# General Zoology

## 1st Year students Physic and Chemistry (English)

## Faculty of Education

## By

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## THE CELL

Cells are the fundamental building blocks of all organisms. For instance, the human body is made up of trillions of cells which provide structure for the body, making the useful from the food, from which, energy is obtained to carry out the organism's biological functions.

**Cell 'Scope of history'**

In 1665, the phrase "cell" used by the English Scientist, Robert Hooke who was the first to describe cells through examining a slice of cork as he noticed that this piece of cork comprised of many tiny square boxes (small rooms) and called them cells. Scientists "150 years later" were able to observe and understand more parts of the cell due to the work of Antonie van Leeuenhoek (1675, a Dutch lens maker) who described the first living cells.

In 1838, Dutch botanist Matthias Schleiden concluded that all plants are composed of cells. A year later, a German zoologist, Theodor Schwaan
postulated that animals are also composed of cells.

In 1855, Rudolph Virchow, a German doctor, declare that all cells must come from other cells by the process of cell division. Work carried out by the three above mentioned scientists was combined into what is now known as the Cell theory that can be phrased as:

All living things are made of cells, the cell is the smallest living thing that can perform all the biological functions of life and all cells must come from pre-existing cells.

Some organisms consist of a single cells = unicellular organism, others are multicellular aggregates of specialized cells. Whether multicellular or unicellular, all organisms must accomplish the same same functions: uptake and processing of nutrients excretion of wastes response to environmental stimuli and reproduction among others.





### Cell Shapes and Cell Size

Cells differ in terms of form and structure depending on their locations in the body and its functions, some of them take different forms. For example, white blood cells moving amebic movement and shaped in various forms, red blood cells are round and smooth making them very flexible, moving easily through the blood vessels, while others have a fixed form, such as sperm cells and egg cells, and neurons (Figure 1).

Cells vary in size from each other. For example, In the human body, cell size ranges between 200 and 15,000 micron (micron =0.001 millimeter). In birds, there are cells you can seen by the naked eye (e.g an egg cells), also there are cells such as neurons to a length of several feet

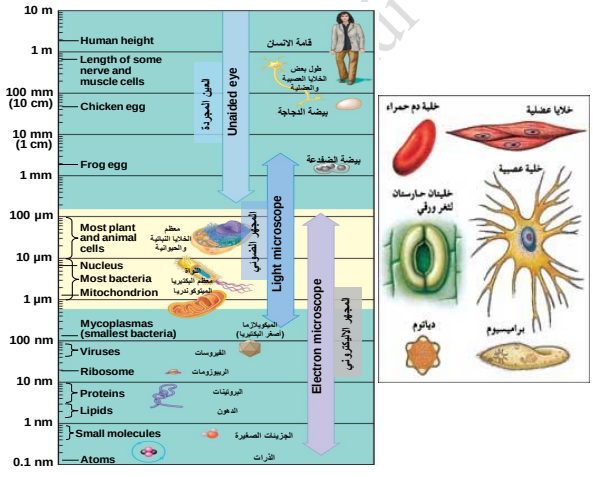



**Figure 1. Cells differ in terms of form and structure, some of them take different forms.**





### Chemical Composition of Living Cells

All living organisms, from microbes to mammals, are composed of chemical substances from both the inorganic and organic world, that appear in roughly the same proportions, and perform the same general tasks. Hydrogen, oxygen, nitrogen, carbon, phosphorus, and sulfur normally make up more than 99% of the mass of living cells, and when combined in various ways, form virtually all known organic biomolecules.

There are four general classes of macromolecules (**Figure 2**) within living cells: nucleic acids, proteins, polysaccharides, and lipids. These compounds, which have molecular weights ranging from 1x103 to 1x106, created through polymerization of building blocks that have molecular weights in the range of 50 to 150.

### Cells studying

Cells can be studied using the Microscopes (light or electrons microscope) and the cell fractionation.

**Light Microscopes**

As most cells are between 1-100 µm in diameter which can be visualized by light microscope (LM) (**Figure 3**) as the visible light is passed through the specimen and then through glass lenses that lenses refract light such that the image is magnified into the eyes or the video screen.Magnification and resolving power: Magnification power = the ratio of an object's image to its real size. Magnification of LM ~ X1,000 while the Resolving power = the measure of the image clarity.

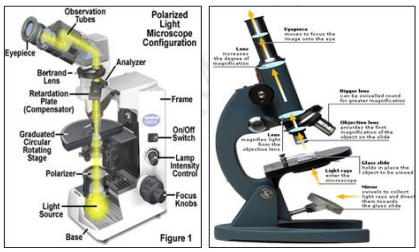
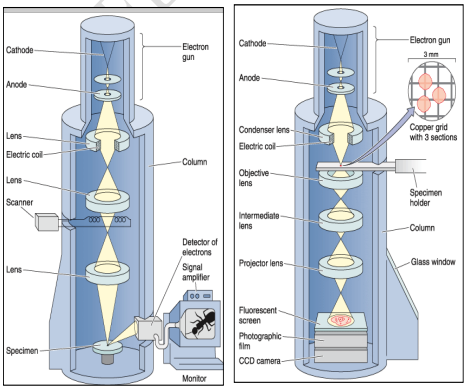



**Figure 4. Normal and polarized light microscopes**

**Electron microscope (EM); There are two types:-**

**1**-The transmission electron microscope (TEM) be used to study the internal ultrastructure of cells, as an electron beam was aimed through the thin section of specimen, then the image was focused and magnified by electromagnet (instead of glass lenses) as shown in Figure 4.

**2**-The scanning electron microscope (SEM) be used to study the surface structure of the cells as sample surface is covered with the thin film of gold, then electron beam excites the electrons on the sample surface. The secondary electrons are collected and focused on a screen and image appeared 3-dimensional (Figure 4).








## Cell Fractionation

Cell fractionation (Figure 5).is the separation of homogeneous sets, usually organelles, from a larger population of cells. Tissue is typically homogenized in an isotonic buffer solution, as well as a pH buffer by use of a variety of mechanisms such as grinding, mincing, chopping, pressure changes, osmotic shock, freeze-thawing, and ultra-sound homogenization. The disrupted cells are centrifuged at different speed and duration to fractionate components of different sizes in order to study their structure, chemical composition and function

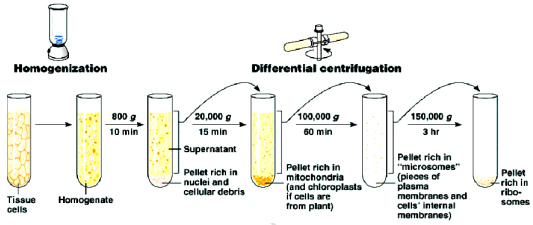



**Figure 5.** Separation of homogeneous sets (organelles) from a larger population of cells using cell fractionation technique.

## Types of cells

There are two main types of cells (Figure 6 and Table 1):

1) Eukaryotes:- The cells, have a nucleus bound by membrane (large structure that controls the workings of the cell because it contains the genes). Both animals and plants have eukaryotic cells (animals, plants, protists, and fungi) which are complex and contain a nucleus and other membrane-bound structures. Cell are in a wide variety of shapes and sizes as they all perform different functions. Regardless the protists and yeasts (single-cell fungi), all eukaryotes are multicellular.

2)-Prokaryotes: The cell does not have a nucleus as eukaryotic cells do. Archaea and bacteria are both prokaryotes, cells so small they are just visible with the light





microscope. Bacteria, are much simpler in structure, colonized the Earth two billion years before eukaryotes. It has no membrane bound nucleus. Both types of cells do share several things in common, they are surrounded by a plasma membrane (a bilayer of phospholipids). This membrane surrounds the cytoplasm that is composed of the fluid and cell's organelles, the specialized structures that perform certain tasks within the cell.

**Table 1** Comparison between Eukaryotes and Prokaryotes cells types

| | Prokaryotes | Eukaryotes |
|---|---|---|
| Nucleus? | NO (nucleoid) | YES |
| Membrane-bound organelles? | NO | YES (Many) |
| Size | 1 - 10 mm | 10 - 50 mm |
| When evolved? | 3.5 billion years ago | 1.5 billion years ago |
| Cytoplasm? | YES | YES |
| Cell membrane? | YES | YES |
| Cell wall? | Some Do | Plants |
| Ribosomes? | YES | YES |
| DNA? | Circular Free Floating | Chromosomes in Nucleus |
| Examples | Bacteria | Plants, Animals, Fungi, and Protist |

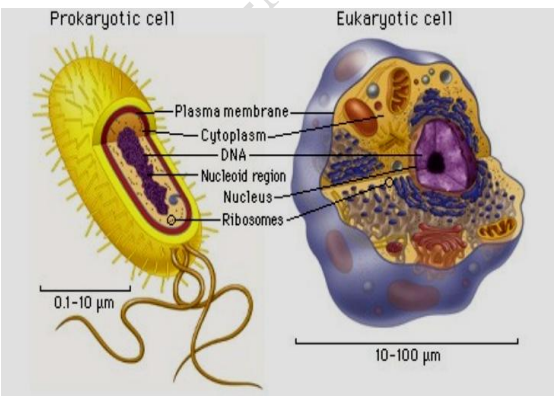



**Figure 6. Two Basic Types of Cells**





## Levels of Organization of Living things

Living things are highly organized and structured, following a hierarchy that can be examined on a scale from small to large (Figure 7). The atom is the smallest and most fundamental unit of matter. It consists of a nucleus surrounded by electrons. Atoms form molecules which are chemical structures consisting of at least two atoms held together by one or more chemical bonds. Many molecules that are biologically important are macromolecules, formed by polymerization. Macromolecules can form aggregates within a cell that are surrounded by membranes; these are called organelles. Organelles are small structures that exist within cells. Examples of these include: mitochondria and chloroplasts, which carry out indispensable functions. In larger organisms, cells combine to make tissues, which are groups of similar cells carrying out similar or related functions. Organs are collections of tissues grouped together performing a common function and present not only in animals but also in plants. An organ system is a higher level of organization that consists of functionally related organs. Mammals have many organ systems. For examle, the circulatory system transports blood through the body to and from the lungs; it includes organs such as the heart and blood vessels.

