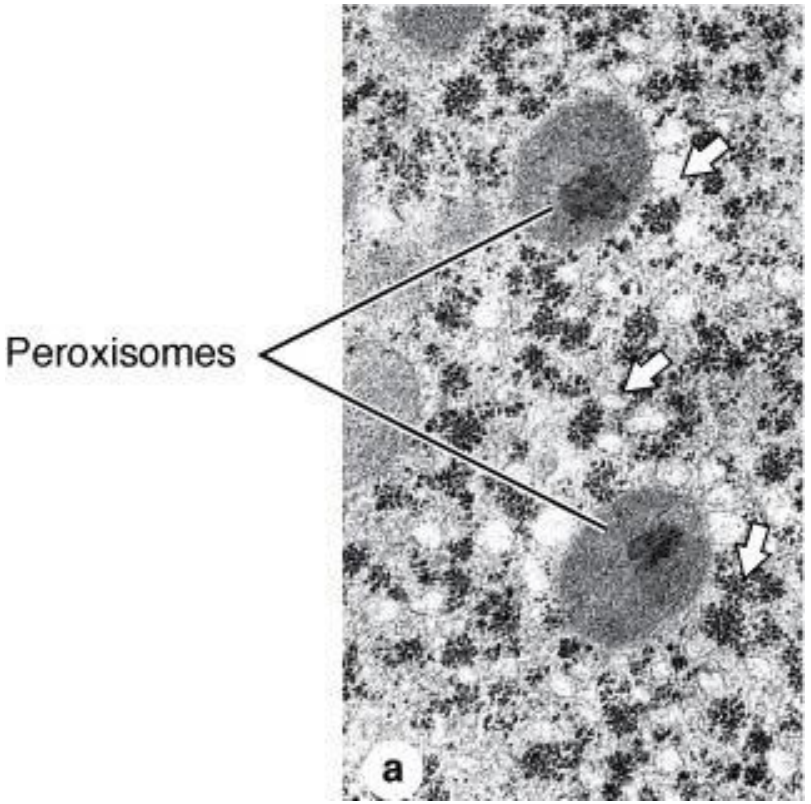
- Cytoplasmic protein complexes not associated with membrane.
- Is a cylindrical structure made of four rings, each composed of seven proteins.
- Presence of Ubiquitin protein.
- At each end is a regulatory particle contains ATPase.
- Function to degrade unneeded or damaged proteins by proteolysis.





Peroxisomes or Microbodies

- Are spherical membranous organelles.
- approximately 0.5 m in diameter.
- They utilize oxygen by oxidize specific substrates by removing hydrogen atoms then transferred to molecular oxygen (O2) .
- does not produce ATP and does not participate directly in cellular metabolism but contain enzymes involved in lipid metabolism.



The Cytoskeleton

Is a complex network of:

(1) microtubules.

(2) microfilaments (actin filaments.(

(3) intermediate filaments.

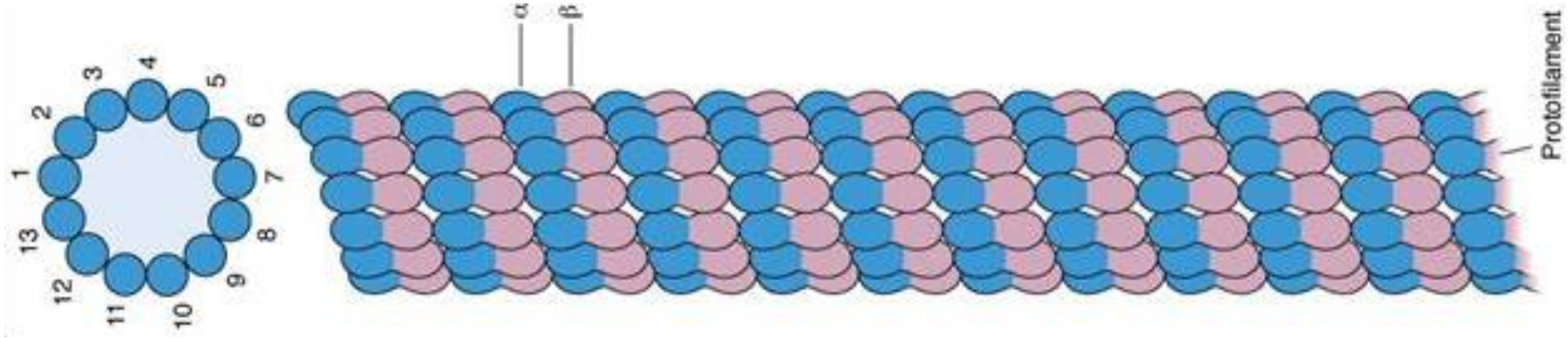
Functions:

- determine the shape of cells,
- helps transport of material within the cell.
- allow the movement of entire cells.

1. Microtubules

- Found in the cytoplasm as **cilia**, **flagella** or **centeriole**.
- outer diameter of 24 nm and a hollow lumen 14 nm wide.

composed of tubulin molecules are arranged to form 13 **protofilaments**



The Cytoskeleton,

*Microtubules **

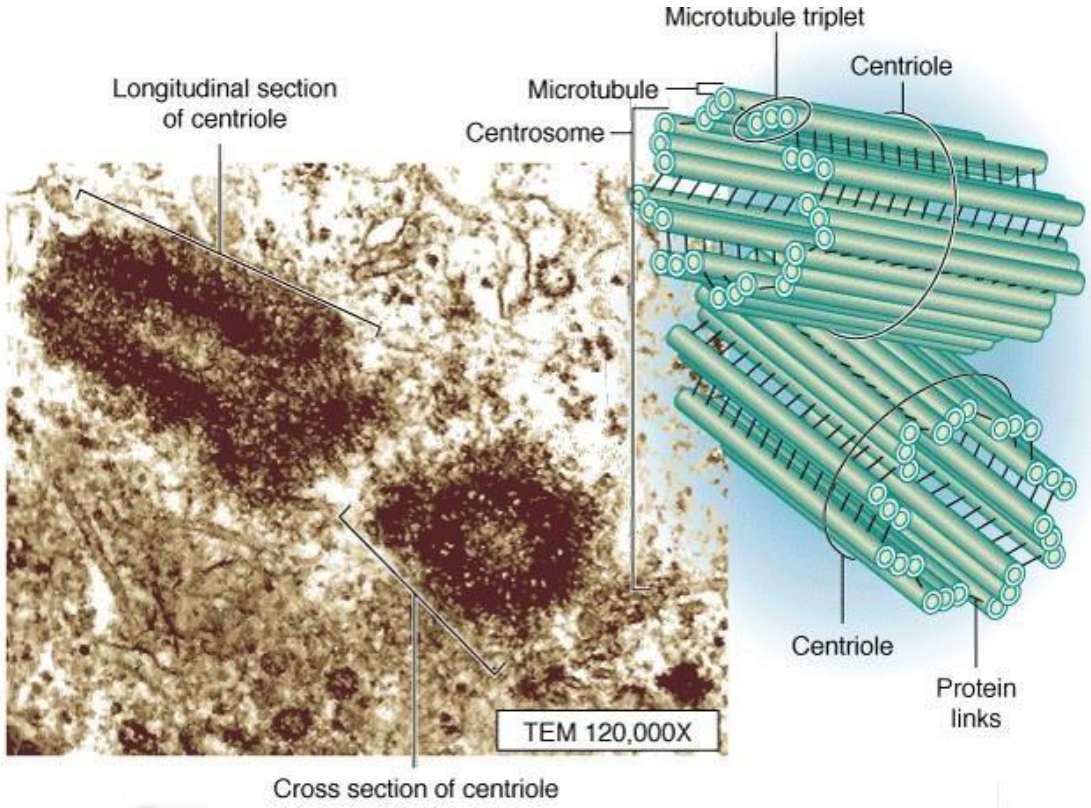
I. Centrioles

- Pair of cenerioles, forming a **centrosome,** are at right angles to each other.
- Wall is made of 9 triplets of microtubules, i.e. 27microtubules.

Functions:

- Essential for cell division.

Formation of cilia and flagella.

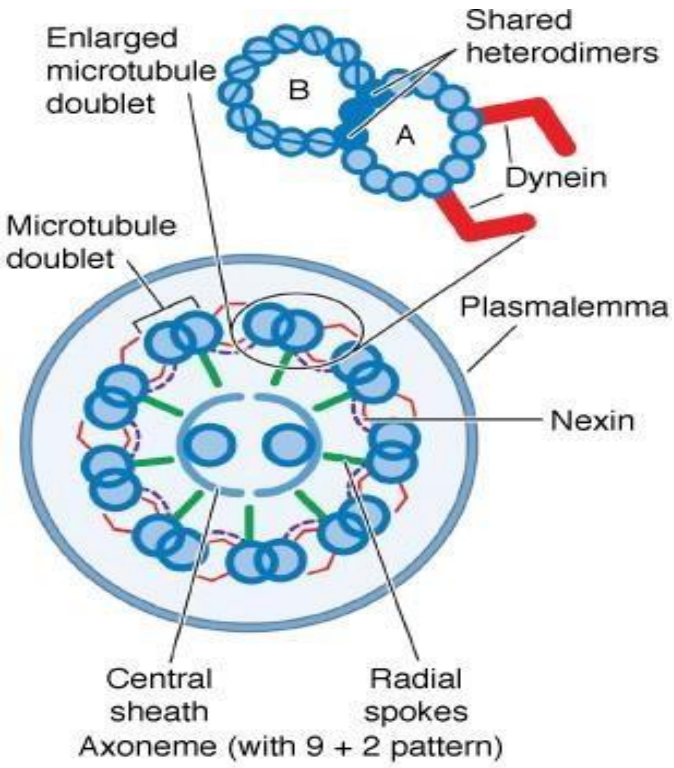


The Cytoskeleton, Microtubules

II.Cilia

- Are motile processes, covered by cell membrane.
- Hair-like striations on the free surface of some cells.
- With basal bodies.
- Cross section named **axoneme**.
- Each axoneme composed of 9 doublets and 2 central singlets of microtubules, i.e. 20 microtubules.
- doublets are linked together by proteins **nexins** and **dynin.**
- a **radial spoke** projecting toward the center.

Function: movement of particles or fluids on the free surface of the cell in one direction.



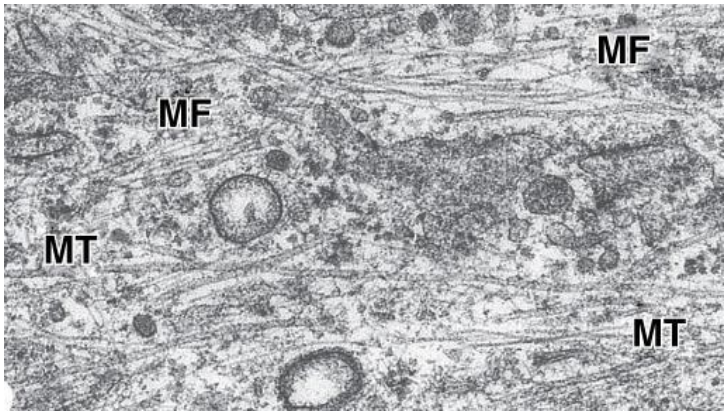
III.Flagella

- Longer and larger than cilia.
- Same structure as cilia.
- Form the tails of sperms.

Function: movement of the sperms.

2.Microfilaments (Actin Filaments)

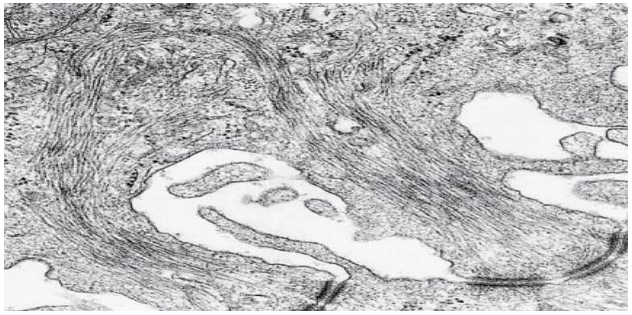
- Contraction in cells results from an interaction between **actin** and its associated protein**, myosin**.
- actin filaments (F-actin) composed of globulin protein
- forming globular **actin subunits** (G-actin(
- arranged as a **double-stranded helix**.
- **treadmilling**.is the movement balance of (G-actin.(



Forms of microfilaments (F-actin) in different cells:

1. In most cells,form a thin network just beneath the plasmalemma giving the cell shape.
2. in skeletal muscle, a stable arrange integrated with thick myosin filaments.
3. in mitotic cells, with myosin form a "purse-string" ring of filaments.
4. In crawling cells as parallel bundles called stress fibers.
5. In the cytoplasm named (cytoplasmic streaming.(

Intermediate Filaments

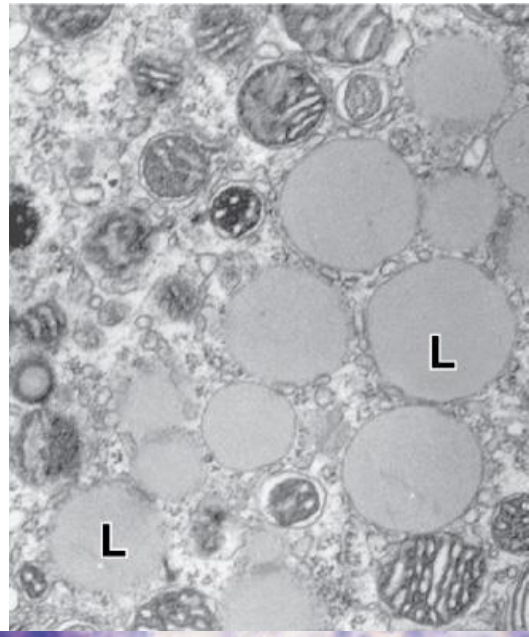


- Intermediate in size 10–12 nm diameter.
- Forms of intermediate filaments in different cells:

Filament Type	Cell Type	Examples
Keratins or Cytokeratins	Epithelium	Both keratinizing and nonkeratinizing epithelia
Vimentin	Mesenchymal Fibroblasts, cells	chondroblasts, macrophages , endothelial cells, vascular smooth muscle
Desmin	Muscle	Striated and smooth muscle (except) vascular smooth muscle
Glial fibrillary acidic proteins	Glial cells	Astrocytes
Neurofilaments	Neurons	Nerve cell body and processes

3.Inclusions

- Are not considered organelles.
- composed of accumulated metabolites or other substances.
- often transitory components of the cytoplasm.
- Nonmotile and with little or no metabolic activity.

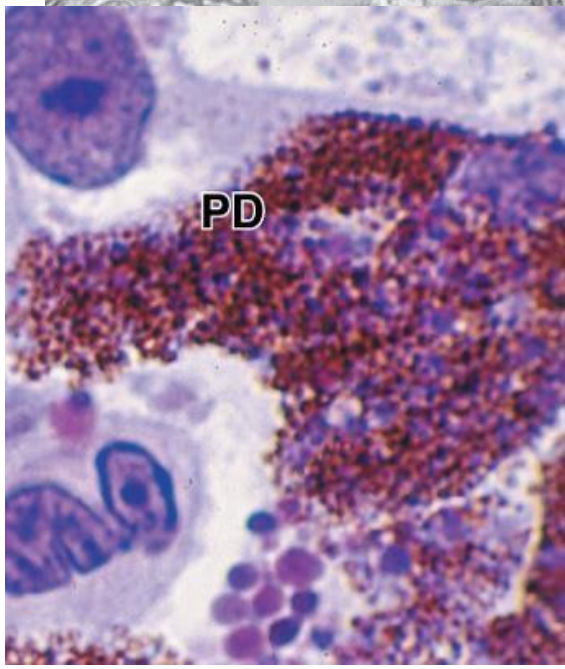


Types:

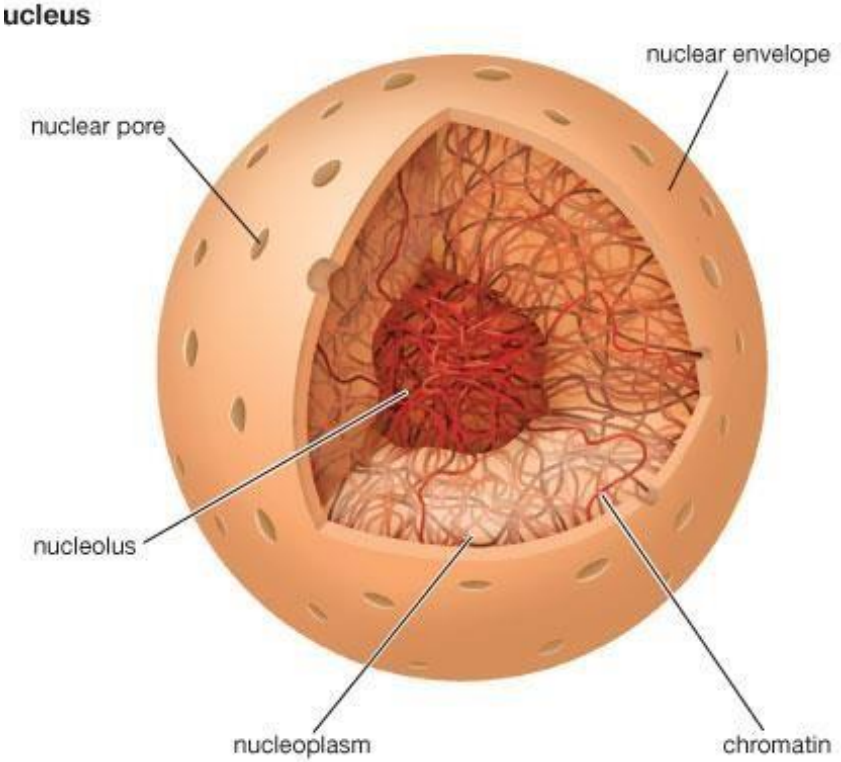
Fat droplets, accumulations of lipid molecules, in adipocytes (fat cells), adrenal cortex cells and liver cells.

Glycogen granules, aggregates of a carbohydrate polymer , in several cell types, mainly liver cells.

Lipofuscin granules, **pigmented** (golden-brown) bodies accumulate with age, e.g. in neurons, cardiac muscle.



The Cell Nucleus



- A rounded or oval structure, usually in the center of the cell.

Composed of;

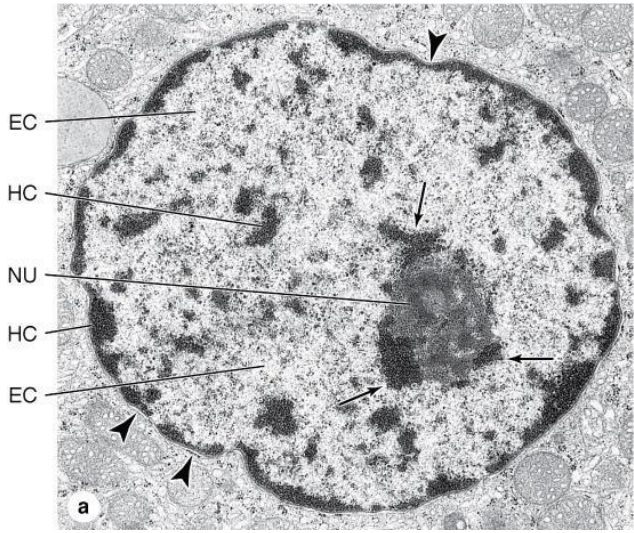
- Nucleolemma (nuclear envelope).
- Nucleoplasm.
- Nucleolus.
- Chromatin, chromosomes.
- Nuclear pores

Nucleus size and shape:

Size and morphology in normal tissue tend to be uniform:

- Liver cells (hepatocytes)are large active cells, have large, well-stained nuclei located in the center of the cytoplasm.
- In cancer cells often have irregular shapes, variable sizes, and atypical chromatin patterns.

The Cell Nucleus



Structure:

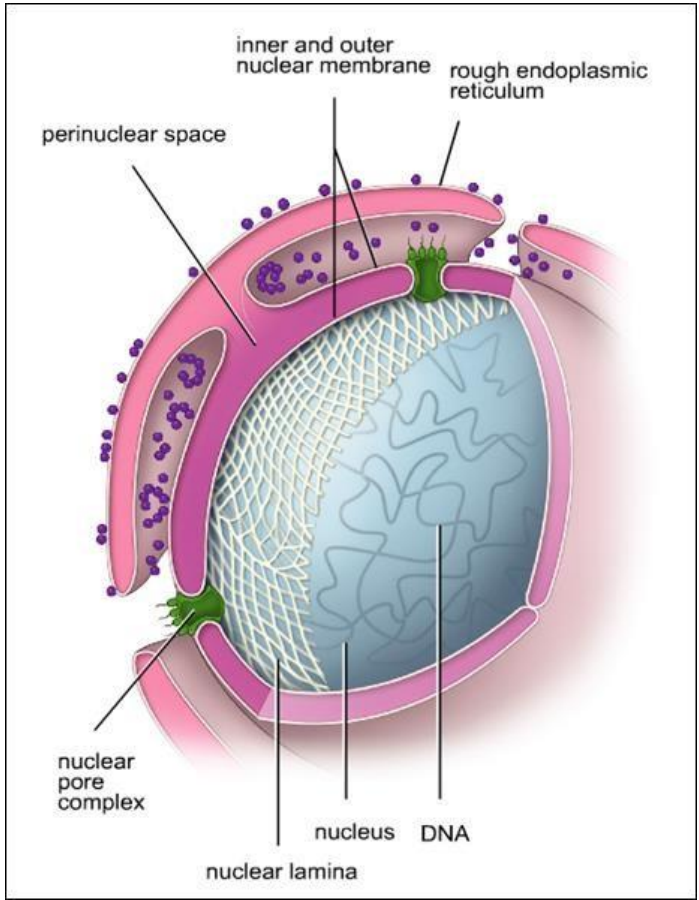
1.Nuclear Envelope:

- Consists of two membranes, separated by a narrow (30–50 nm) **perinuclear space(Isterna):**

a. The outer layer, Polyribosomes are attached and is continuous with endoplasmic reticulum.

- **The inner layer**, attached to a layer of fibrous proteins called the **nuclear lamina** composed of intermediate filaments and lamins A,B,and C proteins.
- With **nuclear pore complexes (NPCs) ,** which regulate the transport between nucleus and cytoplasm.

Each cell contains 3000–4000 pore complexes, each composed of subunits with 30 different NPC proteins or **nucleoporins**



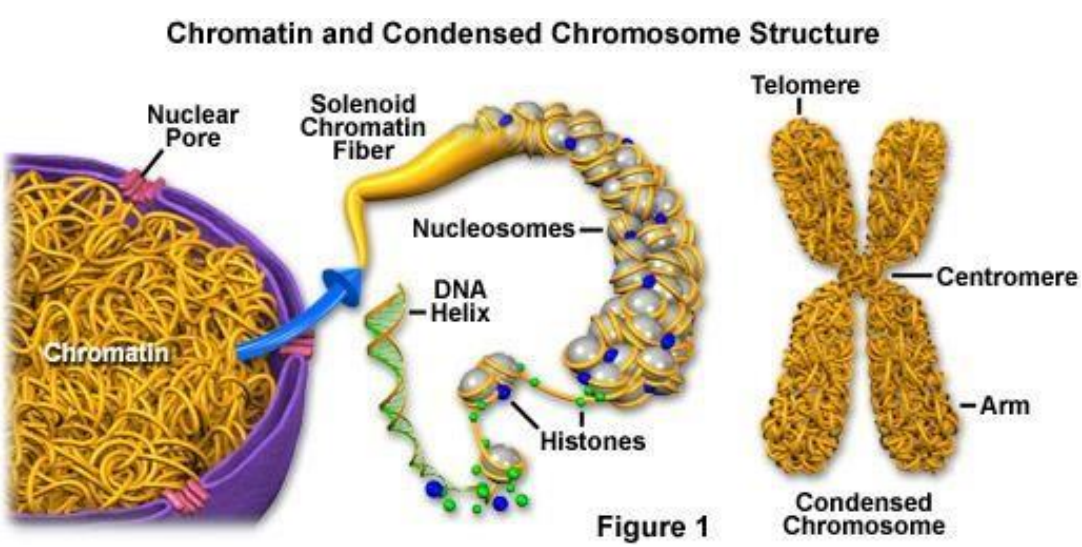
The Cell Nucleus

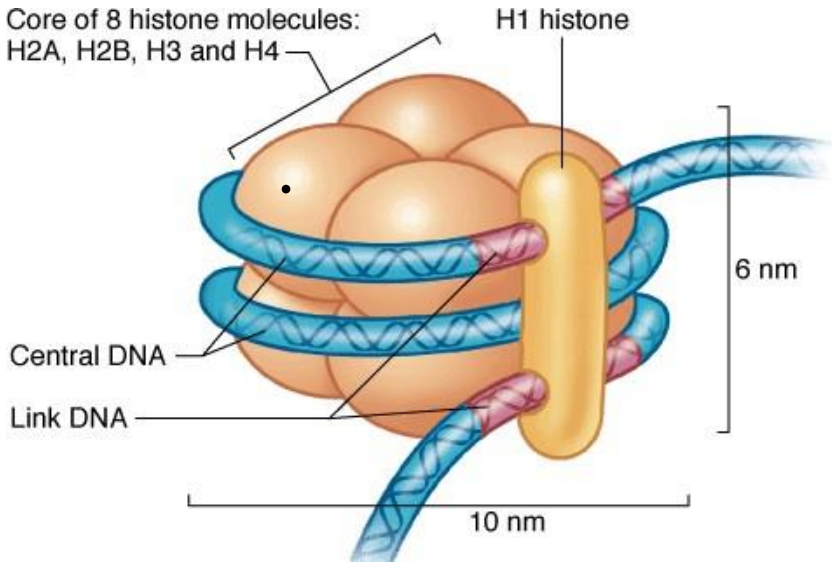
2. Chromatin,

composed of :

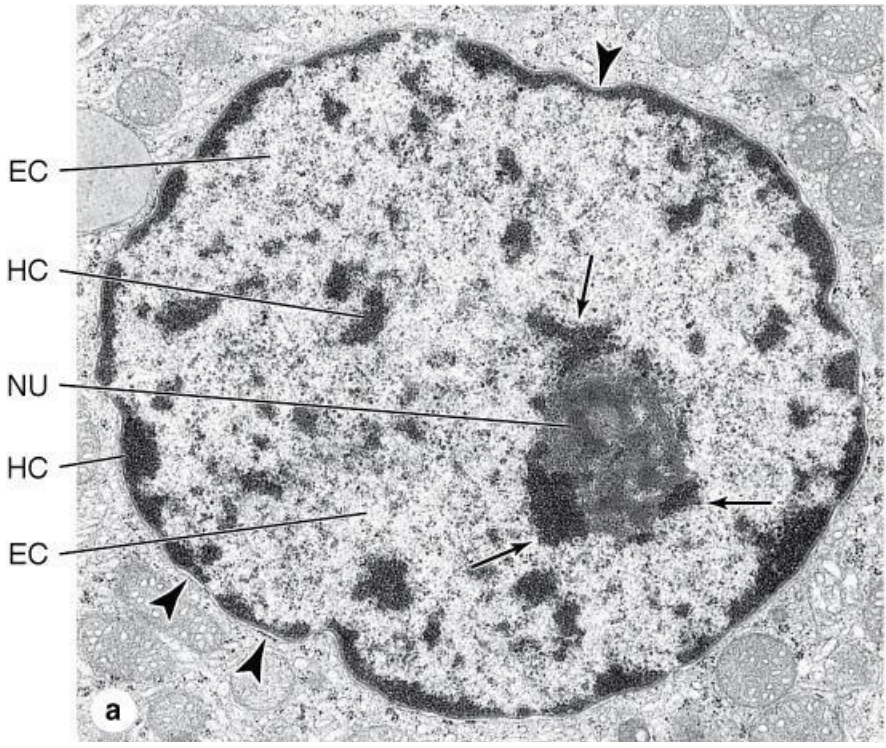
1. coiled strands of DNA bound to:
2. basic proteins called **histones**

- The structural unit of chromatin + histones is called **nucleosome.**
- **Nucleosome,** has eight small histones (two copies each of histones H2A, H2B, H3, and H4), surrounded by DNA with about 150 base pairs, each nucleosome also has a larger linker histone (H1).





The Cell Nucleus



Two types of chromatin:

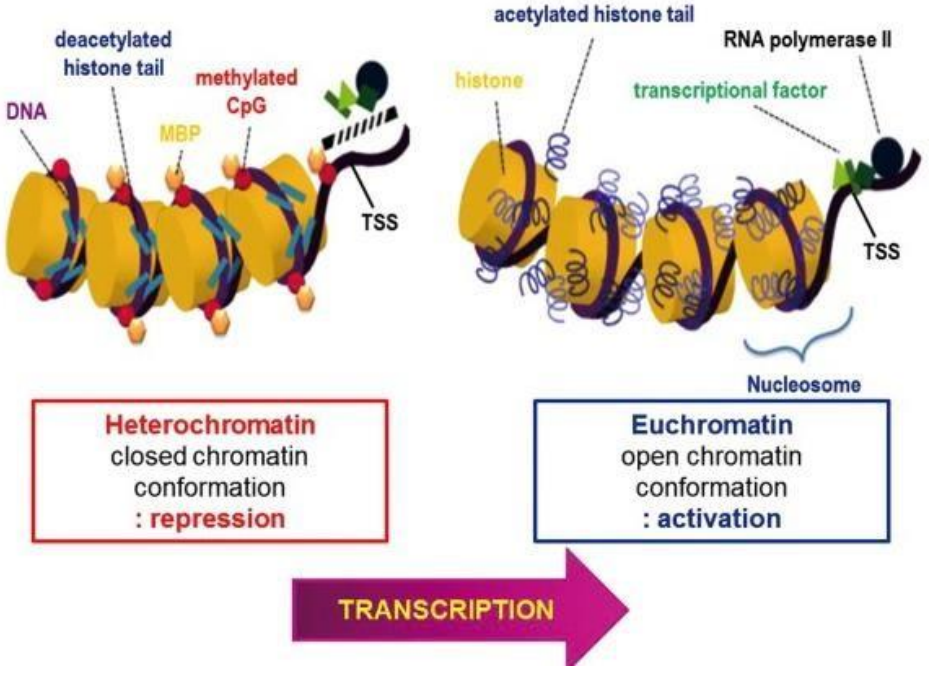
which reflect the degree of chromosomal condensation

I. Heterochromatin (HC), non-active

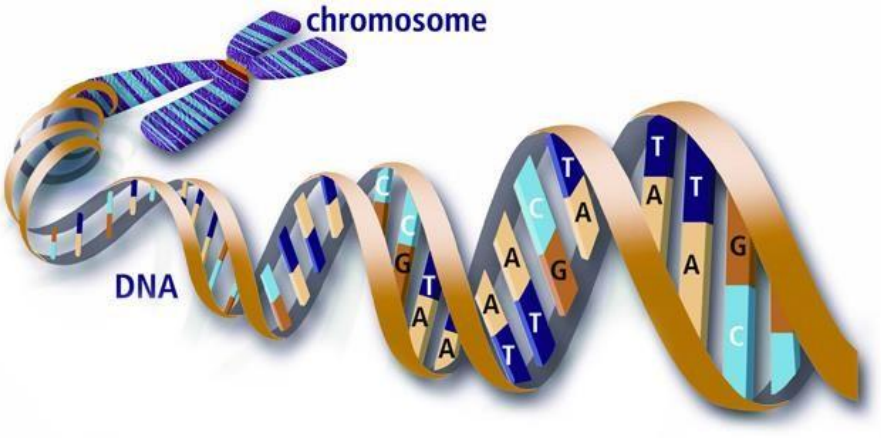
- (condensed chromatin).
- repressive regulation of transcription.
- by EM appears as dense granules.
- By LM as basophilic clumps.

II. Euchromatin(EC), active.

- is loose, less coiled.
- active regulation of transcription.
- By EM appears as finely granular.
- By LM as lightly stained basophilic.



The Cell Nucleus, Chromosome



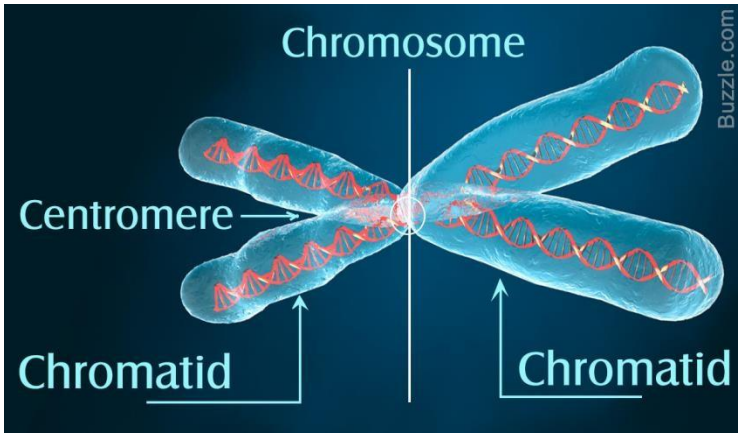
Chromosome

- All cells store genetic information in chromosomes.

Structure

1. Single, long, double-stranded fiber of DNA.
2. Chromatin proteins.

Shape present as two chromatids held together at a narrow point called the **centromere**.



Sex chromatin

- is one of the two X chromosomes present in female cells, called **barr body**.
- genetically inactive.
- No sex chromatin in males.

The Cell Nucleus,

Chromosome

Sex chromosome or heterochromosome

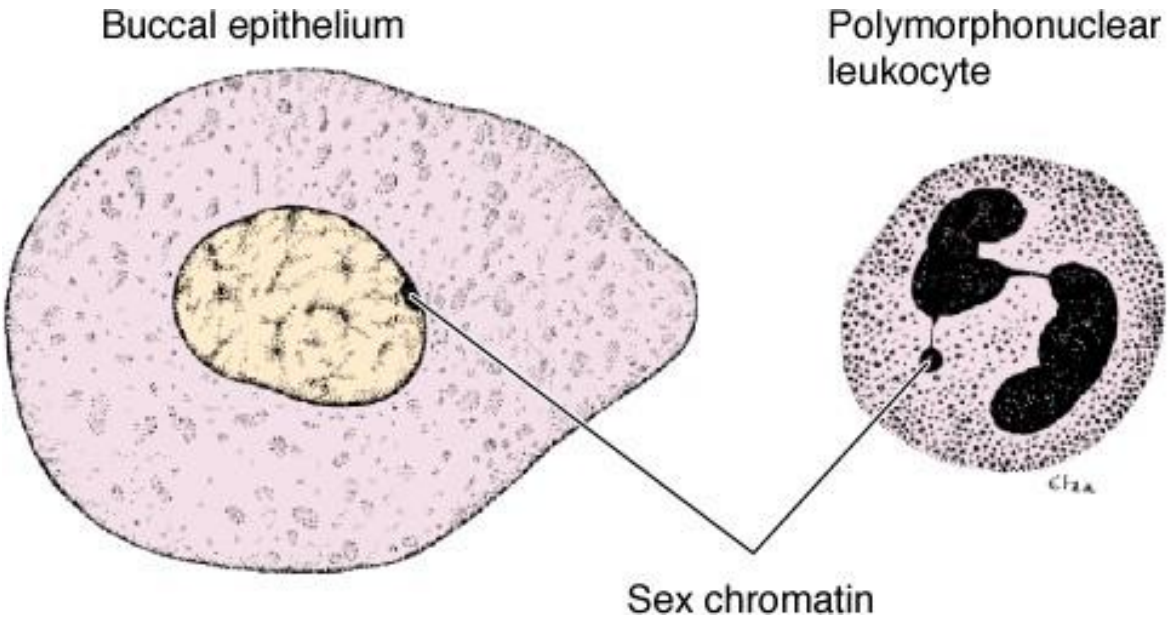
- A pair of **chromosomes** that determine whether an individual is male or female.
- Are designated as X and Y.
- In humans the **sex chromosomes** comprise one pair of the total of 23 pairs of **chromosomes**

- Sex chromosome is tightly coiled and visible in mitotic cycles, whereas the other **X chromosome** is uncoiled and not visible.
- The male cell has one uncoiled X chromosome and one Y chromosome;

The Cell Nucleus,

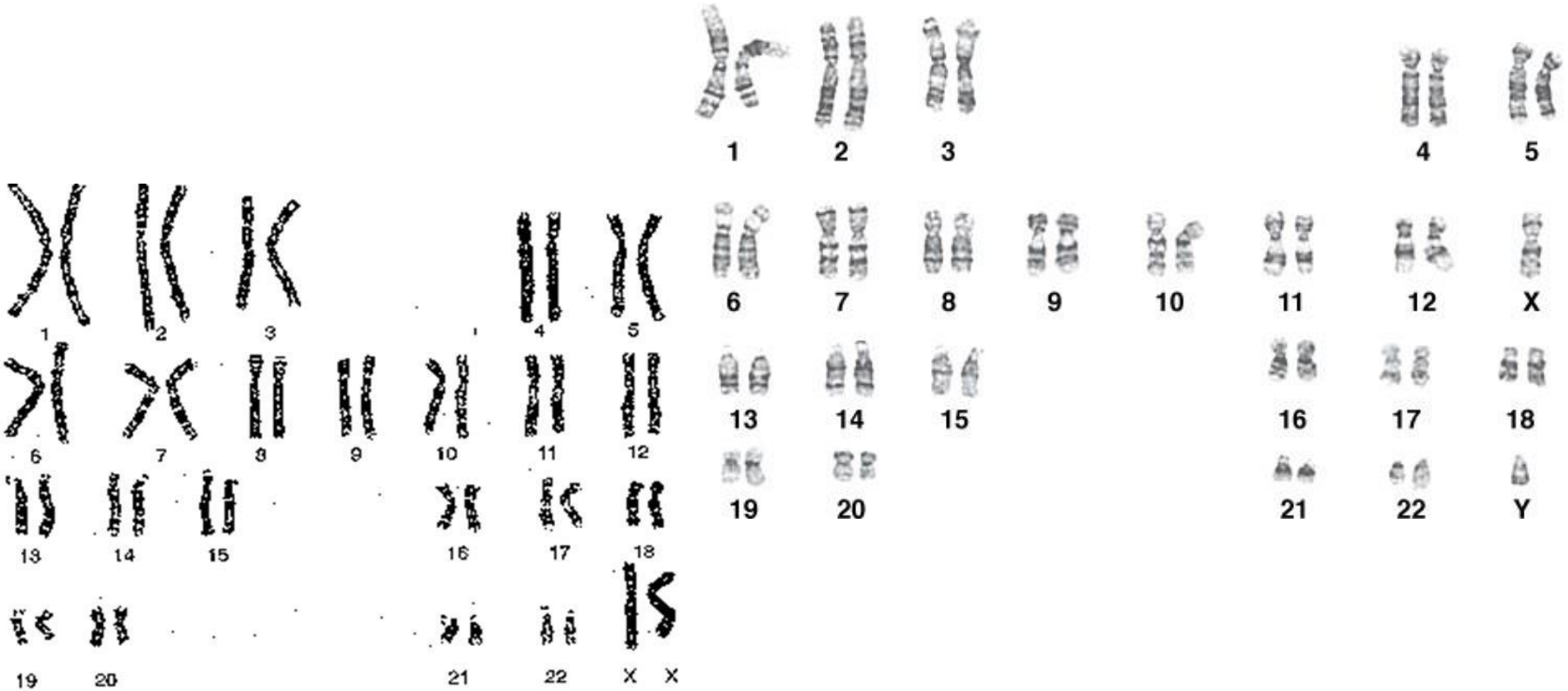
Chromosome

- Sex chromatin can be seen in female epithelial cells lining the mouth and neutrophils.
- in the **oral (Buccal) epithelial cells**, sex chromatin appears as a small granule adhering to the nuclear envelope. These cells are frequently used to study sex chromatin or as a source of nucleated cells for DNA analyses.
- In **neutrophils**, chromatin shape as a drumstick projecting from the nucleus.



Karyotype

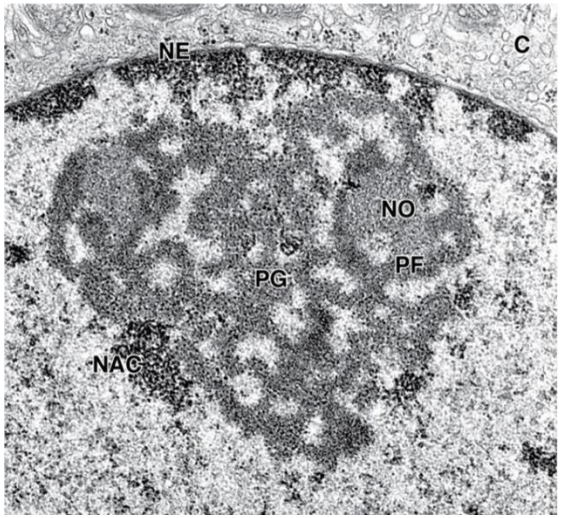
Karyotype, chromosomes are photographed and arranged in bands under the light microscope

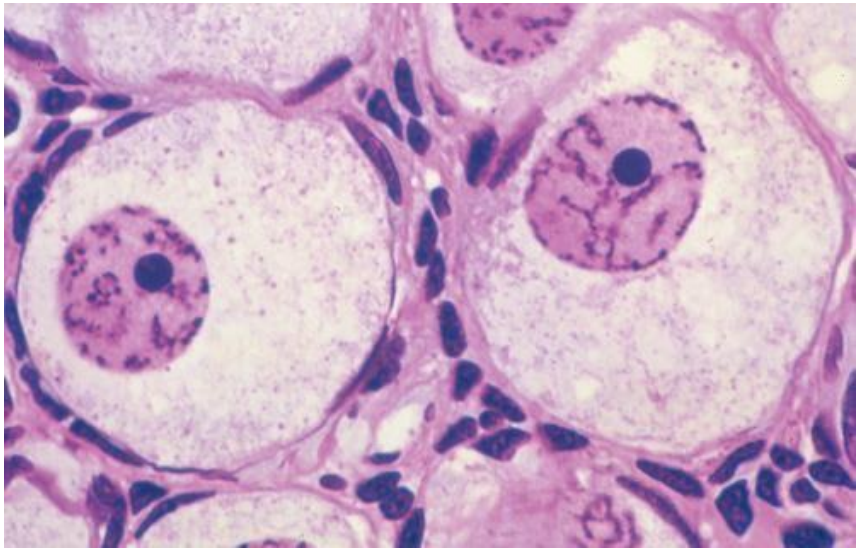


The Cell Nucleus, *Nucleolus*

.3 Nucleolus

- Spherical, present in the nuclei.
- active in protein synthesis.
- Composed of proteins and ribosomal RNA.
- highly basophilic, due to the presence of densely concentrated rRNA which is transcribed, processed, and complexed into ribosomes in the nucleoplasm.





The Cell Nucleus, *Nucleolus*

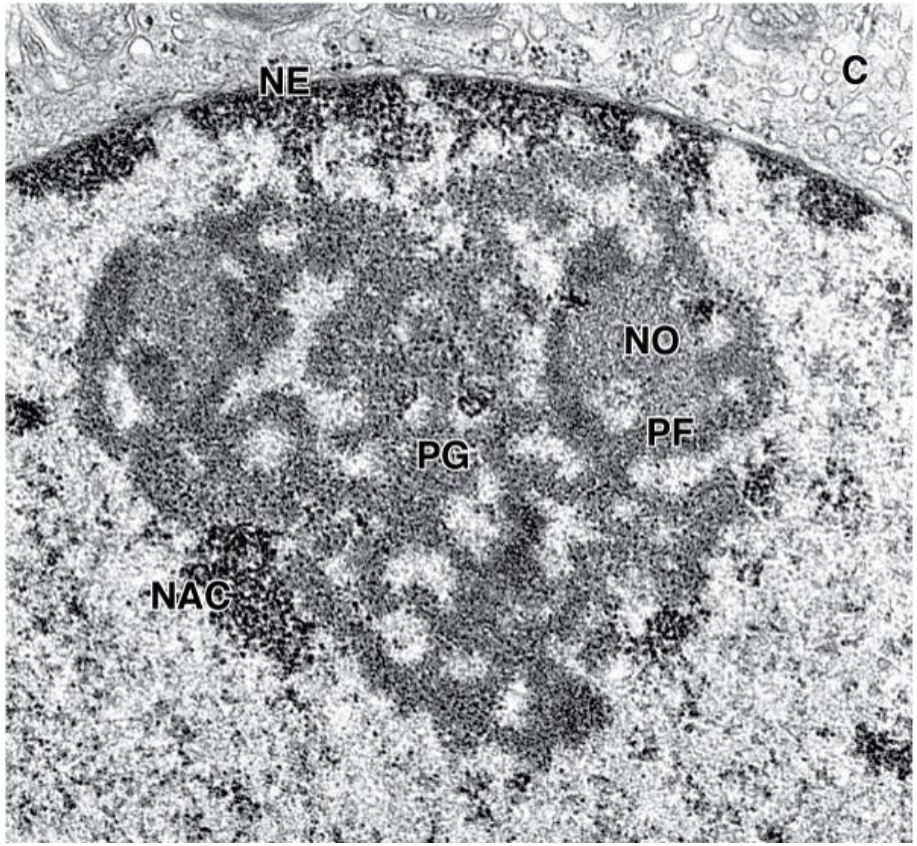
- By EM, appears regions with different staining.

Structure: Regions of nucleoli:

1. **Nucleolar organizer (NO) DNA**, sequences of bases coding for rRNA.
2. **Pars fibrosa (PF)**, are ribonucleoprotein fibers, consists of primary rRNA transcripts.

3.Pars granulose (PG), represent maturing ribosomes

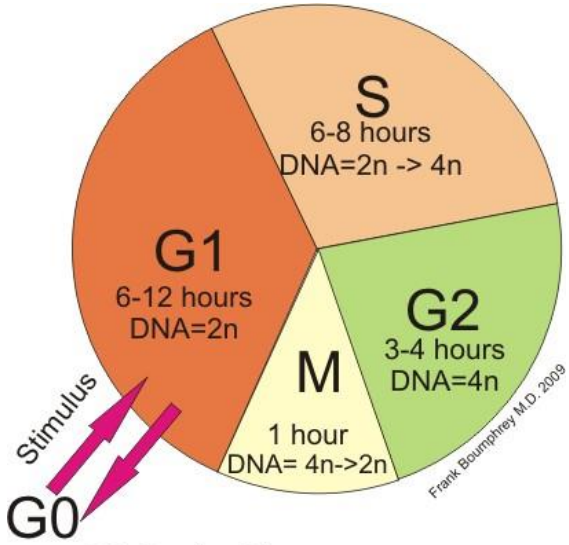
4.Nucleolus-associated chromatin (NAC), heterochromatin attached to the nucleolus ,its functional is unknown



❑ *Nuclear matrix*

- Fills the space between chromatin and nucleoli.

The Cell Cycle



G0: Resting Phase
G1: Growth & Metabolism
S: DNA Replication
G2: Growth of Structural Elements
M: Mitosis

- The cell cycle has four distinct phases:

1. **Mitosis** (cell division)
2. **Three interphase** periods: –(normal cell activity).

Interphase, are three periods:

1) **G_1** (primary growth), the longest.

- the gap between mitosis and DNA replication.
- there is active synthesis of RNA and proteins that control the cell cycle,
- the cell volume which reduced to one-half by mitosis, grows to its previous size.
- **G0 phase** or resting phase(R), the cell is neither dividing.

2) **S** (the period of DNA synthesis, replication) synthesis of DNA and histones.

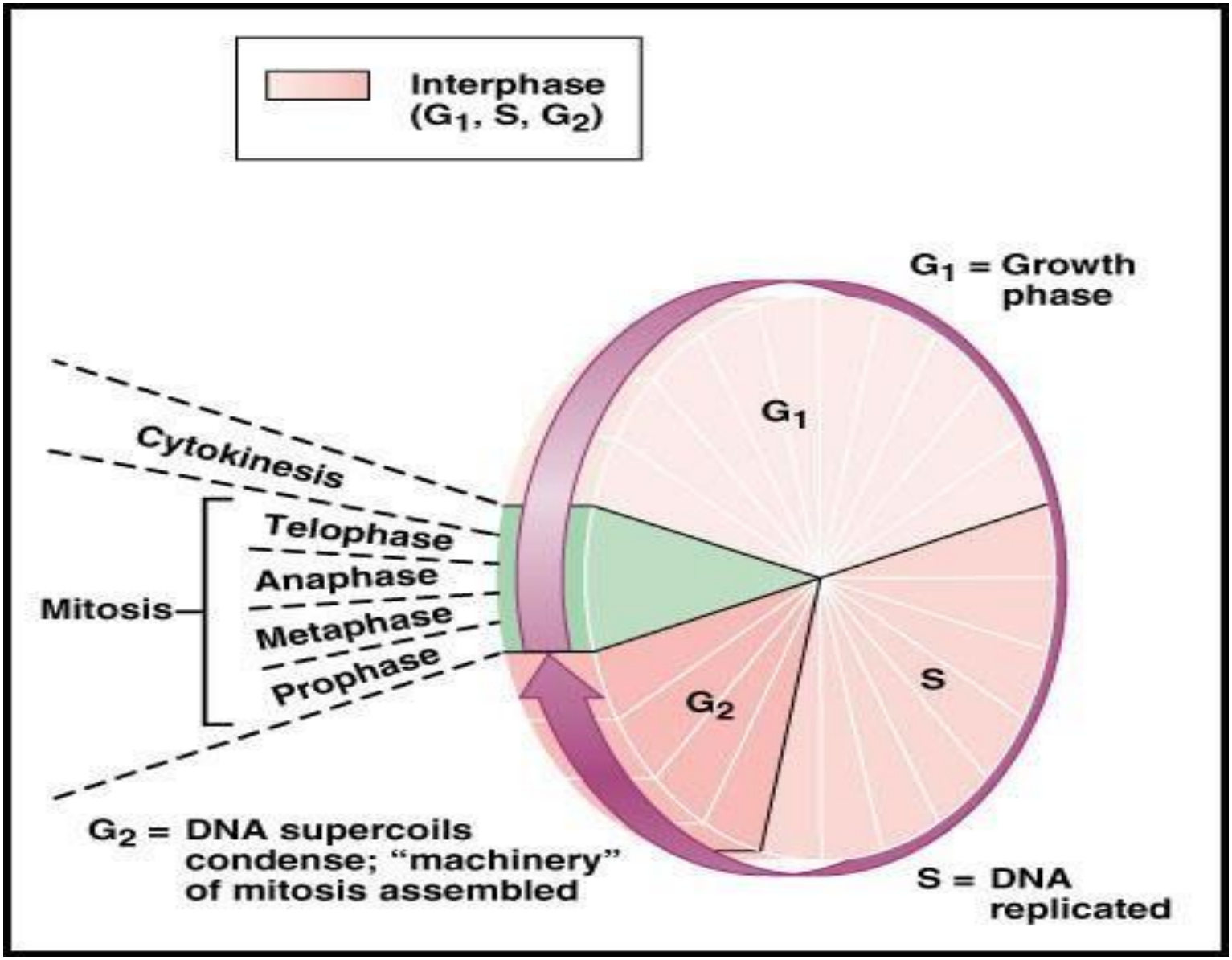
- beginning of centrosome duplication.

3) **G_2** (secondary growth),

- the gap between DNA duplication and the next mitosis.

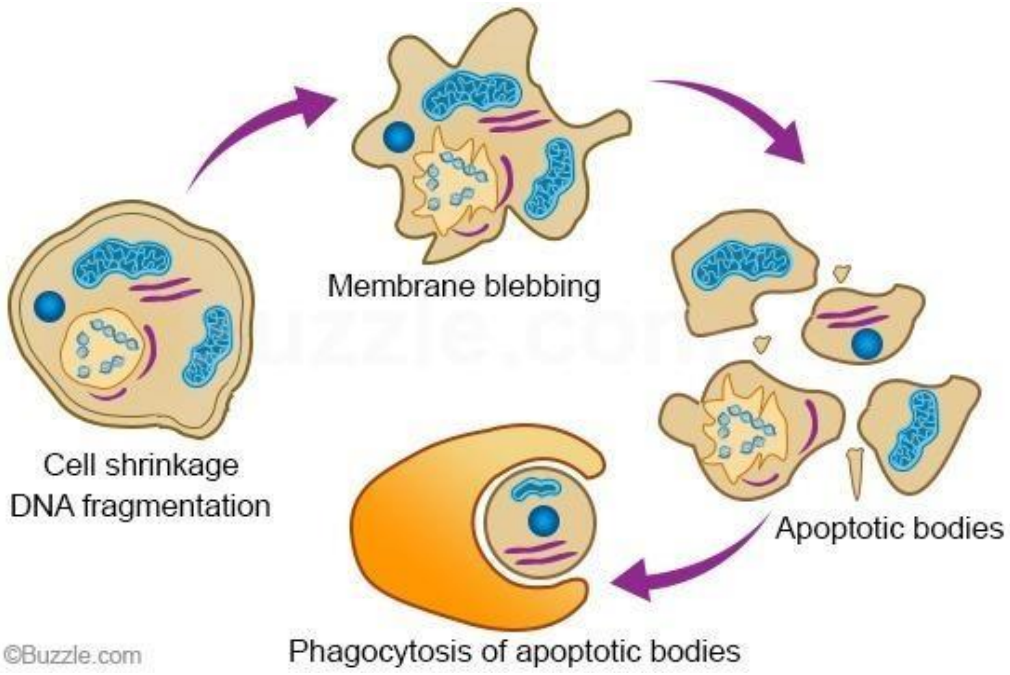
Short period, preparation for mitosis

The Cell Cycle



Apoptosis

- Is the process of programmed cell death.
- occurs rapidly and produces **apoptotic bodies**, which quickly undergo phagocytosis by macrophages.
- It is important for eliminating cells which is blocked by lack of nutrients, or by damage.



- the affected cells are removed without a trace.

Examples of sites of apoptosis:

- T lymphocytes in thymus react against self-antigens
- The mature ovary.
- In developing embryos, (morphogenesis,(formation of the central nervous system

Thank you
Dr.Ali Ashgar

General Histology (Theory) Epithelial Tissues

Medical laboratories technics department

2nd stage 2023-2024

Dr. Ali Ashgar

Epithelial Tissues

Despite its complexity, the organs of the human body are composed of only four basic tissue types:1-epithelial, 2-connective,3- muscular, and4- nervous tissues. Each tissue is an assemblage of similarly specialized cells united in performing a specific function. The basic tissues, each containing 1-extracellular matrix (ECM) 2-cells, associate with one another in the variable proportions and morphologies characteristic of each organ. The main features of the basic tissue types are summarized in the Table.

TABLE **Main characteristics of the four basic types of tissues.**

Tissue	Cells	Extracellular Matrix	Main Functions
Epithelial	Aggregated polyhedral cells	Small amount	Lining of surface or body cavities; glandular secretion
Connective	Several types of fixed and wandering cells	Abundant amount	Support and protection of tissues/organs
Muscle	Elongated contractile cells	Moderate amount	Strong contraction; body movements
Nervous	Elongated cells with extremely fine processes	Very small amount	Transmission of nerve impulses

- 1- Epithelial tissue is present in two forms: as (1) sheets of contiguous cells (epithelia) that cover the body on its external surface and line the body on its internal surface and (2) glands, which originate from invaginated epithelial cells.

- Epithelia are derived from all three embryonic germ layers, although most of the epithelia are derived from ectoderm and endoderm. The ectoderm gives rise to the oral and nasal mucosae, the cornea, the epidermis of skin, and the glands of the skin and the mammary glands. The liver, pancreas, and lining of the respiratory and gastrointestinal tract are derived from the endoderm. The uriniferous tubules of the kidney, the lining of the male and female reproductive systems, the endothelial lining of the circulatory system, and the mesothelium of the body cavities develop from the mesodermal germ layer.

Epithelial tissues have numerous functions

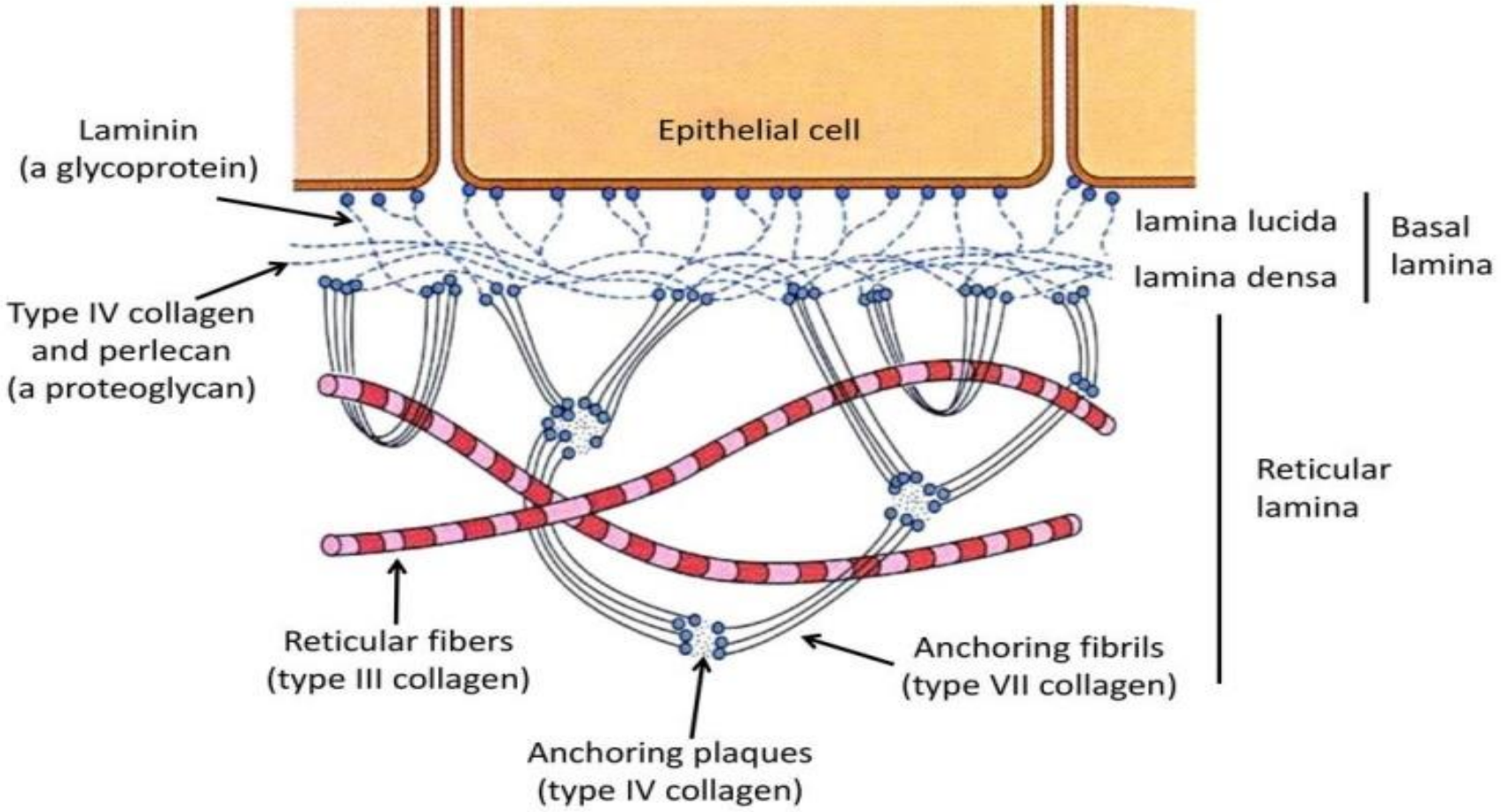
- **Protection** of underlying tissues of the body from abrasion and injury
- **Transcellular transport** of molecules across epithelial layers
- **Secretion** of mucus precursor, hormones, enzymes, and other molecules from various glands
- **Absorption** of material from a lumen (i.e., intestinal tract or certain kidney tubules)
- Control of movement of materials between body compartments via **selective permeability** of intercellular junctions between epithelial cells
- **Detection** of **sensations** via taste buds, retina of the eye, and specialized hair cells in the ear

- The sheets of contiguous cells in the epithelium are tightly bound together by junctional complexes. Epithelia display little extracellular space and little extracellular matrix. Epithelium is separated from the underlying connective tissue by an extracellular matrix, the basement membrane, composed of the basal lamina and the lamina reticularis synthesized by the epithelial cells and cells of the connective tissue. Because epithelium is avascular, the adjacent supporting connective tissue through its capillary beds supplies nourishment and oxygen via diffusion through the basement membrane

Basement Membrane

- The **basement membrane** of all epithelia is a thin extracellular layer of specialized proteins, usually having two parts: a basal lamina and a more fibrous reticular lamina.
- **The basal lamina** is a thin meshwork of type IV collagen and laminin produced by the epithelial cells.
- **The reticular lamina** contains type III collagen and anchoring fibrils of VII collagen, all secreted by cells of the immediately adjacent connective tissue
- Together, these components attach epithelia to connective tissue, regulate (filter) substances passing from connective tissue into epithelia, provide a guide or scaffold during tissue regeneration after injury, and compartmentalize epithelial cells from other tissues.

Components of basement membrane



Classification (types)of Epithelial Membranes

- **Epithelial membranes are classified according to the 1- number of cell layers between the basement membrane and the free surface and by the2- morphology of the surface most epithelial cells (Table). If the membrane is composed of a single layer of cells, it is called *simple epithelium*; if it is composed of more than one cell layer, it is called *stratified epithelium* The morphology of the cells may be squamous (flat), cuboidal, or columnar when viewed in sections taken perpendicular to the basement membrane. Stratified epithelia are classified by the morphology of the cells in their superficial layer only.**

Classification of Epithelia

Type	Shape of Surface Cells	Sample Locations	Functions
Simple			
Simple squamous	Flattened	*Lining:* pulmonary alveoli, loop of Henle, parietal layer of Bowman capsule, inner and middle ear, blood and lymphatic vessels, pleural and peritoneal cavities	Limiting membrane, fluid transport, gaseous exchange, lubrication, reducing friction (thus aiding movement of viscera), lining membrane
Simple cuboidal	Cuboidal	Ducts of many glands, covering of ovary, form kidney tubules	Secretion, absorption, protection
Simple columnar	Columnar	*Lining:* oviducts, ductuli efferentes of testis, uterus, small bronchi, much of digestive tract, gallbladder, and large ducts of some glands	Transportation, absorption, secretion, protection
Pseudostratified	All cells rest on basal lamina but not all reach epithelial surface; surface cells are columnar	*Lining:* most of trachea, primary bronchi, epididymis and ductus deferens, auditory tube, part of tympanic cavity, nasal cavity, lacrimal sac, male urethra, large excretory ducts	Secretion, absorption lubrication, protection, transportation
Stratified			
Stratified squamous (nonkeratinized)	Flattened (with nuclei)	*Lining:* mouth, epiglottis, esophagus, vocal folds, vagina	Protection, secretion
Stratified squamous (keratinized)	Flattened (without nuclei)	Epidermis of skin	Protection
Stratified cuboidal	Cuboidal	*Lining:* ducts of sweat glands	Absorption, secretion
Stratified columnar	Columnar	Conjunctiva of eye, some large excretory ducts, portions of male urethra	Secretion, absorption, protection
Transitional	Dome-shaped (relaxed), flattened (distended)	*Lining:* urinary tract from renal calyces to urethra	Protection, distensible

1. **Simple squamous epithelium** is composed of a single layer of tightly packed, thin, or low-profile polygonal cells. When viewed from the surface, the epithelial sheet looks much like a tile floor with a centrally placed bulging nucleus in each cell . Viewed in section, however, only some cells display nuclei because the plane of section frequently does not encounter the nucleus. Simple squamous epithelia line pulmonary alveoli, compose the loop of Henle and the parietal layer of Bowman capsule in the kidney, and form the endothelial lining of blood and lymph vessels as well as the mesothelium of the pleural, pericardial, and peritoneal cavities

2-simple cuboidal epithelium A single layer of polygon-shaped cells constitutes simple cuboidal epithelium. When viewed in a section cut perpendicular to the surface, the cells present a square profile with a centrally placed round nucleus. Simple cuboidal epithelia make up the ducts of many glands of the body, form the covering of the ovary, and compose many kidney tubules.

3- simple columnar epithelium

The cells of simple columnar epithelium appear much like those of simple cuboidal epithelium in a surface view; when viewed in longitudinal section, however, they are tall, rectangular cells whose ovoid nuclei are usually located at the same level in the basal half of the cell .

Simple columnar epithelium lines much of the digestive tract, gallbladder, and large ducts of glands. Simple columnar epithelium may exhibit a striated border, or microvilli (narrow, finger-like cytoplasmic processes), projecting from the apical surface of the cells. The simple columnar epithelium that lines the uterus, oviducts, ductuli efferentes, and small bronchi is ciliated. In these organs, cilia (hair like structures) project from the apical surface of the columnar cells into the lumen

4- pseudostratified columnar epithelium

As the name implies, pseudostratified columnar epithelium appears to be stratified, but it is actually composed of a single layer of cells. All of the cells in pseudostratified columnar epithelium are in contact with the basal lamina, but only some cells reach the surface of the epithelium Cells not extending to the surface usually have a broad base and become narrow at their apical end. Taller cells reach the surface and possess a narrow base in contact with the basal lamina and a broadened apical surface. Because the cells of this epithelium are of different heights, their nuclei are located at different levels, giving the impression of a stratified epithelium, even though it is composed of a single layer of cells. Pseudostratified columnar epithelium is found in the male urethra, epididymis, and larger excretory ducts of glands .

The most widespread type of pseudostratified columnar epithelium is ciliated, having cilia on the apical surface of the cells that reach the epithelial surface. Pseudostratified ciliated columnar epithelium is found lining most of the trachea and primary bronchi, the auditory tube, part of the tympanic cavity, the nasal cavity, and the lacrimal sac.

Stratified Epithelium

1-Stratified squamous epithelium

Stratified squamous (nonkeratinized) epithelium is thick; because it is composed of several layers of cells only the deepest layer is in contact with the basal lamina. The most basal (deepest) cells of this epithelium are cuboidal in shape, those located in the middle of the epithelium are polymorphous, and the cells composing the free surface of the epithelium are flattened (squamous)—Because the surface cells are nucleated, this epithelium is called nonkeratinized. It is usually wet and is found lining the mouth, oral pharynx, esophagus, true vocal folds, and vagina.

Stratified squamous (keratinized) epithelium is similar to stratified squamous (nonkeratinized) epithelium, except that the superficial layers of the epithelium are composed of dead cells whose nuclei and cytoplasm have been replaced with keratin .This epithelium constitutes the epidermis of skin, a tough layer that resists friction and is impermeable to water. It should be noted that there is another category of stratified squamous epithelium, namely stratified squamous parakeratinized epithelium. This epithelium is similar to stratified squamous keratinized; however, many of its surface-most cells retain their nuclei, though they are pyknotic. Thus, its degree of keratinization of this epithelium is more than that of nonkeratinized and less than that of keratinized stratified squamous epithelium. The epithelium of both the hard palate and gingiva are stratified squamous parakeratinized.

2- Stratified Cuboidal Epithelium

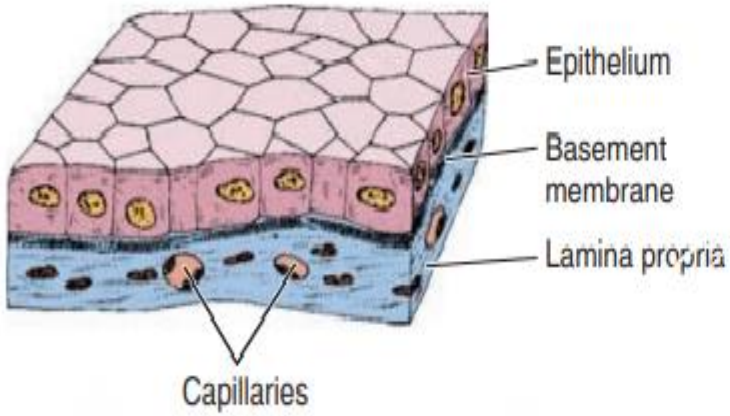
Stratified cuboidal epithelium, which contains only two layers of cuboidal cells, lines the ducts of sweat glands .

3- Stratified columnar epithelium is composed of a low polyhedral to cuboidal deeper layer in contact with the basal lamina and a superficial layer of columnar cells. This epithelium is found only in a few places in the body, namely, the conjunctiva of the eye, some large excretory ducts, and regions of the male urethra.

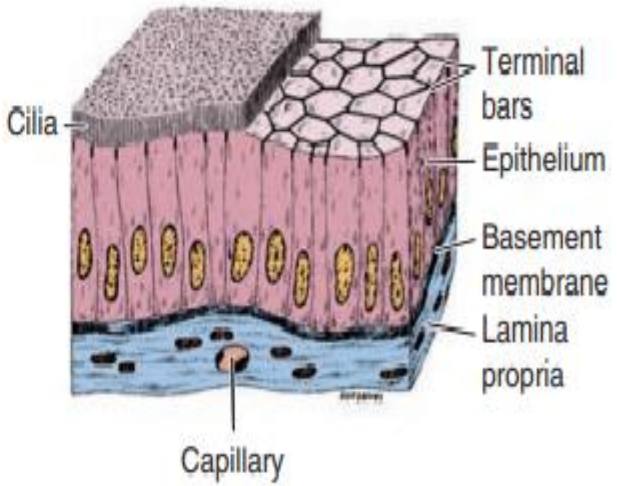
4-Transitional epithelium received its name because it was erroneously believed to be in transition between stratified columnar and stratified squamous epithelia. This epithelium is now known to be a distinct type located exclusively in the urinary system, where it lines the urinary tract from the renal calyces to the urethra. Transitional epithelium is composed of many layers of cells; those located basally are either low columnar or cuboidal cells.

Polyhedral cells compose several layers above the basal cells. The most superficial cells f the empty bladder are large, are occasionally binucleated, and exhibit rounded dome tops that bulge into the lumen These dome-shaped cells become flattened, and the epithelium becomes thinner when the bladder is distended with urine

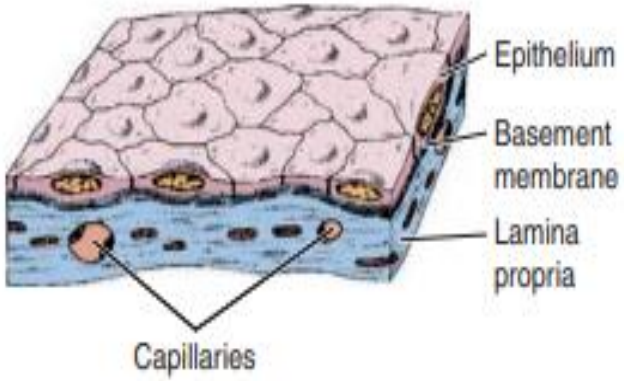
Simple cuboidal epithelium.



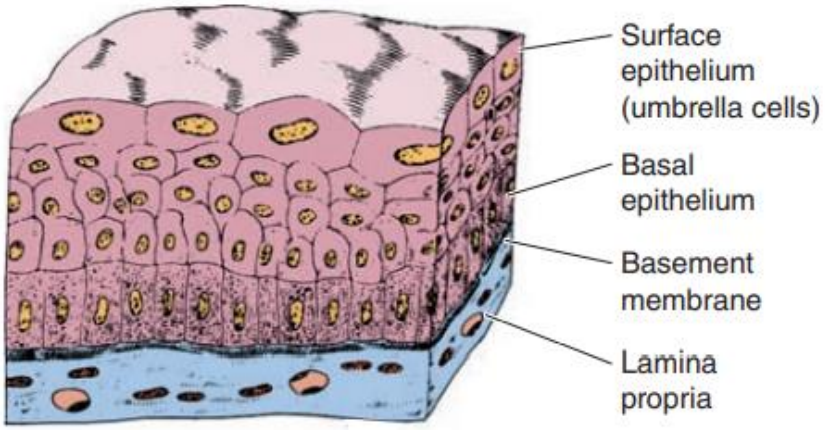
Simple columnar epithelium.



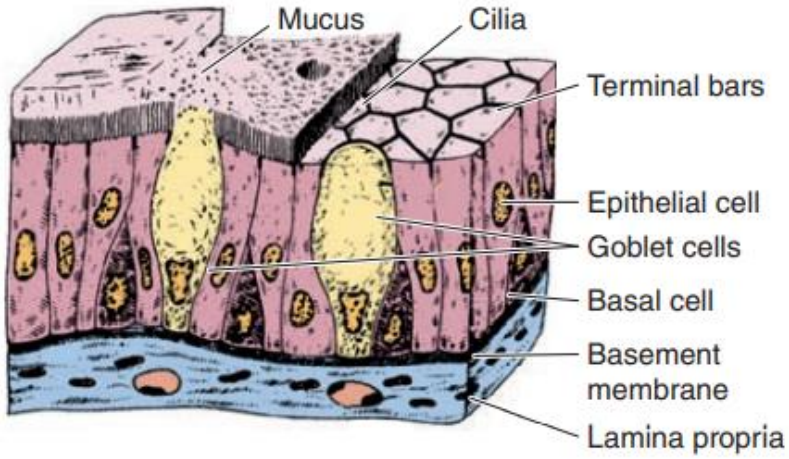
Simple squamous epithelium.



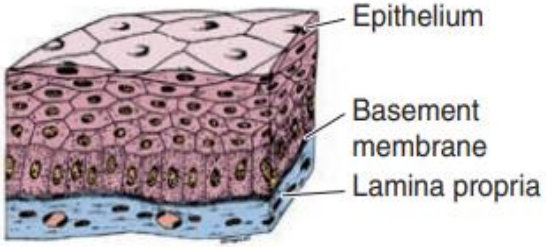
Transitional epithelium or urothelium.



Pseudostratified epithelium.



stratified squamous epithelium



Intercellular Adhesion & Other Junctions

Epithelial cells adhere strongly to neighboring cells and basal laminae, particularly in epithelia subject to friction or other mechanical forces. As shown in Figure and summarized in(Table), lateral surfaces of epithelial cells have complexes of several specialized intercellular junctions with different functions:

- Tight or occluding junctions form a seal between adjacent cells.
- Adherent or anchoring junctions are sites of strong cell adhesion.
- Gap junctions are channels for communication between adjacent cells.

In many epithelia, these junctions are present in a definite order at the apical end of the cells. Tight junctions, also called **zonulae occludens,** are the most apical of the junctions. The term “zonula” indicates that the junction forms a band completely encircling each cell. In TEM the adjacent membranes at these junctions appear fused or very tightly apposed (Figure). The seal between the two cell membranes is due to tight interactions between the transmembrane proteins: **claudin** and **occludin**. they appear as a band of branching strands in the membrane around each cell’s apical end. The intercellular seal of tight junctions ensures that molecules crossing an epithelium in either direction do so by going through the cells (a transcellular path) rather than between them (the paracellular pathway).

The second type of junction is the adherens junction or **zonula adherens** (Figures), which also encircles the epithelial cell, usually immediately below the tight junction. This is an adherent junction, firmly anchoring a cell to its neighbors. Cell adhesion is mediated by cadherins, transmembrane glycoproteins of each cell that bind each other in the presence of Ca2+.

At their cytoplasmic ends, cadherins bind **catenins** that link to actin filaments with actin-binding proteins. The actin filaments linked to the adherens junctions form part of the "terminal web," a cytoskeletal feature at the apical pole in many epithelial cells. Together, the tight and adherent junctions encircling the apical ends of epithelial cells function like the plastic bands that hold a six-pack of canned drinks together.

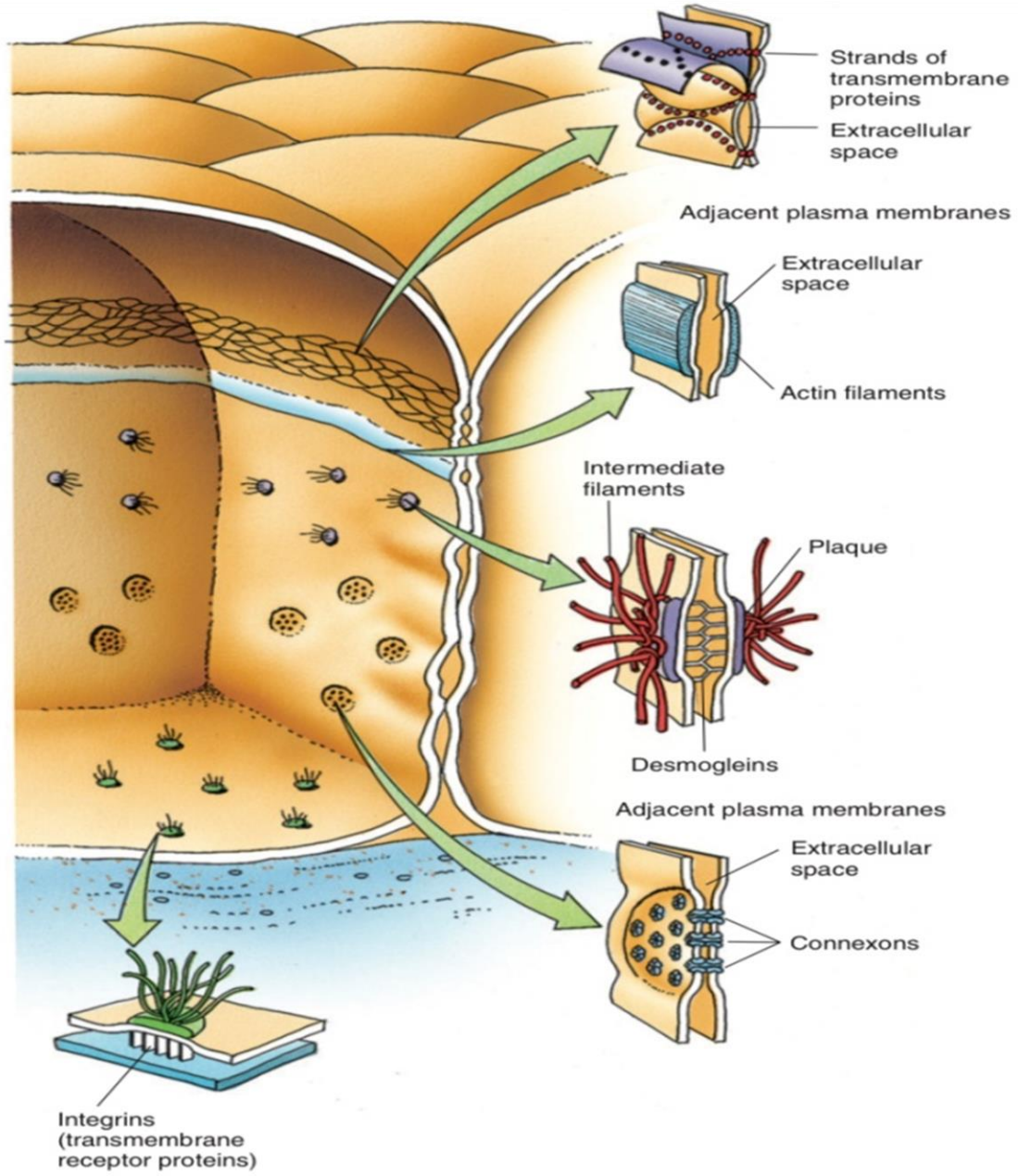
Another anchoring junction is the **desmosome** (Gr., desmos, binding and soma, body) or macula adherens (L. macula, spot). As the name implies, this junction resembles a single "spot-weld" and does not form a belt around the cell. Desmosomes are disc-shaped structures at the surface of one cell that are matched with identical structures at an adjacent cell surface (Figures). Desmosomes contain larger members of the cadherin family called desmogleins and desmocollins.

Epithelial desmosomes attach to cable-like filaments of cytokeratin, sometimes referred to tonofilaments. Such intermediate filaments are very strong and desmosomes provide firm cellular adhesion and strength throughout the epithelium.

Gap junctions, shown in Figure, mediate intercellular communication rather than adhesion or occlusion between cells. Gap junctions are also functionally important in nearly all mammalian tissues. Gap junctions consist of aggregated transmembrane protein complexes that form circular patches in the plasma membrane (Figure).

The transmembrane gap junction proteins, **connexins**, form hexameric complexes called **connexons**, each of which has a central hydrophilic pore about 1.5 nm in diameter. When two cells attach, connexins in the adjacent cell membranes move laterally and align to produce connexons between the two cells ,with each junction having dozens or hundreds of aligned connexon pairs. Gap junctions permit intercellular exchange of molecules with small (<1.5nm) diameter.

On the basal epithelial surface, cells (Figure) attach to the basal lamina by anchoring junctions called hemidesmosomes (Gr. hemi, half + desmos + soma), which can be seen by TEM .These adhesive structures resemble a half-desmosome ultrastructurally, but unlike desmosomes the clustered transmembrane proteins that indirectly link to cytokeratin intermediate filaments are integrins rather than cadherins. The integrins of hemidesmosomes bind primarily to laminin molecules in the basal lamina.



Zonulae occludentes
Extend along entire circumference of the cell. Prevent material from taking paracellular route in passing from the lumen into the connective tissues.

Zonulae adherentes
Basal to zonulae occludentes. E-cadherins bind to each other in the intercellular space and to actin filaments, intracellularly.

Maculae adherentes
E-cadherins are associated with the plaque; intermediate filaments form hairpin loops.

Gap junctions
Communicating junctions for small molecules and ions to pass between cells. Couple adjacent cells metabolically and electrically.

Hemidesmosomes
Attach epithelial cells to underlying basal lamina.

Schematic diagram of junctional complexes, gap junctions, and hemidesmosomes.

Epithelial cell junctions, their major structural features and functions, and medical significance.

Junction	Tight Junction (Zonula Occludens)	Adherens Junction (Zonula Adherens)	Desmosome (Macula Adherens)	Hemidesmosome	Gap Junction (Nexus)
Major transmembrane link proteins	Occludins, claudins, ZO proteins	E-cadherin, catenin complexes	Cadherin family proteins (desmogleins, desmocollin)	Integrins	Connexin
Cytoskeletal components	Actin filaments	Actin filaments	Intermediate filaments (keratins)	Intermediate filaments	None
Major functions	Seals adjacent cells to one another, controlling passage of molecules between them; separates apical and basolateral membrane domains	Provides points linking the cytoskeletons of adjacent cells; strengthens and stabilizes nearby tight junctions	Provides points of strong intermediate filament coupling between adjacent cells, strengthening the tissue	Anchors cytoskeleton to the basal lamina	Allows direct transfer of small molecules and ions from one cell to another
Medical significance	Defects in occludins may compromise the fetal blood–brain barrier, leading to severe neurologic disorders	Loss of E-cadherin in epithelial cell tumors (carcinomas) promotes tumor invasion and the shift to malignancy	Autoimmunity against desmoglein I leads to dyshesive skin disorders characterized by reduced cohesion of epidermal cells	Mutations in the integrin-β4 gene are linked to some types of epidermolysis bullosa, a skin blistering disorder	Mutations in various connexin genes have been linked to certain types of deafness and peripheral neuropathy

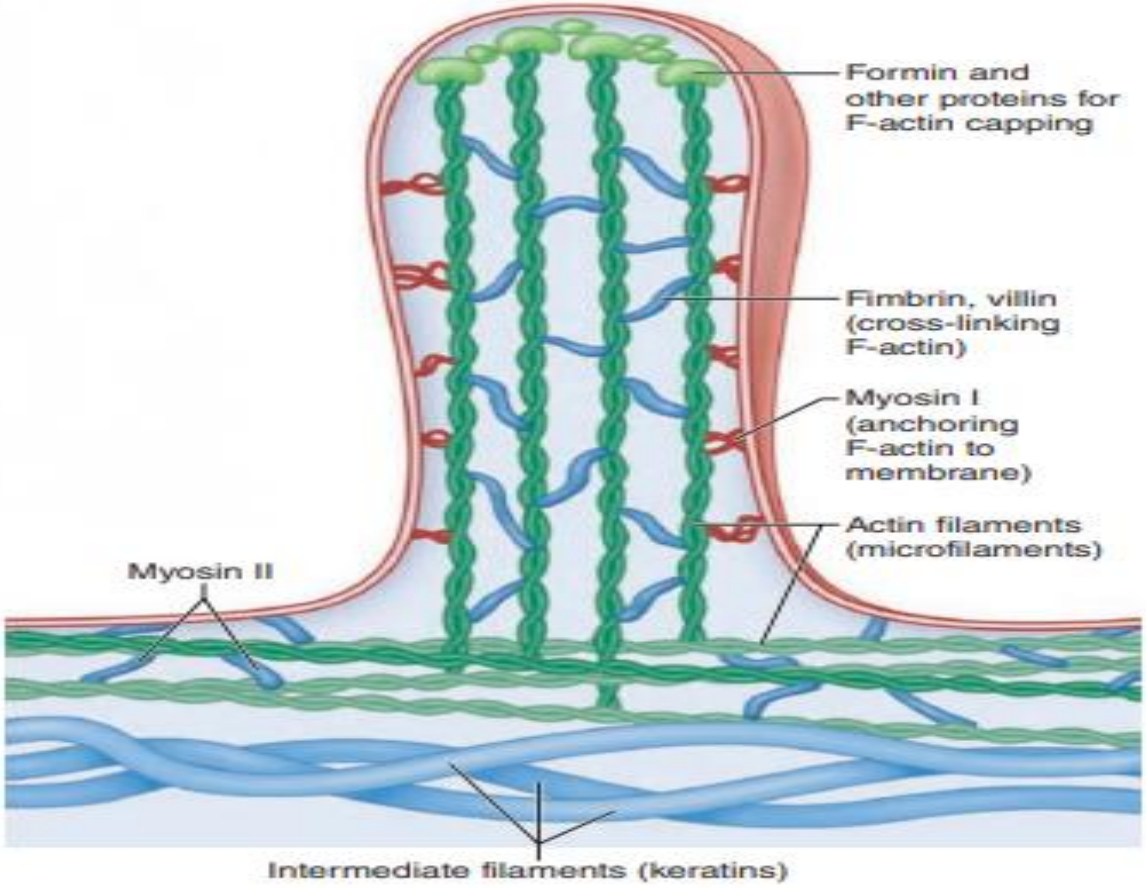
› SPECIALIZATIONS OF THE APICAL CELL SURFACE

The apical ends of many columnar and cuboidal epithelial cells have specialized structures projecting from the cells

Microvilli

Many cells have cytoplasmic projections best seen with the electron microscope. Such extensions usually reflect the movements and activity of actin filaments and are both temporary and variable in their length, shape, and number. However, in epithelia specialized for absorption the apical cell surfaces are often filled with an array of projecting microvilli (L. villus, tuft), usually of uniform length. In cells such as those lining the small intestine, densely packed **microvilli** are visible as a **brush** or **striated border** projecting into the lumen (Figure). The average microvillus is about 1 µm long and 0.1 µm wide, but with hundreds or thousands

present on the end of each absorptive cell, the total surface area can be increased by 20- or 30-fold.Each microvillus contains bundled actin filaments capped and bound to the surrounding plasma membrane by actin-binding proteins (Figure). Although microvilli are relatively stable, the microfilament arrays are dynamic and undergo various myosin-based movements, which help maintain optimal conditions for absorption via numerous channels, receptors, and other proteins in the plasmalemma. The actin filaments insert into the **terminal web** of cortical microfilaments at the base of the microvilli.



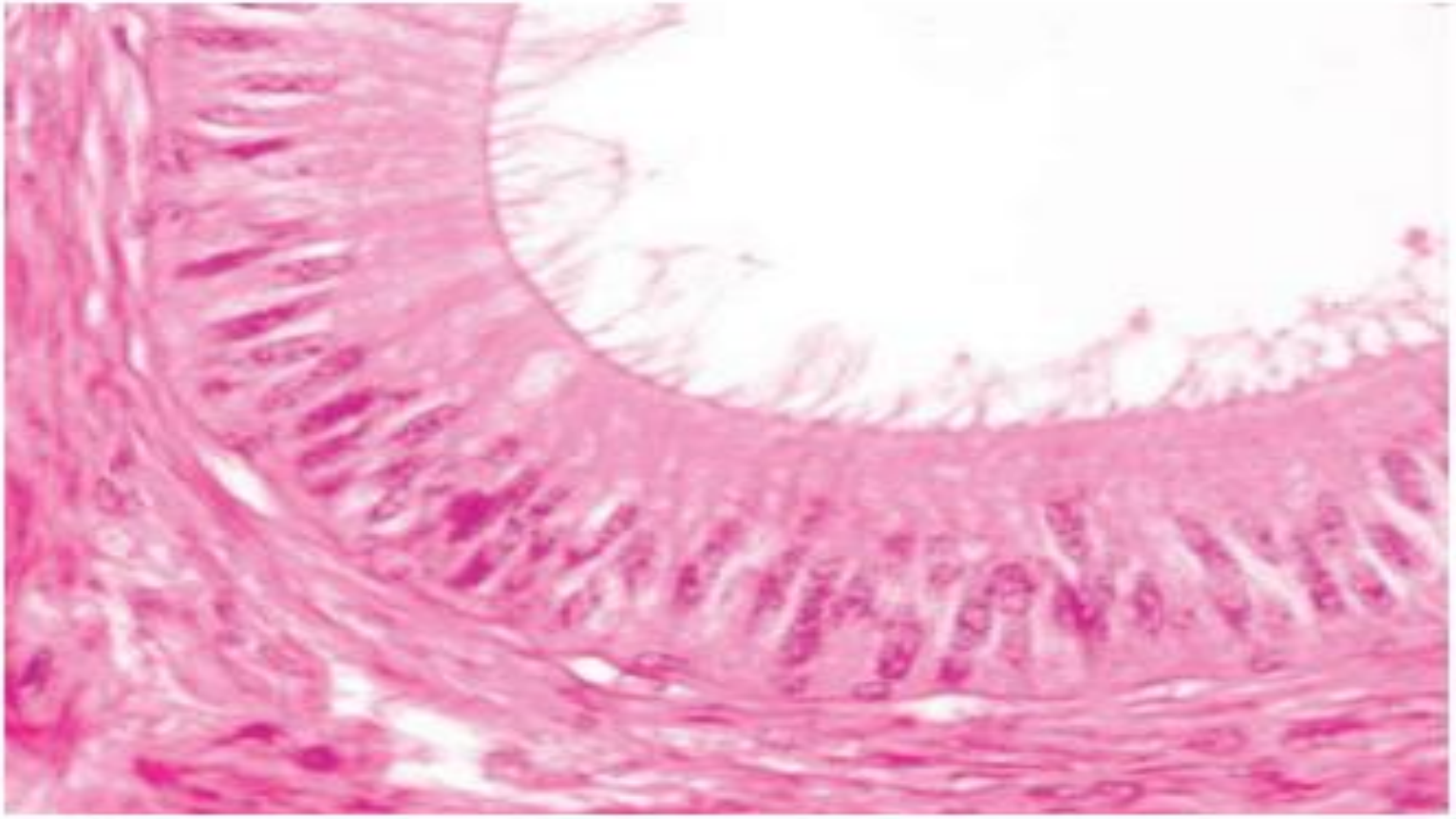
The diagram shows a few microfilaments in a microvillus, with various actin-binding proteins important for F-actin assembly, capping, cross-linking, and movement. Like microfilaments in other regions of the cytoskeleton, those of microvilli are highly dynamic with treadmilling and various myosin-based interactions. Myosin motors import various microvilli components along the actin filaments

2-Stereocilia

Stereocilia are a much less common type of apical process, best seen on the absorptive epithelial cells lining the male reproductive system(Figure). Like microvilli, stereocilia increase the cells' surface area, facilitating absorption. More specialized stereocilia with a motion-detecting function are important components of inner ear sensory cells.

Stereocilia are typically much longer and less motile than microvilli, and may show branching distally.

Stereocilia.



At the apical ends of the tall epithelial cells lining organs such as the epididymis (shown here) are numerous very long stereocilia, which increase the surface area available for absorption. Stereocilia are much longer than microvilli and often have distal branching. (X400; H&E)

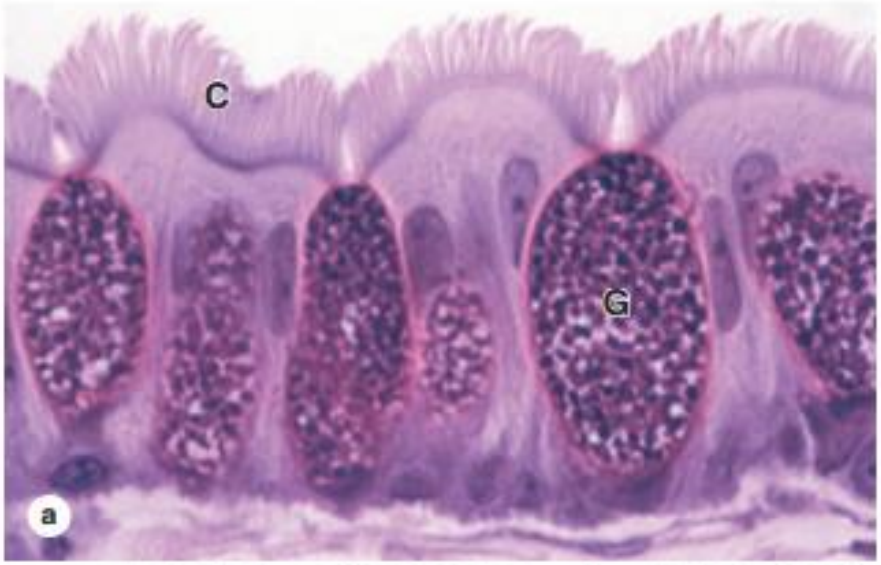
3-Cilia

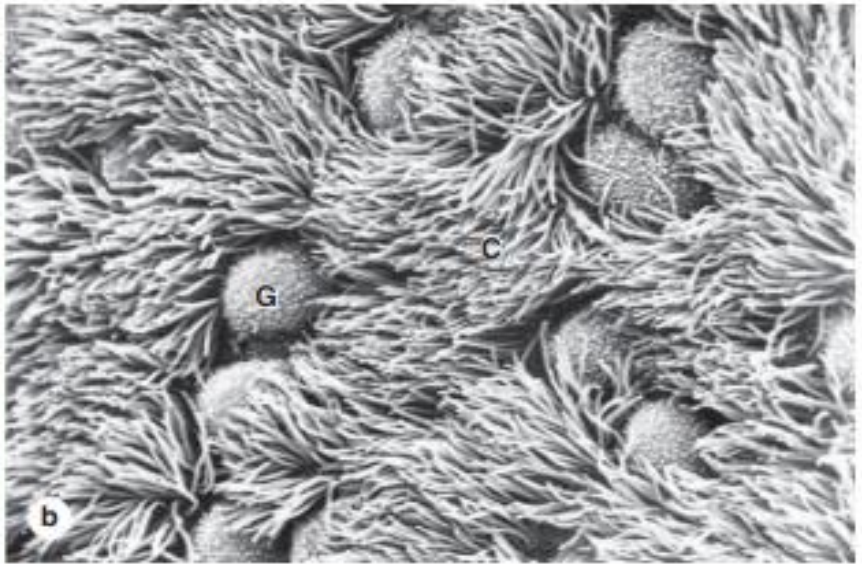
Cilia are long, highly motile apical structures, larger than microvilli, and containing internal arrays of microtubules not microfilaments .

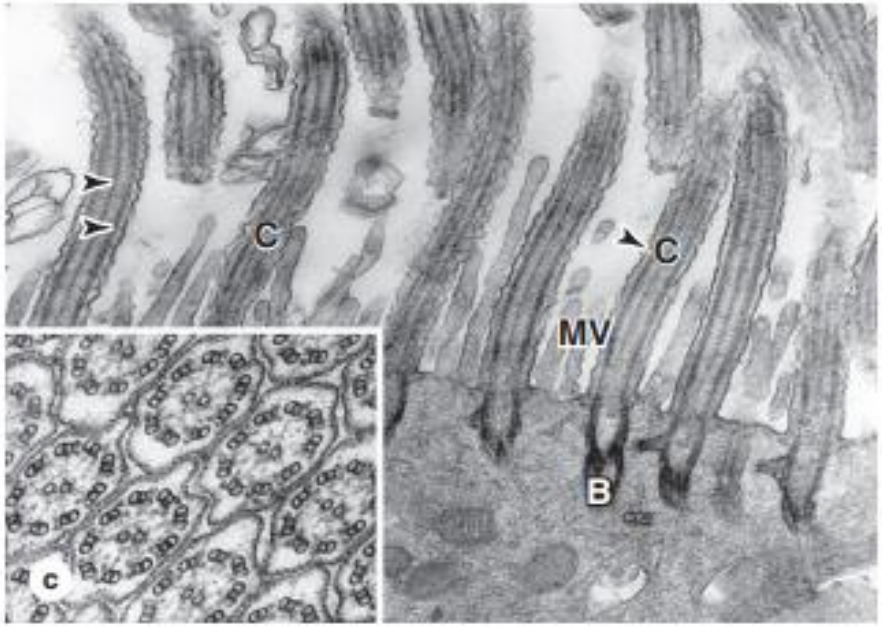
In addition to cilia on epithelial cells, most (if not all) other cell types have at least one short projection called a primary cilium, which is not motile but is enriched with receptors and signal transduction complexes for detection of light, odors, motion, and flow of liquid past the cells.

Motile cilia are abundant on cuboidal or columnar cells of many epithelia. Typical cilia are 5-10 µm long and 0.2 µm in diameter, which is much longer and two times wider than a typical microvillus. As shown in (Figures), each cilium has a core structure consisting of nine peripheral microtubule doublets (in which a few tubulin protofilaments are shared) arrayed around two central microtubules. This 9 + 2 **assembly** of microtubules is called an **axoneme** (Gr. axon, axis + nema, thread).

Microtubules of axonemes are continuous with those in **basal bodies**, which are apical cytoplasmic structures just below the cell membrane (Figures). Basal bodies have a structure similar to that of centrioles, with triplets of microtubules and dynamic tubulin protofilaments forming rootlets anchoring the entire structure to the cytoskeleton. Cilia exhibit rapid beating patterns that move a current of fluid and suspended matter in one direction along the epithelium. Ciliary motion occurs through successive changes in the conformation of the axoneme, The long flagellum that extends from each fully differentiated sperm cell has an axonemal structure like that of a cilium and moves with a similar mechanism.







Epithelial cells lining the respiratory tract have many very well-developed cilia.

(a) By light microscopy cilia (**C**) on the columnar cells appear as a wave of long projections, interrupted by nonciliated, mucus-secreting goblet cells (**G**). (X400; Toluidine blue)

(b) SEM of the apical surfaces of this epithelium shows the density of the cilia (**C**) and the scattered goblet cells (**G**). (X600)

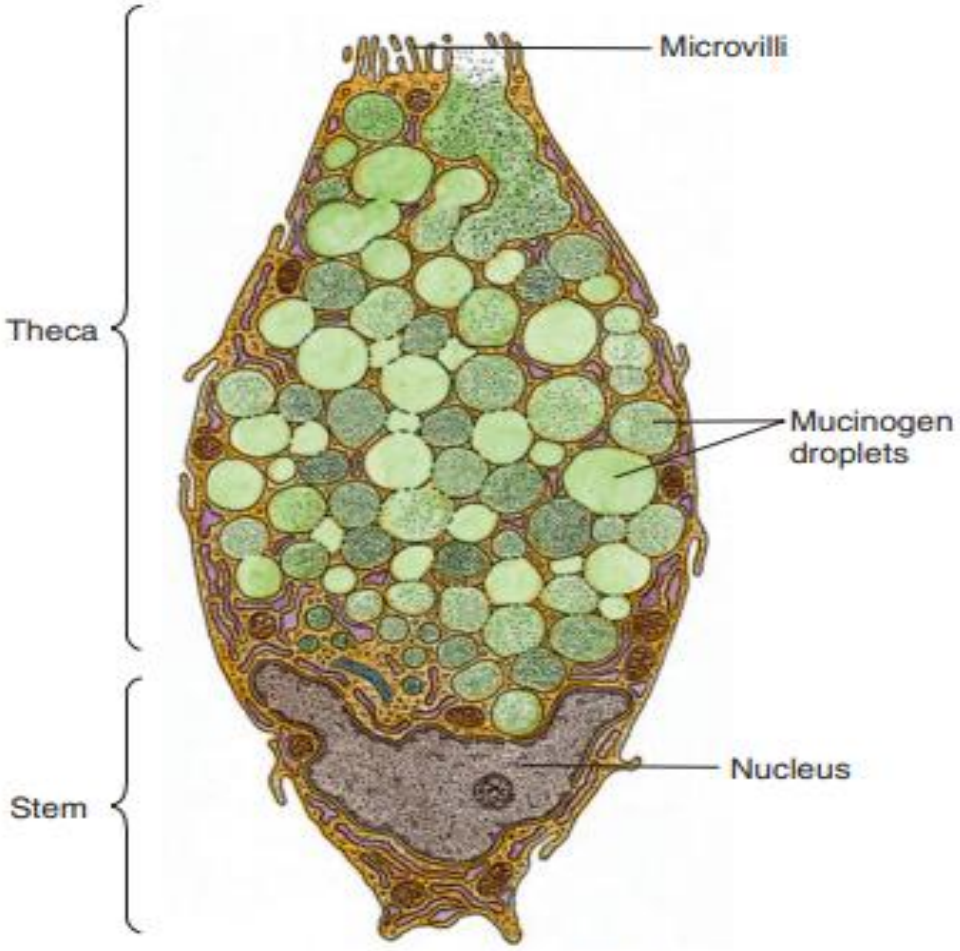
(c) TEM of cilia (**C**) sectioned longitudinally reveals central and peripheral microtubules (arrowheads) of the axonemes, with cross sections (inset) clearly showing the 9 + 2 array of the microtubule doublets. At the base of each cilium is a basal body (**B**) anchoring the axoneme to the apical cytoplasm. Much shorter microvilli (**MV**) can be seen between the cilia. (X59,000; Inset: X80,000)

Secretory Epithelia & Glands

Epithelial cells that function mainly to produce and secrete various macromolecules may occur in epithelia with other major functions or comprise specialized organs called **glands**.

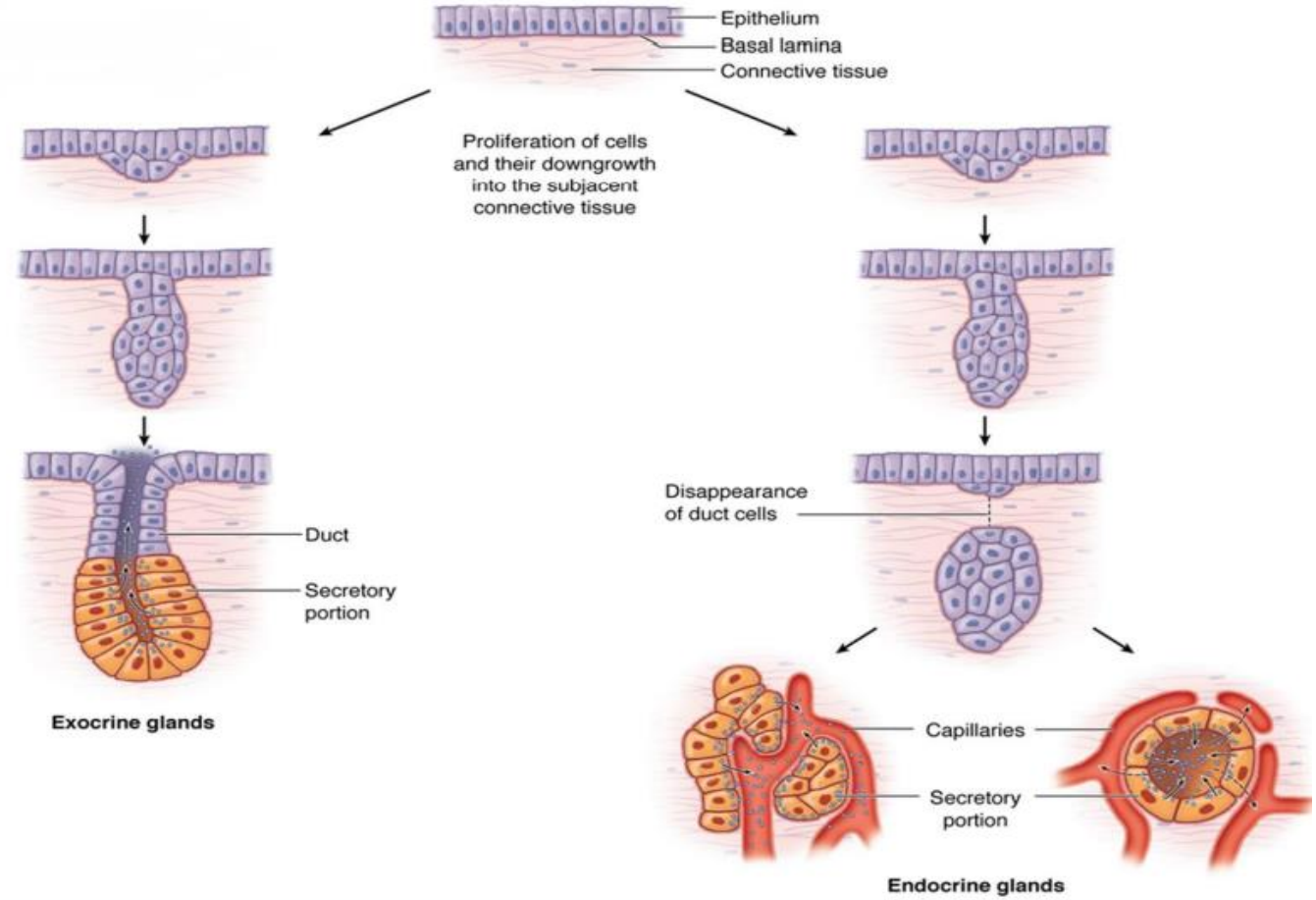
Secretory cells may synthesize, store, and release proteins (eg, in the pancreas), lipids (eg, adrenal, sebaceous glands), or complexes of carbohydrates and proteins (eg, salivary glands). Epithelia of mammary glands secrete all three substances.

Scattered secretory cells, sometimes called unicellular glands, are common in simple cuboidal, simple columnar, and pseudostratified epithelia. An important, easily seen example is the **goblet cell** abundant in the lining of the small intestine (Figure) and respiratory tract (Figure) which secretes lubricating mucus that aids the function of these organs.



Schematic diagram of the ultrastructure of a goblet cell illustrating the tightly packed secretory granules of the theca. (From Lentz TL. *Cell Fine Structure: An Atlas of Drawings of Whole-Cell Structure*. Philadelphia: WB Saunders; 1971.)

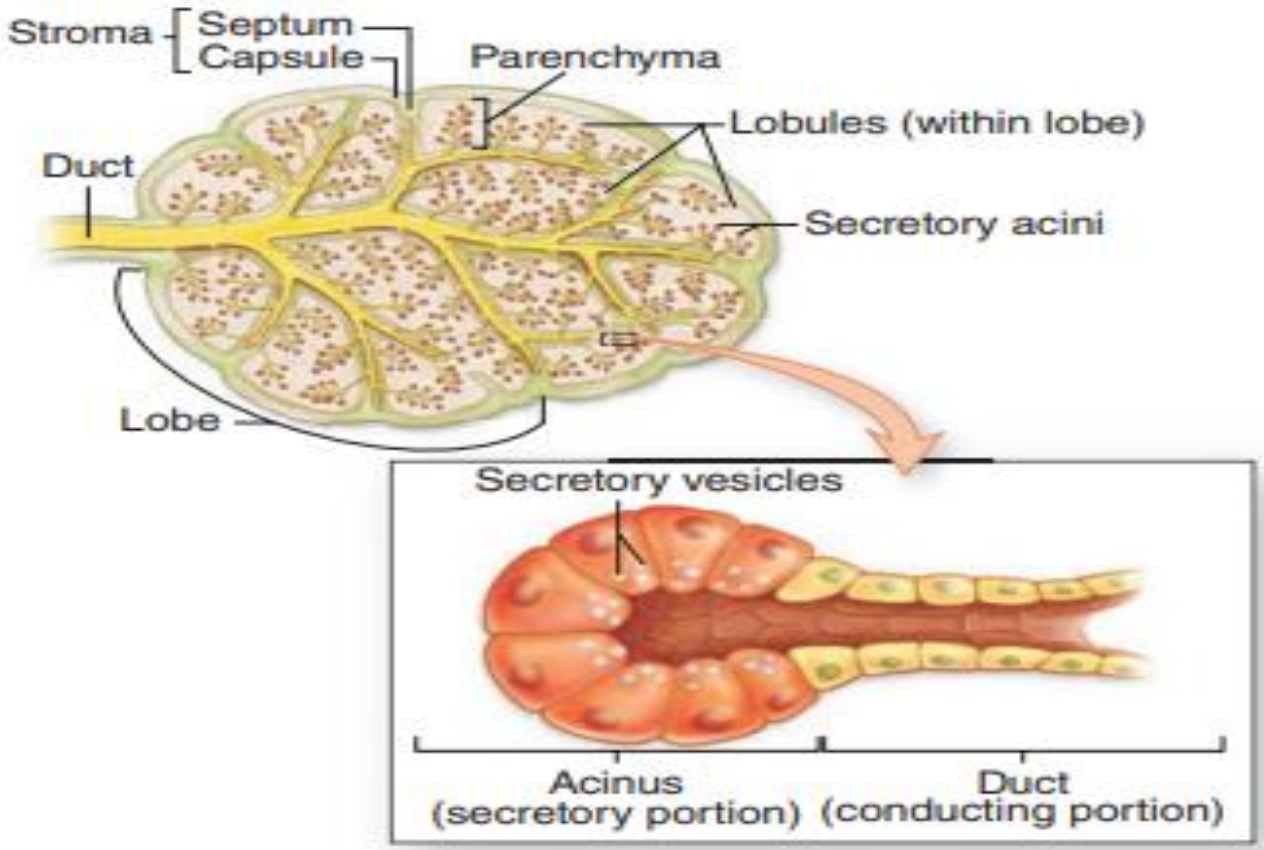
Glands develop from covering epithelia in the fetus by cell proliferation and growth into the underlying connective tissue, followed by further differentiation (Figure). **Exocrine glands** remain connected with the surface epithelium, the connection forming the tubular ducts lined with epithelium that deliver the secreted material where it is used. **Endocrine glands** lose the connection to their original epithelium and therefore lack ducts. Thin-walled blood vessels (capillaries) adjacent to endocrine cells absorb their secreted hormone products for transport in blood to target cells throughout the body.



During fetal development epithelial cells proliferate and penetrate the underlying connective tissue. These cells may—or may not— maintain a connection with the surface epithelium. The connection is maintained to form a duct in exocrine glands; it is lost as endocrine glands develop. Exocrine glands secrete substances to specific organs via duct systems. Endocrine glands produce hormones and are always rich in capillaries. Hormones are released outside the cells and picked up by these blood vessels for distribution throughout the body, where specific target cells are identified by receptors for the hormones. Endocrine glands can have secretory cells arranged as irregular cords (left) or as rounded follicles (right) with lumens for temporary storage of the secretory product

As shown in(Figure), epithelia of exocrine glands are organized as a continuous system of many small **secretory portions** and **ducts** that transport the secretion out of the gland. In larger glands, layers of connective tissue surround the larger ducts, form partitions or septa separating the gland into lobules, each containing secretory units connected to a small part of the duct system, and enclose the entire gland as its capsule (Figure).

FIGURE **General structure of exocrine glands.**



Exocrine glands by definition have ducts that lead to another organ or the body surface. Inside the gland the duct runs through the connective tissue of septa and branches repeatedly, until its smallest branches end in the secretory portions of the gland.

The structures of their secretory portions and ducts allow exocrine glands to be classified as shown schematically in Table.

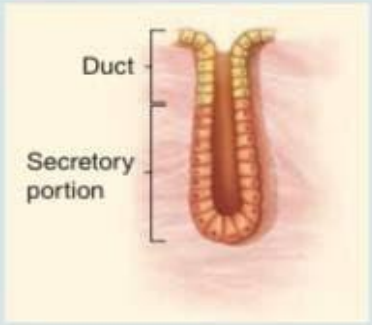
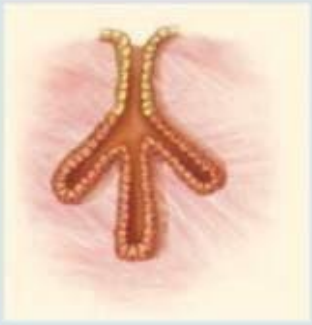
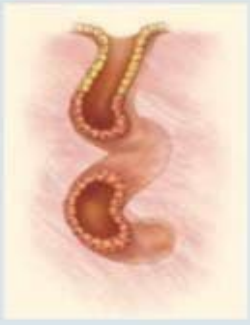
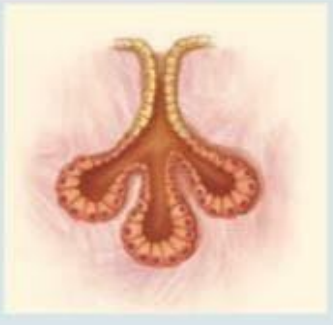
- Glands can be **simple** (ducts not branched) or **compound** (ducts with two or more branches)
- Secretory portions can be **tubular** (either short or long and **coiled**) or **acinar** (rounded and saclike); either type

of secretory unit may be branched, even if the duct is not branched.

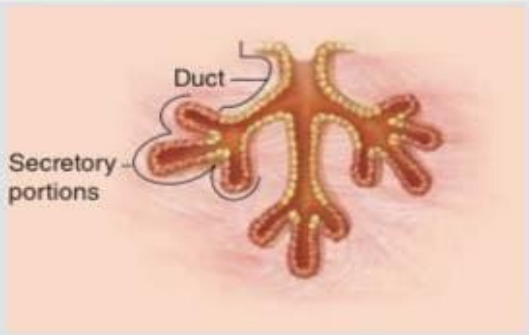
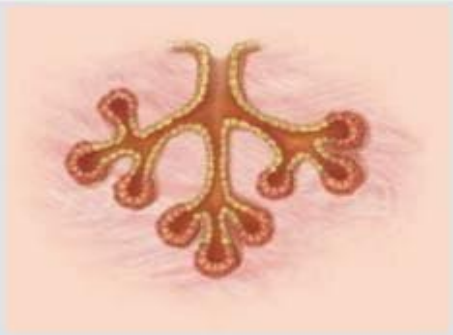
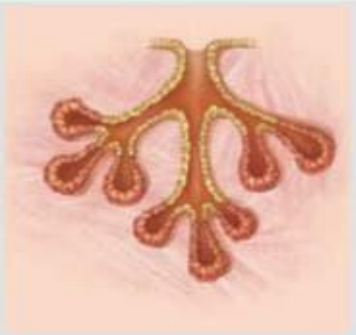
- **Compound** glands can have branching ducts and can have multiple tubular, acinar, or **tubuloacinar** secretory portions.

TABLE **Structural classes of exocrine glands, features of each class, and examples.**

SIMPLE Glands **(Ducts Do Not Branch)**

Class	Simple Tubular	Branched Tubular	Coiled Tubular	Acinar (or Alveolar)	Branched Acinar
					
Features	Elongated secretory portion; duct usually short or absent	Several long secretory parts joining to drain into 1 duct	Secretory portion is very long and coiled	Rounded, saclike secretory portion	Multiple saclike secretory parts entering the same duct
Examples	Mucous glands of colon; intestinal glands or crypts (of Lieberkühn)	Glands in the uterus and stomach	Sweat glands	Small mucous glands along the urethra	Sebaceous glands of the skin

COMPOUND Glands **(Ducts from Several Secretory Units Converge into Larger Ducts)**

Class	Tubular	Acinar (Alveolar)	Tubuloacinar
			
Features	Several *elongated* coiled secretory units and their ducts converge to form larger ducts	Several *saclike* secretory units with small ducts converge at a larger duct	Ducts of both tubular and acinar secretory units converge at larger ducts
Examples	Submucosal mucous glands (of Brunner) in the duodenum	Exocrine pancreas	Salivary glands

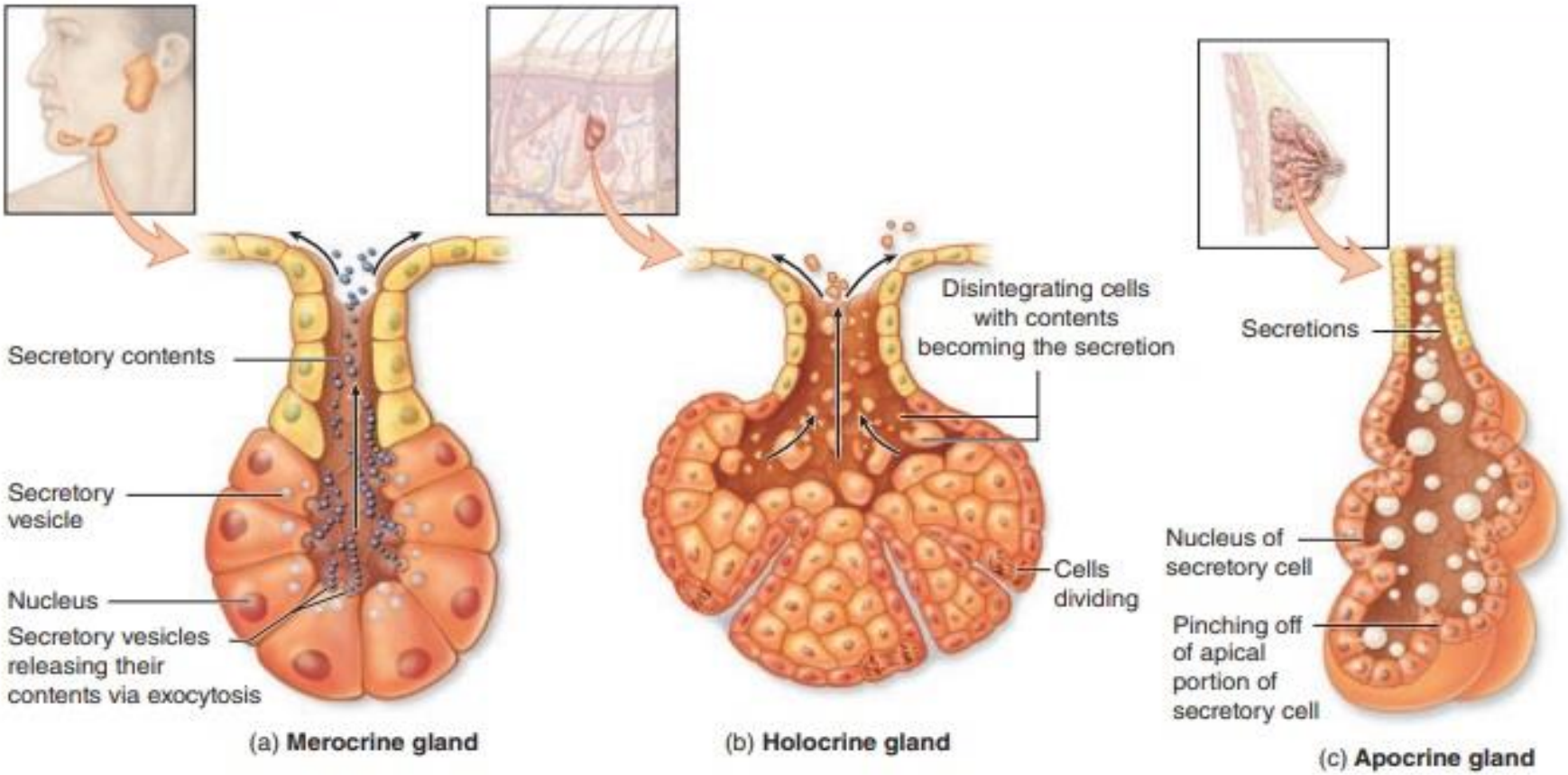
Three basic mechanisms for releasing the product are commonly used by cells specialized for secretion (Figure), and cells engaged in each type of secretion can be distinguished histologically:

1. **Merocrine secretion**: This is the most common method of protein or glycoprotein secretion and involves typical exocytosis from membrane-bound vesicles or secretory granules.

2. **Holocrine secretion**: Here cells accumulate product continuously as they enlarge and undergo terminal differentiation, culminating in complete cell disruption that releases the product and cell debris into the gland's lumen. This is best seen in the sebaceous glands producing lipidrich material in skin.

3. **Apocrine secretion**: Here product accumulates at the cells' apical ends, portions of which are then extruded to release the product together with small amounts of cytoplasm and cell membrane. Lipid droplets are secreted in the mammary gland in this manner .

FIGURE **Mechanisms of exocrine gland secretion.**



Three basic types of secretion are used by cells of exocrine glands, depending on what substance is being secreted.

(a) Merocrine secretion releases products, usually containing proteins, by means of exocytosis at the apical end of the secretory cells. Most exocrine glands are merocrine.

(b) Holocrine secretion is produced by the disintegration of the secretory cells themselves as they complete their terminal differentiation, which involves becoming filled with product. Sebaceous glands of hair follicles are the best examples of holocrine glands.

(c) Apocrine secretion involves loss of membrane-enclosed apical cytoplasm, usually containing one or more lipid droplets. Apocrine secretion, along with merocrine secretion, is seen in mammary glands.

Exocrine glands with merocrine secretion can be further categorized as either **serous** or **mucous** according to the nature of their secretory products, which give distinct staining properties to the cells. Serous cells synthesize proteins that are mostly not glycosylated, such as digestive enzymes. Serous cells stain intensely with basophilic or acidophilic stains. Acini of the pancreas and parotid salivary glands are composed of serous cells

Mucous cells, such as goblet cells. Mucous cells, contain heavily glycosylated proteins called **mucins**. When mucins are released from the cell, they become hydrated and form a layer of mucus. The hydrophilic mucins are usually washed from cells during routine histological preparations, causing the secretory granules to stain poorly with eosin .

Sufficient oligosaccharides remain in developing **mucinogen** granules, however, to allow mucous cells to be stained by the PAS method.

Some salivary glands are mixed **seromucous** glands, having both serous acini and mucous tubules with clustered serous cells

In addition to secretory cells, epithelia of many exocrine glands (eg, sweat, lachrymal, salivary, and mammary glands) contain contractile **myoepithelial cells** at the basal ends of the secretory cells (Long processes of these cells embrace an acinus as an octopus might embrace a rounded boulder Myoepithelial cells are rich in actin filaments and myosins. Strong contractions in these cells serve to help propel secretory products from acini into the duct system. Endocrine glands lack myoepithelial cells and are specialized either for protein or steroid **hormone** synthesis,

Some salivary glands are mixed **seromucous** glands, having both serous acini and mucous tubules with clustered serous cells . The product of such glands is a mixture of digestive enzymes and watery mucus

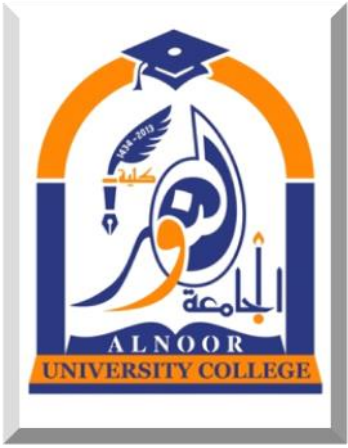
In addition to secretory cells, epithelia of many exocrine glands (eg, sweat, lachrymal, salivary, and mammary glands) contain contractile **myoepithelial cells** at the basal ends of the secretory cells (Long processes of these cells embrace an acinus as an octopus might embrace a rounded boulder. Bound to the basal lamina by hemidesmosomes and connected to the other epithelial cells by both gap junctions and desmosomes, myoepithelial cells are rich in actin filaments and myosins. Strong contractions in these cells serve to help propel secretory products from acini into the duct system. Endocrine glands lack myoepithelial cells and are specialized either for protein or steroid **hormone** synthesis,

Diffuse Neuroendocrine System

The diffuse neuroendocrine system functions to produce paracrine and endocrine hormones.

Widespread throughout the digestive tract and in the respiratory system are endocrine cells interspersed among other secretory cells. These cells, members of the **diffuse neuroendocrine system (DNES),** manufacture various paracrine and endocrine hormones

Thank you



Al-Noor University College.

Medical laboratories technics department.

Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Nervous Tissue .

Dr. Ali Ashgar Abd

Nerve tissue and Nervous system

- The most complex system in the human body
- Formed by network of billons of neurons .
- Each neuron has a thousand **interconnection** → a very complex system for communication
- Nerve tissue is distribute throughout the body, Structurally consist : **Nerve cells** & **Glial cells**
- **Anatomically divided in to :**
- **1. central nervous system (CNS)**
- **2.peripheral (PNS)**

Functional Organization of the Nervous System

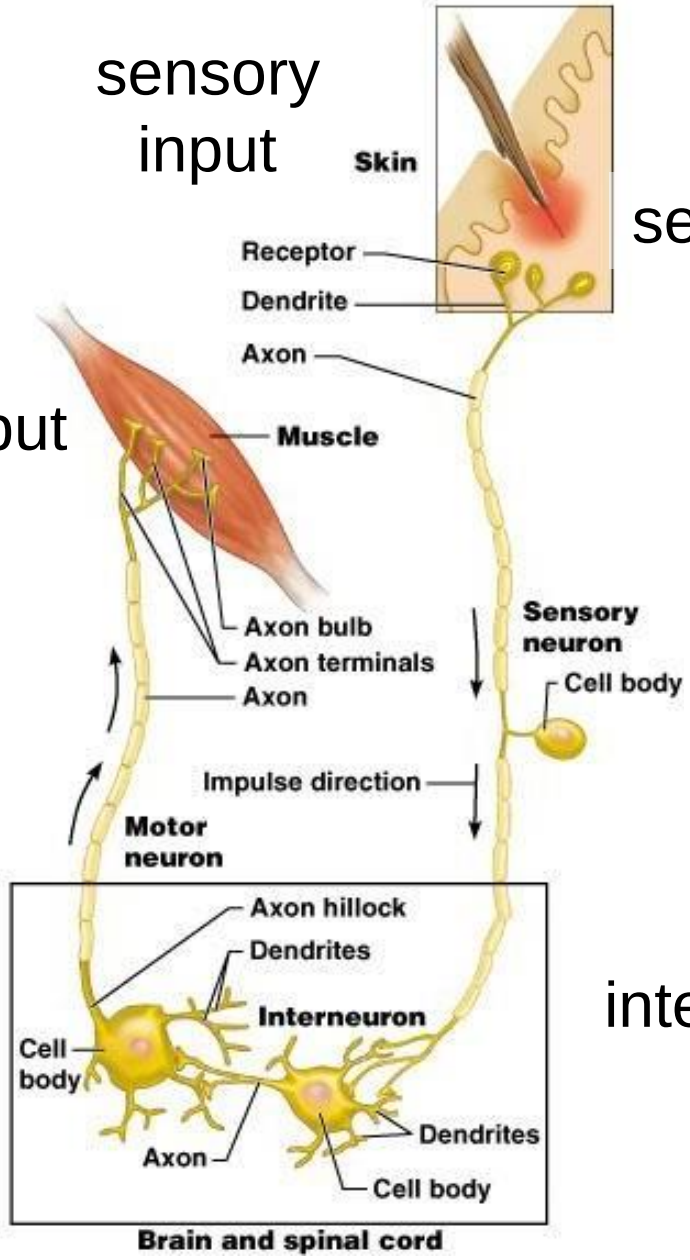
1. **Somatic** (conscious afferent* and efferent, voluntary motor control(
2. **Autonomic** (unconscious efferent, involuntary motor control of internal organs to maintain homeostasis(
   a. **Sympathetic – thoracolumbar division**
   b. **Parasympathetic – craniosacral division**

* Somatic afferents = sensory fibers from skin, muscle, joints, tendons.

Visceral afferents = sensory fibers from visceral organs; However, they are not considered part of the autonomic nervous system, which is entirely efferent.

Function of the nervous system

sensory input



sensory receptor

motor input

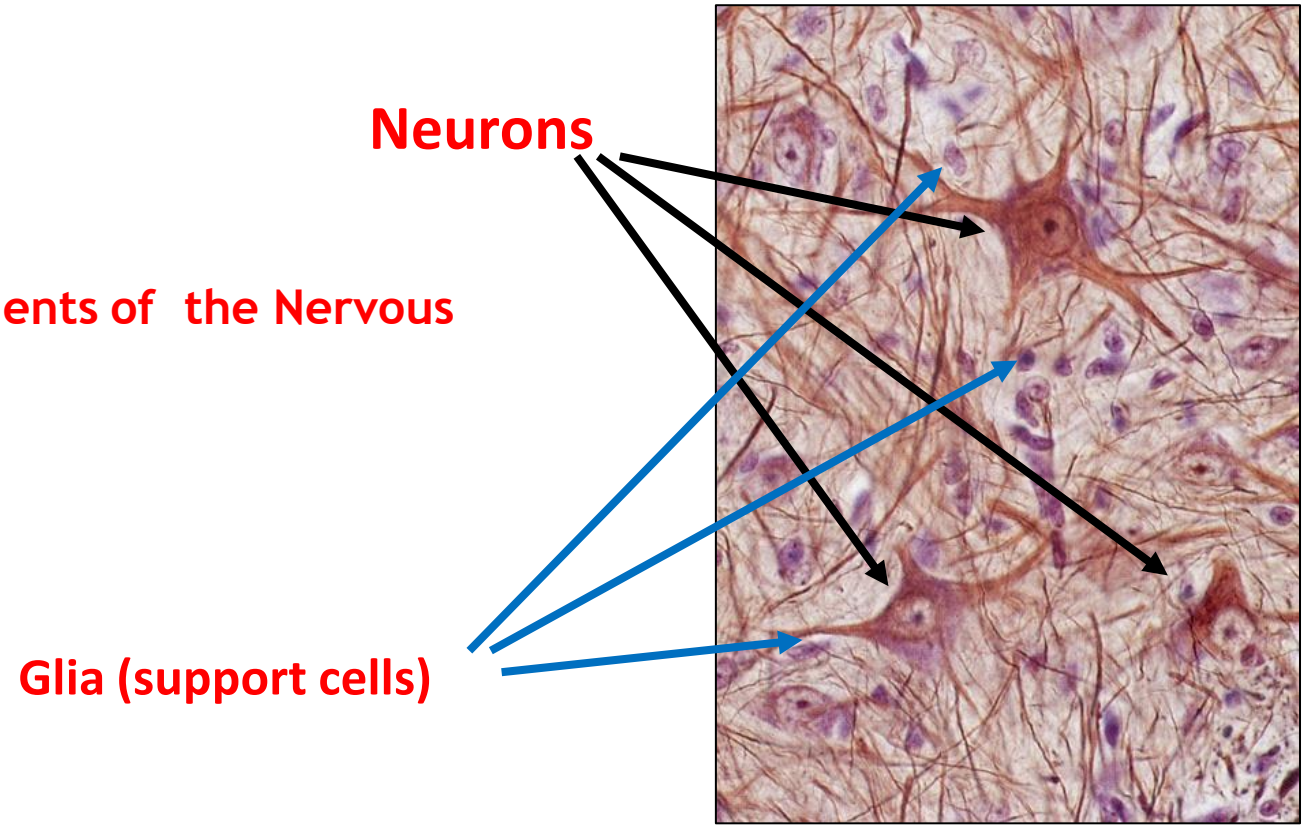
effector

integration

CONTENTS

- Cells of nervous system nerve cells and Neuralgia
- Synaptic communication
- Central nervous system & Peripheral nervous system & associated structures

Cellular Components of the Nervous System



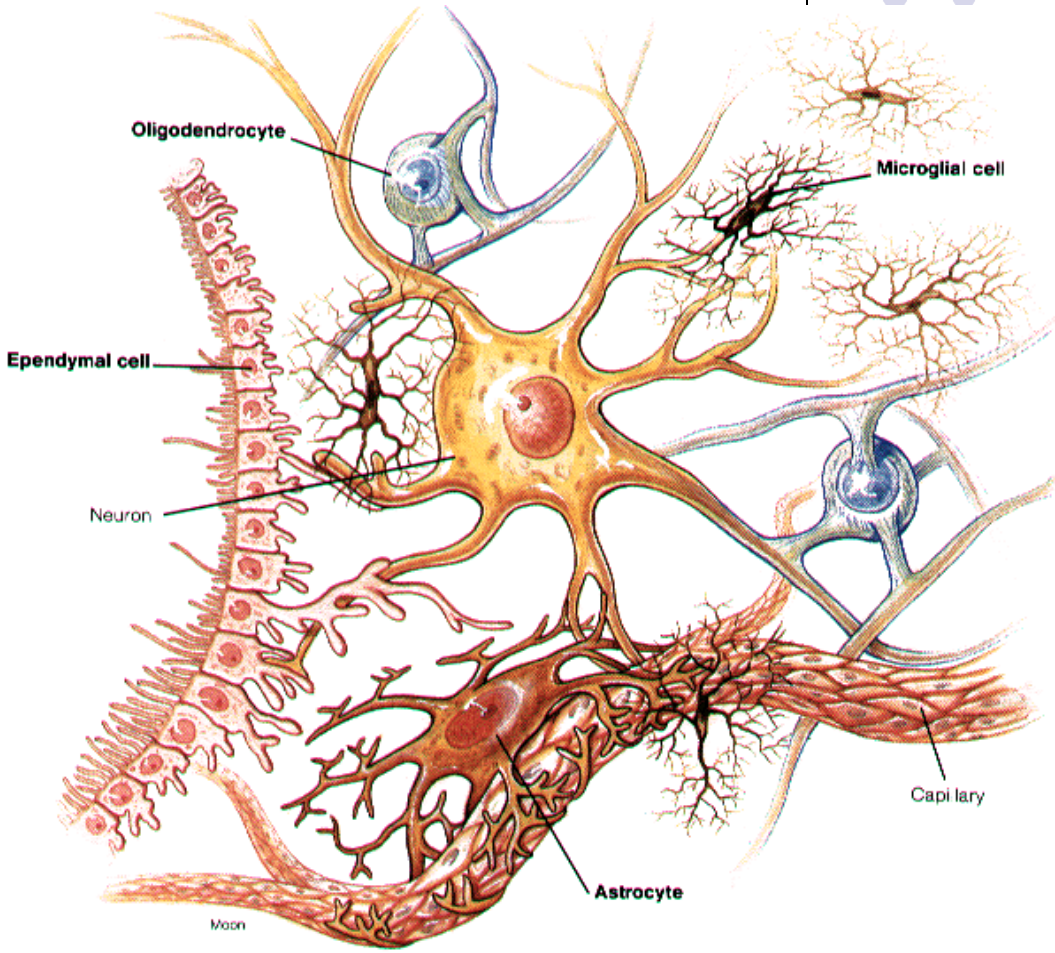
Nervous Tissue: Support Cells(Neuroglia)

- Support cells in the Central Nervous System (CNS) are grouped together as neuroglia
- Neuroglia literally means “nerve glue”
- The function of neuroglia is to support, insulate, and protect the delicate neurons of the brain

Neuroglial Cells

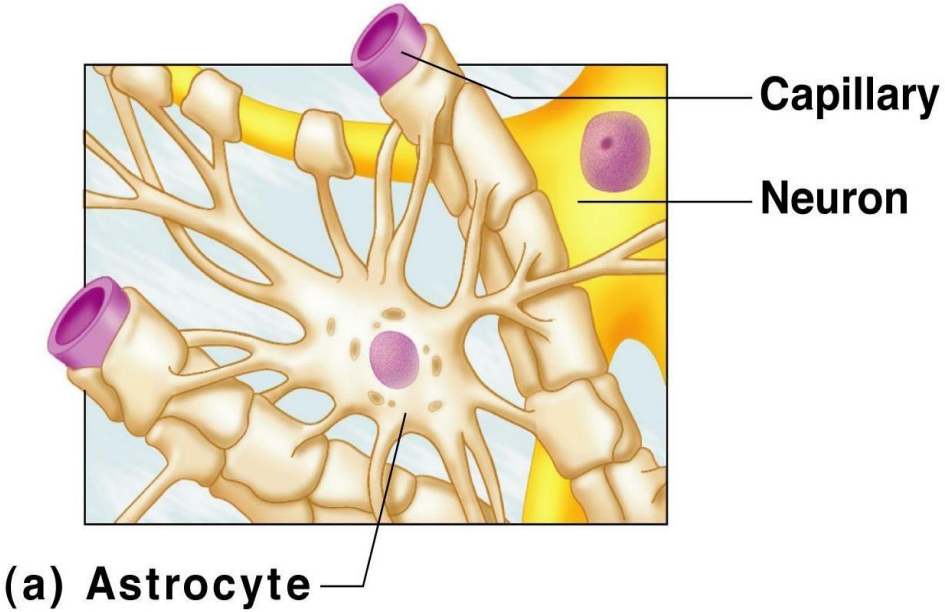
- Half of the volume of the CNS
- Smaller cells than neuron
- 50X more numerous
- Cells can divide
- rapid mitosis in tumor formation (gliomas(

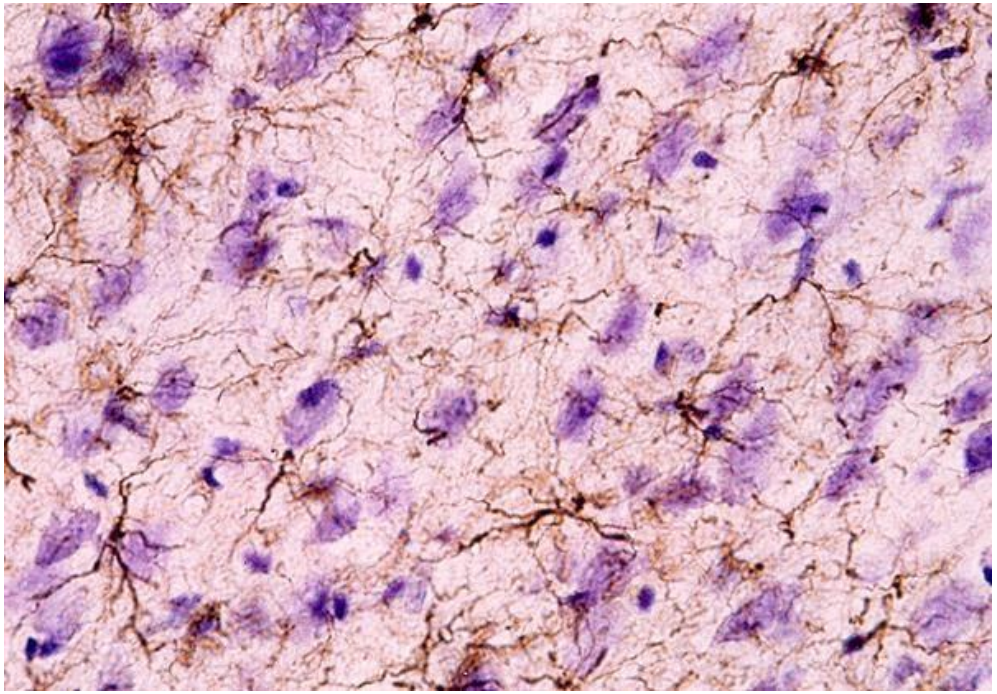
- 4cell types in CNS
  - Astrocytes
  - Microglia
  - Ependymal
  - oligodendrocytes
- 2cell types in PNS
  - Schwann
  - satellite cells



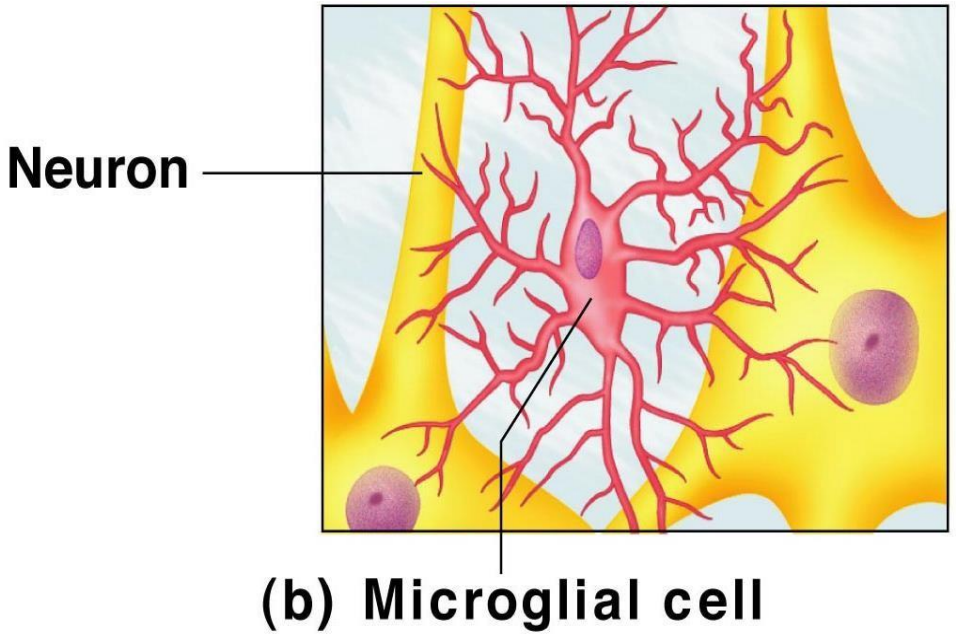
Types of Neuroglia in CNS

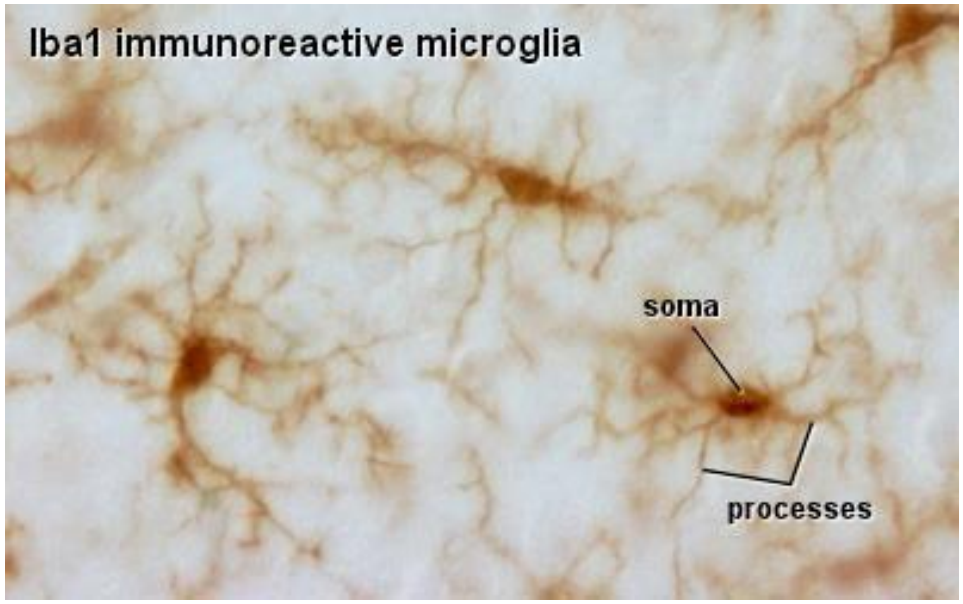
- **Astrocytes**
  - Star-shaped cells
  - Half of all brain tissue
  - Brace neurons; they keep the neurons in contact with their blood supply (capillaries(
  - Control the chemical environment of the brain by mopping up leaked ions



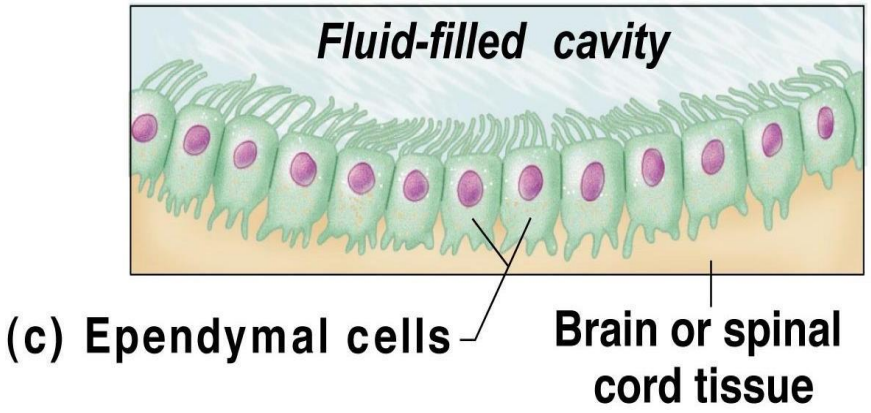


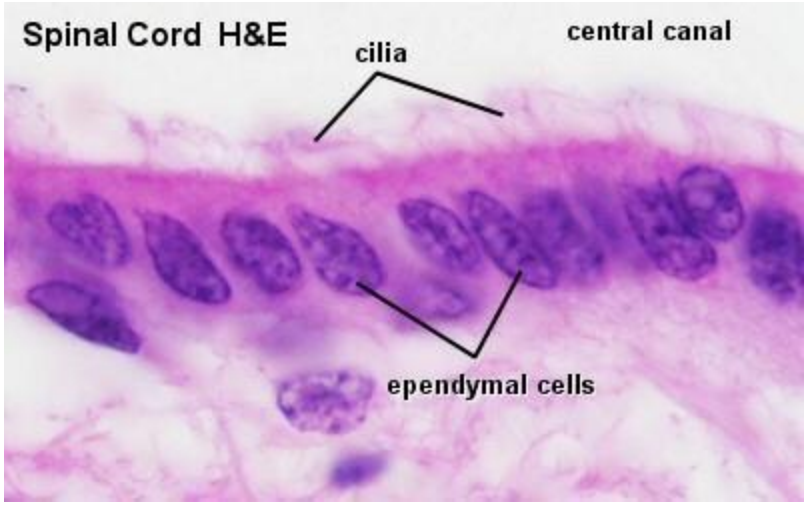
- **Microglia**
  - Spiderlike phagocytes (white blood cells)
  - Dispose of debris like dead brains cells and bacteria





- **Ependymal cells**
  - Lines the cavities of the brain and spinal cord
  - Circulate cerebrospinal fluid by beating their cilia
  - Cerebrospinal fluid fills the space the brain does not take up and forms a protective cushion around the brain and spinal chord





Ependymal cells

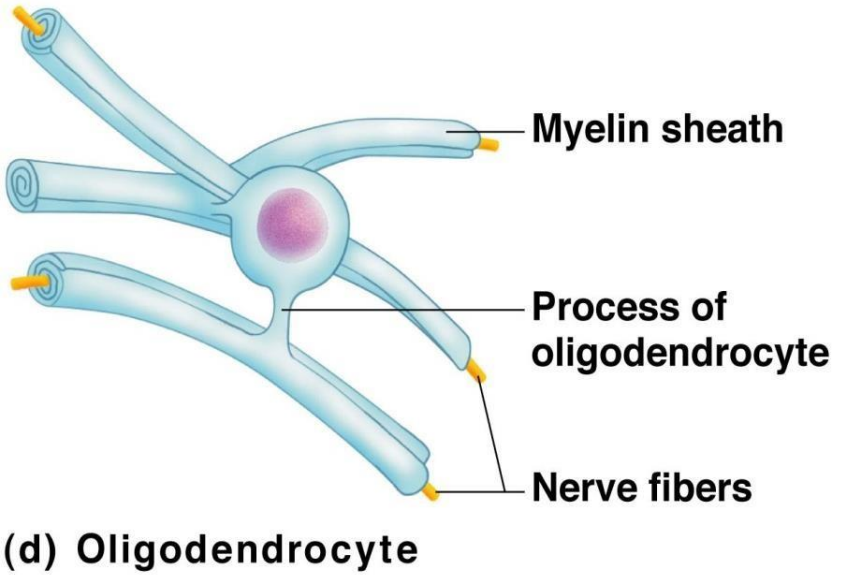
- Forms the epithelial lining of ventricles and spinal cord
- Cubodial or low columnar in shape
- Cells are bound at the luminal surface by epithelial junctional complexes
- The bases of cells taper and break into fine branches which ramify into underlying layer of astrocytic processes
- **Functions**

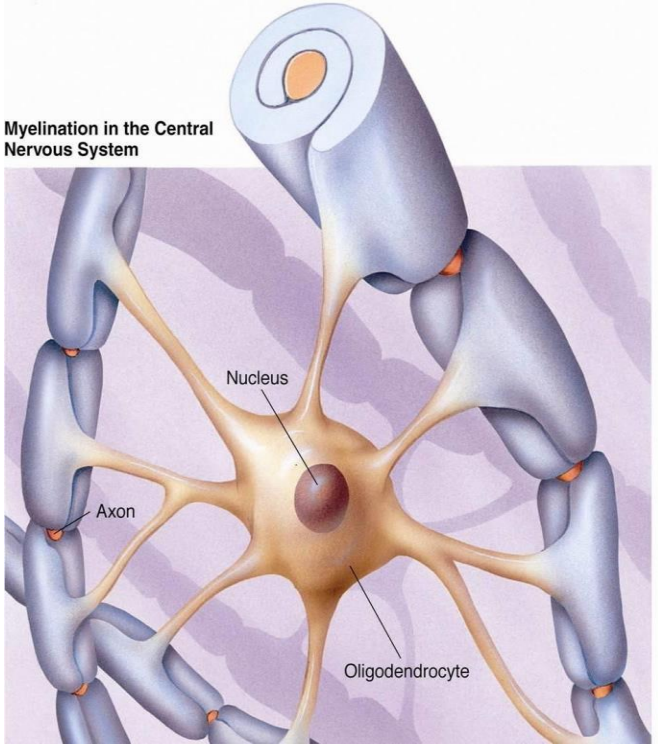
➢ Protection :forms lining of the ventricles of the brain and central canal of the spinal cord.

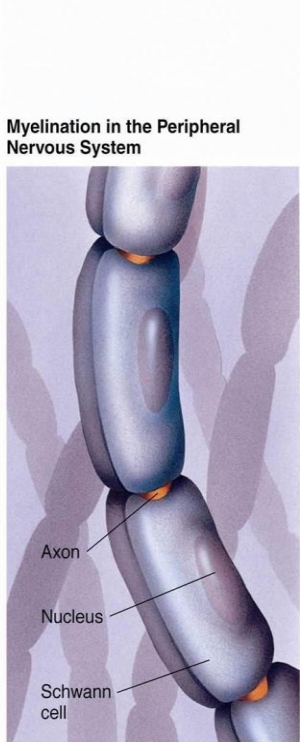
➢ Forms cerebrospinal fluid (CSF)

➢ Aids circulation of cerebrospinal fluid (CSF)

- **Oligodendrocytes**
  - **Wrap around nerve cells in the brain and spinal chord**
  - **Produce myelin sheaths**
  - **Myelin is a fatty, insulation covering the nerve cells; allows for the electrical signal to transmit faster (like wire coating)**



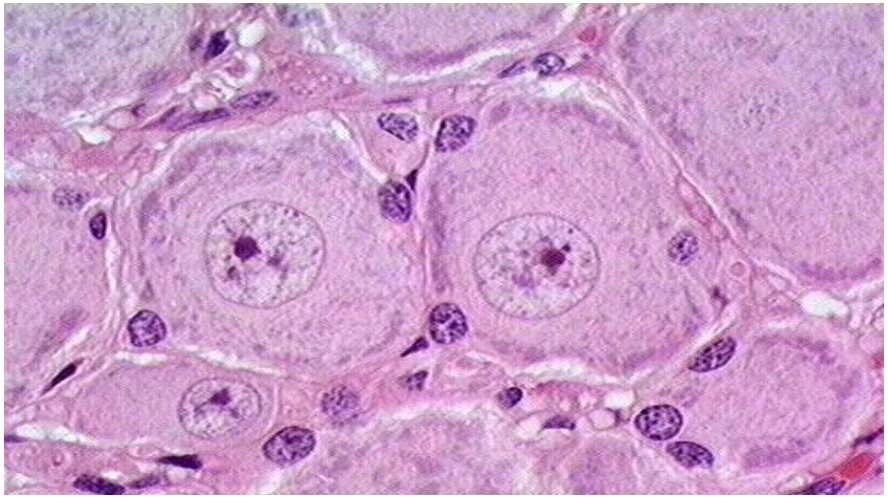


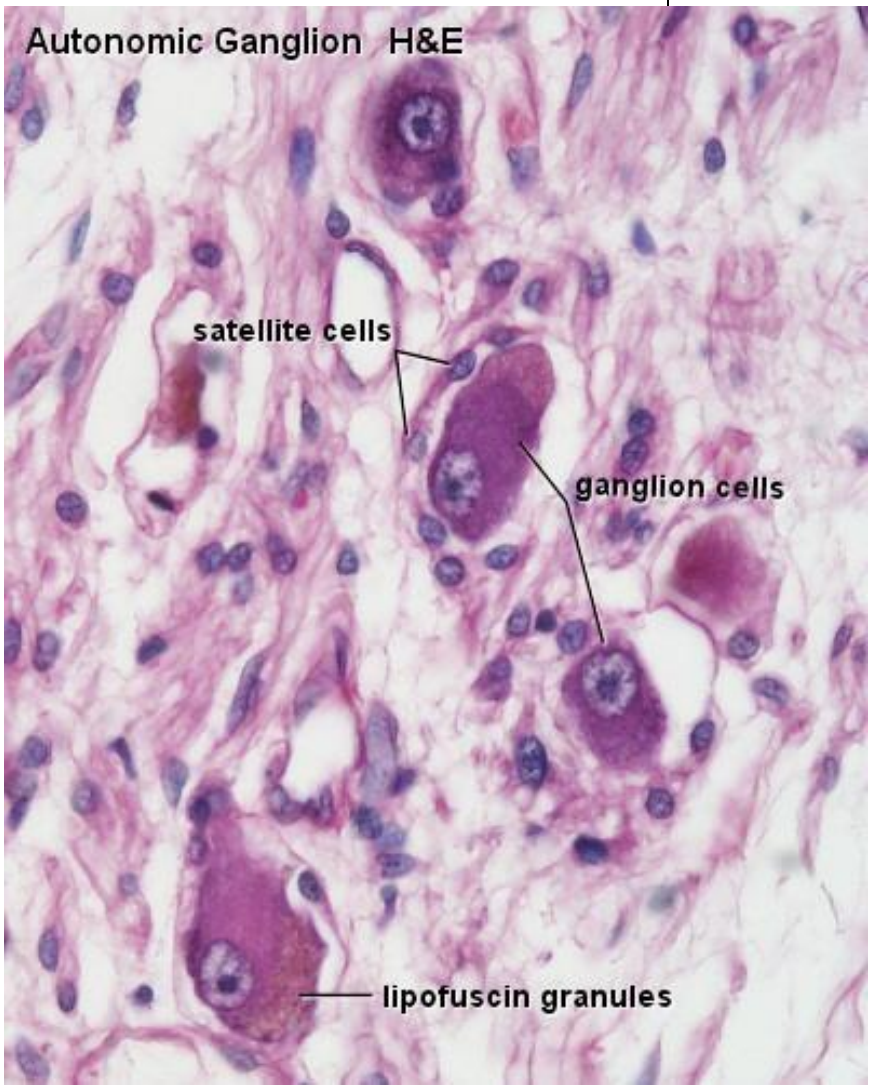


Neuroglial Cells in the PNS

1. Satellite cells

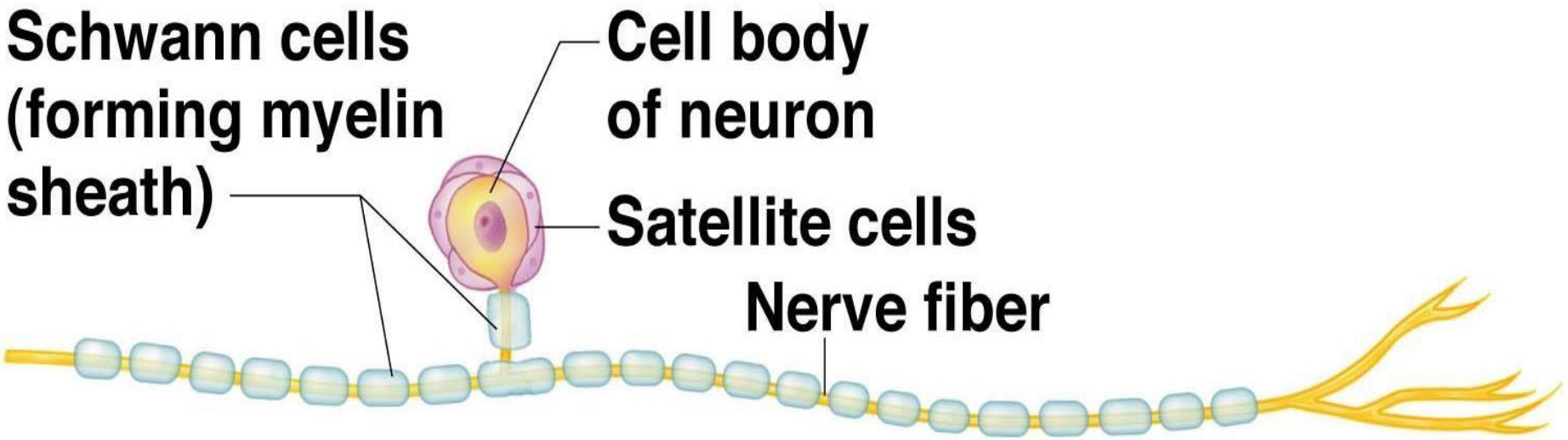
- Protects neuron cell bodies which is where the nucleus of the cell if found





2.Schwann cells

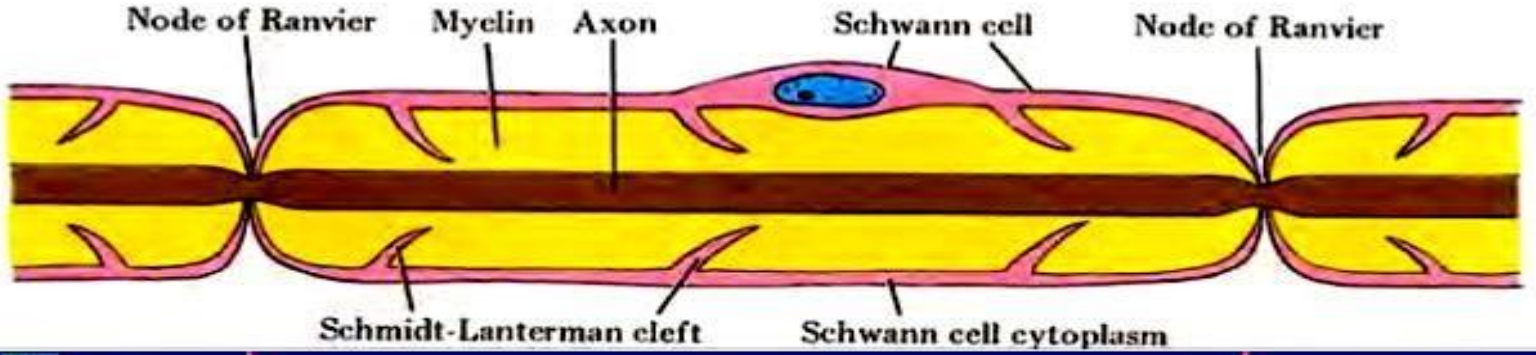
- **Form myelin sheath in the peripheral nervous system (nerves of the body; *not* nerves of the CNS**



Sensory neuron with Schwann cells and satellite cells

Schwann cells

Each Schwann cell myelinates a single internode

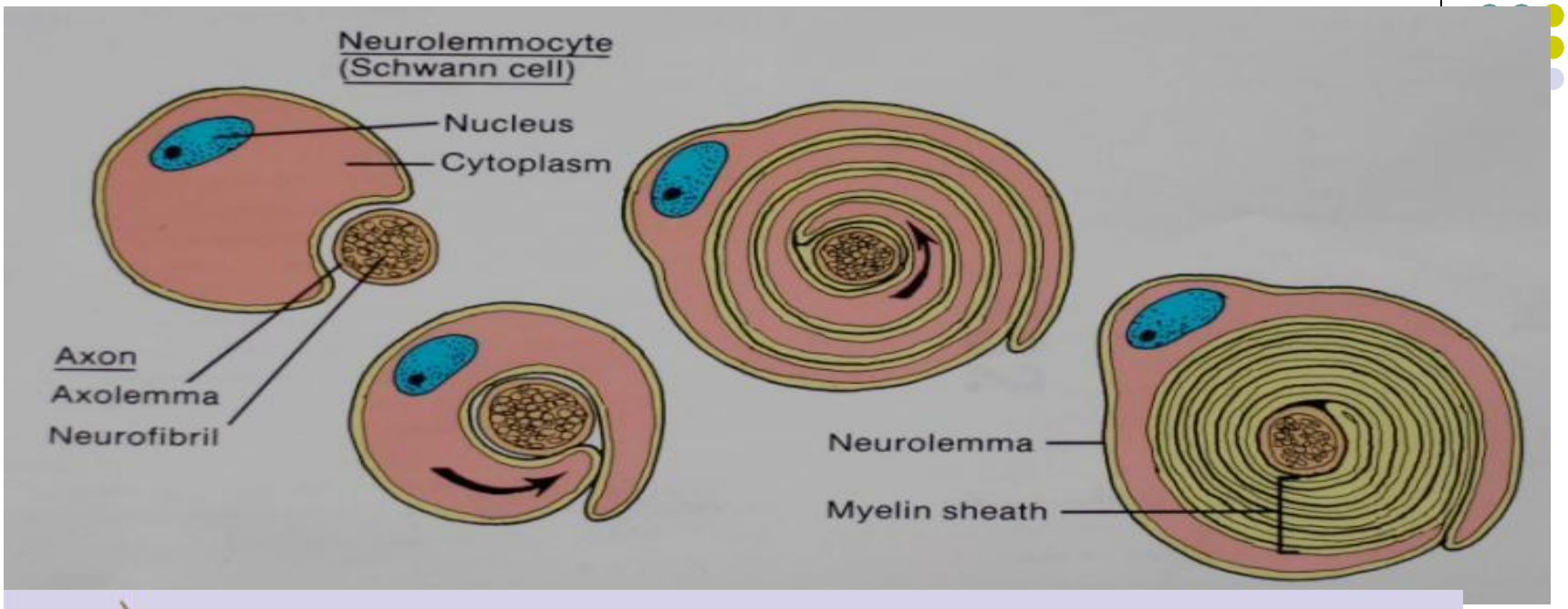


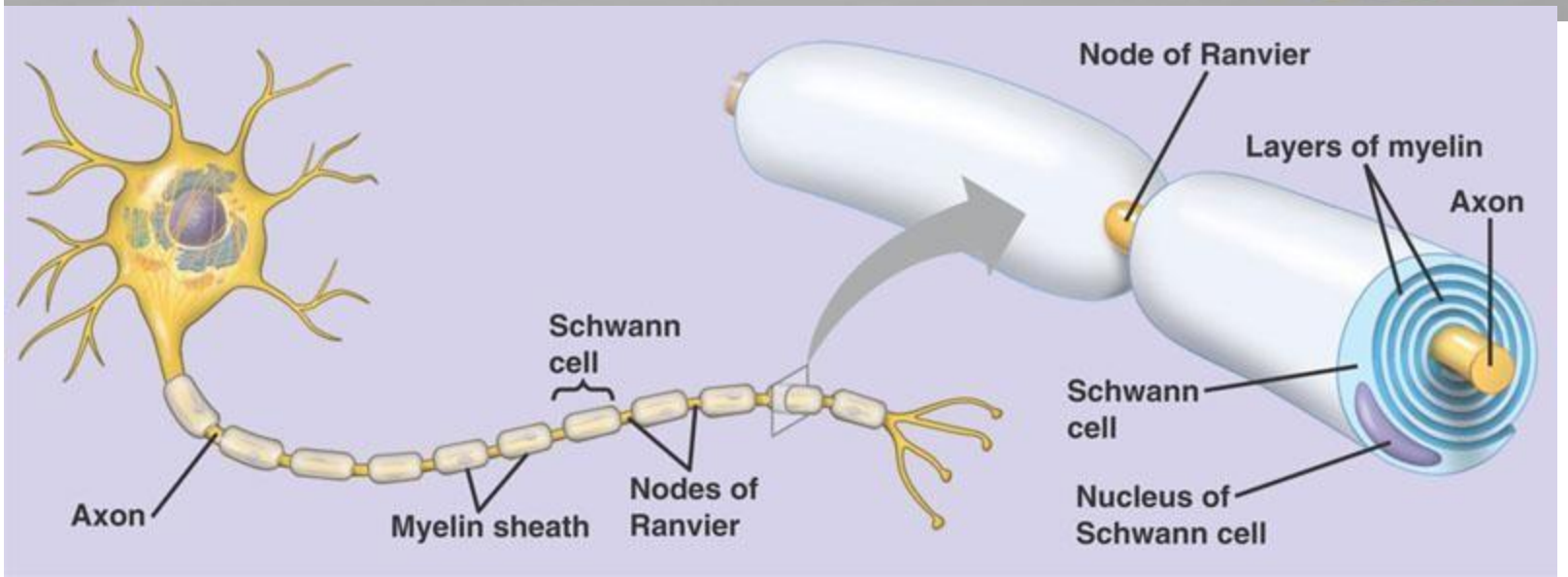
Source Undetermined

Internode length can be up to 1.5 mm in the largest nerve fibers

- Myelin sheath — whitish, fatty material covering axons
  - protects/insulates the cells and increases the transmission rate of nerve impulses
- Schwann cells — produce myelin
- Nodes of Ranvier — gaps in myelin sheath along the axon

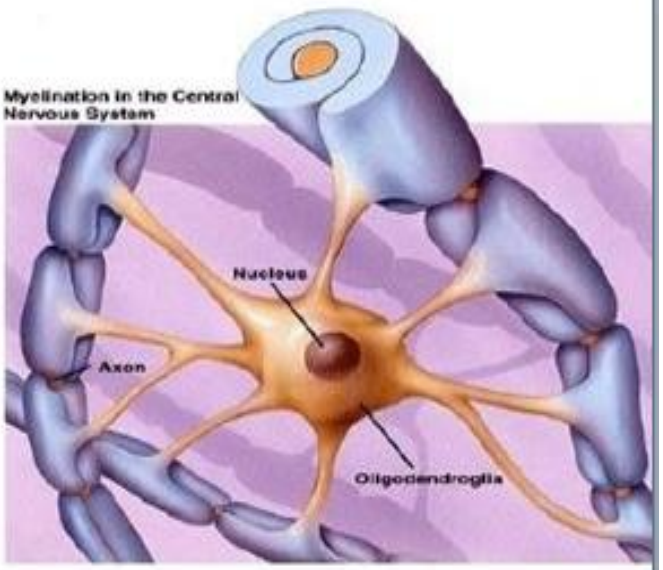
The process of myelination





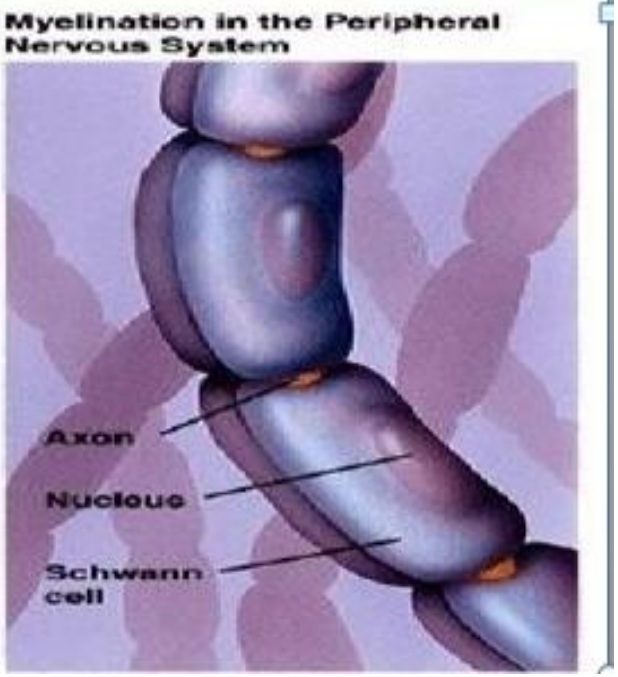
Oligo-dendrocytes

- ✓ produce the myelin sheath which provides the electrical insulation for neurons in CNS



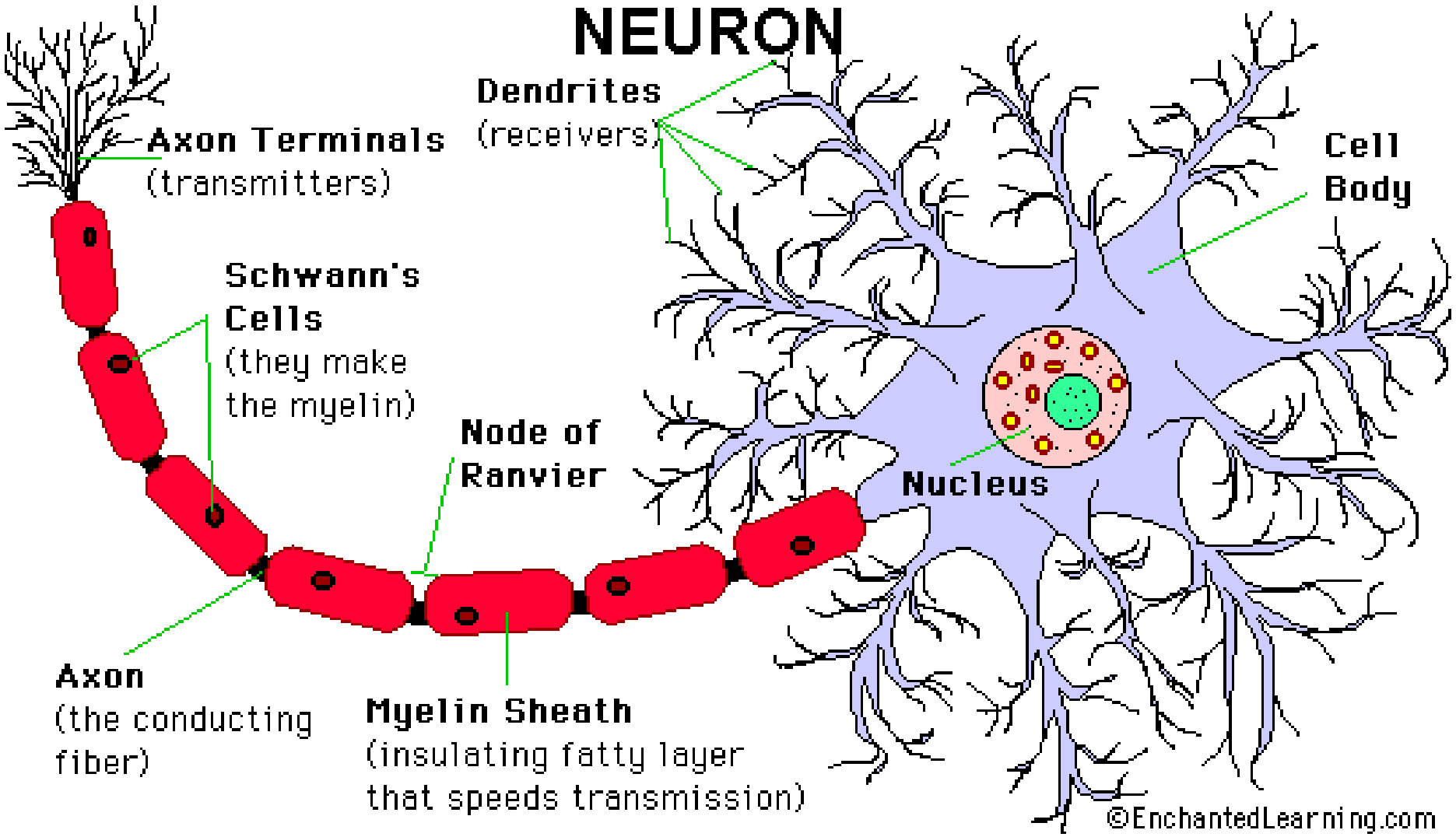
Schwann cells

- ✓ Form myelin sheaths around the larger nerve fibers in PNS.
- ✓ Vital for neuronal regeneration



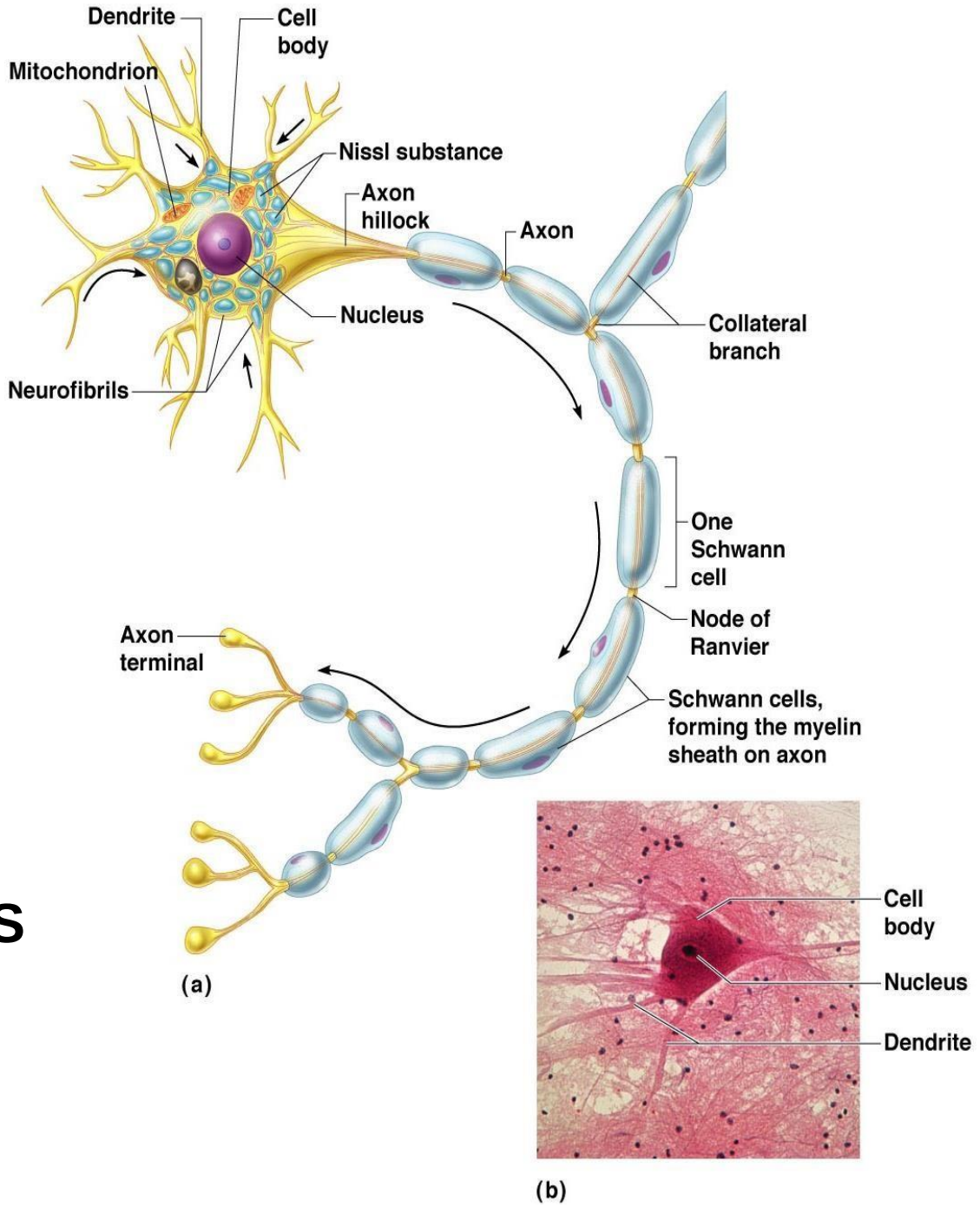
Neurons

- Neurons = nerve cells
  - Cells specialized to transmit messages
  - Major regions of neurons
    - Cell body — nucleus and metabolic center of the cell (main part of nerve cell)
    - Processes — fibers that extend from the cell body
      - can be microscopic or up to 3-4 feet in length


NEURON
Dendrites
(receivers)
Axon Terminals
(transmitters)
Cell
Body
Schwann's
Cells
(they make
the myelin)
Node of
Ranvier
Nucleus
Axon
(the conducting
fiber)
Myelin Sheath
(insulating fatty layer
that speeds transmission)
©EnchantedLearning.com

STRUCTURE OF NEURON

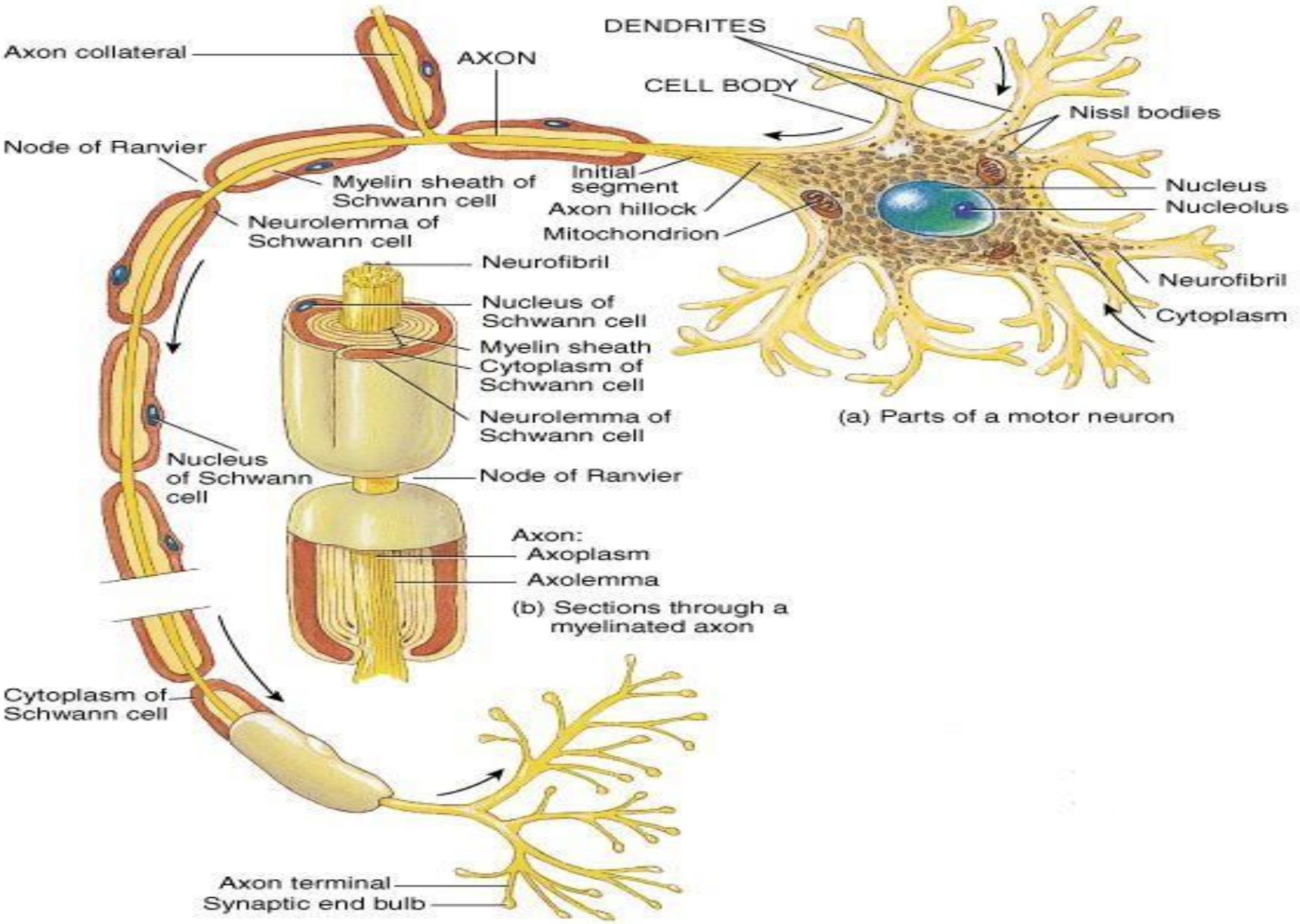
- Principle cells of Nervous Tissue
- **Consist of 3 parts** :
  - **CELL BODY** (perikaryon/soma)
  - **A single AXON**
  - **Multiple DENDRITES**
- ø 5-150 µm



Neuron

- Functional unit of nervous system

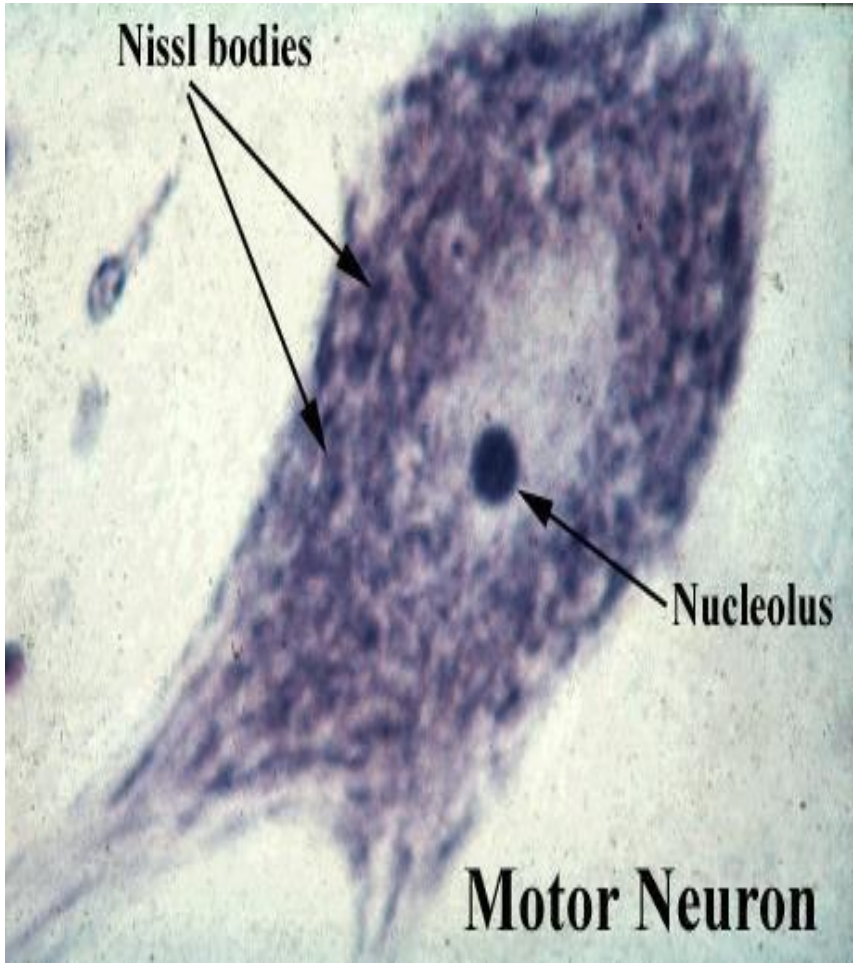
1. Cell body
   a) Nissl bodies
   b) Neurofilaments
   c) Microtubules
   d) Lipofuscin pigment clumps
2. Cell processes
   a) Dendrites
   b) Axons


DENDRITES
Axon collateral
AXON
CELL BODY
Nissl bodies
Node of Ranvier
Initial segment
Myelin sheath of Schwann cell
Nucleus
Axon hillock
Nucleolus
Neurolemma of Schwann cell
Mitochondrion
Neurofibril
Neurofibril
Nucleus of Schwann cell
Cytoplasm
Myelin sheath
Cytoplasm of Schwann cell
Neurolemma of Schwann cell
(a) Parts of a motor neuron
Nucleus of Schwann cell
Node of Ranvier
Axon:
Axoplasm
Axolemma
(b) Sections through a myelinated axon
Cytoplasm of Schwann cell
Axon terminal
Synaptic end bulb

FUNCTION OF NEURON

- Receptive
  - Receptor receive stimuli and tranduce into nerve
    impulse and transferro to other neuron
- Integrative
  - Processing impulse on the higher center
- Motor
  - Initiating motor respons and tranduse impulse to the effector

CELL BODY (PERIKARYON(



- Central portion of the cell
- Generally are polygonal
- Different shape and size → characteristic regions of nervous system
- Contain:
  - Nucleus
  - Perinuclear cytoplasm

ULTRASTRUCTURE OF NEURON

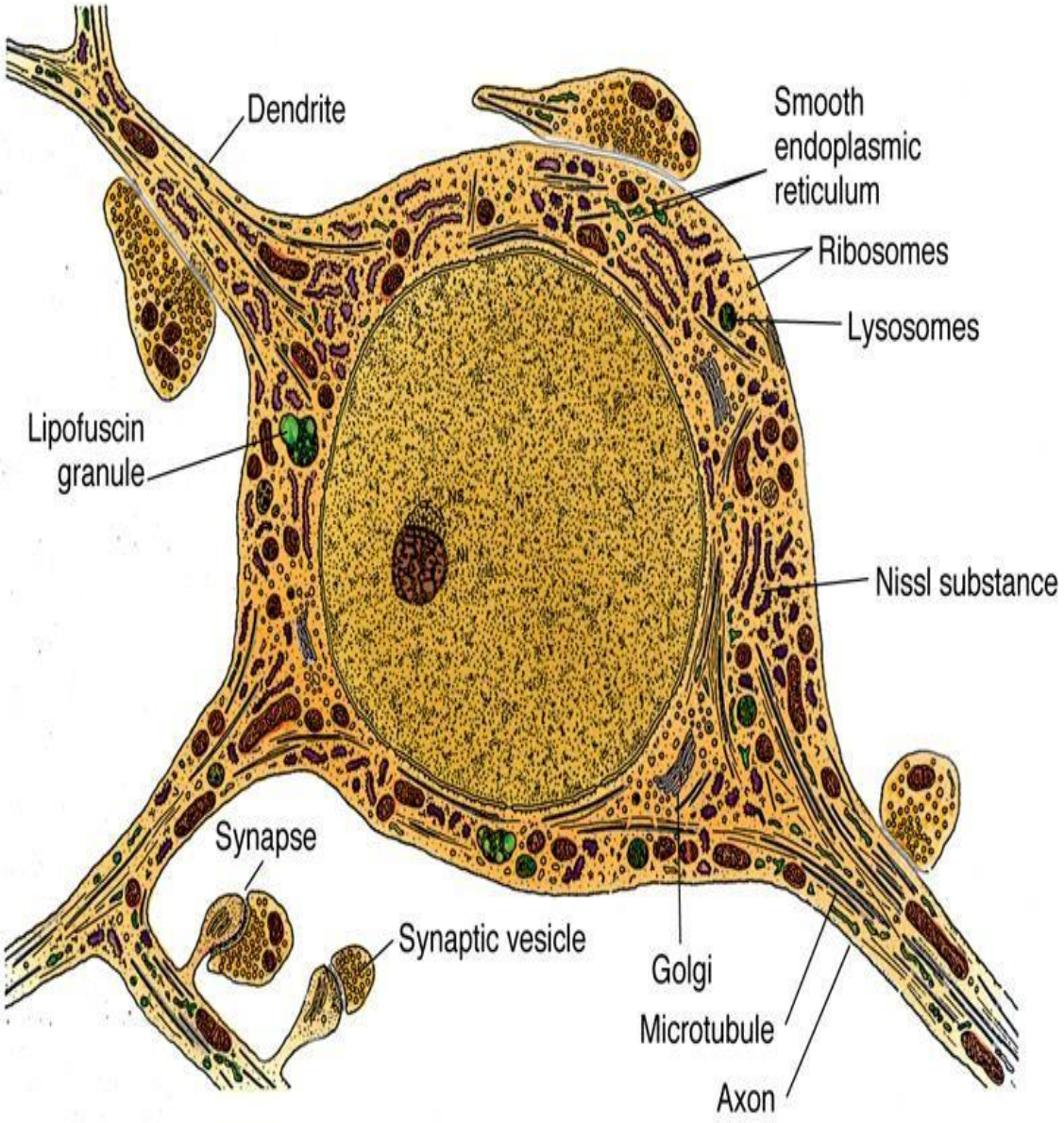
Nucleus:

- large, spherical to ovoid and centraly located
- a single prominent nucleolus
- finely dispersed chromatin
- → **trancriptionaly active**

Cytoplasm:

a. Abundant of R.E.R
b. Polyribosomes
c. Basic dyes (a+b) →**Nissl Bodies**
d. lots of S.E.R.
e. Golgi bodies (perikaryon)

→ **protein secreting cell**

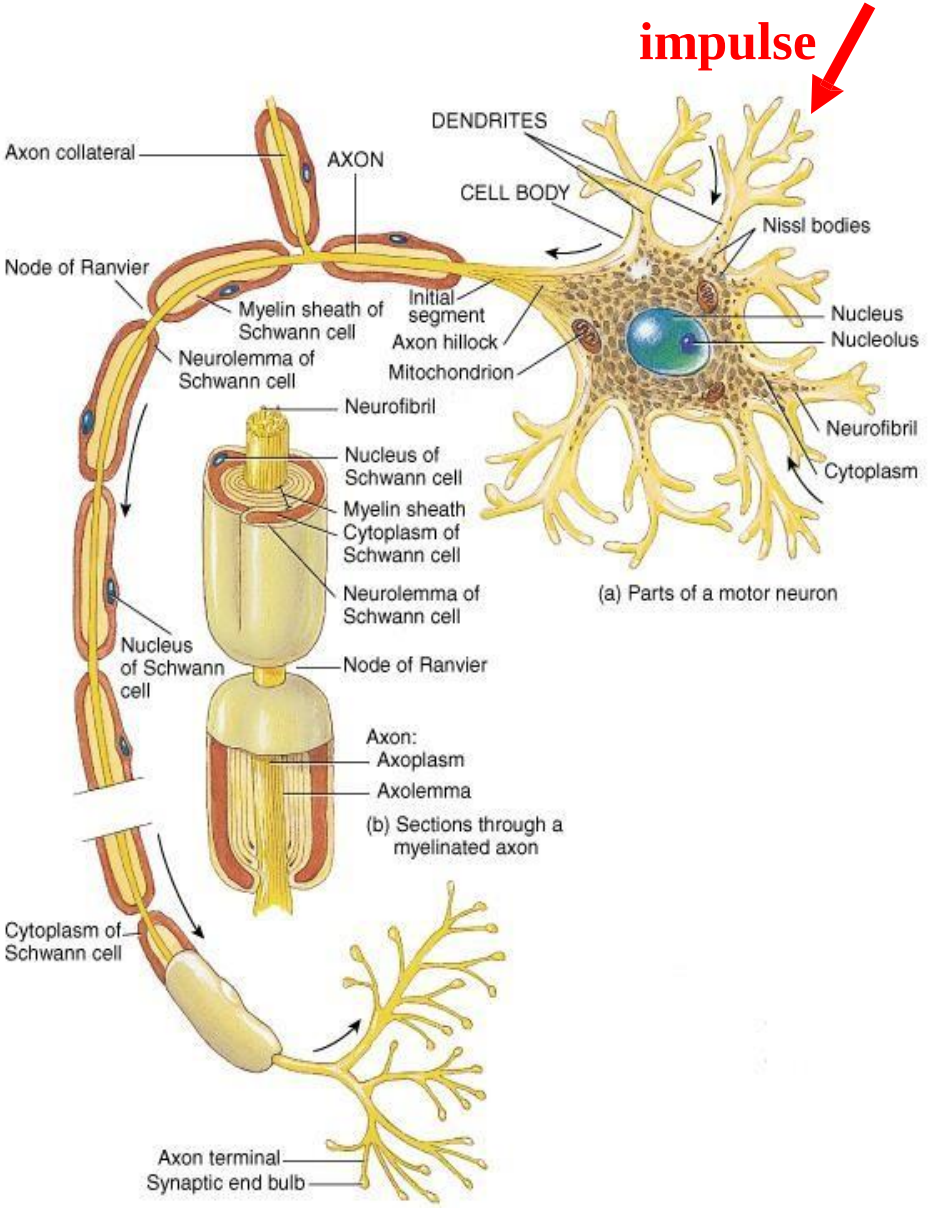


Cytoplasm

a. Many mitochondria, most abundant in axon terminal
b. extensive cytoskeleton → axonal transport
c. <u>One centriole</u> → **do not undergo cell divisions**

Dendrites

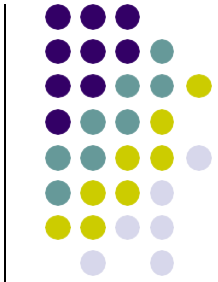
- Conducts impulses towards the cell body
- Typically short, highly branched & unmyelinated
- Surfaces specialized for contact with other neurons
- Contains neurofibrils & Nissl bodies



Axons

- Conduct impulses away from cell body
- Long, thin cylindrical process of cell
- Arises at axon hillock
- Impulses arise from initial segment (trigger zone)
- Side branches (collaterals) end in fine processes called axon terminals
- Swollen tips called synaptic end bulbs contain vesicles filled with neurotransmitters

Structural Classification of Neurons



- Based on number of processes found on cell body

1) multipolar = several dendrites & one axon

- most common cell type

2) bipolar neurons = one main dendrite & one axon

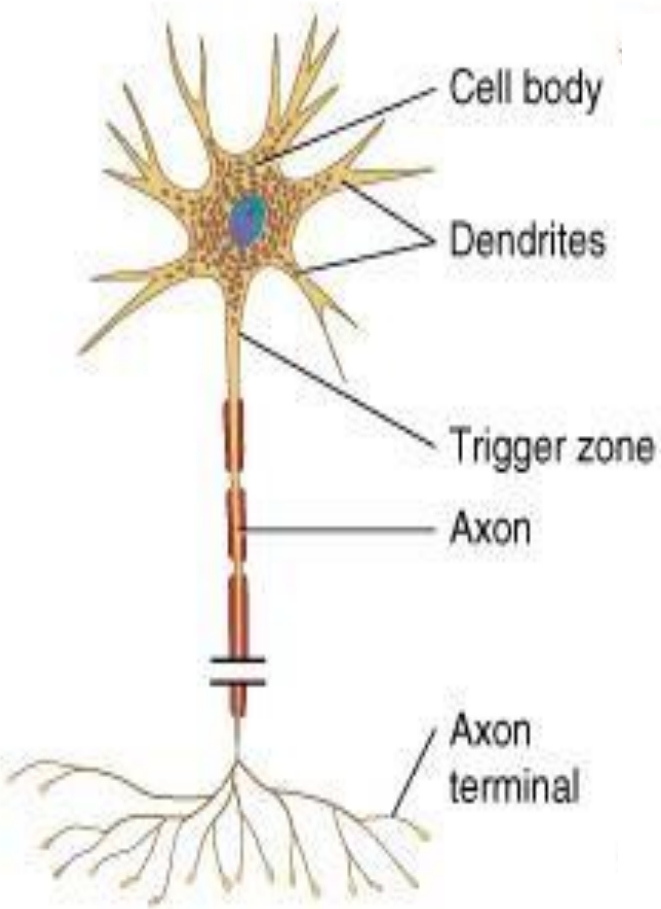
- found in retina, inner ear & olfactory

3) unipolar(pseudunipolar) neurons = one process only(develops from a bipolar)

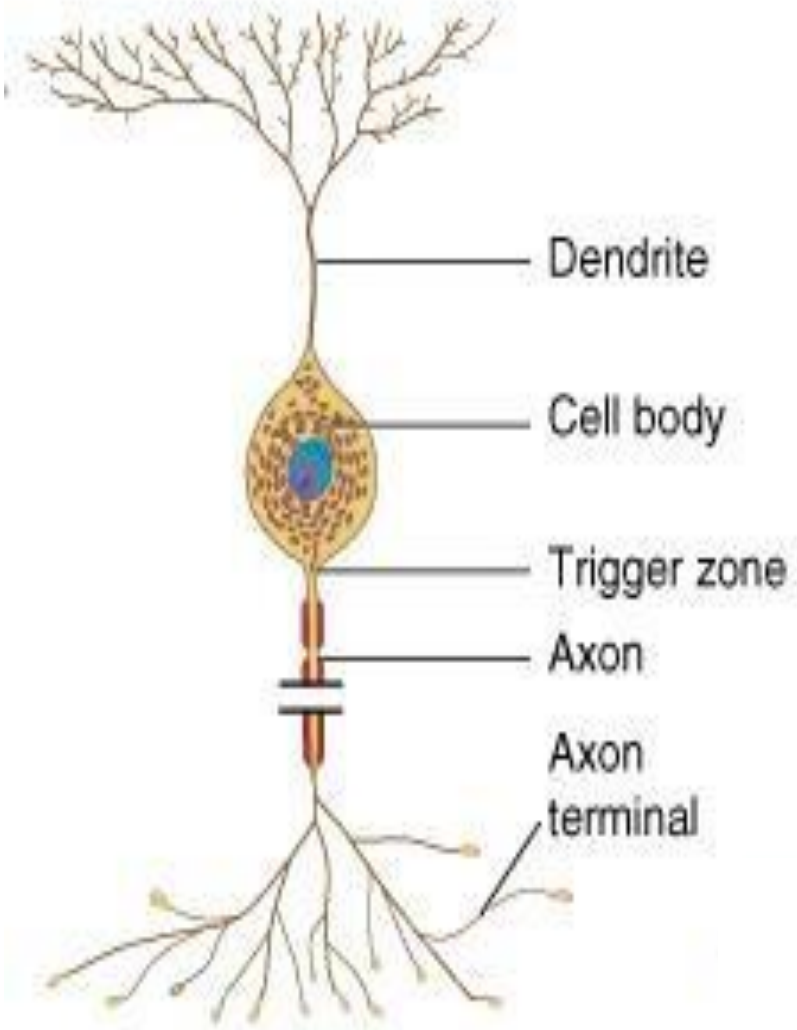
- are always sensory neurons

4) **Anaxonic neurons**

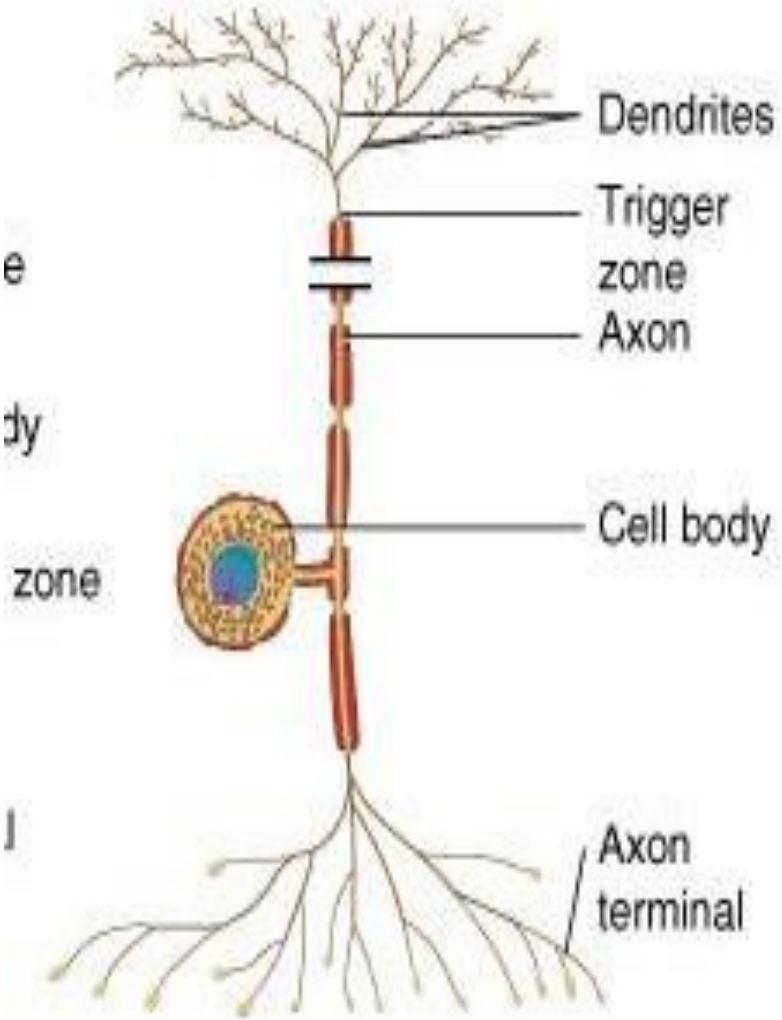
- CNS
- Lack true axon
- Don't produce action potential
- Regulatory function



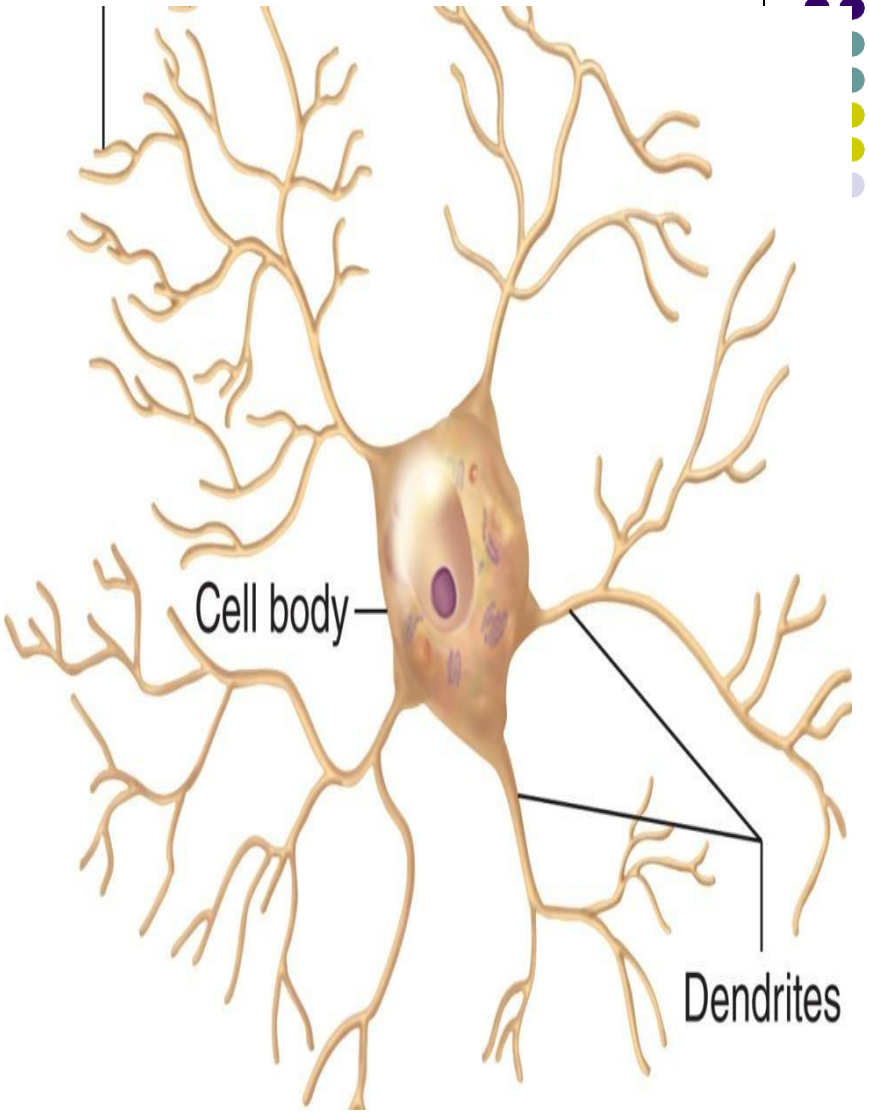
(a) Multipolar neuron



(b) Bipolar neuron



(c) Unipolar neuron



(d) Anaxonic neuron

NEURON GROUPING

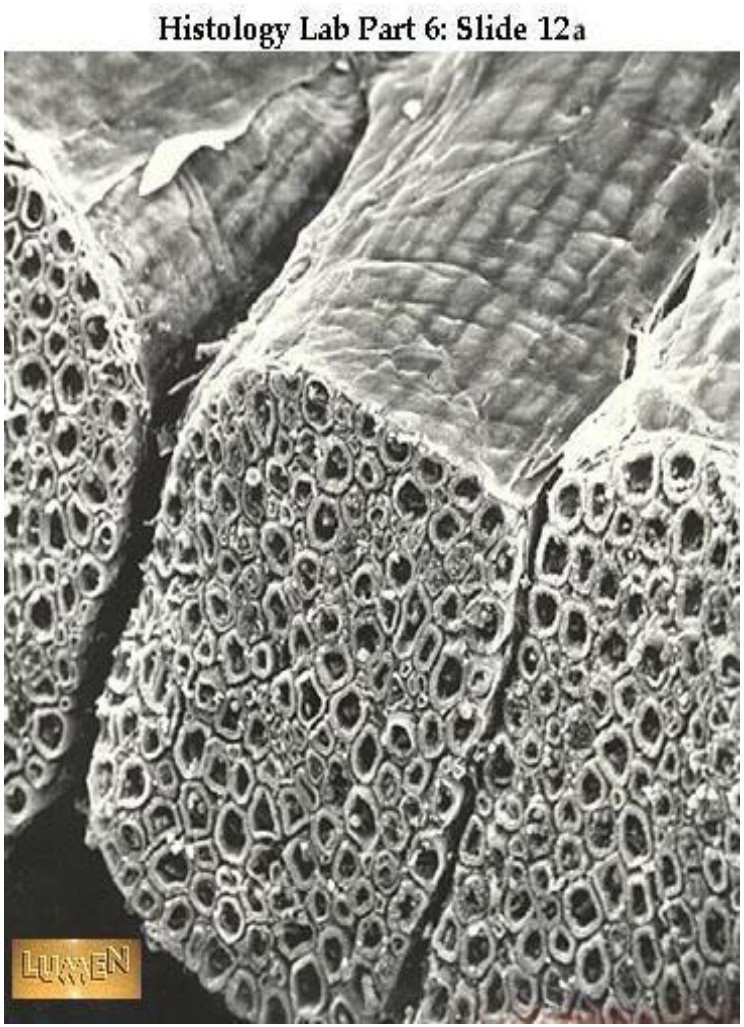
- CORTEX
  - Neuron form six layers on the cerrebrum
  - Form three layers on the cerrebellum
- NUCLEI
  - In subcortical region (thalamus, midbrain, brainstem and spinal cord) neuron form irregular cluster → nuclei
- GANGLION
  - Cluster of neuron outside the CNS

NEURONS CLASSIFICATION:

According to their function:

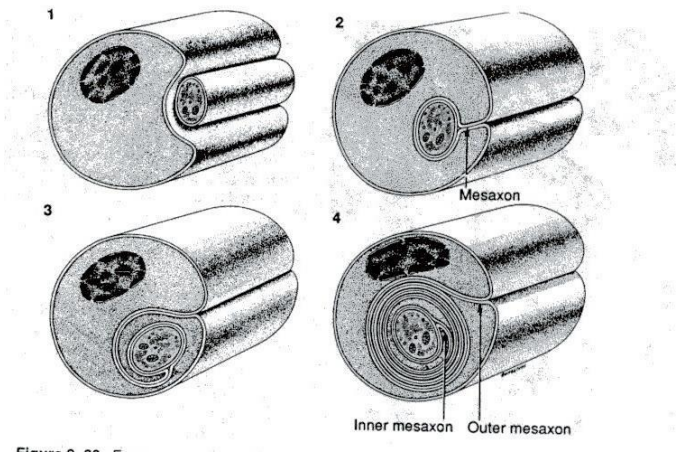
- **Sensory Neuron (afferent)**
  - Receive sensory input → conduct impulses to CNS
- **Motor Neuron (Efferent)**
  - CNS → conduct impulses to muscles, glands and other neurons
- **Interneuron**
  - In the CNS as interconnectors, establish neuronal circuit between sensory and motor neuron

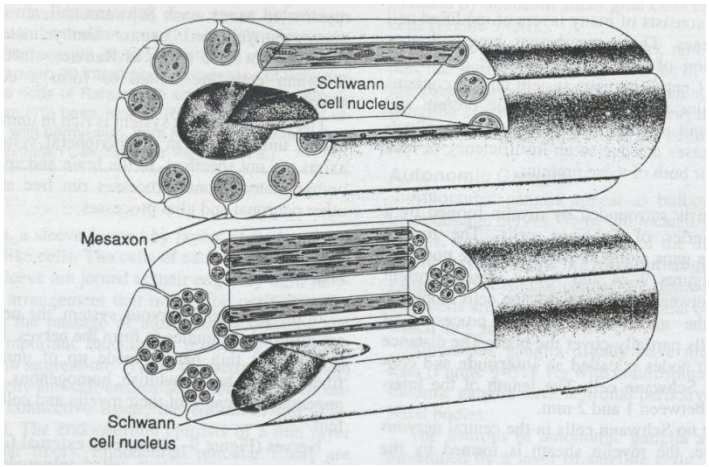
NERVE FIBERS



- Consist of axons enveloped by a special sheath
- Group of fibers constitute the **peripheral nerve**
- Two types:
  - Myelinated fiber
  - Unmyelinated fiber

NERVE FIBERS





- **Myelinated fibers**
  - A single Schwann cell wraps around single axon→ form myelin sheath → **nodes of Ranvier**
- **Unmyelinated fibers**
  - A single Schwann cell envelopes several axon
  - Fibers enveloped within simple clefts of Schwann cells

Myelin formation

- Myelin is not part of the neuron but formed by the ***Neuroglial*** cells.
- Begins during **2nd** trimester of pregnancy and continues well into the **2nd** decade
- Myelin increases the speed of impulse conduction.

Nerve fibers are either:

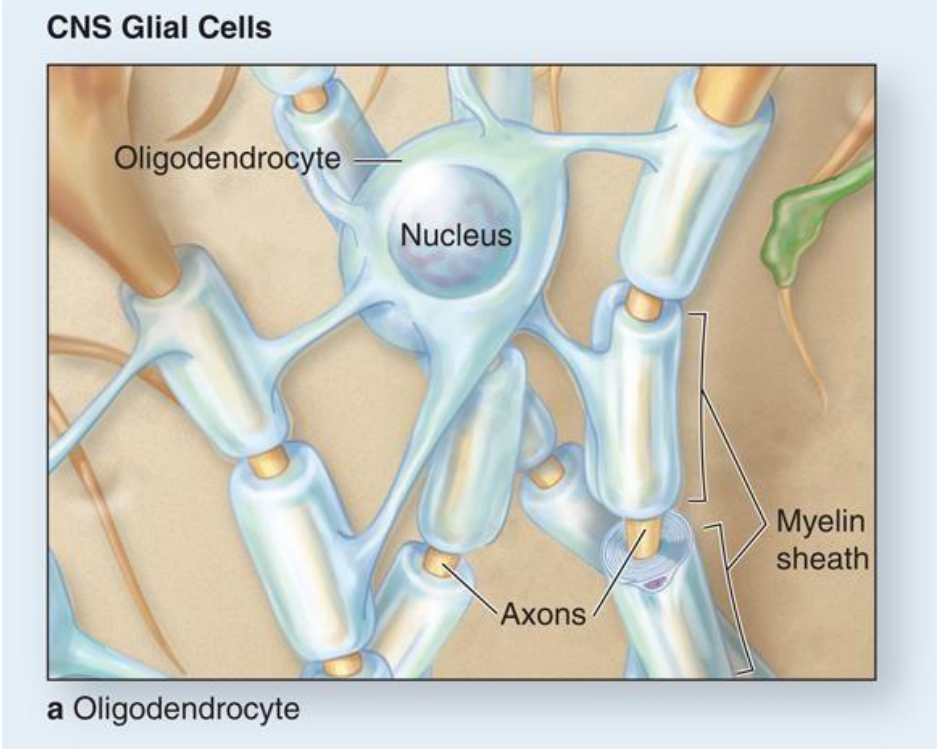
Myelinated: Impulse conduction is saltatory (jumping from node to node) with a maximum speed of 120m/s.

Unmyelinated: Impulse conduction is continuous with a maximum speed 15m/s.

Myelination in the CNS:

*Formed by Oligodendrocytes.

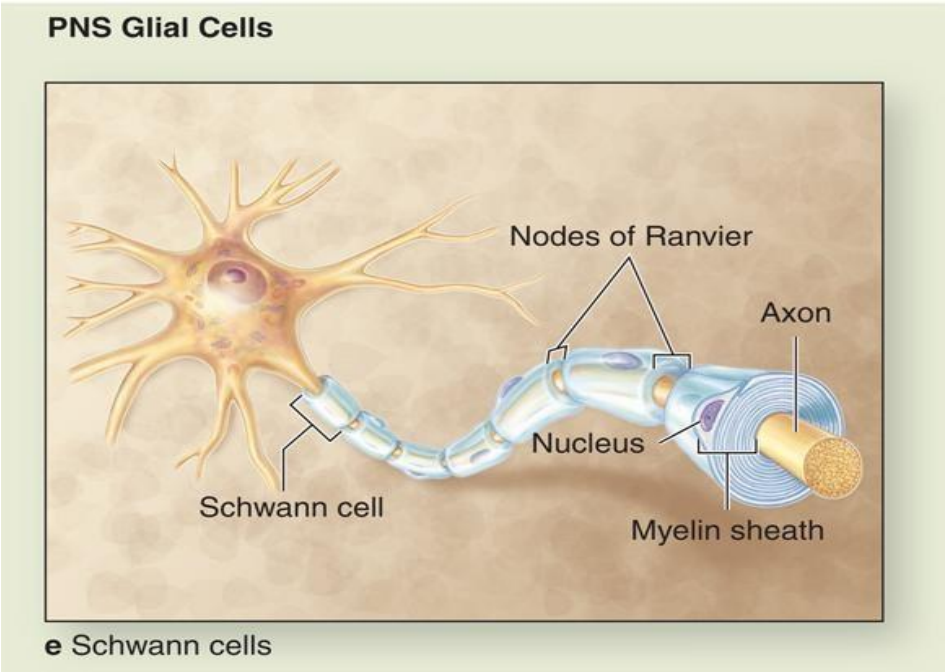
*Each cell can myelinate internodal segments of about 60 axons



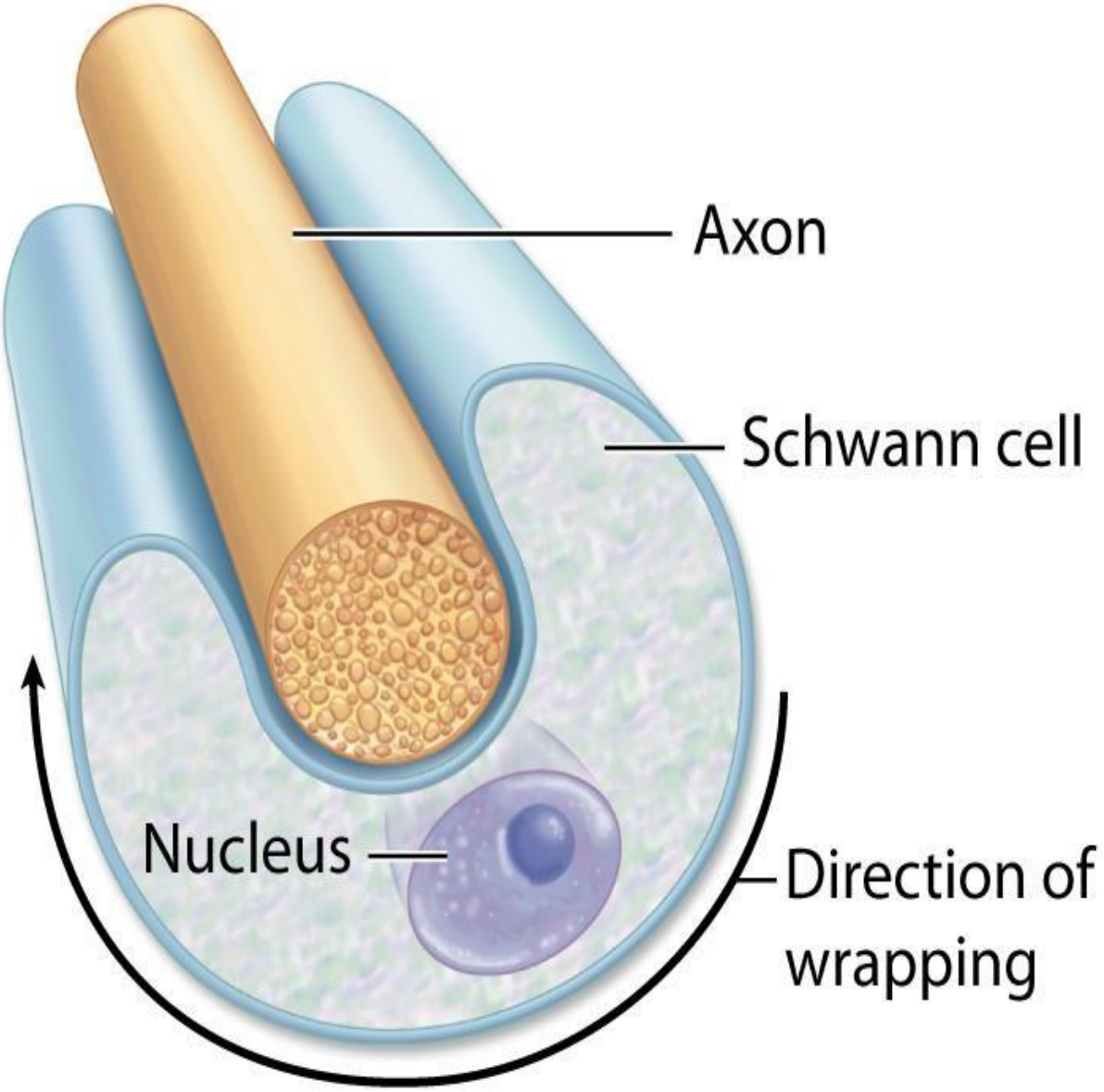
Myelination in the PNS:

*Formed by **Schwann cells**

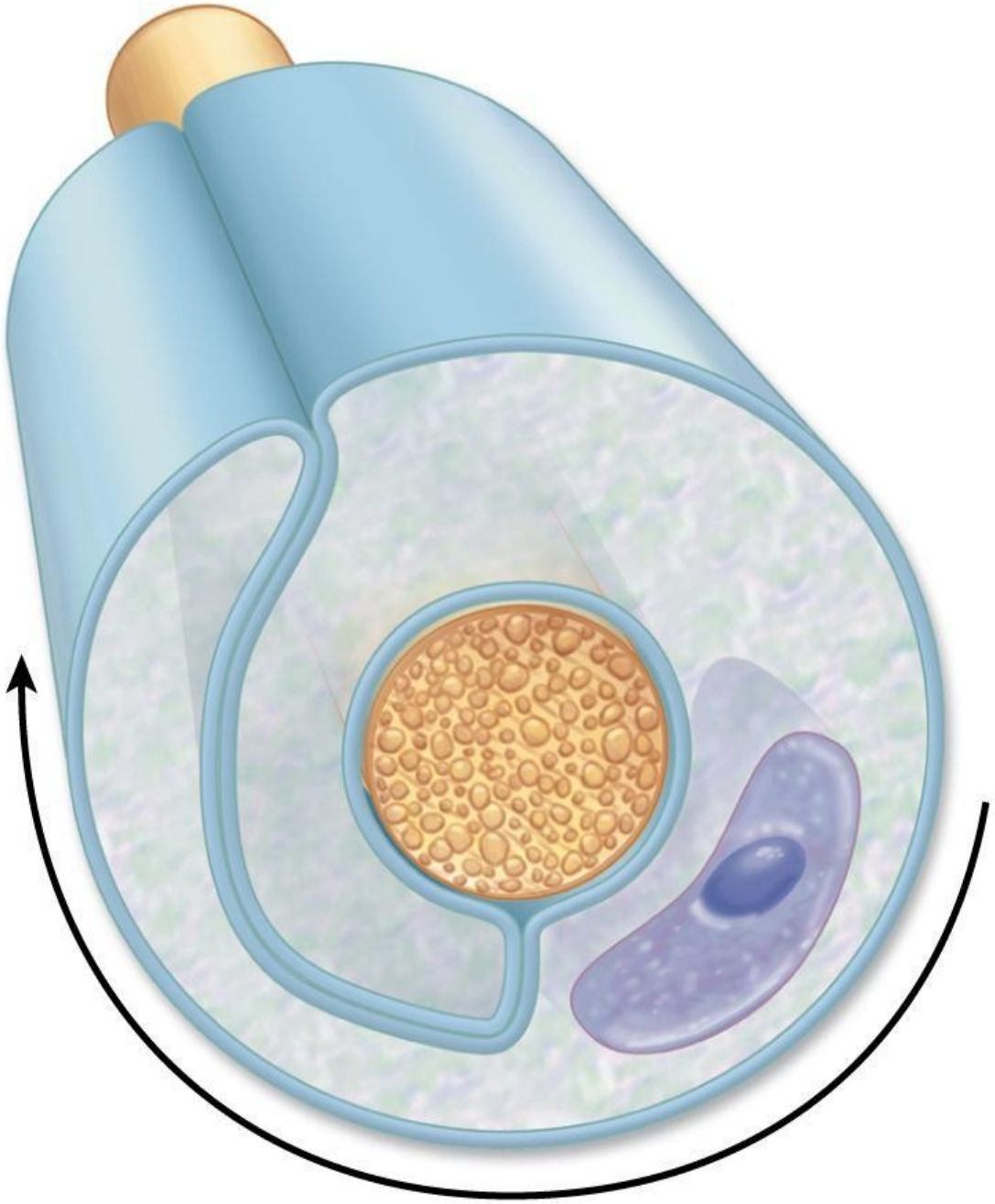
*Each Schwann cell myelinates **only one internodal segment of one axon**



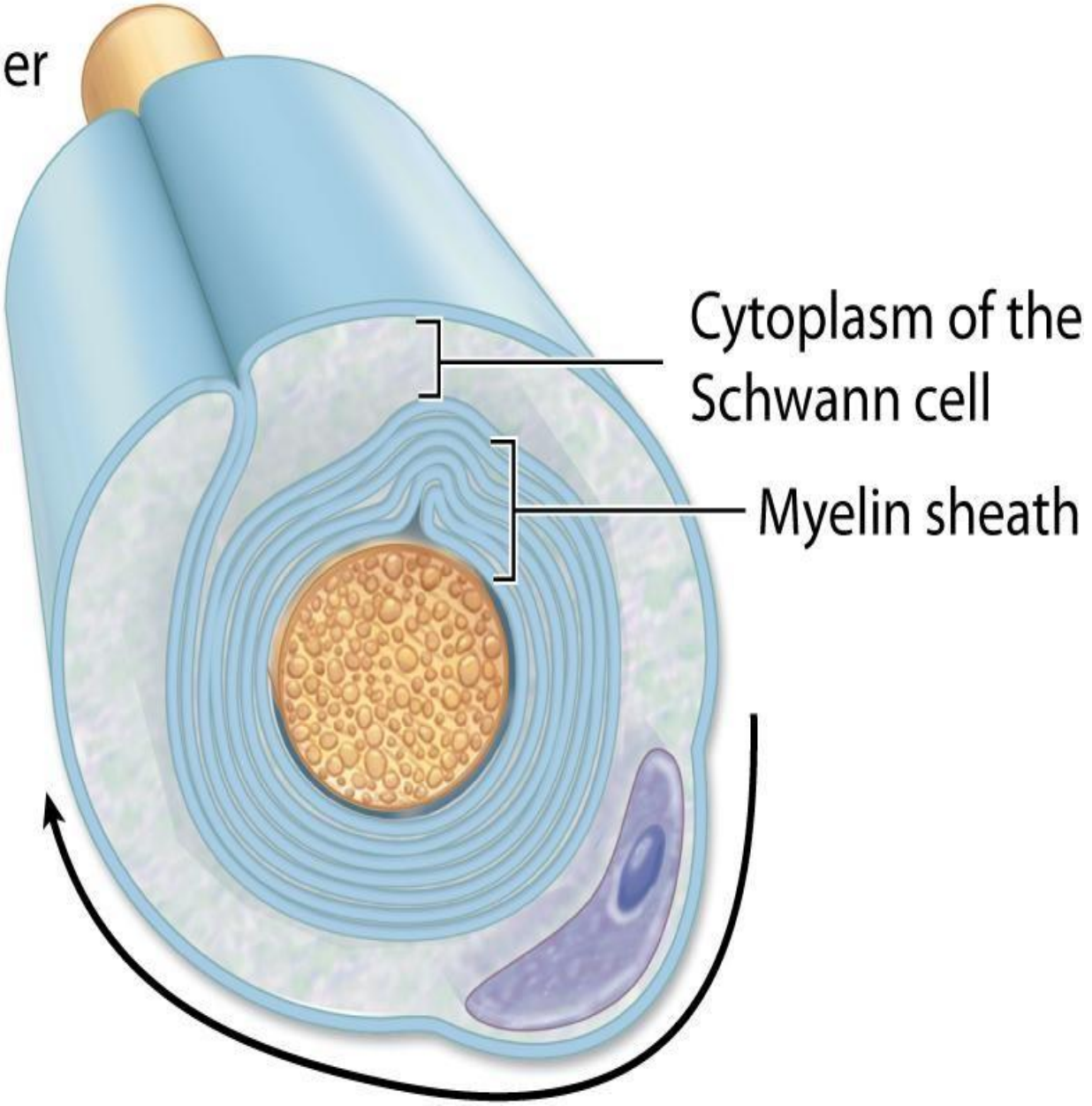
① Schwann cell starts to wrap around a portion of an axon.



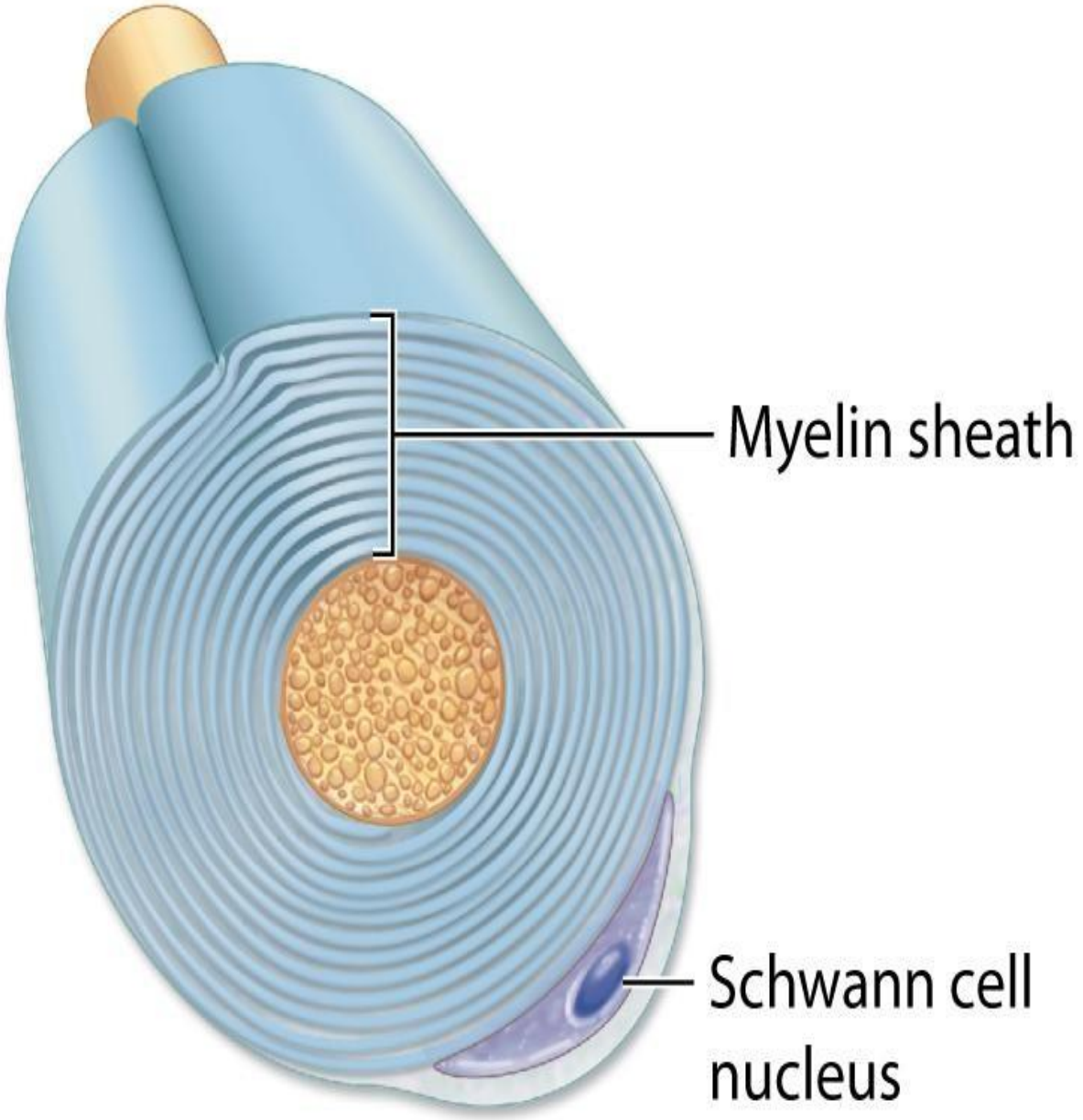
2 Schwann cell cytoplasm and plasma membrane begin to form consecutive layers around axon.



3 The overlapping inner layers of the Schwann cell plasma membrane form the myelin sheath.

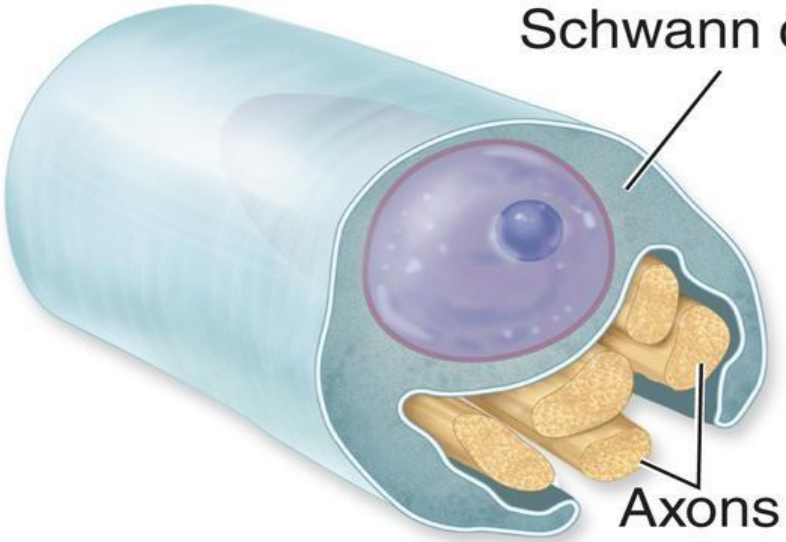


4 Eventually, the Schwann cell cytoplasm and nucleus are pushed to the periphery of the cell as the myelin sheath is formed.

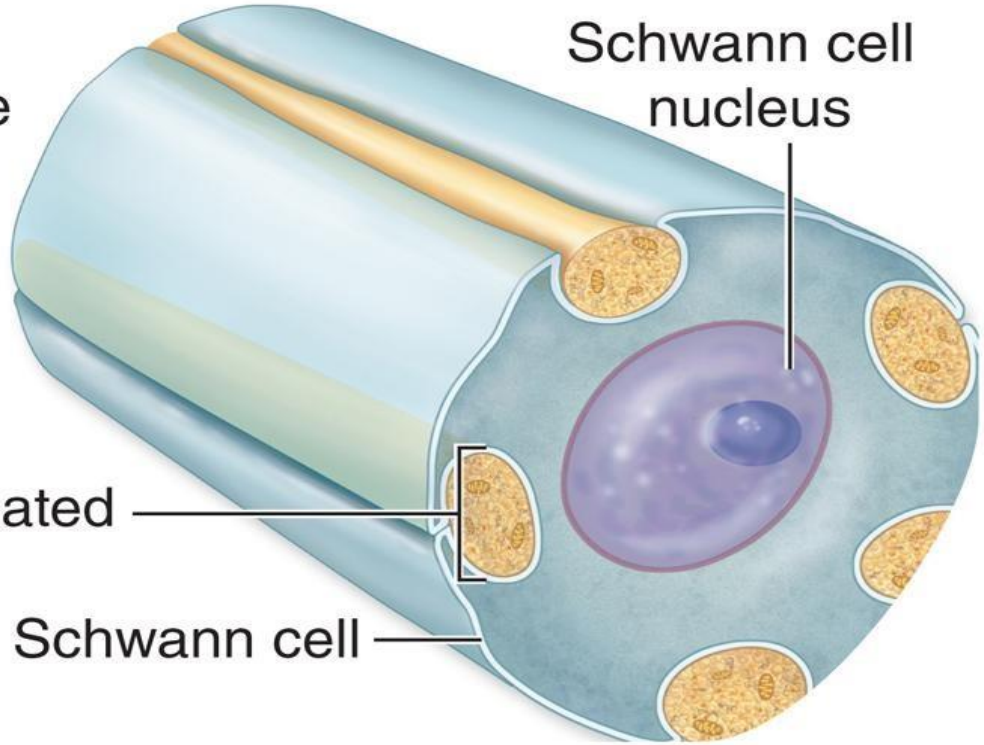


Unmyelinated axons

① Schwann cell starts to envelop multiple axons.



② The unmyelinated axons are enveloped by the Schwann cell, but there are *no* myelin sheath wraps around each axon.



Synaptic Communication

Synapses (Gr. synapsis, union) are sites where nerve impulses are transmitted from one neuron to another, or from neurons and other effector cells. The structure of a synapse ensures that transmission is unidirectional. Synapses convert an electrical signal (nerve impulse) from the **presynaptic cell** into a chemical signal that affects the **postsynaptic cell**. Most synapses act by releasing **neurotransmitters**, which are usually small molecules that bind specific receptor proteins to either open or close ion channels or initiate secondmessenger cascades.

A synapse (Figure)has the following components:

- The presynaptic axon terminal (terminal bouton) contains mitochondria and numerous synaptic vesicles from which neurotransmitter is released by exocytosis

- The postsynaptic cell membrane contains receptors for the neurotransmitter, and ion channels or other mechanisms to initiate a new impulse.

- A 20- to 30-nm-wide intercellular space called the synaptic cleft separates these presynaptic and postsynaptic membranes.

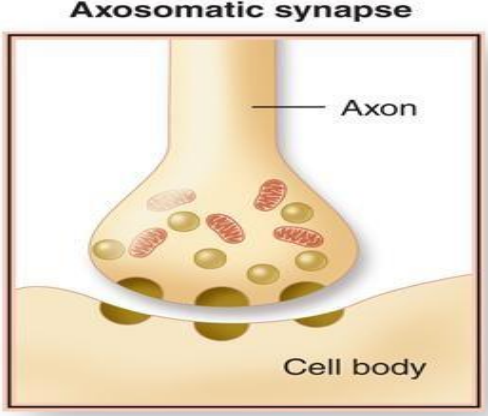
At the presynaptic region the nerve impulse briefly opens calcium channels, promoting a Ca2+ influx that triggers neurotransmitter release by exocytosis or similar mechanisms. Immediately the released neurotransmitter molecules diffuse across the synaptic cleft and bind receptors at the postsynaptic region. This produces either an excitatory or an inhibitory effect at the postsynaptic membrane, as follows:

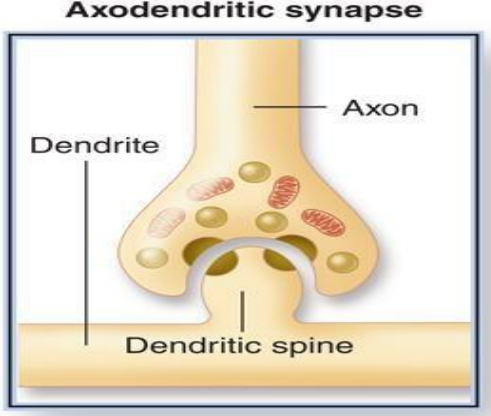
- Neurotransmitters from excitatory synapses cause postsynaptic Na+ channels to open, and the resulting Na+ influx initiates a depolarization wave in the postsynaptic neuron or effector cell as just described.

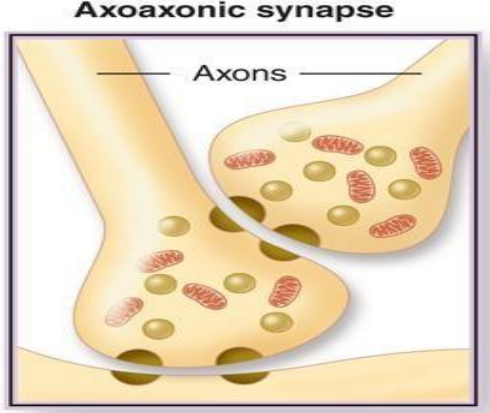
- At inhibitory synapses neurotransmitters open Cl– **or other** anion channels, causing influx of anions and hyperpolarization of the postsynaptic cell, making its membrane potential more negative and more resistant to depolarization.

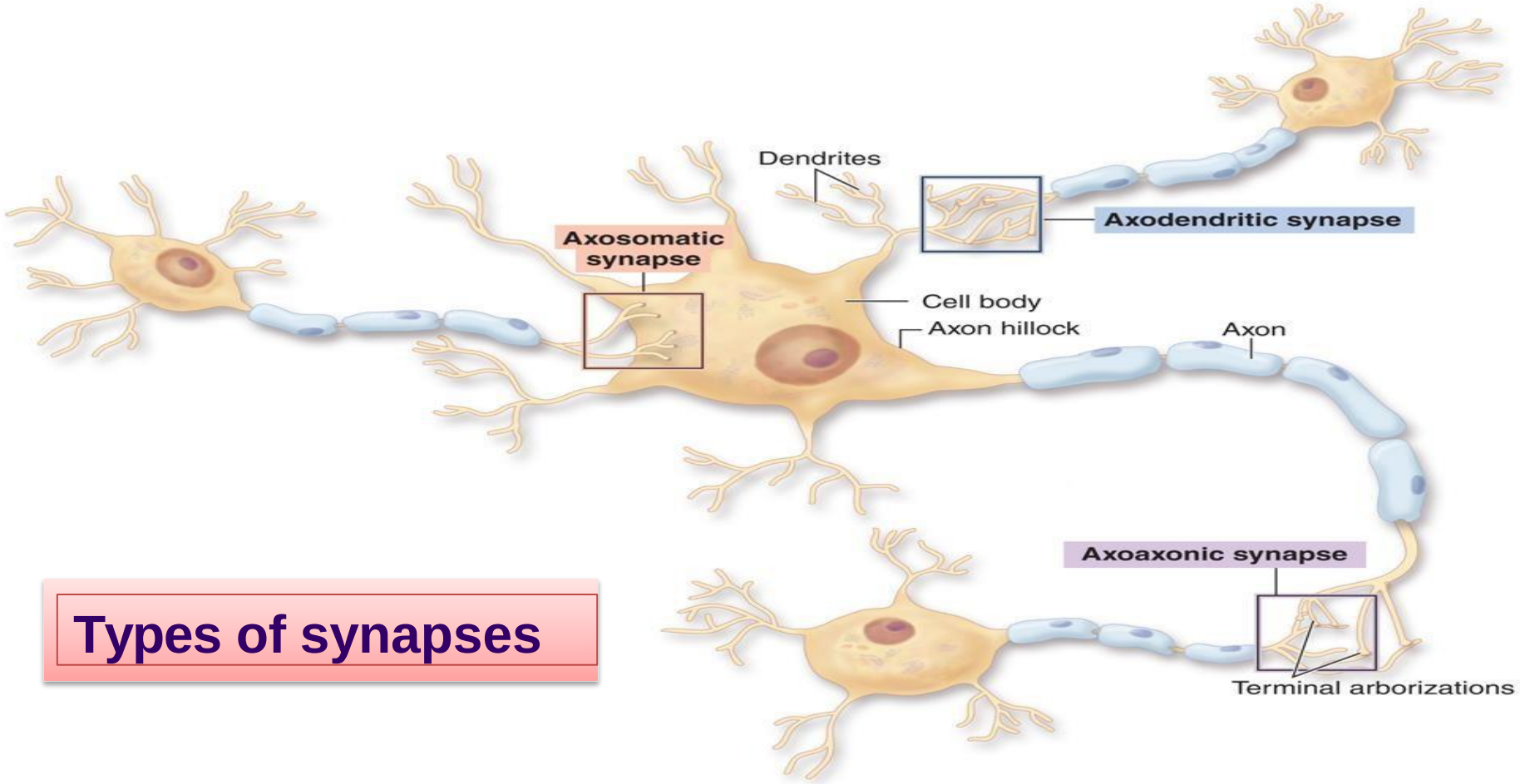
❖ The chemical transmitter used at neuromuscular junctions and some synapses of the CNS is acetylcholine. Within the CNS other major categories of neurotransmitters include the following:

- Certain amino acids (often modified), such as glutamate and γ-aminobutyrate (GABA)
- Monoamines, such as serotonin (5-hydroxytryptamine or 5-HT) and catecholamines, such as dopamine, all of which are synthesized from amino acids
- Small polypeptides, such as endorphins and substance P.



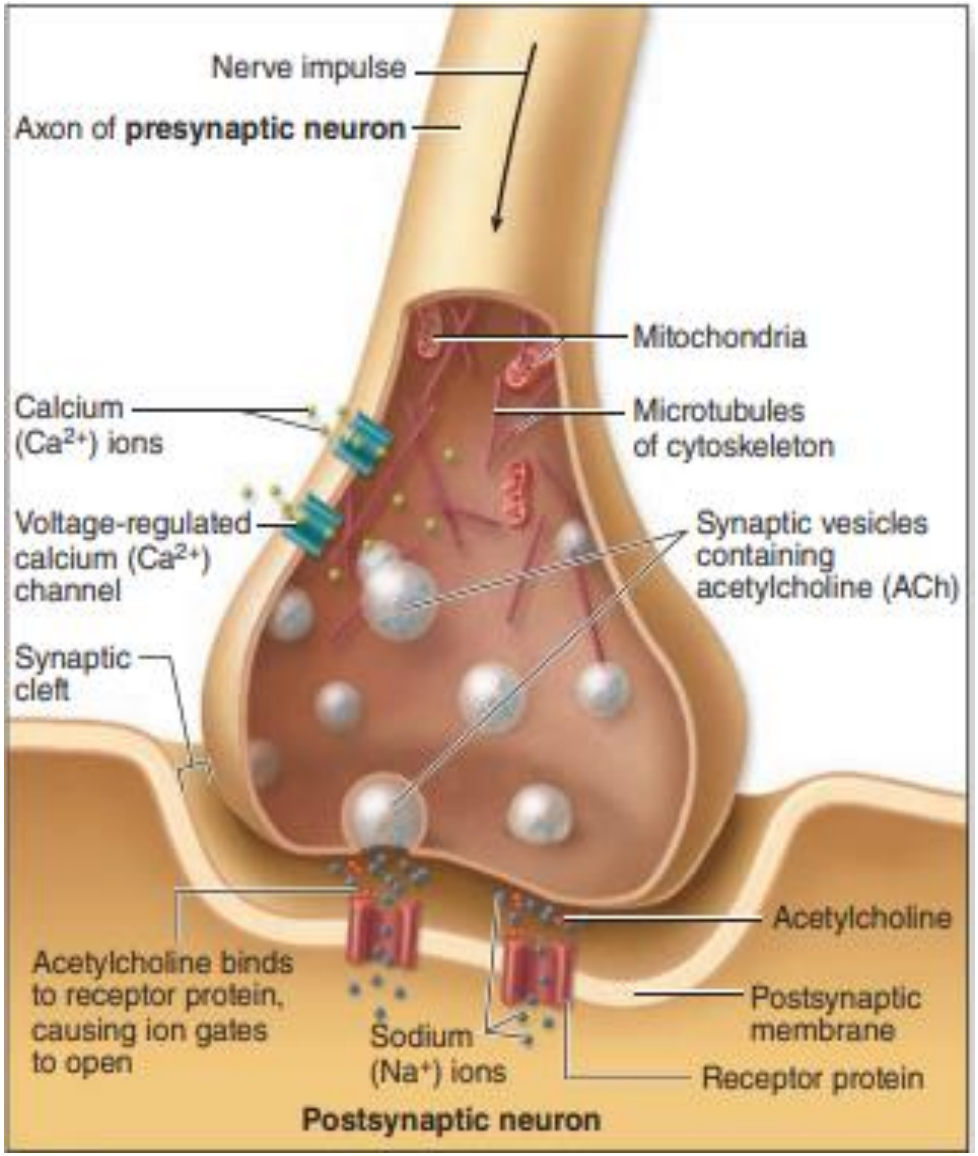




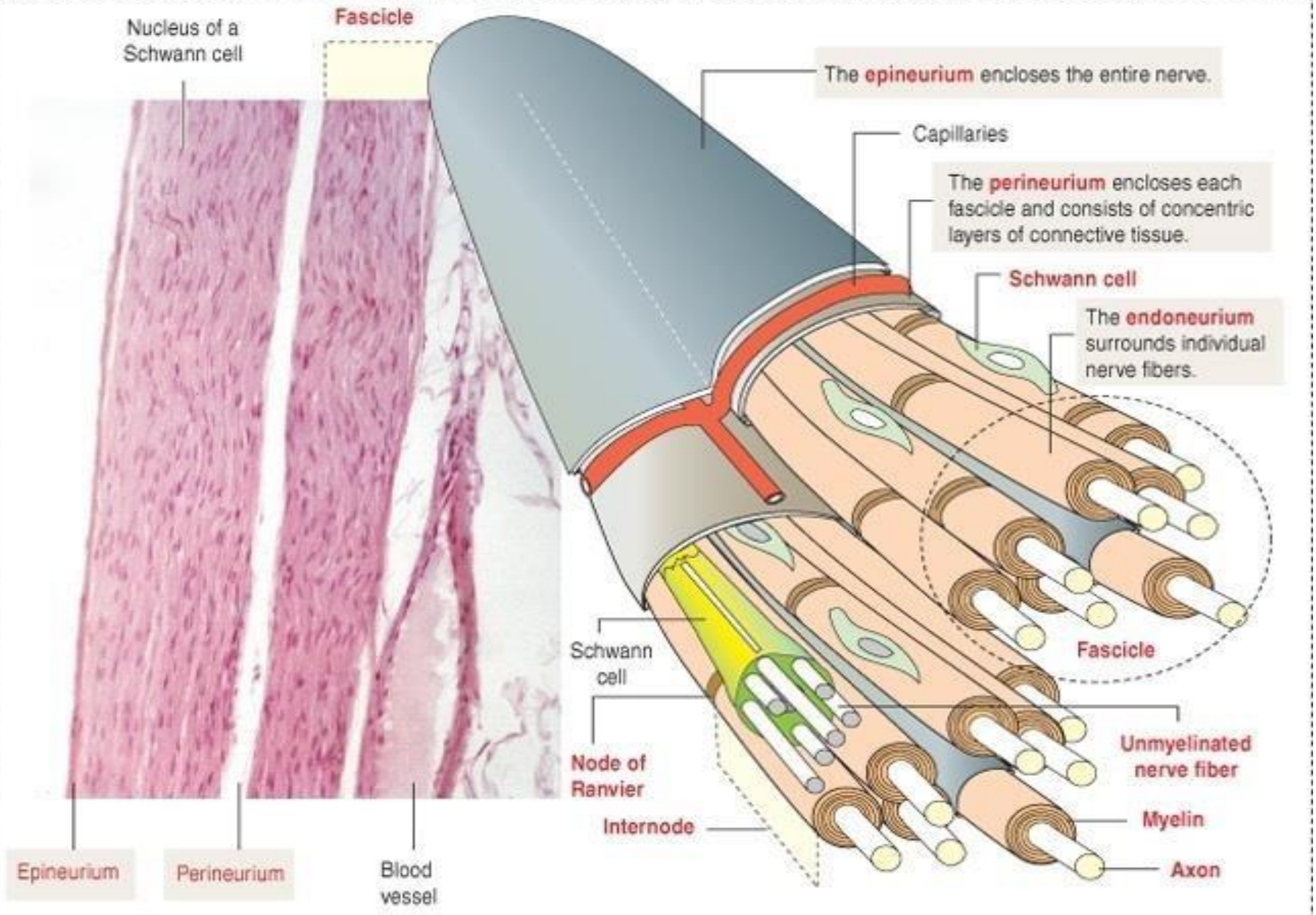


Types of synapses

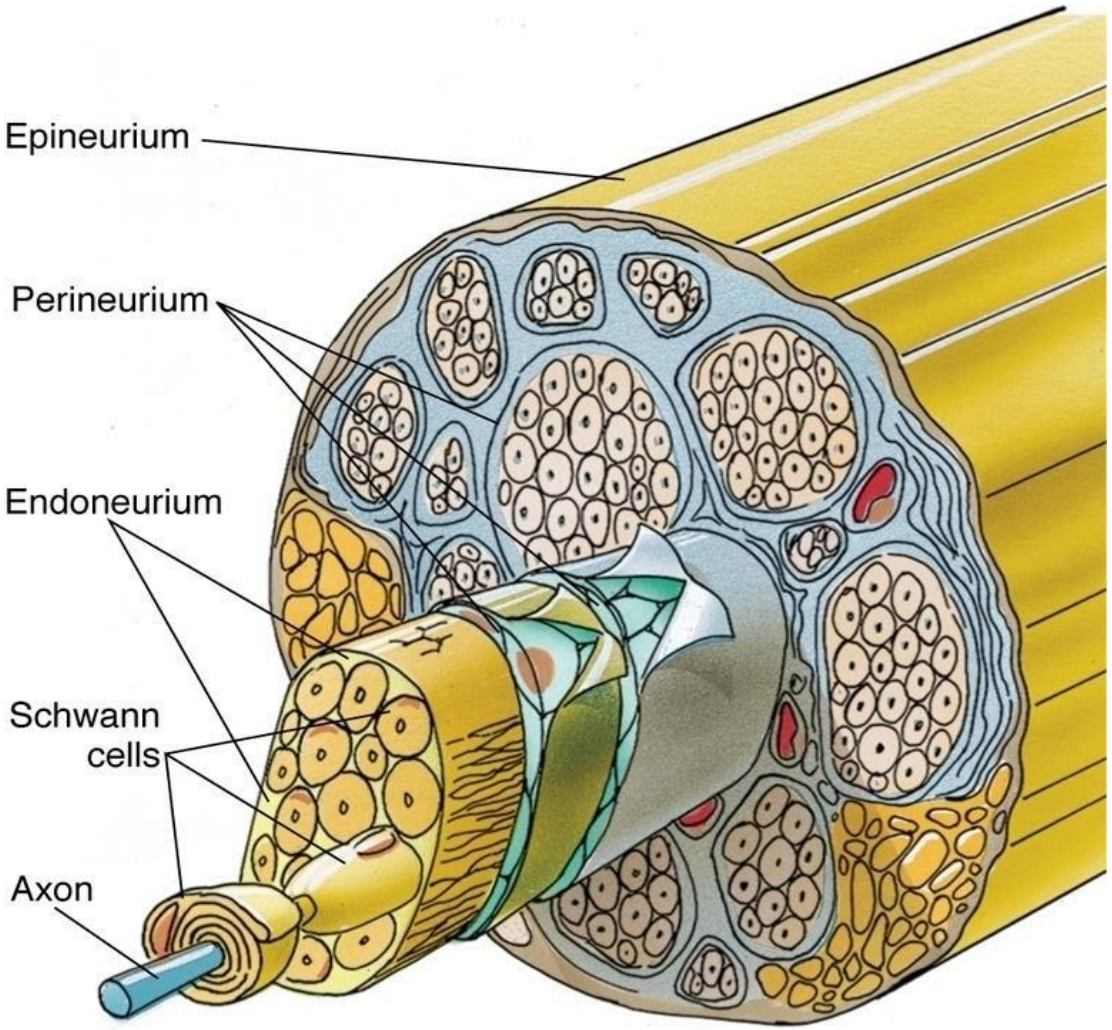
Diagram showing a synapse releasing neurotransmitters by exocytosis from the terminal bouton. Presynaptic terminals always contain a large number of synaptic vesicles containing neurotransmitters, numerous mitochondria, and smooth ER as a source of new membrane. Some neurotransmitters are synthesized in the cell body and then transported in vesicles to the presynaptic terminal. Upon arrival of a nerve impulse, voltage-regulated Ca2+ channels permit Ca2+ entry, which triggers neurotransmitter release into the synaptic cleft. Excess membrane accumulating at the presynaptic region as a result of exocytosis is recycled by clathrinmediated endocytosis, which is not depicted here.



PERIPHERAL NERVE



PERIPHERAL NERVES



CONNECTIVE TISSUE INVESTMENTS (sheaths)of Peripheral Nerve :

- Consist of cranial and spinal nerves connecting brain and spinal cord to peripheral tissues.
- Peripheral nerves consist of parallel bundles of nerve axons, Myelinated or Unmyelinated surrounded by connective tissue sheaths.
- Epineureum
  - Dense collagenous Con.Tissue with thick elastic fiber
  - Prevent damage by overstreching
- Perineureum
  - Dense con. Tissue
  - Layers of epithelioids
  - Isolates neural environment (blood-nerve barrier)
- Endoneureum
  - Loose con. Tissue
  - Regulation of microenvironment of nerve fiber

Thank you

Al-Noor University College.

Medical laboratories technics department.

Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

Skin

Dr. Ali Ashgar Abd

The skin is the largest single organ of the body, typically accounting for 15%-20% of total body weight and, in adults, presenting 1.5-2 m2 of surface to the external environment. Also known as the integument (L. integumentum, covering) or cutaneous layer, the skin is composed of the epidermis, an epithelial layer of ectodermal origin, and the dermis, a layer of mesodermal connective tissue (Figure 1). At the irregular junction between the dermis and epidermis, projections called dermal papillae interdigitate with invaginating epidermal ridges to strengthen adhesion of the two layers. Epidermal derivatives include hairs, nails, and sebaceous and sweat glands. Beneath the dermis lies the subcutaneous tissue or hypodermis (Gr. hypo, under + derma, skin), a loose connective tissue layer usually containing pads of adipocytes. The subcutaneous tissue binds the skin loosely to the underlying tissues. The specific functions of the skin fall into several broad categories:

1-Protective: It provides a physical barrier against thermal and mechanical insults such as friction and against most potential pathogens and other material. The dark pigment melanin in the epidermis protects cell nuclei from ultraviolet (UV) radiation.

2-Sensory: Many types of sensory receptors allow skin to constantly monitor the environment, and various skin mechanoreceptors help regulate the body's interactions with physical objects.

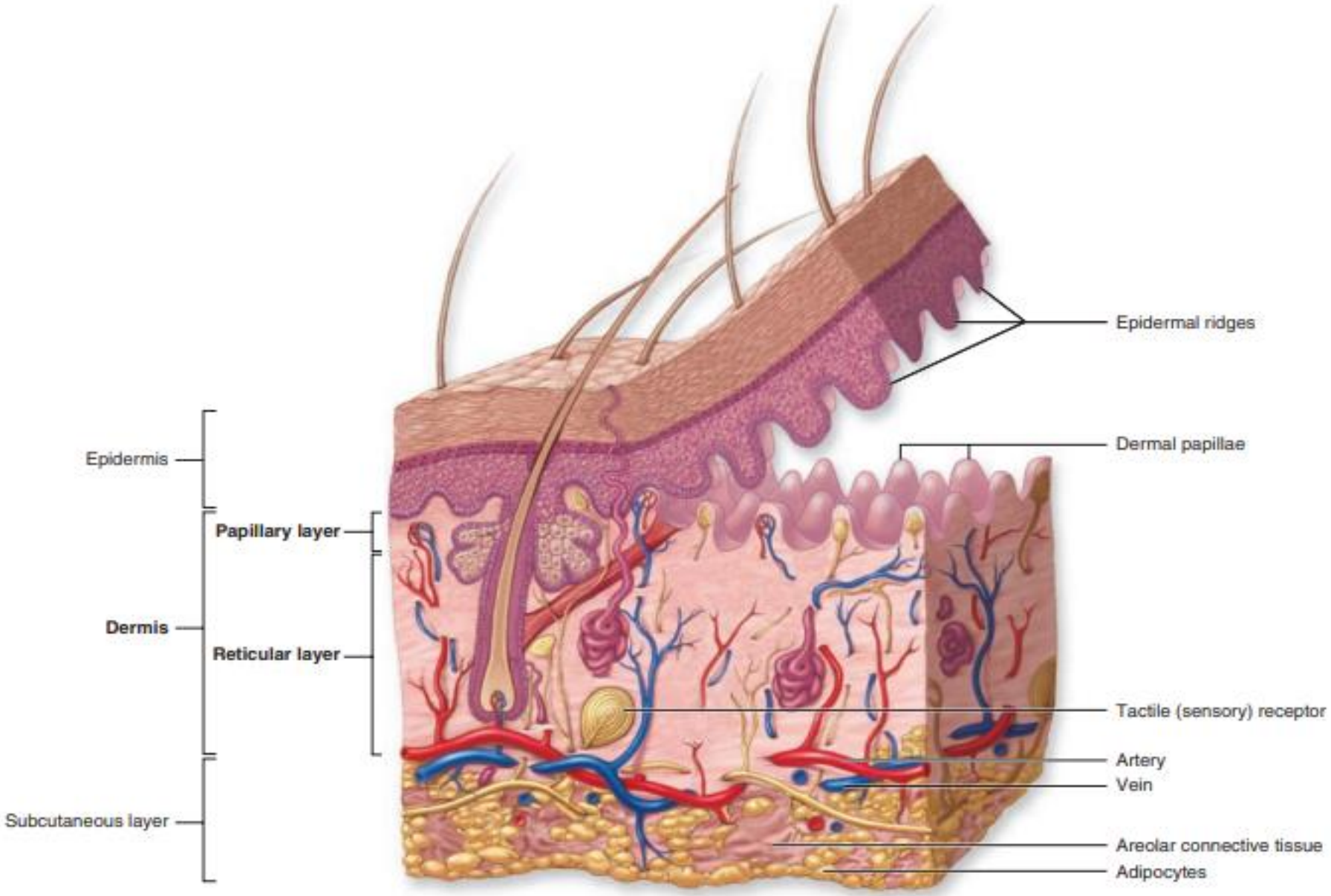
3-Thermoregulatory: A constant body temperature is normally easily maintained thanks to the skin's insulating components (eg, the fatty layer and hair on the head) and its mechanisms for accelerating heat loss (sweat production and a dense superficial microvasculature).

4-Metabolic: Cells of skin synthesize vitamin D3 , needed in calcium metabolism and proper bone formation, through the local action of UV light on the vitamin's precursor. Excess electrolytes can be removed in sweat, and the subcutaneous layer stores a significant amount of energy in the form of fat.

5-Sexual signaling: Many features of skin, such as pigmentation and hair, are visual indicators of health involved in attraction between the sexes in all vertebrate species, including humans.

The dermal-epidermal interdigitations are of the peg-andsocket variety in most skin (Figure 1), but they occur as well-formed ridges and grooves in the thick skin of the palms and soles, which is more subject to friction. These ridges and the intervening sulci form distinctive patterns unique for each individual, appearing as combinations of loops, arches, and whorls, called dermatoglyphs, also known as fingerprints and footprints

Figure 1 : Layers and appendages of skin



The epidermis consists mainly of a stratified squamous keratinized epithelium composed of cells called keratinocytes. There are also three much less abundant epidermal cell types: pigment-producing melanocytes, antigen-presenting Langerhans cells, and tactile epithelial cells called Merkel cells. The epidermis forms the major distinction between thick skin, found on the palms and soles, and thin skin found elsewhere on the body. The designations “thick” and “thin” refer to the thickness of the epidermal layer, which alone varies from 75 to 150 µm for thin skin and from 400 to 1400 µm (1.4 mm) for thick skin. Total skin thickness (epidermis plus dermis) also varies according to the site. For example, full skin on the back is about 4-mm thick, whereas that of the scalp is about 1.5-mm thick. From the dermis, the epidermis consists of four layers of keratinocytes (or five layers in thick skin):

1-Basal layer (stratum basale): Is a single layer of basophilic cuboidal or columnar cells on the basement membrane at the dermal-epidermal junction . and desmosomes bind the cells of this layer together in their lateral and upper surfaces. The stratum basale is characterized by intense mitotic activity. The human epidermis is renewed about every 15-30 days, depending on age, the region of the body, and other factors. An important feature of all keratinocytes in the stratum basale is the cytoskeletal keratins, intermediate filaments about 10 nm in diameter. During differentiation, the cells move upward and the amount and types of keratin filaments increase until they represent half the total protein in the superficial keratinocytes.

2- Spinous layer (stratum spinosum): Is normally the thickest layer, especially in the epidermal ridges and consists of generally polyhedral cells having central nuclei with nucleoli and cytoplasm actively synthesizing keratins.. The keratin filaments assemble here into microscopically visible bundles called tonofibrils, which converge and terminate at the numerous desmosomes holding the cell layers together. The cells extend slightly around the tonofibrils on both sides of each desmosome (and the extensions elongate if the cells shrink slightly during histologic processing), leading to the appearance of many short “spines” or prickles at the cell surfaces. The epidermis of thick skin subject to continuous friction and pressure (such as the foot soles) has a thicker stratum spinosum with more abundant tonofibrils and desmosomes.

3-The granular layer (stratum granulosum): Consists of three to five layers of flattened cells, now undergoing the terminal differentiation process of keratinization. Their cytoplasm is filled with intensely basophilic masses called keratohyaline granules. These are dense, non-membrane-bound masses of filaggrin and other proteins associated with the keratins of tonofibrils, linking them further into large cytoplasmic structures. Characteristic features in cells of the granular layer also include Golgi-derived lamellar granules, small ovoid (100 × 300 nm) structures with many lamellae containing various lipids and glycolipids. Among the last activities of the keratinocytes, the lamellar granules undergo exocytosis, producing a lipid-rich, impermeable layer around the cells. This material forms a major part of the skin's barrier against water loss.

4-The stratum lucidum, found only in thick skin, consists of a thin, translucent layer of flattened eosinophilic keratinocytes held together by desmosomes. Nuclei and organelles have been lost, and the cytoplasm consists almost exclusively of packed keratin filaments embedded in an electron-dense matrix .

5-The stratum corneum consists of 15-20 layers of squamous, keratinized cells filled with birefringent filamentous keratins. Keratin filaments contain at least six different polypeptides Important features. These fully keratinized or cornified cells called squames are continuously shed at the epidermal surface as the desmosomes and lipid-rich cell envelopes break down.

Melanocytes: The color of the skin is the result of several factors:

1- Melanin (responsible for black color)the most important content of keratinocytes.

2- Carotene (responsible for yellow color) .

3- The number of blood vessels in the dermis(as the number exceeds the color will be red).

Eumelanins are brown or black pigments produced by the melanocyte a specialized cell of the epidermis found among the cells of the basal layer and in hair follicles. The similar pigment found in red hair is called pheomelanin (Gr. phaios, dusky + melas, black). Melanocytes are neural crest derivatives that migrate into the embryonic epidermis' stratum basale, where eventually one melanocyte accumulates for every five or six basal keratinocytes (600-1200/mm2 of skin). Several long irregular cytoplasmic extensions from each melanocyte cell body penetrate the epidermis, running between the cells of the basal and spinous layers and terminating in invaginations of 5-10 keratinocytes.

Langerhans Cells:

Antigen-presenting cells called Langerhans cells, derived from monocytes, represent 2%-8% of the cells in epidermis and are usually most clearly seen in the spinous layer. Cytoplasmic processes extend from these dendritic cells between keratinocytes of all the layers, forming a fairly dense network in the epidermis . Langerhans cells bind, process, and present antigens to T lymphocytes.

Because of its location, the skin is continuously in close contact with many antigenic molecules. Various epidermal features participate in both innate and adaptive immunity providing an important immunologic component to the skin's overall protective function.

Merkel Cells:

Merkel cells, or epithelial tactile cells, mechanoreceptors essential for sensing gentle touch. They are abundant in highly sensitive skin like that of fingertips and at the bases of some hair follicles. Joined by desmosomes to keratinocytes of the basal epidermal layer, present in both thick and thin skin. Merkel cells resemble the surrounding keratinocytes , contain few, if any, they are characterized by small, melanosomes. Instead, Golgi-derived dense-core granules concentrated in areas near the basolateral surface where the cells have synaptic contacts with the expanded terminal discs of unmyelinated afferent fibers penetrating the basal lamina Light touch to the skin initiates release of neurotransmitters and sensation from that location.

DERMIS:

The dermis is the layer of connective tissue that supports the epidermis and binds it to the subcutaneous tissue (hypodermis). The thickness of the dermis varies with the region of the body and reaches its maximum of 4 mm on the back. The surface of the dermis is very irregular and has many projections (dermal papillae) that interdigitate with projections (epidermal pegs or ridges) of the epidermis.

A basement membrane always occurs between the stratum basale and the dermis, and follows the contour of the interdigitations between these layers. Nutrients for keratinocytes diffuse into the avascular epidermis from the dermal vasculature through the basement membrane.

Dermis composed of two layers:

1- The thin papillary layer, which includes the dermal papillae, consists of loose connective tissue, with types I and III collagen fibers, fibroblasts and scattered mast cells, dendritic cells, and leukocytes. From this layer, anchoring fibrils of type VII collagen insert into the basal lamina, helping to bind the dermis to the epidermis.

2- The underlying reticular layer is much thicker, consists of dense irregular connective tissue (mainly bundles of type I collagen), with more fibers and fewer cells than the papillary layer. A network of elastic fibers is also present providing elasticity to the skin. Between the collagen and elastic fibers are abundant proteoglycans rich in dermatan sulfate. Both dermal regions contain a rich network of blood and lymphatic vessels. Nutritive vessels form two major plexuses.

The dermis is also richly innervated. Sensory afferent nerve fibers form a network in the papillary dermis and around hair follicles, ending at epithelial and dermal receptors . Autonomic effector nerves to dermal sweat glands and smooth muscle fibers in the skin of some areas are postganglionic fibers of sympathetic ganglia; no parasympathetic innervation is present.

SUBCUTANEOUS TISSUE: The subcutaneous layer consists of loose connective tissue that binds the skin loosely to the subjacent organs, making it possible for the skin to slide over them. This layer, also called the hypodermis or superficial fascia, contains adipocytes that vary in number in different body regions and vary in size according to nutritional state. The extensive vascular supply at the subcutaneous layer promotes rapid uptake of insulin or drugs injected into this tissue.

SENSORY RECEPTORS

Diverse sensory receptors are present in skin, including both simple nerve endings with no Schwann cell . or collagenous coverings and more complex structures with sensory fibers enclosed by glia and delicate connective tissue capsules .The unencapsulated receptors include the following:

1-The Merkel cells, each associated with expanded nerve endings which function as tonic receptors for sustained light touch and for sensing an object’s texture.

2- Free nerve endings in the papillary dermis and extending into lower epidermal layers, which respond primarily to high and low temperatures, pain, and itching, but also function as tactile receptors.

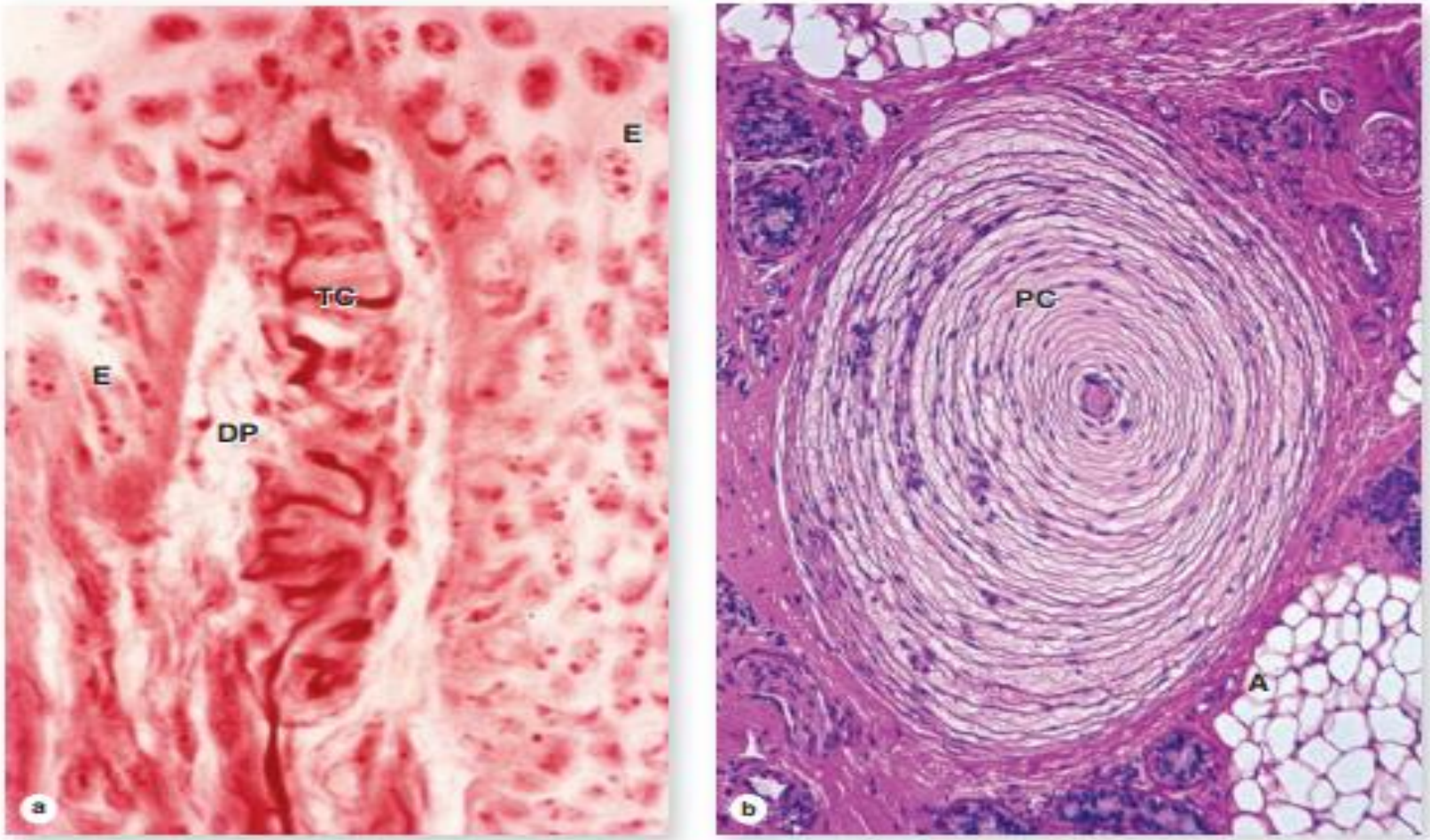
3-Root hair plexuses, a web of sensory fibers surrounding the bases of hair follicles in the reticular dermis that detects movements of the hairs.

The encapsulated receptors are all phasic mechanoreceptors, responding rapidly to stimuli on the skin. Four are recognized in human skin, although only the first two are seen in routine preparations:

1-Meissner corpuscles are elliptical structures, 30-75 µm by 50-150 µm, consisting of sensory axons winding among flattened Schwann cells arranged perpendicular to the epidermis in the dermal papillae (Figure 2). They initiate impulses when light-touch or lowfrequency stimuli against skin temporarily deform their shape. They are numerous in the fingertips, palms, and soles but decline slowly in number during aging after puberty.

2-Lamellated (pacinian) corpuscles are large oval structures, approximately 0.5 mm by 1 mm, found deep in the reticular dermis and hypodermis, with an outer capsule and 15-50 thin, concentric lamellae of flattened Schwann cells and collagen surrounding a highly branched, unmyelinated axon (Figure2). Lamellated corpuscles are specialized for sensing coarse touch, pressure (sustained touch), and vibrations, with distortion of the capsule amplifying a mechanical stimulus to the axonal core where an impulse is initiated. Pacinian corpuscles are also found in the connective tissue of organs located deep in the body, including the wall of the rectum and urinary bladder, where they also produce the sensation of pressure when the surrounding tissue is distorted.

FIGURE 2 Meissner and lamellated (pacinian) corpuscles.



Micrographs show the two most commonly seen sensory receptors of skin.

(a) Meissner tactile corpuscles (**TC**) are specialized to detect light touch and are frequently located in dermal papillae (**DP**), partially surrounded by epidermis (**E**). They are elliptical, approximately 150-µm long, with an outer capsule (from the perineurium) and thin, stacked inner layers of modified Schwann cells, around which course nerve fibers. (X400; H&E)

(b) Lamellated (pacinian) corpuscles (**PC**) detect coarse touch or pressure and are large oval structures, frequently 1 mm in length, found among adipose tissue (**A**) deep in the reticular dermis or in the subcutaneous tissue. Here the outer connective tissue capsule surrounds 15-50 thin, concentric layers of modified Schwann cells, each separated by slightly viscous interstitial fluid. Several axons enter one end of the corpuscle and lie in the cylindrical, inner core of the structure. Movement or pressure of this corpuscle from any direction displaces the inner core, leading to a nerve impulse. (X40; H&E)

3- Krause end bulbs are simpler encapsulated, ovoid structures, with extremely thin, collagenous capsules penetrated by a sensory fiber. They are found primarily in the skin of the penis and clitoris where they sense lowfrequency vibrations.

4- Ruffini corpuscles have collagenous, fusiform capsules anchored firmly to the surrounding connective tissue, with sensory axons stimulated by stretch (tension) or twisting (torque) in the skin.

HAIR

Hairs are elongated keratinized structures that form within epidermal invaginations, the hair follicles (Figure3). The color, size, shape, and texture of hairs vary according to age, genetic background, and region of the body. All skin has at least minimal hair except the glabrous skin of the palms, soles, lips, glans penis, clitoris, and labia minora. The face has about 600 hairs/cm2 and the remainder of the body has about 60/cm2 . Hairs grow discontinuously, with periods of growth followed by periods of rest, and this growth does not occur synchronously in all regions of the body or even in the same area.

The growing hair follicle has a terminal dilation called a hair bulb (Figure3a). A dermal papilla inserts into the base of the hair bulb and contains a capillary network required to sustain the hair follicle. Keratinocytes continuous with those of the basal epidermis cover the dermal papilla. These cells form the matrix of the elongating hair root; the part of a hair extending beyond the skin surface is the hair shaft.

In most thick hairs large, vacuolated, and moderately keratinized cells form the central medulla of the hair root (Figures3b). Heavily keratinized, densely packed cells make up the cortex around the medulla. The most peripheral cells of the hair root comprise the cuticle, a thin layer of heavily keratinized, squamous cells covering the cortex (Figures3c)

The outermost cells of the hair bulb are continuous with the epithelial root sheath, in which two layers can be recognized. The internal root sheath completely surrounds the initial part of the hair root but degenerates above the level of the attached sebaceous glands. The external root sheath covers the internal sheath and extends all the way to the epidermis, where it is continuous with the basal and spinous layers. Separating the hair follicle from the dermis is an acellular hyaline layer, the thickened basement membrane called the glassy membrane (Figure 3a). The surrounding dermis forms a connective tissue sheath.

The arrector pili muscle, a small bundle of smooth muscle cells, extends from the midpoint of the fibrous sheath to the dermal papillary layer (Figure3b). Contraction of these muscles pulls the hair shafts to a more erect position.

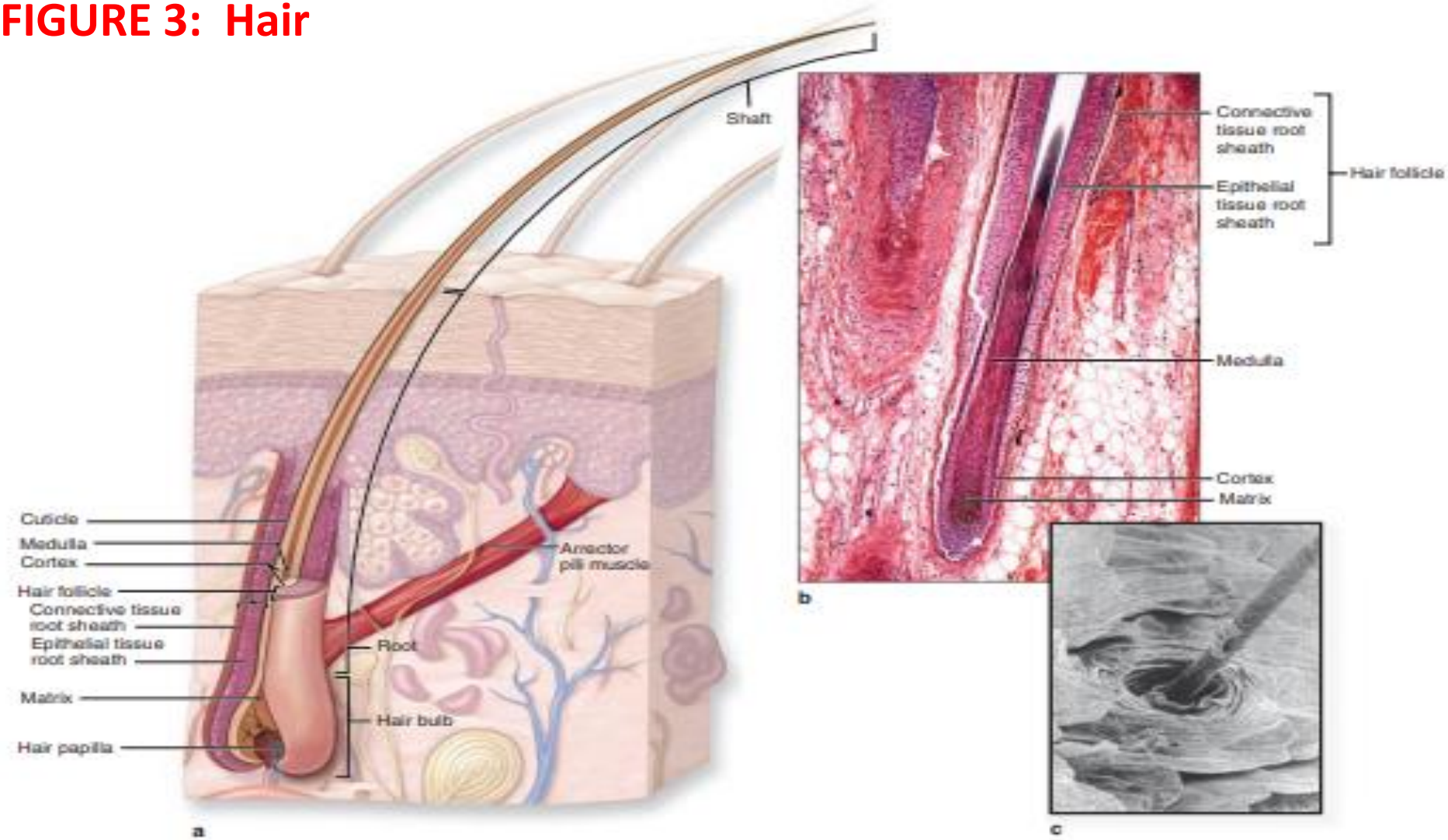
The hair growth cycle has three major phases:

1-A generally long period of mitotic activity and growth (anagen).

2-A brief period of arrested growth and regression of the hair bulb (catagen).

3-A final long period of inactivity (telogen) during which the hair may be shed.

FIGURE 3: Hair



All types of body hair have a similar composition and form in hair follicles derived from the epidermis but extending deep into the dermis.

(a) The diagram shows major parts of a hair and its follicle, including vascularized, nutritive hair dermal **papilla** and the **arrector pili muscle** that pulls the hair erect.

(b) A longitudinal section of a hair root and bulb shows the **matrix**, **medulla**, and **cortex** in the root and the surrounding **epithelial and connective tissue** sheaths. Cells of the hair bulb matrix proliferate, take up melanin granules, and undergo keratinization to differentiate as the three concentric layers of the hair. (X70; H&E)

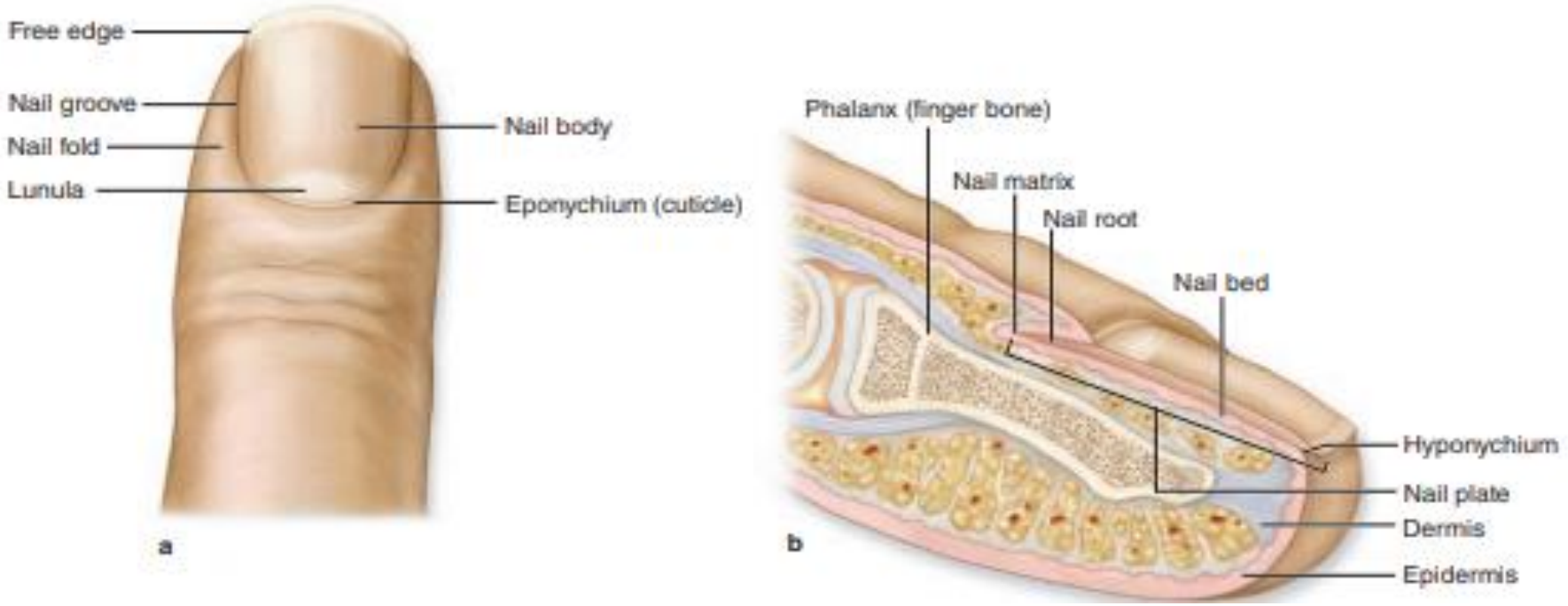
(c) The outermost layer of the hair is the thin **cuticle**, composed of shingle-like cells, shown in this SEM of a hair shaft emerging at the stratum corneum. (X260)

Nalis

Hard plates of keratin on the dorsal surface of each distal phalanx (Figure 4). The proximal part of the nail

is the nail root and is covered by a fold of skin, from which the epidermal stratum corneum extends as the cuticle, or eponychium. The nail plate is bound to a bed of epidermis, the nail bed, which contains only the basal and spinous epidermal layers. The nail root forms from the nail matrix in which cells divide, move distally, and become keratinized in a process somewhat similar to hair formation but without keratohyaline granules. The nail root matures and hardens as the nail plate continuous growth in the matrix pushes the nail plate forward over the nail bed (which makes no contribution to the plate) at a rate of about 3 mm/mo for fingernails and 1 mm/mo for toenails. The distal end of the plate becomes free of the nail bed at the epidermal fold called the hyponychium. The nearly transparent nail plate and the thin epithelium of the nail bed provide a useful window on the amount of oxygen in the blood by showing the color of blood in the dermal vessels

FIGURE 4 Nail



Nails are hard, keratinized derivatives formed in a process similar to that of the stratum corneum and hair.

(a) Surface view of a finger shows the nail's major parts, including the crescent-shaped white area called the **lunula**, which derives its color from the opaque nail matrix and immature nail plate below it.

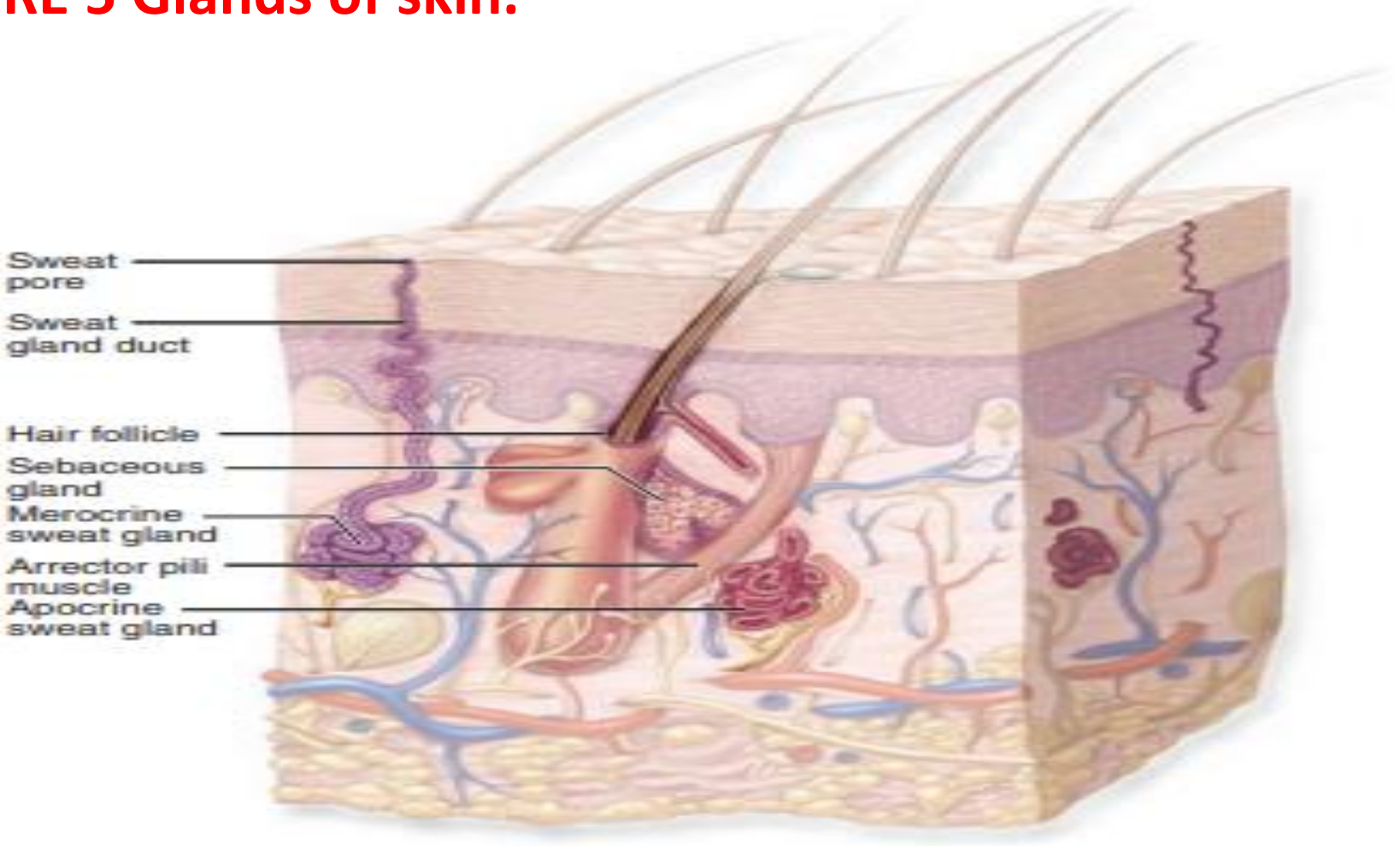
(b) A diagrammatic sagittal section includes major internal details of the growing nail and the hyponychium where the free end of the nail plate is bound to epidermis.

SKIN GLANDS

Sebaceous Glands Sebaceous glands are embedded in the dermis over most of the body, except in the thick, glabrous skin of the palms and soles. There is an average of about 100 such glands per square centimeter of skin, but the frequency increases to 400-900/cm2 in the face and scalp. Sebaceous glands are branched acinar glands with several acini converging at a short duct that usually empties into the upper portion of a hair follicle (Figure5). A hair follicle and its associated sebaceous glands make up a pilosebaceous unit. The stem cell niche of the follicle's bulge region also forms the progenitor cells of the associated sebaceous glands. In certain hairless regions, such as the penis, clitoris, eyelids, and nipples, sebaceous ducts open directly onto the epidermal surface.

The acini of sebaceous glands are the classic example of holocrine secretion. They have a basal layer of flattened epithelial cells on the basal lamina, which proliferate and are displaced centrally, undergoing terminal differentiation as large, lipid-producing sebocytes filled with small fat droplets. Their nuclei shrink and undergo autophagy along with other organelles, and near the duct the cells disintegrate, releasing the lipids as the main secretory product. This product, called sebum, gradually covers the surfaces of both the epidermis and hair shafts

FIGURE 5 Glands of skin.



Skin includes three major types of exocrine glands. **Sebaceous glands** are usually part of a pilosebaceous unit with a hair follicle and secrete oily sebum into the space around the hair root. Thermoregulatory **eccrine sweat glands** empty their secretion onto the skin surface via sweat pores. **Apocrine sweat glands** secrete a more protein-rich sweat into the follicles of hair in skin of the axillae and perineum.

Sweat Glands

There are two types of sweat glands, eccrine and apocrine, with distinct functions, distributions, and structural details. Eccrine sweat glands are widely distributed in the skin and are most numerous on the foot soles (620/cm2). Collectively the 3 million eccrine sweat glands of the average person approximately equal the mass of a kidney and produce as much as 10 L/day, a secretory rate far exceeding that of other exocrine glands. Sweating is a physiologic response to increased body temperature during physical exercise or thermal stress and is the most effective means of temperature regulation of humans. Both the secretory components and ducts of eccrine sweat glands are coiled and have small lumens. The secretory part is generally more pale-staining than the ducts and consists of an unusual stratified cuboidal epithelium with three cell types:

1-clear cells Pale-stainings located on the basal lamina produce the sweat, having abundant mitochondria and microvilli to provide large surface areas. Interstitial fluid from the capillary-rich dermis around the gland is transported through the clear cells, either directly into the gland's lumen or into intercellular canaliculi that open to the lumen.

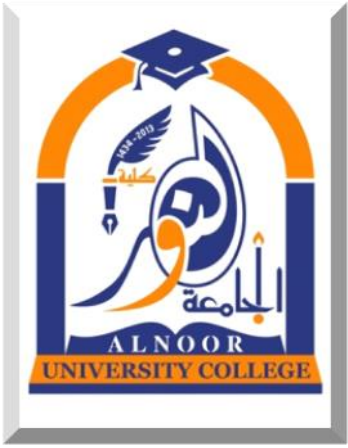
2-Dark cells filled with strongly eosinophilic granules line most of the lumen and do not contact the basal lamina The granules undergo merocrine secretion to release a poorly understood mixture of glycoproteins with bactericidal activity.

3-Myoepithelial cells on the basal lamina contract to move the watery secretion into the duct.

The ducts of eccrine sweat glands have two layers of more acidophilic cells. At the epidermis each duct merges with the stratum basale and sweat flow continues in a spiraling channel through the five epidermal strata to an excretory sweat pore in the skin surface .

Apocrine sweat glands are largely confined to skin of the axillary and perineal regions. The secretory components of apocrine glands have much larger lumens than those of the eccrine glands and consist of simple cuboidal, eosinophilic cells with numerous secretory granules that also undergo exocytosis.

The ducts of apocrine glands usually open into hair follicles at the epidermis. The slightly viscous secretion is initially odorless but may acquire a distinctive odor as a result of bacterial activity. The production of pheromones by apocrine glands is well established in many mammals and is likely in humans, although in a reduced or vestigial capacity. Apocrine sweat glands are innervated by adrenergic nerve endings, whereas eccrine sweat glands receive cholinergic fibers.



Al-Noor University College.

Medical laboratories technics department.

Second Stage / 2022 – 2023.

Lectures of General Histology (Theory).

The lymphoid system

Dr. Ali Ashgar Abd

The lymphoid organs

- The immune system has the ability to distinguish self from non self cells, also has the ability to inactivate or neutralize the foreign molecules such as bacteria, viruses, viral infected cells or tumor cells ……etc. The cells of immune system are:

1- Distributed all over the body

2- Arrange themselves into small spherical nodules called (lymphatic nodules) or

3- Organized into organs.

Antigens: Molecules that are identified by the cells of immune system are called Antigens that may elicit a response of these cells.

Antibodies: Antibodies belong to the immunoglobulin (Ig) protein family, free molecules of antibodies are secreted by plasma cells that arise by proliferation and terminal differentiation of B lymphocytes whose receptors identify and bind specific Antigen.

Mucosa Associated Lymphoid Tissue (MALT):

The mucosa and submucosa of the digestive tract, respiratory tract, genito-urinary tract contain a large amount of lymphatic tissue that are not encapsulated. These include variety of cells like lymphocytes, IgA secreting plasma cells, mast cells, and **(Antigen presenting cells)** APCs.

In addition to lymphatic tissue, there is localized collection of lymphocytes found also in the wall of GIT, Respiratory passages, Genito-urinary tract, etc…, these called lymphatic nodules. Lymphatic nodules are sharply demarcated but also not encapsulated. These nodules are in two types:

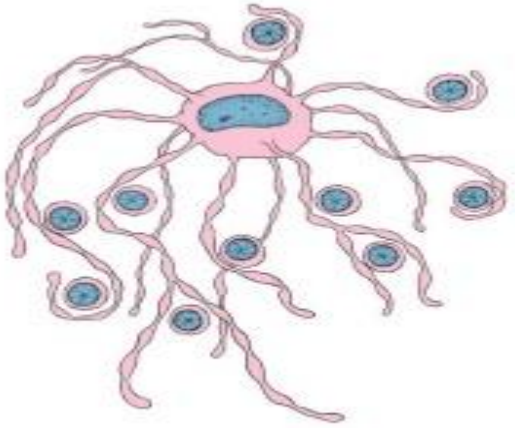
Primary nodule is a collection of small lymphocytes (inactive without germinal centre) and **secondary** nodules which have distinctive features that include the following:

- **Germinal center** is located in the central region of the nodule and appears lightly stained in histologic sections. The germinal center develops when a lymphocyte that has recognized an antigen and undergoes proliferation. The lighter staining is attributable to the large immature lymphocytes **(lymphoblasts)** that it contains. **Follicular dendritic cells (FDCs)** are also present in germinal centers interdispersed between populations of B lymphocytes (see figure below).

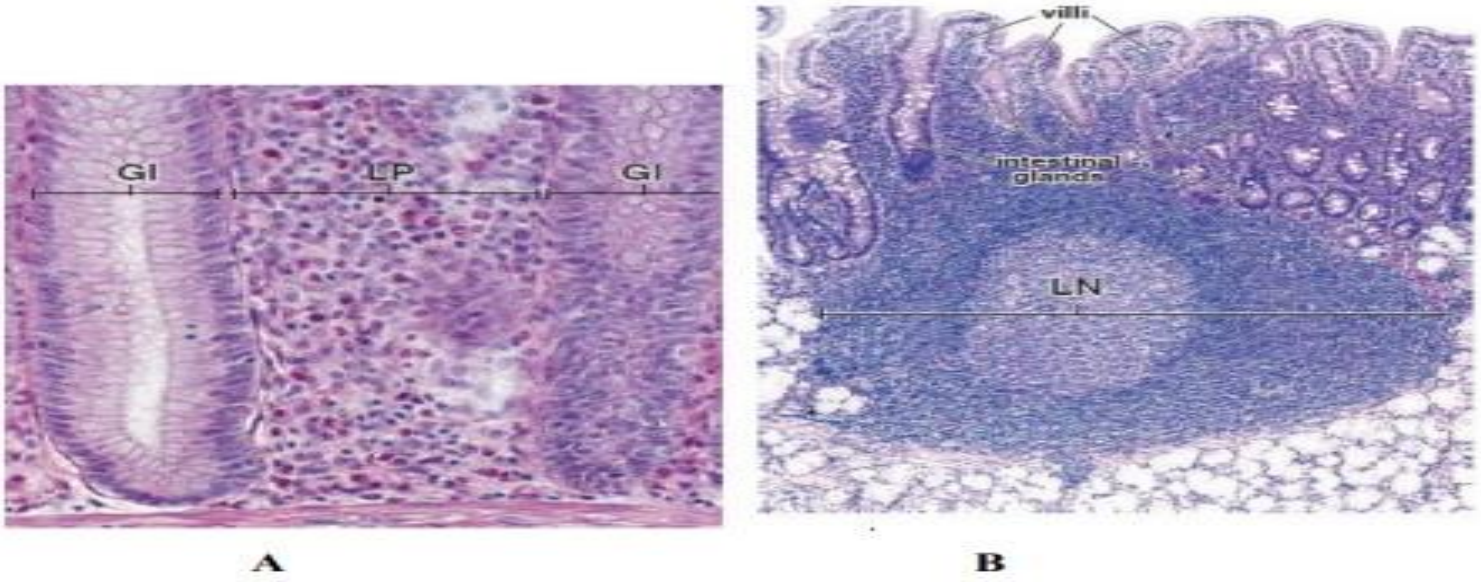
The germinal center is a morphologic indication of lymphatic tissue response to antigen. The presence of a germinal center represents a cascade of events that includes activation and proliferation of lymphocytes, differentiation of plasma cells, and antibody production. Mitotic figures are frequently observed in the germinal center, reflecting the proliferation of new lymphocytes at this site. The number of FDCs and macrophages in the germinal center often increases dramatically after a period of intense response to an antigen.

- **Mantle zone** or **corona** is present that represents an outer ring of small lymphocytes that encircles the germinal center.

In some places these aggregation form a conspicuous structures such as tonsils and peyer's patches of the ileum, similar aggregation are found in the appendix.



Follicular dendritic cell



A: Photomicrograph of diffuse lymphatic tissue. This photomicrograph shows the diffuse lymphatic tissue in the lamina propria (LP) of the large intestine. The lower portion of two intestinal glands (GI) is also evident. The highly cellular, diffuse lymphatic tissue includes fibroblasts, plasma cells, and eosinophils. However, the most abundant cell component, whose presence characterizes diffuse lymphatic tissue, is the lymphocyte, which can be identified by its small, round, dark-staining nucleus.

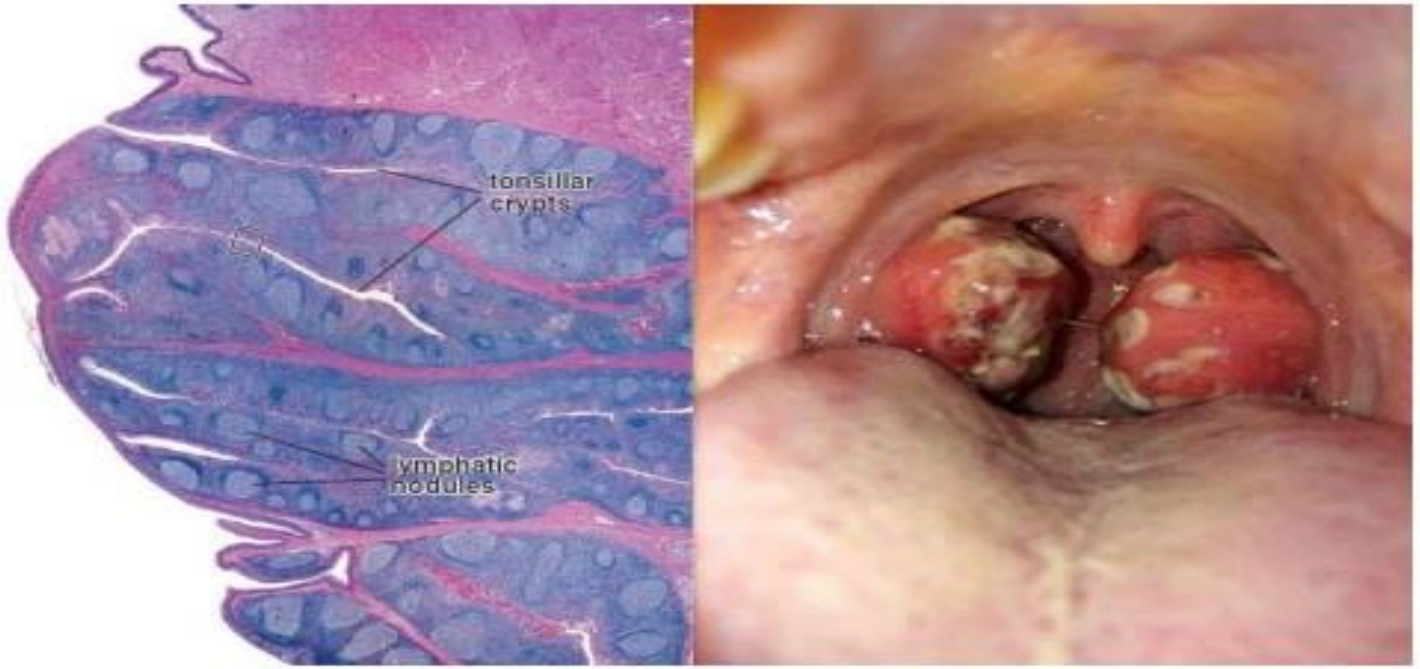
B: Photomicrograph of a lymphatic nodule. This photomicrograph shows a section of the wall of the small intestine (duodenum). Short villi and intestinal glands are present in the upper part of the micrograph. A lymphatic nodule (LN) occupies most of the remainder of the micrograph. The lighter central region of the nodule is the germinal center. The lymphocytes in the germinal center are larger than those in the denser region of the nodule. They have more cytoplasm, so, their nuclei are more dispersed, giving the appearance of a less compact cellular mass.

Tonsils: The tonsils are lymphoid tissues that lie beneath and in contact with the epithelium of the initial portion of the digestive tract. Depending on their location, tonsils in the mouth are called palatine, pharyngeal and lingual.

Palatine tonsils: The two palatine tonsils are located in the lateral wall of the oral part of the pharynx. They are lined with a squamous stratified epithelium. Each tonsil has 10-20 epithelial invagination called crypts, whose lumen contain few desquamated epithelial cells, live or dead lymphocytes and bacteria.

Pharyngeal tonsil: Single tonsil situated in the superior posterior portion of the phaynx. It is covered by respiratory epithelium, it has no crypt.

Lingual tonsil: They are smaller and more numerous than palatine and pharyngeal tonsils, situated at the base of tongue, covered by stratified squamous epithelium and has a single crypt.



A: Photomicrograph of a palatine tonsil This low-magnification photomicrograph shows an H&E–stained palatine tonsil. The stratified squamous epithelium that forms the surface of the tonsil dips into the underlying connective tissue in numerous places, forming tonsillar crypts.

B: Follicular Tonsilitis

Thymus:

Is a central lymphoid organ situated in the mediastinum, the thymus has dual embryonic origin mesodermal and endodermal origin. The thymus originated from branchial epithelium. During development, the epithelium grows caudally and proliferates to form tubular projections.

Multipotential lymphoid stem cell (CFULs) originated from bone marrow and destined to form immunocompetent T lymphocytes which invade the epithelium and occupy the spaces between the epithelial cells.

The thymus has connective tissue capsule which penetrates the parenchyma and divide it into incomplete lobules, so that there is continuity between the cortex and medulla of adjoining lobules. Each lobule has a peripheral dark zone known as cortex and a central light zone called the medulla.

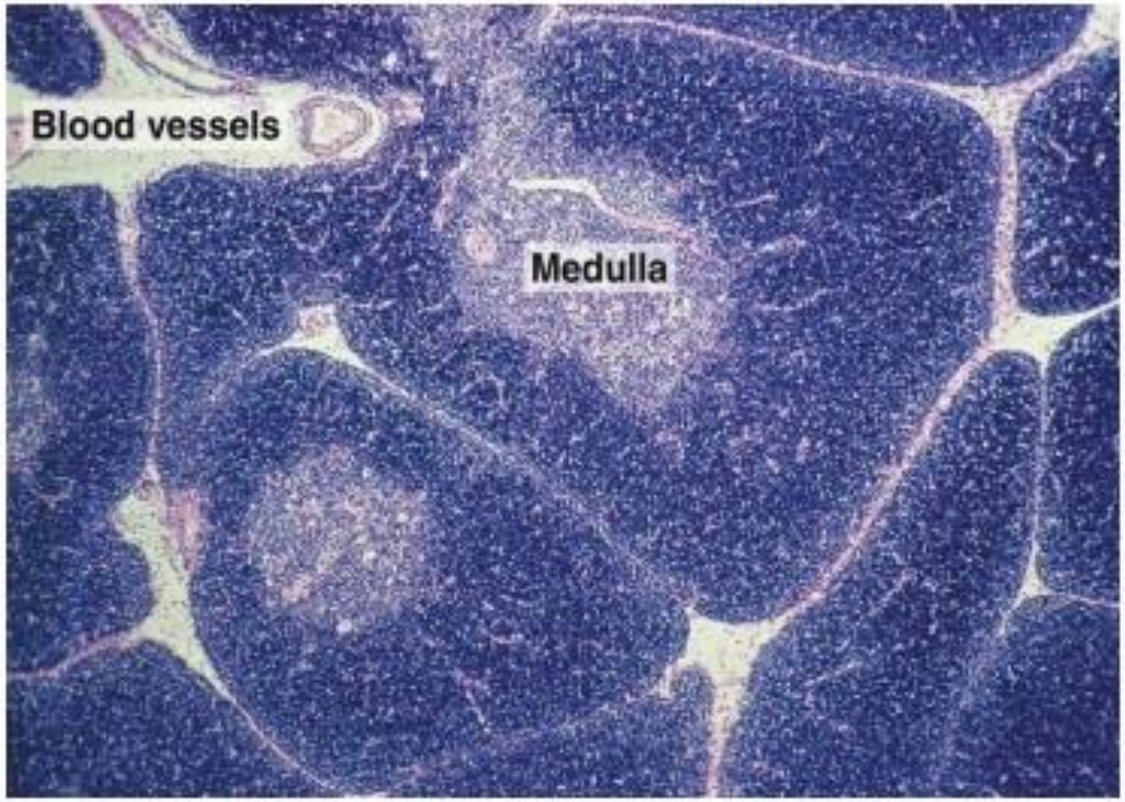


Figure: Photomicrograph of a section of thymus showing the lobules. Two lobules show the dark cortical and the light medullary zones. At the upper left are blood vessels and the connective tissue capsule.

The **cortex** is composed of an extensive population of T cell precursors (also called thymocytes) occupy spaces within an extensive meshwork of epithelioreticular cells. Macrophages are also dispersed among the cortical cells. Because the cortex is richer in small lymphocytes than the medulla, it stains more darkly.

The developing T cells arise from CFU-Ls, which originate in bone marrow. As development proceeds in the thymus, the cells derived from CFU-Ls pass through a series of developmental stages that are reflected by their expression of different CD molecules.

As their name implies, epithelioreticular cells have features of both epithelial and reticular cells.

They provide a framework for the developing T cells; thus, they correspond to the reticular cells and their associated reticular fibers in other lymphatic tissues and organs. Epithelioreticular cells exhibit certain features characteristic of epithelium such as intercellular junctions.

Six types of epithelioreticular cells are recognized on the basis of function: Three types in the cortex and three types in the medulla

1- Type I epithelioreticular cells In essence, type I epithelioreticular cells serve to separate the thymic parenchyma from the connective tissue of the organ. The occluding junctions between these cells reflect their function as a barrier that isolates developing T cells from the connective tissue of the organ—that is, capsule, trabeculae, and perivascular connective tissue.

2- Type II epithelioreticular cells Type II cells compartmentalize the cortex into isolated areas for the developing T cells. Unlike type I cells, type II cells express MHC I and MHC II **(Major histocompatibility molecules, I and II)** which are involved in thymic cell education.

3- Type III epithelioreticular They are located at the boundary of the cortex and medulla. The TEM reveals occluding junctions between sheetlike cytoplasmic processes of adjacent cells. Like type I cells, type III epithelioreticular cells create a functional barrier—in this case, between the cortex and medulla. Like type II cells, they possess MHC I and MHC II molecules.

4-Type IV epithelioreticular cells They are located between the cortex and the medulla close to type III cells. They possess sheetlike processes with occluding junctions between adjacent cells as well as between them and type III cells. In cooperation with type III cells, they create the barrier at the corticomedullary junction.

5- Type V epithelioreticular cells They are located throughout the medulla. Like the type II cells located in the cortex, processes of adjacent cells are joined by desmosomes to provide the cellular framework of the medulla and to compartmentalize groups of lymphocytes. These nuclei contrast markedly with the densely staining lymphocyte nuclei

6- Type VI epithelioreticular cells They form the most characteristic feature of the thymic medulla, the thymic (Hassall's) corpuscles. Thymic corpuscles are isolated masses of closely packed, concentrically arranged type VI epithelioreticular cells that exhibit flattened nuclei. TEM studies of these cells reveal keratohyalin granules, bundles of cytoplasmic intermediate filaments, and lipid droplets. The cells are joined by desmosomes. The center of a thymic corpuscle may display evidence of keratinization. Although the function of thymic corpuscles is not fully understood, it is thought that thymic corpuscles produce interleukins (IL-4 and IL-7) that function in thymic differentiation and education of T lymphocytes.

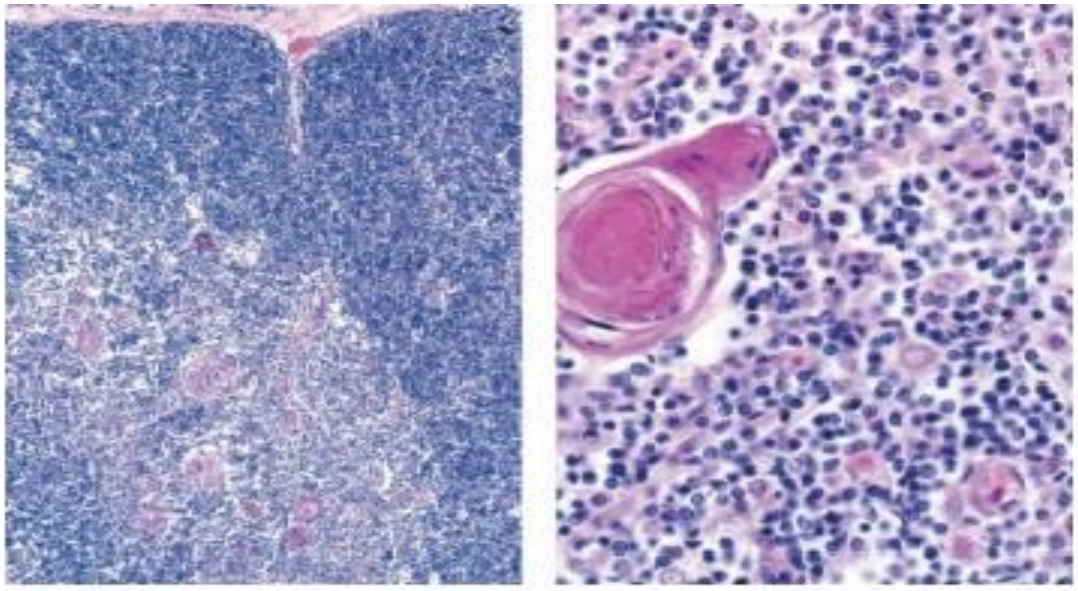


Figure : Illustrates thymic medulla and Hassal's corpuscle

Macrophages reside within the thymic cortex and are responsible for phagocytosis of T cells that do not fulfill thymic education requirements. These T cells are programmed to die before leaving the cortex. Approximately 98% of the T cells undergo this apoptosis and are then phagocytosed by the macrophages.

Although the epithelioreticular cells of the thymic cortex play an important role in the development of immunocompetent T cells, recent evidence shows that T cells at the different stages of differentiation control the microarchitecture of the thymic epithelioreticular cells, a phenomenon called crosstalk. The developing lymphocytes and epithelioreticular cells thus influence each other during T-cell development.

Secretion of the thymus: The thymus produces several proteins that act as growth factors to stimulate the proliferation and differentiation of T lymphocytes.

Development and involution of the thymus: The thymus shows its maximum development immediately after birth and undergoes involution after puberty, in which the lymphoid tissue is replaced by adipose tissue. Despite the processes of involution, the thymus remains capable of producing great number of lymphocytes when stimulated. Involution begins in the cortical areas which gradually become thinner but the process of involution in the medulla started at puberty. Both reticular cells and Hassall's corpuscles are resistant to involution than are lymphocytes. The thymus never disappear completely, it is still present even in very old people.

Spleen:

Is the largest lymphoid organ in the body, is important defense against antigens that reach blood circulation, and it is the site of destruction of aged RBCs and production of activated lymphocytes, so spleen is an important filter and antibody forming organ. In addition to large numbers of lymphocytes, it contains specialized vascular spaces or channels, a meshwork of reticular cells and reticular fibers, and a rich supply of macrophages and dendritic cells. These contents allow the spleen to monitor the blood immunologically.

General structure:

The spleen is surrounded by a capsule of dense connective tissue from which emerge trabeculae which divide the parenchyma or splenic pulp into incomplete compartments.

Splenic pulp:

The splenic pulp has two components the white and red pulp, these names derived from the fact that on the surface of a cut of spleen, white spots are observed (lymphatic nodule).

White pulp:

The splenic artery divides as it penetrate the hilum into trabecular arteries that follow the course of connective tissue trabeculae, when they leave the trabeculae to enter the parenchyma, the arteries are enveloped by a sheath of T lymphocytes called (Periarterial Lymphatic Sheath PALS) which is part of white pulp and one of the **thymic dependant areas,** these vessels are known as central arteries, after coursing through the parenchyma PALS receive large collection of lymphocytes mainly B lymphocyte forming lymphatic nodules,

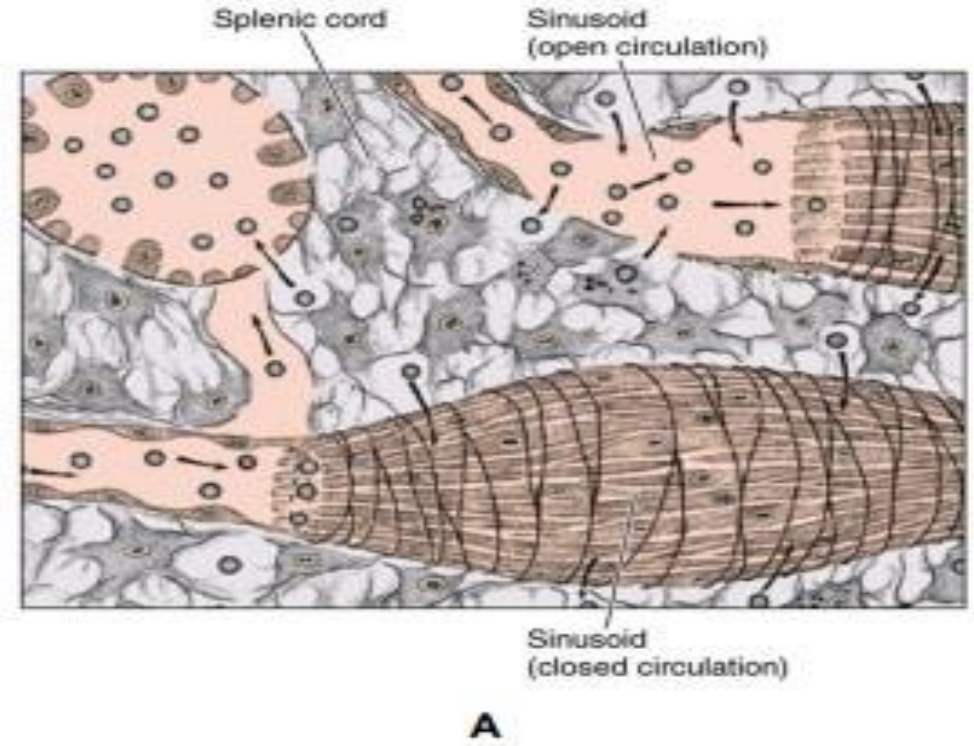
in these nodules, the arteries are now **turned to arteriole and take eccentric position** but it is still called **central artery**, this artery also give numerous radial branches to the surrounding lymphatic tissue.

Surrounding the lymphatic nodule is **marginal zone** which consist of blood sinuses and loose lymphoid tissue, many macrophages and few lymphocytes are present there. This zone plays an important role in immunological activities. After leaving the white pulp the central artery subdivides to form the penicillar arterioles.

Red pulp:

The red pulp is composed from splenic cords and sinusoids, the splenic cords **(cords of Billroth)** contain a network of reticular cells supported by reticular fibers, it contain also T and B cells, macrophages, plasma cells and many blood cells. The splenic cords are separated by irregularly shaped wide sinusoids. Elongated endothelial cells line the sinusoids. The spaces between endothelial cells are small, so only flexible cells are able to pass freely from the red pulp into lumen of sinusoids and vice versa.

Processes of macrophages extend between the endothelial cells and into the lumen of the sinuses to monitor the passing blood for foreign antigens. The sinuses do not possess a continuous basal lamina. Strands of basal lamina loop around the outside of the sinus much like the hoops that loop around the staves of a barrel. These strands are at right angles to the long axes of the endothelial cells.



A: Structure of the red pulp of the spleen, showing splenic sinusoids and splenic cords with reticular cells and macrophages (some macrophages contain ingested material). The disposition of the reticular fibers in the red pulp is illustrated. In the splenic cords they form a 3-dimensional network; in the sinusoids they are mainly perpendicular to the long axis of the sinusoid. Both the open and closed theories of circulation are illustrated. Arrows indicate blood flow and options for movement of blood cells.

Functions of the spleen:

The spleen performs both immune and hemopoietic functions. Because the spleen filters blood as the lymph nodes filter lymph, it functions in both the **immune and the hemopoietic systems.**
Immune system functions of the spleen include:

- Antigen presentation by APCs (mostly dendritic cells and macrophages) and initiation of immune response;
- Activation and proliferation of B and T lymphocytes;

- Production of antibodies against antigen present in circulating blood; and
- removal of macromolecular antigens from the blood. Activation and proliferation of T cells and differentiation of B cells and plasma cells, as well as secretion of antibodies, occur in the white pulp of the spleen; in this regard, the white pulp is the equivalent of other lymphatic organs.

Hemopoietic functions of the spleen include:

- Removal and destruction of senescent, damaged, and abnormal erythrocytes and platelets.

- Retrieval of iron from erythrocyte hemoglobin;
- Formation of erythrocytes during early fetal life; and
- Storage of blood, especially red blood cells, in some species.

Lymph nodes

Lymph nodes are distributed throughout the body along the course of lymphatic vessels. Lymph nodes constitute a series of in-line filter that are important against the microorganism and spread of tumor cells.

All lymph, derived from tissue fluid is filtered by at least one LN. LN are elongated or kidney shaped organs that have convex surface that is the entrance site of afferent lymphatic vessels and a concave depression, the hilum, through which the arteries, and nerves enter and veins and lymphatic vessels leave the organ. They range in size from about 1 mm (barely visible with the unaided eye) to about 1 to 2 cm in their longest dimension. A connective tissue capsule surrounds the lymph node, sending trabeculae into its interior.

Cells of the Reticular Meshwork

The reticular meshwork of the lymph node contains several types of cells that perform different functions in generating immune responses. Several population of cells have been identified:

1. **Reticular cells** synthesize and secrete reticular fibers and the associated ground substance that forms the stroma. Besides their supporting role, they express surface molecules and produce substances that attract T cells, B cells, and dendritic cells.

2. **Dendritic cells (DCs)** are unique bone marrow–derived APCs. DCs monitor the local environment for foreign substances that they then process and present to antigen specific T cells. They are much more efficient in antigen presentation than other APCs and can present virtually any form of protein antigen on both MHC I and MHC II molecules. In the lymph node, DCs are usually localized in T lymphocyte–rich areas.

3. **Macrophages** are both phagocytic and antigen-presenting cells that express MHC I, MHC II, and co-stimulatory molecules

4. **Follicular dendritic cells (FDCs)** have multiple, thin, hairlike branching cytoplasmic processes that interdigitate between B lymphocytes in the germinal centers.

General architecture of the lymph node:

The LN has two regions: cortex and medulla, the cortex is subdivided into **superficial** (nodular) cortex and **deep or paracortical** areas. Lymphocytes in the superficial cortex are organized into nodules **(primary and secondary).** The portion of the cortex between the medulla and superficial cortex is free of nodules; it is called the deep cortex (paracortex). This region contains most of the T cells in the lymph node.

Because of its dependence on the thymus, prenatal thymectomy in animals results in a poorly developed deep cortex. On the basis of this observation, the deep cortex is also called the thymus dependent cortex.

The medulla, the inner part of the lymph node, consists of cords of lymphatic tissue separated by lymphatic sinuses called medullary sinuses. A network of reticular cells and fibers serves as the framework of the parenchyma. In addition to reticular cells, the medullary cords contain lymphocytes (mostly B lymphocytes), macrophages, dendritic, and plasma cells.

The medullary sinuses converge near the hilum, where they drain into efferent lymphatic vessels.

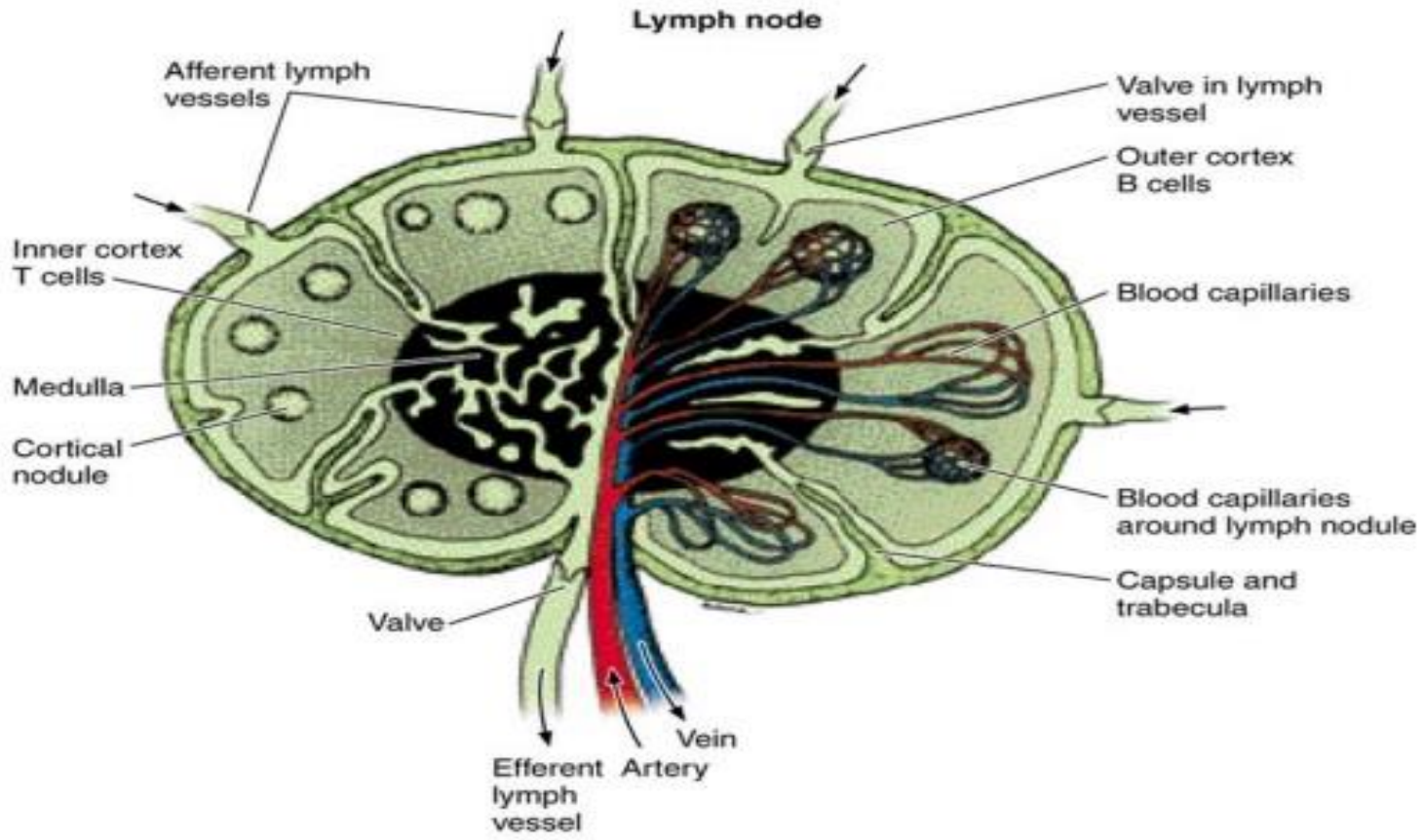


Figure: Schematic representation of the structure of a lymph node. Note the outer and inner cortex, the medulla, and the blood and lymph circulation. Also note that the lymph enters through the convex side of the node and leaves through the hilum. The lymph percolates through the node, exposing its contents to the action of defensive cells (macrophages, lymphocytes, APCs)

The role of lymph node immune response:

Antigens conveyed in the lymph percolate through the sinuses and penetrate the lymph nodules initiate an immune response. Some antigens become trapped on the surface of the follicular dendritic cells, whereas others are processed by macrophages, dendritic cells, and B cells, leading to activation and differentiation of B cells into antibody-producing plasma cells and memory B cells.

The **plasma cells** then migrate to the medullary cords where they synthesize and release specific antibodies into the lymph flowing through the sinuses. Plasma cells account for 1% to 3% of the cells in resting lymph nodules.

Memory B cells may leave the lymph nodes and circulate to various regions throughout the body, where they can proliferate in response to subsequent exposure to their specific antigen.