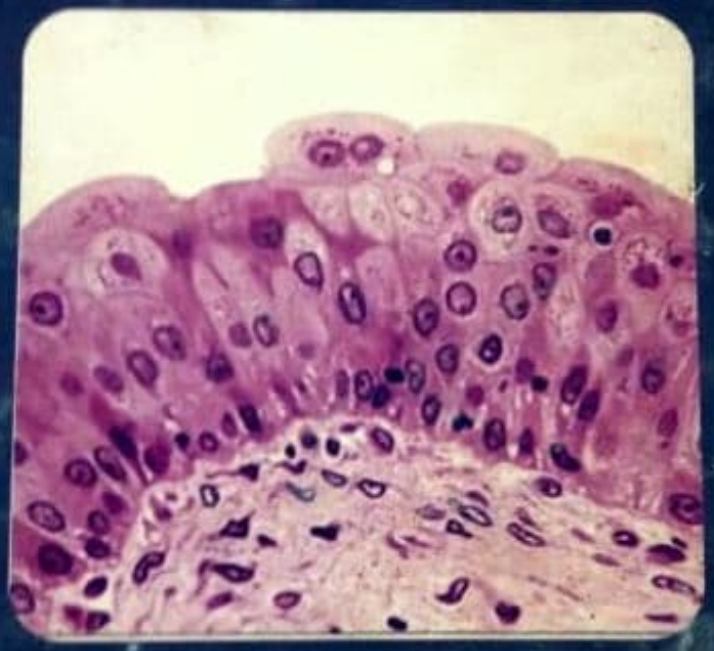
Introduction to Histology and Cell Biology



For First Year Medical Students

First Semester

By Staff Members
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I

Micro-techniques and Microscopy

Intended learning outcomes (ILOs) of the micro-techniques and microscopy

By the end of this unit, the student should be able to:

1. Define micro-techniques.
2. Enumerate the steps of preparation of paraffin sections.
3. Explain the aim of each step of preparation of paraffin sections.
4. Compare between the advantages and the disadvantages of the paraffin method, the celloidin method and the freezing method.
5. Briefly know an idea about the tissue culture technique.
6. Explain the principle of staining with hematoxylin and eosin (H & E).
7. Define vital staining, supra-vital staining, meta-chromatic staining and histo-chemical staining.
8. Define the measurements and units commonly used in histology.
9. Recognize the different parts of the ordinary light microscope.
10. Define the term resolution power.
11. Differentiate between resolution and magnification of microscopes.
12. Summarize the differences between the light microscope and the transmission electron microscope (TEM).
13. Explain electron dense and electron lucent terms.

Micro-techniques: Methods of preparation of tissue sections for microscopic examination and histological study.

- Tissues must be cut to obtain thin sections that are suitable for study with the light and electron microscope. This is done by replacing water present in the tissues by solid substances as paraffin (for light microscope) or plastic resins (for electron microscope) to facilitate tissue sectioning.

The most commonly used measurements and units	
1.0 Millimeter (mm)	1000 Micrometer (µm)
1.0 Micrometer (µm)	1000 Nanometer (nm)
1.0 Nanometer (nm)	10 Angstroms (A)

Methods of preparation of tissue sections for light microscopic examination

I. Paraffin technique

1. Tissue sample

- It is taken by biopsy, surgical excision or postmortem (after death).
- Its size should be not more than 1 cm^3.

2. Fixation of tissues. This must be done immediately.

The most commonly used fixative is 4%Formaldehyde (formalin).

- **The aim of fixation**

a. Preserves the fine structure of the tissues.
b. Prevents autolysis by inhibition of hydrolytic enzymes of lysosomes.
c. Stop the bacterial effect, so it prevents putrefaction.
d. Hardens the tissues due to coagulation of proteins.
e. Increases the affinity of tissues to staining effect **(mordant effect)**.

3. Dehydration

- The tissue sample is placed in ascending grades of alcohol (from 50%, 70%, 90% to 100% alcohol).
- Aim: Gradual removal of water from tissue spaces to be replaced by alcohol. (Gradual dehydration prevents shrinkage of tissues).

4. Clearing

- The tissue sample is treated with clearing agents e.g. xylol. As the tissue is infiltrated with xylol, it becomes transparent (clear).
- Aim: To replace alcohol with xylol which is miscible with paraffin.

5. Impregnation

- Xylol-penetrated tissue is placed in melted soft paraffin, in an oven (at 50- 55°C).
- Aim: Melted soft paraffin replaces xylol and infiltrates the tissue.

6. Embedding

- Tissue sample is placed and oriented in melted hard paraffin (at 55- [illegible] C) and then left to cool.
- Aim: to form hard paraffin block.

7. Sectioning

- Using microtome, 5 to 8 μm thin sections are cut.
- Aim: Thin sections allow light transmission and avoid superimposition of cells.

8. Mounting

- Sections are mounted on glass slides and left to dry in incubators at 37°c.

9. Staining

- Staining is usually done in aqueous media, and wax has to be removed and replaced by water. This is done by passing sections through:

1- Xylol to remove paraffin.
2- Descending grades of alcohol (100%, 90%, 70%, 50%).
3- Water.

- Aim: to distinguish the various tissue components as:
  1. Unstained sections having uniform optical density.
  2. The various tissue components of the cell have a selective affinity to stains.

Advantages and disadvantages of paraffin technique

Advantages of paraffin technique	Disadvantages of paraffin technique
1- It takes short time (few days). 2- Easily stained. 3- Thin serial sections are obtained	Not suitable for demonstration of: 1- Lipid (as it is dissolved by solvent e.g. xylol). 2- Enzymes in histo-chemical stains (as most enzymes are destroyed by heat).

II. Freezing technique

Method

1- The tissue is fixed by rapid freezing (using liquid nitrogen or carbon dioxide).
2- Sectioning is carried out by a Cryostat (a freezing microtome).
3- Staining with the required stain.

Advantages and disadvantages of freezing technique

Advantages of freezing technique	Disadvantages of freezing technique
1- Rapid, within few minutes so, used to study specimens during surgical procedures. 2- Suitable for demonstration of lipid and enzyme in histo-chemical staining.	1- Thick sections, more than 10 µm. 2- Serial sections are difficult to be obtained. 3- Not easy to be stained.

III. Celloidin technique

- Tissue is infiltrated by celloidin substance instead of paraffin.

Advantages and disadvantages of Celloidin technique

Advantages of Celloidin technique	Disadvantages of Celloidin technique
1- Used for large pieces of tissues. 2- Better preservation of tissues (no heat is used)	1- Takes long time (6-8 weeks), 2- Thick sections are obtained. 3- No serial sections. 4- Difficult to be cut and stained

Tissue culture

Tissue culture generally refers to the growth of living cells, which are separated fr tissue of a multicellular organism outside the body (*in vitro*). Culturing of cells specific growth medium. Tissue culture is an important tool for studying the biolo cells. It provides an *in vitro* model of the tissue in a well defined environment which easily manipulated and analyzed. Different types of cells and tissues can grow in c They include connective tissue elements such as fibroblasts, skeletal and cardiac m epithelial tissue (liver, breast, skin, kidney) and many different types of tumor cells.

Uses of cell culture

1- Studying cell growth, multiplication and differentiation, as well as in cancer resea
2- Studying the effects of new drugs, viruses and radiation on cells.
3- Studying the process of aging.
4- Studying the effect of nutrition on the cells.
5- Cultivation of viruses for vaccine production (e.g. polio, rabies, chicken pox).

6- In cytogenetics research & determination of human karyotypes (the number and morphology of an individual chromosomes).

N.B: Cultured cells are examined using **phase contrast microscopes.**

Staining

1. **Basic stains**
   - Bind with acidic components of the tissue such as nucleic acids.
   - **Basophilic structures:** Tissue components that have an affinity to basic stains e.g. nucleus, ribosome, rough endoplasmic reticulum and matrix of the cartilage.
   - **Examples of basic dyes:** Hematoxylin, toluidine blue and methylene blue.

2. **Acidic stains**
   - Bind with basic components of the tissue.
   - **Acidophilic structures:** Tissue components that have an affinity to acidic stains e.g. cytoplasmic protein, collagen fibers, muscle fibers, mitochondria and secretory granules.
   - **Examples of acidic dyes:** Eosin and orange G.

❖For routine uses, the combination of **hematoxylin and eosin (H&E)** is the most commonly used stain.

- **Hematoxylin** is of plant origin, it stains basophilic structure blue purple color.
- **Eosin** is a synthetic substance. It stains the acidophilic structures pink to red- color.

3. **Neutral stains**
   - These are compounds of an acidic dye and basic dye.
   - The tissue may show affinity for the acidic dye, the basic dye, and for the whole compound.
   - e.g. **Leishman's stain** can be used to differentiate between blood cells that contain acidic, basic or neutral granules.

4. **Meta-chromatic staining**
   - Staining of tissue components with a color, different from the color of the original dye. This is due to interaction of the dye and tissue component.
   - e.g. Staining of mast cells with **toluidine blue** gives red to purple color.

5. **Histo-chemical staining**
   - Special chemical reactions are used for localization of a particular tissue component.

- **e.g.** Periodic acid Schiff reaction (PAS) for demonstration of glycogen, Sudan black and Sudan III for demonstration of lipid in frozen sections.

6. **Vital staining technique**
   - This means staining of living cells inside the living body.
   - **e.g.** injection of **trypan blue** into experimental animals, the dye is rapidly engulfed by phagocytic cells (**macrophages**).

7. **Supra-vital staining technique**
   - This means staining of living cells outside the body.
   - **e.g.** staining of **mitochondria** in a fresh state using **Janus green B**. Staining of **reticulocytes** (immature RBCs.) with **brilliant cresyl blue**.

MICROSCOPY

I. The light microscope LM

- It is used to examine stained sections by using natural or electric light as a source of illumination.
- Components
  - **Condenser:** collects and focus light that illuminates the object.
  - **Objective lens** (low power x10, high power x40, oil immersion x100) enlarges and projects the object image into ocular lens.
  - **Ocular lens** (eye piece x5, x10, x15) further magnifies the image and project it onto viewer's retina.

Magnification power of microscope

equals magnification power of objective lens x magnification power of ocular lens.

Magnifying power of LM = 1000 - 1500 times.

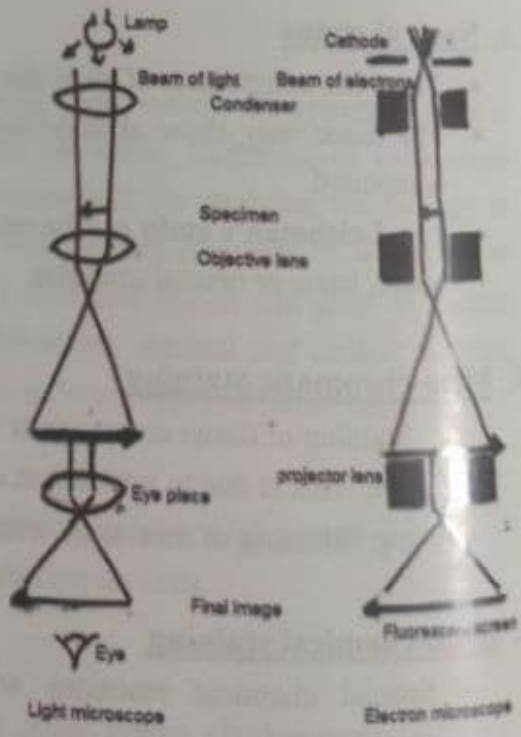
➢ The magnification is of value only when accompanied by high resolution.

Resolution

The smallest distance between two adjacent particles at which they can be seen as separate objects,

The resolving power of L.M. = 0.2 µm.

The resolving power of the eye = 0.2 mm.



II. Electron microscope (EM)

A) Transmission electron microscope (TEM)

It is used to study fine structures with high resolution (0.1nm) that allows very thin sections to be observed with details at magnifications up to 120,000 times.

The principle of TEM

1- The source of illumination is a beam of electrons. Electrons are emitted from cathode and attracted toward anode. They pass through a central opening in the anode forming a constant beam of electrons.

2- Electro-magnetic lenses that detect the beam of electrons.
   - **Condenser**: focus the beam of electrons on the sections.
   - **Objective lens:** magnifies the image.
   - **Projector lens:** further magnifies the image and project it onto fluorescent screen or photographic film.

- Electron-dense areas of the specimen appear black as they scatter the beam of electrons.
- Electron-lucent areas of the specimen appear white as they allow electrons to pass. So, the resulting image is always black and white.

➢ Preparation of tissues for electron microscope

1- **Tissue sample:** not more than $1mm^3$.
2- **Fixation:** 4% cold glutaraldehyde in buffer (overnight), followed by fixation in 1% osmic acid for 1 hour.
3- **Dehydration**: in alcohol.
4- **Clearing** in propylene-oxide.
5- **Embedding:** in Epoxy resin
6- **Sectioning:** ultra-thin sections (60-80) nm are cut using an ultra-microtome, equipped with glass or diamond knives.
7- **Mounting:** on small round copper grids.
8- **Staining:** Heavy metal salts, e.g. uranyl acetate and lead citrate combine with tissue components, rendering some of them more electron-dense than the others.

B) Scanning electron microscope (SEM)

- It is used to show pseudo-three dimensional views of the surfaces of cells, tissues and organs.
- A very narrow electron beam is moved (scanned) from point to point across the surface of the specimen.

Summary

Microtechniques: are methods of preparation of tissue sections for microscopical examination. It includes paraffin technique, frozen technique and celloidin technique.

- Paraffin technique is the most commonly used as it takes few days and thin serial sections are easily obtained.
- Frozen technique used for urgent diagnosis, lipid demonstration and histo-chemical study.
- Of all dyes combination of **hematoxylin and eosin** is the most commonly used.
- **Hematoxylin (basic dye)** stains acidic tissue components into blue-purple color. **Basophilic structures**, as nucleus and ribosomes, have a high affinity to basic dye
- **Eosin (acidic dye)** stains basic tissue components pink. **Acidophilic structures** have high affinity to acidic dye such as cytoplasmic proteins and collagen fibers.
- **Neutral dyes** stains acidic, basic and neutral tissue components, as in blood stains.
- **Metachromasia** is a property of certain tissue components to change the color of some basic stains.
- **Vital stains:** is staining living cells inside the living body.
- **Supra vital stains:** is staining living cells outside the body.
- **Histo-chemical stains:** specific chemical reactions are used for detection of a particular tissue component.
- There are 2 types of microscopy, **light microscope and electron microscope**.
- Electron microscope includes:
  1- **Transmission electron microscope** (TEM), in which a beam of electrons passes through the specimen.
  2- **Scanning electron microscope** (SEM), in which a beam of electrons is moved across the surface of the specimen.

Comparison between Light microscope and Transmission Electron microscope

	Light microscope (LM)	Transmission EM
1- Source of illuminations	- A beam of light from an electric lamp or day light.	- A beam of electrons from the cathode
2- Lens	- Glass	- Electromagnetic
3- Final image is projected onto	- Viewer's retina	- Fluorescent screen
4- Magnification	- 1000-1500 times	- Up to120,000 times
5- Resolving power	- 0.2 µm	- 0.1nm
6- Thickness of sections	- Thin sections of 5-8µm thick	- Ultra thin sections, less than 1µm, 60-80 nm
7- Embedding	- In paraffin	- In epoxy resin

References

1- **Mescher, A.L. (2016)**: Junqueira's Basic Histology: Text and Atlas 14th edition. McGraw-Hill, New York, Chicago, London, Madrid, New Delhi, Seoul, Sydney.
2- **Ross M.H. and Pawlina, W. (2015)**: Histology: A Text and Atlas: With Correlated Cell and Molecular Biology 7th edition. Lippincott Williams and Wilkins.

Questions

Answer the following questions

1. What are the advantages and disadvantages of the freezing method?
2. Explain the terms electron dense and electron lucent.
3. State the differences between the light microscope and the transmission EM.
4. Define meta-chromatic staining, vital staining and supra-vital staining.

M.C.Qs: Select the single correct answer

1- Fixation of the tissue is essential to:

a. Remove water from the tissue.
b. Preserve the fine structure of the tissue.
c. Replace alcohol by xylol.
d. Keep the cells alive.
e. Make the tissue transparent.

2- Which of the following is a clearing agent?

a. Xylol.
b. Alcohol.
c. Formalin.
d. Soft Paraffin.
e. Hard Paraffin.

3- All of the following are basophilic structures EXCEPT:

a. Nucleus.
b. Smooth endoplasmic reticulum.
c. Rough endoplasmic reticulum.
d. Ribosomes.
e. Matrix of the cartilage.

4- What is the total magnification achieved with a Light microscope?

a. Magnification of the objective lens.
b. Magnification of the ocular lens.
c. Magnification of the ocular lens added to magnification of the objective lens.
d. Magnification of the ocular lens multiplied by magnification of the objective lens.
e. Magnification of the objective lens divided by magnification of the ocular lens.

The Cell

II

Intended learning outcomes (ILOs) of the cytology.

By the end of this unit, the student should be able to:

1- **The Cytoplasm:**

- List the components of the cytoplasm.
- Define the cytoskeleton and the cytosol.
- List the types of membranous and non-membranous organelles.
- Describe the structure and correlated functions of the cell membrane.
- Define endocytosis and exocytosis.
- Describe the structure and correlated functions of the membranous organelles.
- Define proteasome structure and function.
- Describe the structure and correlated functions of non- membranous organelles.
- Compare between the centrioles, the cilia and the flagella.
- List the organelles involved in protein synthesis in the cells.
- Classify the different cell inclusions.
- Compare between the organelles and the inclusions.
- Integrate the structure-function relationship of the different cell organelles.
- Correlate between the defective structure of some cell organelles and the occurrence of some diseases.

2- **The Nucleus:**

- List the components of the nucleus.
- Describe the structure and correlated functions of the nuclear envelope, nucleolus, chromatin and nuclear sap.
- Compare between the extended chromatin (euchromatin) and the condensed chromatin (heterochromatin).
- List the nuclear changes indicating cell death.
- Define the programmed cell death (Apoptosis).

- The cell is the structural and functional unit of any tissue. Cells are composed of protoplasm, which consists of nucleus and cytoplasm.
- **Prokaryotic cell**: cell lacking a nuclear envelope e.g. only in bacteria.
- **Eukaryotic cell**: cell having a true nucleus which is surrounded by a nuclear envelope separating DNA from the cytoplasm.
- The cells perform their different specialized functions during the interphase.

The Cytoplasm

► Components of the cytoplasm

1. The cytosol or cytoplasmic matrix.
2. The different kinds of organelles.
3. Inclusions.
4. Cytoskeleton.

1. The cytosol or cytoplasmic matrix

This is the part of cytoplasm between the organelles and inclusions.

It is a colloidal solution composed of soluble proteins, amino acids, carbohydrates and enzymes.

Minerals and ions, useful in metabolic reactions, are also present.

2. The different kinds of organelles

- **Definition:** These are minute living structures, permanently present in the cytoplasm and designed to perform specific functions. They are essential for life.
- **Classification:** Organelles are classified into membranous and non-membranous according to whether they have membranes or not.

a. Membranous organelles

These are surrounded by membranes. They include the following:

1. The cell membrane (plasmalemma).
2. Endosomes and Coated vesicles
3. Mitochondria.
4. Endoplasmic reticulum: rough and smooth.
5. Golgi apparatus.
6. Secretory vesicles.
7. Lysosomes
8. Peroxisomes.

b. Non-membranous organelles

These have no membranes, and include the following organelles:

1. Ribosomes.
2. Microtubules
3. Centrioles
4. Filaments.

3. Cytoplasmic inclusions

These include non-living substances stored in the cytoplasm. They are not permanently present. They are classified as:

a. Stored food:

1. Glycogen.
2. Lipids.

b. Pigments: There are several types, classified as follows:

1. **Exogenous pigments** e.g. Carotene and carbon particles.
2. **Endogenous pigments**, formed in the body, and include:
   - -Hemoglobin.
   - -Hemosiderin.
   - -Bilirubin.
   - -Melanin.
   - -Lipofuscin (Lipochrome pigments).

4. Cytoskeleton

This is formed of a complex system of interconnected microtubules, intermediate filaments and microfilaments which supports the cytoplasm, determines the shape of the cell and it plays an important role in the intracellular transport of organelles, vesicles and macromolecules.

Membranous Organelles

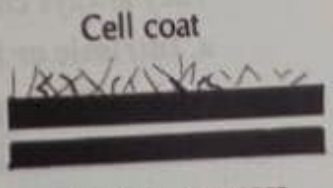
1- The Cell Membrane (plasmalemma or plasma membrane)

It is the outer limiting membrane of the cell which is too thin to be distinguished with the light microscope.

► **LM appearance** of the cell boundary is due to oblique cut or due to condensation of stain on the cell coat.

► **EM appearance**

- It has a trilaminar (3-layered) appearance. Its thickness is 8-10 nm.
- It is composed of an outer dark membrane, inner dark membrane and a middle light layer. Such arrangement is called **unit membrane**.
- A fuzzy electron-dense layer is seen attached to the outer aspect of the cell membrane, representing the **cell coat**.
- The **trilaminar** appearance is due to deposition of osmium on the hydrophilic aspects of the membrane on either side of the lipid bilayer.



Trilaminar appearence

► The molecular structure of cell membrane

Basically, it is formed of proteins and a lipid bilayer with carbohydrates.

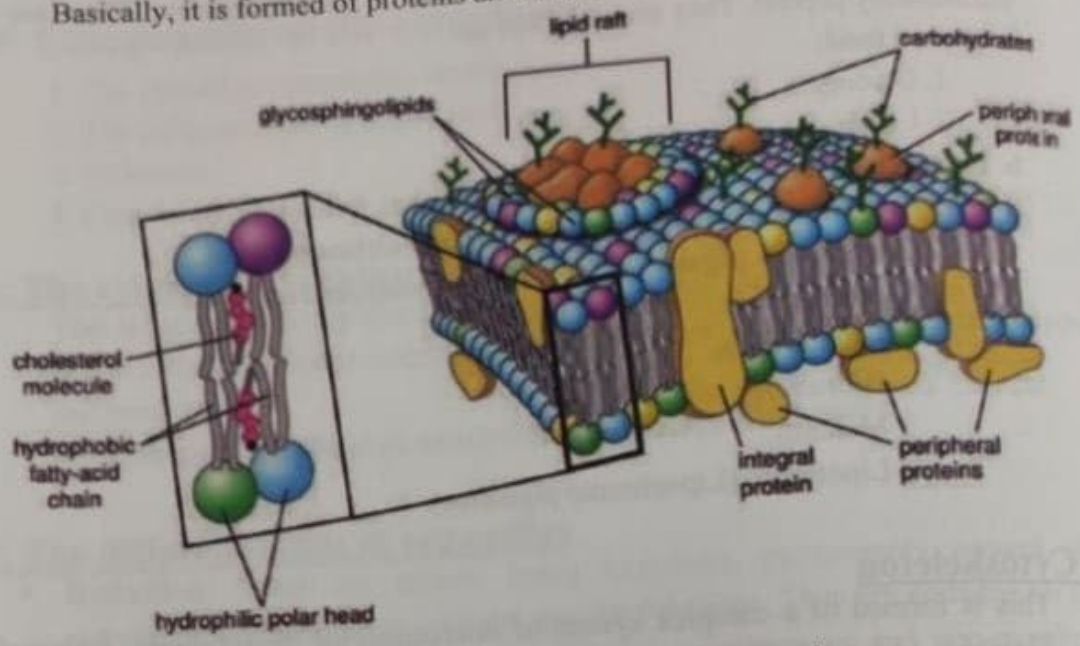


Figure showing structure of the cell membrane

•Lipid Contents

- The lipid bilayer is mainly formed of phospholipids and cholesterol molecules.

a. Phospholipid molecules:

- They are arranged perpendicular to the cell membrane.
- Each phospholipid molecule is formed of a hydrophilic polar head (has great affinity for aqueous solution) which is directed towards the surface of the cell membrane (intracellular or extracellular) and hydrophobic tail (has no affinity for aqueous solution) which is directed inwards.

b. Cholesterol molecules:

- They are present on both sides of the cell membrane.
- Cholesterol molecules have a stabilizing effect, helping to keep t phospholipid molecules packed together and increase the rigidity of t cell membrane.

•Protein contents

Proteins are a major molecular constituent of the cell membrane (about 50%)

They always change their position and are arranged in 2 different ways:

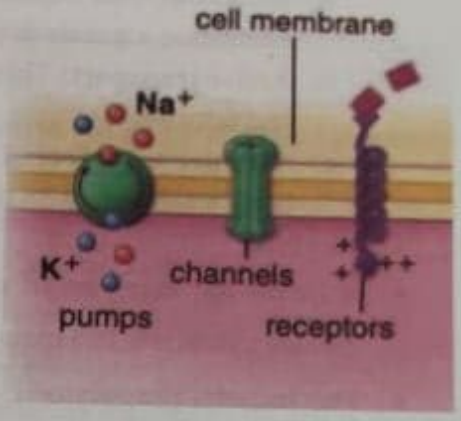
a. Intrinsic or integral membrane proteins:

- These proteins are embedded in the lipid bilayer.
- Some integral proteins extend across the cell membrane from one si the other. These are called **transmembrane proteins**.

- Each molecule has a non-polar **hydrophobic region** (that serves to anchor the molecule firmly to the central core of the cell membrane) and a **polar hydrophilic** region.

Functions:

1. They constitute **ion channels** (for passive transport of certain water-soluble molecules into the cells.) **and ion pumps** (for active transport of ions)
2. They act as receptors controlling the passage of certain substances (e.g. hormones) into the cells.



b. Extrinsic or peripheral membrane proteins:

- These are loosely bound to both inner and outer surfaces of the cell membrane.
- They lack the non-polar portion (necessary to attach them firmly to the central core of the cell membrane).
- **Function:** they act as cytoskeleton.

•The carbohydrate contents (cell coat or glycocalyx)

- The cell coat is a thin coat of glycoproteins and glycolipids on the outer aspect of the cell membrane.
- It is formed of oligosaccharides attached to the outer ends of:
  a. Most of the outward-facing proteins constituting glycoproteins.
  b. Some of the outward-facing lipid molecules forming glycolipids.
- By LM, it is PAS positive.
- By EM, it appears as a fuzzy coat.

Functions

1- It has a key role in cell recognition and cell adhesion.
2- It shares in the formation of the basement membrane.
3- It serves as specific cell receptor.

Differences between the outer and inner aspects of the cell membrane

1. The-cell coat is present on the outer surface only.
2. Different lipid components in both layers.
3. Different proteins in both layers.
4. Receptors are present only on the outer surface of cell membrane.

► Functions of the cell membrane

1. **Exchange of substances between the cell and its surrounding by several ways:**
   a. **Diffusion:** This depends on the concentration gradient on either side of the membrane e.g. ions & gases.
   b. **Active transport:** This requires energy to take place e.g. amino acids, sugars and fatty acids.
   c. **Selective transport:** This occurs due to the presence of specific receptors to certain substances on the outer aspect of the cell membrane.
2. **Endocytosis**

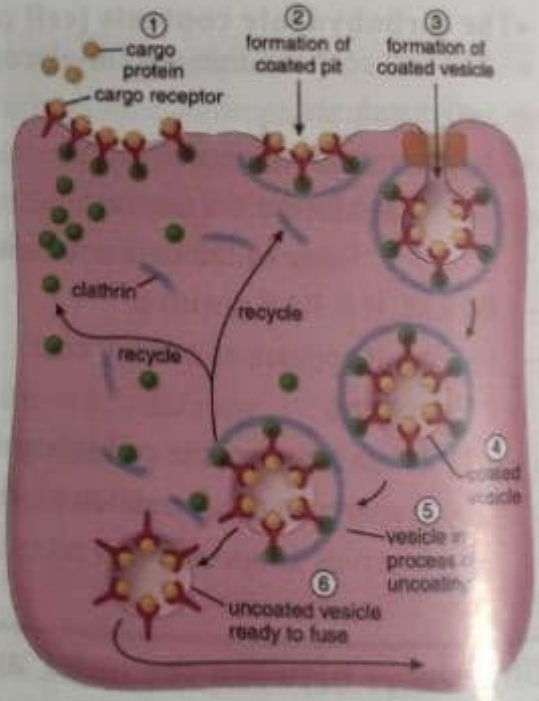
- It means the ingestion of certain substances from the surrounding environment into the cytoplasm in a membrane limited vesicle.
- This includes phagocytosis, pinocytosis and receptor mediated endocytosis.