## Cell Structure and Components

A typical eukaryotic cell (**Figure 8**) is surrounded by a plasma membrane and contain a membrane-bound nucleus and organelles. Unlike the eukaryotic plant and fungi cells; animal cells do not have a cell wall because this rigid cell wall allowed animals to develop a greater diversity of cell types, tissues, and organs.

**The cell is composed of two basic parts**: cytoplasm (Gr. kytos, cell, + plasma, thing formed) and nucleus (L. nux, nut). Individual cytoplasmic components are usually not clearly distinguishable in common hematoxylin and eosin-stained preparations. The nucleus, however, appears intensely stained dark blue or black.

### Cytoplasm

The cytoplasm of eukaryotic cells is divided into several distinct compartments by membranes that regulate the intracellular traffic of ions and molecules. These

compartments concentrate enzymes and the respective substrates, thus increasing the efficiency of the cell. **The Cell organelles and components as follows:**

**Plasma Membrane:** In prokaryotes, it is the inner layer of protection surrounded by a rigid cell wall. Eukaryotic animal cells have only the membrane to contain and protect their contents and regulate the passage of molecules in/out of the cells.

**Nucleus and Nucleolus:** The nucleus is the control center of the cell. It contains/is the place of the cell's hereditary material (Genetic components) and coordinates the cell's activities, which include growth, intermediary metabolism, protein synthesis, and reproduction (cell division). The Nucleolus is a dense region of ribonucleic acid (RNA) in the nucleus and is the site of ribosome formation.

**Endoplasmic Reticulum:** A network of sacs which that manufactures, processes, and transports chemical compounds for use inside and outside of the cell. It is connected to the double-layered nuclear envelope (nuclear membrane), providing a pipeline between the nucleus and the cytoplasm.

**Golgi Apparatus:** The Golgi apparatus is the distribution and shipping department for the cell's chemical products. It modifies proteins and fats built in the endoplasmic reticulum and prepares them for export to the outside of the cell.

**Ribosomes:** All living cells contain ribosomes, tiny organelles composed of approximately 60 percent RNA and 40 percent protein. In eukaryotes, ribosomes are four strands of RNAs. In prokaryotes, they consist of three strands of RNAs.

**Mitochondria:** Mitochondria are oblong shaped organelles that are found in the cytoplasm of every eukaryotic cell. In the animal cell, they are the main power generators, converting oxygen and nutrients into energy.

**Lysosomes:** The main function of these micro bodies is digestion. Lysosomes break down cellular waste products and debris from outside the cell into simple compounds, which are transferred to the cytoplasm as new cell-building materials.

**Endosomes and Endocytosis**: Endosomes are membrane-bound vesicles, formed via a complex family of processes collectively known as endocytosis, and found in





the cytoplasm of virtually every animal cell. The basic mechanism of endocytosis is the reverse of what occurs during exocytosis or cellular secretion. It involves the invagination (folding inward) of a cell's plasma membrane to surround macromolecules or other matter diffusing through the extracellular fluid.

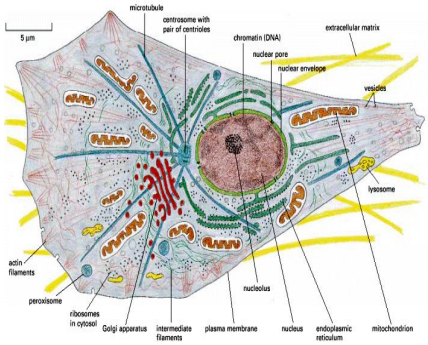
**Peroxisomes:** Microbodies are a diverse group of organelles that are found in the cytoplasm, roughly spherical and bound by a single membrane. There are several types of microbodies but peroxisomes are the most common.

**Microfilaments:** Microfilaments are solid rods made of globular proteins called actin. These are an important component of the cytoskeleton.

**Microtubules:** These straight, hollow cylinders are found throughout the cytoplasm of all eukaryotic cells (prokaryotes don't have them) and carry out a variety of functions, ranging from transport to structural support.

**Centrioles:** Centrioles are self-replicating organelles made up of nine bundles of microtubules and are found only in animal cells. They organize cell division, but aren't essential to the process.

**Cilia and Flagella**: For single-celled eukaryotes, cilia and flagella are essential for the locomotion of individual organisms. In multicellular organisms, cilia function to move fluid/materials past an immobile cell, also a cell or group of cells.








**Intermediate Filaments:** Intermediate filaments are a very broad class of fibrous proteins that play an important role as both structural and functional elements of the cytoskeleton. Ranging in size from 8 to 12 nanometers, intermediate filaments function as tension-bearing elements to help maintain cell shape and rigidity.

### The Plasma Membrane

The outermost component of the cell, separating the cytoplasm from its extracellular environment, is the plasma membrane (plasmalemma). Although the plasma membrane defines the external limit of the cell, a continuum exists between the interior of the cell and extracellular macromolecules using integrins proteins that are linked to both cytoplasmic cytoskeletal filaments and extracellular matrix components. Through these linkages there is a constant exchange of influences, in both directions, between the extracellular matrix and the cytoplasm.

**Plasma Membrane Structure**

All eukaryotic cells are enveloped by a limiting membrane composed, cholesterol, proteins, and chains of oligosaccharides covalently linked to phospholipid and protein molecules. Membranes range from 7.5 to 10 nm in thickness and consequently are visible only in the electron microscope. The line between adjacent cells sometimes seen with the light microscope is formed by plasma membrane proteins of the cells plus extracellular material, which together can reach a dimension visible by light microscopy. Because all membranes have this appearance, the 3-layered structure was designated the unit membrane (Figure 9).

Membrane phospholipids, such as phosphatidylcholine (lecithin), consist of two non-polar (hydrophobic or water-repelling) long-chain fatty acids linked to a charged polar (hydrophilic or water-attracting) head group. Cholesterol is also present, often at nearly a 1:1 ratio with the phospholipids in plasma membranes.

Membrane phospholipids are most stable when organized into a double layer (bilayer) with their hydrophobic fatty acid chains directed toward the middle away from water and their hydrophilic polar heads directed outward to contact water on





both sides (Figures 9/10). Cholesterol molecules insert among the close packed the phospholipid fatty acids, restricting their movement, and thus modulate the fluidity and movement of all membrane components. The lipid composition of each half of the bilayer is different. For example, in red blood cells phosphatidylcholine and sphingomyelin are more abundant in the outer half of the membrane, whereas phosphatidylserine and phosphatidylethanolamine are more concentrated in the inner half. Some of the lipids, known as glycolipids, possess oligosaccharide chains that extend outward from the surface of the cell membrane and thus contribute to the lipid asymmetry.

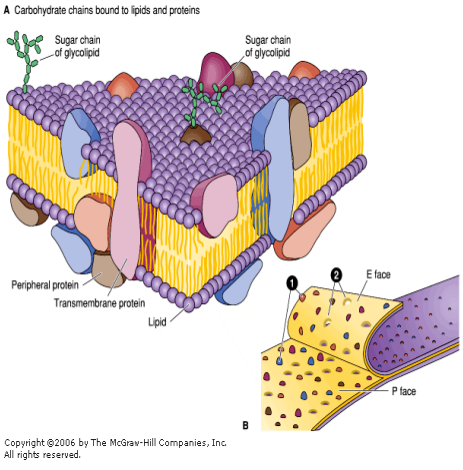



**Figure 10.The fluid mosaic model of membrane structure**.

**A:** The fluid mosaic model of membrane structure. The membrane consists of a phospholipid double layer with proteins inserted in it (integral proteins) or bound to the cytoplasmic surface (peripheral proteins). Integral membrane proteins are firmly embedded in the lipid layers. Some of these proteins completely span the bilayer and are called transmembrane proteins, whereas others are embedded in either the outer or inner leaflet of the lipid bilayer. The dotted line in the integral

membrane protein is the region where hydrophobic amino acids interact with the hydrophobic portions of the membrane. Many of the proteins and lipids have externally exposed oligosaccharide chains. **B:** Membrane cleavage occurs when a cell is frozen and fractured (cryofracture). Most of the membrane particles (1) are proteins or aggregates of proteins that remain attached to the half of the membrane adjacent to the cytoplasm (P, or protoplasmic, face of the membrane). Fewer particles are found attached to the outer half of the membrane (E, or extracellular, face). For every protein particle that bulges on one surface, a corresponding depression (2) appears in the opposite surface. Membrane splitting occurs along the line of weakness formed by the fatty acid tails of membrane phospholipids, since only weak hydrophobic interactions bind the halves of the membrane along this line. (Modified and reproduced, with permission, from Krstíc RV: Ultrastructure of the Mammalian Cell. Springer-Verlag, 1979.)







**Plasma Membrane Transport Process**

There are three types of transport systems operating to move substances across membranes (Figure 11). These are Passive Transport, Facilitated Transport and Active Transport. The first two mechanisms employ the power of diffusion and do not require energy for operation.

**1-Passive Transport**: Diffusion is a Passive Transport system. Diffusion processes ultimately achieve equal concentration of molecules on either side of the membrane, but, as noted above, polar substances have difficulty diffusing across lipid bilayer membranes. Food substances, such as sugars do not diffuse across membranes with sufficient speed to meet a cell's energy needs.

**2-Facilitated Transport** (Facilitated Diffusion) uses specific molecules to enable the transfer of substrate across a membrane and reach equilibrium. Ultimatelly, Facilitated Diffusion is the same as simple diffusion-equal concentration of a material on both sides of a membrane. The difference, however, is that Facilitated Diffusion speeds achievement of the equilibrium dramatically. Note that movement of materials across a membrane do not refer to just the cell membrane. Organelle membranes (such as the nucleus or mitochondrion) too pose the same barriers to diffusion as the cell membrane.

**3-Active Transport**

Active transport processes usually work against a concentration gradient, pumping molecules from a lower concentration on one side of the membrane to a higher concentration on the other side of the membrane. In some cases, the gradient can be formidable. For example of calcium across the membranes of the sarcoplasmic reticulum, which is maintained at a ratio of 30,000 to 1. If there were not pumping systems capable of selectively pumping to this extent, the Delta G value of +26.6 kJ/mol would preclude its formation naturally. Active transport mechanisms employ specific protein molecules variously called carriers, permeases, porters, translocases, translocators, and transporters.

Cells expend energy in order to build concentration gradients of ions (for example, Na+ and K+). This electrochemical potential gradient represents energy that can





also be utilized for the purposes of the cell. As we shall see later, mitochondria harvest energy from a proton gradient they create in order to make ATP in oxidative phosphorylation. Energy from electrochemical potential gradients is also used by the cell to drive transport of molecules across membranes.

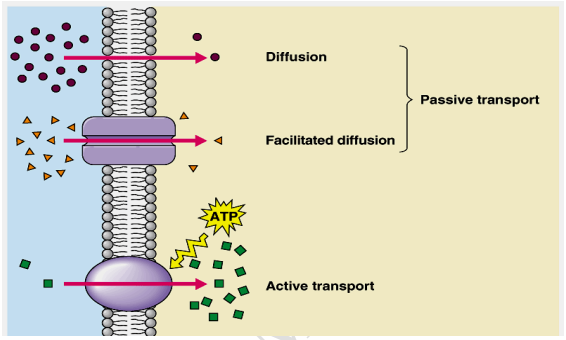



**Figure 11. Plasma Membrane Transport Process**

## Endocytosis

Bulk uptake of material also occurs across the plasma membrane in a general process called endocytosis, which involves folding and fusion of this membrane to form vesicles which enclose the material transported. Cells show **three general types of endocytosis** (**Figure 12**).

**1-Phagocytosis**. Phagocytosis literally means "cell eating." Certain white blood cells, such as macrophages and neutrophils, are specialized for engulfing and removing particulate matter such as bacteria, protozoa, dead cells, and unneeded extracellular constituents. When a bacterium becomes bound to the surface of a neutrophil, cytoplasmic processes of the cell are extended and ultimately surround





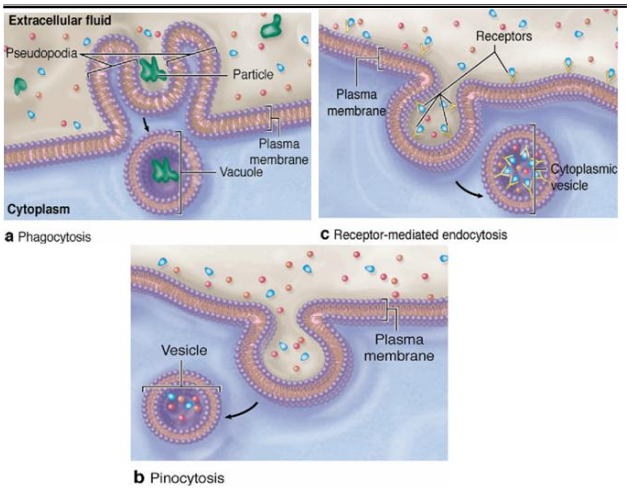



**Figure 12. Three major forms of endocytosis.**

**Endocytosis is a process** in which a cell takes in material from the extracellular fluid using dynamic movements and fusion of the cell membrane to form cytoplasmic,membrane-enclosed structures containing the material. Such cytoplasmic structures formed during endocytosis fall into the general category of vesicles or vacuoles.

**(a) Phagocytosis** involves the extension from the cell of large folds called pseudopodia which engulf particles, for example bacteria, and then internalize this material into a cytoplasmic vacuole or phagosome.

**(b) In pinocytosis** the cell membrane invaginates (dimples inward) to form a pit containing a drop of extracellular fluid. The pit pinches off inside the cell when the cell membrane fuses and forms a pinocytotic vesicle containing the fluid.

**(c) Receptor-mediated endocytosis** includes membrane proteins called receptors which bind specific molecules (ligands). When many such receptors are bound by their ligands, they aggregate in one membrane region which then invaginates and pinches off to create vesicle or endosome containing both the receptors and the bound ligands

the bacterium. The membranes of these processes meet and fuse, enclosing the bacterium in an intracellular vacuole, a phagosome.

**2-Fluid-phase Endocytosis**. In fluid-phase **pinocytosis** "**cell drinking**", with a mechanism comparable to that of phagocytosis, smaller invaginations of the cell membrane form and entrap extracellular fluid and anything it has in solution. Pinocytotic vesicles (about 80 nm in diameter) pinch off inwardly from the cell surface. In most cells such vesicles usually fuse with lysosomes (see the section on lysosomes later in this chapter). In the lining cells of capillaries (endothelial cells), however, pinocytotic vesicles may move to the cell surface opposite their origin. There they fuse with the plasma membrane and release their contents outside the cell, thus accomplishing bulk transfer of material across the cell. This process is termed transcytosis.

**3-Receptor-mediated Endocytosis**. Receptors for many substances, such as low-density lipoproteins and protein hormones, are integral proteins of the cell membrane. Binding of the ligand (a molecule with high affinity for a receptor) to its receptor causes widely dispersed receptors to aggregate in special membrane regions called coated pits. The electron-dense coating on the cytoplasmic surface of the membrane is composed of several polypeptides, the major one being clathrin. In a developing coated pit clathrin molecules interact like the struts in a geodesic dome, forming that region of cell membrane into a cage-like invagination that is pinched off into the cytoplasm, forming a coated vesicle (Figure 13) carrying the ligand and its receptor.

In all these endocytotic processes, the vesicles or vacuoles produced quickly enter and fuse with the endosomal compartment, a dynamic system of membranous vesicles (Figure 13) and tubules located in the cytoplasm near the cell surface (early endosomes) or deeper in the cytoplasm (late endosomes). The clathrin molecules separated from the coated vesicles recycle to the cell membrane to participate in the formation of new coated pits. The membrane of endosomes contains ATP-driven H+ pumps that acidify their interior. While phagosomes and





pinocytotic vesicles soon fuse with lysosomes, molecules penetrating the endosomal compartment after receptor-mediated endocytosis may take more than one pathway (Figure 14). The acidic pH of early endosomes causes many ligands to uncouple from their receptors, after which the two molecules are sorted into separate vesicles. The receptors may be returned to the cell membrane to be reused.

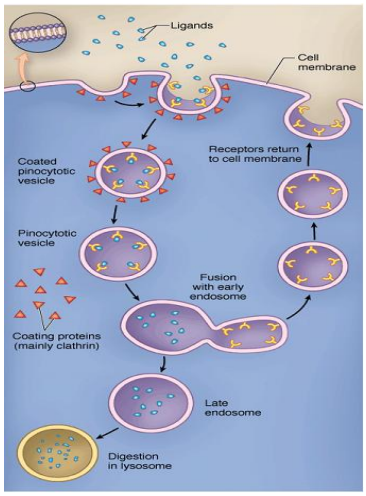



**Figure 14.** Endocytosis and membrane trafficking. Ligands, such as hormones and growth factors, are internalized by receptor-mediated endocytosis, which is mediated by the cytoplasmic peripheral membrane proteinclathrin or other proteins which promote invagination and temporarily coat the newly formed vesicles. Such coated vesicles can be identified by TEM. After detachmentof the coating molecules, the vesicle fuses with one or more vesicles of the endosomal compartment, where the ligands detach from their receptors and are sorted into other vesicles. Vesicles of membrane with empty receptors return to the cell surface and after fusion the receptors are ready for reuse. Vesicles containing the free ligands typically fuse with lysosomes. The cytoskeleton with associated motor proteins is responsible for all such directional movements of vesicles.





**Exocytosis**

In exocytosis a membrane-limited cytoplasmic vesicle fuses with the plasma membrane, resulting in the release of its contents into the extracellular space without compromising the integrity of the plasma membrane (Figure 15). Often exocytosis of stored products from epithelial cells occurs specifically at the apical domains of cells, such as in the exocrine pancreas and the salivary glands. The fusion of membranes during exocytosis is a highly regulated process involving interactions between several specific membrane proteins. Exocytosis is triggered in many cells by transient increase in cytosolic Ca2+.

During endocytosis, portions of the cell membrane become endocytotic vesicles; during exocytosis, the membrane is returned to the cell surface. This process of membrane movement and recycling is called membrane trafficking (Figures 20). Trafficking and sorting of membrane components occur continuously in most cells and are not only crucial for cell maintenance but also physiologically important in processes such as reducing blood lipid levels.

**Signal Reception and Transduction**

Cells in a multicellular organism need to communicate with one another to regulate their development into tissues, to control their growth and division, and to coordinate their functions. Many cells form communicating junctions that couple adjacent cells and allow the exchange of ions and small molecules. Through these channels, also called gap junctions, signals may pass directly from cell to cell without reaching the extracellular fluid. Soluble extracellular signaling molecules bind receptor proteins only found on their target cells. Each cell type in the body contains a distinctive set of receptor proteins that enable it to respond to a complementary set of signaling molecules in a specific, programmed way (Figure 15). Such signaling can different routes.

*In endocrine signaling, the signal molecules (called hormones) are carried in the blood to target cells throughout the body.





* **In paracrine signaling**, the chemical mediators are rapidly metabolized so that they act only on local cells very close to the source.

***In synaptic signaling**, a special kind of paracrine interaction, neurotransmitters act only on adjacent cells through special contact areas called synapses.

***In autocrine signaling,** signals bind receptors on the same cell type that produced the messenger molecule. *In juxtacrine signaling, important in early embryonic tissue interactions, signaling molecules remain part of a cell's surface and bind surface receptors of the target cell when the two cells make direct physical contact.

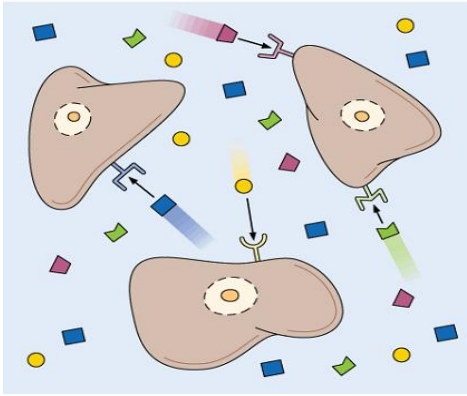


**Figure 15. Receptors and their ligands**

Cells respond to certain external chemical signals that act as ligands, such as hormones and lipoproteins, according to the library of receptors they have. Such receptors are always proteins, typically transmembrane proteins. In this schematic representation, three cells appear with different receptors. The extracellular environment is shown to contain several ligands, which can interact only with the appropriate specific receptors. Considering that the extracellular environment contains a multitude of molecules, it is important that ligands and the respective receptors exhibit complementary morphology and great binding affinity.

## Endoplasmic Reticulum

The cytoplasm of eukaryotic cells contains an anatomising network of intercommunicating channels and sacs formed by a continuous membrane which encloses a space called a cisterna. In sections cisternae appear separated, but high-resolution microscopy of whole cells reveals that they are continuous. This membrane system is called the endoplasmic reticulum (ER) as shown in Figure 16. In many places the cytosolic side of the membrane is covered by polyribosomes synthesizing protein molecules which are injected into the cisternae. This permits the distinction between the two types of endoplasmic reticulum: rough and smooth.

### Rough Endoplasmic Reticulum

Rough endoplasmic reticulum (RER) is prominent in cells specialized for protein secretion, such as pancreatic acinar cells (digestive enzymes), fibroblasts (collagen), and plasma cells (immunoglobulins). The RER consists of saclike as well as parallel stacks of flattened cisternae (Figure 16), limited by membranes that are continuous with the outer membrane of the nuclear envelope. The name "rough endoplasmic reticulum" refers to the presence of polyribosomes on the cytosolic surface of this structure's membrane. The presence of polyribosomes also confers basophilic staining properties on this organelle when viewed with the light microscope.

The principal function of the RER is to segregate proteins not destined for the cytosol. Additional functions include the initial (core) glycosylation of glycoproteins, the synthesis of phospholipids, the assembly of multichain proteins, and certain posttranslational modifications of newly formed polypeptides.

### Smooth Endoplasmic Reticulum

Smooth endoplasmic reticulum (SER) also takes the form of a membranous network within the cell; however, its ultrastructure differs from that of RER in two ways. First, SER lacks the associated polyribosomes that characterize RER. SER membranes therefore appear smooth rather than granular. Second, its cisternae are more tubular and more likely to appear as a profusion of interconnected channels





of various shapes and sizes than as stacks of flattened cisternae (Figures 16). Additionally, SER is continuous with the RER.

SER is associated with a variety of specialized functional capabilities. In cells that synthesize steroid hormones (eg, cells of the adrenal cortex), SER occupies a large portion of the cytoplasm and contains some of the enzymes required for steroid synthesis. SER is abundant in liver cells, where it is responsible for the oxidation, conjugation, and methylation processes employed by the liver to degrade certain hormones and neutralize noxious substances such as barbiturates. Another important function of SER is the synthesis of phospholipids for all cell membranes.

## Ribosomes

Ribosomes are small electron-dense particles, about 20 x 30 nm in size. They are composed of four types of rRNA and almost 80 different proteins. There are two classes of ribosomes. One class is found in prokaryotes, chloroplasts, and mitochondria; the other is found in eukaryotic cells. Both classes of ribosomes are composed of two different-sized subunits (Figure 17).

In eukaryotic cells, the RNA molecules of both subunits are synthesized within the nucleus. Their numerous proteins are synthesized in the cytoplasm and then enter the nucleus and associate with rRNAs. Subunits then leave the nucleus, via nuclear pores, to enter the cytoplasm and participate in protein synthesis. Ribosomes are intensely basophilic because of the presence of numerous phosphate groups of the constituent rRNA that act as polyanions. Thus, sites in the cytoplasm that are rich in ribosomes stain intensely with basic dyes, such as methylene and toluidine blue. These basophilic sites also stain with hematoxylin.

The individual ribosomes (Figure 18) are held together by a strand of mRNA to form polyribosomes (polysomes). The message carried by mRNA is a code for the amino acid sequence of proteins being synthesized by the cell, and the ribosomes play a crucial role in decoding, or translating, this message during protein synthesis. Proteins synthesized for use within the cell and destined to remain in the cytosol (eg, hemoglobin in immature erythrocytes) are synthesized on polyribosomes existing as isolated clusters within the cytoplasm. Polyribosomes





that are attached to the membranes of the endoplasmic reticulum (via their large subunits) translate mRNAs that code for proteins that are segregated into the cisternae of the reticulum. These proteins can be secreted (eg, pancreatic and salivary enzymes) or stored in the cell (eg, enzymes of lysosomes, proteins within granules of white blood cells [leukocytes]). In addition, integral proteins of the plasma membrane are synthesized on polyribosomes attached to membranes of the endoplasmic reticulum.

## Mitochondria

Mitochondria (Gr. mitos, thread, + chondros, granule) are spherical or filamentous organelles tend to accumulate in parts of the cytoplasm at which the utilization of energy is more intense, such as the apical ends of ciliated cells, in the middle piece of spermatozoa, These organelles transform the chemical energy of the metabolites present in cytoplasm into energy that is easily accessible to the cell. About 50% of this energy is stored as high-energy phosphate bonds in ATP molecules, and the remaining 50% is dissipated as heat used to maintain body temperature. Through the activity of the enzyme ATPase, ATP promptly releases energy when required by the cell to perform any type of work, whether it is osmotic, mechanical, electrical, or chemical.

## Structure of Mitochondria

Mitochondria have a characteristic structure under the electron microscope (Figure 19). They are composed of an outer and an inner mitochondrial membrane; the inner membrane projects folds, termed cristae, into the interior of the mitochondrion. These membranes enclose two compartments. The compartment located between the two membranes is termed the intermembrane space. The inner membrane encloses the other compartment—the intercristae, or matrix, space. Compared with other cell membranes, mitochondrial membranes contain a large number of protein molecules. Most mitochondria have flat, shelflike cristae in their interiors (Figure 19), whereas cells that secrete steroids (eg, adrenal gland) frequently contain tubular cristae. The cristae increase the internal surface area of





mitochondria and contain enzymes and other components of oxidative phosphorylation and electron transport systems.

The number of mitochondria and the number of cristae in each mitochondrion are related to the energetic activity of the cells in which they reside. Thus, cells with a high-energy metabolism (eg, cardiac muscle, cells of some kidney tubules) have abundant mitochondria with a large number of closely packed cristae, whereas cells with a low-energy metabolism have few mitochondria with short cristae.

Between the cristae is an amorphous matrix, rich in protein and containing circular molecules of DNA and the three varieties of RNA. In a great number of cell types, the mitochondrial matrix also exhibits rounded electron-dense granules rich in Ca2+. Although the function of this cation in mitochondria is not completely understood, it may be important in regulating the activity of some mitochondrial enzymes; another functional role is related to the necessity of keeping the cytosolic concentration of Ca2+ low. Mitochondria will pump in Ca2+ when its concentration in the cytosol is high. Enzymes for the citric acid (Krebs) cycle and fatty acid -oxidation are found to reside within the matrix space.

### Mitochondrial genome

The DNA isolated from the mitochondrial matrix is double stranded and has a circular structure, very similar to that of bacterial chromosomes. These strands are synthesized within the mitochondrion; their duplication is independent of nuclear DNA replication. Mitochondria contain the three types of RNA: ribosomal RNA (rRNA), messenger RNA (mRNA), and transfer RNA (tRNA). Mitochondrial ribosomes are smaller than cytosolic ribosomes and are comparable to bacterial ribosomes. Protein synthesis occurs in mitochondria, but because of the reduced amount of mitochondrial DNA, only a small proportion of the mitochondrial proteins is produced locally. Most are encoded by nuclear DNA and synthesized in polyribosomes located in the cytosol.

Mitochondrial inheritance is maternal, because few, if any, mitochondria from the sperm nucleus remain in the cytoplasm of the zygote. In the case of nuclear DNA

defects, inheritance may be from either parent or both parents. Generally, in these diseases the mitochondria show morphological changes.

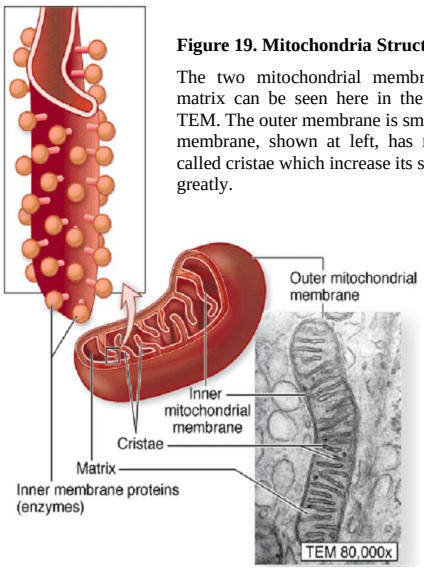



**Figure 19. Mitochondria Structure.**

The two mitochondrial membranes and central matrix can be seen here in the diagram and the TEM. The outer membrane is smooth and the inner membrane, shown at left, has many sharp folds called cristae which increase its surface area greatly.

## Energy production and ATP synthesis

The chemiosmotic theory suggests that ATP synthesis occurs at the expense of a flow of protons across this globular unit (Figure 31).The globular structures are a complex of proteins with ATP synthetase activity that, in the presence of ADP plus inorganic phosphate and energy, forms ATP. Membrane proteins guide the small electron carrier molecules through closely packed enzyme complexes so that the electrons move sequentially along the chain.





Electron transfer is coupled with oriented proton uptake and release which causes protons to accumulate in the intermembrane space (Figure 19). This produces an electrochemical gradient across the inner membrane. Other membrane-associated proteins make up the ATP synthase system, forming 10 nm, multisubunit globular complexes on stalk-like structures densely packed on the matrix side of the inner membrane. Through this enzyme complex runs a hydrophilic pathway that allows protons to flow down the electrochemical gradient, crossing the membrane back into the matrix. Passage of protons through this narrow channel causes rapid spinning of specific polypeptides in the globular ATP synthase complex, converting the energy of proton flow into the mechanical energy of protein movement. Mechanical energy is stored in the new phosphate bond of ATP by other subunit polypeptides that bind ADP and inorganic phosphate. A steady torrent of protons along the gradient allows each of these remarkable synthase complexes to produce more than 100 molecules of ATP per second.

**Medical Application**

Several mitochondrial deficiency diseases have been described, and most of them are characterized by muscular dysfunction. Because of their high-energy metabolism, skeletal muscle fibres are very sensitive to mitochondrial defects. These diseases typically begin with drooping of the upper eyelid and progress to difficulties in swallowing and limb weakness. DNA mutations or defects that can occur in the mitochondria or the cell nucleus cause them.





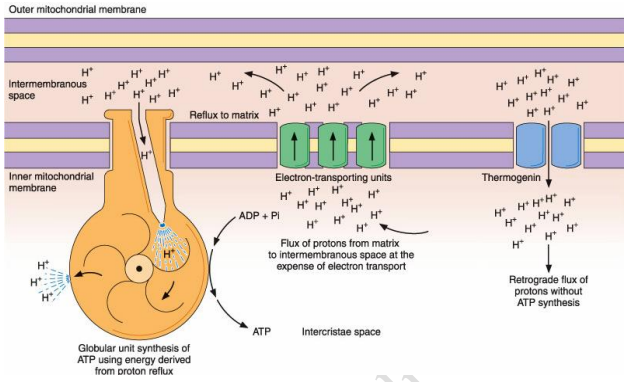



**Figure 20.** The chemiosmotic theory of mitochondrial energy transduction. Middle: The flux of protons is directed from the matrix to the intermembranous space promoted at the expense of energy derived from the electron transport system in the inner membrane. Left: Half the energy derived from proton reflux produces ATP; the remaining energy produces heat. Right: The protein thermogenin, present in multilocular adipose tissue, forms a shunt for reflux of protons. This reflux, which dissipates energy as heat, does not produce ATP.

## Golgi Apparatus

The highly dynamic Golgi apparatus, or Golgi complex, completes posttranslational modifications and then packages and addresses proteins synthesized in the RER. This organelle, named for histologist Camillo Golgi who discovered it in 1898, is composed of smooth membranous saccules in which these functions occur (Figures 21). In polarized secretory cells with apical and basal ends, such as mucus-secreting goblet cells, the Golgi apparatus occupies a characteristic position between the nucleus and the apical plasma membrane. The Golgi apparatus generally shows two distinct sides structurally and functionally, which reflects the complex traffic of vesicles within cells. Near the Golgi, the RER can be seen budding off small transport vesicles that shuttle newly synthesized proteins to the Golgi apparatus for further processing. The Golgi saccules nearest





this point make up the **entry** or **cis face**. On the opposite side of the Golgi network, which is the **exit** or **trans face**, larger saccules sometimes called condensing vacuoles can be seen to accumulate (Figure 21). These structures bud from the maturing saccules and generate vesicles that carry completed protein products to organelles away from the Golgi. The Golgi apparatus is important for glycosylation, sulfation, phosphorylation, and limited proteolysis of proteins as well as initiates packing, concentration, and storage of secretory products as shown in Figure 22.

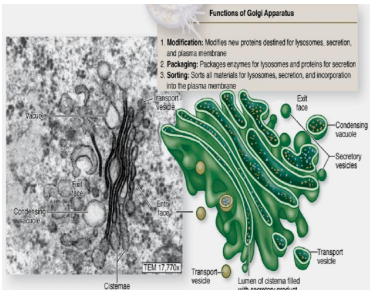



**Figure 21.** The Golgi apparatus is a highly plastic, morphologically complex system of membrane vesicles and cisternae in which proteins and other molecules made in the ER undergo modification and maturation and then are sorted into specific vesicles destined for different roles in the cell:

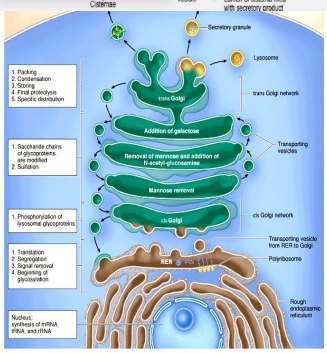



**Figure 22. Summary of Golgi apparatus structure and function.** Summary of the main events occurring during protein trafficking and sorting from the rough ER through the Golgi complex. Numbered at the left are the main molecular processes that take place in the compartments shown. In the trans Golgi network, the proteins and glycoproteins combine with specific receptors that guide them to the next stages toward their destinations. On the left side of the drawing is the returning flux of membrane, from the Golgi to the endoplasmic reticulum.

**Golgi biochemicals main destinations**

There are three main destinations for biochemicals released from the trans Golgi network: In each case the destination is clearly linked to function, these are:

**1-Inside the cell**: '**lysosome line**'About 40-50 different biochemicals despatched from the Golgi apparatus in vesicles are destined for delivery to the lysosomes.

**2-The plasma membrane**, '**Continuous secretion line'**. Vesicles containing biochemicals for continuous secretion flow to and fuse with the plasma membrane. This group of secretions will contribute to the biochemicals of the extracellular matrix, act as chemical signals to other cells, and provide proteins for the repair and replacement of the plasma membrane.

**3-Outside the cell**, '**Regulated secretion line'** Vesicles and chemicals of this group are produced in specialist secretory cells. They move from the trans Golgi network (TGN) towards the plasma membrane but accumulate in number before reaching the membrane.

## Lysosomes

Lysosomes are sites of intracellular digestion and turnover of cellular components. Lysosomes (Gr. lysis, solution, + soma, body) are membrane-limited vesicles (Figure 23) that contain about 40 different hydrolytic enzymes and are particularly abundant in cells with great phagocytic activity (eg, macrophages, neutrophils). Although the nature and activity of lysosomal enzymes vary depending on the cell type, the most common are acid hydrolyases such as proteases, nucleases, phosphatase, phospholipases, sulfatases, and-glucuronidase.

Lysosomal hydrolases are synthesized and segregated in the RER and subsequently transferred to the Golgi apparatus, where the enzymes are further modified and packaged in vacuoles that form lysosomes.

Material taken from the cellular environment by endocytosis is digested when lysosomes fuse with the membrane of the phagosome or pinocytotic vesicle. The endocytosed material mixes with the hydrolytic enzymes, a proton pump in the lysosomal membrane is activated to lower the internal pH, and digestion follows.





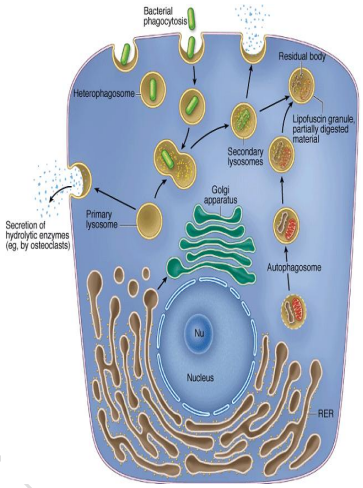



**Figure 23. Lysosomal functions.**

Synthesis of the digestive enzymes occurs in the rough ER, enzymes packaged in the Golgi apparatus. Heterophagosomes are formed by the fusion of the phagosomes and lysosomes. Autophagosomes are formed after nonfunctional or surplus organelles become enclosed with membrane resulting structure fuses with a lysosome. Products of digestion can be excreted from the cell by exocytosis. Residual bodies can accumulate in long-lived cells and be visualized as lipofuscin granules.

There are three pathways to degradation in lysosomes (Figure 24), each pathway leads to the intracellular digestion of materials derived from a different source. The compartments resulting from the three pathways can sometimes be distinguished morphologically.

**1-Phagocytosis** is the ingestion of larger extracellular material such as foreign invading microbes.

**2-Endocytosis** is the ingestion of macromolecules where receptor proteins are recycled from the cell surface.

**3-Autophagy** wherein old or unneeded organelles or proteins, or microbes that have invaded the cytoplasm are delivered to the lysosome. Autophagy may also lead to autophagic cell death, a form of programmed self-destruction, or autolysis, of the cell, which means that the cell is digesting itself.





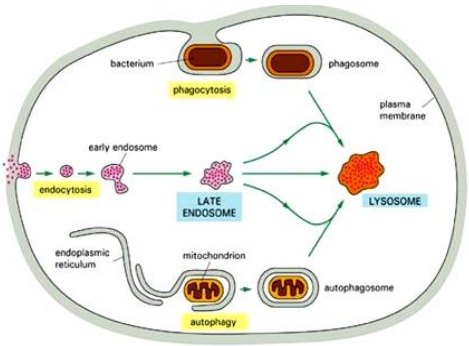



**Figure 24. The three pathways to degradation in lysosomes**

**Proteasomes**

The proteasome is a cylindrical structure made of four stacked rings, each composed of seven proteins including proteases. Proteasomes are abundant cytoplasmic protein complexes not associated with membrane, each approximately the size of the small ribosomal subunit. They function to degrade denatured or otherwise nonfunctional polypeptides. Proteasomes also remove proteins no longer needed by the cell and provide an important mechanism for restricting activity of a specific protein to a certain window of time. Whereas lysosomes digest bulk material introduced into the cell, or whole organelles and vesicles, proteasomes deal primarily with proteins as individual molecules.

**Medical Application**

Failure of proteasomes or other aspects of a cell's protein quality control can allow large aggregates of protein to accumulate in affected cells. Such aggregates may adsorb other macromolecules to them and damage or kill cells. Aggregates released from dead cells can accumulate in the extracellular matrix of the tissue. In the brain this can interfere directly with cell function and lead to





neurodegeneration. Alzheimer disease and Huntington disease are two neurologic disorders caused initially by such protein aggregates.

**Peroxisomes or Microbodies**

All animal cells (except erythrocytes) and many plant cells contain peroxisomes, a class of small organelles (≈0.2–1 μm in diameter) bounded by a single membrane (Figure 25) [Glyoxisomes are similar organelles found in plant seeds that oxidize stored lipids as a source of carbon and energy for growth]. Peroxisomes contain several oxidases enzymes that use molecular oxygen to oxidize organic substances, in the process forming hydrogen peroxide ($H_2O_2$), a corrosive substance. Peroxisomes also contain copious amounts of the enzyme catalase, which degrades hydrogen peroxide to yield water and oxygen [$2H_2O_2 \rightarrow 2H_2O + O_2$], the free Oxgen oxidizes various potentially toxic molecules as well as prescription drugs, particularly in the large and abundant peroxisomes of liver and kidney cells.

The energy released during peroxisomal oxidation is converted to heat, and the acetyl groups are transported into the cytosol, where they are used in the synthesis of cholesterol and other metabolites.

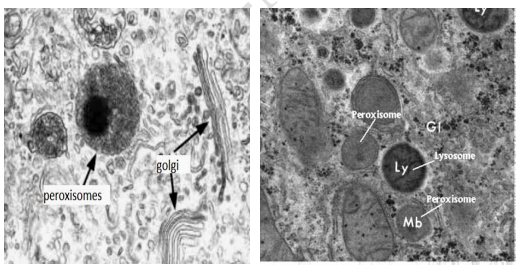


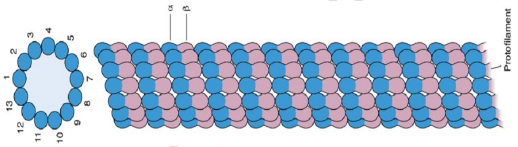

**Figure 25.** Peroxisomes (or microbodies) are small spherical, membranous organelles, containing enzymes that use $O_2$ to remove hydrogen atoms from substrates, typically fatty acids, in a reaction that produces hydrogen peroxide ($H_2O_2$) which must be broken down to water and $O_2$ by another enzyme, catalase

**Cytoskeleton**

The cytoplasmic cytoskeleton is a complex network of (1) microtubules, (2) microfilaments (actin filaments), and (3) intermediate filaments. These protein structures determine the shape of cells, play an important role in the movements of organelles and cytoplasmic vesicles, and also allow the movement of entire cells.

**Microtubules**

Within the cytoplasmic matrix of eukaryotic cells, there are fine tubular structures known as microtubules (Figures 26). Microtubules are also found in cytoplasmic processes called cilia and flagella. They have an outer diameter of 24 nm, with a dense wall 5 nm thick and a hollow lumen. Microtubules are variable in length, but they can become many micrometers long. Two or more microtubule are linked by protein arms or bridges, and are important in cilia and flagella **(Figure 26).**




**Figures 26.** Molecular organization of a microtubule. Microtubules are rigid structures which assemble from heterodimers of α and β tubulin. Tubulin molecules are arranged to form 13 protofilaments, as seen in the cross section in the upper part of the drawing. Orientation of the tubulin dimmers results in structural polarity of the microtubule. Microtubules elongate or rapidly shorten by the addition or removal of tubulin at the ends of individual protofilaments.

**Functional role of microtubules.**

Cytoplasmic microtubules are stiff structures that play a significant role in the development and maintenance of cell shape. They are usually present in a proper orientation, either to effect development of a given cellular asymmetry or to maintain it. Procedures that disrupt microtubules result in the loss of this cellular asymmetry.

Microtubules also participate in the intracellular transport of organelles and vesicles. Examples include axoplasmic transport in neurons, melanin transport in pigment cells, chromosome movements by the mitotic spindle, and vesicle





movements among different cell compartments. In each of these examples, movement is related to the presence of complex microtubule networks, and such activities are suspended if microtubules are disrupted. The transport guided by microtubules is under the control of special proteins called motor proteins, which use energy to move molecules and vesicles. They provide basis for several complex cytoplasmic components as centrioles, basal bodies, cilia, and flagella.

**Centrioles**

Centrioles are cylindrical structures composed primarily of short, highly organized microtubules (Figure 27). Each centriole shows **nine sets** of microtubules arranged in triplets sharing a common wall. Close to the nucleus of non dividing cells is a ***centrosome*** (Figure 26) made of a pair of centrioles surrounded by a granular material. In each pair, the long axes of the centrioles are at right angles to each other. Before cell division, more specifically during the S period of the interphase, each centrosome duplicates itself so that now each centrosome has two pairs of centrioles. During mitosis, the centrosomes divide in two, move to opposite poles of the cell, and become organizing centers for the microtubules of the mitotic spindle.

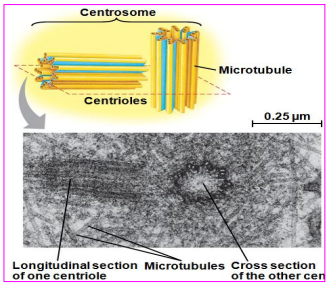
**Cilia and flagella** are motile processes, covered by cell membrane, with a highly organized microtubule core. Ciliated cells typically possess a large number of cilia, each about 2–3 m in length. Flagellated cells have only one flagellum, with a length close to 100 m. In humans, the spermatozoa are the only cell type with a flagellum. The main function of cilia is to sweep fluid from the surface of cell sheets. Both cilia and flagella possess the same core organization.

**Medical Application**

Some normal blood-forming cells and the epithelial cells that cover the digestive tract show a high rate of proliferation and are adversely affected by chemotherapy. Several mutations have been described in the proteins of the cilia and flagella. They are responsible for the immotile cilia syndrome, the symptoms of which are immotile spermatozoa, male infertility, and chronic respiratory infections caused by the lack of the cleansing action of cilia in the respiratory tract.

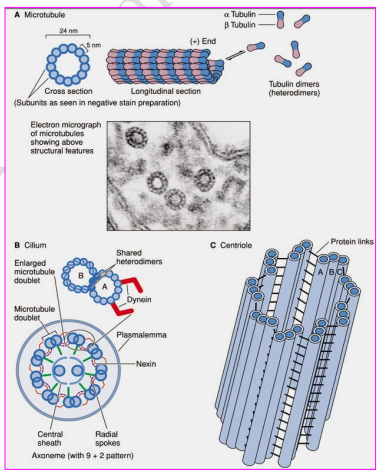







**Figures 26. Centrosome.** The centrosome is the microtubule-organizing center for mitotic spindle and consists of paired centrioles.TEM reveals the two centrioles in a centrosome exist at right angles to one another in a dense matrix of free tubulin subunits and other proteins. Each centriole consists of nine microtubular triplets. In a poorly understood process, the centrosome duplicates itself and is divided equally during a cell's interphase, each half having a duplicated centriole pair. At the onset of mitosis, the two daughter centrosomes move to opposite sides of the nucleus and become the two poles of the mitotic spindle of microtubules attaching to chromosomes.

**Figures 27.** Schematic representation of microtubules, cilia, and centrioles. A: Microtubules as seen in the electron microscope after fixation with tannic acid in glutaraldehyde. The unstained tubulin subunits are delineated by the dense tannic acid. Cross sections of tubules reveal a ring of 13 subunits of dimers arranged in a spiral. Changes in microtubule length are due to the addition or loss of individual tubulin subunits. B: A cross section through a cilium reveals a core of microtubules called an axoneme consisting of two central microtubules surrounded by nine microtubule doublets. In the doublets, microtubule A is complete and consists of 13 subunits, whereas microtubule B shares two or three heterodimers with A. When activated by ATP, the dynein arms link adjacent tubules and provide for the sliding of doublets against each other. C: Centrioles consist of nine microtubule triplets linked together in a pinwheel-like arrangement. In the triplets, microtubule A is complete and consists of 13 subunits, whereas microtubules B and C share tubulin subunits.








**Microfilaments (Actin Filaments)**

Contractile activity in muscle cells results primarily from an interaction between two proteins: actin and myosin. Actin is present in muscle as a thin (5–7 nm in diameter) filament composed of globular subunits organized into a double-stranded helix (Figure 28). Structural and biochemical studies reveal that there are several types of actin and that this protein is present in all cells. Within cells, microfilaments can be organized in many forms.

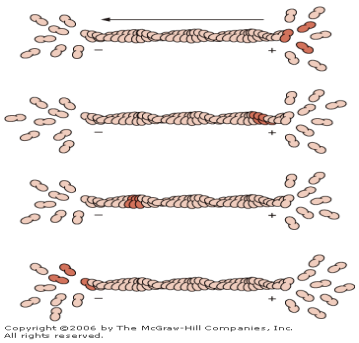
1-In skeletal muscle, they assume a paracrystalline array integrated with thick (16-nm) myosin filaments.

2-**In most cells**, actin filaments form a thin sheath just beneath the plasmalemma, called the cell cortex. These filaments appear to be associated with membrane activities such as endocytosis, exocytosis, and cell migratory activity.

3-**Actin filaments** are intimately associated with several cytoplasmic organelles, vesicles, and granules. The filaments are believed to play a role in moving and shifting cytoplasmic components (cytoplasmic streaming).

4-**Actin filaments** are associated with myosin and form a "purse-string" ring of filaments whose constriction results in the cleavage of mitotic cells.

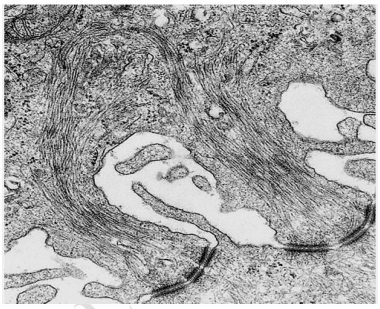
5-**In most cells,** actin filaments are found scattered in what appears to be an unorganized fashion within the cytoplasm.




**Figures 28.** The cytosolic actin filament. Actin dimers are added to the plus (+) end and removed at the minus (–) end, dynamically lengthening or shortening the filament, as required by the cell. (Redrawn and reproduced, with permission, from Junqueira LC, Carneiro J: Biologia Celular e Molecular, 6th ed. Editora Guanabara, 1997.)

**Intermediate Filaments**

In addition to microtubules and the thin actin filaments, eukaryotic cells contain a class of filaments intermediate in size between the other two. In comparison with microtubules and actin filaments, intermediate filaments are much more stable and vary in their protein subunit structure in different cell types. Several proteins that form intermediate filaments have been isolated and localized by immunocytochemical means (Figures 29a,b).



**Figures 29.** Electron micrograph of a skin epithelial cell showing intermediate filaments of keratin associated with desmosomes

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

**Figure 29b.** Examples of Intermediate Filaments Found in Eukaryotic Cells.





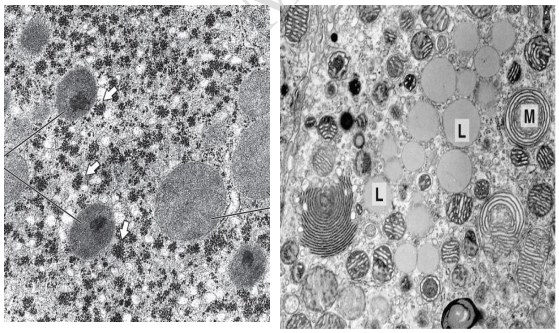
**Cellular inclusions.**

Inclusions are cytoplasmic structures or deposits filled with stored macromolecules and are not present in all cells. Unlike organelles, cytoplasmic inclusions are composed mainly of accumulated metabolites or other substances and are often transitory components of the cytoplasm.

-**Fat droplets**, accumulations of lipid molecules that are prominent in adipocytes (fat cells), adrenal cortex cells, liver and other cells (Figure 30).

-**Glycogen granules**, aggregates of a carbohydrate polymer in which glucose is stored and are also visible in several cell types, mainly liver cells, in the form of irregular clumps of PAS-positive or electron-dense material (Figure 30). They are not enclosed with membrane.

-**Lipofuscin granules**, small pigmented (golden-brown) bodies present in many cells, but which accumulate with age in stable nondividing cells (eg, neurons, cardiac muscle). Lipofuscin granules contain a complex mixture of material derived from residual bodies after lysosomal digestion.




**Figures 30.** Section of drenal gland showing lipid droplets (L) and abundant anomalous mitochondria (M). A liver cell showing glycogen deposits as accumulations of electron-dense particles (arrows). The dark structures with a dense core are peroxisomes. Mitochondria (M) are also shown.





## The Nucleus

The nucleus contains a blueprint for all cell structures and activities, encoded in the DNA of the chromosomes. It also contains the molecular machinery to replicate its DNA and to synthesize and process the three types of RNA ribosomal (rRNA), messenger (mRNA), and transfer (tRNA). Mitochondria have a small DNA genome and produce RNAs to be used in this organelle, but the genome is so small that it is not sufficient even for the mitochondrion itself. On the other hand, the nucleus does not produce proteins; the numerous protein molecules needed for the activities of the nucleus are imported from the cytoplasm.

**Components of the Nucleus**

The nucleus frequently appears as a rounded or elongated structure, usually in the center of the cell (Figures 31, 32). Its main components are the **nuclear envelope, chromatin**, **nucleolus, and nuclear matrix**. The size and morphological features of nuclei in a specific normal tissue tend to be uniform. In contrast, the nuclei in cancer cells have an irregular shape, variable size, and atypical chromatin patterns.

**Nuclear Envelope**

The Nuclear Envelope (Figure 33) surrounds the nuclear material and consists of two parallel membranes separated from each other by a narrow perinuclear cisterna. These membranes fuse at intervals, forming openings in the nuclear envelope called nuclear pores. It has two membranes:-

**A. Outer nuclear membrane**

This membrane is about 6 nanometers (nm) thick.It faces the cytoplasm and is continuous at certain sites with the rough endoplasmic reticulum (RER). There is a loosely arranged mesh of intermediate filaments (vimentin) surrounds the outer nuclear membrane on its cytoplasmic aspect. The Ribosomes stud the cytoplasmic surface of the outer nuclear membrane, these ribosomes synthesize proteins that enter the perinuclear cisterna.

**B. Inner nuclear membrane**

The inner nuclear membrane is about 6 nm thick. It faces the nuclear material but is separated from it and supported on its inner surface by the nuclear lamina, a fibrous lamina that is 80-300 run thick and composed primarily of lamins A, B,





and C. These intermediate filament proteins help organize the nuclear envelope and perinuclear chromatin. Additionally, they are essential during the mitotic events, when they are responsible for the disassembly and reassembly of the nuclear envelope by Phosphorylation and dephosphorylation.

**C. Perinuclear cisterna**

The perinuclear cisterna is located between the inner and outer nuclear membranes and is 20-40 nm wide. It is continuous with the cisterna of the RER. It is perforated by nuclear pores at various locations.

**D. Nuclear pores**

The nuclear pores average 80 nm in diameter and are associated with the nuclear pore complex (NPC); they are formed by fusion of the inner and outer nuclear membranes; and they permit passage of certain molecules in either direction between the nucleus and cytoplasm via a 9-nm channel opening.

**E. The NPC** are protein subunits surrounding the nuclear pore (Figure 33). Structurally, it is composed of nearly 100 proteins, some of which are arranged in eight-fold symmetry around the margin of the pore. The nucleoplasmic side of the pore exhibits a nuclear basket, whereas the cytoplasmic side displays fibers extending into the cytoplasm. A transporter protein is located in the central core and is believed to be responsible for transporting proteins into and out of the nucleus via receptor-mediated transport.

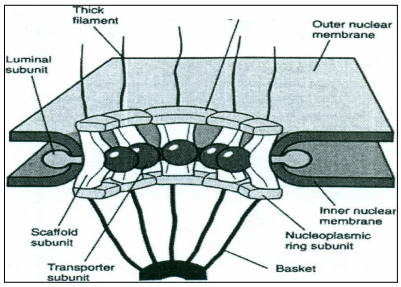



**Figure 33**. Diagram of the nuclear pore complex. (Modified with permission from Alberts B, Bray D, Lewis J, et al: Molecular Biology of the Cell, 3rd ed. New York, Garland Publishing, 1994.

A) The cytoplasmic ring is

located around the cytoplasmic margin of the nuclear pore and is composed of eight subunits, each possessing a filamentous fiber extending into the cytoplasm may serve as a staging area prior to protein transport.

B) The nucleoplasmic ring is located around the nucleoplasmic margin of the nuclear pore and is composed of eight subunits. Extending from this ring into the nucleoplasm is a basket-like structure, the nuclear basket. It is thought to have a function in RNA transport.

C) The middle ring is interposed between the cytoplasmic and nucleoplasmic rings. Eight transmembrane proteins project into the lumen of the nuclear pore, anchoring the complex into the pore rim

**Function of the NPC**

**The NPC** permits passive movement across the nuclear envelope via a 9- to l l-nm open channel for simple diffusion. Most proteins, regardless of size, pass in either direction only by receptor-mediated transport. These proteins have clusters of certain amino acids known as nuclear localization segments (NLS) that act as signals for transport.

**Nucleolus**

The nucleolus is a spherical structure that is rich in rRNA and protein. It is usually basophilic when stained with hematoxylin and eosin. The nucleolus consists of three distinct components (Figure 32):

**1-Nucleolar organizer regions** (NORs), portions of chromosomes (in humans, chromosomes 13, 14, 15,21, and 22) where rRNA genes are located; these regions are involved in reconstituting the nucleolus during the G 1 phase of the cell cycle

**2-Pars fibrosa** are composed of 5-nm fibrils surrounding the fibrillar centers and contain transcriptionally active DNA and the rRNA precursors that are being transcribed

**3-Pars granulosa** are composed of 15-nm maturing ribosomal precursor particles. Additionally, the nucleolar matrix is a fiber network participating in the organization of the nucleolus.





**Function of the nucleolus**

The nucleolus is involved in the synthesis of rRNA and its assembly into ribosome precursors. The nucleolus also sequesters certain nucleolar proteins that function as cell-cycle checkpoint signaling proteins. Three cell-cycle regulator proteins have been identified within the nucleolus, where they remain sequestered until their release is required for targets in nucleus and /or cytoplasm.

**Chromatin**

Chromatin, in non dividing nuclei, is in fact the chromosomes in a different degree of uncoiling. According to the degree of chromosome condensation, two types of chromatin can be distinguished with both the light and electron microscopes (Figures 32).

**1-Heterochromatin** (Gr. heteros, other, + chroma, color), which is electron dense, appears as coarse granules in the electron microscope and as basophilic clumps in the light microscope.

**2-Euchromatin** is the less coiled portion of the chromosomes, visible as a finely dispersed granular material in the electron microscope and as lightly stained basophilic areas in the light microscope.

Chromatin is composed mainly of coiled strands of DNA bound to basic proteins (histones). The basic chromatin structural unit 'nucleosome' (Figure 34), which consists of a core of four types of histones: two copies each of histones H2A, H2B, H3, and H4, around which are wrapped 166 DNA base pairs. An additional 48-base pair segment forms a link between adjacent nucleosomes, and another type of histone (H1 or H5) is bound to this DNA. This organization of chromatin has been referred to as "beads-on-a-string." Nonhistone proteins are also associated with chromatin, but their arrangement is less well understood. The next higher order of organization of chromatin is the 30-nm fiber (Figure 35). In this structure, nucleosomes become coiled around an axis, with six nucleosomes per turn, to form the 30-nm chromatin fiber. There are higher orders of coiling, especially in the condensation of chromatin during mitosis and meiosis.





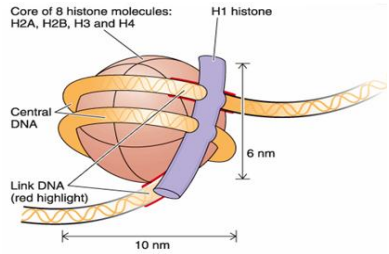



**Figure 34** Schematic representation of a nucleosome. This structure consists of a core of four types of histones (two copies of each) H2A, H2B, H3, and H4 and one molecule of H1 or H5 located outside the DNA filament.

The chromatin pattern of a nucleus has been considered a guide to the cell's activity. In general, cells with light nuclei are more active than those with condensed, dark nuclei. In light-stained nuclei (with few heterochromatin clumps), more DNA surface is available for the transcription of genetic information. In dark-stained nuclei (rich in heterochromatin), the coiling of DNA makes less surface available.

Careful study of the chromatin of mammalian cell nuclei reveals a heterochromatin mass that is frequently observed in female cells but not in male cells. This chromatin clump is the sex chromatin and is one of the two X chromosomes present in female cells.

The X chromosome that constitutes the sex chromatin remains tightly coiled and visible, whereas the other X chromosome is uncoiled and not visible. Evidence suggests that the sex chromatin is genetically inactive. The male has one X chromosome and one Y chromosome as sex determinants; the X chromosome is uncoiled, and therefore no sex chromatin is visible.

## Cellular aspects of Cancer

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Normal cells are





constantly subject to signals that dictate whether the cell should divide, differentiate into another cell or die.

Cancer cells develop a degree of autonomy from these signals, resulting in uncontrolled growth arid proliferation. If this proliferation is allowed to continue and spread, it can be fatal. In fact, almost 90% of cancer-related deaths are due to tumour spreading — a process called metastasis. This disease that involves changes or mutations in the cell genome. These changes (DNA mutations) produce proteins that disrupt the delicate cellular balance between cell division and quiescence, resulting in cells that keep dividing to form cancers.

### Cancer is Clonal in Origin

Current dogma States that cancer is a multi-gene, multi-step disease originating from a single abnormal cell (clonal origin) with an altered DNA sequence (mutation). Uncontrolled proliferation of these abnormal cells is followed by a second mutation leading to the mildly aberrant stage. Successive rounds of mutation and selective expansion of these cells results in the formation of a tumour mass (Figures 41a,b).Then, subsequent rounds of mutation and expansion leads to tumour growth and progression, and spreading to other parts of the body (metastasis). Death as a result of cancer is due to the invading, eroding and spread of tumours into normal tissues due to uncontrolled clonal expansion of these somatic cells.

Evidence as a clonal expansion model. Glucose-6.phosphate dehydrogenase (G6PD) enzyme has two forms, G6PD-A and G6PD- B, which differ from each other by 1 single amino acid. Some people have cells that contain either type A or type B but no cell contains both, hence tissues are a mosaic of cells with these two types. Individuals who develop Chronic Myeloid Leukacmia (CML-a blood cancer) contain cancerous mycloid cells which all contain only one type of the

enzyme, either type A or type B, but never both, clearly demonstrating that cancers are clonal in origin as shown in figure 42.

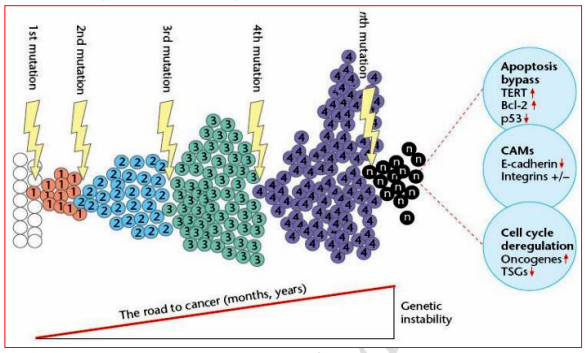



**Figure 41a**. Overview of the road to cancer. Cancer is a multi-gene, multi-step disease originating from single abnormal cell (clonal origin). Cells may acquire mutations in genes that control proliferation, such as proto-oncogenes and/or tumor suppressor genes. Each new mutation may provide a selective advantage for this cell, leading to 'clonal expansion'. Cellular properties changed in this process include cell cycle deregulation, apoptosis prevention and cell adhesion properties (CAMs–Cellular adhesion molecules). Image from Alison, MR, Cancer. Encyclopedia of LifeSciences,2001. Reproduced with permission from John Wiley & Sons.

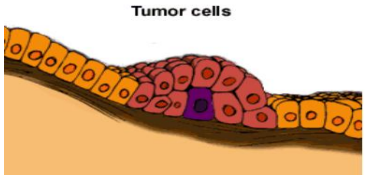
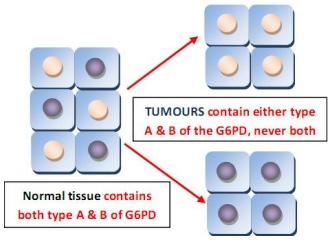



**Figure 41b**. