Block 102-PMS

Principles of microscopic and macroscopic structures

Histology 2026

Contents

Histology and Cytology

• Definition of Histology: "Histo" comes from Greek which means "tissue" "Ology" comes from Greek which means "branch of knowledge"

• Definition of Cytology: "Cyto" comes from Greek which means "cell"

• Histology requires the use of "Microscopes" to view the structures under increasing magnifications. Because most tissues and organs are too thick for light to pass through, thin translucent sections are cut from them and placed on glass slides for microscopic examination of the internal structures. For tissue preparation for light microscope, the paraffin technique is the most commonly used technique.

Paraffin technique

Steps as follow:

1. ***Fixation*** using solution of formaldehyde (formalin).

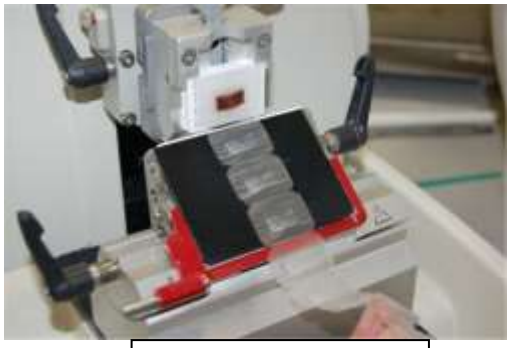
Aims of fixation:

- Prevent autolysis by stabilizing lysosomes of the cells preserving tissue structure.
- Fixation kills bacteria thus preventing putrefaction.
- Hardens the tissue to facilitate cutting.

2. **Washing** in running tap water.
3. **Dehydration:** removing water by passing the tissue through increasing concentrations of ethyl alcohol (from 0 to 100%), this occurs gradually to prevent sudden tissue shrinkage.
4. **Clearing:** the alcohol is replaced with xylene, which is a paraffin solvent. Xylene also makes the tissue transparent.

5. Impregnation and Embedding: using hot oven, the tissue is placed in warm paraffin wax (55-60 C) to fill the spaces between cells.

6. Sectioning: serial thin sections (5-7 µm thickness) are cut using rotatory microtome and then mounted on a slide.



Rotatory microtome

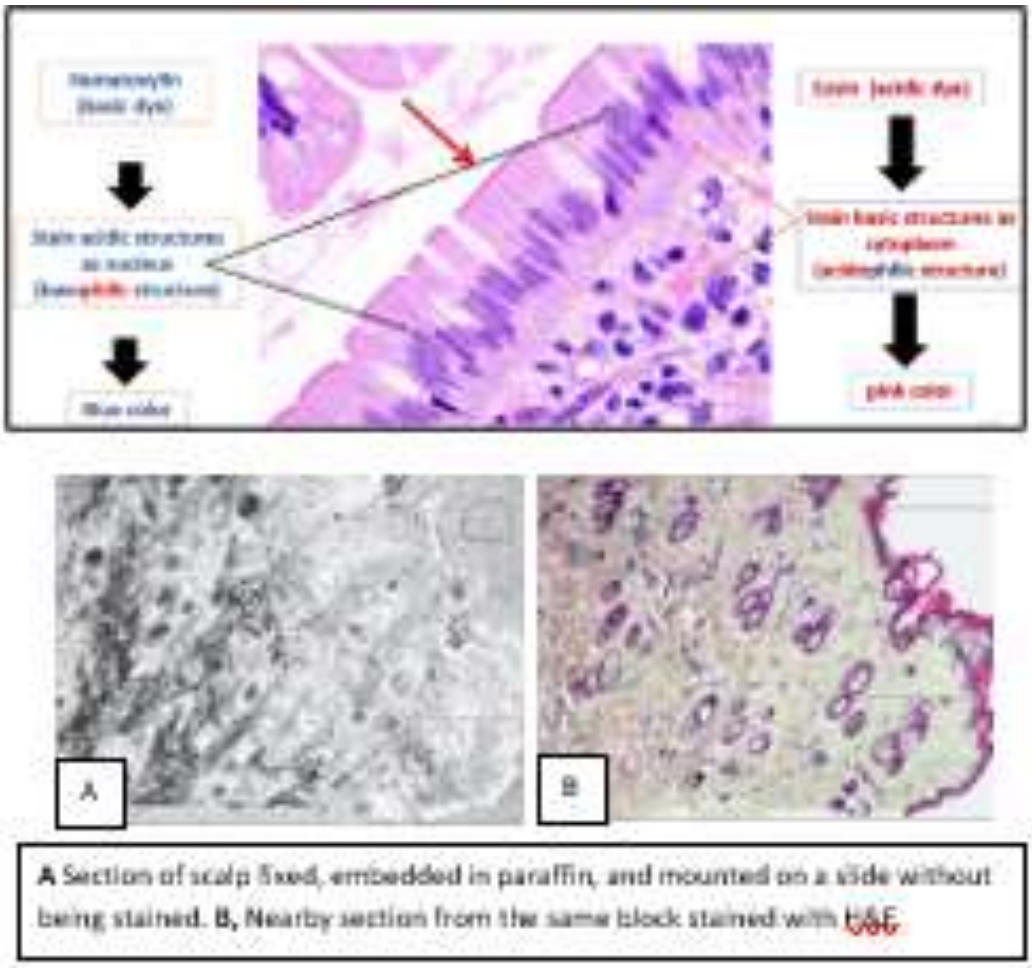
7. Staining: unfortunately, most staining solutions are aqueous, so to stain the sections, the wax has to be dissolved and replaced with water (rehydration). The sections are passed through xylene, and then decreasing strengths of alcohol (100% to and finally

water). Once stained, the section is then dehydrated once again, and placed in xylene and a coverslip is placed to protect the sample.

Hematoxylin and eosin (H&E)

Both are the universally used stains for routine histological examination of tissue sections.

Hematoxylin	Eosin
Basic dye that stains acidic components of the cell (nucleus) giving blue color (basophilia)	Acidic dye that stains the cell cytoplasm giving reddish pink color (acidophilia)



A Section of scalp fixed, embedded in paraffin, and mounted on a slide without being stained. B, Nearby section from the same block stained with H&E

Clinical applications:

Biopsies are tissue samples removed during surgery or routine medical procedures then processed for microscopic analysis in a pathology laboratory.

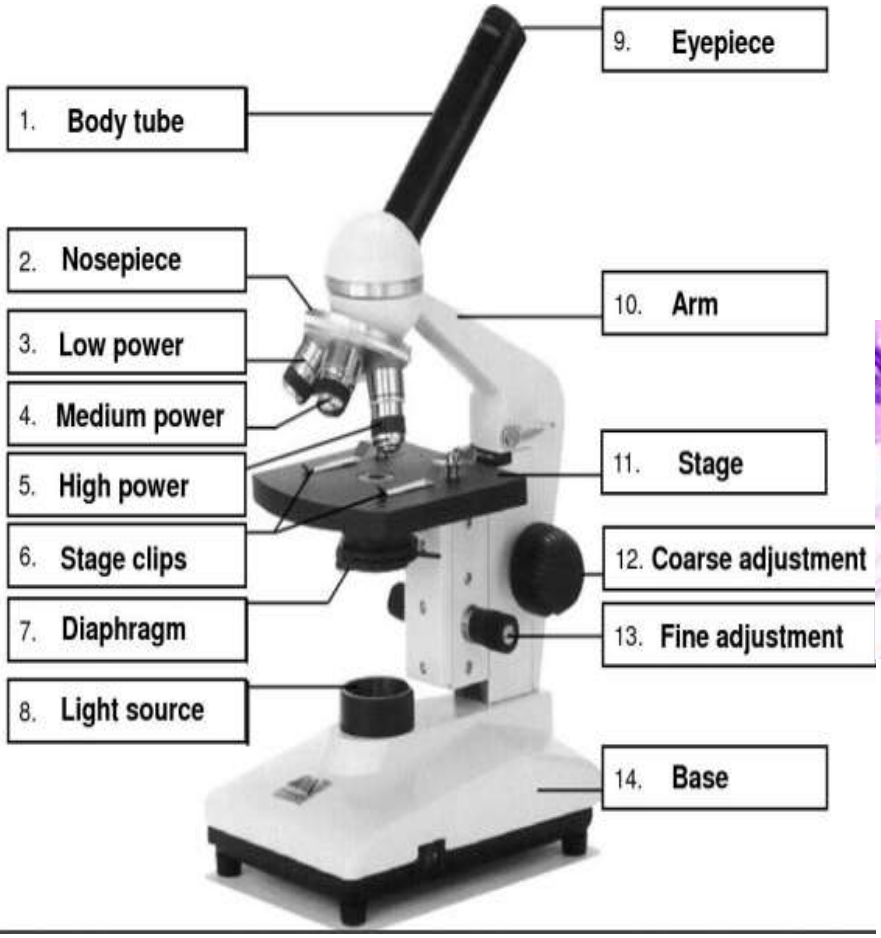
N.B: sometimes intra-operative consultation and immediate pathological reports (especially in tumor surgery) might be needed for rapid decision (takes only minutes) during the surgery, so a much more rapid processing method (**freezing technique)** is used. In freezing technique, biopsy is rapidly frozen in liquid nitrogen then sectioned using a cryostat.

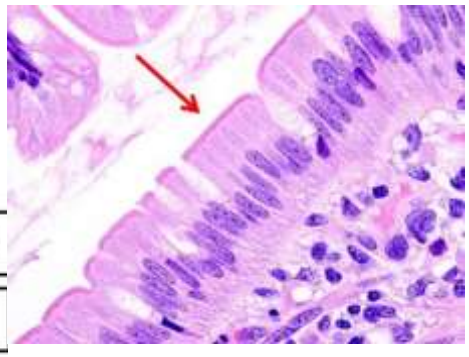
Types of microscopes

Light microscopes:

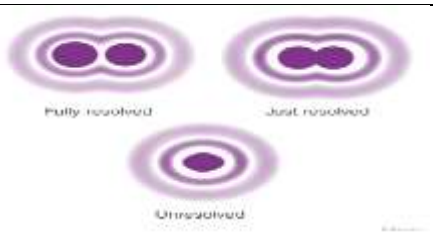
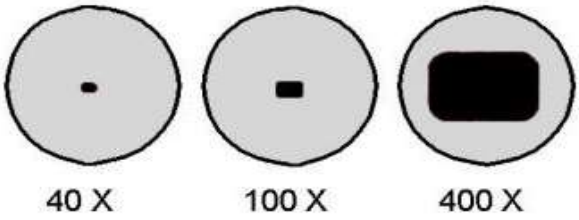
- ***Bright-Field microscope:***

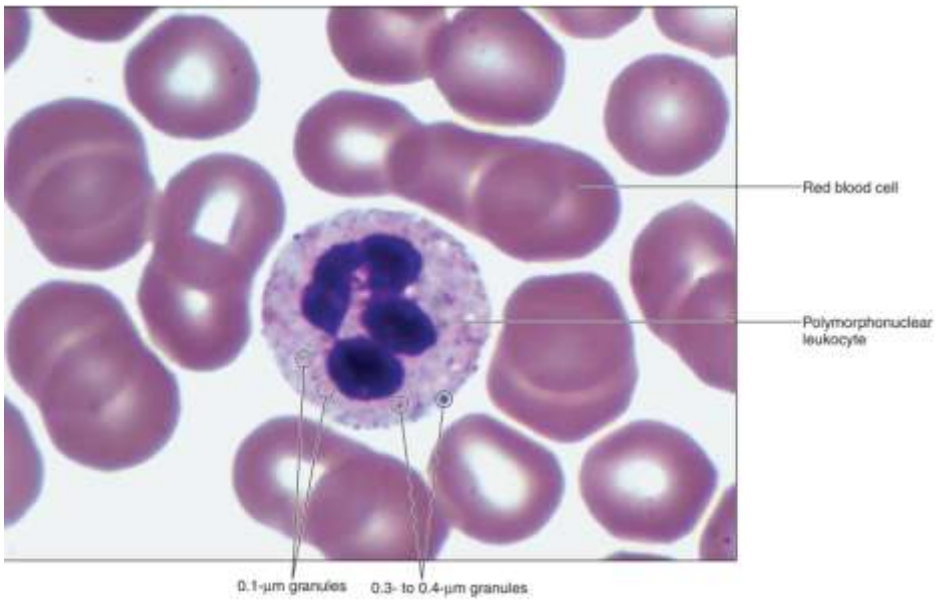
It is the most common and widely used microscope in histology.





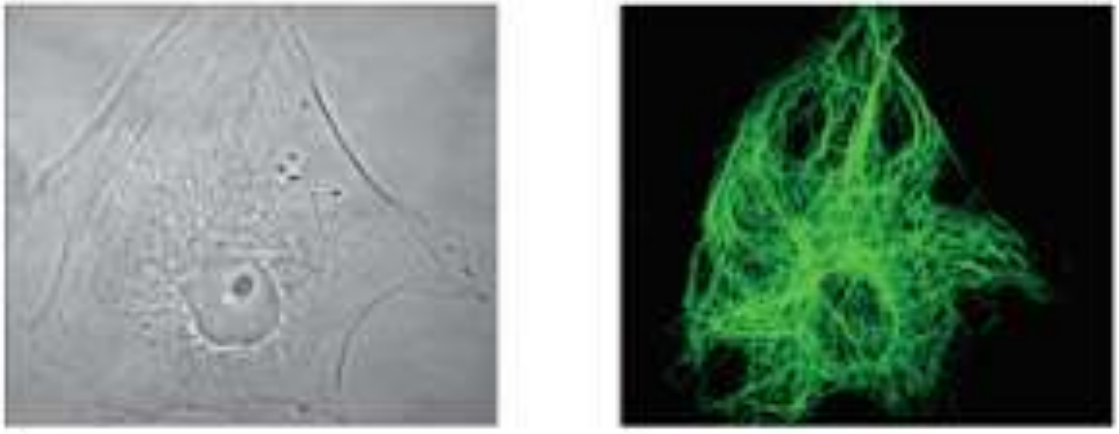
Resolution and magnification

Resolving power	Magnification power
• The ability of microscope to show two points very close to each other as two separate points.	• The ability of microscope to magnify objects. • Magnification power = Power of ocular x objective lens
	
• For light microscope is 0.2 µm. • For electron microscope is 0.2 nm	• For light microscope: nearly 1500-2000 • For electron microscope: nearly 500000



White blood cell from the peripheral circulation (1600×). This micrograph illustrates the limit of resolution of the light microscope.

- ***Fluorescence microscope:*** tissues are stained using a fluorescent dye then examined with the immunofluorescence microscope in the dark.
- ***Phase-Contrast Microscope:*** this microscopy is a technique most commonly used to examine living, unstained cells growing in laboratory tissue culture plates.



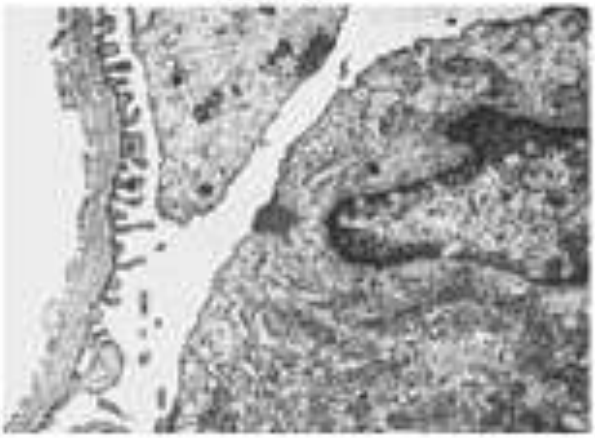
A B

A Phase-contrast image of an epithelial cell from a rat kangaroo grown in tissue culture. **B,** The same cell as seen in an immunofluorescence microscope after the cell was stained with an antibody to the intermediate filament protein vimentin.

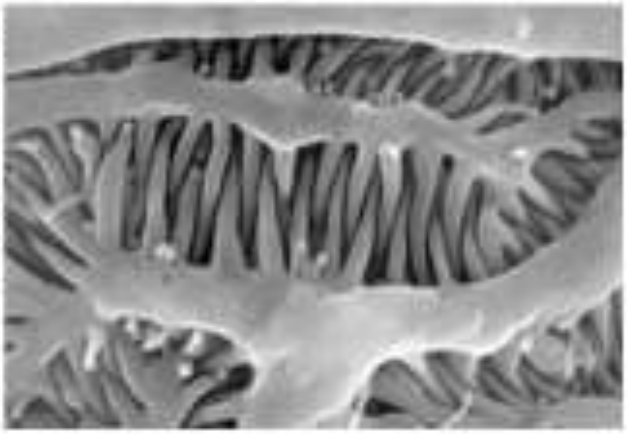
Electron microscopes:

Transmission and scanning electron microscopes are based on the interaction of tissue components with beams of electrons. The wavelength in an electron beam is much shorter than that of light, allowing a 1000-fold increase in resolution.

Transmission electron microscope (TEM)

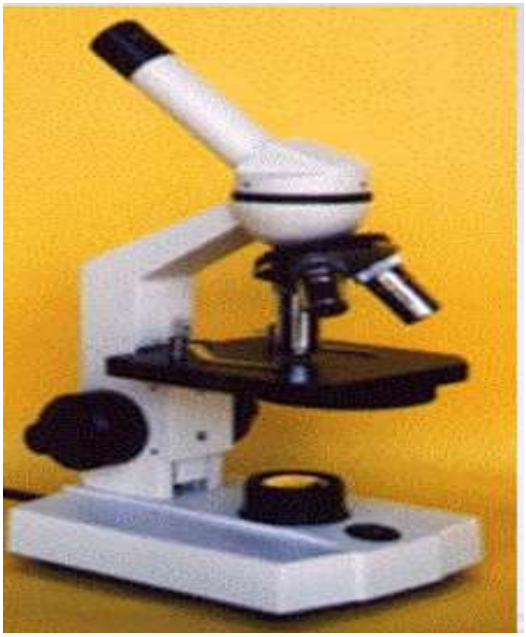


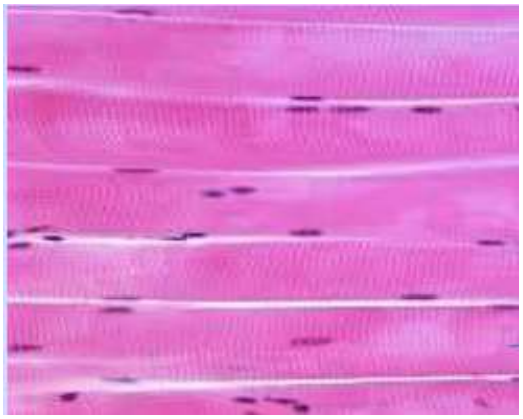
Scanning electron microscope (SEM)



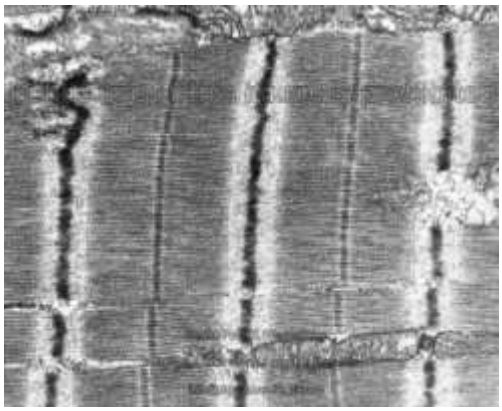
Comparison between light and electron microscopes

Light microscope (compound)	Electron microscope
Small	Large and non-portable
Relatively inexpensive	Expensive
Does not need a lot of training	Training is required
Colored image	Black and white image
Specimen can be alive and unharmed	Specimen must be dead
Lower resolving power	Greater resolving power
Lower magnification	Greater magnification





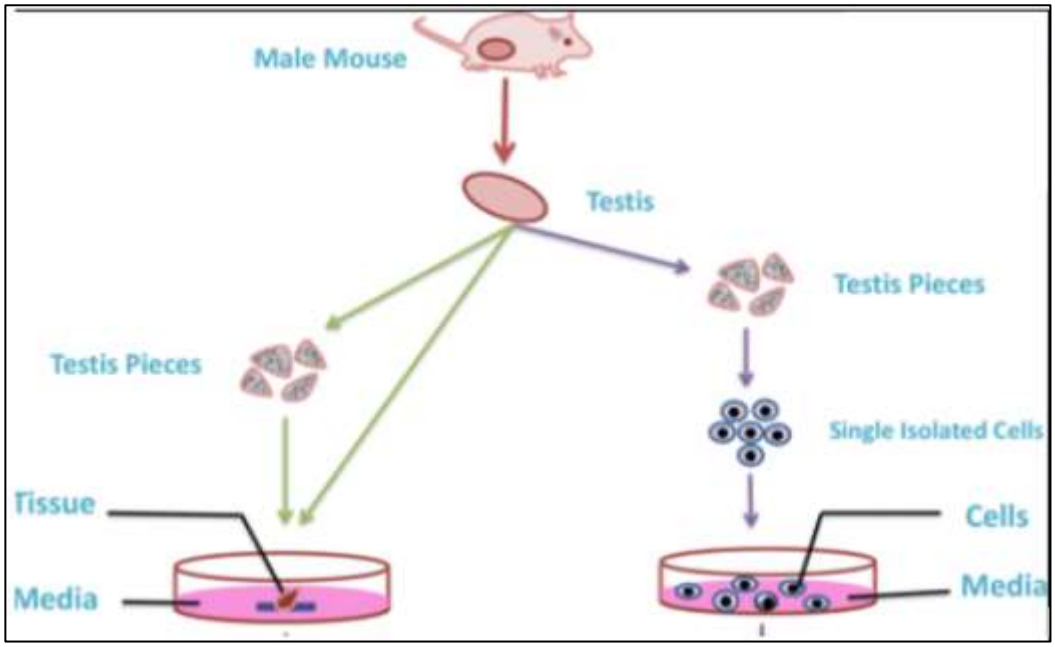
Skeletal muscle by light microscopy



Skeletal muscle by electron microscopy

Cell & tissue culture:

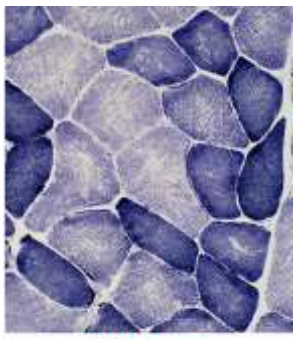
- Cell culture refers to the removal of cells from an animal and their subsequent growth in a favorable artificial environment (in vitro).
- Cell culture allows the direct observation of cellular behavior under a phase-contrast microscope.
- It is essential for many experiments which are technically impossible to be performed in intact animals.



Medical application:

- ***Cell biology:*** cell culture supplies biologists with different cells for different experiments.
- ***Karyotyping*** (will be discussed later).
- ***Cancer research*** for novel chemotherapeutic drug screening or interactions between cancer cells and the immune system.
- ***Virology*** for virological studies and vaccine production which requires the culture of infected cells to obtain virus proteins.
- ***Regenerative medicine*** through using of cultured stem cells, tissues or organ to replace damaged cells and tissues in patients suffering from organ failure.
- ***Manufacturing of biopharmaceuticals*** as the production of antibiotics or therapeutic hormone formulations (e g. to treat growth hormone deficiency in children).

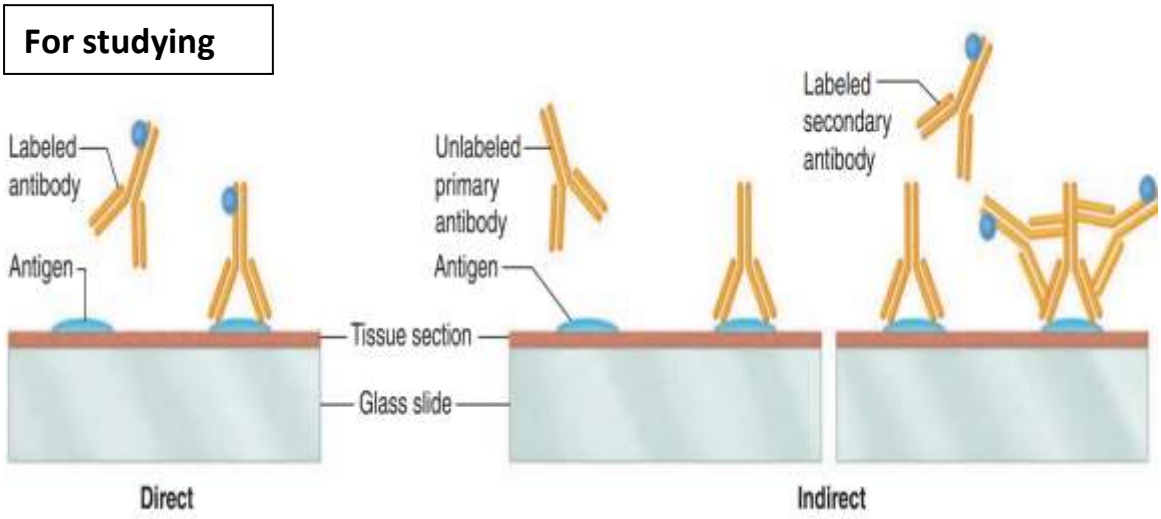
Enzyme histochemistry (cytochemistry): it is a method for localizing cellular structures using a specific enzymatic activity present in those structures. To preserve the endogenous enzymes, histochemical procedures usually use unfixed or mildly fixed tissue, which is sectioned on a cryostat to avoid adverse effects of heat and organic solvents which are commonly used in paraffin technique.



SDH enzyme

Immunohistochemistry: labeled antibodies are routinely used in immunohistochemistry to identify and localize many specific proteins, not just those with enzymatic activity that can be demonstrated by histochemistry**.**

For studying

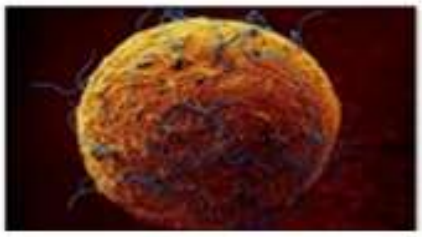


The cell

The structural and functional unit of all living tissues.

Size: In human there is wide variation cell size. Smallest cell is sperm cell, largest cell is ovum and longest is nerve cell.

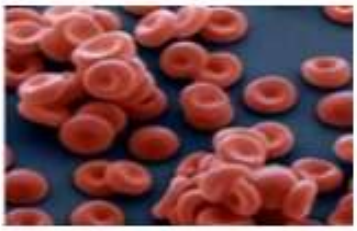
Smallest cell
Sperm cell
Size: 5 µm



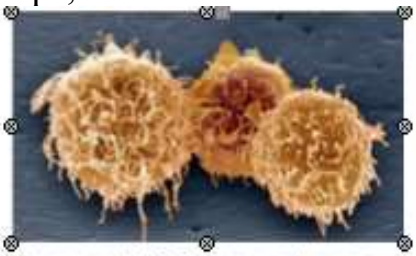
Largest cell
Ovum cell
Size: 120 µm

Longest cell
Nerve cell
Size: 1 m

Shape: Varies according to the function of cells as in RBCs which is circular biconcave, WBCs changeable shape, and nerve cell which is branched



Human RBCs are circular biconcave for easy passage through human capillaries.



Human WBCs can change their shape to engulf the microorganisms that enter the body.

Nerve cells are branched to conduct impulses from one point to another.

Structure of the cell

Organization of the cell:

1. Cytoplasm: Everything inside a cell between the plasma membrane and the nucleus; consists of cytosol, organelles and inclusions.

2. Nucleus: The genetic control center of a eukaryotic cell

- **Cytosol:** Jelly-like substance composed of mainly water and found between the cell membrane and nucleus. The cytoplasm makes up most of the "body" of a cell and is constantly steaming.
- **Organelles:**
  1. ***Membranous organelles:*** Cell membrane, Mitochondria, Endoplasmic Reticulum, Golgi apparatus, Lysosome, Peroxisome and Vesicle.

  2. ***Non membranous organelles:*** Ribosomes, centrioles and cytoskeleton.

- **Inclusions:** Non-essential for vitality of the cells.

Structure of the cell

Cytoplasm

Organelles
(Essential-for cell vitality)

A. Membranous

1. Cell membrane
2. Mitochondria
3. Endoplasmic reticulum
4. Golgi apparatus
5. Lysosomes
6. Peroxisomes
7. Coated vesicles

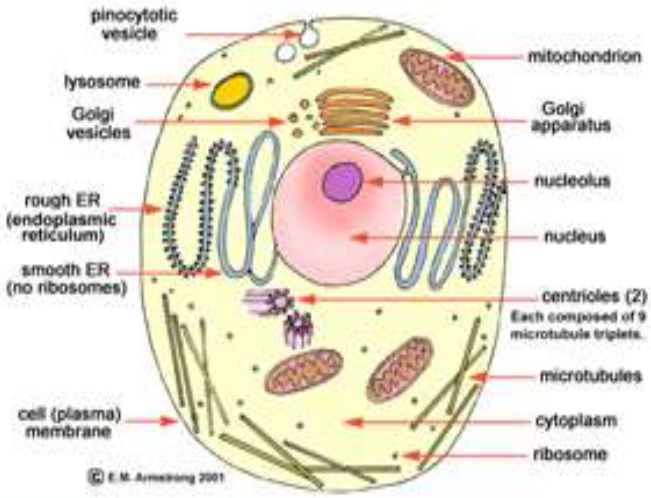
B. **Non-Membranous**

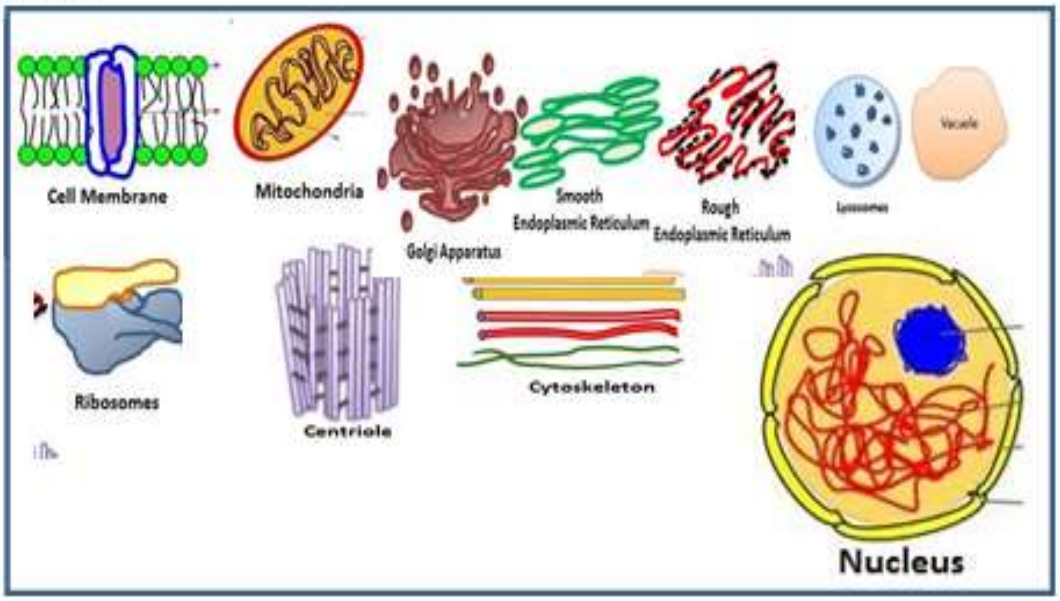
1. Ribosomes
2. Microtubules
3. Filaments

Nucleus

Inclusions
(Not essential-for cell vitality)

A. Stored food
B. Pigments
C. Crystals





Membranous Organelles

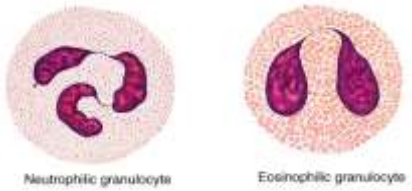
ILOS (intended learning outcomes):
By end of this chapter students should be able to:-

- Define cell organelles and classify them.
- Describe the structure of cellular organelles by the light and electron microscope.
- Correlate the structure of each organelle to its function.
- Define the integration between cell organelles in performing cellular activities
- Demonstrate the clinical correlations of different cell organelles

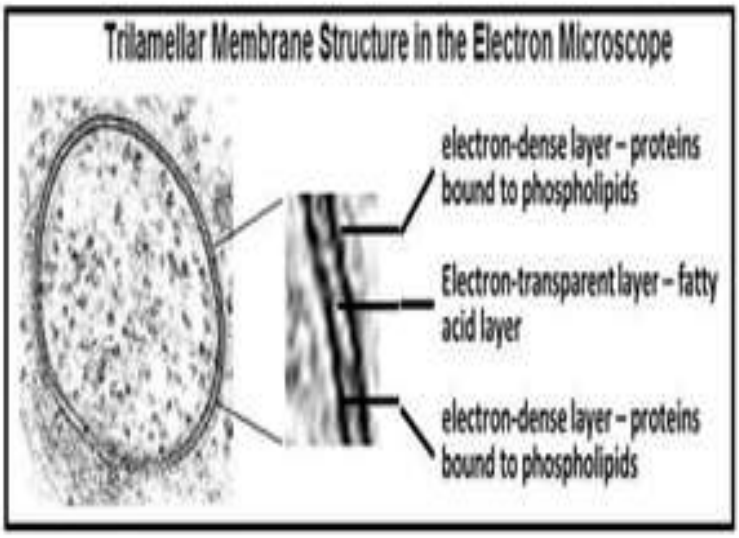
1. Cell membrane

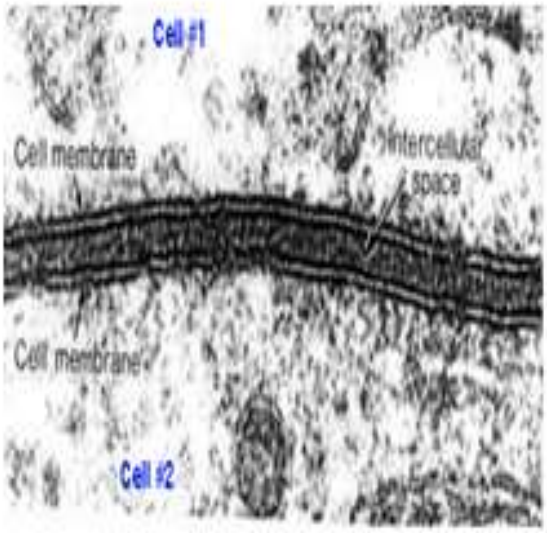
Definition: A living membrane forming the outermost cover of the cytoplasm (plasma membrane). It surrounds the membranous organelles (Unit membranes)

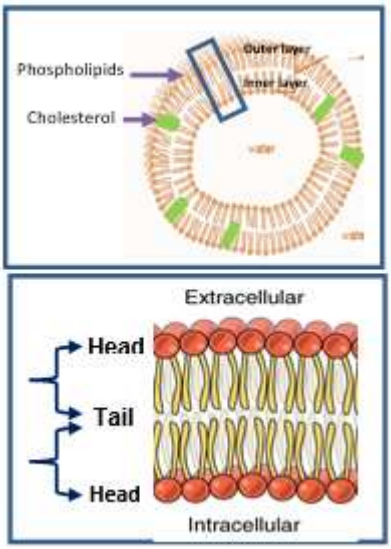
Structure:
LM: Cannot be seen by H&E because it is very thin (5-10 nm)



EM: Cell membrane is 5-10 nm thick. It appears as two densely stained layers separated by a lighter zone, thus creating a trilaminar appearance.







Biochemical structure: Cell membranes are made up of:

1. Lipids (30%):

A. Phospholipids: are the main constituents of cell membranes. Each phospholipid molecule consists of:

- *The head end:* Enlarged end in which the **phosphate** portion is located. **Polar hydrophilic** (soluble in water) end directed **peripherally** forming the dark staining parts of the membrane seen by EM.
- *The tail end:* Two thin tails. **Non-polar, hydrophobic,** directed to the center forming the light staining intermediate zone.

Phospholipids arrangement in the cell membrane explains the Trilamellar EM structure

B. Cholesterol provides stability to the membrane.

2. Proteins (60%):

A. Integral (intrinsic-transmembrane) proteins: Occupy the entire thickness of the membrane and may project out of both surfaces. Act as channels through which ions pass. Act as receptor enzymes

B. Peripheral (extrinsic) proteins: Present on both surface of the cell. Attached to integral proteins or phospholipid layer. Usually associated with cytoskeleton, so maintain cell shape. Have a role in transport.

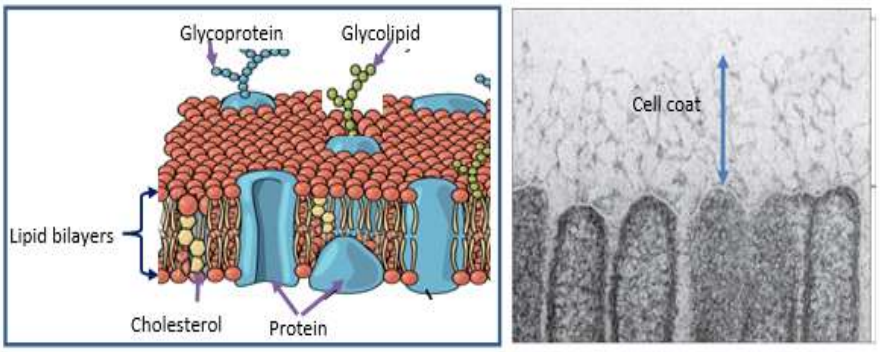
C. Carbohydrates (10%): Present at the external surface of the membrane.

A. **Glycoproteins:** Carbohydrate molecules are attached the proteins.

B. G**lycolipids**: Carbohydrate molecules attached to phospholipid.

Cell coat (glycocalyx)

Formed by glycoproteins and glycolipids on the external surface of cell membrane.

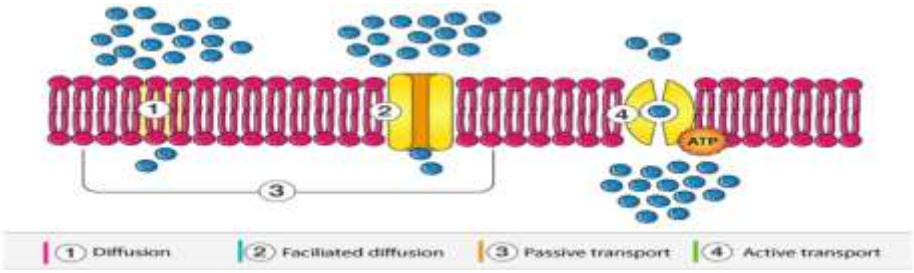


Functions of cell coat:

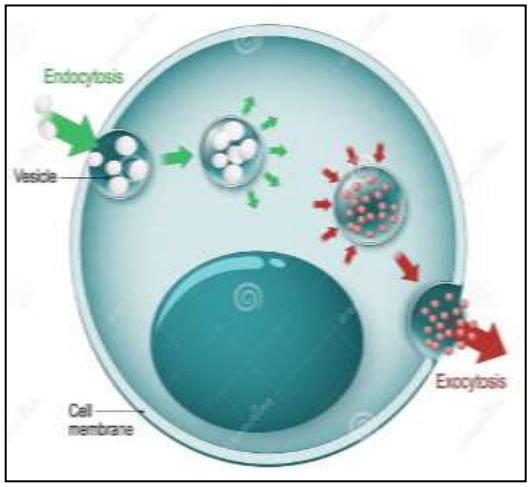
1. Protection of the cell.
2. It contains special adhesion molecules which enable the cell to adhere to specific types of cells, or to specific extracellular molecules.
3. It contains antigens. As in erythrocytes, the glycocalyx contains blood group antigens.
4. Most molecules in the glycocalyx are negatively charged causing adjoining cells to repel one another. This force of repulsion maintains the 20 nm interval between cells.

Function of cell membrane:

1. **Passive Transport**
   - *A. Simple Diffusion:* water, oxygen and other molecules move down a concentration gradient (from high to low concentration).
   - *B. Facilitation Diffusion:* assisted by proteins (channel or carrier)
   - *C. Osmosis*: Diffusion of water against concentration gradient, from low concentration solution to high concentration solution.
2. **Active Transport:** occurs against concentration gradient. Requires energy (ATP): *Sodium-Potassium Pump***:** pumps out 3 sodium ions for every 2 potassium taken in against gradient



3. **Bulk transport:**
   - *A. Endocytosis***:** taking substances into the cell. The cell membrane surrounds the molecule, invaginates and then separates to form an endocytic vesicle, includes:
   - **Pinocytosis** engulfment of water.
   - **Phagocytosis** engulfment of solids particles.
   - *B. Exocytosis:* pushing substances out of the cell, such as removal of waste produced within the cytoplasm. Membrane enclosed vesicles approach the cell membrane and fuse with its internal surface. The vesicle ruptures releasing molecule to the exterior.



4. **Support the cell and help maintain its shape.**

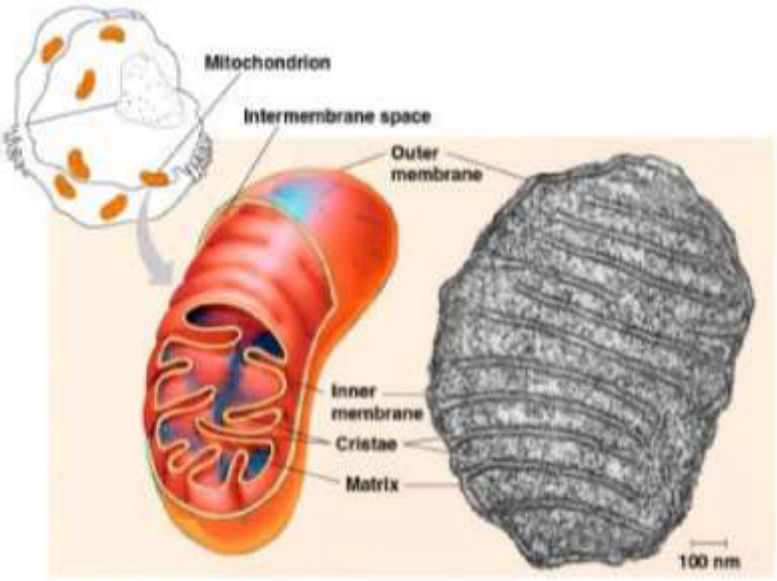
2. Mitochondria
(Powerhouse of the cell)

Definition: membranous organelle, concerned with energy production. Their number varies from one thousand in liver cells (active) to few mitochondria in fat cells (inactive).
LM: Cannot be seen by H&E. Visualized by special stains e.g. iron hematoxylin.
EM: Two membranes and two spaces

A. Two membranes

1. Outer smooth membrane.

2. Inner membrane: Folded into **cristae** to increase surface area. Cristae show **elementary particles**, which carry respiratory enzymes responsible for energy production.



B. Two Spaces

1. Outer (Intermembrane) space:
Narrow space between the inner and outer membrane

2. Inner space (Inter-cristae, matrix space): The interior of the mitochondria is filled with a matrix rich in protein and contains lipids, RNA, circular DNA, ribosomes, enzymes and dense granules rich in Ca2+.

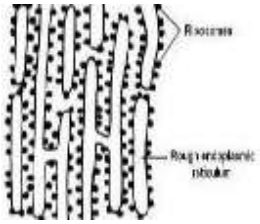
N.B: New mitochondria originate from preexisting mitochondria by growth and subsequent division (**binary fission)** of the organelle itself.

Functions:
1. Providing the cell by energy by generation of ATP.
2. Maintain calcium levels of the cell.
3. Play important role in process of **apoptosis (program cell death).**

Clinical application

Mitochondrial Disease:
Mitochondrial dysfunction reduces energy production by the mitochondria. Mitochondrial disease causes damage to the cells of brain, heart, liver, muscles and kidney. Symptoms include muscle weakness, loss of motor control, and pain. Other symptoms gastro-intestinal disorders, poor growth, cardiac disease and liver disease.

A. Rough Endoplasmic Reticulum (RER)

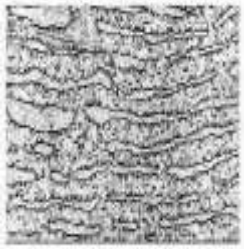


Definition:
RER is a series of connected parallel flattened tubules with ribosomes attached to its surface.

Site: Increases near the nucleus and the Golgi apparatus.

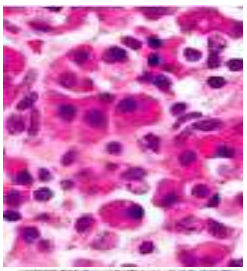
LM: By H&E, RER if increased in the cell shows cytoplasmic basophilia due to the presence of ribosomes

EM: connected parallel flattened tubules (cisternae) with ribosomes on the surface.



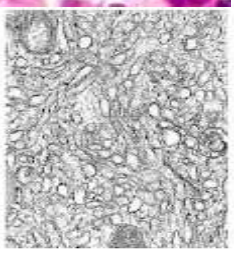
Functions:
1. Proteins synthesis
2. Lysosomal enzymes synthesis and origin of lysosomes

B. Smooth Endoplasmic Reticulum (SER)



Definition: Branching anastomosing smooth tubules. In muscle SER is well-developed specialized and called **Sarcoplasmic Reticulum**.

LM: By H&E, if increased in the cell shows cytoplasmic acidophilia.

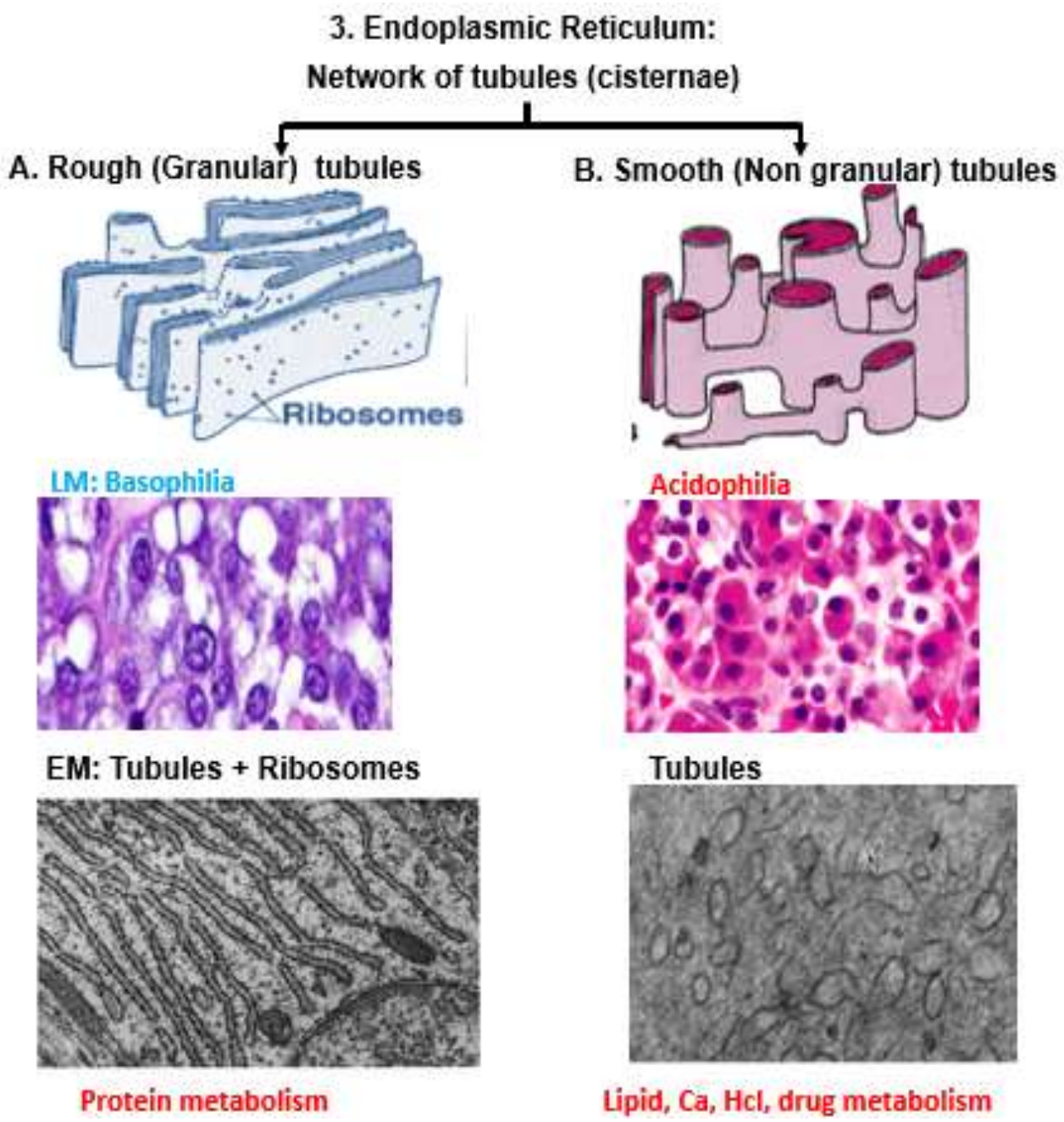


EM: Branching anastomosing tubules or flattened vesicles with no ribosomes on the surface.

Functions:
1. **Lipid synthesis:** In the steroid-secreting cells as in adrenal cortex. SER is responsible for the synthesis and repair of membranes.
2. **Glycogen metabolism**: Enzymes regulating glycogen metabolism are associated with SER membrane e.g. in liver cells.
3. **Regulation of mineral metabolism** e.g. HCL production in the stomach.
4. **Calcium storage:** in the skeletal and cardiac muscle fibers to control muscle contraction.
5. **Drug detoxification:** Due to the presence cytochrome P450 enzyme in the SER membrane especially in the liver cells.

Medical application:

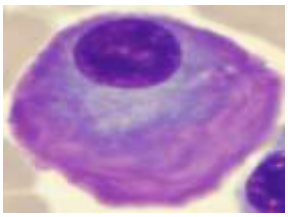
Underdeveloped SER in liver cells in **newborn infants causes jaundice**. **Jaundice** is caused by accumulation of bilirubin which is normally metabolized by **SER enzymes** in liver cells and excreted as bile**.**



4. Golgi complex (Apparatus)

Definition:
Responsible for packing and sorting macromolecules such as proteins and lipids.

LM:
Cannot be seen by H &E. In cell with deeply basophilic cytoplasm of the protein secreting cells as plasma cell, its position appears as non-stained area called Negative Golgi Image**.**
It can be visualized only by using special stains.

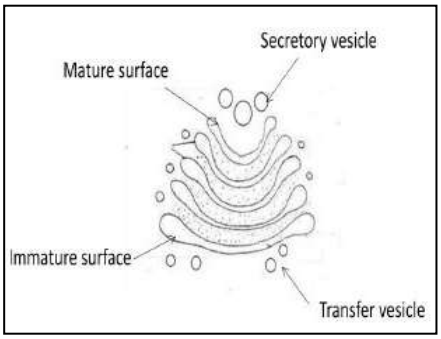


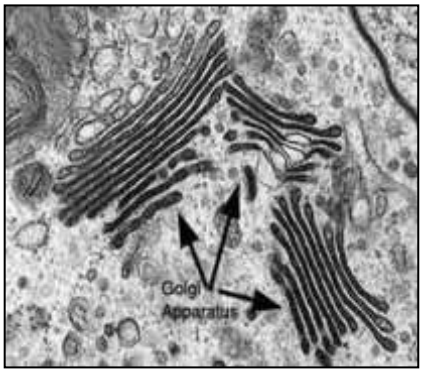
EM: Golgi complex is formed of:

1. **Golgi stack:** Formed of 3-6 flattened sacs called cisternae. Each stack has a convex immature surface facing the nucleus called (Cis Face) and a concave mature surface towards the cell membrane called (Trans Face).

2. **Transfer (microvesicles):** Derived from rough endoplasmic reticulum and fuse with the convex surface.

3. **Secretory (macrovesicles)**: Formed by budding from mature Golgi surface. Exocytosed out-side the cell or remain inside as lysosomes.





Functions:

1. Protein modification by the adding of carbohydrates and phosphate to proteins.

2. Lysosomes formation, share with RER.

3. Maintaining and renewal cell membrane and cell coat through exocytosis.

5. Lysosomes

Definition:
Membrane bound vesicles containing hydrolytic enzymes increase in cells with phagocytic activity such as macrophage.

LM:Can not seen by H&E. Can be detected by immunohistochemical techniques.

EM:

1. **Primary lysosomes** appear spherical homogenous electron-dense vesicles.
2. **Secondary lysosomes** appear spherical heterogeneous electron-dense vesicles as they contain digested elements.

Formation of lysosomes:

- Lysosomal enzymes are synthesized and segregated in the **RER**.
- Then they transferred to the Golgi complex as **transfer vesicles.**
- In the Golgi complex enzymes are modified and packed as **lysosomes**.

Types of lysosomes:

1) Primary Lysosome:

Lysosomes that have not entered into a digestive process appear as homogenous vesicle.

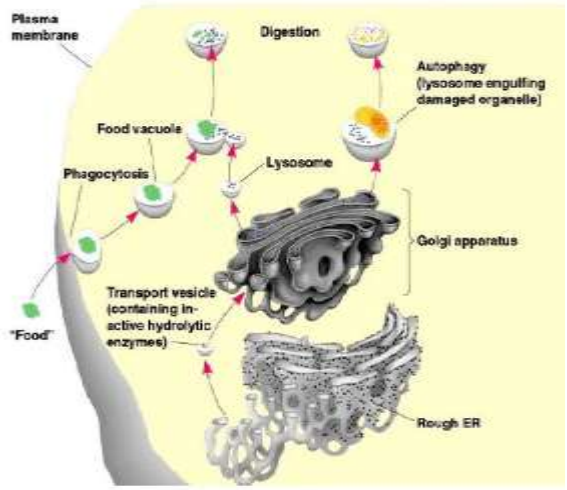
2) Secondary Lysosomes:

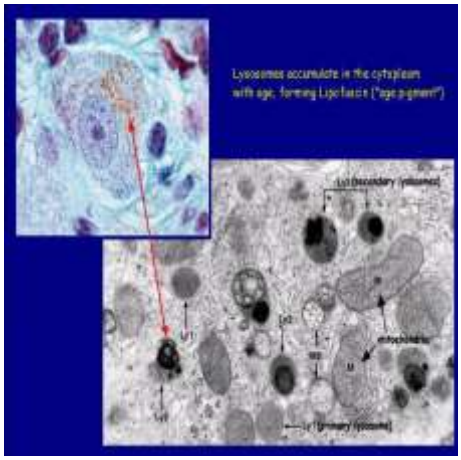
Lysosomes that have entered into a digestive process include three subtypes.

a) Heterophagosome, lysosome fuses with endocytosed **solid Particles** (phagosome)

b) Multivesicular body, lysosome fuses with endocytosed **fluid droplets** (pinocytotic vesicle).

c) Autophagosome, lysosome fuses with **autophagic vacuoles** containing bits of the own cellular membranes.





Fate of the digested material:

1. Digested nutrients: diffuse back to the cytoplasm for cellular reuse.
2. Indigestible compounds: **Residual bodies** extruded outside by exocytosis.

N.B: In some long-lived cells (e.g. neurons, heart muscle), large quantities of residual bodies accumulate and are referred to **as lipofuscin, or age pigment.**

Functions of lysosome: Digestion

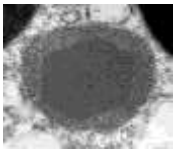
1. **Digestion** of **material** engulfed from **outside the cell** example bacteria.
2. **Digestion** of **material** from **inside the cell** such as old mitochondria. Keep cell healthy
3. **Digestion** of **completely breakdown cells** that have died (**autolysis).**
4. **Release enzymes** outside to destroy material around the cell such as in osteoclast.

Lysosomal storage disorders: In these diseases, a specific **lysosomal enzyme** is absent or inactive, and certain molecules as glycogen are not digested. As a result, these substances accumulate in the cells, interfering with their normal functions

6. Peroxisomes (Microbodies)

Definition:

Small membrane-bound organelles contain **oxidative enzymes**.



Functions:

1. Peroxisomes oxidize specific organic substrates producing **hydrogen peroxide (H2O2)** that is very damaging to the cell. H2O2 is eliminated by the enzyme catalase, which is present in peroxisomes
2. Catalase degrades several toxic molecules and drugs, particularly in liver and kidney
3. Peroxisomes contain enzymes involved in **lipid metabolism**.

7 . Secretory Granules

They are originally granules derived from RER and containing secretory proteins. These are transported to the immature face of Golgi stack, then to the mature face to bud off from them as secretory granules. These granules migrate to the apical pole of the secretory cells to exocytosis**.**

LM: They appear as an apical acidophilic area.

EM: Membrane-bound electron dense granules in the apical pole of secretory cells.

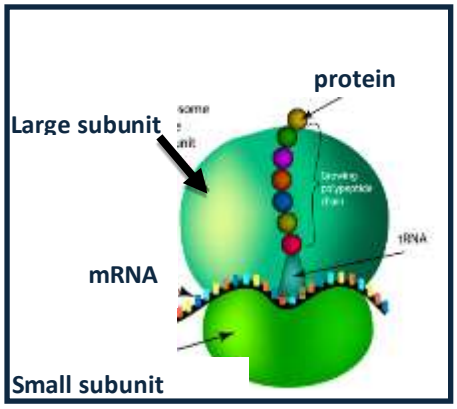
Functions:

Addition of new cell membrane to replace the apical membranes lost in the process of endocytosis.

B. Non-Membranous Cell Organelles

The organelles that have no membranes
They include:

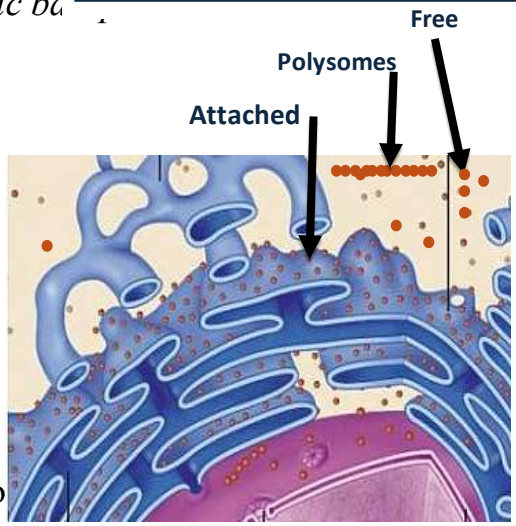
1. **Ribosomes.**
2. **Filaments**
3. **Microtubules**



1. Ribosomes

Definition: Non-membranous, site of protein synthesis
Origin: Formed in the nucleolus and pass to the cytoplasm
Number: More in protein synthesizing cells
LM: Not seen by H&E *but* when abundant shows *cytoplasmic ba*

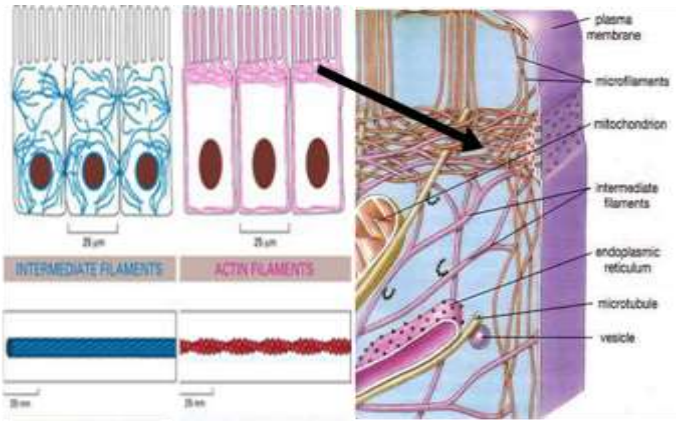
EM: 2 subunits a small and a large unites.
Types of ribosomes:
1. **Free**: scattered diffusely & singly
2.**Polysomes**: linked together by a strand of mRNA
3. **Attached**: bind to the outer surface of rER



Function of ribosomes: Protein synthesis:

- Free ribosomes: Form proteins for local use in the cell
- Attached ribosomes: Form proteins for export by secretio

2. Filaments



A. Thick (myosin**)**: in muscle fibre

B Thin (Microfilaments-actin**)**: in muscle fibre

Actin filaments, they are thin thread like structures about 6-7 nm in diameter and of variable length, they are present in muscle cells.

Functions of microfilaments:

- They are supportive elements in cells.
- Responsible for muscle contraction.
- Movement of some cells (amoeboid movement).

- **B. Intermediate:** Long unbranched filaments, their average diameter **10 nm**.

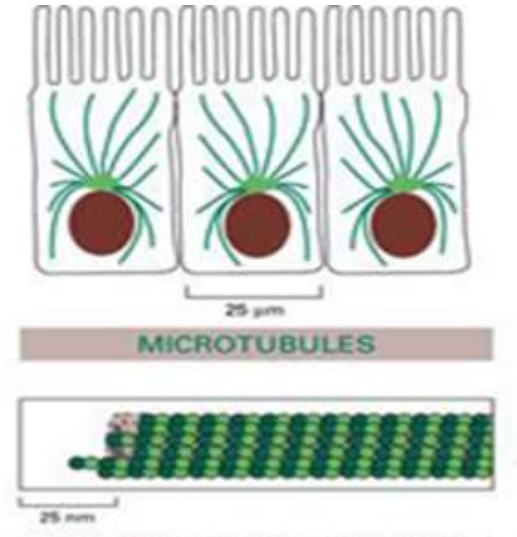
They are of different subtypes:

- Keratin, in epidermis of the skin.
- Vimentin, in fibroblasts.
- Desmin, in smooth muscle.

N.B Diameter of intermediate filament is intermediate between actin thin filaments and myosin thick filaments.

NB: Cytoskeleton of the cell includes microtubules, intermediate and thin filaments

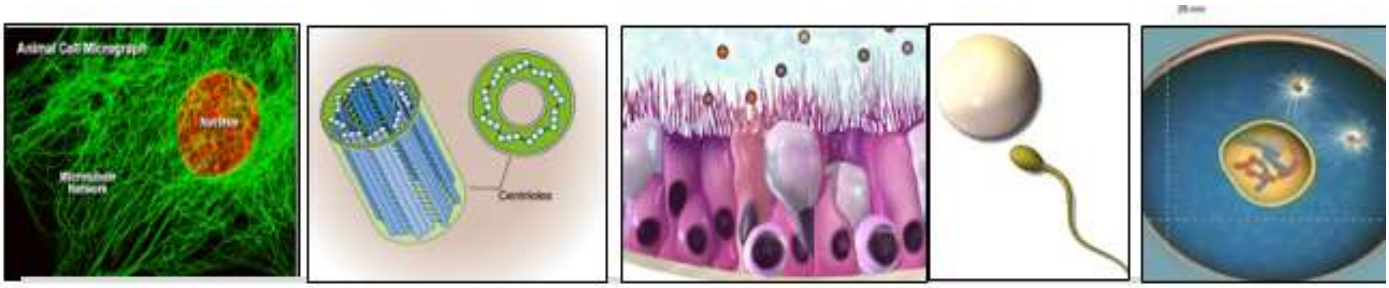
2. Microtubules



Hollow, cylindrical tubules, about 25nm in diameter with variable length.

Function:

1. Form the cytoskeleton of the cell.
2. Form centrioles
3. Form cilia and flagellum.
4. Form mitotic spindle during mitosis to guide movement of chromosomes.



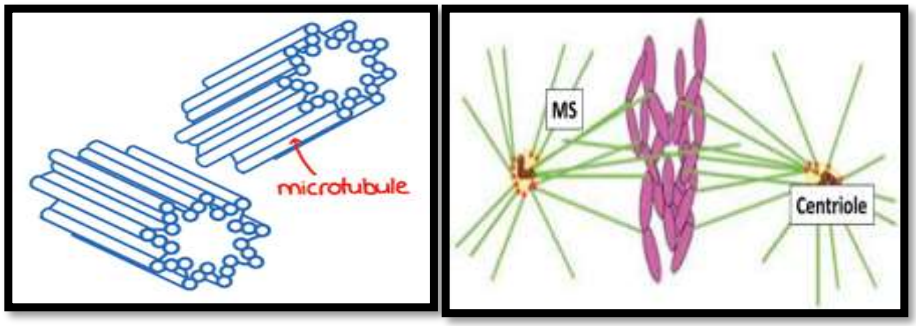
Cytoskelton *Centriole* *Cilia* *Flagella* *Mitotic spindle*

Centriole: A pair of cylindrical rods oriented at a right angel to each other near nucleus. Seen in the cells that can divide.

Each centriole consists of **9 bundles** of microtubules.

Each bundle is called triplets as it is composed of 3 microtubules.

Functions of centrioles: during cell division, centrioles duplicate and each pair move to the opposite poles of the cell forming the microtubule organizing center (MTOC) and the mitotic spindle.



Cytoplasmic inclusions

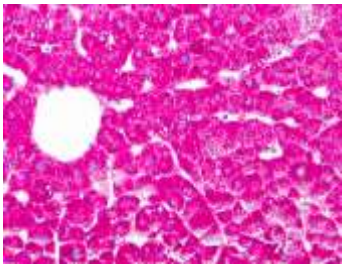
Definition: Non-living temporary cytoplasmic component resulting from cell activities.

Organelles	Inclusions
Metabolically active	Inert
Permanent	Temporary
Essential	non-essential for vitality
Like body organs	Storage food
e.g. mitochondria	e.g. glycogen

Types of inclusions are:

A. Stored food e.g. carbohydrates and lipids

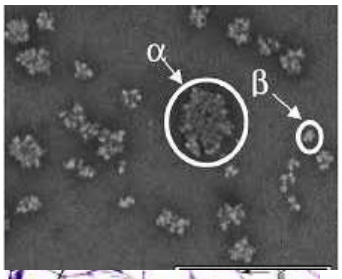
B. Colored pigments
C. Crystals



A. <u>Stored food:</u>

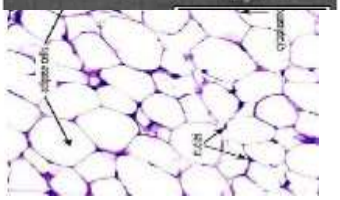
1. **Carbohydrates:** are stored in cells in the form of glycogen for energy reserve, especially in liver and muscle cells.

LM: Glycogen can be stained by PAS or Best's carmine method.



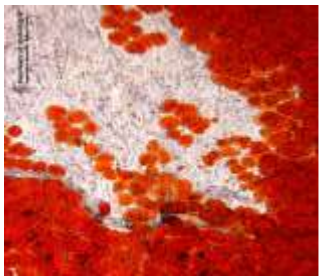
EM: Glycogen particles appeared as electron dense particles.

Clinical application:
Glycogen storage disorders: The inability to degrade glycogen leads to the accumulation of glycogen in the cells.

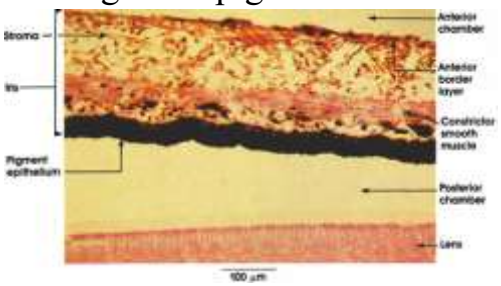


2. **Lipids: are stored in fat cells.**

LM: H & E stain adipocytes (fat cells) appears like a signet ring appearance. contains a large lipid globule and cytoplasm is rim with the nucleus pushed out to the periphery. Can be *visualized using special stains such as Sudan III, Sudan black, and osmium tetroxide.*



B. <u>Pigments:</u>
Results in coloration of tissues. It may be induced by endogenous or exogenous pigment.



❖ **Endogenous:** are formed by cells and include:

1. ***Hemoglobin*:** the most important pigment in the body, Formed in RBCs.
2. ***Melanin*:** causes coloration of skin, hair, and iris. Formed by melanocytes.
3. ***Lipofuscin***: accumulated as residual bodies in cells of nerve, heart, and liver.

❖ **Exogenous:** Reaches the cell from outside, include:

1. ***Carotene***: in vegetables such as orange pigment of carrots and this can color fats in cells as it is lipid soluble.

2. ***Carbon* particles:** present in tobacco smoke, can reach lung tissue in heavy smokers where it was phagocytosed by dust cells.
3. ***Tattoo* marks:** when vital stains (i.e., trypan blue) introduced by special needles into the skin they produce permanent coloration.

C-Crystals:

- Crystals resulting from protein metabolism. May accumulate in the cell in high concentrations e.g. uric acid crystals in gout disease
- Clinical application: Gout is a kind of arthritis caused by deposition of uric acid crystals in the joints. This leads to attacks of painful arthritis, kidney stones, kidney failure.

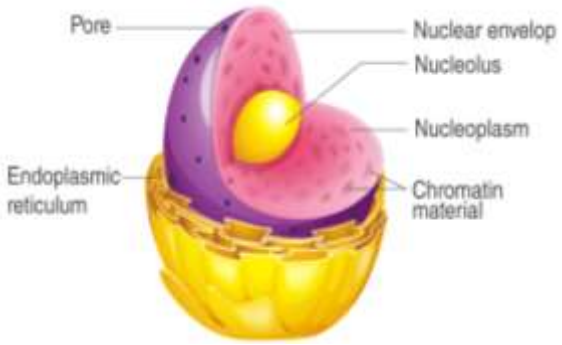
Nucleus

Definition: A membrane-bounded organelle present in eukaryotic cells.
Number: Most of eukaryotic cells have one nucleus**.** Nuclei are absent in e.g. red blood corpuscle. Some cells have two (binucleated) e.g. liver cells or more than two nuclei e.g. skeletal muscle.

Shape: Usually large rounded or oval

Site: Often near the cell's center.

Functions:
Control center of the cell
It stores the hereditary material DNA.
It is the site of DNA replication.
It is the site for synthesize and process RNAs.
It Coordinates the cell´s activities which includes growth, metabolism, protein synthesis, and reproduction (cell division).
It controls gene expression and mediates the replication of DNA during the cell cycle.



Structure:

1. **Nuclear membrane (envelop)**
2. **Nucleolus**
3. **Nucleoplasm**
4. **Chromatin** (DNA and its associated proteins)

1. Nuclear membrane (envelop)

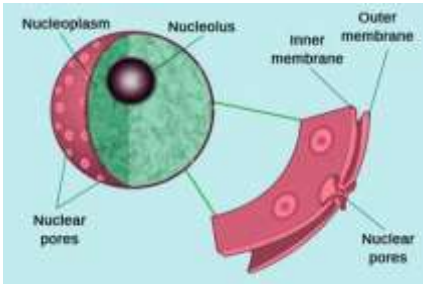
A double membrane that encloses the nucleus

Consists of 2 parallel membranes, separated by a narrow space (perinuclear space), and perforated with pores.

A. ***The outer membrane*** faces cytoplasm and is rough, continuous with RER.

B. ***The inner membrane*** is fibrillar due to its attached peripheral chromatin.

Nuclear pores:



The two nuclear membranes fuse at intervals forming openings called nuclear pores. Pores are closed by a thin diaphragm.

The diameter of the pore proper is usually about 55–70 nm.

The number of pores is 3000-4000 per nucleus depending on the cell activity.

Pores regulate the movements of macromolecules, RNAs and proteins into and out of the nucleus. Small molecules can move passively through the pores, but larger molecules move actively. This movement of molecules is known as nuclear transport.

Functions of the nuclear membrane:

Nuclear pores control molecules transport between the cytoplasm and the nucleus. RNA is selectively transported into the cytoplasm, and proteins are selectively transported into the nucleus.

2. Nucleolus

Definition:

Non membranous spherical basophilic bodies found inside the nucleus.

These are the sites at which ribosomes are assembled.

Nucleoli are most prominent in cells that are synthesizing large amounts of protein.

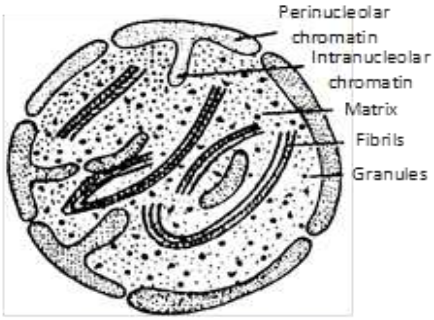
Number: Most nuclei have only one nucleolus in the nucleus, but some nuclei have multiple nucleoli.

EM:

Light area: matrix.

1. **Dark area:** consists of 3 parts:

- ***Nucleolar organizer region*** consists of DNA molecule in the center that directs rRNA formation.
- ***Pars fibrosa:*** filaments of newly formed rRNA surrounding the nucleolar organizer region.
- ***Pars granulosa:*** accumulation of newly formed ribosomal subunits.



Ultrastructure of a Nucleolus

Functions:

DNA in the center directs formation of rRNA that passes to pars fibrosa then to granulosa where then tightly packed and combine with protein forming ribonucleoprotein→ nuclear sap → nuclear pore→ cytoplasm.

The nucleolus is thought to have other roles, as it contains a number of proteins unrelated to rRNA and ribosome synthesis. It is thought to play a role in activities such as DNA damage repair, cell cycle regulation and RNA editing.

N.B. tRNA & mRNA are formed in nucleus.

2. <u>Nucleoplasm</u>

Highly viscous semiliquid that fills the empty space in the nucleus and contains fibrillary structure (nucleoskeleton) that supports nuclear membrane, pore complexes, and hold heterochromatin to inner nuclear membrane.
It acts as a media for movement of mRNA, tRNA and rRNA toward nuclear pores.

3. <u>Chromatin:</u>

Chromatin is a complex formed of DNA, RNA and proteins forming the genome.
In eukaryotic chromosome; DNA : Histone ratio is roughly 1:1. Chromatin basic structure is essentially the same in nearly all eukaryotes. Its fundamental role is to package the genome in a compact to fit inside the nucleus.

LM: appear as basophilic granules and threads.

EM: There are two types:

A. **Euchromatin**: less compact, lightly stained, contain genes that are frequently expressed by the cell and more prominent in active cells e.g. protein forming cells.

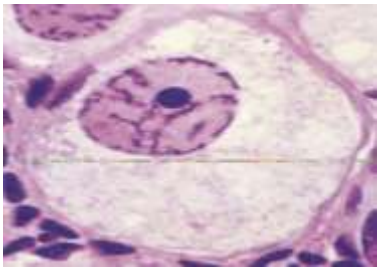
B. Heterochromatin: more compact form, darkly stained contains DNA that is infrequently expressed prominent in inactive cells e.g. lymphocytes.

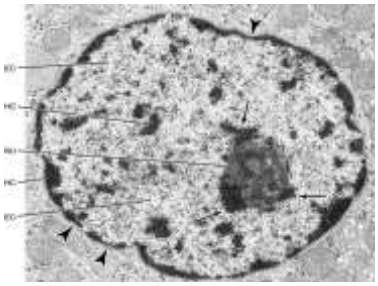
Types of heterochromatin

1. ***Peripheral***:
   Present on the inner surface of nuclear membrane.
2. ***Nucleolus associated chromatin***(NAC)
3. ***Chromatin Island:*** present between nucleolus and nuclear membrane.

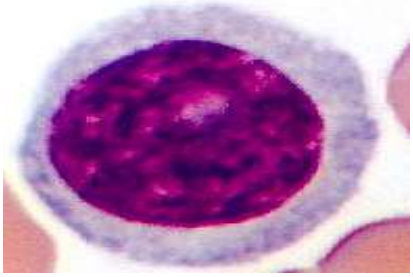
NB: The LM and EM of the nucleus varies from cell to cell depending on the cell activity and on the predominant type of chromatin.

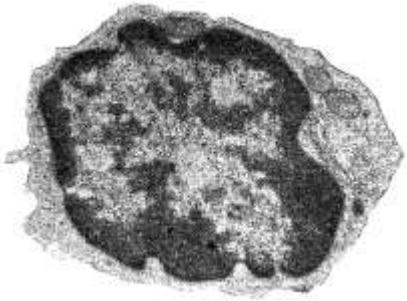
Active cell
Increase euchromatin.
LM: Pale nucleus
EM: Euchromatic





Inactive cell
Increase heterochromatin.
LM: Dark nucleus
EM: Heterochromatic





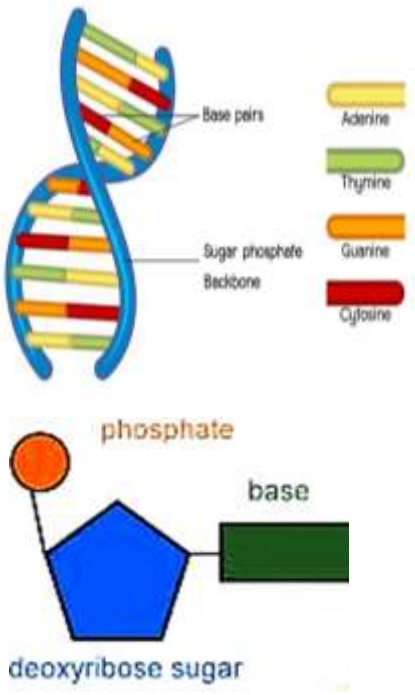
Functions of chromatin:

1. Stores genetic information.
2. Direct formation of protein inside the cell by formation of the 3 types of RNA.

Nucleic acids

1. DNA

DNA molecule is formed of a large number of chemical compounds called nucleotides, linked together in a very long chain.



These chains are arranged like a ladder, twisted into the shape of a winding staircase, called a double helix.

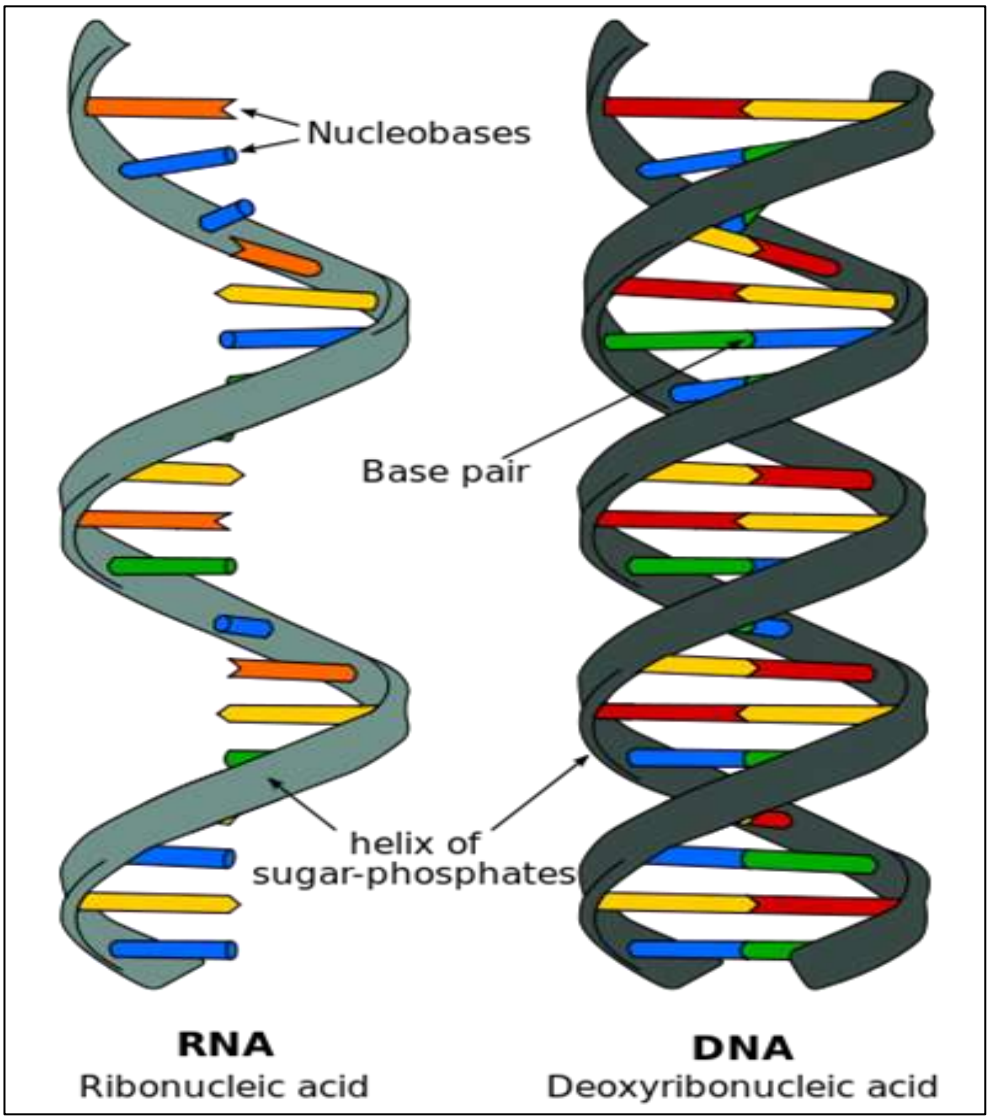
Each nucleotide is formed of 3 units:

A. A sugar molecule called deoxyribose
B. A phosphate group (P)
C. One of four nitrogenous bases.
   Adenine (A), guanine (G), thymine (T) and cytosine (C).

2. RNA

Structure of RNA: The same as DNA but differs in:

	DNA	RNA
Function	Carry all genetic information.	Translates these genetic in formations into assembled protein
Appearance	Double helix	Single strand
Sugar	Deoxyribose	Ribose
Bases &pairing	A & G & C & T (A-T) and (G-C)	A & G & C & U (A-U) and (C- G)
Location	Inside nucleus and mitochondria	Nucleus & cytoplasm and ribosome
Types	Only one type	3 types

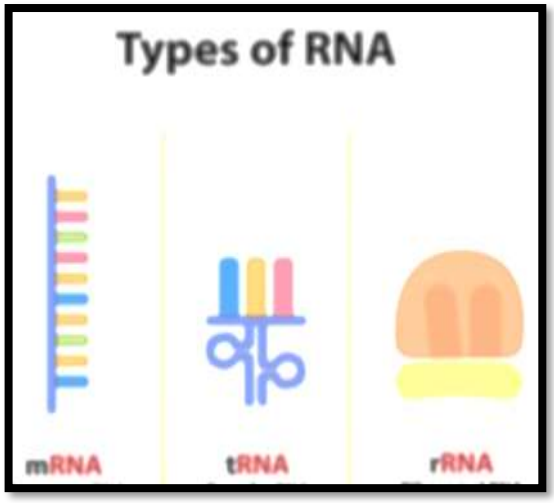


Types of RNA:

1. **mRNA:** formed from DNA in nucleus, carry the genetic 3 letter codons called the secret language to ribosome.

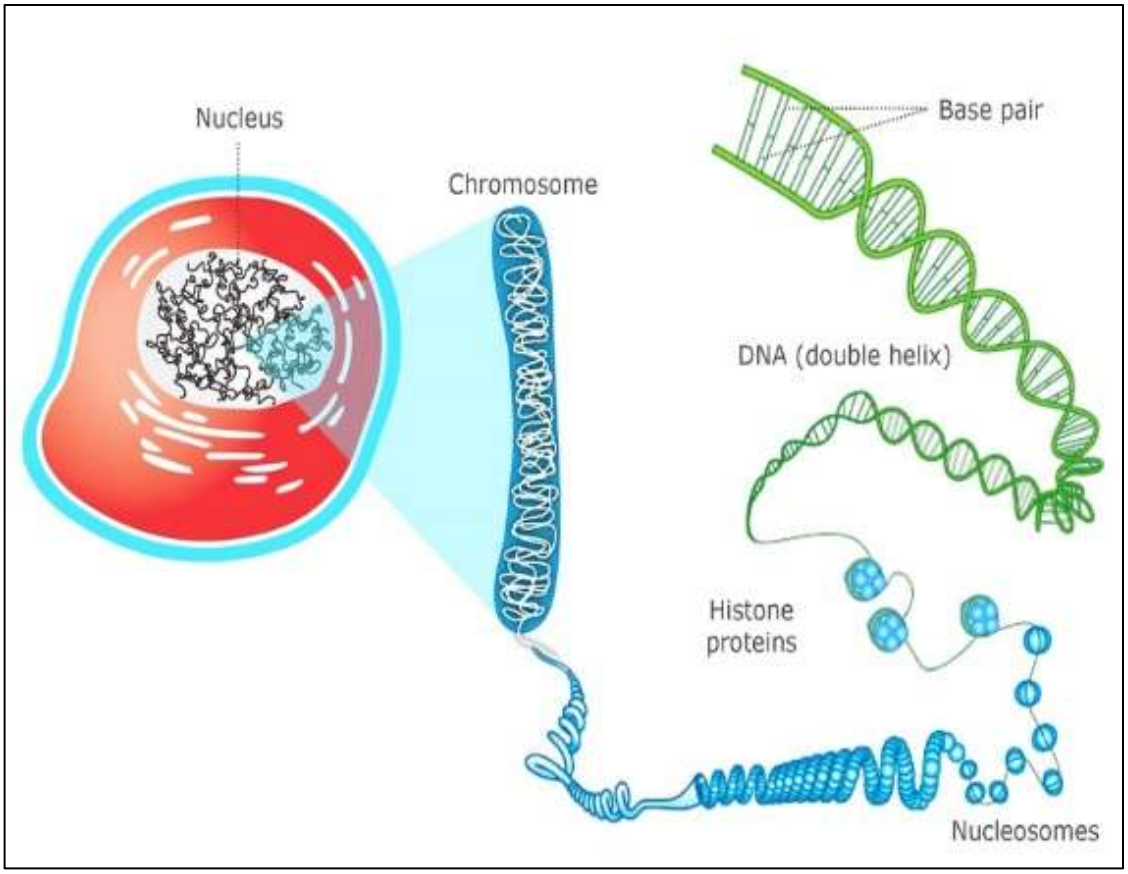
2. **tRNA:** has 2 arms, brings the wanted amino acid to ribosome.

3. **rRNA:** act as a factory for protein synthesis.



Chromosomes

Each eukaryotic cell contains about 6 billion base pairs (information encoded) in DNA structure, which has a total length of about 1.8 meter. The length of the DNA molecule is 100,000 times longer than the nuclear diameter. Therefore, the DNA must be highly folded and tightly packed in the cell nucleus. This is accomplished by the formation of a unique nucleoprotein complex called chromatin. The chromatin complex consists of DNA and structural proteins (***histone protein*** and nonhistone proteins). Further folding of chromatin, such as that which occurs during mitosis, produces structures called **chromosomes**. Each human cell contains 46 chromosomes. A unique feature of chromatin packaging is that it permits the transcriptional machinery to access those regions of the chromosomes that are required for gene expression.



Structure of chromosome

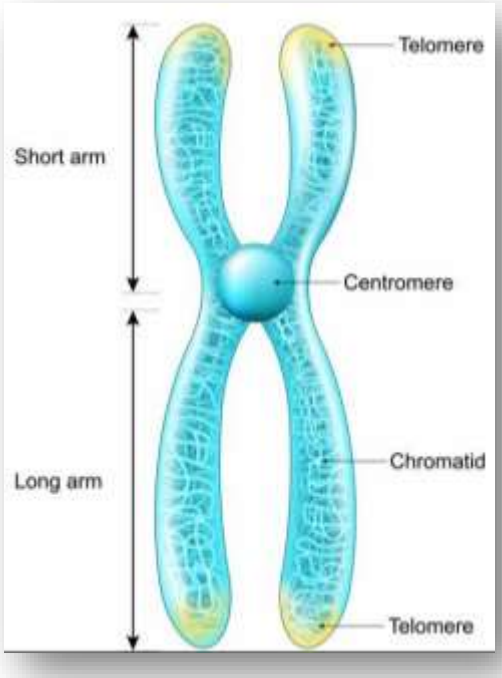
- At Metaphase stage of cell division, each chromosome appears to be longitudinally divided into two identical parts, each of which is known as 'Chromatid' (chromosomes are not visible in interphase).

- Each chromatid has short (p) arm and long (q) arm.

- Centromere is the region where the two sister chromatids of a chromosome appeared to be held together.

- Kinetochores are the attachment point for spindle fibers which help to pull apart the sister chromatids during cell division.

- The two ends of a chromosomes are known as 'Telomeres.'



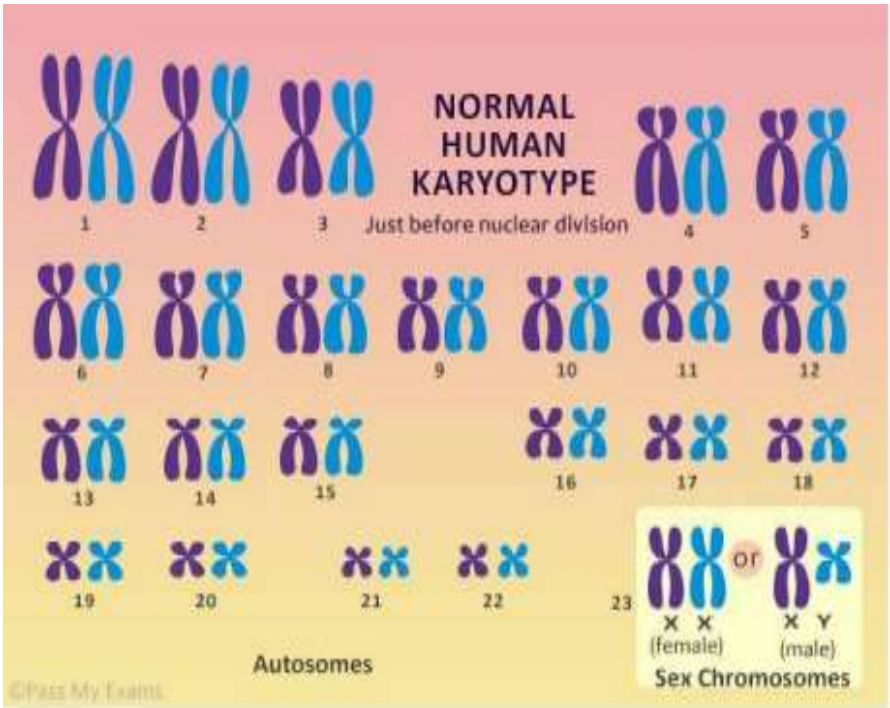
- Telomere contains many repeats of short identical DNA sequence.

- The sequence is (TTAGGG).
- It preserves chromosomes.
- Telomeres shorten with each cell division. Recent studies indicate that telomere length is an important indicator of the lifespan of the cell.
- It is kept long and healthy by telomerase enzyme.
- Telomere shortening resulting from the decrease in telomerase activity which is usually related to aging.

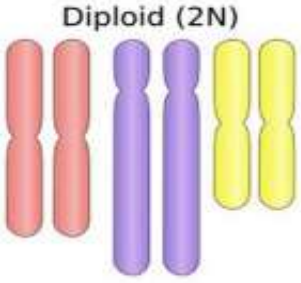
Number of chromosomes

Chromosomes have specific numbers in each species e.g. Humans have 46 chromosomes while dog has 78 & fruit fly has 8 chromosomes.

- In human, each somatic cell contains 23 pairs of chromosomes, for a total of 46, 22 of these pairs called autosomes, look the same in both males and females. The 23rd pair, the sex chromosome, differs between males and females. Females have 2 copies of the X chromosome, while males have one X and one Y chromosome.



Haploid and diploid number of chromosomes

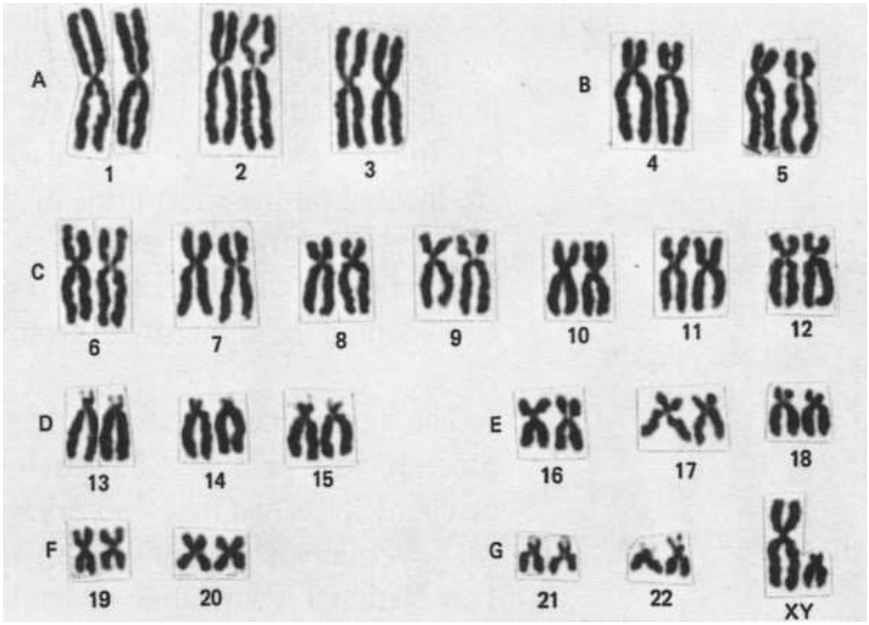
Haploid	Diploid
One set of chromosomes	Two sets of chromosomes
In human, number (n)= 23	In human, 2n = 46
In human, gametes (sperm and ova) are haploid	In human, all body cells (other than gametes) are diploid
	

Types of chromosomes according to position of centromere

- *Metacentric*: centromere in the center→2 equal arms.
- *Sub metacentric*: the centromere is slightly offset from the center→ 2 unequal arms.
- *Acrocentric*: centromere is severely offset from the center→ very short and very long arms.
- *Telocentric*: centromere is at the end→ long arms only, not in human

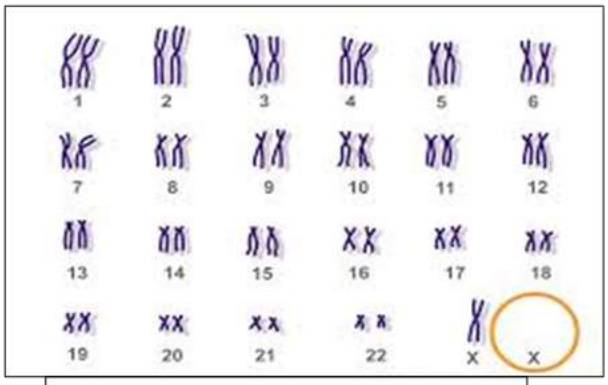
Karyotyping:

- It is the general appearance of the complete set of chromosomes in the cells, mainly including their sizes, numbers, and shapes.
- A **karyogram** or **idiogram** is a graphical depiction of a karyotype, wherein chromosomes are generally organized in pairs, ordered by size (from largest to smallest), position of centromere for chromosomes of the same size and the banding pattern.
- Any nucleus can be used to make karyotype (as Lymphocytes or skin cells).
- Sampling cells before birth (Amniocentesis, Chorionic villus sampling) could be used for karyotyping.

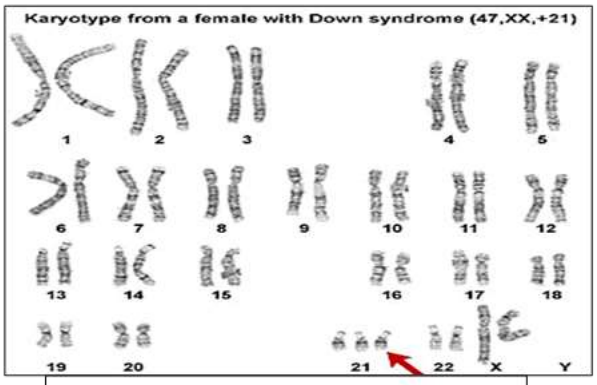


Information Obtained from a Karyotype

- Number of chromosomes.
- Sex chromosome content.
- Presence or absence of individual chromosomes.
- Nature and extent of numerical chromosomal abnormalities as Down syndrome (trisomy 21) and Turner syndrome (45 xo) as shown in figures below.

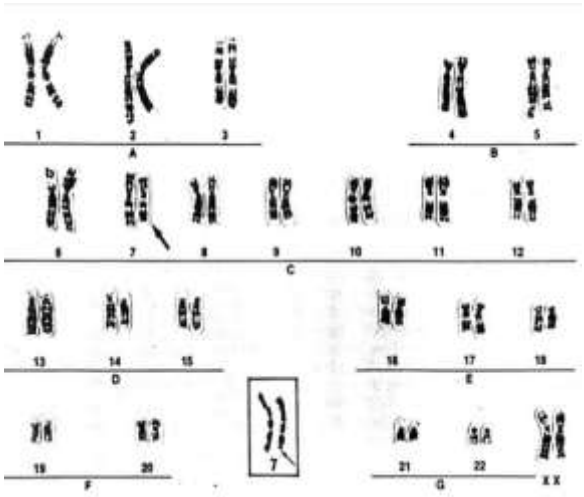


Abnormal karyotypes, Turner syndrome 45 xo



Abnormal karyotypes, Down syndrome (trisomy 21)

- Detect structural abnormalities including any change in the normal structure of the chromosomes.



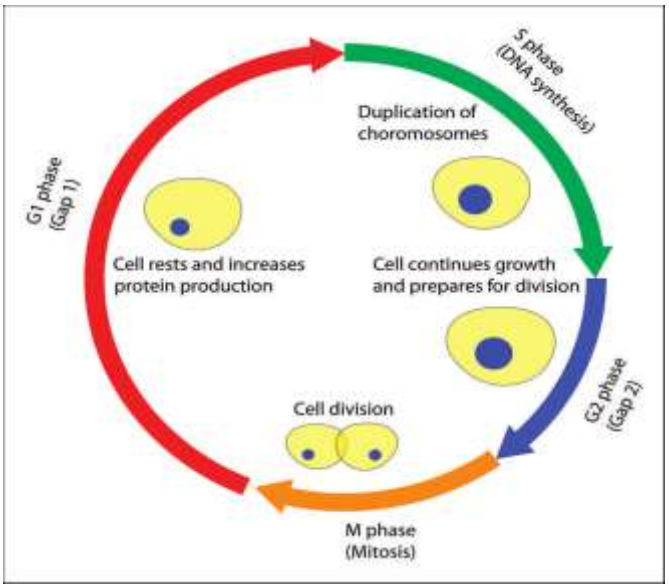
Deletion of bands q33-35 in one of the long arms of chromosome 7 [arrow]

Cell cycle and Cell death

Cell cycle, or cell-division cycle:

Is the series of events in the cell that end by cell division producing two daughter cells.

Phases of cell cycle



A. ***Interphase***: during which the cell grows and accumulate nutrients needed for mitosis and DNA duplication.

B. ***The mitosis (M)*** phase: Cell splits itself into two distinct daughter cells.

A. Interphase: It is divided into G1 , S ,and G2 phases. The duration of each phase varies in different types of cells. In human somatic cells, the cell cycle lasts about 18 hours, and the G1 phase takes up about 1/3 of that time.

1. <u>G1 phase</u>*:* During this phase, the cell grows in size and synthesizes mRNA and proteins (histones) required for DNA synthesis. It is particularly important in cell cycle because it determines whether a cell commits to division or to leaving cell cycle. After this phase cell either move to S phase to complete division or G0 phase which is a state of dormancy with no further division and no proliferating.

2. <u>S Phase</u>*:* Includes DNA synthesis and histone synthesis.

3. <u>G2 phase:</u> A period of rapid cell growth and protein synthesis during which the cell prepares itself for mitosis and cytokinesis. G2 phase is not a necessary part of the cell cycle, as some cell types as cancer proceed directly from DNA replication to mitosis.

M Phase: A nuclear division (mitosis) followed by a cell division (cytokinesis), the time interval between 2 mitotic divisions is the interphase.

<u>Stages of mitosis:-</u>

<u>1-Prophase</u>

- ***Nuclear envelope:*** fragmentation and disappearance

- ***Chromosomes:*** condensed and visible due to DNA duplication during S phase. Chromosome is formed of two chromatid joined at centromere region by kinetochore protein complex.
- ***Cenrtosomes*** move to the opposite pole of the cell.

2- Metaphase

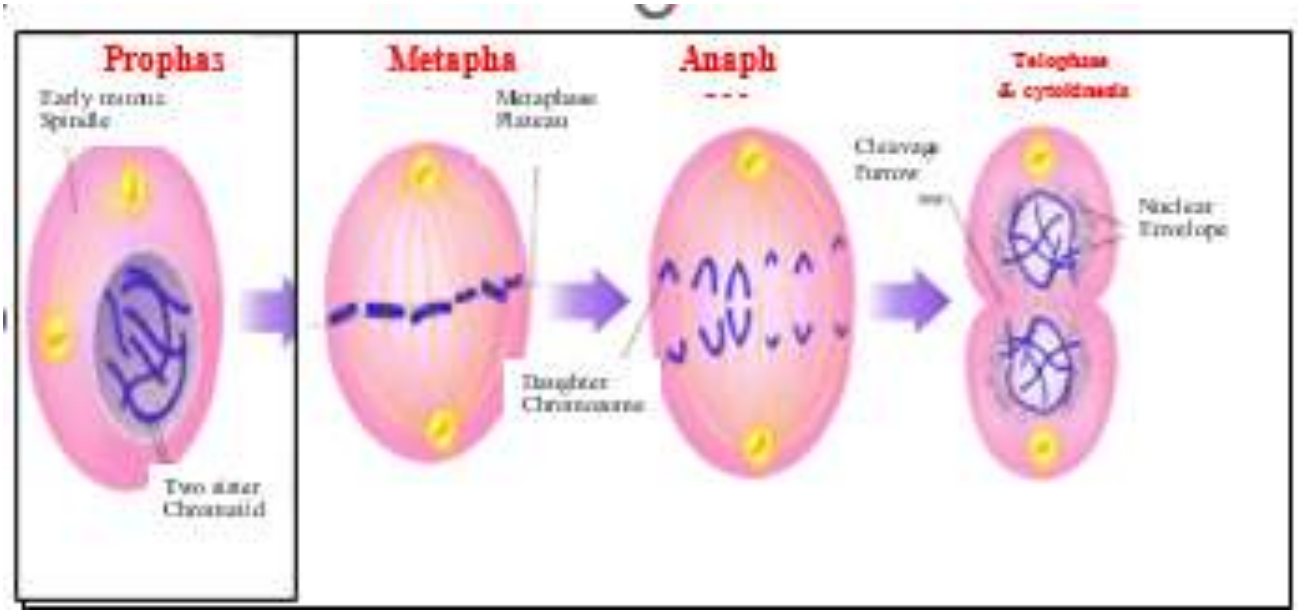
Chromosomes arranged in the equatorial of the cell and attached to the dynamic microtubules of the spindle.

3- Anaphase

- The spindle splits the chromatids, each chromatid migrates to the opposite pole of the cell and forms future chromosome.
- Due to dynamic movement of the spindle microtubules two sister chromatids are further apart.

4- Telophase

- Two sets of chromosomes are at spindle pole and assume their uncoiled state.
- Spindle microtubules depolymerized and start to disappear.
- Formation of constriction ring (f –actin & myosin) split the cell into two.



G0 (G zero): A cell may leave the cell cycle, temporarily or permanently at G1 and enters a stage designated G0.

A G0 cell is usually terminally differentiated and will never reenter the cycle. They are busy conducting their functions in the organism until they die e.g. secretion, attacking

pathogens. Some differentiated cells, such as those of the liver, re-enter the cycle under certain conditions. While others such as muscle and nerve cells, are terminally differentiated.

Cell death (apoptosis and necrosis)

Apoptosis is a naturally occurring programmed and targeted cause of cellular death by which redundant or defective cells are rapidly eliminated in a manner that does not provoke a local inflammatory reaction in the tissue.

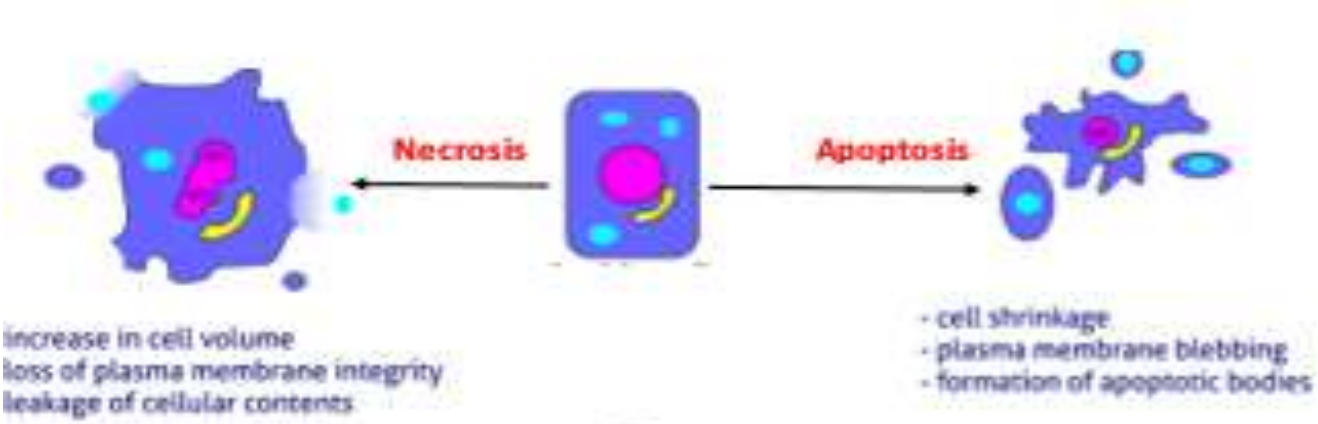
Necrosis is a form of cell injury which results in the premature death of cells in living tissue by autolysis, Necrosis is caused by factors external to the cell or tissue, such as infection, or trauma which result in the unregulated digestion of cell components While apoptosis often provides beneficial effects to the organism, necrosis is Almost always detrimental and can be fatal.

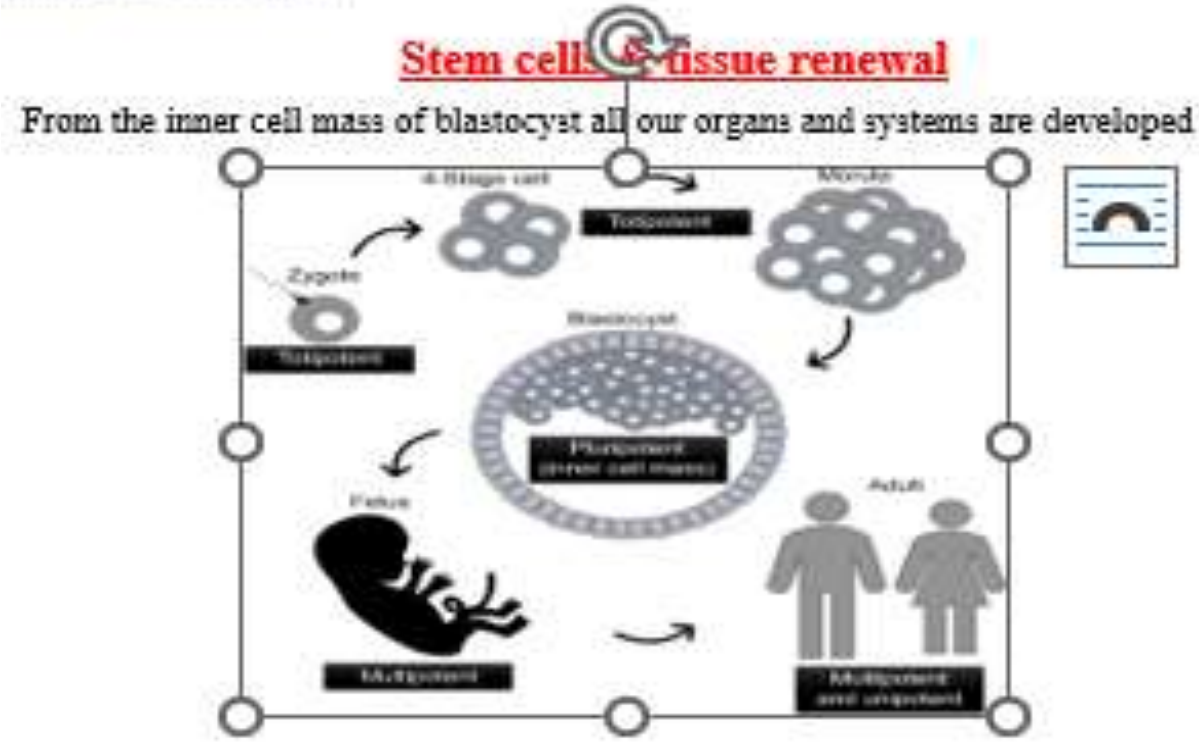
Morphological features of apoptosis

1. Chromatin aggregation
2. Nuclear and cytoplasmic condensation
3. Partition of cytoplasm and nucleus into membrane bound vesicles (apoptotic bodies) which contain ribosomes, morphologically intact mitochondria, and nuclear material.
4. No inflammatory response is elicited.

Morphological features of necrosis

1. ***Cell lysis:*** Cell swell and rupture.
2. ***Cell membrane***: Breakdown
3. ***Inflammatory response:*** In vivo, necrotic cell death is often associated with extensive tissue damage resulting in an intense inflammatory response.





Criteria of stem cells:

1. They are blank or unspecialized cells.
2. Capable of dividing and renewing themselves for long period.
3. They have a potential to differentiate and give rise to specialized cell types.
4. Their plasticity and regenerative ability.

Types of stem cells

According to their differentiating ability

1. **Totipotent stem cells**: Have high potency, capable of differentiating into any type of cell in an organism as the early cells of a fertilized egg.

2. **Pluripotent stem cells:** Can only progress to cells from any of the three germ layers (mesoderm, endoderm, and ectoderm). Pluripotent stem cells are located in the inner mass of the blastocyst.
3. **Multipotent stem cells:** Produce only closely related cells. Hematopoietic stem cells can only produce red and white blood cells (including platelets).
4. **Oligopotent stem cells:** Produce a few types of cells e.g. myeloid stem cells produce neutrophils and eosinophils.
5. **Unipotent stem cells:** Produce cells of their own type along a single lineage.

According to their Source

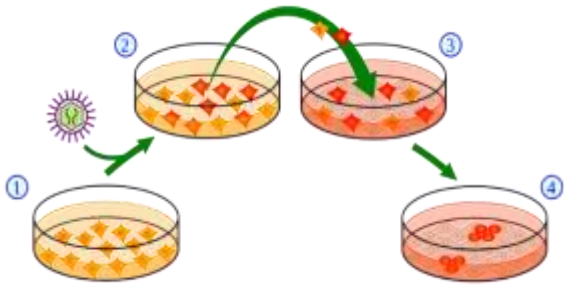
1. Embryonic Stem Cells: Derived from embryos (4 to 5 days old). Located within an inner cell mass of the blastocyst.

2. Mature/Adult Stem Cells: In various tissues, they replace dead cells.

- ***Hematopoietic Stem Cells*** (HSCs) in the bone marrow form the entire spectrum of blood cells
- ***Mesenchymal Stem cells*** In bone marrow and cord blood. They develop into a number of specialized cells including chondrocytes, adipocytes, and osteoblasts.
- ***Neural stem cells they*** produce progeny cells that ultimately differentiate giving rise to neurons, astrocytes, and oligodendrocytes.
- ***Epithelial stem cells*** are also capable of self-renewal while continually developing into various mature cells that serve different functions.
- ***Stem cells in the skeletal muscle***.
- ***Adipose- derived stem cell***.

Induced pluripotent stem cells (IPS) embryonic genes are introduced into the adult somatic cells which convert them into stem-like cells

NB: 2012 ***professor Shiny Yamanaka*** has won Nobel Prize as he transformed adult skin cells to embryonic like stem cells that can differentiate into any other cell type.



1. Adult skin cells.
2. Embryonic gene introduced to adult skin cells.
3. New cells express embryonic gene.
4. Stem cells.

Progenitor cells

When stem cells divide and produce a slightly differentiated form of themselves, it is called a progenitor cell. They considered as the transitional stage between stem cells and fully differentiated cells.

Differences	Stem cells	Progenitor cells
Self-renewal	Unlimited	limited
Cell- potency	Totipotent – pluripotent	Uni or oligopotent
Differentiation	Undifferentiated	Mild- differentiated
Origin	Inner cell mass of blastocyst	Stem cells

Classification of tissues according to regeneration

Most tissues undergo cell turnover with slow cell division and cell death. Some tissues are exceptions, as their differentiated cells cannot undergo mitosis. Capacity for mitosis within a tissue through differentiated cells or a reserve stem cells, determine its potential to regeneration.

1. ***Labile tissue:*** continuously lost and replaced by maturation from tissue stem cells and by proliferation of mature cells e.g. epithelium of skin and intestine.
2. ***Stable tissue***: Cells of these tissues (in the G0 stage of the cell cycle) these cells are capable of dividing in response to injury or loss of tissue mass such as liver, kidney, and pancreas.
3. ***Permanent tissue:*** the cells of these tissues are considered to be terminally differentiated and non-proliferative in postnatal life. Majority of neurons and cardiac muscle cells. Thus, injury to the brain or heart is irreversible and results in a scar because neurons and cardiac muscle cannot regenerate.

Importance of stem cell and their applications

1. Can be used for the generation of experimental models of systems (Heart muscle cells beating in a petri dish).
2. Adult stem cell-based therapy, as bone marrow transplant for treatment of leukemia.
3. Embryonic stem cell therapy for spinal cord injuries.
4. Stem cells for drug delivery and gene therapy.
5. Stem cell secretome (macrovesicles and exosomes) in clinical trials.

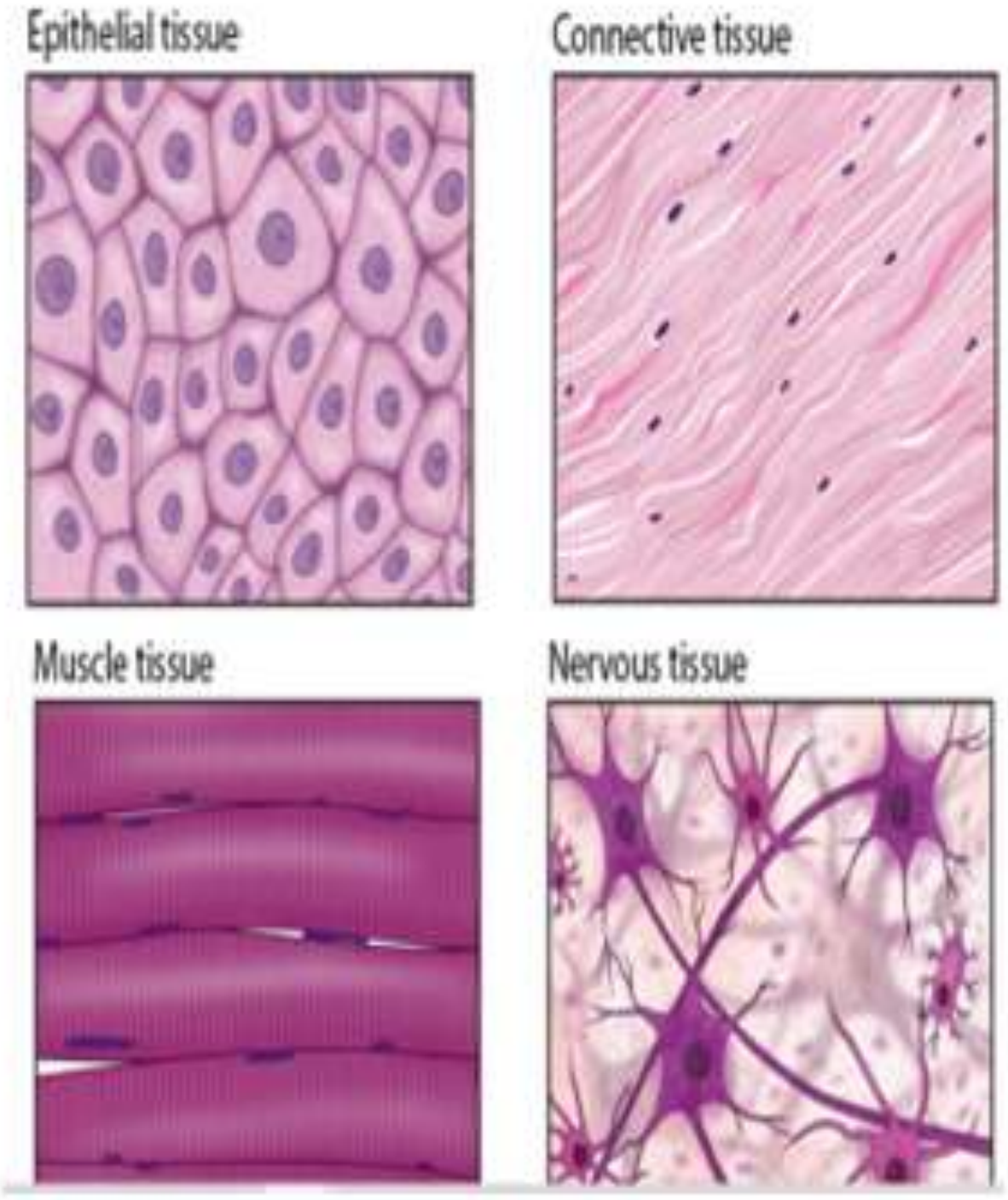
Challenges in stem cell therapy

1-Contamination.
2-Poor differentiation.
3-Mutations and gene aberrations.
4-Stem cell induced teratomas and tumors.

Challenges in stem cell research and therapy in developing countries

1-Poor facilities and infrastructure.
2-Lack of skilled well trained researchers.
3-No governmental support.
4-Low income of most population.
Private source funding, international collaboration , and promotions of exchange studies help to solve most of the problems.

Tissues of the body

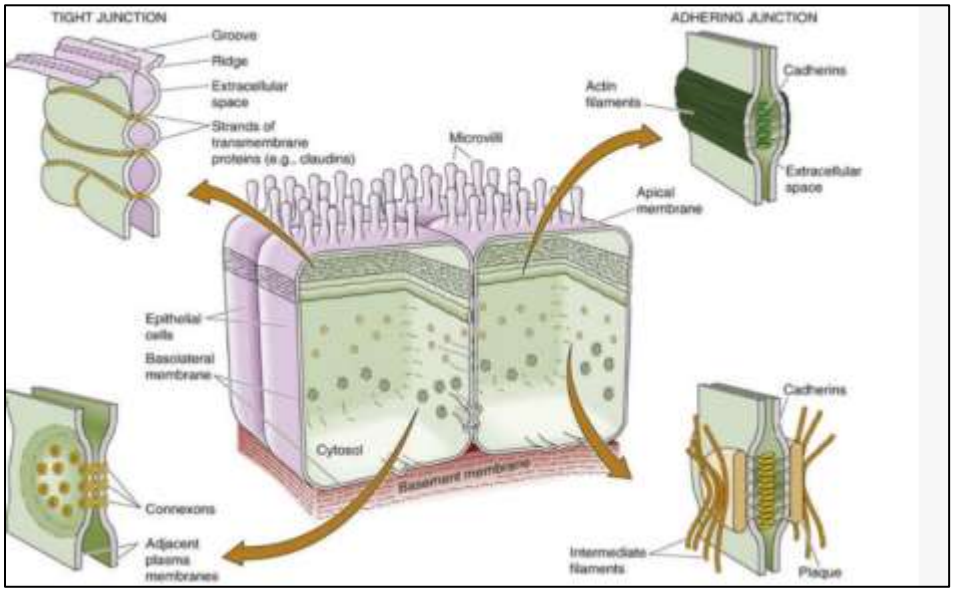


1. Epithelial tissue

Epithelium tissue is a layer of cells covering body surfaces, lining hollow organs and form glands and sensory organs.

General characters of epithelium

- ❖ Cells are tightly packed with little extracellular space
- ❖ Cells are attached to each other by cell junctions.
- ❖ Cells rest on basement membrane connecting them to the underlying CT.
- ❖ Have morphological polarity i.e., apical portion differs from basal portion.
- ❖ Perform different functions; protection, secretion and sensory functions
- ❖ Avascular (have no blood vessels)
- ❖ Innervated, rich in nerves.
- ❖ Cells can divide and renew (e.g. skin)



Classification of epithelium:

1. Covering and lining (Surface) epithelium:

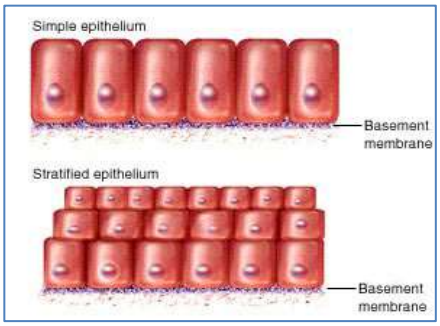
Covers surfaces and lines blood vessels, tubes and cavities.

2. Glandular (Secretory) epithelium: Forms glands.

3. Neuroepithelium: Concerned with special senses e.g smell, taste, hearing, and vision.

1. Covering and lining (Surface) epithelium

Classified according to the number of cell layer and shape of the cell:



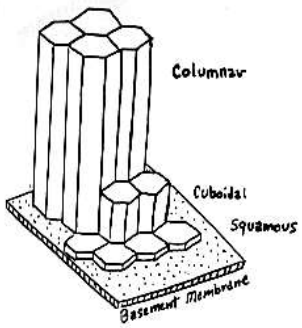
I. According to the number of cell layers:

A. **Simple epithelium**: formed of single cell layer.

B. **Stratified epithelium**: formed of two or more cell layers.

II. Shape of the cells:

A. **Squamous:** Formed of flat (spindle-shaped) cells with central flattened nuclei.



B. **Cuboidal:** Formed of cubical cells with central rounded nuclei.

C. **Columnar**: Formed of tall rectangular cells with basal oval nuclei.

A. Simple epithelium:

1. Simple squamous:

Shape of Cells: Flattened

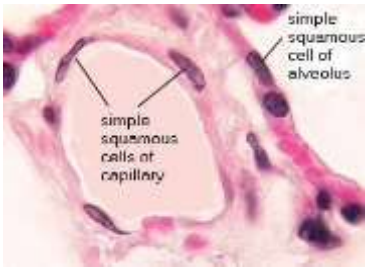
Sites :

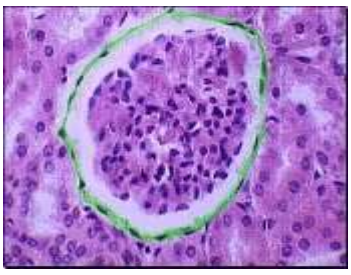
Blood and lymphatic vessels lining (Endothelium).

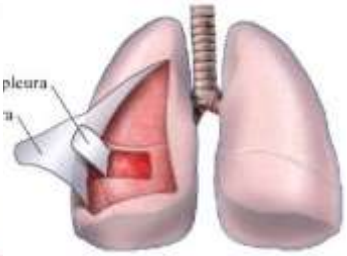
Body cavities: **p**ericardial, **p**eritoneal and **p**leural cavities lining (***Mesothelial)***

Bowman's capsule in the kidney

Alveoli in the lung.





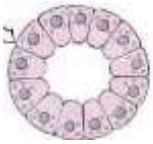


Functions:

Fluid transport

Gaseous exchange

Lubrication for movement of visceral organs

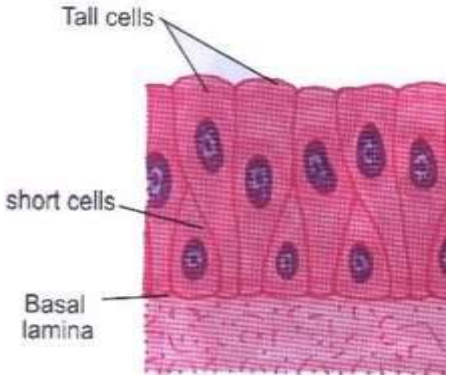



2. Simple cuboidal:
***Shape of Cells*:** Cubical
Sites: Thyroid follicles
***Functions*:** Secretion

3. Simple columnar:
Shape of Cells: Columnar
Sites:
Digestive system: Stomach and intestine

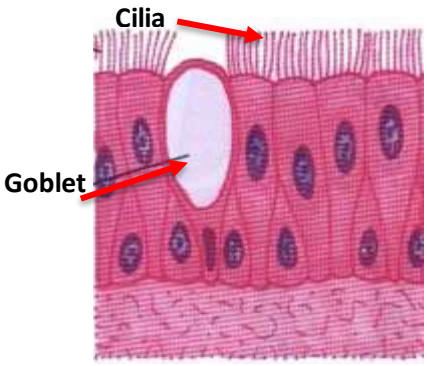
Functions:
Secretion as in stomach
Absorption as in intestine

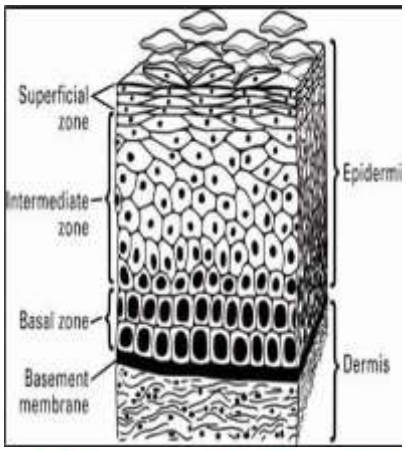
4. Simple columnar ciliated:
Shape of Cells: Columnar with cilia on apical surface.
Sites:
Female genital system: Fallopian tubes



5. Pseudo-stratified columnar:
Shape of Cells: Apparently formed of two layers of cells but actually formed of a single layer. **All** cells rest on the basement membrane, **some** cells reach the surface while **others** do not reach the surface. Thus, nuclei appear at different levels.
Sites:
Male genital system: Vas deferens and prostate

6. Pseudo-stratified columnar ciliated:
Shape of Cells: Pseudo-stratified columnar with cilia or stereo cilia (long microvilli) on apical surface.
Sites:
Upper respiratory passages (with goblet cells)
Male genital system: Epididymis with stereocilia
Functions: Protection, secretion and transportation.





b) Stratified epithelium:

Formed of more than one layer.

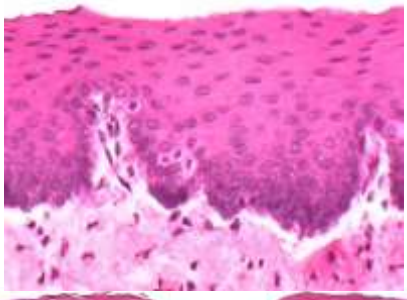
Basal layer: Columnar cells

Intermediate layers: Cubical or polyhedral

Superficial layer: Squamous, cubical, or columnar (type based on this)

Functions:

Protection



1. **Stratified squamous non-keratinized:**

Shape of surface cells: Squamous

Sites:

Digestive tract: Oral cavity, esophagus anal canal

Female genital tract: Vagina,

So in opening on the body surface: Cornea, vagina, anal canal

2. **Stratified squamous keratinized:**

Shape of surface cells: Squamous, covered keratin.

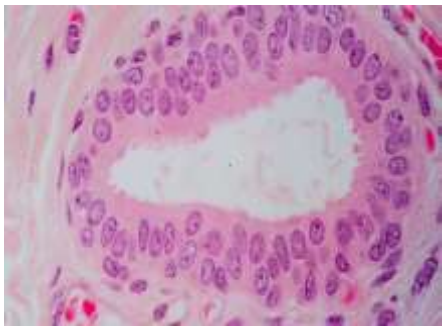
Sites:

Skin

3. **Stratified cuboidal:** Uncommon in human

Shape of surface cells: Cuboidal

Sites: Ducts of sweat glands.



4. **Stratified columnar non ciliated:** Uncommon

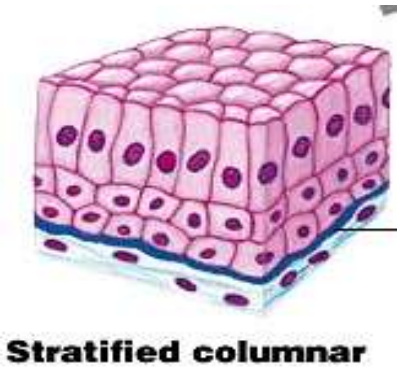
Shape of surface cells: Columnar

Sites: recto anal junction

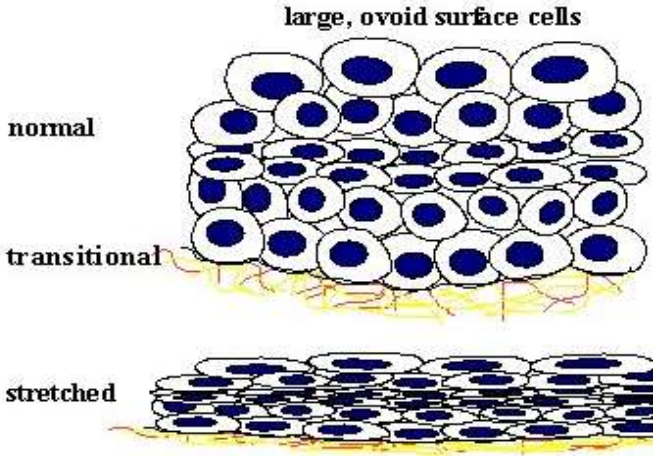
5. **Stratified columnar ciliated:** Uncommon

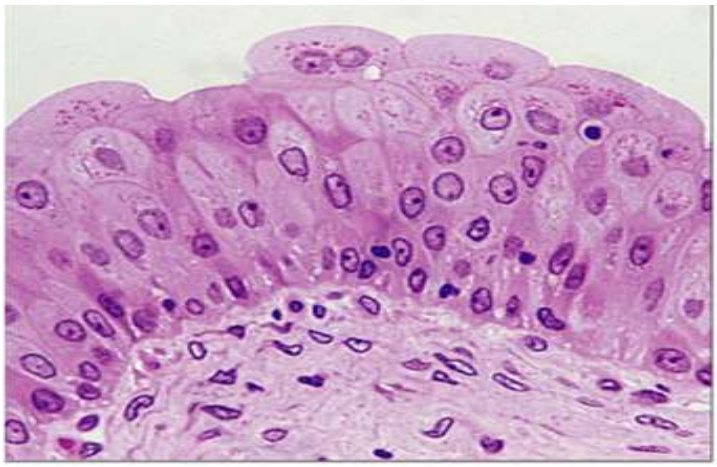
Shape of surface cells: Columnar

6. Transitional epithelium:



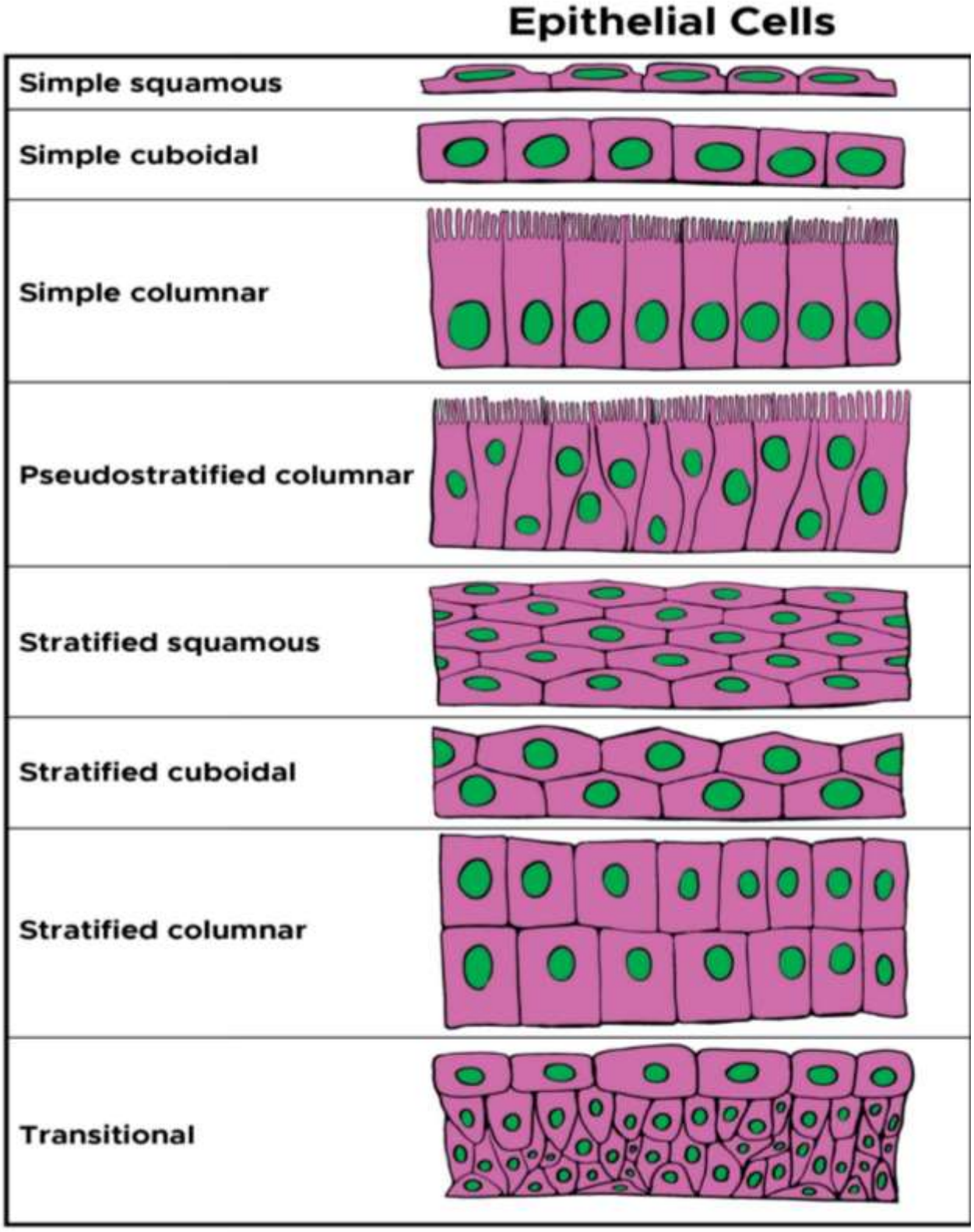
Cell shape changes according organ state.
Basal layer: Cubical or low columnar.
Intermediate layers: Polyhedral.
Superficial layer: Dome-shape cells, that change to flattened cells to allow stretching without rupture of cells.
Sites: Urinary tract including ureter, urinary bladder.
Superficial cells are modified to protect from the harmful effects of urine.





Clinical applications:

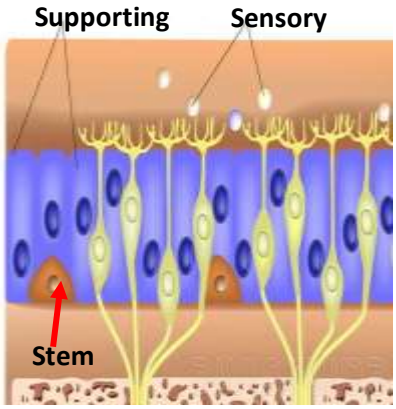
Metaplasia: Epithelial cells change to different epithelial type.
Tumors: abnormal cell proliferation which can be benign or malignant.
Carcinomas: are malignant tumors that arise from epithelium Adenocarcinomas are tumors that arise from glandular epithelial cells.


Epithelial Cells
Simple squamous
Simple cuboidal
Simple columnar
Pseudostratified columnar
Stratified squamous
Stratified cuboidal
Stratified columnar
Transitional

Neuroepithelium

Neuroepithelium is a modified epithelium of a specific sensory organ.

Structure



1. **Sensory (hair) cells:** Columnar cells with hairlets on apical surfaces. A basal surface is surrounded by sensory nerve fibers.
2. **Supporting cells:** Tall elongated between sensory cells
3. **Stem (Basal) cells:** Near basement membrane between other two cell types. They give rise to other cell types.

Sites:

Taste sensation in tongue: **Taste** buds

Smell sensation in nose: **Olfactory** epithelium

Hearing sensation in ear: **Cochlea** of inner ear.

Functions: It acts as a sensory receptor for special sense stimuli**.**

Glandular epithelium

Gland: formed of one or more cells.
Epithelium modified perform secretion.
Secretion: Exocytotic release of products outside the cell.
Molecules of the secretion may store in membrane-bound secretory vesicles.

Development of secretory epithelium

During fetal life, from surface epithelium by cell proliferation and invasion of underlying CT followed by differentiation.

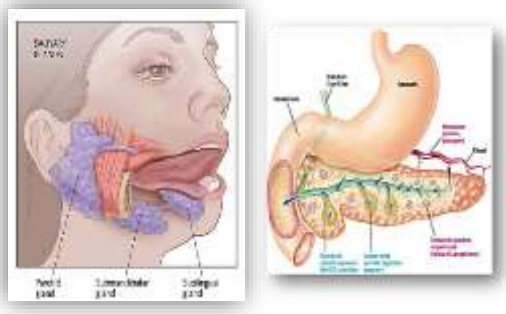
Classification of Glands: According to:

1. Number of secretory cells:

Unicellular: single cell, e.g goblet cells.
Multi-cellular: more than one cell.

2. Presence or absence of ducts:

Endocrine glands: (ductless) **e.g. Thyroid gland**
Exocrine Glands through ducts. **e.g. Salivary glands**
Mixed endocrine and exocrine: Pancreas.

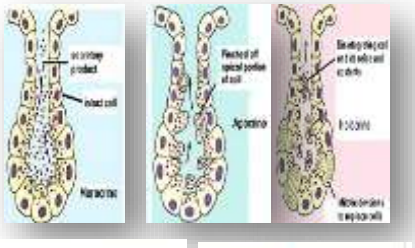


3. Type of secretion:

Serous: Watery liquid secretions rich in protein e.g serous acini of pancreas and parotid
Mucous: Viscous e.g goblet cells and mucous acini of sublingual salivary gland
Mixed: Sub-mandibular gland has both mucous and serous secreting cells.
Waxy: Wax-like creamy e.g glands of external ear.
Mineral: HCl secretion in the stomach.
Hormones: Gonads; ovary and testis.
Watery: Sweat gland.

4. Mode of secretion:

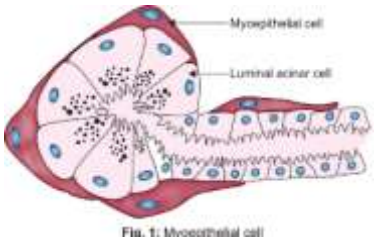
Merocrine: Most common. Secretions by exocytosis with no changes or loss of any part of cell e.g. pancreatic acinar cells.
Apocrine: Apical part detached with secretion. e.g. lactating mammary gland.
Holocrine: Whole cell destructed with secretion. e.g. sebaceous gland in the skin.



5. Shape of secretory unit:

Tubular: Secretory portion tube shaped.
Alveolar (Acinar): Flask shaped.
Tubulo-alveolar: Tube ends in sac like dilatation.

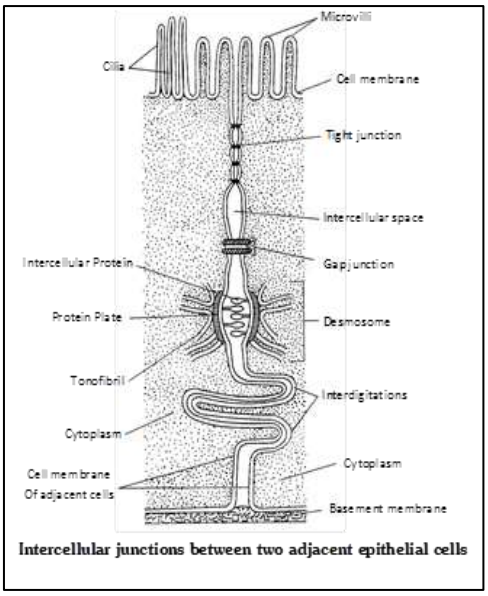
Myoepithelium (Basket cells): Epithelial in origin. Specialized with contraction ability. Surround acini and ducts of many glands. Contain actin and myosin for contractility. They help to expel secretion and also have supporting function.



Modifications of the cell membrane

1. Lateral modifications

A. Junctional complex.
B. Gap junction.
C. **Interdigitations**.



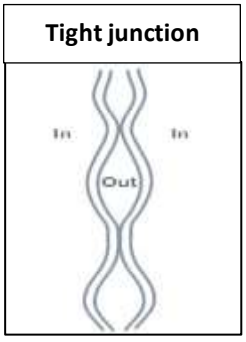
Intercellular junctions between two adjacent epithelial cells

A. Junctional complex:

It joins adjacent Epithelial cells firmly at their margins.
It regulates para cellular traffic and stabilize the tissue.
It is formed of a series of three junctions from above downward:

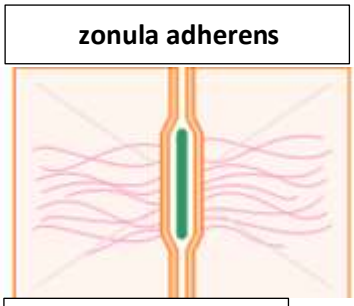
1. ***Tight junction*** (zonula occludens)
2. ***Intermediate junction*** (zonula adherens)
3. ***Desmosome*** (macula adherens)

1. Tight junction (zonula occludens):



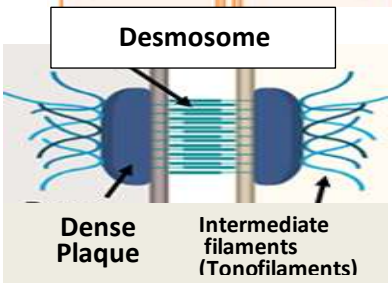
- It is formed by complete fusion of the outer leaflets of the opposed cell membranes of the adjacent cells at certain points.
- It acts as a perfect seal preventing any intercellular diffusion of materials.

2. Intermediate junction (zonula adherens):



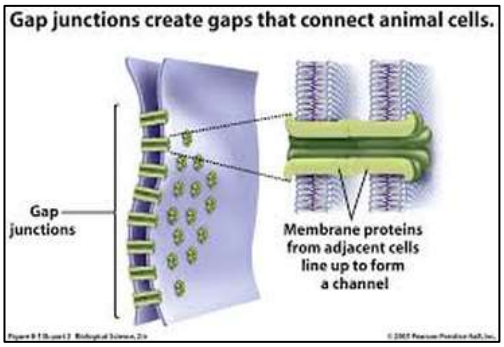
- Regular intercellular space about 15-20 nm containing a dense filamentous material " adhesive effect".
- Microfilaments inserted into cytoplasm related to cell membranes at junction to provide an additional support.

3. Desmosome (macula adherens):



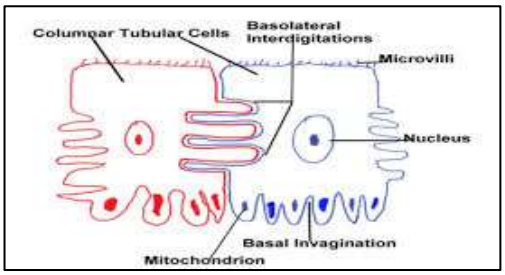
- Inter-cellular space about 20-25 nm, filled with an electron- dense lamina. On the cytoplasmic side: a disk-shaped dense material called plaques.
- Tonofilaments appear to loop through the plaques.
- This very strong junction provides support for cells exposed to mechanical stress e.g. epidermal cells & cardiac muscle cells.

B. Gap junction (nexus):



- Adjacent cells separated by tiny gaps of about 2 nm.
- Consists of accumulation of trans-membrane protein complexes that form circular patches in the plasma membrane
- Allows ions and small molecules to pass between cells for electrical coupling and functional coordination e.g. smooth, and cardiac muscle fibers & nerve cells.

C. Interdigitations:

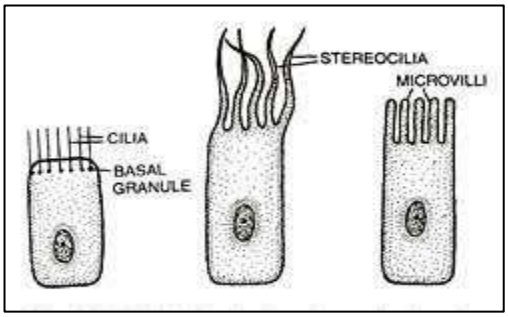


Parallel cell membranes highly folded and interlocked

Functions: Increase the surface area for ion transport

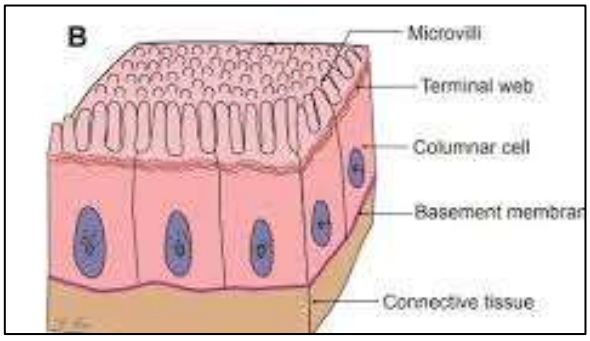
Sites: Cells of convoluted tubules of kidney.

2. Apical modifications of epithelial cells



A. Microvilli
B. Cilia
C. Flagella
D. Stereo cilia

A. Microvilli: Finger like projections of the apical surface of absorptive and secretory cells



Site: Intestinal lining and renal tubule lining cells

LM: Appear as brush border on the apical surface

EM: Projections formed by cell membrane folding

Functions: Increase the surface area of the absorptive and secretory cells

B. Cilia:

Hair like projection of the apical surface of cells

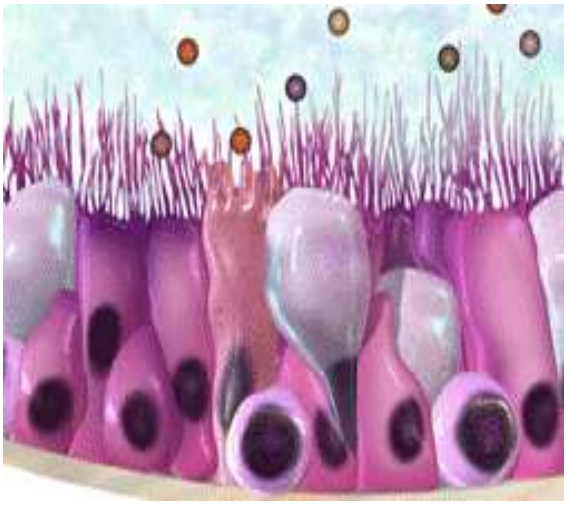
LM: Appear as acidophilic striations on the apical surface

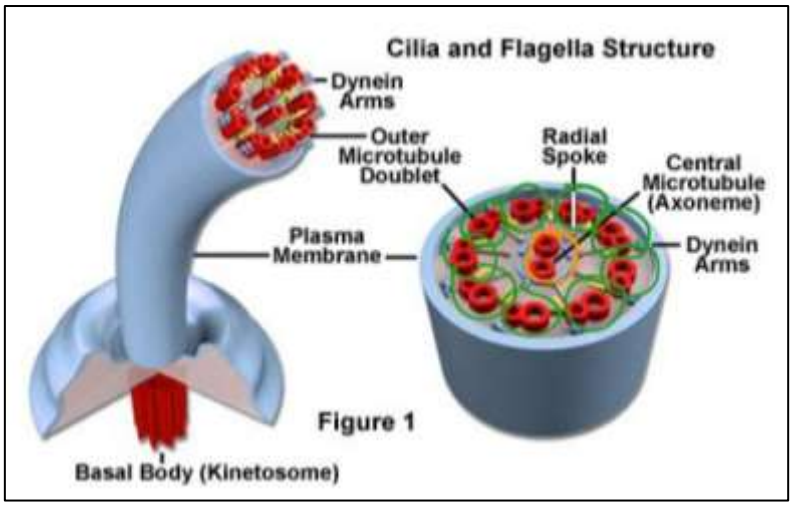
EM: Formed of three parts:

- **Shaft** (axoneme): Formed of 9 doublets of microtubules arranges in a ring around a central pair of singe microtubules

- **Basal body** (kinetosome):): Formed of 9 triplets of microtubules at the base of the cilium. Resembles the structure of the centriole.
- Rootlet: Formed of dynamic tubulin protofilaments extending downward to fix the cilium to the cytoskeleton.

*Functions***:** cilia are motile structures move in one direction to push fluids like mucus in respiratory epithelial lining, or push small bodies like ova in Fallopian tube epithelial lining.





C. Flagella:

Are cilia-like structures, but are longer.

Forms the tail of mature sperm to facilitate its movement.

D. Stereo cilia:

Not true cilia but very long microvillus

Sites: Epididymis in male genital system and hair cells of the inner ear.

Formed of tonofilaments not microtubules.

3. Basal modifications:

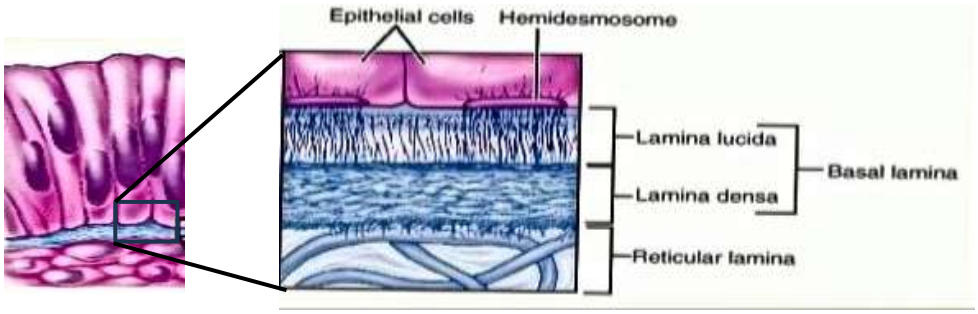
A. Basement membrane

B. Hemidesmosome
C. Basal infoldings

A. Basement membrane:
A narrow non cellular zone between epithelial cells and underlying connective tissue.

Structure:
1. Basal lamina: Formed by epithelial cells and composed of:
Lamina lucida (formed of glycoprotein)
Lamina densa (formed of collagen IV network).

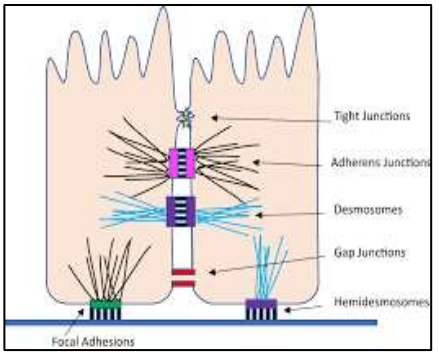
2. Reticular lamina: Formed by connective tissue cells
Composed of reticular fibers (collagen III).



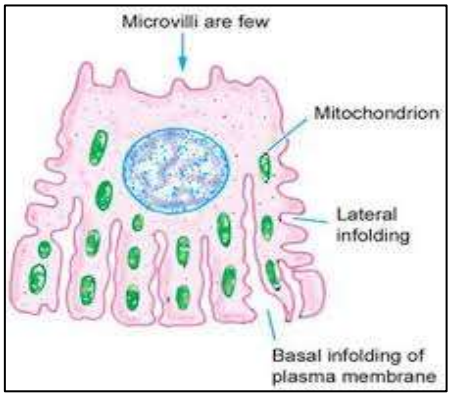
***LM*:**
H&E: Poorly stained, visualized by special stains
Special stains: Van Gieson stained red
PAS stained magenta red
Silver stained brown.
***EM*:**
Lamina lucida: appear electron lucent
Lamina densa: appear electron dense
Reticular lamina: thicker, diffuse layer

***Functions of basement membrane*:**
1. Anchors epithelial cell to underlying tissues
2. Provides structural support and polarity to epithelial cells
3. Provides mechanical barrier preventing malignant cells invading underlying tissues.

B. **Hemidesmosome.**
Resemble half desmosomes
Functions:
Provides a strong binding between the basal surface of the epithelial cells and the underlying basement membrane



D. Basal infoldings:
Basal infoldings of the basal cell membrane.
Usually have associated mitochondria
Functions: Rapid transport of ions.
Sites: Renal tubules



Connective tissue

Connective tissue consists of cells that are widely separated by varying amounts of extracellular matrix. The extracellular substance consists of fibers embedded in a ground substance.

Origin: Mesodermal origin

Characteristics of connective tissue:
1. Formed of widely separated several types of cells within large amount of matrix.
2. Rich in blood vessels, nerves and lymphatics.

Functions:
- ***Mechanical support*:** connective tissues connect and hold tissues and organs in place.

- ***Nutritional support****:* provides media through which nutrients are transported from capillaries -that lie in the intercellular substance- to the cells. It provides a passage for blood vessels and nerves to organs and tissues.
- ***Immunological protection:*** The principal cell types involved in immunological defense are found within connective tissue (as macrophage cells, plasma cells, etc.…..) and the ground substance that prevents the spread of infection. Connective tissue is the usual site for inflammation and edema.
- ***Fat:*** storage site.

Connective tissue is composed of:

A- Connective tissue cells.

B- Extracellular matrix:

- Ground substance
- Fibers

Types of connective tissue:

A. Embryonic connective tissues:
1. Mesenchymal connective tissue.
2. Mucous connective tissue.

B. Connective tissue proper:
1. Loose (areolar) connective tissue.
2. Dense connective tissue (regular and irregular).
3. Reticular tissue.
4. Adipose tissue.

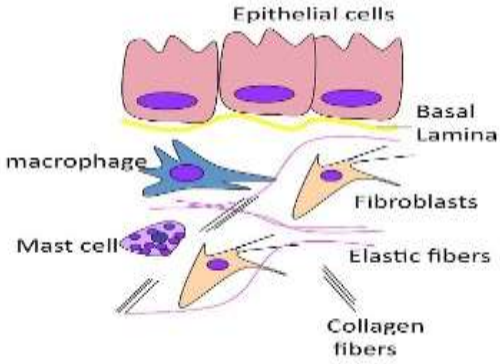
C. Specialized connective tissue: 1. Cartilage. 2. Bone. 3. Blood

Connective tissue cells

A) Fixed cells: stable and long population cells which include:

- ❖ Mesenchymal cells
- ❖ Fibroblasts & fibrocytes
- ❖ Fixed Macrophages (Histocytes)

- Reticular cells
- Fat cells
- Endothelium
- Pericytes



B) Free cells (wandering):

- Free macrophage cells
- Plasma cell
- Mast cells
- Leukocytes

Undifferentiated Mesenchymal cells (UMCs)

Undifferentiated cells that can differentiate into other types of CT cells and blood cells in the bone marrow.

Sites: Mesenchymal tissue in embryo, umbilical cord and small population of these pluripotential cells is found in adult tissues.

LM: They are small fusiform or branched cells with dark nuclei

EM: few amounts of cytoplasmic organelles, and heterochromatic nucleus

Functions: Differentiate to CT cells, blood cells, smooth muscles and endothelium

Fibroblasts

The most abundant CT cell.

Origin: UMCs.

LM: It is flattened or fusiform in shape with a centrally placed nucleus and presents numerous processes. Young and active fibroblast possess open faced nucleus with prominent nucleolus and abundant basophilic cytoplasm.

EM: show criteria of protein forming cells (abundant rough endoplasmic reticulum, prominent Golgi apparatus and mitochondria.)

Functions:

1. Fibroblasts produce all types of fibers (collagen, elastic and reticular) and the amorphous ground substance.

2. They help in the healing of wounds by continued proliferation and subsequent formation of connective tissue components. In the process of repair, fibroblasts are capable of contraction (thus, named myofibroblasts) due to the presence of cytoskeletal proteins that are normally found in smooth-muscle cells. These myofibroblasts participate in wound repair by contracting the edges of the wound.

Fibrocytes

When the fibroblasts become old and inactive, they are converted into fibrocytes.

LM: flattened with few processes, oval dark nuclei, and less basophilia of cytoplasm.

EM: scanty organelles and heterochromatic nucleus

Functions: change to active fibroblast during healing & after wound

Macrophages (Histiocyte)

Origin: monocytes of the blood.
These cells are less numerous than the fibroblasts

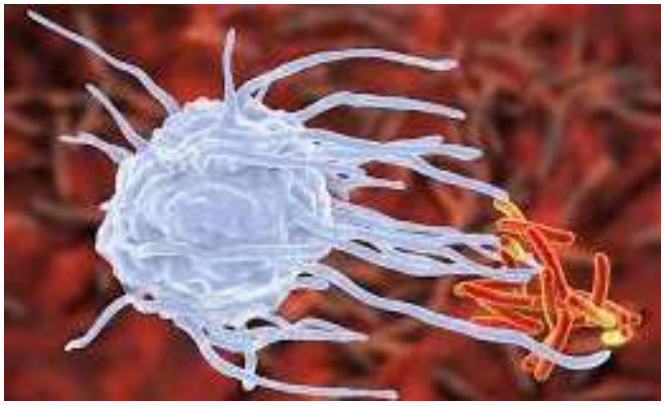
LM: Large cell with irregular cell boundary and variable shapes due to pseudopodia. It possesses dark hyperchromatic kidney-shaped (indented) nucleus and acidophilic cytoplasm. It can be stained by vital dyes such as trypan blue.

EM: irregular cell outlines with pseudopodia, the cytoplasm contains numerous lysosomes, residual bodies, and many mitochondria.
Resting macrophages are fixed to the reticular fibers of the connective tissue. When active, they become free, assume ovoid outline, and undergo amoeboid movements.

Functions:

1. The macrophages phagocytose and digest particulate organic materials, foreign bodies or invading micro-organisms and bacteria thereby eliminate them from the body.

1. In spleen: they phagocytose worn out RBCs.
2. They are antigen presenting cells to lymphocytes.
3. In inflammation, they phagocytose cellular debris.
4. They fuse → multinucleated giant cell to face large foreign body or physiologically present as in osteoclasts of bone.



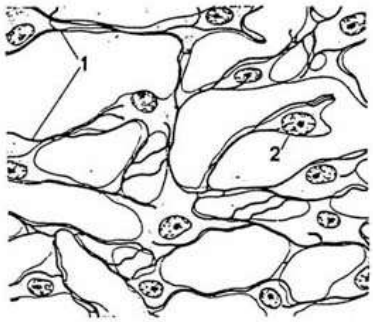
NB: Melanophore cells:

Site: Dermis of skin

LM& EM: macrophage cells engulfing melanin pigment.

Functions: the connective tissue macrophages in dermis engulf melanin pigments from disintegrating or aging melanocytes.

Reticular cells



Reticular cells are a type of fibroblast that synthesizes collagen type-III to produce reticular fibers.

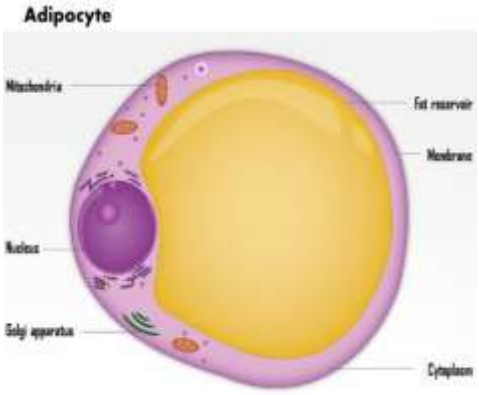
LM: branched flattened cells with poorly staining nuclei and cytoplasm

Functions:

1. They produce reticular fibers to maintain thin networks of fibers that are a framework for most organs providing structural support.
2. Phagocytic: can ingest and remove the bacteria.
3. They act as stem cells

Fat cells

Origin: UMCs



LM: Each cell is spherical or polygonal, consists of peripheral rim of cytoplasm with an eccentric nucleus and contains a large central lobule of fat.
-By H & E, the cell is 'signet-ring' in appearance as fat is dissolved by alcohol used during tissue preparation.
-By frozen sections:
a) Sudan III stain →stained with orange color
b)Sudan black stain →black color.

EM: Few ribosomes, rER, sER, Golgi, mitochondria, and large fat droplet.

Functions:
1. Storage of fat and giving body contour.
2. Support organs as in perinephric fat.
3. Heat insulation.
4. Secretion of hormones as: Leptin which inhibits appetite and Adiponectin which increases insulin sensitivity of skeletal muscle cells.

Endothelial cells

Origin: UMCs

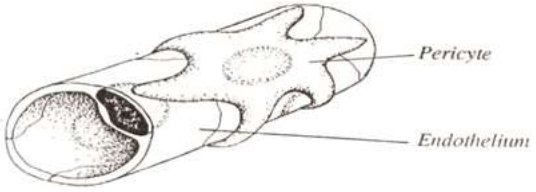
LM: They are the simple squamous epithelial cells that line blood vessels.

Functions: they produce special type of collagen (type IV). They also produce their own basal lamina. So endothelial cells are considered as one of the connective tissue cells.

Pericytes:

Origin: UMCs.

Site: found around blood capillaries and venules.



LM: flattened and branched cells with many processes with oval and pale nucleus

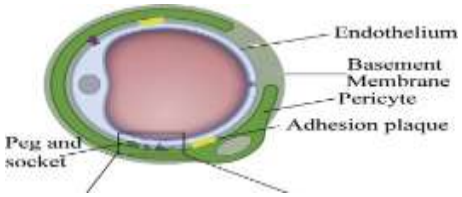
EM: Has few organelles & numerous gap junctions and seen between the endothelial cells and their basal laminae (basement membrane).

Functions:

a- After injury it can differentiate to:

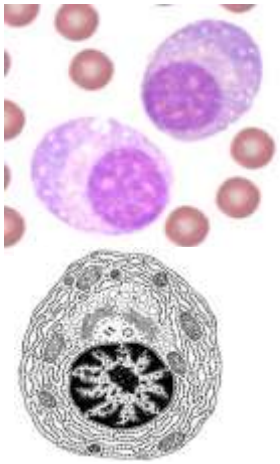
1- Fibroblast 2- Endothelium 3- Smooth muscle cells.

b- It can contract (contains actin and myosin) &cause vasoconstriction



Plasma cells

Origin: Plasma cells are activated B-lymphocytes (when the latter are exposed to antigens). Plasma cells form a small population in bone marrow.



LM: rounded cells without any process, with intense basophilic cytoplasm showing – ve Golgi area and acidophilic granules called Russel bodies (Ig antibodies).

EM: The cytoplasm is rich in RER, numerous ribosomes, mitochondria and prominent supranuclear Golgi complex. The nucleus is eccentric in position and typically presents clumps of chromatins in a radiating manner, resembling 'cart-wheel' or clock face in appearance.

Functions:

1. The plasma cells liberate humoral antibodies to counter-act the action of antigens and help in the defense mechanism of the body.

N.B. The plasma cells are not present at birth but appear in the postnatal life. Therefore, the antibody formation of the newborn is minimum.

Mast cells

Origin: UMCs

Site: Mast cells are present in the CT especially in fibrous capsule of the liver, along the blood vessels, beneath the mucosa of alimentary and respiratory tracts, and in other parts of the body.

LM: Mast cell is rounded in shape and presents a central nucleus. The cytoplasm is closely packed with large membrane-bound basophilic granules, which stain metachromatically with toluidine blue. Granules become purple colored when treated with toluidine blue. Histochemically, the granules contain heparin, histamine, eosinophil chemotactic factors and neutrophil chemotactic factors.

EM: ribosomes, RER, large Golgi, mitochondria, and larger membrane bound granules.

Functions:

1. The mast cells liberate heparin which is anticoagulant that prevents fibrinogen from clotting into fibrin. This may explain the presence of mast cells near blood vessels.
2. The mast cells produce histamine, which promotes capillary leakage, edema, and contraction of smooth muscles. Sometimes the antibodies (IgE) are adsorbed on the surface of the mast cells and fail to move. When the specific antigen enters the body, antigen-antibody reaction may take place on the surface of the mast cell. Eventually the mast cell releases the histamine which produces anaphylactic or allergic reactions.
3. Secretion of eosinophil and neutrophil chemotactic factors which attract leukocytes.

Leukocytes

Neutrophils, basophils, eosinophils, lymphocytes and monocytes are wandering cells that may migrate from the blood stream to the connective tissue. These cells protect the tissues against invasion from microorganisms.

B. Extracellular matrix

1. **Ground substance:** colorless, gel-like substance which is highly hydrated.

Form the background material within which other connective tissue elements are embedded. It is the major component of connective tissue. Secreted mainly by fibroblasts. It consists of glycoproteins, proteoglycans, and glycosaminoglycan or acid mucopolysaccharide (hyaluronic acid). Its fluid is derived from capillaries, similar to blood plasma except for the absence of plasma proteins.

Functions:

1- Acts as a medium for the transfer of nutrients & waste materials between connective tissue cells and blood.

2- Acts as physical barrier prevents the spread of microorganisms.

2. Connective tissue fibers

The extracellular matrix contains fibers made out of protein. The fibres can vary in diameter, and in the way in which they are 'woven' into a network. For example, in tendons, the fibers run parallel to resist forces in the direction in which the muscle produces force. In bone they are arranged in alternating parallel layers. Whereas GAGs are good at resisting compressive forces, fibers are good at resisting tensile forces. There are two main types of fiber; **collagen,** and **elastin**.

1. Collagen fibers
2. Elastic fibers
3. Reticular fibers

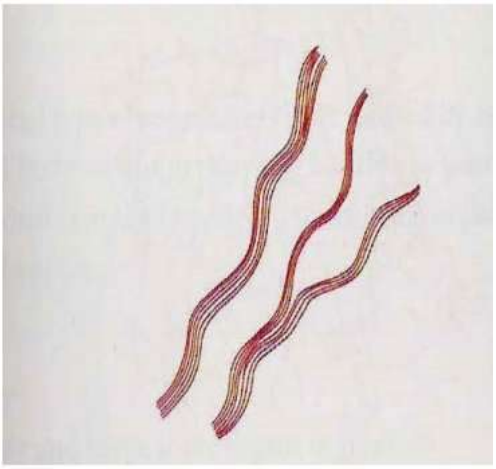
1. Collagen fibers

The most common fibrous protein in the body. It is the most abundant protein in mammals - 25% of total protein body mass. It is white in fresh state and it strongly resists a pulling force (greater tensile strength than steal).
They are flexible but not elastic. Collagen fibers present a cord- or tape-shape 1-10 µm wide and run a wavy course in tissues. These fibers consist of closely packed thin collagen fibrils (30-100 nm thick in ordinary tissues of mammals) and are present in all types of connective tissue.

LM: They are arranged into wavy bundles formed of smaller fibers. The bundles may branch, but the individual fibers do not. They are acidophilic, they stain pink with H&E; best differentiated as green with Masson's trichrome stain.

Collagen Fibre

- *White* colour when fresh
- Do not branch,wavy
- present in bundle
- *Collagen protein* forms Fibres
- Fibres composed of fibril made of microfibrils
- Micro fibrils made up *tropocollagen-striations*
- Synthesized by *fibroblast*



Types: about 15 kinds of collagen are known.

1. ***Type I:*** in the form of bundles, constitutes 90% of all collagens. This type is found in bone, skin, tendon, ligaments, cornea etc.
2. ***Types II***: in the form of fibrils present in cartilage (hyaline and elastic).
3. ***Types III***: in the form of fibers, present in reticular fibers.
4. ***Types IV & V***II form networks in the basal lamina.

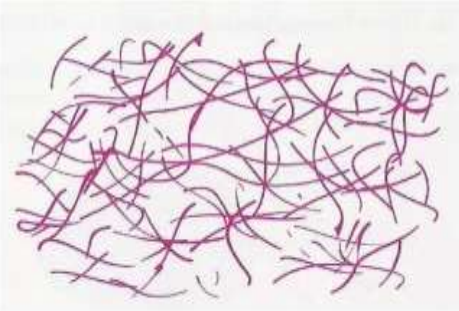
2. Reticular fibers

The reticular fibers are composed of type III collagen. Unlike the thick and coarse collagenous fibers, reticular fibers branch and anastomose forming a fine reticulum. Such networks are widespread among different tissues and form supporting frameworks in the liver, lymphoid organs, capillary endothelia, and muscle fibers.
LM: very thin fibers (cannot be seen by H&E) and stained dark brown or black by silver (argyrophilic).

Sites: The fibers are commonly present in the reticular connective tissue, stroma of organs and particularly in association with basement membranes.

Reticular fibre

- Structurally similar to collagen fibres
- Are very thin immature collagen fibre
- Actively branch to form delicate network therefore named Reticular
- Form supportive framework of lymphoid tissue
- Stained black by silver salts (argyrophillic)
- Composed of Collagen Type III



3. Yellow elastic fibers

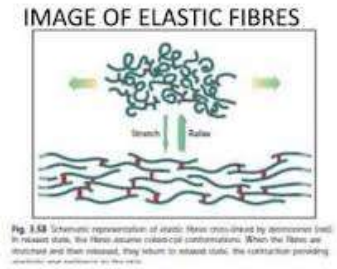
- The fibers are thin arranged in a plexus, branch and anastomose with a diameter of about 0.2 to 2 µm. These fibers are yellow in fresh state, stretch easily and recoil to original position. It contains elastin and fibrillin.

LM: elastic fibers are stained reddish brown with orcein.

Sites: tunica media of large blood vessels and in elastic ligaments.

Elastic fibre

- Yellow in color when fresh
- Composed of elastin protein
- Singly present
- Branched and anastomose forming a network
- Can be stretched (one and a half times)
- Synthesized by fibroblast and smooth muscle cells in blood vessels
- Found in ligamentum flava, ligamentum nuchae, large arteries



Types of connective tissue proper:

A. Loose connective tissues:

1. Loose areolar connective tissue
2. Adipose connective tissue
3. Reticular connective tissue
4. Mucoid connective tissue

B. Dense Connective Tissue:

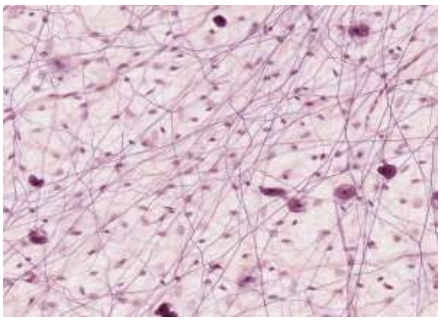
5. White Fibrous Tissue
6. Yellow Elastic Tissue

1. Loose areolar connective tissue

It is the commonest type, so called ordinary. It consists of loose arrangement of all types of CT cells (especially fibroblast and macrophage) & all types of fibers (especially collagen) in large quantity of extracellular material. The amount of matrix gives an impression of air spaces presence, so called areolar connective tissue.

Distribution:

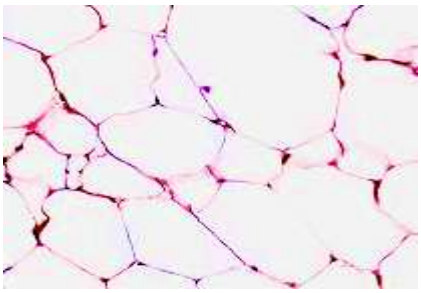
- In the papillary dermis of skin, around blood vessels.
- In the lamina propria and submucosa of digestive tract.
- Fill the spaces between different tissues.



Functions:

- Act as packing material for organs.
- It appears in those areas where considerable amount of mobility is required.

- Contains many transient cells responsible for inflammation, allergic reactions, and the immune response.
- Contains blood vessels and small nerve fibres.



2. **Adipose Connective Tissue:** There are two types of adipose tissue:

A. **White fat:** which is formed of aggregation of unilocular fat cells (with a large fat vacuole) in lobes separated by loose CT containing vessels, nerves, lymphatics.

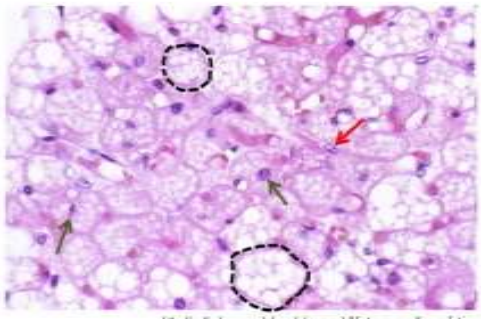
Sites: subcutaneous tissue and yellow bone marrow.

Functions:

1. Provides a store house of fat.
2. Acts as cushion in many sites and provides contour in others.
3. Helps to conserve the body heat.
4. Provides packing material around some viscera to keep them in position, such as peri-nephric fat.

B. **Brown fat**: formed of small fat cells with multiple lipid droplets (multilocular). It appears brown due to:

- ↑ mitochondria rich in cytochrome oxidase pigment.
- Very rich in blood capillaries.

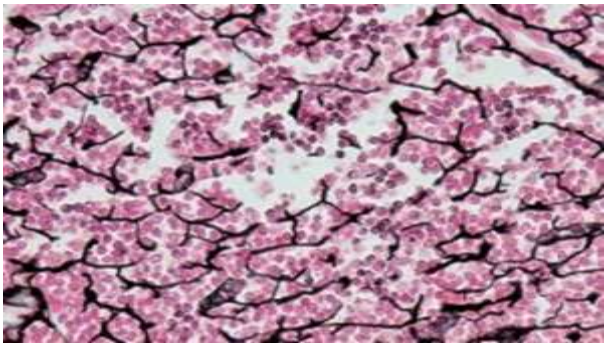


Sites: in fetuses and newborns to provide heat, protect from cold. (In adults, it is restricted to inter scapular, axillary, and mediastinal regions).

N.B.

- Fat accumulates in the body by hyperplasia or hypertrophy of adipocytes.
- Adipocytes contain enzymes that catalyze fatty acid synthesis from glucose during nutritional excess. In mitochondria and endoplasmic reticulum, fatty acids are transformed to triglycerides, then transported into central fat vacuole via liposomes.

3. Reticular Tissue



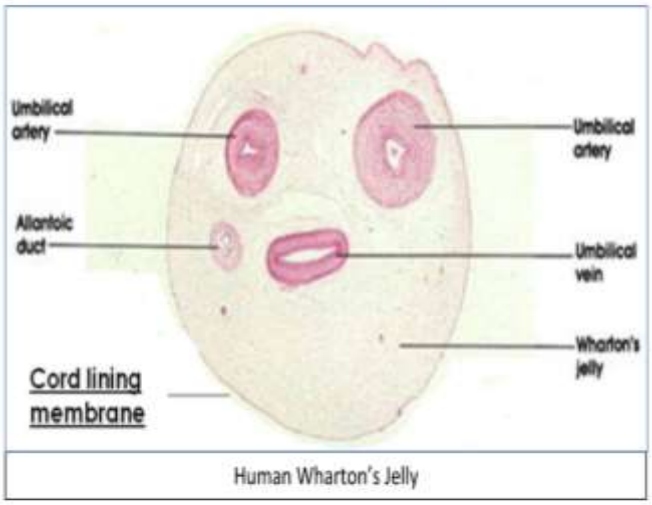
It consists of anastomosing networks of reticular fibers and reticular cells.
L/M: It stains brown with silver.
Sites: forms the stroma of lymph nodes, spleen, liver, kidneys, lungs, bone marrow, etc.

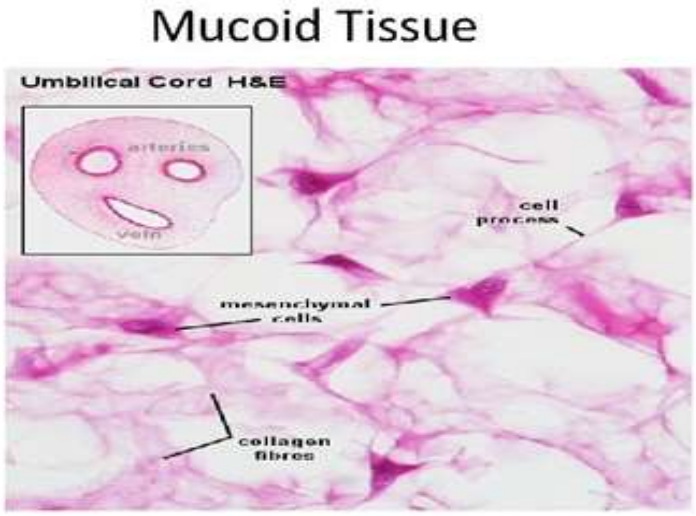
4. Mucoid Tissue:

It is embryonic connective tissue with abundant jelly like matrix, few collagen fibers, few fibroblasts (with long anastomosing processes) and numerous mesenchymal stem cells. It protects nearby structures from pressure.

Sites:

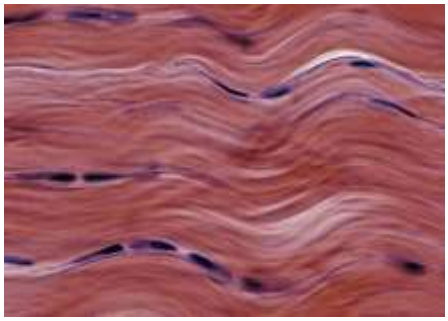
- Wharton's jelly of the umbilical cord.
- Pulp of the developing teeth.
- Vitreous body of the eyeball.





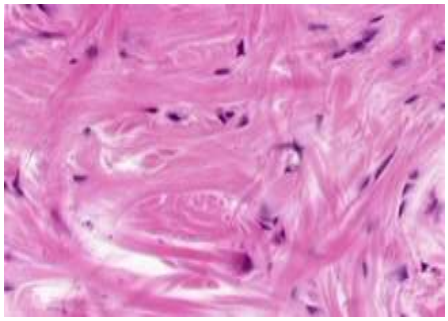
5. White Fibrous Tissue

In this tissues, collagen fibers predominate in the form of bundles in few amount of ground matrix, and contain few modified fibroblast called tendon cells. It appears in response to tensile strain.



Types:

- **Regular:** regular collagen bundles, resist stretch in one direction: as cornea, tendons.



- **Irregular**: irregular bundles, resist stretch in different directions: as sclera, capsules of organs.

6. Yellow Elastic Tissue

In this tissue, elastic fibers are predominant with few fibroblasts.

Sites: It forms elastic membranes as in aorta. Also, in elastic ligaments as ligamentum flavum between vertebrae (to facilitate movement and ligamentum nuchae for neck movement).**Cartilage**

Function of cartilage:

1. Bearing mechanical stresses.
2. Support soft tissue.
3. Shock-absorbing and sliding area for joints to facilitate bone movements.
4. Development and growth of long bones before and after birth.

General characters of cartilage:

1. Cartilage extracellular matrix has a firm (rubbery) consistency that allows the tissue to bear mechanical stresses without permanent distortion.
2. Cartilage is avascular and gets its nutrition from surrounding CT capillaries by diffusion or by means of synovial fluid from joint cavities.
3. Cartilage has no lymphatic vessels or nerves.
4. All types of cartilages except articular-hyaline and fibrocartilage, are covered by perichondrium.

Structure of cartilage: As other types of CT it has the following components:

A. Cells:

1. Chondrogenic cells
2. Chondroblasts
3. Chondrocytes

B. Matrix: consists of

*1. **Fibers:*** (depending on the type of cartilage)

- Collagen type I and II.
- Elastic

*2. **Ground Substance:***

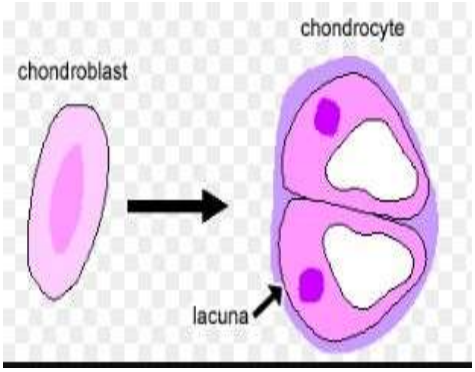
- Hyaluronic acid.
- Proteoglycan.
- Glycoprotein.

A. Cells of cartilage

1. Chondrogenic cell

They are spindle-shaped cells derived from mesenchymal cells. Their cytoplasm is sparse, and display a small Golgi apparatus, a few mitochondria, some profiles of rough endoplasmic reticulum (RER), and **an abundance of free ribosomes**. They are present in the inner layer of perichondrium. These cells can differentiate into both chondroblasts and osteoprogenitor cells.

2. Chondroblasts



Form chondrocytes in the growing cartilage matrix.

Site: at the periphery of cartilage.

LM: oval cells with basophilic cytoplasm and vesicular nuclei.

EM: chondroblasts show all the features of protein synthesizing cells; abundant rER, prominent Golgi apparatus, numerous mitochondria, and euchromatin.

Functions:

1. These cells are extremely important in chondrogenesis due to their role in forming both the Chondrocytes and cartilage matrix which will form cartilage.
2. Chondroblasts are called chondrocytes when they embed themselves in the cartilage matrix until they completely surrounded by the matrix forming what is called lacunae.

3. Chondrocytes

They are the mature cartilage cells derived from chondroblast. It synthesizes and secretes the extracellular matrix.

LM: large, flattened cells with their long axis parallel to the surface. Towards the interior, they become rounded. They have vacuolated basophilic cytoplasm.

EM: their characters are similar to features of protein synthesizing cells. The cytoplasm contains lipid droplets and glycogen.
Young chondrocytes can divide inside lacunae once or twice to form cell nests. --- Mature chondrocytes do not divide.

N.B. Because cartilage matrix is avascular, chondrocytes respire under low-oxygen tension. Hyaline cartilage cells metabolize glucose mainly by anaerobic glycolysis

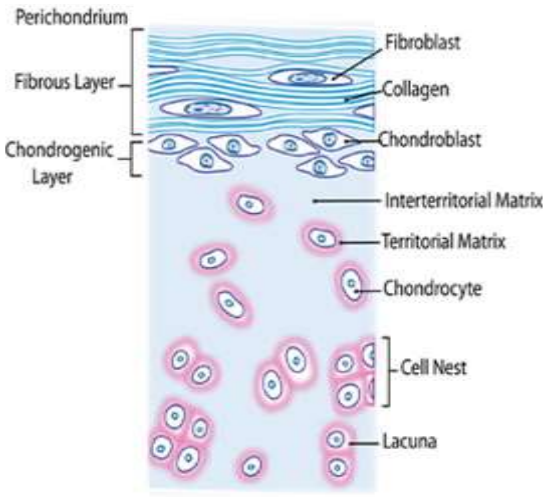
Functions:
Synthesis of the components of cartilage matrix.

Types of Cartilage:
1. Hyaline cartilage.
2. Elastic cartilage.
3. Fibrocartilage.

1. Hyaline cartilage

The most abundant type,

Sites: It is found in:
- Temporary embryonic skeleton
- Epiphyseal plate
- Articular surfaces of various synovial joints.
- In the wall of large respiratory passages (trachea, bronchi).
- Ends of ribs, where they articulate with the sternum.



Structures:

1. **Cells**:
   - Chondrogenic cells
   - Chondroblasts
   - Chondrocytes: which are lying in groups inside lacunae. Each lacuna is generally occupied by a single cell, but during the division of the cells it may contain two, four, or eight cells.

2. **Matrix**: is mostly made up of
   - Type II collagen
   - Hydrated gel of proteoglycan: **aggrecans**
   - Multiadhesive glycoprotein: chondronectin

The proteoglycan makes the matrix generally basophilic and the thin collagen fibrils are barely discernible

Perichondrium:

- Hyaline cartilage is covered externally by a fibrous membrane, called the perichondrium (not in articular cartilage). This membrane contains vessels that provide the cartilage with nutrition. It is essential for nutrition and growth.
- It consists of 2 layers:

A. The outer layer is formed of type I collagen fibers and fibroblast.

B. The inner layer is composed of chondrogenic cells and chondroblasts.

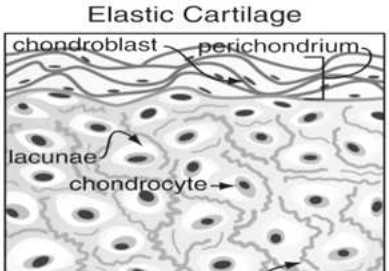
N.B Hyaline cartilage degenerates when the chondrocytes hypertrophy and die and the matrix begins to calcify. This process is a normal and integral part of **endochondral bone formation**; however, it is also a natural process of **aging**, often resulting in less mobility and in joint pain.

2. Elastic cartilage

Elastic cartilage is also called yellow cartilage.

Sites: It is found in:

- Ear pinna
- External auditory canal
- Eustachian tube
- Epiglottis



Structure of elastic cartilage:
Elastic cartilage is histologically similar to hyaline cartilage but it differs from hyaline cartilage in:

- Its matrix contains many elastic fibers and few collagen fibers type II. These yellow elastic fibers give elastic cartilage great flexibility so that it is able to withstand repeated bending.

3. Fibrocartilage

Sites: It is found in:
- The intervertebral discs
- Pubic symphysis
- Semilunar cartilage of knee joint

- Chondrocytes appear singly or in groups arranged in rows.
- Matrix is acidophilic because it contains large amount of collagen type I with little proteoglycan.
- It has no perichondrium.
- It is strong and resists stretching due to its high content of collagen fibers.

Growth of cartilage
The growth is performed by 2 methods:

1. Appositional growth:
- Deposition of new cartilage on the surface of existing cartilage.

- It occurs through mitotic division of the chondroblasts in the inner layer of perichondrium, which leads to the formation of new cells that secrete matrix. This process adds new layers to the cartilage from outside.

2. Interstitial growth:
- Formation of new cartilage within an existing cartilage.
- Results chondrocyte division in the center of the cartilage, leading to the formation of cell nests, which secrete matrix and causing growth of the cartilage from its center.
- Interstitial growth occurs only in the early phase of hyaline cartilage formation. articular cartilage which lacks a perichondrium and in the epiphyseal plates of long bones.

Cartilage repair

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

Bone

Bone is a special type of CT with hard matrix.

Function of bone:

1. Forms body skeleton and protects vital organ.
2. Acts as a store of Ca and other ions.
3. Contains bone morrow, the factory of blood cells.

Structure of bone:

A. Cells:

1. Osteogenic or osteoprogenitor cells
2. Osteoblasts
3. Osteocytes
4. Osteoclasts

B. Matrix

1. ***Organic component***
   - **Mainly type I collagen fibers** "90% of organic matrix".
   - **Ground substance**: proteoglycans and small glycoprotein as osteopontin and osteocalcin.
2. ***Inorganic component:***
   Calcium, phosphorous, bicarbonates, citrate, sodium, potassium, and sodium.

External and internal surfaces of all bones are covered by connective tissue of the periosteum and endosteum respectively

A. Periosteum: Two layers:

1. **Outer fibrous**: dense CT formed mainly of collagen fibers and fibroblasts. It contains blood and nerve supply of bone.
2. **Inner Cellular**: osteogenic cells (stem cell) and osteoblasts.

B. Endosteum

1. Single delicate layer of osteogenic cells.
2. Lines marrow cavities, canals of compact bone, and trabeculae of spongy bone.

Bone Cells

1. Osteogenic or osteoprogenitor

Origin: Mesenchymal stem cells.

Site: In periosteum and endosteum.

LM: Flattened cells, slightly basophilic cytoplasm, and lightly stained elongated nucleus.

Functions: Differentiate into osteoblasts and at low oxygen tension may change into chondrogenic cells so considered as bi-potential cells.

2. Osteoblasts

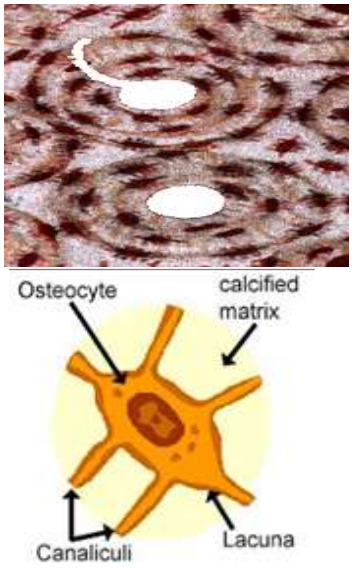
The bone-forming cells.

LM: Large oval cells with short fine processes and strong basophilic cytoplasm (-ve Golgi image above nucleus).

EM:
Abundant RER and free ribosomes.
Well-developed Golgi apparatus with numerous mitochondria.

Functions:
1. Secretion of bone matrix.
2. Calcification (mineralization) of bone matrix.

3. Osteocytes *(The bone maintaining cell)*



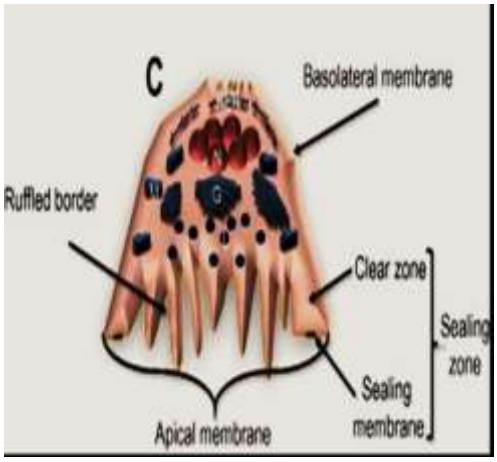
Origin: Formed by osteoblasts trapped in lacunae and surrounded by calcified matrix.

LM: Small, branched cells present inside lacunae, weak basophilic cytoplasm, and oval nuclei.

EM:RER, Golgi apparatus, ribosomes, and mitochondria.
Cytoplasmic processes extend through canaliculi in bone matrix to contact processes of neighboring cells by gap junctions.

Functions: Osteocytes maintain the calcified
Matrix. The extensive lacunar-canalicular network of these cells and their communication with all other bone cells allow osteocytes to act as detectors of microdamage in bone and help regulate bone remodeling.

4. Osteoclasts



Bone-eating cells.
origin from the fusion of bone marrow-derived monocytes.

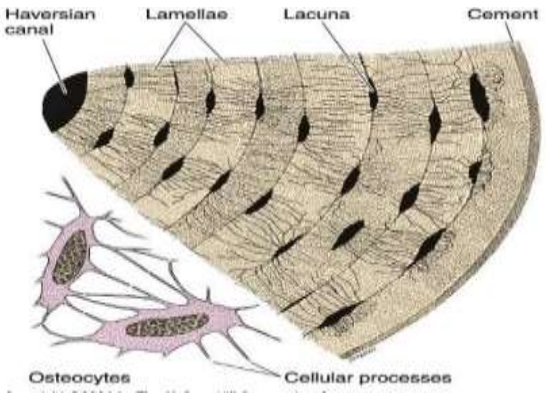
Site: Occupy shallow depressions in bone matrix called *"Howship's lacunae".*

LM:
Large cell with striated (ruffled) border.
Strongly acidophilic cytoplasm.
Multinucleated (5- 50 nuclei).

EM:
Ruffled border: numerous cell membrane infoldings.
C**lear zone** just below ruffled border**.** Rich in microfilaments lacking other organelles.
Central zone of cytoplasm contains numerous lysosomes and mitochondria.

Functions:
1. Resorb bone by releasing lysosomal hydrolases into extracellular space.
2. Secrete collagenases to digest organic component
3. Secrete organic acids for dissolution of calcium salts

Types of bone



1. Compact Bone.
2. Cancellous bone (spongy bone)

1. Compact bone: Dense, hard and without cavities. In outer layer of all bones
(especially shaft of long bones)

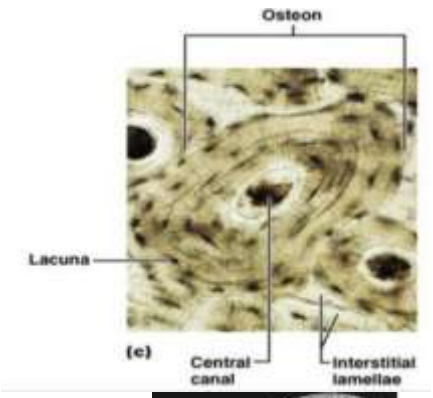
Structure:
1. Haversian system.
2. Circumferential (O&I) lamellae.
3. Interstitial lamellae.

4. Periosteum
5. Endosteum

1. Haversian system (osteon): Structural unit of compact bone formed of:

A. Haversian canal: loose CT rich in blood vessels and nerves. runs parallel to long axis of bone.

B. Concentric bone lamellae: calcified osteoid tissue arranged in layers (4-20 layers) around haversian canals. Osteocytes are arranged concentrically between lamellae.

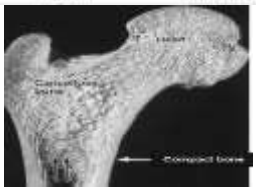


2. Circumferential Lamellae: Calcified osteoid tissue arranged:

A. Parallel to endosteum (inner circumferential).

B. Parallel to periosteum (outer circumferential) lamellae.

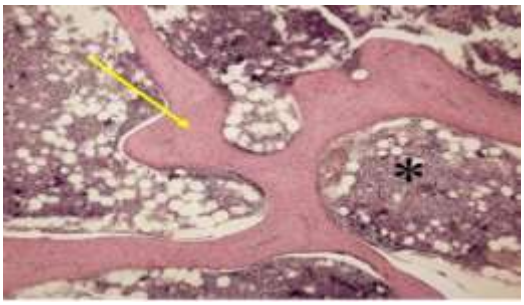
3. Interstitial Lamellae: Irregularly arranged lamellae in-between haversian systems.



Volkmann's Canals: Oblique or transverse channels through which blood vessels and nerves travel from periosteum and endosteum to haversian canals.

Sharpey's Fibers: Collagen fibers arise from periosteum, at sites of tendons and ligaments attachment, to anchor them strongly to extracellular matrix of bone.

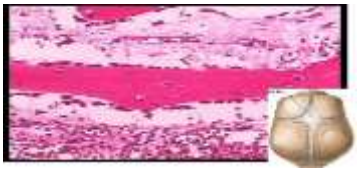
2. Cancellous Bone



Spongy-like meshwork with cavities.

Site: interior of all bones mainly flat bones.

Structure:
Irregular trabeculae of bone tissue
NO Haversian system.
Numerous interconnecting marrow spaces
Osteocytes are irregularly arranged in bone lamellae.



Ossification

1. Intra-membranous
2. Intra- cartilaginous (1ry and 2ry)

1. Intra-membranous ossification`

Occurs around the 8th week of gestation in humans. Occurs in flat bones of skull, face, and clavicle. With no cartilage template but in the center of mesenchymal tissue. Primary center of ossification appears in which mesenchymal cells differentiate into osteogenic cells and the blood vessels are increased.

The osteogenic cells divide to form osteoblasts, which form bone matrix.
Osteoblasts that are surrounded by bone matrix are now called osteocytes.

Thus, the mesenchymal membrane is changed into spongy bone.

Stages:

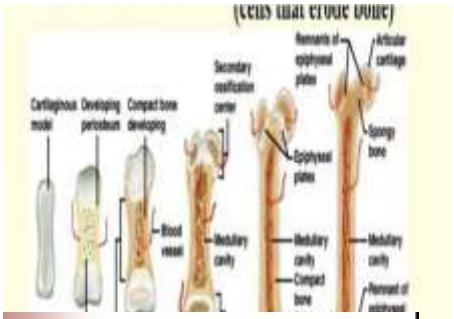
1. Some of elongated mesenchymal cells migrate and aggregate in specific areas where bone is destined to form.
2. Mesenchymal membrane becomes more vascularized and mesenchymal cells change into osteogenic cells, which divide forming osteoblasts.
3. Osteoblasts secrete collagen and other components of bone matrix (osteoid).
4. With time matrix becomes calcified and osteoblasts with inter-connected cytoplasmic processes through canaliculi are now termed osteocytes.
5. New bone extends from the center of ossification outwards in a radial manner forming interlacing bone trabeculae.
6. Vascular tissue fills spaces between trabeculae to form bone marrow spaces thus spongy bone formed. Surrounding mesenchymal cells differentiate into osteogenic cells, which form endosteum.
7. Osteogenic cells in the tissue covering bone plates form periosteum.
8. Some of the Osteogenic cells in periosteum change into osteoblasts which can deposit bone layers from outside forming parallel lamellae of comp

2. Endochondral ossification:

It occurs in the 12th week of gestation and continues in early adult life. In long bones in which a temporary cartilaginous model of the future bone is first formed. The cartilage is destroyed and then replaced by new bone. This process involves the development of primary and secondary centers of ossification.

The primary center of ossification

In diaphysis of the cartilaginous model in early fetal life:



The 2ry center of ossification

Develops at epiphysis after birth in a sequence similar to the described for the primary center.

The epiphyseal plate:

During growth of long bone the epiphyseal plates have a characteristic histological appearance. The following zones are found in the epiphyseal plate from epiphysis to diaphysis.

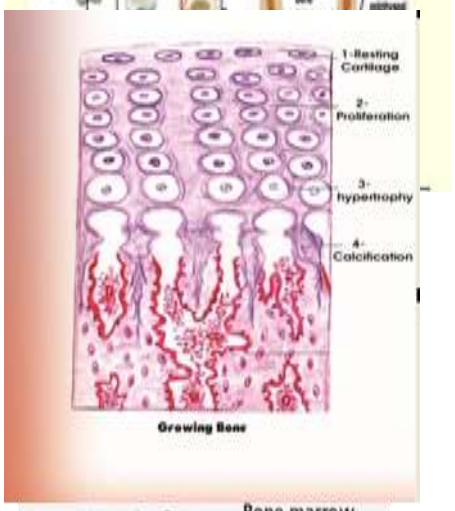
1- Resting zone: It is present next to the epiphyseal cartilage. It is a layer of hyaline cartilage. The covering perichondrium of this cartilage is very rich in osteogenic cells and blood vessels.

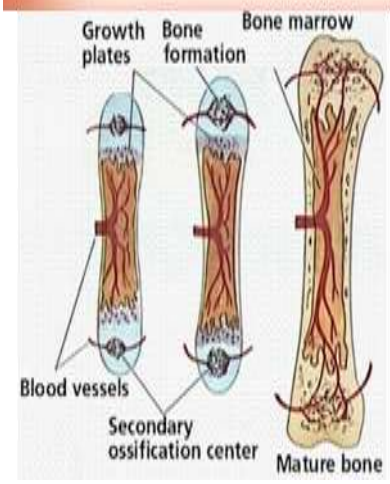
2- Proliferative zone:
chondrocytes divide rapidly and form columns parallel to the long axis of the bone.

3- Hypertrophic zone:
chondrocytes accumulate glycogen and increase in size, while the matrix between them is reduced. They produce alkaline phosphatase, which is concerned with the calcification of intercellular matrix.

4- Calcification zone: the thin septa of cartilage matrix become calcified by the deposition of hydroxyl-apatite ($Ca_{10}(PO_4)_6(OH)_2$). Calcification prevents the nutrients from diffusion through the matrix leading to degeneration of chondrocytes.

5- Ossification zone: blood capillaries & osteogenic cells invade the cavities left by chondrocytes. Osteogenic cells differentiate into osteoblasts, which deposit bone matrix over the calcified cartilage. generally associated with partial resorption of bone tissue and simultaneous lying down of new bone.





Growth of long bones

Complex process. =diaphyseal shaft increases in length as a result of osteogenic activity of the epiphyseal plate and increases in width as a result of formation of new bone by periosteum on the external surface. =At the same time, bone is removed from the internal surface causing the bone marrow cavity to increase in diameter.

When the cartilage of the epiphyseal plate stops growing, it is replaced by bone tissue around age 20.

Bone remodeling:

Lifelong process (mature bone tissue removed from skeleton (process called bone resorption) and new bone tissue formed (ossification). It is a dynamic process regulated by osteoblasts and osteoclasts.

Repair of bone fractures:

At the site of fracture, bone matrix is destroyed, and bone cells die. The damaged blood vessels produce a localized hemorrhage with formation of a blood clot.

During repair, the blood clot, cells, and damaged bone Matrix are removed by macrophages.

Osteoprogenitor cells in the endosteum and periosteum undergo intense proliferation forming a cellular (granulation) tissue surrounding the fracture and penetrating between the extremities of the fractured bone.

Small cartilage fragments appear in the cellular tissue, which then undergoes Endochondral ossification.

Bone is also formed by intramembranous ossification.

Repair process is done by irregular trabeculae of primary bone, which unites the extremities of the fractured bone forming a bone callus.

Normal stresses imposed on the bone during repair serve to remodel the bone callus.

The primary bone tissue of the callus is gradually resorbed and replaced by secondary bone restoring the original bone structure.