*1- **Phagocytosis**:* The cells are able to engulf solid particles (e.g. bacteria) within a vesicle forming a phagocytic vesicle or **phagosome.** This is done by specialized cells e.g. neutrophils and monocytes.

*2- **Pinocytosis:*** The cell engulfs a small amount of extra-cellular fluid forming **pinocytotic vesicle.**

*3- **Receptor mediated endocytosis (RME):*** It is the selective uptake of certain macromolecules (e.g. hormones) by certain cells that have in their cell membrane specific receptors for these macromolecules.

In receptor mediated endocytosis, **receptors** are associated with **Ligands** extracellularly and with **Clathrin coat** intracellularly.



Once the receptors are bound with appropriate ligands, they pinch off from the plasma membrane and became coated inside the cytoplasm with **clathrin, forming coated vesicles**. Once the vesicle has formed, the clathrin coat is lost. Each vesicle has 1000 receptors for different molecules.

Fate of Ligand and Receptor:

1- Both ligand and receptor are degraded. e.g.: Growth factor receptor complex.
2- Both ligand and receptor are recycled to the cell membrane. e.g.: Transferrin receptor complex.
3- The ligand is degraded, and receptor is recycled to the cell membrane. e.g.: Low density lipoprotein.
4- Both ligand and receptor are transported across the cell membrane. e.g.: IgA receptor complex.

Functions of receptor mediated endocytosis:

1- Nutritional: as in case of the uptake of certain substances required by the cell as iron and low-density lipoprotein.
2- Transfer of large molecules across the cell as IgA.
3- Host defense.

Clinical Application:

In case of **Type II diabetes mellitus**, the cell receptors become desensitized to insulin.

3. Exocytosis

It is the extrusion of the contents of a membranous vesicle from the inside of the cell to the extra-cellular fluid. The membrane of the vesicle fuses with the cell membrane.

4. Sodium pump

It is an active process by which Na is pumped outside the cell whereas K is picked up into the cytoplasm.

- It forms the basis for depolarization and spread of nerve impulse.
- It is performed by the integral membrane proteins.

5. The functions of the cell coat which serves as a specific cell receptor. It also plays a key role in cell recognition, cell adhesion and in the formation of basement membrane.

6 Antigenic specificity

The cell membrane is provided with receptors which can recognize specific antigens and combine with them.

NB. All membranous organelles are surrounded by membranes which have almost the same structure of that of the cell membrane.

2. Endosomes

- These are membrane bound vesicles associated with the **endocytotic pathway.**
- The **Endosomes** which are located in the cytoplasm near the plasma membrane are called **early endosomes** while those which are located deeper in the cytoplasm are called **late endosomes.**

1- Early Endosomes:

- These are group of vesicles and tubules beneath the plasma membrane forming network. They have low acidic content **(pH 6)** which is essential to separate the ligands from their receptors.
- If the content of the early endosome needs degradation, it will be transferred to the late endosomes.

2- Late Endosomes:

- They are group of vesicles that lie deeper in the cytoplasm with higher acidic content, **(pH 5.5)** They help to prepare their content for destruction by lysosomes.

Multivesicular Bodies:

These are group of vesicles that transport substances between early and late endosomes.

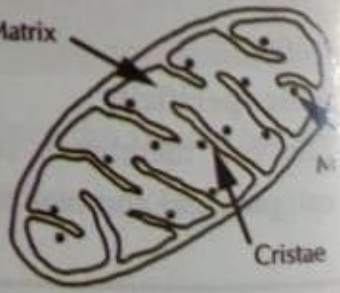
3. Mitochondria

► Definition

These are membranous organelles. They may be termed power houses of the cell.

► LM appearance:

- In the living cells, mitochondria could be seen moving by using the **phase contrast microscope**.
- The mitochondrial membranes contain a large number of protein molecules and they are responsible for much acidophilia of the cytoplasm.



- Special staining methods e.g. silver stains, and **supravital stains** e.g. Janus green B are used to show them outside the body.
- They appear ovoid or elongated or filamentous.
- Their number varies according to energy requirements of the cell, being very high in liver cells and much less in lymphocytes.
- Within the cell, they lie close to the part of the cell having the highest energy requirements.
- Mitochondria change shape constantly and move and grow in-vitro.
- Renewal of mitochondria is a continuous process that occurs through **fission division**.

► EM appearance

- It is the largest organoid (1μmin diameter and 5-10 μm in length).
- Each mitochondrion is bounded by double membranes separated by inter-membrane space.
- The **outer membrane** is smooth and fairly permeable to most small molecules.
- The **inner membrane** is highly selective. It is provided with cristae or folds which are shelf-like projections of variable number, size and shape. They are rich in enzymes involved in oxidative phosphorylation and ATP production.
- Cristae may have a tubular appearance e.g. in steroid hormone-secreting cells as in cells of the adrenal cortex.
- The **Matrix** fills the interior of the mitochondrion. It is rich in enzymes involved in citric acid cycle and oxidation of fatty acids. The matrix also contains electron dense granules which represent calcium ions accumulation. It also contains DNA, mRNA, t RNA and ribosomes.

► Functions of mitochondria

1. They are sites of energy production within the cell. Energy is stored as ATP, which is an energy-rich, compound.
2. Mitochondria play a role in the regulation of calcium metabolism.
3. Mitochondria of the steroid secreting cells contain enzymes involved in steroid synthesis.
4. Mitochondria can synthesize some of its own proteins because it contains DNA mRNA, t RNA and ribosomes.

NB. - **Self renewal** of mitochondria occurs by simple division (fission).

-The life span of the mitochondria is 10 days.

► Structure and function relationship

- The mitochondria tend to accumulate at parts of the cytoplasm with higher energy requirement e.g. basal parts of ion transporting cells.
- The cristae increase the surface area of the inner mitochondrial membrane. They are rich in enzymes of oxidative phosphorylation.
- The total number of mitochondria and the number of cristae in each mitochondrion is related to the cell activity. It is higher in cells with high energy metabolism e.g. muscle cells.

► Medical application

Deficiencies of mitochondrial enzymes lead to impairment of the functions of many tissues, mainly the muscle and nervous tissues. This is because of the high energy requirement of these tissues.

4- The Endoplasmic Reticulum

► Definition

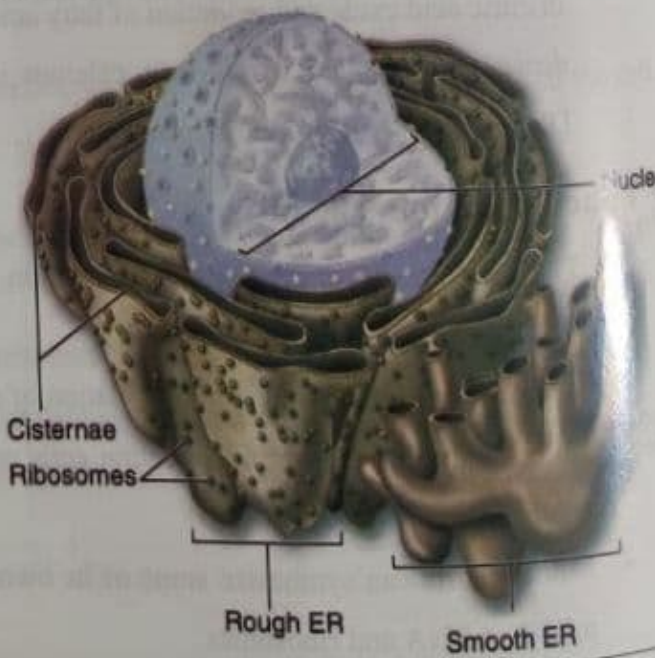
This is a network of interconnected membranous structures.

► It is classified into 2 main kinds

a. Rough endoplasmic reticulum (rER)

b. Smooth endoplasmic reticulum (sER)

They differ in structure, distribution and function.



a. The Rough Endoplasmic Reticulum

▶ The LM appearance:

- They do not appear distinctly.
- Their places appear as regions of localized basophilia.
- Sites: They are abundant in protein secreting cells e.g., fibroblasts, osteoblasts and plasma cells.

▶ EM appearance

- The rough endoplasmic reticulum (rER) appears as interconnected flattened membranous sacs (**cisternae**) parallel to each other.
- Their outer limiting membranes are studded with ribosomes.
- They are also connected with the smooth ER and the outer nuclear membrane.

▶ Function

- Synthesis of the secretory proteins, cell membrane proteins and lysosomal enzymes by their **attached ribosomes.**
- Packing and release of the synthesized proteins to the immature face of Golgi apparatus as **transfer vesicles.**

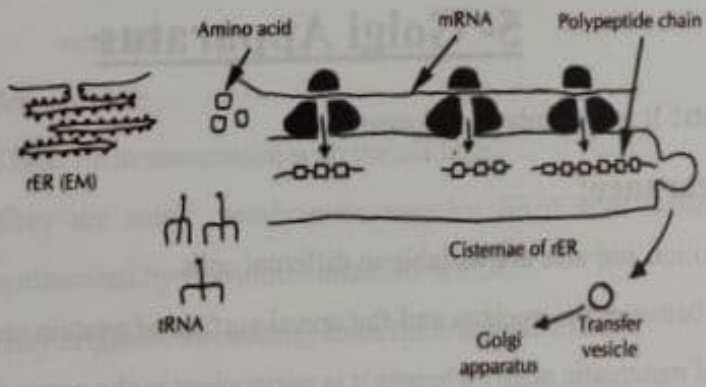


Figure showing protein synthesis in rER

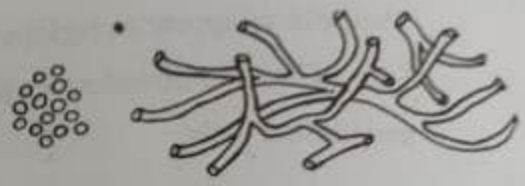
▶ Structure and function relationship

1. Ribosomes are attached to the cisternae of the rough endoplasmic reticulum.
2. The polypeptide chain (protein) that is synthesized by ribosomes is delivered to the lumen of rER.
3. These proteins are transferred to the Golgi apparatus via the **transfer vesicles.**

b. The Smooth Endoplasmic Reticulum

► **LM appearance:** Not seen

► **EM appearance:**



- They consist of branching and anastomosing tubules.
- It is continuous with the rER.
- The limiting membrane is smooth (no attached ribosomes).
- It is prominent in cells concerned with synthesis of lipids, steroid and glycogen e.g. cells of liver and adrenal cortex.

► **Functions:**

1. Lipid synthesis: It forms intracellular lipids and cholesterol derivatives.
2. Detoxification of drugs e.g. barbiturates.
3. Glycogen synthesis in the liver and muscle.
4. Regulation of intracellular calcium as in skeletal muscle where release of calcium from the lumen of sER leads to contraction and re-uptake of calcium leads to relaxation.

5- Golgi Apparatus

► **Definition:** It is a membranous organelle.

► **LM appearance:**

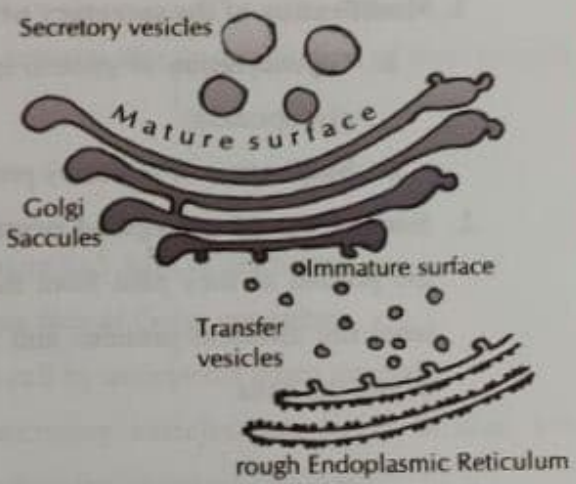
- Its position and size are variable in different cells.
- It lies between the nucleus and the apical surface of protein secreting cells (e.g. cells of pancreatic acini) whereas it is perinuclear in the nerve cells.
- In H & E stained-sections, it may appear as an unstained area in the cytoplasm called **negative Golgi image** e.g.in plasma cells and osteoblasts.
- By silver stain, it appears as dark brown network.

► EM appearance:

It is formed of Golgi saccules, transfer vesicles and secretory vesicles

1.Golgi saccules:

- These represent the main structural unit.
- They are flattened membranous vesicles having saucer like shape. They are arranged in stacks (3-10), one above the other.
- The saccules at the top and bottom are fenestrated.
- The saccules are interconnected.



- Each stack has:
  a. **Cis (immature) face** which is convex and associated with rER and transfer vesicles.
  b. **Transface (mature)** which is concave and associated with secretory vesicles.

2. Transfer vesicles:

- These lie in association with the cis face.
- They are small membranous vesicles filled with protein that is newly synthesized by ribosomes attached to rER.
- They originate as budding from the cisternae of rER.

3. The secretory vesicles:

- These are large membrane bound vesicles associated with the trans face of Golgi apparatus.
- They contain concentrated protein secretion.
- They originate as budding from the saccules at **trans face**.

► EM appearance:

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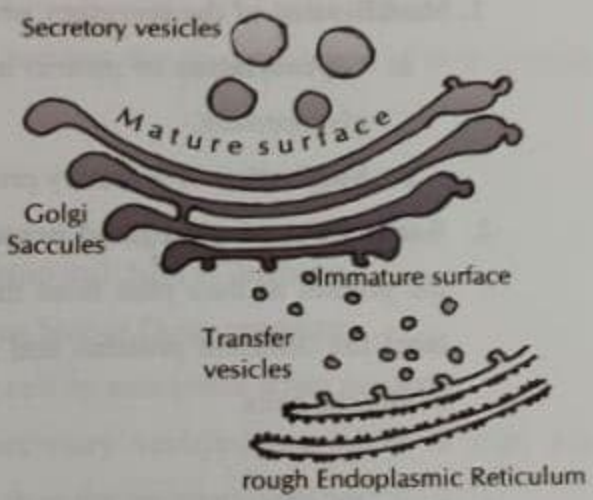

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3. The secretory vesicles:

- These are large membrane bound vesicles associated with the trans face of Golgi apparatus.
- They contain concentrated protein secretion.
- They originate as budding from the saccules at **trans face**.

- They may be extruded outside the cell as secretory products or remain as lysosomes or cell membrane proteins.

► Functions of Golgi apparatus:

Proteins are synthesized by ribosomes of rER then delivered to the cis face of Golgi via the transfer vesicle.

1. Modification of the secretory products:

a. **Glycosylation** of protein molecules i.e. addition of carbohydrate forming glycoprotein.

b. **Sulphation** of secretory protein.

2. **Sorting out of segregated proteins:** by addition of certain chemical groups to the protein as they pass from the cis to the trans face. These chemical groups label the different proteins and serve to address them to the appropriate sites within the cells.

3. **Packaging of sorted out proteins.** The secretory products of the cell are packaged in membranes as:

a. Secretory vesicles (to be discharged out as secretory product).

b. Acid hydrolase enzymes are packaged into lysosomes.

c. Cell membrane proteins (transferred to the cell membrane).

4. **It plays a role in membrane recycling in the cell** where new membranes are added **to the cis face** and old membranes are removed as the secretory vesicles at the **trans face**.

5. **It plays a role in prohormone processing and lipoprotein secretion** e.g. in liver cells.

NB.

- Golgi apparatus cannot synthesize proteins as it lacks ribosomes.
- Proteins are synthesized by ribosomes of rER then delivered to the cis face of Golgi apparatus via the transfer vesicles.
- Concentration, modification, sorting out and packing of the proteins are the functions of Golgi apparatus.

6. Secretory Vesicles

► Definition

These are membrane limited vesicles containing concentrated secretory products of the cell.

► LM appearance:

They appear as red granules in H & E sections due to coagulation of their protein content.

► EM appearance:

- These are membrane-bounded vesicles (up to 1.5μm in diameter).
- They originate as budding from the trans face of Golgi apparatus.
- Their content is discharged outside the cell by exocytosis when needed.
- **Prosecretory granules** (**immature** secretory vesicles) are larger in size, less electron-dense with more fluid content than the secretory vesicles.
- Fluid extraction causes concentration of contents giving mature secretory vesicles.
- **Zymogen granules** are secretory vesicles containing digestive enzymes.

7. Lysosomes

► Definition

These are spherical membranous vesicles containing numerous hydrolytic enzymes.

► LM appearance:

- Lysosomes cannot be distinguished in H & E stained sections.
- They can be demonstrated by **histochemical methods** i.e. **acid phosphatase technique** because they are studded with acid hydrolase enzymes.
- Variable number in different cells (numerous in **macrophages**).

► EM appearance:

- Lysosomes are spherical membrane bounded vesicles.
- They have **variable** electron dense content.

- Each Lysosome is surrounded by **a unique membrane** that resists digestion by its own hydrolytic enzymes

► The lysosomal membrane is characterized by the following:

a) Unusual **unique lipid (phospholipids)** content that resists the activity of the hydrolytic enzymes

b) **Highly glycosylated membrane proteins**. The sugar molecules cover the entire luminal surface of these proteins, thus protect them from digestion by the hydrolytic enzymes

c) **Proton pumps** that transport H+ into lysosomal lumen to maintain low, acidic PH media which is essential for activation of the hydrolytic enzymes.

d) **Transport proteins** that transport the final products of digestion to the cytoplasm, where they are **utilized** by the cell or **exocytosed outside the cell**.

► Formation of the lysosomes:

- The hydrolytic enzymes are synthesized by the ribosomes attached to the **rER**.
- These enzymes are delivered to the lumen of the rER.
- They are then separated from rER as **transfer vesicles** which will fuse with the cis face of the **Golgi apparatus,** where they are modified, sorted and enclosed within a membrane.
- These hydrolytic enzymes will be transferred from Golgi apparatus to late endosomes. The specific proteins of the lysosomal membrane are also transmitted to the late **endosomes**.
- The late endosomes then mature into lysosomes.

Three different pathways deliver materials for digestion into the lysosome:

1) Extracellular large particles as bacteria, cell debris are engulfed by phagocytosis. **phagosome** receives hydrolytic enzymes to become a late endosome which matures into a lysosome.

2) Extracellular small particles are internalized by **pinocytosis and receptor-mediated endocytosis**. These particles follow the endocytotic pathway through early and late endosomes and finally degraded in lysosome.
3) Intracellular particles as **old organelles** and **unwanted cytoplasmic proteins** are isolated from cytoplasmic matrix, surrounded by a membrane then transported to the lysosomes where they are degraded. This process is called **autophagy.**

The digested particles (nutrients) will diffuse through the lysosomal membrane into the cytosol to be used by the cell.

The undigested particles (debris) are retained within the vacuole, which is now called the **residual body.**

- The **residual body** either remains within the cytoplasm or becomes extruded outside the cell by **exocytosis**.
- **With advancing age**, the residual bodies accumulate in the cells of some tissues as brown **lipofuscin** granules e.g. in cardiac muscle and nerve cells.

NB.

- **Autophagy** is a process by which the cell uses its lysosomes to get rid of an old non-functioning organelle or other unwanted cellular structures which becomes surrounded by a membrane.

- The **phagosome** is a vesicle containing solid substance taken within the cell from outside.

- The **autophagosome** is a vesicle containing old non-functioning organelle or unwanted cellular structures surrounded by a membrane.

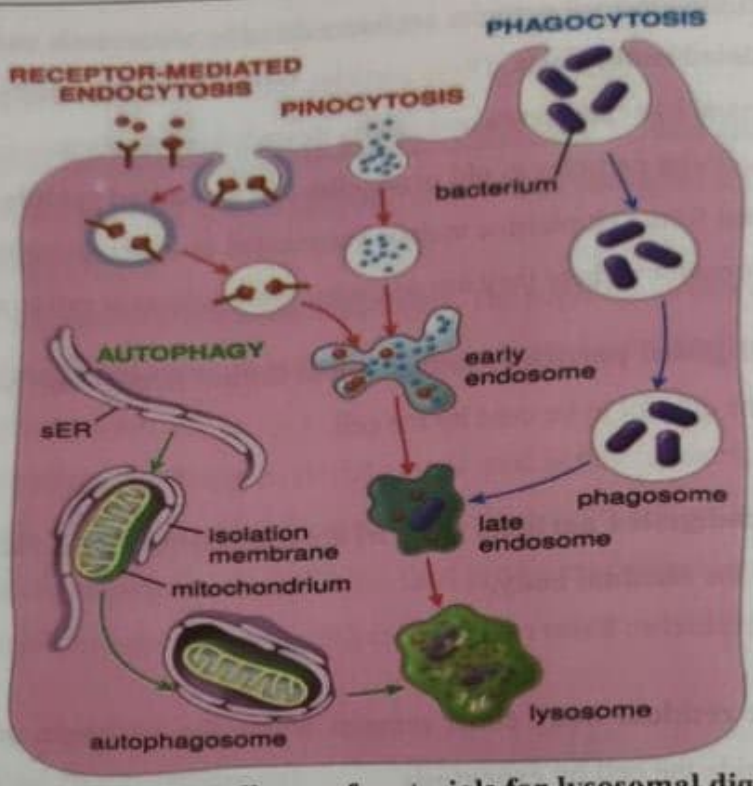


Figure showing delivery of materials for lysosomal digestion

► Functions of lysosomes

1- Intracytoplasmic digestion of micro-organisms or macromolecules ingested by the cell from the external environment.

2- Degradation of old non-functioning organelles.

3- Transformation of inactive prohormones into active hormones.

The cytoplasmic components are protected from the lysosomal enzymes as follows:

1-The enzymes are surrounded by the lysosomal membrane.

2- The lysosomal enzymes are inactive at the pH of the cytosol.

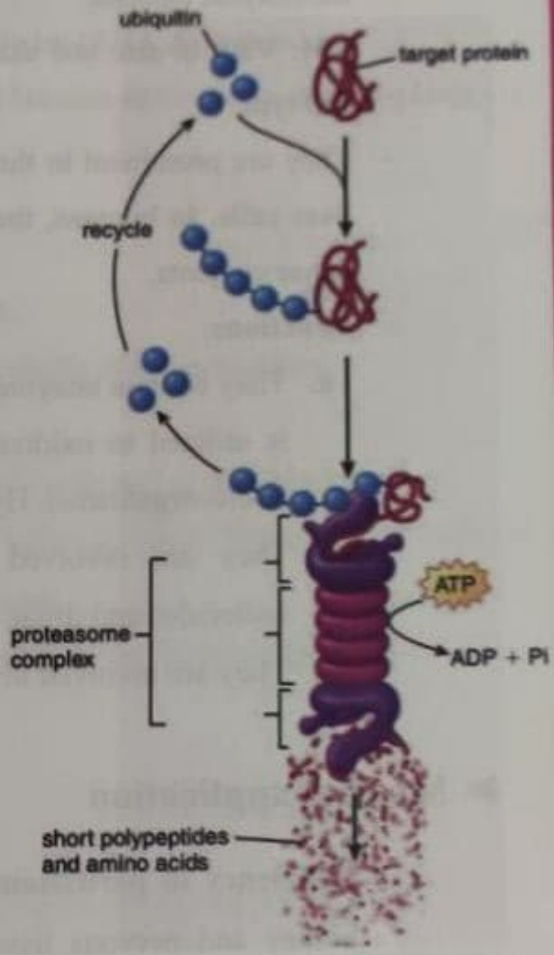
► Medical application

- **Hypoxia** leads to release of lysosomal hydrolytic enzymes leading to cell digestion.
- Lysosomal enzymes are responsible for autolysis of the body after death (**post mortem autolysis**).

- Deficiency **of Lysosomal enzymes** lead to accumulation of undigested substances within the cells interfering with their normal functions e.g. **glycogen storage disease** (characterized by growth abnormalities).

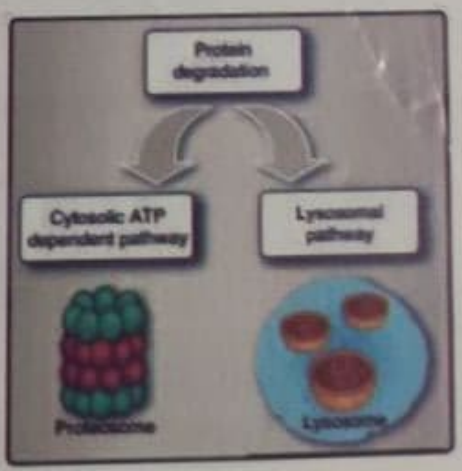
N.B. Proteasomes

- Proteasomes are cytoplasmic protein complexes not surrounded by membranes.
- They contain complex enzyme system that can destroy abnormal proteins without involvement of lysosomes.
- Proteins selected for degradation are tagged with molecules of ubiquitin (a special type of protein).
- Proteasomes deal with short lived proteins while lysosomes degrade proteins with long half-lives.



- **Function:**
  - Proteasomes are used by cells to destroy abnormal proteins.
  - They also degrade normal short-lived regulatory proteins that need to be rapidly inactivated and degraded such as mitotic cyclins that regulate cell cycle progression.

- **Medical application:**
  - Malfunction of proteasomes leads to a decrease in protein degradation with subsequent accumulation of defective proteins in the cytoplasm e.g Alzheimer's disease.



8. Peroxisomes or microbodies

- These are membranous organelles rich in oxidative enzymes e.g. catalase and amino acid oxidases.
- They can divide by binary fission.
- **LM**: visible by histochemical reaction for the enzyme catalase.
- **EM**: Vary in size and shape according to cell type.
- They are prominent in the kidney and the liver cells. In humans, they have electron dense contents.

- **Functions**:
  - **a.** They contain enzymes needed for formation of hydrogen peroxide (which is utilized to oxidize many potentially toxic metabolites and to kill the micro-organisms). Hydrogen peroxide is broken down by catalase.
  - **b.** They are involved in the metabolism of various potentially toxic molecules and drugs in liver and kidney e.g. formaldehyde and alcohol.
  - **c.** They are involved in lipid metabolism (B oxidation of fatty acids).

► Medical application

Deficiency in peroxisomal enzymes leads to sever impairment of the liver, kidney and nervous tissues. This is due the accumulation of various toxic molecules and metabolites in such tissues.

Non-membranous organelles

1. Ribosomes

► Definition

- Ribosomes are non-membranous organelles.
- They are formed of ribonucleoprotein particles (RNA & protein).
- They are synthesized in the nucleolus and become delivered to the cytoplasm via the nuclear pores.

► LM appearance:

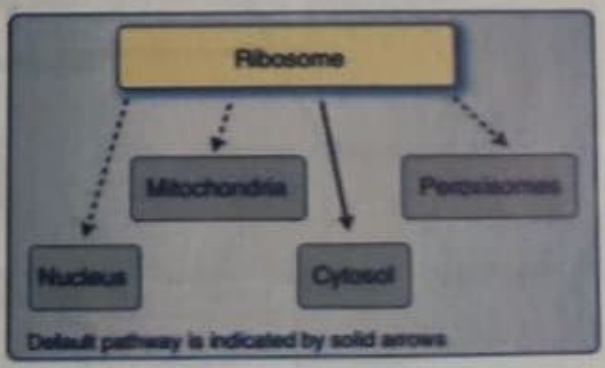
- They cannot be seen due to their small size.
- However, they are responsible for the basophilia of the cytoplasm.
- **Cytoplasmic basophilia may be**:
  a. **Diffuse** e.g. malignant cells, embryonic cells and erythroblasts.
  b. **Localized** in a certain part of the cell e.g. basal basophilia in cells of pancreatic acini.
  c. **Spotty,** in the form of basophilic patches, as in Nissl granules of nerve cells.

► EM appearance:

- They appear as electron dense granules (20-30 nm in diameter).
- Each ribosome is formed of two subunits; a large subunit and a small subunit.
- Types of ribosomes:

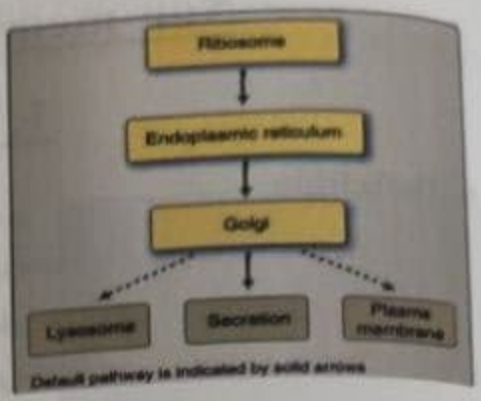
a. Free ribosomes:

- Free particles within the cytoplasm.
- A group of ribosomes may be linked together by a molecule of mRNA forming a bead -like structure called **polysomes (polyribosomes)**.



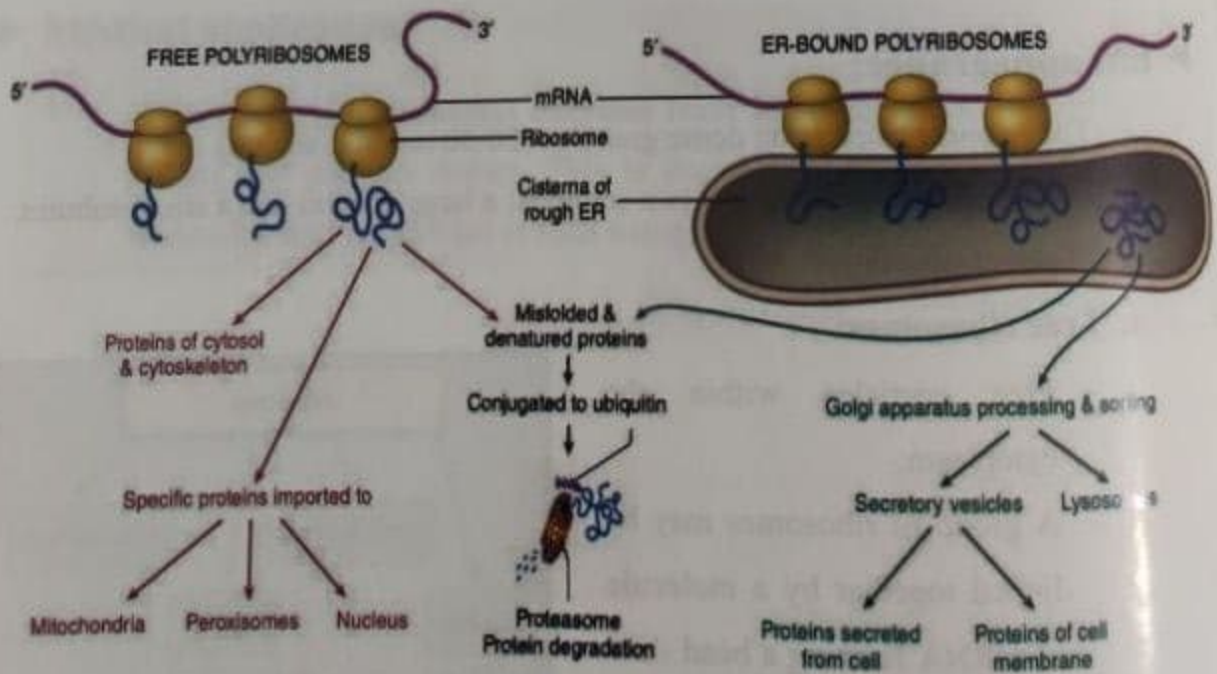
b. Attached ribosomes:

- These are attached to the outer surface of the rER by their large subunits.
- Ribosomes may appear also attached to the outer nuclear membrane.



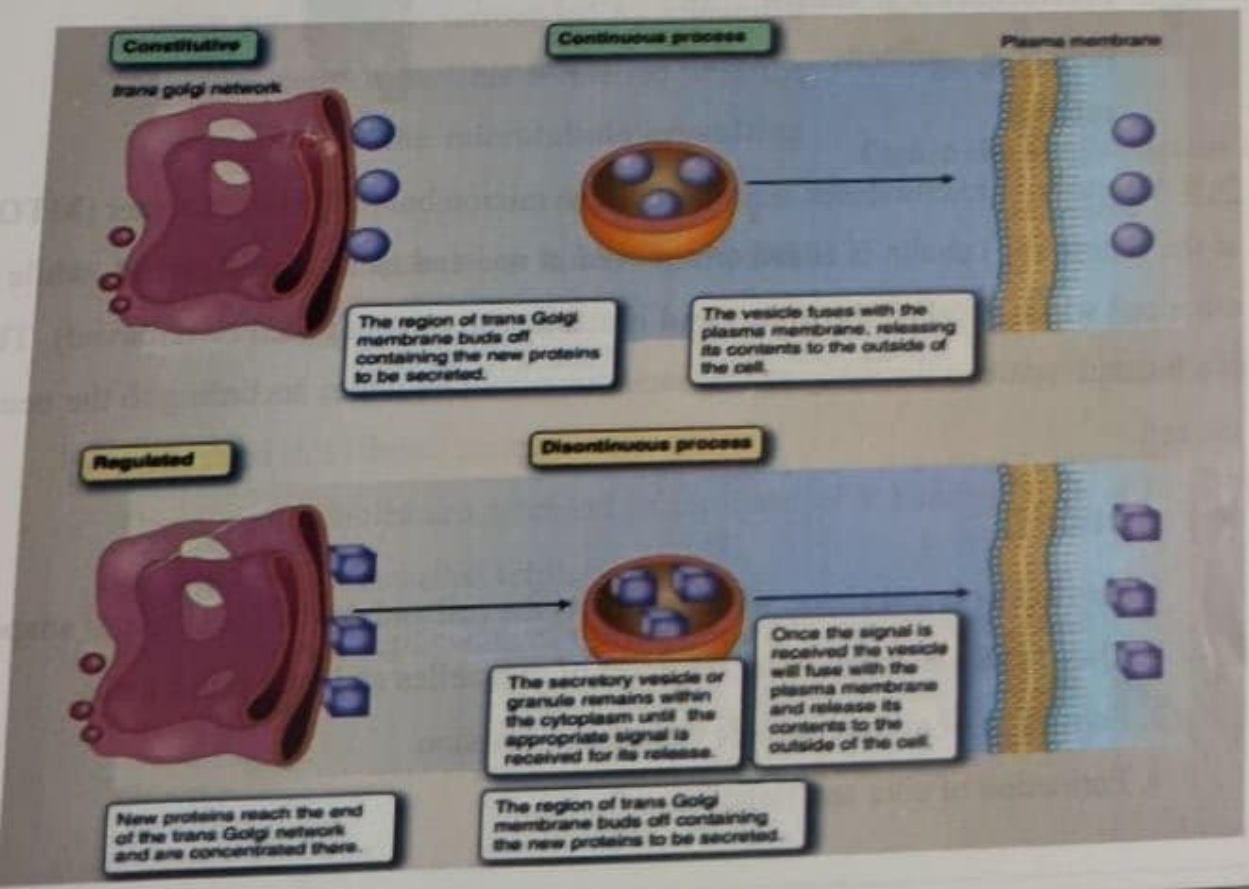
► Function:

- Ribosomes are concerned with **protein synthesis**. They provide sites for amino acid linking to form polypeptide chains i.e. proteins.
- The proteins which are synthesized by the **free ribosomes** will function in the nucleus, mitochondria, peroxisomes or are kept inside the cytoplasm to be used to build up the cell.
- The proteins which are synthesized by the **ribosomes attached to the rER** are packed by the Golgi apparatus into either secretory proteins, plasma membrane proteins or lysosomal enzymes.



N.B. Protein trafficking

- Proteins are synthesized either on free ribosomes or on ribosomes bound to the rough endoplasmic reticulum.
- Ribosomes bind to rER when proteins they are synthesizing contain a signal sequence or a leader sequence. Ribosomes remain free when proteins they are synthesizing lack this sequence.
- The default pathway for proteins synthesized on bound ribosomes is to enter the lumen of rER, then move to the Golgi complex and then to be secreted from the cell.
- Proteins destined to function in lysosomes receive a Mannose-6-phosphate tag in the Golgi.
- Proteins secreted from the cell are released either in a constitutive or in a regulated manner.
    - Example of constitutive secretion is extracellular matrix proteins including collagen and elastin.
    - Example of regulated secretion is insulin which is released from B cells in the islets of Langerhans in the pancreas only in response to elevated levels of blood glucose.
- Proteins synthesized on free ribosomes will remain in the cytosol unless they contain a tag to direct them to the nucleus, mitochondria or peroxisomes.



2. Microtubules

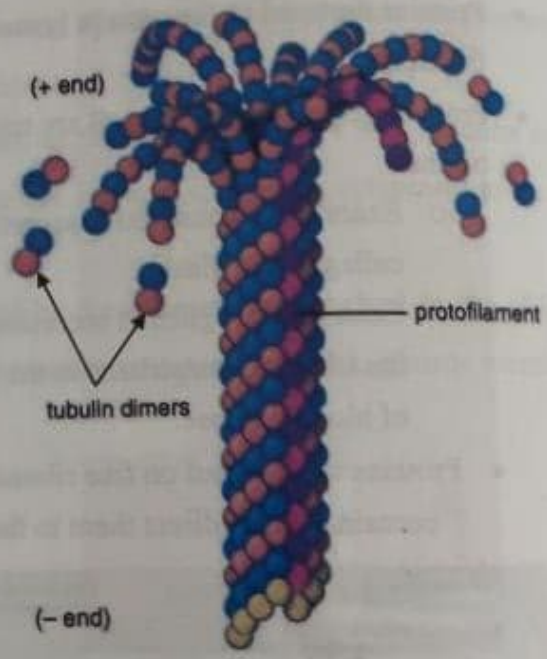
► **Definition:** They are tubular non-membranous organelles.

► **LM appearance:**

- They do not appear easily in ordinary sections.
- They appear by special staining methods e.g. fluorescent antitubulin.
- They are present in cilia, centrioles and flagella.

► **EM appearance:**

1. They appear as slender tubular structures of variable length but fixed diameter (25 nm).
2. They appear as tiny circles in section.
3. The wall of each microtubule is formed of 13 thread-like structures called **protofilaments.**
4. Protofilaments consist of protein subunits called **tubulin.**



N.B Assembly of microtubules is initiated in the microtubule-organizing center (MTOC) at the centrioles. Tubulin is added or removed at one end called the **plus end**, while the other end which is called the **minus end** is stabile (no tubulin added or removed). There is a balance between assembly and dissociation of microtubules according to the need of the cell.

► **Functions:**

1. They act as cytoskeleton which supports the cell and determines the cell shape.
2. They facilitate intracellular transport of organelles and macromolecules.
3. Formation of mitotic spindle during cell division.
4. Formation of cilia and flagella.

► **Medical application:**

Antimitotic drugs e.g. **colchicine** can stop mitosis as they prevent the development of the mitotic spindle (because they bind to tubulin and prevent its addition at the plus end).

Uses of antimitotic (Cytotoxic) drugs:

1-In karyotyping.

2- In treatment of cancer.

3. The centrioles

► **Definition:** Are non-membranous organelles.

► **LM appearance:**

They appear as 2 dots close to the nucleus with special stains e.g. iron hematoxylin.

► **EM appearance:**

- Close to the nucleus of non-dividing cells, the two centrioles appear perpendicular to each other and they are surrounded by a granular electron dense area. This is referred to as the **centrosome or the microtubule organizing center (MTOC)**.
- Each centriole appears as a hollow cylinder (0.2 X 0.5μ).
- The wall of each cylinder consists of 27 longitudinally arranged microtubules embedded in a fibrous matrix.
- These microtubules are arranged in the form of 9 bundles, each is formed of three microtubules called **triplets**.
- Before mitosis, duplication of the two centrioles occurs at S phase.

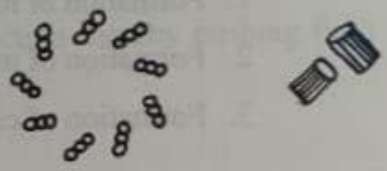
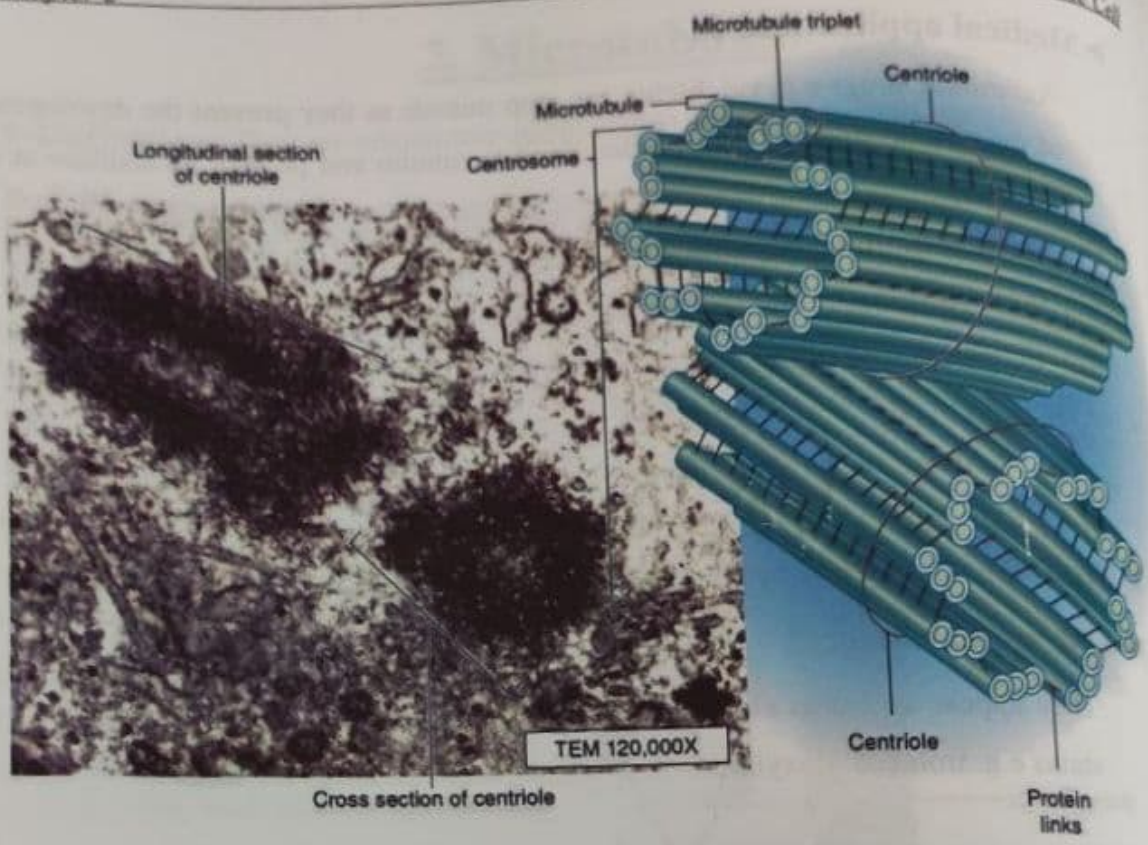


Figure showing structure of centrioles



► **Functions of centriole:**

1. Formation of microtubules by MTOC.
2. Formation of mitotic spindle during cell division.
3. Formation of cilia and flagella.

The Cilia and flagella

A. Cilia

► **Definition:**

They are motile hair like processes extending from the free surface of certain cells e.g. in the respiratory system.

► **LM:**

They are fine hair -like processes extending from the free surface of cert

► **EM:** Each cilium is formed of a basal body, a shaft, and rootlets

a. Basal body

- Its structure is identical to that of the centriole (formed of 27 microtubules arranged as **9 triplets**).
- The basal body is organized from the centriole and then migrates to the free border of the cell.

b. Shaft or axoneme

- It is formed of 18 microtubules arranged as 9 bundles, 2 tubules each i.e.**9 doublets.**
- The central part of the shaft contains two more tubules called **singlets**.
- The shaft is covered by a membrane.

c. Rootlets

These are minute fibers which anchor the basal body to the cytoplasm.

► Function of the cilia

Cilia beat over the surface of epithelium in one direction thereby pushing fluid or even small particles by rhythmic movement.

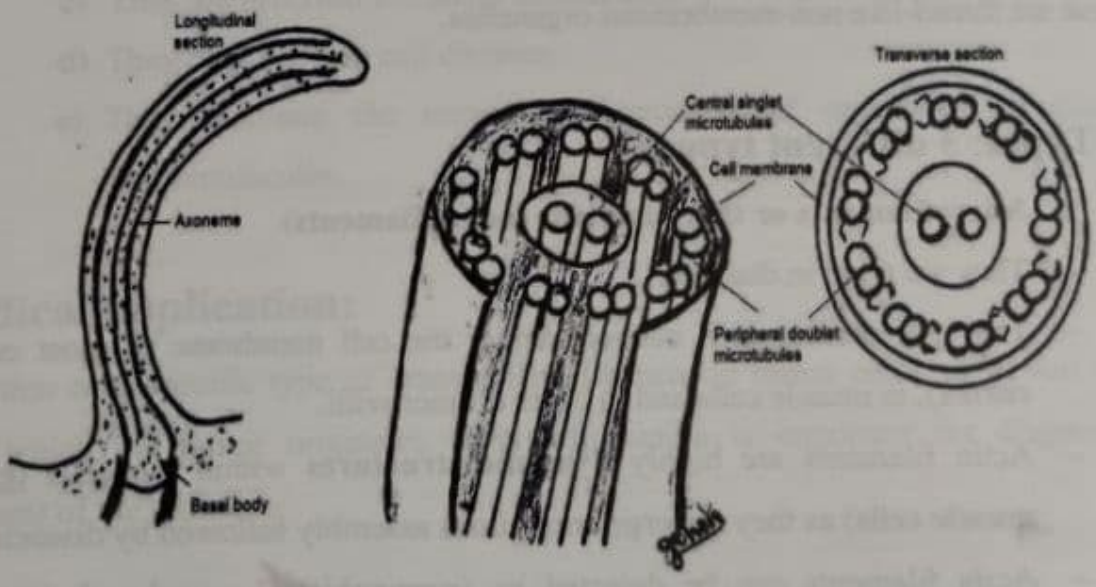


Figure showing structure of cilia

► **Differences between centrioles and shafts of cilia:**

1. In the shaft of cilia there are 9 doublets and 2 singlets in the center.
2. Cilia are covered by cell membrane.

B. Flagella

- Flagella have the same structure as cilia.
- It is single and longer than cilia.
- It has whip like movement.
- Site: the sperm has a single flagellum

Medical application

Immotile cilia syndrome is due to congenital lack of the dynein arms which provide energy for movement in cilia and flagella. This is characterized by immotile cilia (of the respiratory system) and flagella (of the sperms), leading to chronic respiratory tract infection and male sterility.

4. Filaments

► Definition

These are thread-like non-membranous organelles.

► Types: 3 different types.

1. **Microfilaments or thin filaments (actin filaments)**

- They are 6 nm in diameter.
- They are present as a network under the cell membrane of most cells (**cell cortex**), in muscle cells and in cores of microvilli.
- Actin filaments are highly **dynamic structures** within the cells (except in **muscle cells**) as they undergo continuous assembly followed by dissociation.
- Actin filaments can be detected by immunohistochemical techniques (using antibodies against actin).

2. **Thick filaments:** or **myosin** filaments. They are 15 nm in diameter and are found in striated, smooth and cardiac muscles. It is an actin binding protein.

2. **Intermediate filaments:** Their diameter is 10 nm. This group of filaments is heterogenous, with variable functions and distribution.

► **Types of intermediate filaments:**

a) Desmin e.g. in striated and smooth muscle.
b) Keratins e.g.in epithelial cells.
c) Neurofilaments e.g. in nerve cells.
d) Vimentin e.g.in fibroblasts and vascular smooth muscles.
e) Glial filaments e.g.in neuroglia cells.
f) Nuclear lamina: associated with the inner membrane of nuclear envelope.

► Functions:

a) Together with the microtubules they form the cytoskeleton which supports the cell and serves to keep its shape.
b) They help to ensure equal distribution of the tensile forces throughout the cells e.g. in smooth muscles and keratinocytes of skin.
c) They are involved in muscle contraction.
d) They play a role in cell division.
e) They facilitate the intracellular transport of organelles, vesicles and macromolecules.

Medical application:

Detection of a specific type of intermediate filament in tumor cells can reveal the cell from which the tumor originates. This information is important for diagnosis and treatment of the tumor.

Cytoplasmic inclusions

► **Definition**

These are aggregations of non-living material within the cytoplasm which are either products of cell metabolism or taken inside the cell from the outside. They include stored food and pigments.

A) Stored food

Only carbohydrates and fats are stored as inclusions.

1. Carbohydrates

These are stored mainly in the liver cells and muscle cells as glycogen.

► **LM appearance:**

- Irregular unstained spaces in H& E stained sections.
- They are stained purple with **PAS** and red with **Best's carmine.**

► **EM appearance:**

Glycogen appears in two different forms:

1-Alpha particles: aggregation of electron dense particles forming rosettes e.g. in the liver cells.

2-Beta particles: discrete single granules e.g. in muscle cells.

2. Fats or lipids

Fats are stored in fat cells and in liver cells.

► **LM appearance:**

Fat appears as empty round spaces with regular sharp edges in H & E sections. The fat droplets dissolve during preparation. Special stains are used for their demonstration e.g. Sudan III.

► **EM appearance:**

They appear as large round droplets which are moderately electron dense with no limiting membrane.

B) Pigments

► Classification:

Pigments are either exogenous or endogenous

1. Exogenous pigments:

These are taken into the body from the outside.

► Types:

a. **Carotene:** These are fat soluble orange compounds. When taken in, carotene colors the body components which contain fat.

b. **Dust and carbon particles:** Inhaled dust and carbon particles cause dark to black coloration of the lungs e.g. smoker's lung.

c. **Minerals:** Certain minerals can cause pigmentation of tissues, when taken by mouth or through the body surface e.g. lead. Tattoo marks are made of inorganic pigments.

2. Endogenous pigments

They are synthesized inside the body.

a. Hemoglobin and its derivatives:

- This is the most abundant endogenous pigment in the body.
- It is an iron-containing pigment of red blood corpuscles.

b. Melanin:

This is a brown to black pigment that is found in the skin, hairs, eyes and it is formed by melanocytes.

c. Lipofuscin pigment:

- It is a lipid material of golden brown color.
- It is found in the very long-lived cells e.g. neurons and cardiac muscle fibers.
- They represent wear and tear pigments which resist digestion by lysosomal enzymes and accumulate in the form of **residual bodies**.

The Nucleus

- It is the storage compartment for DNA that code for protein synthesis.
- It carries the genetic information and performs the same functions in all cells.

I. The interphase nucleus

General features

All nuclei have the same components. However, there are some variations in size, shape and number in different cells.

- **Shape**: the nucleus may be rounded, ovoid, elongated, kidney-shaped or segmented.
- **Number**: most cells have one nucleus (**mononucleated**), some cells have two nuclei (**binucleated**), and others have multiple nuclei (**multinucleated**).

Components of the nucleus

The nucleus is formed of:

1. Nuclear envelope
2. Nuclear matrix
3. Chromatin
4. Nucleolus

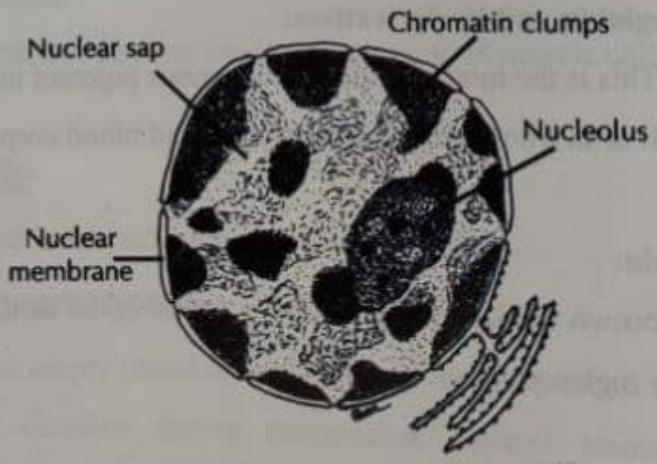
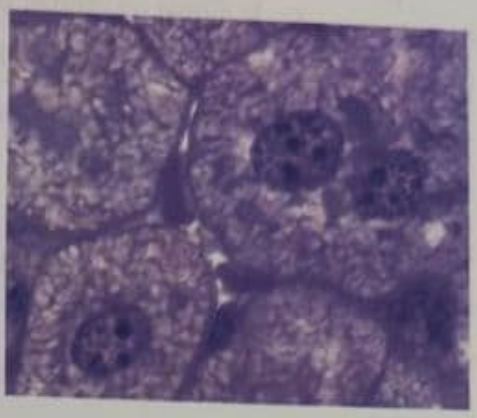


Figure showing components of the nucleus

1. The nuclear envelope



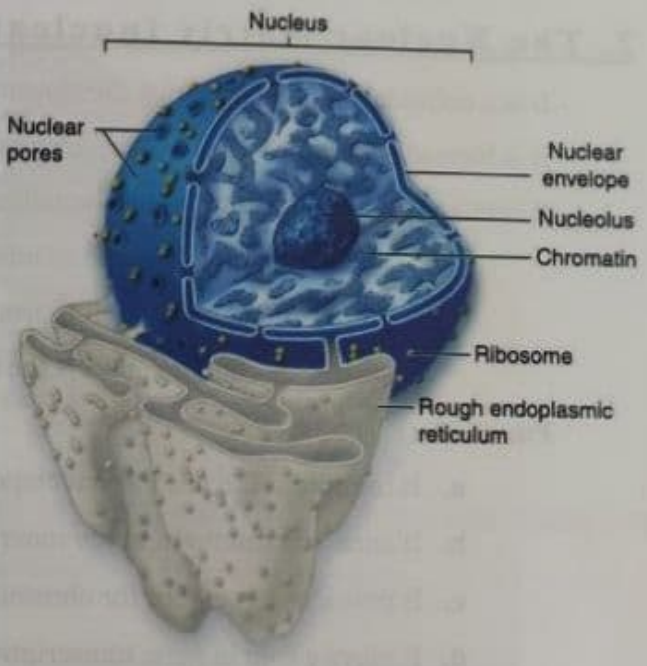
The LM appearance:

It appears as a basophilic line. The basophilia is due to:

1. The chromatin attached to its inner aspect.
2. The ribosomes attached to its outer aspect.

The EM appearance

The nuclear envelope consists of two membranes (8nm thick) separated by a narrow **perinuclear space** (25nm wide). Each membrane has a unit membrane structure.



1. The **outer membrane** is continuous with the rER and is covered with **polyribosomes**.
2. The **inner membrane** is attached to peripheral chromatin. It is supported by a network of intermediate filaments called **nuclear lamina**.

- The nuclear envelope contains minute circular openings called the **nuclear pores** (80-100 nm in diameter).
- The number of these nuclear pores is about 3000-4000.
- The inner and outer membranes of the nuclear envelope fuse at the periphery of each nuclear pore.

The Nuclear Pore Complex (NPC)

- It is a short cylindrical channel crossing the nuclear pore from the nucleus into the cytoplasm.

- **Function of the nuclear pore complex:**
  - It allows exchange of ions and molecules between the nucleus and the cytoplasm. Ions and small molecules pass through the nuclear pores passively, but passage of larger molecules requires energy (i.e. active process).

Functions of the nuclear envelope:

1- It segregates the content of the nucleus from the cytoplasm.

2- It controls the exchange of ions and molecules between the nucleus and the cytoplasm through the nuclear pore complex e.g. histone protein and ribosomal RNA subunits.

2. The Nuclear matrix (nuclear sap)

- It is a colloidal solution in which the chromatin is suspended.
- It is formed of proteins, metabolites, enzymes and minerals.
- It contains fibrillar structure which includes:
  - **a.** Nuclear lamina adherent to inner surface of the nuclear envelope.
  - **b.** Fibrous network extending from the nuclear lamina into the interior of the nucleus and it supports the nucleolus.

Functions:

- **a.** It reinforces the nuclear envelope and the NPC.
- **b.** It anchors chromatin to the inner nuclear membrane.
- **c.** It provides a medium for chromosomal duplication.
- **d.** It plays a role in gene transcription.

3. Chromatin

It is a complex basophilic material from which chromosomes are composed during cell division.

Chromatin is formed of:

1. DNA.
2. Strongly basic protein, namely histones.
3. Less basic non-histone proteins.

– Proteins provide structural and functional organization for the chromatin.

– The DNA molecule, which is several centimeters long, can be compacted into chromosome, which is very much shorter than the DNA molecule.

- **Function of the nuclear pore complex:**
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Compaction or shortening of the DNA

It is achieved by winding of DNA molecule around a spool of histones. This leads to 10000-fold reduction in length of a single DNA molecule.

Nucleosome

It is the basic structural unit of chromatin. It is formed of 4 types of histone proteins and DNA molecule wrapped around the proteins. The nucleosomes are very dynamic structures, this is essential to allow transcription of the genetic information of DNA.

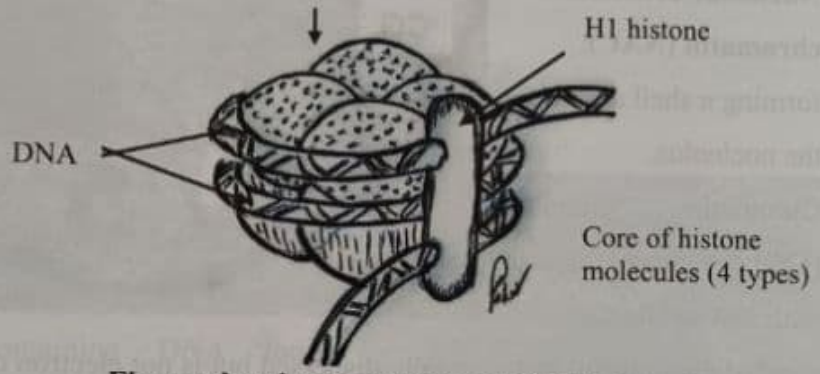


Figure showing components of Nucleosome

► **LM:**

Chromatin is too thin to be visible by the LM but the highly coiled and folded parts (**condensed chromatin**) appear as coarse or fine basophilic granules.

► **Classification of chromatin**

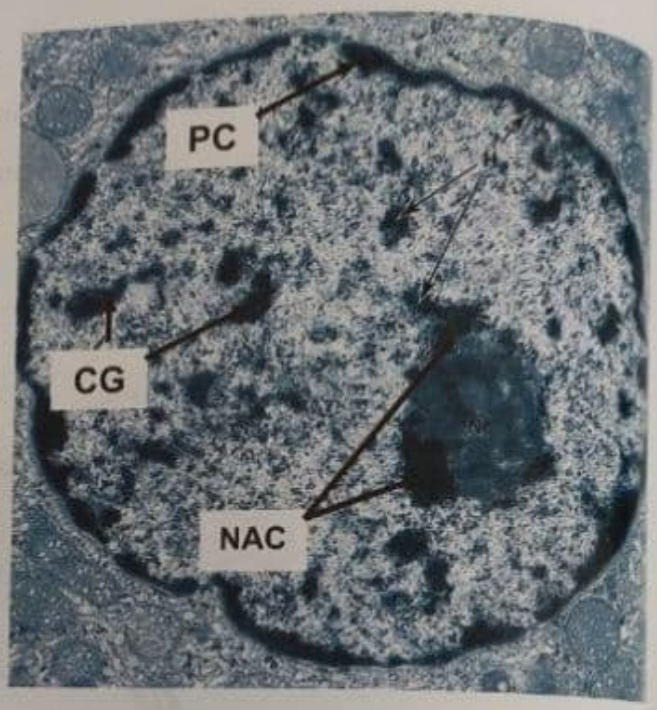
Chromatin is classified into two main types:

1. **Extended chromatin (Euchromatin).**
   - -It is formed of uncoiled chromatin thread.
   - - It is genetically active i.e.it carries functioning (active) genes.
   - - LM: cannot be seen
2. **Condensed chromatin (Heterochromatin)**
   - - It is the coiled part of the chromatin.
   - - It is genetically inactive i.e. it carries non-functioning (inactive) genes.
   - - LM: it appears as basophilic coarse granules.

► **EM appearance of the nuclear chromatin**

Under the EM, chromatin appears as one of the followings:

1. Condensed chromatin appears as granular electron-dense masses that distributed in three sites:



a. **Peripheral chromatin (PC)**: distributed on the inner aspect of the inner membrane of nuclear envelope.

b. **Nucleolus-associated chromatin (NAC)**: forming a shell around the nucleolus.

c. Chromatin granules **(CG)** or clumps: appear with LM as islands.

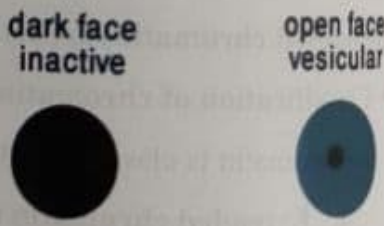
2. Extended chromatin: this is widely dispersed but is not electron dense.

3. Gradation between both kinds.

N.B.

Vesicular (Open face) nucleus

A nucleus which appears as a vesicle with an apparent nucleolus. It contains mainly extended chromatin e.g. the nucleus of the nerve cell.



Condensed (inactive) nucleus

A deeply stained nucleus with an unapparent nucleolus. It contains mainly condensed chromatin e.g. nucleus of the lymphocyte.

4. The Nucleolus

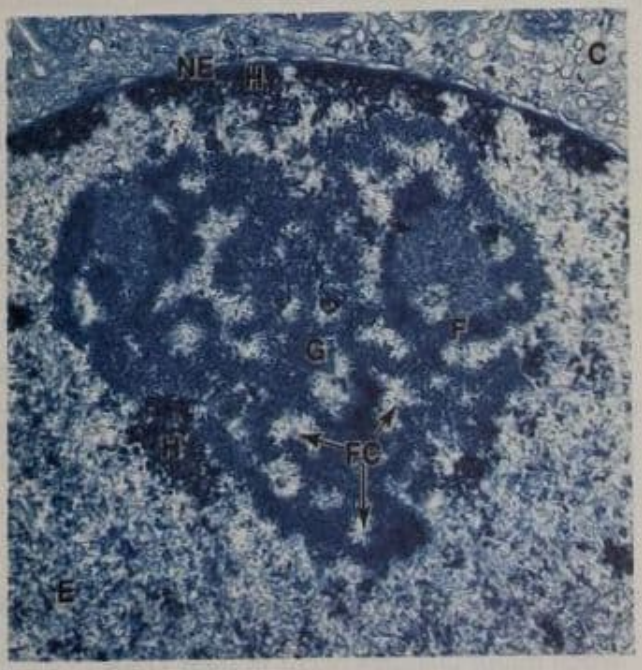
It is a rounded structure very rich in RNA.

► LM appearance:

- It may be seen as one or more round basophilic masses.
- The cause of the basophilia is the high content of rRNA.
- Nucleoli are prominent in cells actively synthesizing proteins (e.g. **nerve cells**) and in rapidly dividing cells.

► EM appearance:

- It appears as an irregular mass, not limited by a membrane.
- It shows light and electron dense areas.
- The light areas are filled with nuclear sap.
- The electron dense areas are formed of:



a. **Nucleolar organizer regions (FC)**: one or more pale staining regions containing **DNA loops** that direct rRNA formation i.e. the **ribosomal RNA genes.**

b. **Pars fibrosa (F)**: filamentous material surrounding the nucleolar organizer regions. It consists of newly formed rRNA.

c. **Pars granulosa (G)**: newly formed rRNA are conjugated with protein to form ribonucleoprotein. It has granular appearance, and this represents maturing ribosomal subunits.

N.B. The nucleolus associated chromatin is a small amount of heterochromatin that associates the nucleolus. It has unknown function.

► **Function of the nucleolus:**

–It is the site of **transcription of rRNA** which is concerned with protein synthesis.

The **ribosomal subunits** are exported to the cytoplasm through the nuclear pores.

N.B. Relatively inactive cells have condensed chromatin and unapparent nucleoli whereas, highly active cells have extended chromatin and prominent nucleoli.

► Nuclear changes indicating cell death

1. **Pyknosis:** this is shrinkage of nuclear material which appears darkly-stained.
2. **Karyorrhexis:** the nucleus disintegrates into tiny fragments.
3. **Karyolysis:** the nucleus dissolves and disappears.

Apoptosis

- It is programmed single cell death.
- It occurs in living tissues to regulate cell renewal & growth.
- The nucleus undergoes pyknosis, karyorrhexis then karyolysis.
- The cytoplasm is fragmented into small vesicles which are rapidly engulfed by adjacent cells or macrophages.
- Apoptosis occurs in the embryo (for shaping of developing organs) and in the thymus (to destroy **T lymphocytes** which can react against self-antigens).

Medical application

Apoptosis is a protective mechanism against cancer as most cells undergo apoptosis when major changes occur in their DNA.

Summary

- **The cell** is the structural unit of any tissue. It consists of nucleus and cytoplasm.
- **The cytoplasm** is composed of the cytosol, cytoskeleton, organelles and inclusions.
- **Cytoskeleton** is formed of a complex system of interconnected microtubules, intermediate filaments and microfilaments.
- **Organelles** are minute living structures essential for life, and they perform specific functions. They are classified into membranous and non-membranous.
- **The cell membrane** has a trilaminar appearance by EM. It is formed of lipid bilayer, carbohydrates and proteins.
- **Mitochondria** are membranous organelles. They can be demonstrated with silver and supravital stains. By EM, each mitochondrion is bounded by double membranes. The outer membrane is smooth. The inner membrane is provided with cristae. They are concerned with energy production.
- **The Golgi apparatus** is a membranous organelle. By silver stain, it appears as dark brown network. By EM, it is formed of Golgi saccules, transfer vesicles and secretory vesicles. It is responsible for modification, packaging and sorting out of secretory proteins.
- **The endoplasmic reticulum** is a network of membranous structures. There are two types: rough endoplasmic reticulum (**rER**) and smooth endoplasmic reticulum (**sER**). By LM, rER imparts for basophilia of the cytoplasm. By EM, its membranes are studded with ribosomes. Its function is synthesis of the secretory proteins and lysosomal enzymes (by the attached ribosomes). By EM, sER consists of anastomosing tubules with no attached ribosomes. It is involved in lipid and glycogen synthesis, detoxification of drugs and in regulation of intracellular calcium.
- **Lysosomes** are membranous organelles. By LM, they can be demonstrated by histochemical methods. By EM, lysosomes have variable electron dense content.
- **Proteasomes** are cytoplasmic protein complexes concerned with degradation of abnormal proteins.
- **The non-membranous organelles** include ribosomes, microtubules, centrioles and filaments.
- **Ribosomes** are formed of RNA and protein. With LM, they impart for the basophilia of the cytoplasm. By EM, they appear as electron dense granules. They may be free or attached to the surface of rER. Ribosomes are concerned with protein synthesis.
- **The proteins which are synthesized by free ribosomes will function in the nucleus, mitochondria, peroxisomes or are kept inside the cytoplasm to be used to build up the cell. The proteins which are synthesized by attached ribosomes are packed by Golgi apparatus into either secretory proteins, plasma membrane proteins or lysosomal enzymes.**
- **Microtubules** appear by EM as tubular structures. They act as cytoskeleton and facilitate intracellular transport of organelles.

- **The centriole** could be seen with LM with special stains e.g. iron hematoxylin. In EM, each centriole appears as a hollow cylinder. The wall of each cylinder consists of 27 microtubules arranged as 9 triplets. The centriole is involved in the formation of microtubules, mitotic spindle cilia and flagella.
- **The cilia** are motile hair like processes extending from the free surface of some cells. By EM, each cilium is formed of a basal body, a shaft, and rootlets. The structure of the basal body is identical to that of the centriole. The shaft consists of nine microtubules (arranged as 9 doublets) surrounding two central microtubules. The Flagella have the same structure as that of the cilia.
- **Filaments** are thread-like non-membranous organelles. There are three types of filaments: microfilaments, thick filaments and intermediate filaments. The filaments are involved in formation of the cytoskeleton, muscle contraction and cell division.
- **Cytoplasmic inclusions** are non-living substances stored in the cytoplasm. They include stored food and pigments. Carbohydrates are stored mainly in the liver cells and muscle as glycogen.
- **Glycogen** can be stained with PAS and Best's carmine. By EM, glycogen appears as electron dense particles.
- **Fats** are stored by fat cells and liver cells. By LM, fat can be detected by Sudan III. By EM, fats appear as round moderately electron dense droplets with no limiting membrane.
- **Pigments** are either exogenous (e.g. dust and minerals) or endogenous (e.g. hemoglobin, melanin and lipofuscin).
- **The nucleus** consists of nuclear envelope, nuclear matrix, chromatin and nucleolus.
- **The nuclear envelope** consists of two membranes separated by a perinuclear space. The outer membrane is covered with ribosomes. The inner membrane has attached peripheral chromatin. The nuclear envelope is interrupted by pores.
- **The nuclear matrix** is a colloidal solution, formed of proteins, metabolites, enzymes and minerals.
- **The nucleolus** is a rounded structure rich in RNA. By LM. It may be seen as round basophilic mass. By EM, it appears as an irregular mass with light and electron dense areas. Nucleoli are prominent in cells actively synthesizing protein.
- **The chromatin** is a basophilic material, formed of DNA, histones, non-histone proteins, and a small amount of mRNA. Chromatin is classified into extended chromatin **(euchromatin)** and condensed chromatin **(heterochromatin)**.

References:

1. **Gartner L.P. & Hiatt J.L. (2014):** Color Textbook of Histology, 6th edition. W.B. Saunders, Philadelphia, London, New York, Sydney, Toronto.

2. **Mescher, A.L.(2016):** Junqueira's Basic Histology: Text and Atlas14th edition.McGraw-Hill, New York, Chicago, London, Madrid, New Delhi, Seoul, Sydney.
3. **Ross M.H. and Pawlina, W. (2015):**Histology: A Text and Atlas: With Correlated Cell and Molecular Biology 7th edition. Lippincott Williams and Wilkins.

Answer the following questions

1-Discuss the structure and correlated function of mitochondria.

2-Compare between rER and sER (LM, EM and functions).

3-Give reason for each of the following:

A. The basophilia of the nucleolus.

B. The trilaminar appearance of the cell membrane by EM.

C. The stored fat appears as empty spaces within the cell By LM.

MCQs: Select the single correct answer

1-The ribosome is characterized by the following:

a- It is surrounded by a membrane

b- It appears acidophilic by LM.

c- It is formed of RNA and protein.

d- It is formed of DNA and protein.

e- By EM, it is formed of 2 large subunits

2-The lysosomal enzymes are synthesized by:

a. Mature face of the Golgi complex.

b. Smooth endoplasmic reticulum.

c. Rough endoplasmic reticulum.

d. Immature face of Golgi complex.

e. Free ribosomes.

III

Epithelial Tissue

Intended learning outcomes (ILOs) of the epithelial tissue:

By the end of this chapter the student should be able to:

1- Describe the general characteristics of the epithelial tissue.
2- List the types of epithelial tissue.
3- Describe the structure and correlated functions of each type of epithelial tissue.
4- Classify Glandular epithelium according to the presence or absence of duct systen exocrine and endocrine glands.
5- Classify the exocrine glands according to the number of cells, the type of the secret the branching of the duct system, the shape of the secretory portion and the mod secretion of glands.
6- Define polarity of epithelial cells.
7- List the specializations of the different epithelial cell surfaces: apical, lateral and ba
8- Describe the structure and function of specializations of the different epithelial surfaces.
9- Describe the structure and correlated functions of the different types of the junctions.
10- Mention examples of sites of the different types of the cell junctions.
11- Describe the structure of the junctional complex.
12- Describe the structure and correlated functions of the taste bud.
13- Realize the effect of chronic irritation on structure of epithelium (metaplasia).

- The human body is composed of four basic tissues: Epithelial, Connective, Musc and Nervous tissues.
- These tissues exist in association with one another forming different organs systems.
- **Main characters of the epithelial tissue:**
  - Epithelial tissue is composed mainly of cells with little intercellular substances.
  - Epithelium covers surfaces (covering epithelium) or lines cavities.
  - The cells lie on a basement membrane which separates the epithelium from underlying connective tissues.
  - No blood vessels or lymphatics enter in between the cells (avascular), but nerves

- Nourishment of epithelial tissue occurs by diffusion of nutrients and oxygen from the blood vessels present in the underlying connective tissue.
- Epithelial cells are continuously renewed and replaced.
- Epithelial tissue may be derived from ectoderm, mesoderm or endoderm.

Functions of the epithelial tissue

1. Protection (e.g. skin)
2. Selective permeability (e.g. endothelium)
3. Secretion (e.g. glands)
4. Absorption (e.g. intestinal epithelium)
5. Detection of sensations (e.g. taste bud)

Classification of Epithelial Tissue

I-Surface epithelium:

A) Simple epithelium:

1) Simple squamous epithelium
2) Simple cuboidal epithelium
3) Simple columnar epithelium
4) Pseudo-stratified columnar epithelium

B) Stratified epithelium:

1) Stratified squamous epithelium
2) Stratified cuboidal epithelium
3) Stratified columnar epithelium
4) Transitional epithelium

II-Glandular epithelium: whose cells have a secretory function.

III-Neuroepithelium: The cells have a sensory function.

IV-Myoepithelium: The cells have a contractile function.

I - Surface epithelium

- Covers surfaces or lines cavities
- Classified according to the number of cell layers into:
  - **A.** Simple epithelium: formed of a single layer of epithelial cells.
  - **B.** Stratified epithelium: formed of two or more layers of epithelial cells.

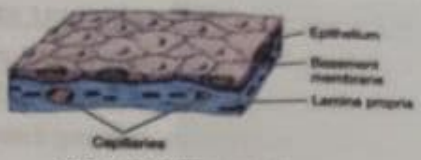
A-Simple epithelium:

Single layer of cells lying on a basement membrane. According to the shape of the cells, it is further classified into:

1-Simple squamous epithelium:

- Formed of one layer of flat cells. Each cell has thin cytoplasm and a flat bulging nucleus.

- **Sites**:
  - Lining the blood vessels (endothelium).
  - Lining the serous membranes: pleura, pericardium and peritoneum (mesothelium).
  - Lining the lung alveoli.



Simple squamous epithelium

- **Functions**: 1) Respiratory function in lung alveoli (Gas exchange)
  2) Active transport by pinocytosis (endothelium)
  3) It forms a thin and smooth surface in blood vessels.
  4) It facilitates movement of the viscera (mesothelium).

2-Simple cuboidal epithelium:

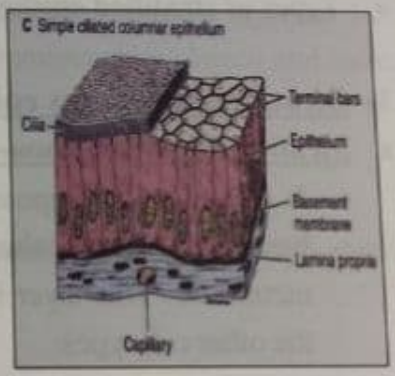
- Formed of a single layer of cubical cells, resting on a basement membrane.
- Each cell has a single rounded central nucleus.
- **Sites**:
  - Lining thyroid follicles.
  - Lining ducts of glands e.g. salivary glands.
  - Covering anterior surface of the lens of the eye.
  - Surface covering of infantile ovary.

Simple cuboidal epithelium

- **Functions**:1) Covering surfaces or lining ducts.
  2) Secretion of hormone in thyroid follicles

3-Simple columnar epithelium:

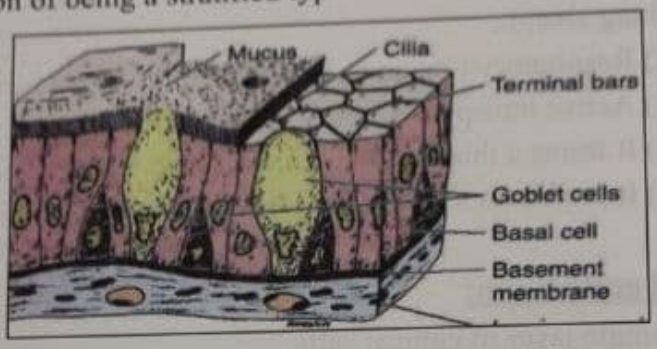
- Formed of a single layer of columnar cells.
- Each cell has a single, basal oval nucleus.
- **Types and sites**:
  - **Unmodified columnar cells:** in excretory ducts of the salivary glands.
  - **Modified columnar cells**: (secretory, absorptive or ciliated):
    a. **Secretory columnar**: Lining epithelium of the stomach.
    b. **Absorptive columnar:** have apical microvilli to increase the surface area for absorption e.g. the lining epithelium of the small intestine.
    c. **Ciliated columnar:** the free surface is supplied by cilia e.g. uterus, fallopian tube and bronchioles of lung.



Simple columnar epithelium

4-Pseudostratified columnar epithelium:

- The cells are overcrowded, but they all rest on the basement membrane. Some cells appear short and not reaching the surface. The nuclei appear at different levels giving a false impression of being a stratified type.



Pseudo stratified columnar ciliated with goblet cells (Respiratory epithelium)

- **Types and sites**:
  a. Non-ciliated: Large ducts of salivary glands and male urethra.
  b. Ciliated: The surface of the cells is provided by cilia and usually associated with goblet cells e.g. trachea and bronchi.
  c. With stereocilia: The surface of the cells is provided by tall immotile cilia called stereocilia. **By E/M**: they appear as long microvilli.

Sites: Epididymis in the male genital system.

B-Stratified epithelium

- Formed of more than one layer of cells.
- **Types of stratified epithelium**:

1- Stratified squamous epithelium:

a. Stratified squamous non-keratinized epithelium:

- It is thick and composed of several layers of cells. The basal cells are columnar and lie on a basement membrane. This layer is responsible for regeneration of the other cell types.
- The intermediate cells are polygonal in shape which gradually flatten to become thin squamous cells at the surface.

Stratified squamo on – keratinized epit m

- **Sites**: It is found in wet surfaces of all openings leading to the skin such a oral cavity, tongue, oesophagus, cornea, anal canal and vagina.
- **Function**: Protection of the underlying tissue.

b. **Stratified squamous keratinized epithelium:**

- It is similar to the stratified squamous non-keratinized epithelium, but the flat cells of the top layer are changed into non-living layer of keratin. **Sites**: Epidermis of the skin.
- **Function**: This type is tough, resists friction and is impermeable to water.

Stratified squamou keratinized epitheliu

2- Stratified cuboidal epithelium:

- The cells in uppermost layer are cubical in shape.
- **Sites**: Cells lining the ducts of sweat glands of the skin.

Stratified cuboidal epithelium

3-Stratified columnar epithelium:

- The cells in the uppermost layer are columnar cells.
- **Types and sites**:

a. Non-ciliated: Large ducts of salivary glands, fornix of conjunctiva, penile part of male urethra.

b. Ciliated: Fetal esophagus.

Stratified columnar epithelium

4-Transitional epithelium:

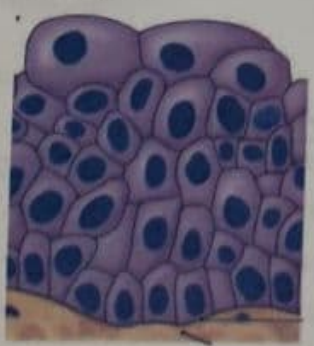
- It is highly specialized to withstand a great degree of distension.
- **Sites**: In the urinary system: Pelvis of the kidney, ureters, urinary bladder an prostatic urethra.
- **Function**: Distensible property

In empty state, it is formed of 6-8 layers of cells:

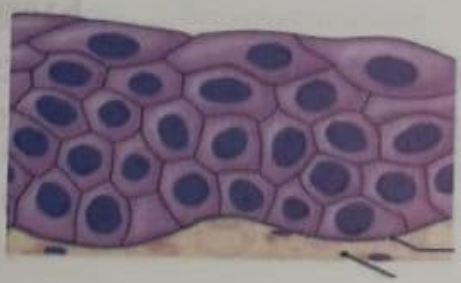
-Basal columnar cells resting on a thin basement membrane, middle layer of 3- polyhedral cells and superficial dome shaped cells, sometimes binucleated and hav convex upper border called facet cells.

In the stretched state:

- The superficial cells become flattened.
- The cells in the middle layer glide on each other and become arranged in abou 2-3 layers.



Transitional epithelium in an empty bladder



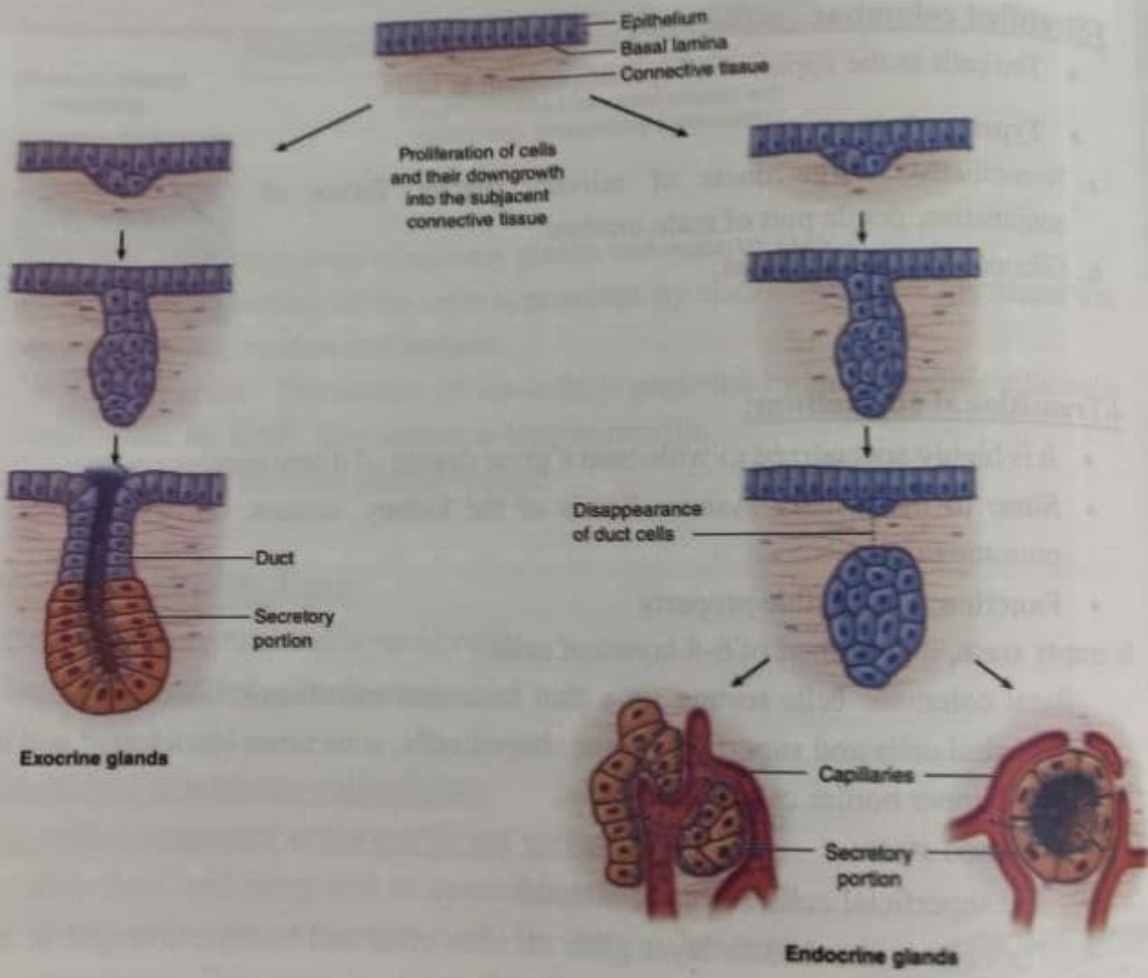
Transitional epithelium in a stretched bladder

II - Glandular epithelium

- It is a special type of epithelium characterized by its secretory function.
- Glands originate from epithelial cells that leave the surface and penetrate into the underlying connective tissue

Types of glandular epithelium:

- **Exocrine glands:** the cells deliver their secretion through ducts, as salivary glands.
- **Endocrine gland:** the cells deliver their secretion directly into the blood stream (ductless glands) as thyroid and pituitary glands.
- **Mixed glands:** these glands contain both exocrine and endocrine portions as pancreas



Exocrine glands

Exocrine glands can be classified according to various criteria:

1-According to the number of cells into:

Unicellular: e.g. goblet cells

Multicellular: e.g. salivary glands

Goblet cells

Unicellular glands

- **Sites**: The gland is formed of one cell only scattered individually in the epithelial lining of the digestive tract and parts of the respiratory tract.
- **Light Microscopy (L/M):** Goblet cell is flask in shape with a slender base and an expanded apex due to presence of mucous granules. These granules are not stained by H&E but stained by PAS. The cytoplasm is basophilic and the nucleus is basal.
- **Electron microscopy (E/M):** The basal part contains the nucleus, ribosomes, rER, Golgi complex and mitochondria. Apical part is rich in mucous secretory granules.
- **Function:** Mucous secretion.

Goblet cell

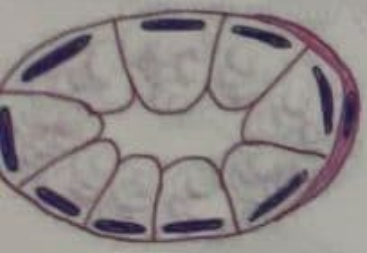
Multicellular glands

Classification:

A. According to the type of secretion:

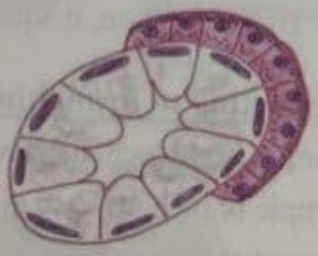
1. **Mucous glands**: secrete a viscous thick secretion containing mucin.
2. **Serous glands:** secrete a watery secretion containing proteins and rich in enzymes as parotid gland.
3. **Mixed glands (Sero-mucous acinus):**

Secrete both mucus and serous secretions. It is formed of a mucous acinus, surrounded partially by a small cap of serous secretory cells. The cap is called a serous demilune or serous crescent or crescent of Gianuzzi. The secretions of the serous cells reach the lumen of the mucous acinus through narrow intercellular canaliculi between the mucous cells, e.g. submandibular salivary gland



Mucous acinus

Serous acinus



Sero-mucous acinus

ands of special nature: the secretion may be:

- Waxy secretion: ceruminous glands of the external ear.
- Watery secretion of the lacrimal glands.
- Fatty secretion of the sebaceous glands.

Comparison between mucous and serous acini:

	Mucous acinus	Serous acinus
Size	• Relatively large in size.	• Relatively smaller than mucous acinus.
Lumen	• Wide.	• Narrow.
Lining cells	• Formed of cuboidal cells that have well-defined boundaries.	• Formed of pyramidal cells that have ill-defined cell boundaries.
Cytoplasm	• Pale basophilic and vacuolated (due to its mucus contents)	• Basal basophilia due to rER. Apical acidophilic secretory granules.
Nucleus	• Each cell contains a single flattened basal nucleus.	• Each cell contains a single rounded nucleus, near the center.
Secretion	• Mucus (a viscous thick secretion)	• Watery containing enzymes.

- In any of the three types (mucous, serous or sero-mucous acini) there is a special type of epithelial cells (Myoepithelial cells) placed between the secretory cells and the basement membrane.
- Myoepithelial cells are more in the mucous and mixed acini than in the serous acini.

Myoepithelial cells:

- It is a special type of epithelium.
- The cell has long branching processes which surround the cells of the secretory unit like a basket, so it is called basket cells.
- It is placed between the secretory cells and their basement membrane.
- The cytoplasm contains contractile elements (actin, myosin and intermediate filaments) hence called myoepithelial cells.
- By contraction, it squeezes the secretion from the secretory unit to the duct.

B. According to branching of their ducts:

- Simple (unbranched): have non-branching ducts.
- Simple branched: have simple branched ducts
- Compound: have branching ducts.

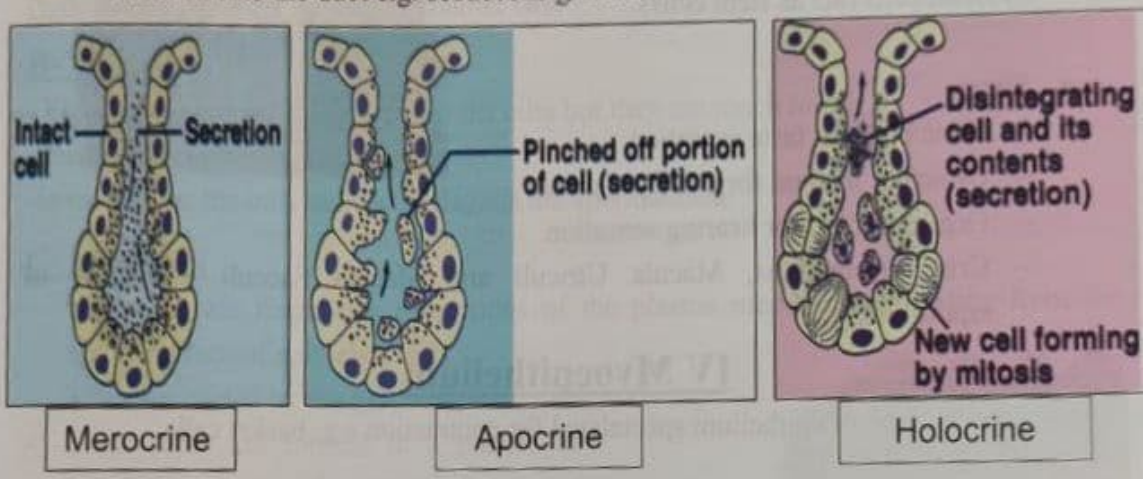
C. According to the shape of the secretory portion:

- Tubular: the secretory part is tubular in shape.
- Acinar or Alveolar: the secretory part is rounded or flask shaped.
- Tubulo-alveolar: the secretory part has the shape of a tubule that terminates by an alveolus.

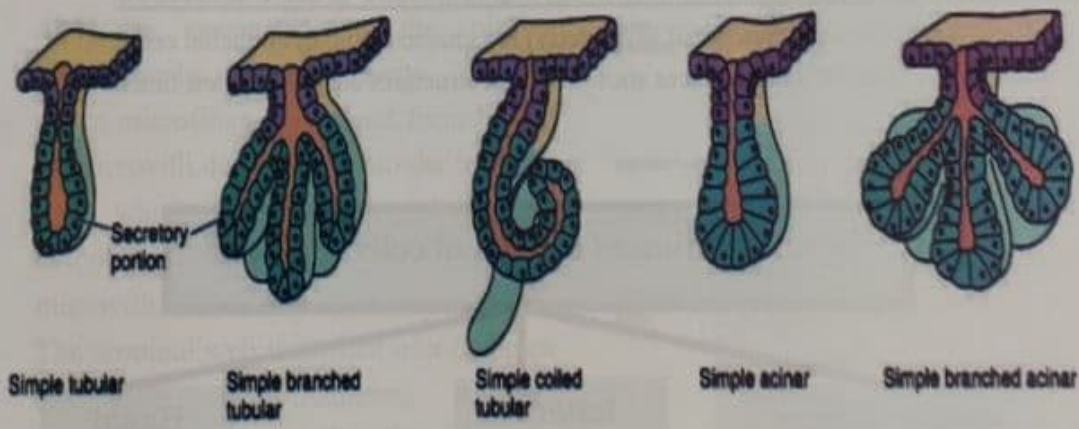
NB. These types of secretory units may have branched or non-branched duct system.

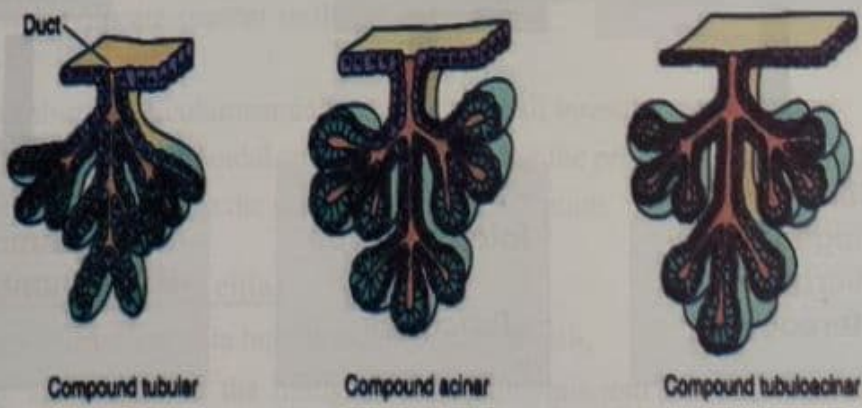
D. According to the mode of secretion:

1. **Merocrine (eccrine) glands:** The secretory cells release their contents by exocytosis with no loss of the cytoplasm or cell membrane e.g. salivary glands.
2. **Apocrine glands:** Part of the cytoplasm of the secretory cells is released along with the secretory contents. e.g. lactating mammary glands.
3. **Holocrine glands:** The secretory cell together with its accumulated secretion is released into the duct e.g. sebaceous glands of the skin.



Classification of glands according to the mode of secretion





Classification of exocrine glands according to the shape of secretory portion and branching of their ducts

III Neuroepithelium

- It is a special type of epithelium which is modified to receive stimuli of special sensations and convert them into nerve impulses.
- Neuroepithelium has three main types of cells:
  1) Sensory cells for receiving stimuli.
  2) Supporting cells.
  3) Basal cells (act as stem cells).

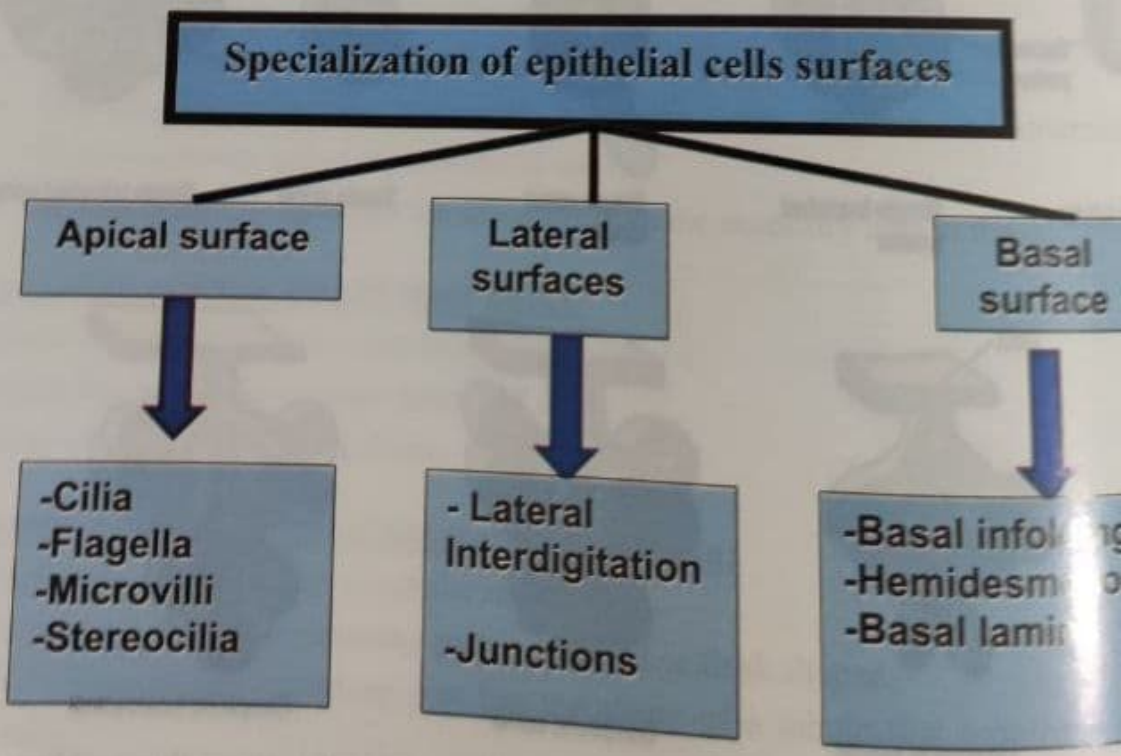
- **Sites:**
  - Taste buds for taste sensation.
  - Olfactory mucosa for smell sensation.
  - Organ of Corti for hearing sensation.
  - Crista Ampullaris, Macula Utriculi and Macula Sacculi for sense equilibrium.

IV Myoepithelium

It is a special type of epithelium specialized for contraction e.g. basket cells.

Polarity and specializations of Epithelial Cell Surfaces

- Polarity (structural and functional asymmetry) is a characteristic of epithelial cells.
- Each of the different three surfaces show different structures adapted to their functions.



Specializations of the Apical Surface of Epithelial Cells

A- Cilia

- Cilia are hair like motile structures extending from the free surfaces of some cells.
- Each cilium is covered by plasma membrane and is composed of:a basal body, rootlets and an axoneme.

N.B. Revise structure of cilia in chapter two.

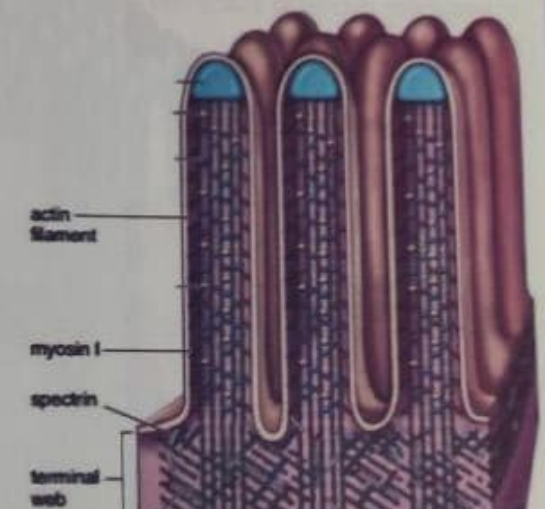
B- Flagella

- Flagella are similar in structure to the cilia but they are much longer.
- Each cell has only one flagellum.
-In mammals, the only cells with flagella are spermatozoa.

C- Microvilli

- Microvilli are finger-like projections of the plasma membrane extending from the apical surface of epithelial cells.
- They are coated by the glycocalyx.
- Their cores are formed of a bundle of approximately 30 parallel actin microfilaments which run longitudinally and are connected to the plasma membrane by myosin filaments.
- Actin microfilaments extend from the tip of microvilli downwards into the terminal web which is located in the apical cytoplasm just below the base of microvilli.

The terminal web is formed of a complex of actin microfilaments, spectrin molecules and intermediate filaments.



Sites: Microvilli are present in the apical surface of:

1. The absorptive columnar cells lining the small intestine.
2. The absorptive cuboidal epithelial cells lining the proximal tubules of the kidney.

Function: They increase the surface area for absorption.

Stereocilia (immotile cilia)

- Steriocilia are not cilia but they are long microvilli.
- They are present in the lining of the epididymis and vas deferens of the male reproductive tract.
- **Function:** They increase the surface area for fluid absorption

Specializations of Lateral Surface of Epithelial Cells

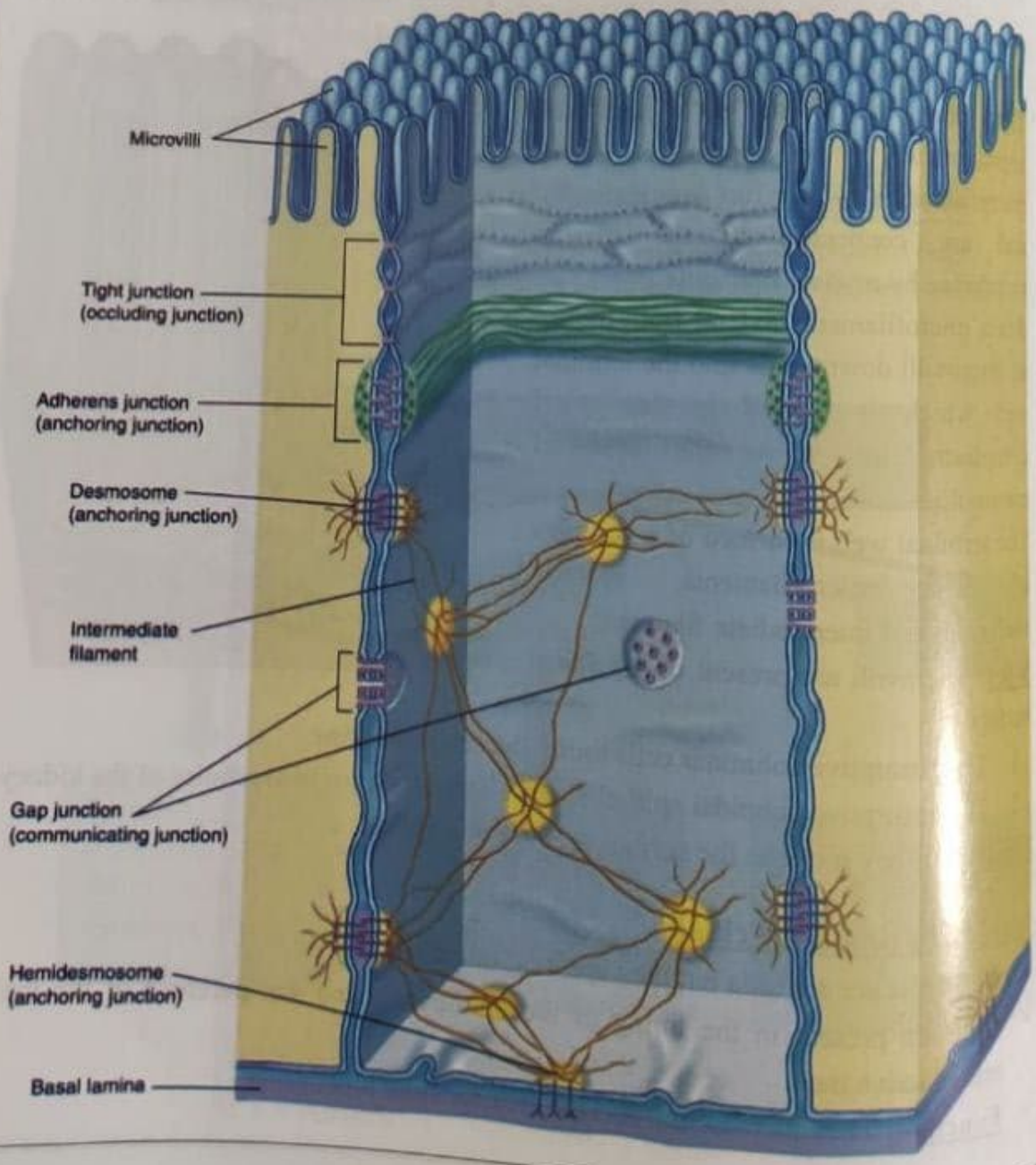
- Lateral surfaces specializations answer the question (How the cells are linked together?)
- Specializations of the lateral surfaces of epithelial cells include:

a. **Lateral interdigitations**: they are finger-like projections that interlock adjacent epithelial cells together.

b. **Cell junctions**

1. If the junction extends around the entire cell circumference it is called **Zonula.**
2. If the junction forms a strip-shaped or band- shaped it is called **Fascia.**
3. If the junction forms a small circular or spot like it is called **Macula.**

Types of cell junctions



1. Occludens (tight) junctions

- The term occludens refers to membrane fusion that closes off the intercellular space.
- The cell membranes of the adjoining cells come very close to each other and their outer layers fuse together giving the pentalaminar appearance by EM (3electron dense and 2 electron light).

Types of occludens junction

A. Zonula occludens or continuous tight junction

- The junction encircles the entire circumference of the cell like a belt.
- It is present in the intestinal columnar cells near the apex forming good seal.
- It is also found between the endothelial cells of blood capillaries in brain tissue.

➢ **Function:**

1) It prevents passage of toxic and harmful materials to brain tissue
2) It prevents passage of molecules and ions through the space between intestinal cells.

B. Fascia occludens:

- The junction between the adjacent cells is strip-shaped.
- It is found between endothelial cells of blood capillaries except in brain capillaries.

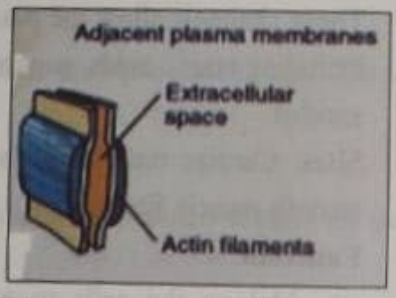
2. Adhering Junctions

- Lateral borders of adjacent cells are connected together by a strong adhesion or bond.

Types of adhering junctions:

A. Zonula adherens (Belt desmosomes)

- It surrounds the entire circumference of the cell.
- The two adjacent cell membranes are separated by intercellular space of 15-20 nm.
- The intercellular space is filled with filamentous material formed of glycoprotein (cell coat material) which is believed to be the binding force between the cells.



- The opposing cell membranes are reinforced on the cytoplasmic surface by a dense plaque to which numerous actin filaments are inserted.
- The zonula adherens present just beneath the zonula occludens and encircles the cell e.g. columnar cells lining the small intestine.

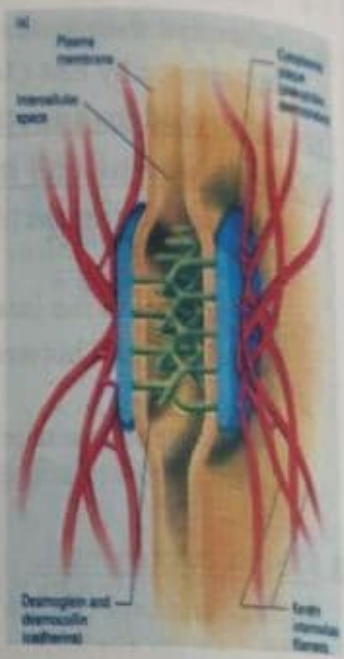
Functions:

- It prevents separation of cells.

B. Fascia adherens

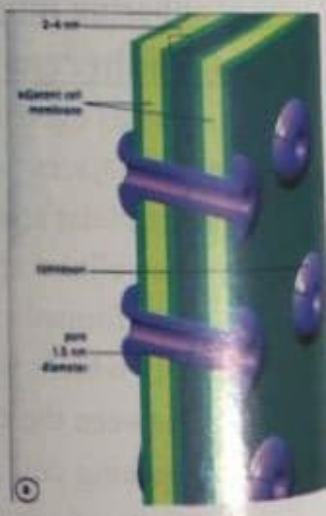
- It is similar to the zonula adherens, but it is ribbon like.
- It is found in the intercalated discs of cardiac muscle fibers.

C. Macula adherens (desmosomes)



- It appears as a circular or a spot-like junction.
- The adjacent cells are separated by a space of 15-30 nm.
- The intercellular space is occupied by an electron lucent filamentous material with a thin vertical electron dense line located in the middle. This filamentous material is the transmembrane linker proteins that extend across the intercellular space.
- The vertical electron dense line represents interconnections between the filamentous materials.
- On the cytoplasmic surface of each cell, an electron dense plaque is present.
- Keratin intermediate filaments (tonofilaments) loop into and out of the dense plaque from the cytoplasm.
- **Site**: Prickle cell layer in the epidermis of the skin.
- **Function**: firm adhesion between cells because it joins the intermediate filaments to the plasma membrane at regions of cell to cell adhesion.

3. Gap junction (Communicating junction or nexus)



- The two adjacent membranes are separated by a narrow space 2-3 nm.
- This narrow gap is crossed by multiple tiny channels (called connexons).
- The wall of each channel is lined by 6 closely packed transmembrane protein.
- These channels allow the passage of ions, small molecules including amino acids, sugars and steroids from one cell to another.
- **Sites**: Cardiac muscle fibers, nerve cells, bone cells and smooth muscle fibers.
- **Function**:
  - Making the cells to act together in a coordinated manner.
  - They transmit impulses at certain synapses.

Junctional complex

- Junctional complex binds some cells close to their luminal surface e.g. intestinal epithelial cells.
- It is formed of three junctions:

1. Zonula occludens junction: present close to the luminal surface of the cell.
2. Zonula adherens junction: just below the zonula occludens.
3. Macula adherens or desmosomes: just below the previous two junctions.

N.B. Gap junction is not a part of junctional complex.

Specializations of the Basal Surface of Epithelial Cells

A- Basal lamina

- Most of the epithelial cells are separated from the connective tissue by an extracellular material called basal lamina.
- It is only seen by electron microscopy. It is 20-100 nm thick.
- It is not found only in epithelial tissue, but also where cell types come into contact with connective tissue such as muscle fibers, fat cells and Schwann cells of the nervous tissue.

N.B. Basement membrane structure will be discussed later in connective tissue chapter.

B- Hemidesmosomes

- They resemble one-half of a desmosome.
- They are formed of a dense plaque in the basal cytoplasm which is linked to the underlying basal lamina by a transmembrane protein (integrin). Tonofilaments are attached to the dense plaque.
- **Site and function**: This type of junction binds the epithelial cells to the underlying basement membrane.

C- Basal plasma membrane infoldings

- The basal plasma membrane of some cells has multiple infoldings. These infoldings are associated with mitochondria.
- They increase the surface area.
- They are common in ion transporting cells e.g. distal convoluted tubules of the kidney.

Medical application:

- Under certain abnormal conditions (chronic irritation), one type of epithelial tissue may undergo transformation into another type. This is called **Metaplasia**.
  In heavy smokers, the ciliated pseudostratified columnar epithelium lining the bronchi is changed to stratified squamous.

Summary

- Epithelial tissue is formed mainly of cells with minimal intercellular substances.
- It is classified into surface, glandular, neuroepithelium and myoepithelium.
- Surface epithelium is classified into simple and stratified.
- Simple epithelia include squamous, cuboidal, columnar and pseudostratified columnar.
- Stratified epithelia include stratified squamous keratinized and non-keratinized, transitional, stratified cuboidal and columnar.
- Glandular epithelium is formed from invagination of epithelium into the underlying connective tissue. They are classified into exocrine, endocrine and mixed glands.
- Exocrine glands can be classified according to: Number of cells, mode of secretion, type of secretion, shape of their secretory portion and the branching of the excretory ducts.
- Neuroepithelium is a special type modified to receive stimuli of some special sensations and convert them to electrical impulses e.g. taste buds.
- Myoepithelium surrounds the cells of the secretory units.
- Specializations of the apical epithelial cell surfaces include: cilia, flagella and microvilli.
- Specializations of the lateral cell surfaces include: lateral interdigitations and cell junctions.
- Specializations of the basal cell surfaces include: basal lamina, hemidesmosomes and basal infoldings.
- There are 3 types of cell junctions: tight (occluding), adhering and gap junctions.
- Functions of epithelial tissue include: protection, secretion, sensation and absorption.

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2. **Mescher, A.L. (2016)**: Junqueira's Basic Histology: Text and Atlas 14thedition.McGraw-Hill, New York, Chicago, London, Madrid, New Delhi, Seoul, Sydney.
3. **Ross M.H. and Pawlina, W. (2015):**Histology: A Text and Atlas: With Correlated Cell and Molecular Biology 7th edition. Lippincott Williams and Wilkins.

Answer the following questions

1- Enumerate the types of simple epithelium and describe one of them.
2- Describe the structure and correlated function of gap junction.
3- Classify the glands according to its mode of secretion.
4- Compare between mucous and serous acini in a table form.

MCQs: Select the single correct answer

1- Which of the following is a character of the epithelial tissue?

a. It is formed mainly of fibers.
b. The cells lie on a basement membrane
c. It never regenerates.
d. It is penetrated by blood vessels.
e. The cells are widely separated.

2- Which of the following structures is lined by transitional epithelium?

a. Epidermis of the skin
b. Small intestine
c. Tongue
d. Ureter
e. Trachea

3- Tonofilaments are attached to the dense plaque in:

a. Belt desmosomes
b. Desmosomes
c. Zonula occludens
d. Fascia occludens
e. Fascia adherens

IV Connective Tissue

Intended learning outcomes (ILOs) of the connective tissue:

By the end of this unit, the student should be able to:

1- **Define** the general characteristic, functions and structure of the connective tissue
2- **Classify** types of connective tissue.
3- **Describe** the histological structure (LM and EM) correlated to functions of different types of the connective tissue cells with medical correlation.
4- **Correlate** between degranulation of mast cells and immediate hypersensitivity reaction
5- **Compare** between unilocular and multilocular fat cells as regards structure and function.
6- **Correlate** between the structure, staining abilities and function of different connective tissue fibers.
7- **Describe** steps of intracellular and extracellular collagen fibers formation.
8- **Define** the main extracellular matrix (ECM) components and their functions.
9- **Describe** structure and functions of basement membrane
10- **Correlate** between structures, sites and functions of different types of connective tissue.
11- **Compare** between white and brown adipose tissue as regards structure, sites and functions.
12- Recognize the effect of vitamin C deficiency on collagen synthesis

General characters of the connective tissue:

- Connective tissue is mesodermal in origin.
- It connects, binds and supports other tissues and organs.
- It is formed of cells separated by a good amount of extracellular matrix (ECM) which is formed of fibers and ground substances.
- It is penetrated by blood vessels, lymphatics and nerves.
- It is separated from other tissues by a basement membrane.

Types of connective tissue:

1. **Connective tissue proper:** loose (areolar) and dense (regular and irregular) connective tissues.
2. **Specialized connective tissue:** elastic connective tissue, reticular connective tissue, adipose connective tissue, cartilage, bone and blood.

3. **Embryonic connective tissue:** Mesenchymal and mucous (mucoid) connective tissues.

Functions of CT

1- It provides form and support to the body and organs
2- It connects other tissues and cells together.
3- It aids in defense and protection
4- It is a medium for exchange of nutrients and waste products
5- In certain sites as in adipose tissue, it stores fat for cushioning and thermoregulation

Connective tissue structure

The components of the connective tissue are:

I- Connective tissue cells.
II- Extracellular matrix formed of:
A- Fibers B- Ground substance

I-Connective tissue cells

1- Undifferentiated mesenchymal cells (UMCs)
2- Pericytes
3- Fibroblasts
4- Reticular cells
5- Macrophages
6- Mast cells
7- Plasma cells
8- Fat cells (adipocytes)
9- Pigment cells
10-Extravasated leucocytes.

Cells of the connective tissue are classified according to their **shape** into:

Branched cells
UMC
Pericyte
Fibroblast
Reticular cell
Macrophage
Pigment cell

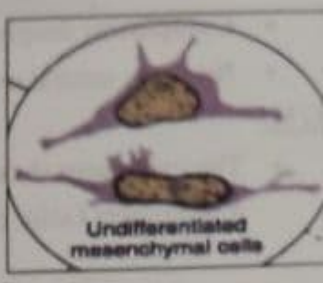
Oval or rounded cell
Mast cell
Plasma cell
Fat cell
Extravasated leucocytes

Undifferentiated Mesenchymal Cell (UMC)

Site: Embryonic mesenchymal tissue.

L/M:

- **Shape:** branched with long cytoplasmic processes.
- **Cytoplasm**: basophilic.
- **Nucleus**: large, oval with prominent nucleolus.



E/M:

- Ribosomes, rER, small Golgi and few mitochondria.

Function:

1- Can differentiate to other connective tissue cells
2- Can produce all types of connective tissue proper and the specialized connective tissue: cartilage, bone and blood
3- Can develop into other structures: smooth muscle fibers and endothelial cells

Pericytes

Origin: UMCs

Sites: Pericytes partially surround the endothelium of the blood capillaries and smal venules. They usually lie between the endothelial cells and their basement membrane.

L/M:

- **Shape**: branched cells with long cytoplasmic processes.
- **Cytoplasm**: basophilic.
- **Nucleus**: large vesicular.

E/M: The cytoplasm contains ribosomes, rER, a small Golgi, mitochondria, myosin an actin.

Functions:

- After tissue injuries, pericytes proliferate and differentiate to form smooth muscles, fibroblasts and endothelial cells in new vessels.
- Contractile function to facilitate flow of blood in blood capillaries.

Fibroblasts

Origin: UMCs, pericytes.

Sites: most common cell in the C.T.

Types:

1. Active fibroblasts.
2. Inactive fibroblasts (fibrocytes)

1. Active fibroblasts:

L/M:

- **Shape**: branching cells with multiple processes.
- **Cytoplasm:** deeply basophilic.
- **Nucleus**: central oval, with prominent nucleolus.

E/M:

- The cytoplasm shows characters of protein secretory cells: abundant rER, a prominent Golgi complex and mitochondria

Functions:

- Synthesis of connective tissue fibers.
- Synthesis of ground matrix (glycosaminoglycans and glycoproteins).
- Growth of connective tissue
- Healing and repair of injured connective tissue

2. Fibrocytes:

L/M:

- **Shape**: small spindle shaped cells with less cytoplasmic processes.
- **Cytoplasm**: pale basophilic.
- **Nucleus**: small elongated and deeply stained nucleus.

E/M: Fewer organelles.

Function:

- Change to active fibroblast in time of need e.g. wound healing.

N.B. In adults, fibroblasts undergo cell division only when there is need for additional fibroblasts as during wound healing.

Myofibroblasts

- They are an activated form of fibroblasts associated with repair
- They have actin and myosin, so they have well-developed contractile functio
- They help in wound contraction

Reticular Cells

Origin: UMCs.

Site: hematopoietic and lymphoid tissues.

L/M:

- **Shape:** small branched cells.

- **Cytoplasm**: basophilic.
- **Nucleus:** central rounded and vesicular.

E/M: The cytoplasm contains ribosomes, rER, Golgi and mitochondria.

Functions:

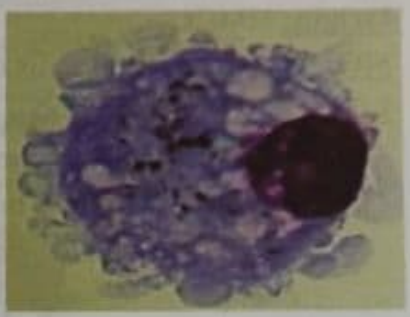
- Formation of reticular fibers.
- Phagocytosis of cellular debris.

Macrophages

Origin: blood monocytes.

Sites and types of macrophages:

- Macrophages (Histiocytes) in connective tissue.
- Kupffer cells in the liver.
- Dust cells in the lung.
- Langerhans cells in the skin.
- Macrophages of the spleen and lymph node.
- Microglia in CNS.



L/M:

- **Shape**: large cells with irregular outlines.
- **Cytoplasm**: pale basophilic.
- **Nucleus**: single eccentric and kidney shaped.
  - **Vital stain:** Macrophages can be stained by vital staining method. Trypan blue dye is injected in the subcutaneous tissue of a living animal. When the tissue is examined by light microscope, the engulfed (phagocytosed) particles of the dye are seen in the cytoplasm of macrophages.
  - **Histochemical stain:** Macrophages can be stained by histochemical stain for acid phosphatase enzyme.

E/M:

- They have irregular surface with protrusions and indentations.
- The cytoplasm contains lysosomes, phagocytic vacuoles, Golgi complex, mitochondria, rER, microtubules and microfilaments.

Functions:

- **Phagocytosis**: they phagocytose foreign particles, bacteria and microorganisms. They also phagocytose dead cells and tissue debris. So, they play an important role in early stage of repair after tissue damage.

- **Immunity:** act as antigen presenting cells (uptake, processing and presentation of antigens for lymphocytes)
- **Secretion**: of various enzymes for extracellular matrix breakdown.

- Macrophages may increase in size and fuse to form **multinucleated giant** to remove large particulate matter.

Pigment Cells

Origin: UMCs.

Site: Iris of the eye, dermis of the skin.

L/M:

- **Shape**: small branched cells.
- **Cytoplasm**: full of brown melanin granules.
- **Nucleus**: small deeply stained rounded nucleus.

Functions:

- Protect the tissues from the harmful effects of ultraviolet rays.

Pigment cells do not need special stains because they have their own colors.

Mast Cells

Origin: Progenitor cells in the bone marrow. The progenitor cells circulate in blood cross the wall of venules and capillaries to reach the connective tissue.

Types and sites:

-Perivascular mast cells are found in skin and mesenteries

-Mucosal mast cells in the mucosa lining the digestive and respiratory tracts

The granule content of the two populations differs somewhat

L/M:

- **Shape**: oval or rounded cells.
- **Cytoplasm**: basophilic and contains basophilic granules.
- **Nucleus**: central, spherical and may be masked by the granules.
- Mast cells granules are metachromatically stained by toluidine blue dye

E/M:

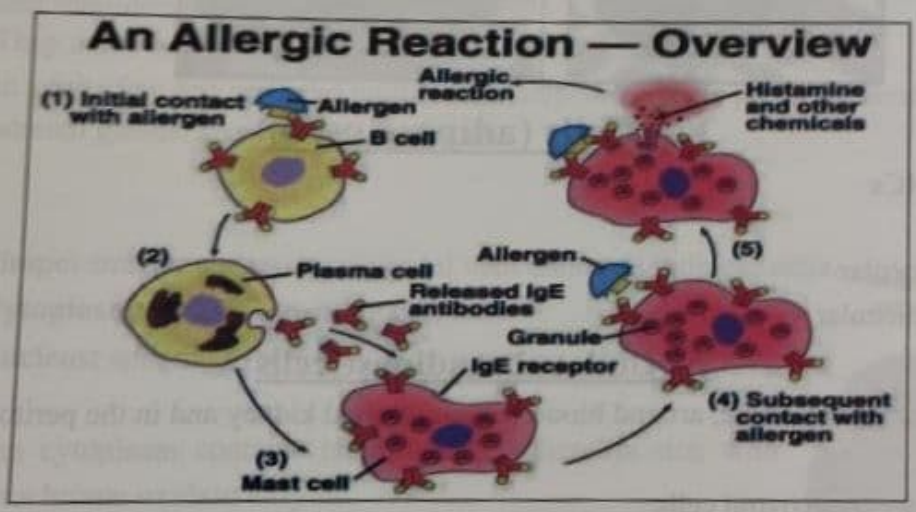
- The cytoplasm contains Golgi complex, rER, mitochondria, membrane bound granules.
- Folded surface that contains specific receptors for IgE.

Functions:

- Synthesis, storage and secretion of: heparin, histamine, eosinophil chemotactic factor (ECF-A), neutrophil chemotactic factor (NCF) and prostaglandins.
- Release of these chemical mediators stored in mast cells leads to **allergic reaction (Immediate hypersensitivity reaction)**
  (Immediate because it occurs within a few minutes)

Sequence of events in allergic reaction:

- **First exposure to antigen** results in activation of B lymphocytes. The activated B lymphocytes differentiate into plasma cells. The plasma cells secrete Ig E which binds to mast cells receptors.
- **Second exposure to the same antigen:** The antigen binds to IgE on the surface of mast cells which results in degranulation of mast cells and release of various mediators which promotes the allergic reaction.



Plasma Cells

Origin: activated B-lymphocytes.

Site: in connective tissue

L/M:

- **Shape**: oval or rounded cells.
- **Cytoplasm**: deeply basophilic and contains negative Golgi image (unstained area in the cytoplasm indicating the site of Golgi complex).
- **Nucleus**: single rounded and eccentric. It contains clumps of heterochromatin which is distributed peripherally giving it the characteristic cart wheel or clock face appearance.

E/M:

- The cytoplasm shows characters of protein secretory cells: rich in rER, well developed Golgi and mitochondria.

N.B In mature plasma cells, acidophilic granules are seen in the cytoplasm called Russell bodies. They may represent that plasma cell is going to degenerate or they may represent large accumulation of secretion in the rER.

Function:

- Synthesis and secretion of antibodies (immunoglobulins).

The antigens stimulate B lymphocytes ⟶ plasmablasts ⟶ plasma cells (secrete immunoglobulins).

Fat Cells (adipose cells)

Origin: UMCs.

Types:

A) Unilocular

B) Multilocular

A- Unilocular adipose cells

Sites: Subcutaneous tissue, around blood vessels, around kidney and in the peritoneum.

L/M:

- **Shape:** large ovoid cells.
- **Cytoplasm:** contains a large single fat droplet, pushing the cytoplasm and nucleus against the cell membrane.
- **Nucleus:** eccentric and flat.
- In H&E stained sections, fat is dissolved during preparation and fat cells appear empty with thin rim of cytoplasm and peripheral flat nucleus giving the cells the characteristic signet ring appearance.
- Fats can be stained by:

Sudan III ⟶ orange

Sudan black ⟶ black

E/M:

- The cytoplasm contains sER, mitochondria, small Golgi, few rER and polyribosomes.
- Adipocytes are surrounded by a thin external lamina containing type IV collagen.

Functions:

- Synthesis and storage of fat.
- Heat insulation.
- Supporting function e.g. fat cells around the kidney.

B- Multilocular adipose cells

Sites:

- In new born, multilocular adipose cells from 2-5% of body weight (back, neck and shoulders)
- They are reduced during childhood and adolescence
- In adults few and scattered multilocular adipose cells are present around kidney, adrenal glands, aorta and mediastinum.

L/M:

- **Shape:** smaller and more polygonal than unilocular adipose cells.
- **Cytoplasm:** contains small fat droplets.
- **Nucleus:** spherical.

Multilocular adipose cell

E/M:

- The cytoplasm contains numerous mitochondria rich with cytochrome oxidase enzyme.
- Few rER, ribosomes and sER.

Function:

- Heat generation.

Extravasated Leucocytes

Leucocytes (neutrophils, eosinophils, lymphocytes, basophils and monocytes) leave the blood stream to enter the connective tissue to perform specific functions.

II-Extracellular matrix

A- Connective tissue fibers

- Fibers are elongated structures formed of proteins.
- There are three main types of connective tissue fibers:
  1. Collagen fibers.
  2. Elastic fibers.
  3. Reticular fibers.
- Collagen and reticular fibers are formed of protein collagen.
- Elastic fibers are composed mainly of protein elastin.

o Collagen fibers are tough and provide tensile strength.

o Elastic fibers allow for stretch.

o Reticular fibers make networks.

1-Collagen fibers

Collagen fibers in fresh state are white in color.
They are not stretchable, but the wavy bundles can be straightened.

Collagen fibers are synthesized by:

- Fibroblasts.
- Chondroblasts in cartilage.
- Osteoblasts in bone.
- Odontoblasts in teeth.

❖ Collagen is formed of protein polypeptide molecules.
❖ Each protein polypeptide molecule is composed of a chain of three amino acids Lysine, proline and hydroxyproline.
❖ Each three protein polypeptide chains are wound together in the form of a triple helix called tropocollagen.

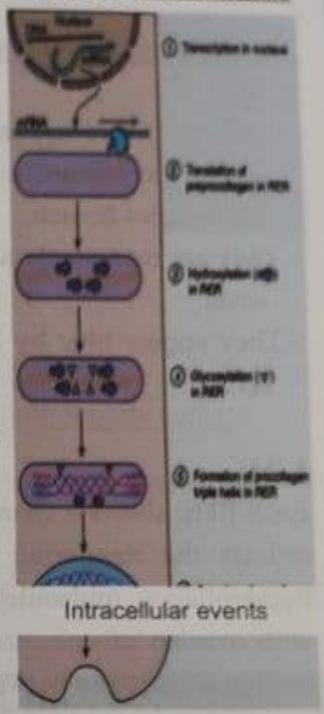
Synthesis of collagen

- The following steps are for type I which accounts for 90% of all body collagen
- It involves intracellular and extracellular events

I. Intracellular events

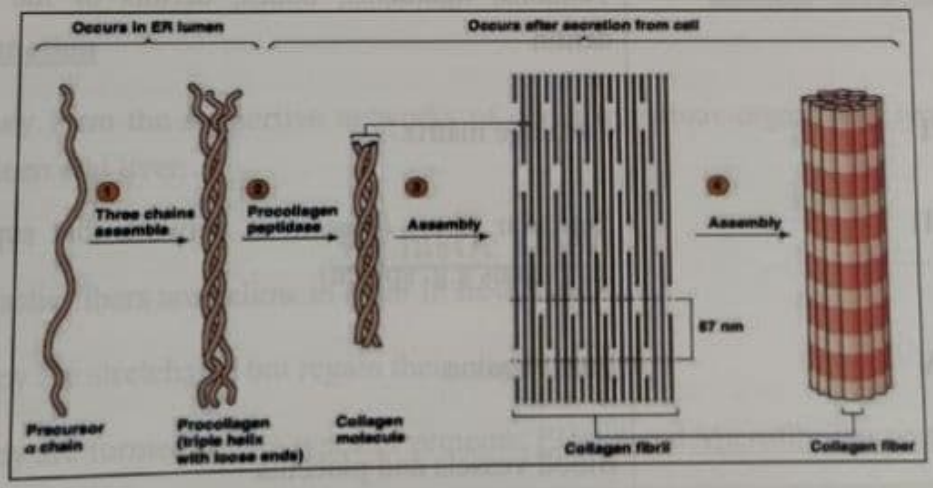
1) Messenger RNA is synthesized from a template of DNA in fibroblast nucleus

2) mRNA molecules enter the cytoplasm and attach to ribosomes of RER
3) Ribosomes translate the nucleotide sequence of mRNA into polypeptide α chains (pre-procollagen)
4) Pre-procollagen α chains with propeptides at both ends are trans-located into cisternae of RER.
5) Hydroxylation of some prolines and lysines in RER that requires O_2, Fe^{2+} and vitamin C as cofactors.
6) Glycosylation of selected hydroxylysin
7) Three alpha chains form a triple helix to form procollagen
8) Transport of procollagen to Golgi saccules by transfer vesicles
9) Packaging of procollagen in secretory vesicles.
10) Release procollagen by exocytosis


Intracellular events

II. Extracellular events

- Procollagen peptidases remove the terminal propeptides
- Procollagen (tropocollagen) → collagen molecules
- Collagen molecules → collagen fibrils
- Collagen fibrils → collagen fibers → bundles



Medical application

Scurvy (vitamin C deficiency)

Reduced hydroxylation step in RER due to vitamin C deficiency.

-Bleeding gums
-Loose teeth
-Poor wound healing
- Poor bone development

Histological appearance:

L/M

- Collagen fibers appear as thick, non-branching fibers that run in wavy, branching bundles (Fibers do not branch, but the bundles branch.
- They are moderately acidophilic, so they can be stained by eosin.
- They appear blue by Mallory stain and green by Masson stain.

E/M:

Each fibril shows a characteristic **axial periodicity** which reflects the staggering of tropocollagen molecules i.e. tropocollagen molecules are arranged in parallel rows with overlap of one quarter the length of the molecules leaving a short gap between them.

Types of collagen

- According to amino acids sequences, there are at least 20 types of collagen fibers:

Major types	Site
Type I	Tendons, ligaments, bones, dermis of the skin, dentin
Type II	Cartilage matrix
Type III	Reticular fibers (present in network that supports the organs e.g. spleen)
Type IV	Basal lamina
Type V	Blood vessels and placenta

Function of collagen fibers

-Collagen fibers are the key element of all connective tissues, as well as epith ial basement membranes and the external laminae of muscle and nerve cells.

-All types of collagen fibers are extremely strong and resistant to shearing and tearing forces.

Medical application

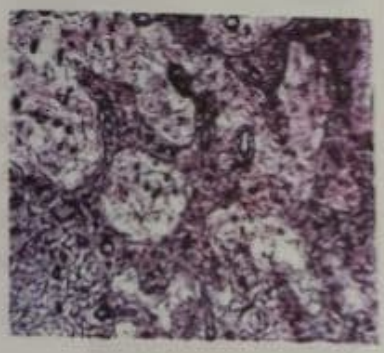
Keloid

Local swelling caused by abnormal large amounts of collagen that forms in scars of the skin

2-Reticular fibers

- They are formed of type III collagen.
- They are synthesized by fibroblasts, reticular cells and smooth muscle cells.
- They are formed of a central core of type III collagen which is surrounded by glycoprotein.
- **By L/M:**

- Reticular fibers form branching and anastomosing networks.
- They can be stained by silver and PAS.



- **By E/M:**

- They show axial periodicity because they are a type of collagen.

- **Function**

- They form the supportive networks of parenchymatous organs e.g. lymph node, spleen and liver.

3-Elastic fibers

- Elastic fibers are yellow in color in fresh state.
- They are stretchable but regain their original length.
- They are formed of two types of proteins: Elastin and Microfibrillar protein.
- Elastic fibers are synthesized by fibroblasts, smooth muscle cells in large arteries and chondrobasts in elastic cartilage.

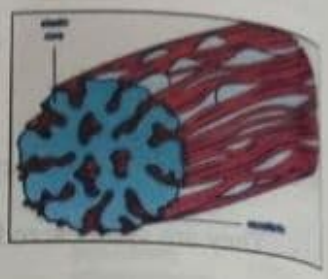
- **By L/M**

- They appear thin, straight and branching.
- They are mildly acidophilic (take the pink color of eosin).

- They can be stained reddish brown color by orcein stain and yellow color by Van Gieson stain.

- **By E/M:**

- Elastic fibers do not show axial periodicity. Each fiber is composed of a core of elastin protein surrounded by a sheath of microfibrils.



- Elastic fibers are not made of fibrils

- **Function:** They give elasticity to the tissue.

B- Ground substance

- Ground substance is highly hydrated, transparent and it fills the space between cells and fibers.

-It is viscous, so it acts as **lubricant** and a **barrier** to the penetration of bacteria.
- Ground substance is a complex mixture of:
  - Glycosaminoglycans (GAGs): The most abundant type is **hyaluronic acid**
  - Proteoglycans
  - Glycoproteins

-It is secreted mainly by fibroblasts.

Medical application

-Hyaluronic acid and proteoglycans form a barrier against bacterial penetration of tissues due to their high viscosity.

- Bacteria that produce hyaluronidase enzyme reduce the viscosity of connective tissue ground substance and have greater invasive power.

- *Hyaluronidase enzyme hydrolyses Hyaluronic acid and disassembles proteoglycans.*

Interstitial fluid

- In addition to the ground substance of connective tissue, a small quantity of interstitial fluid is also present.
- It is derived from the blood capillaries and is important for cells vitality.

Basement Membrane

It is a membrane that separates between the connective tissue and other tissues as epithelial, nervous and muscle tissues.

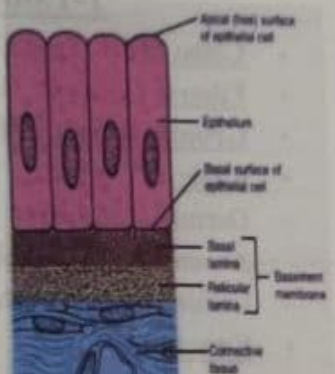
By LM: Can be seen as a homogenous membrane stained positive by PAS stain due its high content of glycoproteins.

By EM, It is formed of:

A- Basal lamina

B- Lamina reticularis

A. Basal lamina



- It is a thin meshwork of type IV collagen and laminin
- It is visible only by **E/M.**
- It is produced by the epithelial cells
- It consists of **TWO** zones:

1. Outer lamina lucida
2. Inner lamina densa

1. **Lamina lucida:**

- Pale zone next to the basal cell membrane of epithelia.
- It is formed mainly of glycoprotein **laminin**. It also contains **integrins** that project from the epithelial cell membrane into the basal lamina

2. **Lamina densa:**

- It is a more electron dense zone facing the underlying connective tissue
- It is formed of **Type IV collagen**

Basal lamina in nonepithelial cells is called external lamina

- Muscle cells, adipocytes and Schwann cells exhibit basal lamina.
- It delineates them from the surrounding connective tissue
- It serves as semipermeable barriers for regulating macromolecules exchanges between these cells and connective tissue.

B. Lamina reticularis

- It is present between the basal lamina and the underlying connective tissue.
- It is formed of type III collagen and type VII collagen (anchoring fibrils) which attach the basal lamina to the lamina reticularis.

- It is formed by the connective tissue i.e. fibroblasts.
- **Functions:**

➢ It supports and binds the cells to connective tissue
➢ It acts as diffusion barrier between connective tissue and other tissues.

Types of connective tissue

1-Loose (areolar) Connective Tissue

- **Cells:** Most of the C.T cells (fibroblasts, macrophages, plasma cells .....)
- **Fibers:** Collagen, elastic, reticular fibers.
- **Ground substance:** moderate in amount
- **Sites:**
  - Dermis of the skin.
  - Around blood vessels and nerves.
  - Lamina propria of the gastro-intestinal tract and urinary tract.
- **Functions**

➢ It wraps and cushions organs.
➢ Its macrophages phagocytose bacteria.
➢ Holds and conveys tissue fluid.

2-Dense Collagenous Connective Tissue

Contains most of the same components found in loose connective tissue, except that it has many more collagen fibers and fewer cells. It is formed of two types:

A) Dense irregular collagenous connective tissue

- **Cells:** Mainly fibroblasts and fibrocytes.
- **Fibers:**

  The coarse collagen fibers interwoven into a meshwork that resists stretch from all directions. The fibroblasts and fibrocytes are present in between the collagen fibers.
- **Ground substance:** Formed of glycosaminoglycans, and glycoprotein
- **Sites**
  - Capsules of organs e.g. the liver and the spleen.
  - Periosteum.
  - Perichondrium.
  - Sclera of the eye.
  - Dermis of the skin.

B) Dense regular collagenous connective tissue

- **Cells:** Mainly fibroblasts and fibrocytes,
- **Fibers:** Mainly Collagen type I. The collagen bundles are densely packed and oriented into parallel rows to allow for resistance to prolonged or repeated stresses exerted in the same direction.
- **Ground substance:** very little in amount and formed of glycosaminoglycans and glycoproteins.
- **Sites:**
  - Tendons, ligaments, cornea of the eye.

3-Elastic Connective Tissue

- **Cells:** Mainly fibroblasts.
- **Fibers:**
  Mainly elastic fibers are arranged parallel to one another and form either thin sheets or fenestrated membranes.
- **Ground matrix:**
  Formed of glycosaminoglycans and glycoproteins.
- **Stain:**
  -Yellow by Van Gieson stain.
  -Brown by orcein stain.
- **Sites:**
  - Ligamentum flavum.
  - Ligamentum nuchae.
  - Vocal ligament.

4- Reticular Connective Tissue

- **Cells:** Reticular cells and macrophages.
- **Fibers:** Reticular fibers that form mesh-like networks.
- **Ground substance:** Formed of glycosaminoglycans and glycoproteins
- **Stain:** Silver stain.
- **Sites:** Stroma of lymphoid tissue, bone marrow, liver and kidney.

5- Adipose Connective Tissue

It is classified into two types according to whether it is composed of unilocular or multilocular adipose cells.

A) White (unilocular) adipose connective tissue.

B) Brown (multilocular) adipose connective tissue.

A) White (unilocular) adipose connective tissue.

- Formed of unilocular adipocytes.
- Almost all adipose tissue in adults is white adipose tissue.
- It is subdivided into incomplete lobules by partitions of CT containing the blood vessels and nerves.
- Reticular fibers form a fine network that supports fat cells and bind them together.
- **Sites:**

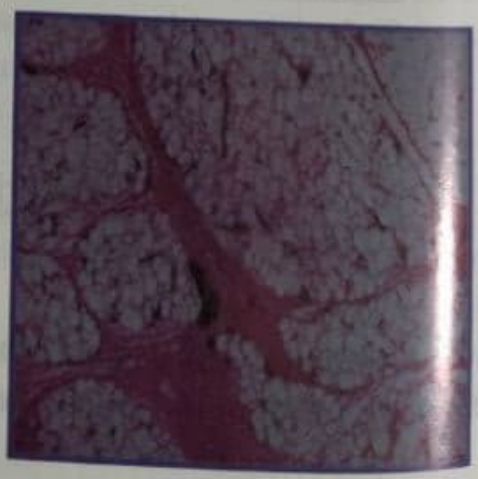
Distribution of this tissue changes throughout childhood and adult life.

- Subcutaneous tissue
- Around the hip, buttocks and abdominal wall
- Around the kidney, heart and blood vessels.
- Mammary glands

- **Colour:** White
  Yellow when diet is rich in carotenes
- **Functions:**
  - Heat insulation
  - Keeps some organs in place
  - Subcutaneous fat helps shape the body surface and in palms and soles acts as shock absorbers
  - It also functions as endocrine organ???????
- It is the only source of hormone **leptin** which helps regulate the appetite.

B-Brown adipose tissue

- It represents 2- 5% of weight of new born body weight
- **Sites:** back, neck and shoulders
- It is greatly reduced during childhood and adolescence. In adults it is found only in scattered areas; around kidney, adrenal glands and aorta
- **Structure:**
  It is formed of multilocular adipocytes
  Tissue is subdivided by partitions of CT into lobules.



- **Colour:** Brown due to:

1. Abundant mitochondria containing cytochrome pigment
2. Rich in blood capillaries

- **Functions**
  - Production of heat
  - New born babies exposed to a colder environment than in the uterus. Brown fat in babies protects them from cold

6- Embryonic Connective Tissue

A) Mesenchymal Connective Tissue:

- Present only in the embryo.
- **Cells:** UMCs.
- **Fibers:** few collagen fibers type I&III.
- **Ground substance:** gel-like amorphous ground substance.
  Function: contains stem cells for all adult connective tissue cells

B) Mucous (Mucoid) Connective Tissue:

- **Cells:** Scattered fibroblasts.
- **Fibers:** Few collagen, elastic and reticular fibers.
- **Ground substance:** Jelly-like formed mainly of hyaluronic acid and glycoproteins (Wharton's jelly).
- **Sites:**

  -Umbilical cord.

  -Vitreous humor of the eye.

  -Pulp cavities of young teeth which represent postnatal source of mesenchymal stem cells

Summary

- Connective tissue (CT) is formed of cells and extracellular matrix formed of fibers and ground substance.
- Types of connective tissue are: connective tissue proper, specialized and embryonic connective tissues.
- Fibers of connective tissue include collagen, elastic and reticular fibers.
- Cells of connective tissue are classified according to their shapes into: Branched cells: UMC, pericytes, macrophages, fibroblasts, pigment cells, reticular cells and rounded or oval cells: mast cells, plasma cells, adipose cells and extravasated leucocytes.
- Basement membrane is formed of two parts, basal lamina and lamina reticularis.
- Types of connective tissue proper include: loose (areolar) and dense (regular and irregular) collagenous connective tissues.
- Specialized types of connective tissue include elastic CT, reticular CT, adipose CT, cartilage, bone and blood.
- Embryonic connective tissue includes mesenchymal and mucous (mucoid) connective Tissue.

References

1. **Gartner L.P. & Hiatt J.L. (2014):** Color Textbook of Histology, 6th edition, W.B Saunders, Philadelphia, London, New York, Sydney, Toronto.
2. **Mescher, A.L.(2016)**: Junqueira's Basic Histology: Text and Atlas14th edition.McGraw-Hill, New York, Chicago, London, Madrid, New Delhi Seoul, Sydney.
3. **Ross M.H. and Pawlina, W. (2015):**Histology: A Text and Atlas: With Correlated Cell and Molecular Biology 7th edition. Lippincott Williams and Wilkins.

Answer the following questions

1) Describe the structure and correlated functions of:

A) Mast cell.

B) Plasma cell.

C) Macrophage.

D) Fibroblast

2) In a table form, write three histological differences between:

A) Unilocular and multilocular adipose cells.

B) Collagen and elastic fibers.

MCQs: Select the single correct answer

1) Which of the following connective tissue cells are derived from B-lymphocytes?

a. Plasma cells.
b. Adipocytes.
c. Pigment cells.
d. Fibroblasts.
e. Macrophages.

2) Collagen fibers are synthesized by:

a. Adipose cells.
b. Mast cells.
c. Fibroblasts.
d. Macrophages.
e. Plasma cells.

3) Elastic fibers:

a. Make a supportive network.
b. Can be stained by silver.
c. Thin, long and branching fibers.
d. Show axial periodicity by E/M.
e. Appear blue by orcein stain.

Overview

V

Blood

- Blood is a special type of connective tissue.
- Blood volume is about five liters.
- It is formed of **blood cells** (45% of blood volume) and **plasma** (55%).

Erythrocytes or red blood corpuscles (RBCs)

➢ **Shape:**

- ***Non-nucleated***, biconcave disc-shaped corpuscles
- Having a **thick periphery** and a **thin center**.

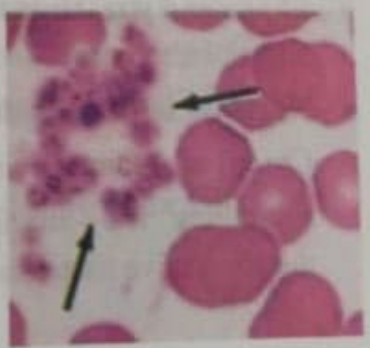
➢ **Size:** The normal diameter ranges from 6-9 μm (average 7.5 μm).

➢ **Structure and composition:**

- Mature RBCs ***lack*** nucleus and organelles.
- Contain water and enzymes. One third of its content is haemoglobin (Hb) which is an **oxygen** carrying protein.
- **Inner surface** of cell membrane is associated with cytoskeleton proteins to maintain the biconcave shape of RBCs.
- **Outer surface** is covered by carbohydrate-rich glycocalyx (cell coat) which is responsible for blood grouping (A, B, AB & O).

Blood Platelets (Thrombocytes)

- **Shape:** oval biconvex disks **lacking nuclei**.
- **Origin:** They are cell fragments derived by budding from a large cell called **megakaryocyte** present in the bone marrow.



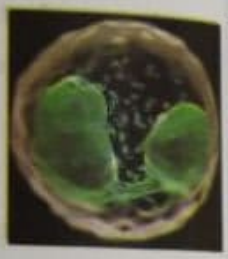
Leucocytes or white blood cells (WBCs)

- They are true cells having nuclei and organelles.
- They migrate to the tissue where they perform their functions.
- Leucocytes are classified according to ***presence or absence of specific*** granules into:
  1. **Granular leucocytes** including: neutrophils, eosinophils and basophils.
  2. **Agranular or non-granular leucocytes** including: lymphocytes and monocytes.

Neutrophils: (Polymorphnuclear leucocytes)

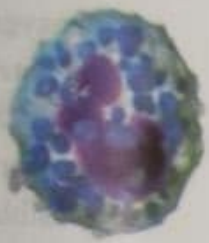
- **Shape and size:** rounded cells, 10 – 12 μm in diameter.
- **Nucleus:** is multilobed, segmented and deeply stained formed of 3 to 5 lobes interconnected by delicate chromatin strands.
- **Cytoplasm:** pale heavily populated with fine granules.
- **Functions:** ***phagocytosis*** of invading organisms in acute inflammation.

Eosinophils



- **Shape and size**: rounded cells, 12-15 μm in diameter.
- **Nucleus:** is bilobed, formed of two lobes connected by chromatin thread.
- **Cytoplasm:** is packed with numerous large, refractile and acidophilic granules.
- **Functions:** control the local response in ***allergic reaction*** and play a role in the defense against certain types of ***parasites.***

Basophils



- **Shape and size:** rounded cells, 10-12 μm in diameter.
- **Nucleus:** is S- shaped or irregular in shape.
- **Cytoplasm:** is packed with large basophilic granules masking the nucleus.
- **Functions:** release histamine and heparin in ***allergic*** reaction.

Monocytes

- **Shape and size**: large rounded cells, 12-20μm in diameter (the largest leucocytes)
- **Nucleus**: large and kidney-shaped.
- **Cytoplasm:** faint grayish blue (frosted glass)
- **Functions**: They are highly ***phagocytic*** cell. They migrate to the connective tissue and differentiate into ***macrophages***.

Lymphocytes

- **Shape:** rounded cells
- **Nucleus:** large, central, rounded and condensed
- **Cytoplasm:** A thin rim of pale *basophilic cytoplasm* is present around the nucleus.
- **They are classified according to their size into:**
  1. **Small lymphocytes:** 6-8 µm in diameter representing majority of lymphocytes in blood (92%). There are two types of small lymphocytes B and T lymphocytes.
  2. **Medium-sized lymphocytes:** 10-15 µm in diameter representing few blood lymphocytes. They are activated from small lymphocytes.
  3. **Large lymphocytes**: 15-18 µm in diameter, they are present in lymphatic tissue. Some are called natural killer cells (NK).
- **They are classified according to their function into:**
  1. **B lymphocytes**: 15%
  2. **T lymphocytes**: 80%
  3. **Natural killer cells**: 5%
- **Functions of lymphocytes:** they are the key cells in immune system
  - **B lymphocytes**: are responsible for the **humoral immunity**. They are activated when exposed to an antigen. Some of these cells will differentiate to **plasma** cells producing antibodies. Other cells will remain inactive as **memory** cells which become activated when re-exposed to the same antigen.
  - **T lymphocytes:** are responsible for the **cell mediated immunity,** either destroy foreign cells by direct contact or helping B lymphocytes.

Bone Marrow (Myeloid tissue)

Structure of bone marrow:

a) **C.T. stroma:** formed of reticular network perforated by arterioles, venules and blood sinusoids.

b) **Blood sinusoids:** are irregular dilated blood channels, lined with fenestrated endothelial cells. They have no or discontinuous basement membrane.

c) **Fixed cells:** including: Stromal reticular cells, Fibroblasts, fat cells, macrophages and bone cells of the endosteum (osteogenic cells, osteoblasts and osteoclasts).

d) **Free cells:** are the developing blood cells in different stages of development, including the megakaryocytes.

❖ **Megakaryocyte:** is a giant cell having large lobulated deeply-stained nucleus and basophilic cytoplasm.

Types:

1. Red active bone marrow.
2. Yellow inactive bone marrow.

Red active bone marrow:

- Is present in newborns and adults.
- **Sites:** in newborns: in most of bones and in adults: epiphysis of the long bones, ribs, body of vertebrae and sternum.
- **Functions:** Production of different types of blood cells, destruction of erythrocytes and storage of iron in macrophages.

Yellow inactive bone marrow:

- Is present in adults.
- **Site:** in diaphysis (shaft) of long bones.
- Is formed mainly of fat cells giving to it the yellow color.
- **Function:** storage of fat and can regain its activity at time of need (e.g. haemorrhage).

Smooth Muscle Fibers

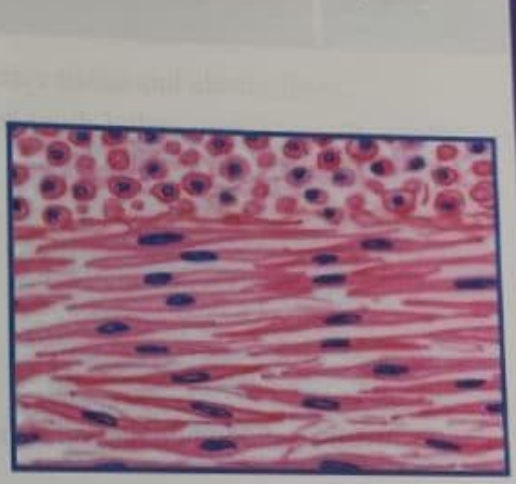
The fibers are involuntary and not striated

► General characters

In the prenatal life, it develops from undifferentiated mesenchymal cells (UMC).
In the postnatal life, it develops from **pericytes** present in the walls of capillaries.

- **Site:**
  1. The wall of blood vessels.
  2. The wall of viscera e.g. GIT, respiratory and genito-urinary systems.
- **Size:** Length varies from **30 µm**. as in the wall of blood vessels up to **500 µm** as in the wall of uterus. The diameter is 8 µm.

► LM structure



- **Shape**: The fibers are fusiform and are arranged in bundles surrounded by connective tissue sheath.
- **The nucleus** is rod shaped and single.
- **The cytoplasm** is acidophilic with dark granules called **dense bodies.**
- Each muscle fiber is surrounded by a **basement membrane**.

► EM structure

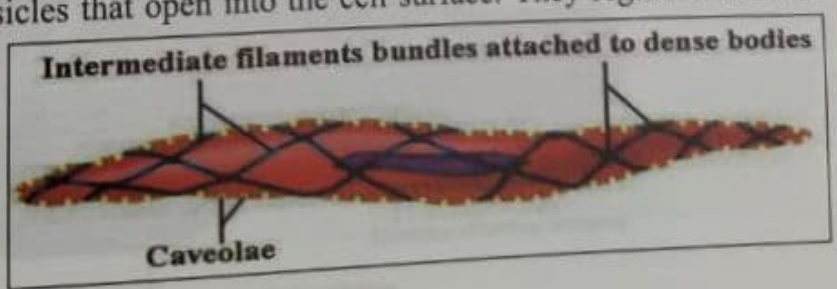
The cytoplasm contains organoids e.g. mitochondria, Golgi apparatus, ribosomes, sER (sarcoplasmic reticulum), rER, microfilaments and inclusions e.g. glycogen.

a. **Filaments:**
   - Actin and Myosin
   - Intermediate filaments include:
     1- Desmin presents in all smooth muscles.
     2- Vimentin is in smooth muscle of blood vessels.

The filaments are arranged haphazardly and overlap each other. This overlap explains the presence of **dense bodies**.

b. **Caveolae** are rows of vesicles that open into the cell surface. They regulate calcium pump to permit muscular contraction.

c. **Gap junctions** which allow rapid conduction of impulses between the muscle fibers



► Growth and regeneration

Growth occurs by:

1- Hypertrophy to increase in width.

2- Proliferation by mitotic division of the smooth muscle fibers.

Regeneration occurs by:

1- Division of the smooth muscle fibers.

2- Differentiation of pericytes.

► Medical application

Abnormal proliferation of smooth muscle fibers and their production excess collagen contribute to formation of atherosclerotic plaques in aorta and coronary arteries in aging humans.

Blood Vascular System

- There are three types of blood vessels: arteries, veins and connecting vessels between arteries and veins (capillaries, sinusoids and arteriovenous anastomosis).
- **The general structure of the wall of any blood vessel (except capillaries) is formed of three layers:**

I. Tunica intima:

It is the innermost layer and is formed of:

a) Endothelium: a single layer of flat endothelial cells resting on basement membrane.

b) Subendothelial layer: formed of loose connective tissue and elastic fibers.

C) Internal elastic lamina: it is a fenestrated (with holes) membrane of elastic fibers separating the intima from the media.

II. Tunica media:

It is the middle layer and is formed of:

a) Circularly arranged smooth muscle fibers.

b) Elastic lamellae.

c) External elastic lamina: which is a fenestrated elastic membrane separates the media from the adventitia.

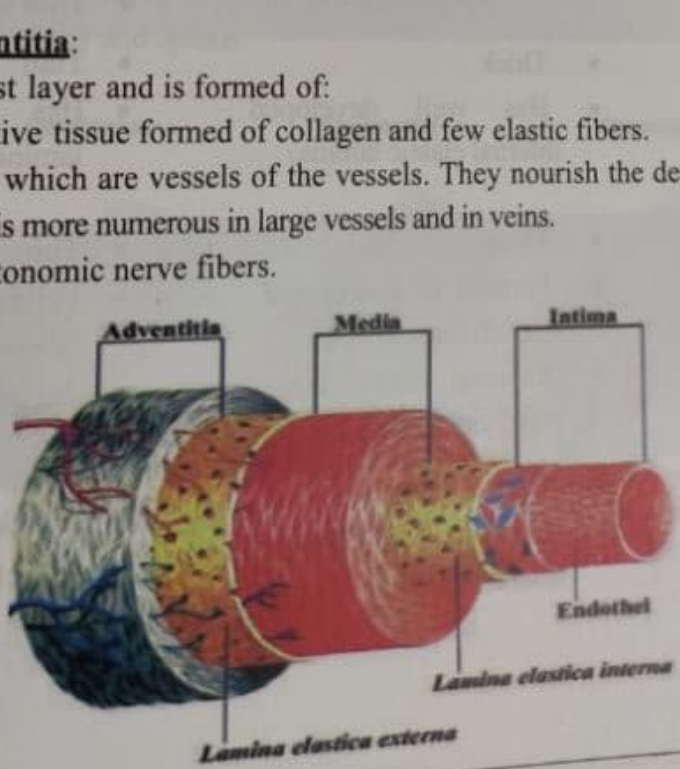
III. Tunica adventitia:

It is the outermost layer and is formed of:

a) Loose connective tissue formed of collagen and few elastic fibers.

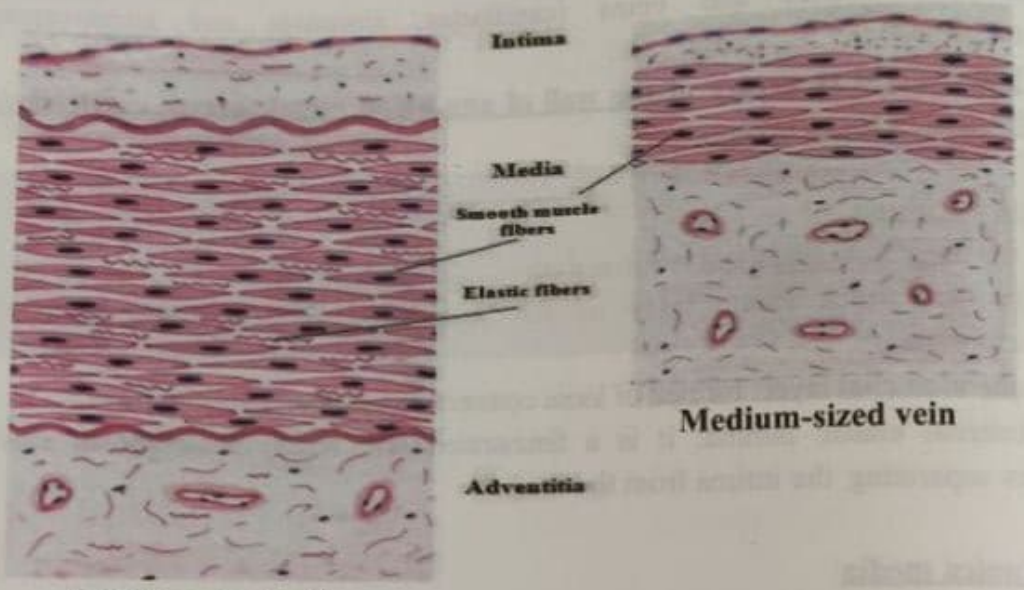
b) Vasa vasorum which are vessels of the vessels. They nourish the deep layers of the vessels. It is more numerous in large vessels and in veins.

c) Network of autonomic nerve fibers.



- The structure of the three layers of a blood vessel and their relative proportions vary in different vessels

Structure of medium sized artery and vein



Medium-sized vein

Medium-sized artery

	Artery	Vein
Wall and lumen	• Narrow patent lumen • Thick wall	• Wide irregular collapsed lumen • Thin wall
Tunica intima	• Thick • Has well developed internal elastic lamina.	• Thin • Has no internal elastic lamina.
Tunica media	• Thick. • Formed of elastic and smooth muscle fibers. • External elastic lamina may be present.	• Thin. • Formed of smooth muscle fibers. • No external elastic lamina.
Tunica adventitia	• Thin • Contains some elastic fibers.	• Thick. • No elastic fibers.

Capillaries

- They branch and anastomose forming the capillary network or bed.
- **LM:** the capillary wall is formed of:
  - A **single layer** of endothelial cells joined by tight junction.
  - A continuous basement membrane on which the endothelial cells rest. It splits to enclose the **pericytes.**

Types of capillaries:

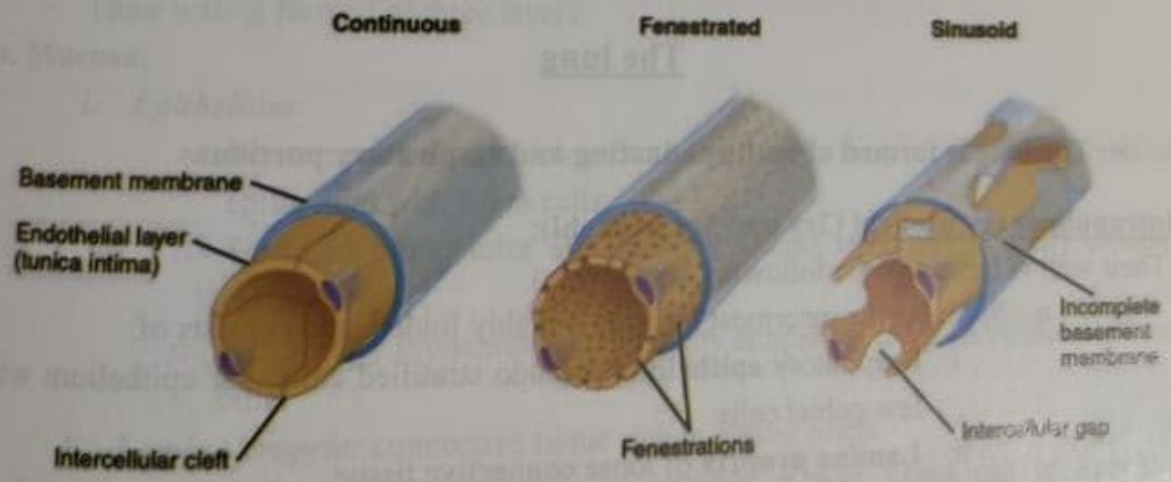
1. **Continuous capillaries:**
   They have continuous endothelial lining, e.g. skeletal muscles and cerebral capillaries.
2. **Fenestrated capillaries:**
   The endothelial cells are perforated by holes, e.g. glomerular capillaries and in endocrine glands.

Function of capillaries:

- Exchange of gases and metabolites between blood and different tissues.

Blood Sinusoids:

- These are dilated irregular blood channels.
- Endothelial cells are separated by wide gaps (slits) and are perforated by holes.
- The endothelial cells rest on discontinuous basement membrane.
- Macrophages are present along its wall with no pericytes.
- Sites: bone marrow, liver and spleen.



The Respiratory System

The respiratory System is divided into two portions:

Conducting portions	Respiratory portions
- Nose (nasal cavity / nasal sinuses) - Nasopharynx - Larynx - Trachea - Bronchial tree: * Extrapulmonary bronchus (1ry bronchi). * Intrapulmonary bronchus (2ry&3ry bronchi). - Bronchioles: * Preterminal bronchioles. * Terminal bronchioles.	(Where Gas Exchange Takes Place) - Respiratory bronchioles - Alveolar ducts. - Alveolar sacs. - Alveoli

Functions of the conducting portion:

1-Conduction of air

2- Air conditioning:

- **Filters:** Cleaning, purification and trapping large particles: by nasal hairs a mucous
- **Adjust temperature:** by blood capillaries
- **Adjust humidity:** by respiratory mucosa and seromucous glands

The lung

➢ **The lung is formed of both conducting and respiratory portions**

Intrapulmonary bronchi (2ry and 3ry bronchi):

Their wall is formed of the following layers:

a. **Mucosa:** the innermost layer. It is highly folded, and consists of:
   i. Respiratory **epithelium**, pseudo stratified columnar epithelium w few goblet cells.
   ii. **Lamina propria** of loose connective tissue.
b. **Muscle Layer**: spirally arranged bundles of smooth muscles.
c. **Adventitia:** the outer layer. It is composed of connective tissue contain supporting plates of hyaline cartilage, muco-serous glands and lympho follicles.

Figure showing the wall of intrapulmonary bronchus.

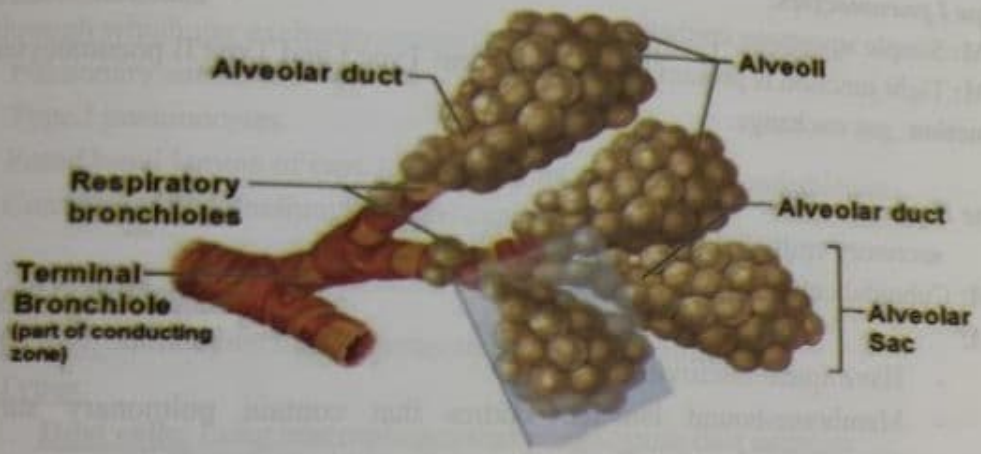


Figure showing respiratory portion of the lung

Bronchioles

- Their wall is formed of three layers:

a. Mucosa:

i. Epithelium:

- Pre-terminal bronchioles are lined by simple columnar ciliated epithelium with Clara cells
- Terminal bronchioles are lined by simple columnar partially ciliated epithelium.
- Respiratory bronchioles are lined by simple cuboidal epithelium with no cilia.

ii. ***Lamina propria:*** connective tissue rich in elastic fibers

b. Muscle layer: Crisscrossing bundles of smooth muscle in oblique direction.

c. Adventitia: fibroelastic C.T ***it does not contain*** glands, lymphatic follicles, cartilage.

Alveolar duct:

- Its wall is interrupted by numerous openings of alveoli and alveolar sacs.
- Lined by low cubical epithelium surrounded by ***elastic*** and ***reticular*** fibers.

Alveolar sacs:

- Groups of alveoli open into a common central space.
- Lined by simple squamous epithelium surrounded by reticular and elastic fibers.

Alveoli:

- They are the basic structural and functional unit of gas-exchange in the lung.
- Lined by alveolar epithelium (type I and type II pneumocytes).

Alveolar epithelium:

(1) Type I pneumocytes:

L/M: Simple squamous epithelium.

E/M: Tight junction is present between adjacent Type I and Type II pneumocytes.

Function: gas exchange.

(2) Type II pneumocytes:

secretory epithelial cell.

L/M: Cuboidal cells, bulging into the lumen.

E/M:

- Have apical microvilli.
- Membrane-bound lamellar bodies that contain pulmonary surfactant (phospholipid material).

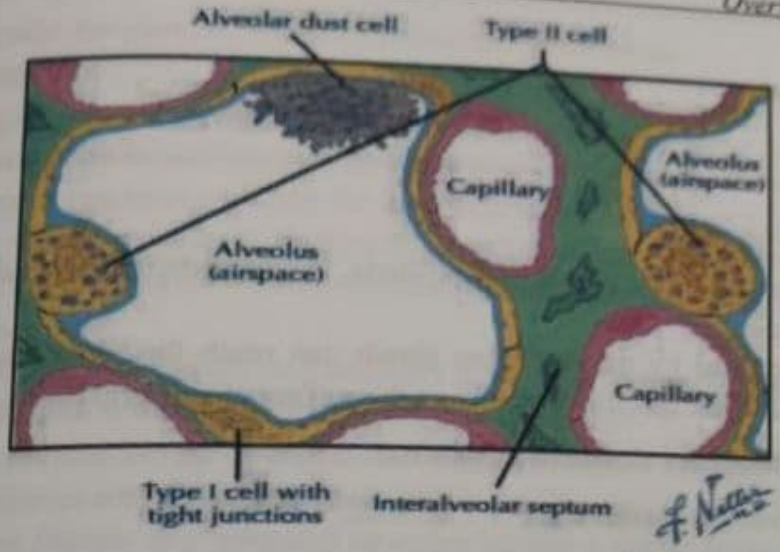
Function:

- Synthesize and secrete pulmonary ***surfactant***.
- They can ***divide*** and ***regenerate*** both types of pneumocytes

N.B: Cilia are absent from alveolar epithelium, and thus dust-trapped particles are removed by ***alveolar macrophage*** (dust cell).

Interalveolar Septum:

- It is the partition between two adjacent alveoli.
- It is formed of: -
  1. Alveolar epithelium on either side (Type I and type II pneumocytes)
  2. Capillary network.
  3. alveolocapillary basement membrane.
  4. Network of connective tissue fibers, connective tissue cells and extravasated leucocytes.



Blood – Air barrier:

Area through which gas exchange occurs. It is formed of:

1. Pulmonary surfactant.
2. Type I pneumocytes.
3. Fused basal lamina of type I pneumocytes and capillary endothelium.
4. Continuous endothelium of blood capillaries.

Alveolar Macrophages:

- **Origin:** Monocytes that migrates to the lung interstitium.
- **Types:**
  1. **Dust cells:** Lung macrophages that phagocytose dust particles.
  2. **Heart failure cells:** Lung macrophages that phagocytose extravasated blood in cases of congestive heart failure.

The Endocrine System

• INTRODUCTION:

- The endocrine glands are glands with no ducts. They secrete hormones directly into the bloodstream.
- Hormones secreted by the endocrine glands can reach their target cells due to the presence of their specific receptors on the surface of that target cells.

- Endocrine glands are classified as follows:

A. Pure endocrine glands e.g:

1. Pituitary gland.
2. Thyroid gland.
3. Parathyroid glands
4. Adrenal glands
5. Pineal gland.

B. Mixed (endocrine tissue within exocrine glands) e.g.:

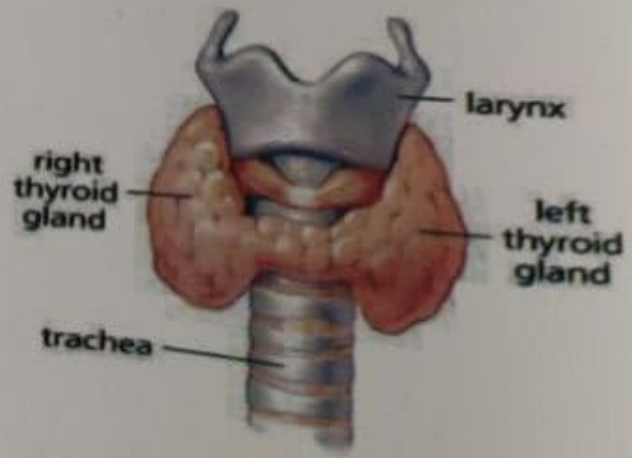
1. Pancreas (islets of Langerhans).
2. Liver cells
3. Sex glands: Male: Interstitial cells of Leydig in the testis
   Female: corpus luteum in the ovary.

C. Scattered and isolated cells:

- Certain hormones are secreted by cells present in various organs e.g.:
  a. Enteroendocrine cells within epithelium of G.I.T and respiratory tracts.
  b. Epithelial reticular cells in thymus.
  c. Juxtaglomerular cells of the kidney.

The Thyroid Gland

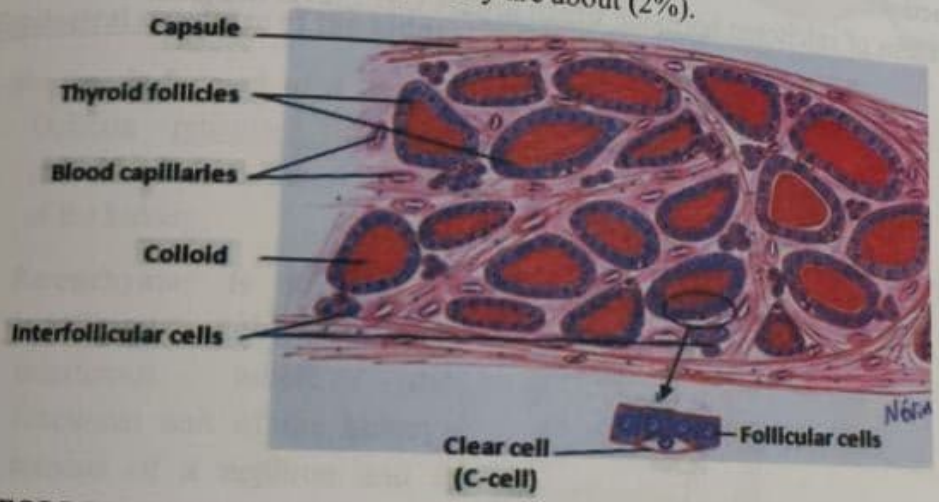
- It is present in the anterior part of the neck. It's formed of two lobes connected together by a narrow isthmus. The two lobes are found one on each side of the trachea



- **Histologically**, the gland is formed of stroma and parenchyma:
  - **Stroma:**
    - The gland is covered by two capsules:
    - The outer one is continuous with the pretracheal fascia.
    - The inner one (true capsule): It's thin and consists of fibroelastic connective tissue which sends septa dividing the gland into ill- defined lobules.
    - There is a delicate network of reticular fibers that support the parenchyma.
  - **Parenchyma:**
    - It is formed of epithelial cells arranged in the form of follicles (**thyroid follicles**).
    - Each follicle is surrounded by a basement membrane.
    - These follicles are the structural and functional units of the gland.
    - The follicles are surrounded by extensive capillary plexus.
    - Thyroid follicle is a spherical structure having a lumen filled with acidophilic PAS positive colloid (formed mainly of thyroglobulin).

- **<u>The lining of the follicle is formed of 2 types of cells:</u>**

1. **Follicular cells:** They constitute the majority (98%).
2. **Parafollicular cells (C cells):** They are about (2%).



1. FOLLICULAR CELLS:

- **LM:**
  - The histological appearance of thyroid follicle and follicular cells reflects the state of functional activity of the gland.
  - In a normal functioning follicle, they are cuboidal cells with basophilic cytoplasm and central rounded nuclei with prominent nucleoli.
  - In **hyperactive follicles**, they are columnar cells. The size of the follicle is smaller with little amount of colloid.
  - In **hypoactive follicles,** they are flattened cells due to the distension of the follicle with a large amount of colloid.
  - These cells lie on basement membrane (BM) surrounded by reticular fibers containing the blood capillaries.

- **EM:**
- Apical microvilli and junctional complexes at the lateral borders.
- Well-developed rER., prominent supranuclear Golgi apparatus, apical secretory vesicles, numerous mitochondria and lysosomes.

- **Function:**
- Synthesis, storage and release of thyroid hormones (T3 and T4).

2. PARAFOLLICULAR CELLS = C CELLS:

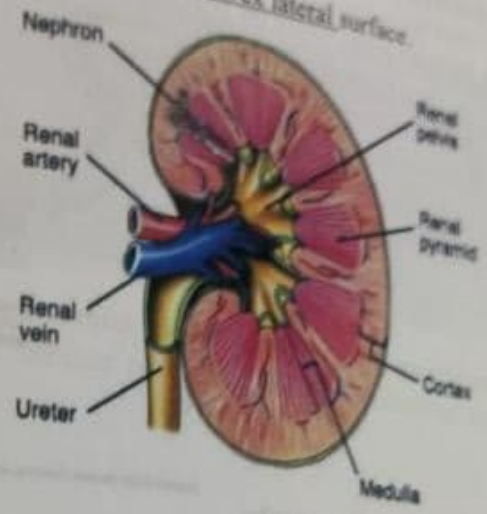
- **LM:**
- They appear larger and paler than the follicular cells.
- They are large rounded cells that have central spherical nuclei.
- They are present between the B.M and the follicular cells, but they do not reach the lumen.

- **EM:**
- Besides the small organelles, there are secretory granules with variable electron density.

- **Function:**
- Synthesis of calcitonin hormone which lowers Ca++ level in blood.

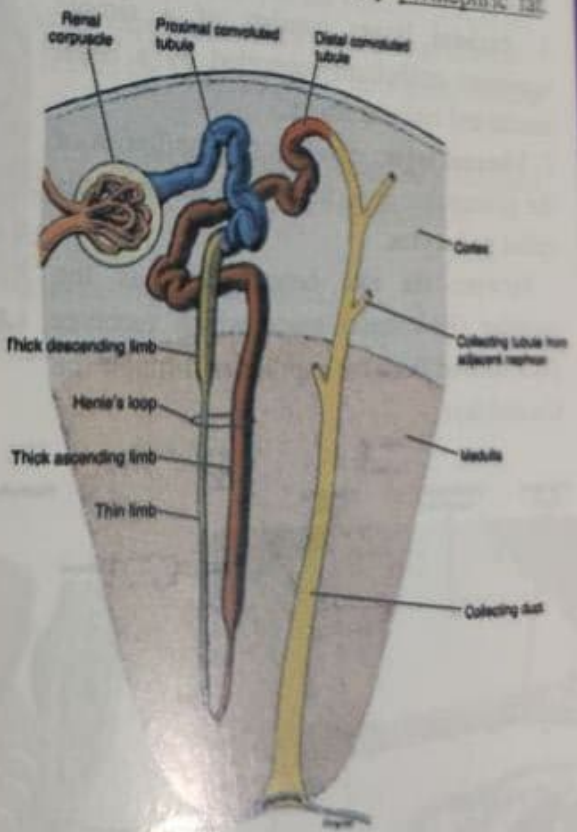
The Kidney

- **General structure of the kidney:**
  - It is **bean shaped** with concave medial border and convex lateral surface.
  - It is divided into **outer cortex** that contains mainly renal corpuscles and convoluted tubules and **inner medulla** that consists mainly of collecting tubules.
  - Hilum: is a concavity on the medial border of the kidney where arteries, veins, lymphatic vessels and nerves of the kidney enter and leave.



Histological structure of the kidney:

1. **Stroma: is formed of a capsule of loose C.T** and surrounded by perinephric fat. Delicate reticular tissue is present between the structures of the kidney.



2. **Parenchyma: is formed of uriniferous tubules.** Each uriniferous tubule (the functional unit of the kidney) consists of a nephron and a collecting tubule.

The **nephron**:

Each nephron consists of:

1- Renal corpuscle
2- Proximal convoluted tubule (PCT)
3- Loop of Henle
4- Distal convoluted tubule (DCT)

Renal Corpuscle (Malpighian Corpuscle):

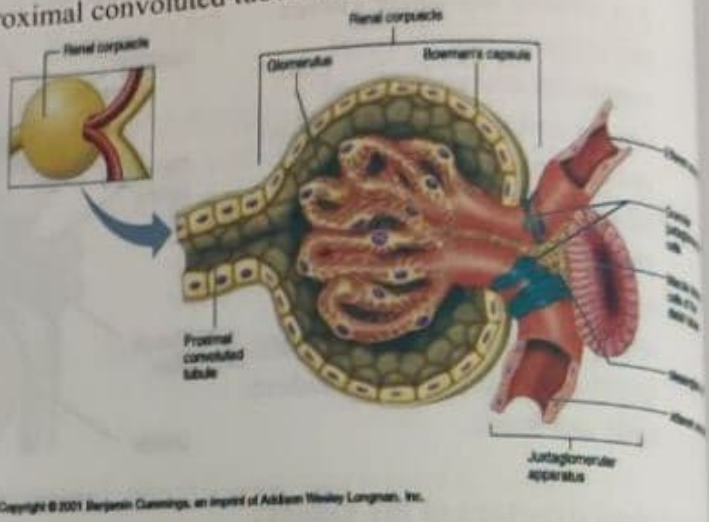
- It is a dilated spherical structure about 200 um in diameter.
- Filtration of blood occurs in it forming the glomerular filtrate.
- It has two poles:

i. Vascular pole: where afferent arteriole enters and efferent arteriole leaves the corpuscle.

ii. Urinary pole: where the proximal convoluted tubule begins.

- **It is formed of:**

a. Bowman's capsule
b. Glomerulus: tuft of capillaries
c. Mesangial cells.



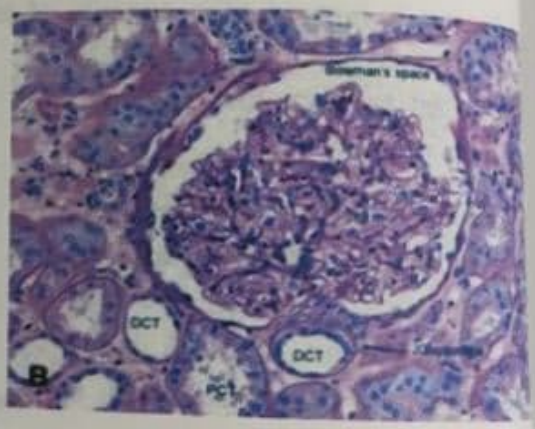
A- Bowman's capsule:

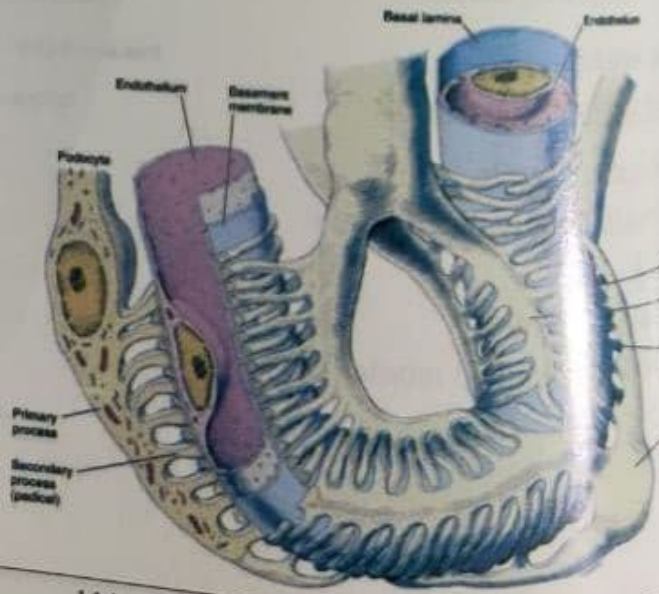
Is formed of two layers:

1- **Parietal layer:** consists of a simple squamous epithelium supported by a basal lamina and reticular fibers.

2- **Visceral layer:** envelops the capillaries of the glomerulus. It is formed of special cells called **podocytes.**

Between the two layers, there is the capsular (Bowman's) space which receives fluid filtered from the capillaries through the visceral layer.





Visceral layer of Bowman's Capsule:

- **Podocytes** are modified simple squamous cells that line the visceral layer of Bowman's capsule.
- Each cell is stellate-shaped. They have several **primary processes**. Each primary process gives rise to numerous **secondary processes called pedicles which end by feet firmly** placed on the basement membrane of glomerular capillaries.
- There are minute gaps between the pedicles called **filtration slits covered by a diaphragm 6 nm thick (arrows)**

- Between the podocyte and the glomerular capillaries, there is a **thick glomerular basement membrane** derived from the fusion of basal laminae of both capillary endothelium and podocyte.

B- Glomerular capillaries:

- The afferent arteriole (carries non-filtered blood) enters at the vascular pole of the renal corpuscle and divides into about 50 capillaries which drain into an efferent arteriole (carries filtered blood) that leaves the renal corpuscle through its vascular pole.
- The glomerular capillaries are lined with fenestrated simple squamous endothelial cells surrounded by a basement membrane. The fenestrae are not closed by diaphragm.
- The glomerular basement membrane is continuous and thick.

The Digestive System

The digestive system is composed of:

I) **The oral cavity:**
That includes lips, cheeks, tongue, teeth and palate.

II) **The gastrointestinal tract:**
That comprises oropharynx, esophagus, stomach, small intestine, large intestine, rectum and anal canal.

III) **The gut associated glands:**
These are salivary glands, liver and pancreas.

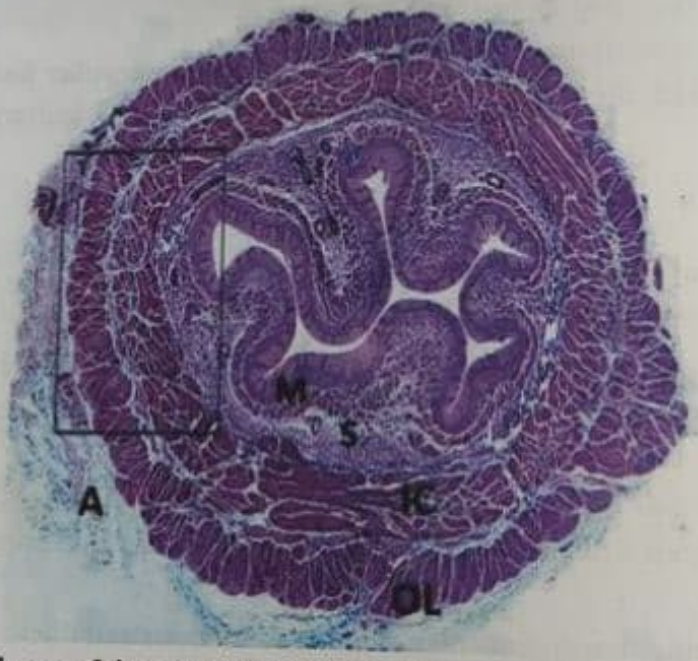


Figure showing the layers of the gastrointestinal tract. M=mucosa, S=submucosa, IC=inner circular, OL=outer longituidinal, A=adventitia.

The Gastrointestinal tract

The wall of the gastrointestinal tract is formed of four layers:

1. Mucosa: The innermost layer, it is formed of three layers:

a) **Surface Epithelium:** The epithelium is variable according to the function.
   i. ***Protective:*** stratified squamous in esophagus, anal canal
   ii. ***Secretory:*** simple columnar in stomach.
   iii. ***Absorptive:*** columnar absorptive in intestine.

b) **Corium (Lamina propria):** It is a layer of loose areolar connective tissue. It contains blood vessels, nerves, lymphatics, glands and gut associated lymphatic tissue *(GALT)*.

c) **Muscularis mucosa:** thin layer of smooth muscle fibers arranged as inner circular and outer longitudinal layer.

2. Submucosa:

a) Loose connective tissue that contains blood vessels and gut associated lymphatic
b) Submucosal nerve plexus.
c) Mucous secreting glands are present ***only*** in esophagus and duodenum.

3. Muscularis externa (Musculosa):

a) Formed of smooth muscles arranged in two layers; inner circular and outer longitudinal layer.
b) Nerve plexus is present between the inner and outer circular layers.
c) Blood and lymphatic vessels.

Exception:

i. **In esophagus:** skeletal muscles are present in upper third, mixed in middle third.
ii. **Fundus:** Innermost oblique layer is present.
iii. **Colon:** the fibers of the outer longitudinal layer are arranged in three columns called taenia coli.

4. Serosa or adventitia:

It is the outer coat of the tube and is formed of loose connective tissue rich in blood vessels and nerves.

a) Serosa is present in intraperitoneal organs where organs are covered by peritoneum formed of mesothelial cells (Simple squamous epithelium).
b) Adventitia is present in retroperitoneal organs lacking mesothelial cells.

The Liver

- The liver is a compound tubular gland having both **endocrine** and **exocrine** functions.
- ***Exocrine function***: as the liver secretes bile through bile ducts.
- ***Endocrine function:*** the liver secretes plasma proteins, lipoproteins and glucose directly into blood.
- **Structure of the liver:**
  The liver is formed of connective tissue stroma and parenchyma.

1-Stroma of the Liver: It is formed of:

a) **Capsule:** C.T. cells and fibers covered by peritoneum.
b) **Trabeculae:** C.T. cells and fibers, very thin in human & thick in animals (pig).
c) Network of **reticular fibers** and cells.

2-Parenchyma of the Liver:

Formed of liver cells and can be defined in three ways:

A. Classic Liver Lobule:

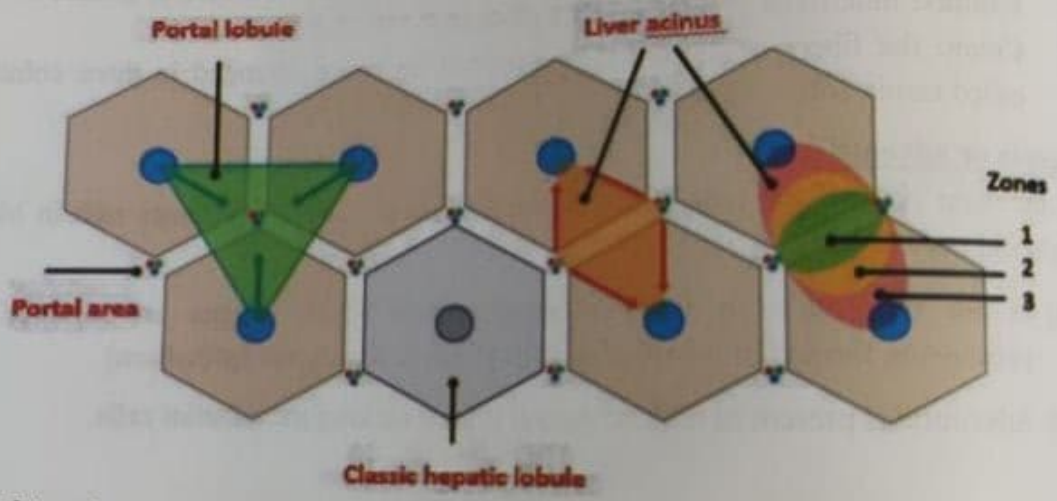
a. Hexagonal mass of liver tissue with central vein in the center and portal tract at its periphery.
b. Formed of plates and cords of branching and anastomosing liver cells (Hepatocytes) separated by blood sinusoids

B. Portal lobule:

Triangular mass of liver containing liver tissue from three adjacent hepatic lobules which have a common portal tract and drain their bile secretion into same branch of bile duct.

C. Liver acinus:

Ovoid mass of liver cells from two adjacent classic hepatic lobules, which surround a central vascular core (branch from hepatic artery and portal vein). It is subdivided into three zones (Zone I, II and III) based on relation of hepatocytes to central vascular core.



Portal tract:

- Connective tissue ***found*** at some of the corners of the classic hepatic lobule.
- ***Contains*** a branch of portal vein, hepatic artery, bile duct and lymphatic vessel.

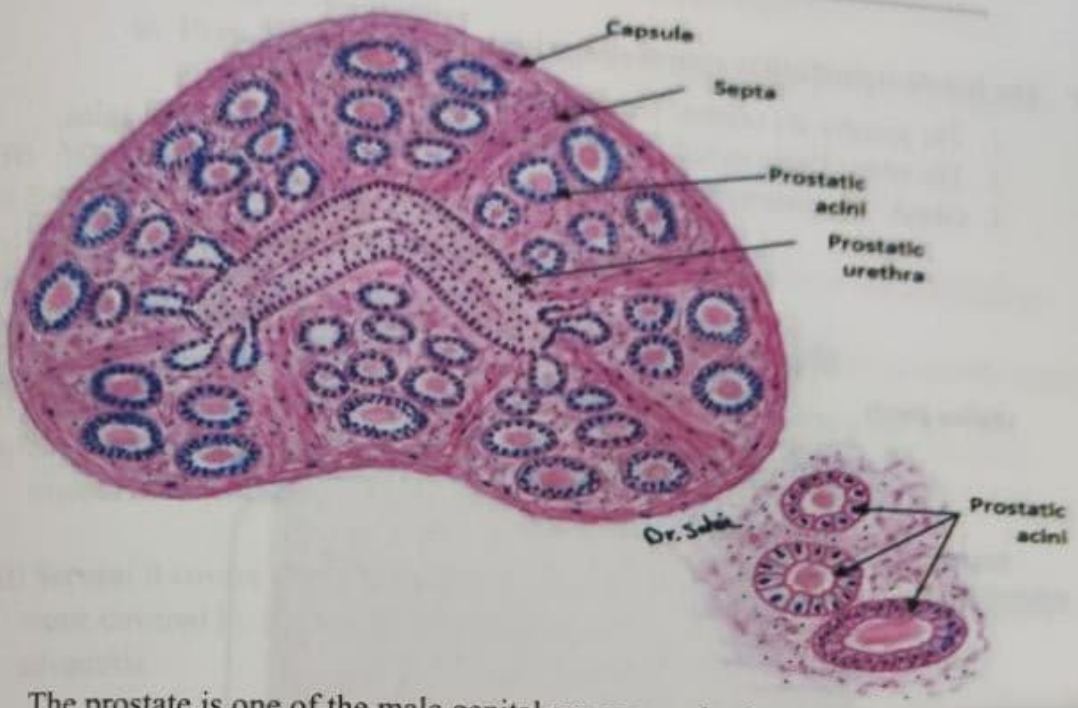
Hepatic blood sinusoids:

- Irregular blood channels present between plates of liver cells.
- Lined by two types of cells: fenestrated endothelial cells and Von Kupffer cells.

Hepatocytes:

- **Shape:** Large polygonal cells.
- **Nucleus:** central, rounded and vesicular (25% binucleated)
- **Cytoplasm:** acidophilic with some basophilic granules (rER and free ribosomes) Vacuolations are due to glycogen and lipid.
- They have **high proliferative** capacity.

The Prostate



- The prostate is one of the male genital accessory glands.
- It is formed of stroma and parenchyma:

A- Stroma: that consists of:

1. Capsule of thin fibroelastic layer with smooth muscle fibers.
2. Septa that divide the glands into lobes.
3. Reticular C.T. that supports the parenchyma.

B- Parenchyma:

- It is formed of prostatic acini (glands) surrounding a V-shaped urethera.
- The prostatic acini are classified into:
  - i) Mucosal (small) acini: that lie close to the urethra.
  - ii) Submucosal acini: that lie peripheral to the mucosal acini.
  - iii) Main (large) acini: in the periphery of the prostate gland.
- The ducts of these acini open into the lumen of the urethra.
- The lining epithelium of the acini and their ducts is simple cubical, simple columnar or pseudo-stratified columnar according to the gland activity.
- In old men, the lumen of the acini may contain calcified bodies, called prostatic concretions or **corpora amylacea**.

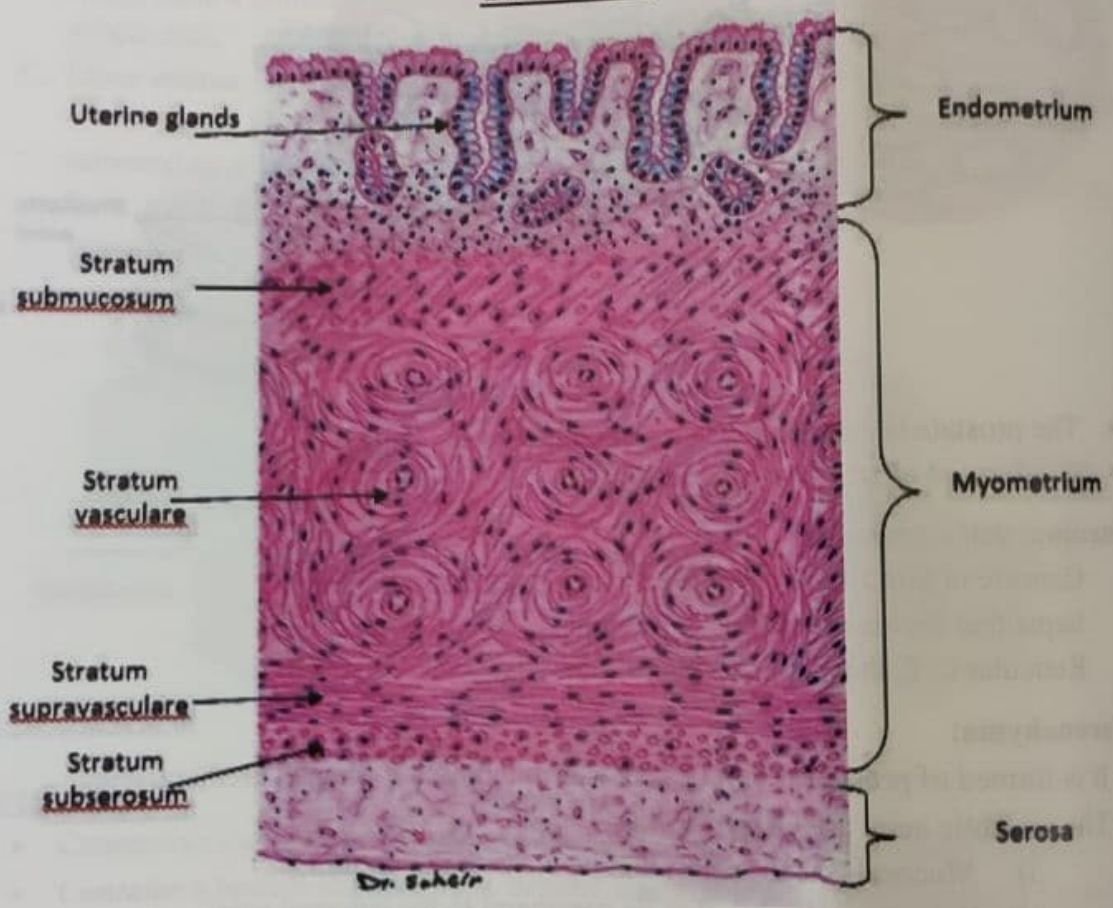
- **Function:**

Secretion of alkaline milky fluid rich in proteolytic enzymes, acid phosphatase, amylase, citric acid, fibrinolysin and lipids.

The Female Reproductive System

- **The female reproductive system comprises:**
  1. The primary sex organs: The two ovaries.
  2. The tubes: Those include two Fallopian tubes, the uterus and the vagina.
  3. Gland: The mammary gland.

The Uterus



The wall of the uterus is formed of the following layers:

I) **Endometrium:** It consists of:

a) **Epithelium**: It is simple columnar cells, partially ciliated and partially secretory.

b) **Lamina propria (Corium)**: a layer of connective tissue contains:

- Uterine glands lined by simple columnar epithelium.
- Stromal (decidual) cells, stellate cells attached to each others.
- Collagen and reticular fibers.
- Uterine blood vessels.
- Granular leucocytes, lymphocytes and macrophages.

endometrium is <u>divided into two parts</u>:

a) **Superficial part**: it is the superficial parts of the uterine glands and the surface epithelium. It is supplied by the spiral arteries. It is shed off during menstruation.

b) **Deep basal part**: it is formed of deep parts of the glands. It is supplied by straight arteries. It is the permanent layer.

II) Myometrium:

It forms the main thickness of the uterine wall. It includes:

a) **Stratum submucosum**: the inner layer. It is formed of oblique and longitudinal smooth muscle fibers.

b) **Stratum vasculare**: that is the thickest middle layer; it is formed of smooth muscle fibers arranged as fiqure "8" around the blood vessels.

c) **Stratum supravasculare**: formed of circularly arranged smooth muscle fibers.

d) **Stratum subserosum**: is the outmost layer, formed of longitudinally arranged smooth muscle fibers.

III) Serosa: it covers only the fundus of the uterus. It is formed of loose connective tissue covered by flat squamous cells. The body of the uterus is covered by adventitia.

Cervix of the Uterus

- The cervix is the lower part of the uterus. Its wall is formed of:

I) Mucosa: which comprises:

a) Epithelium: simple columnar mucous secreting cells. It changes into stratified squamous epithelium to line the vagina.

b) Corium: formed of connective tissue which contains mucous secreting glands.

II) The wall of the cervix is formed of collagenous tissue, many elastic fibers and few smooth muscle fibers.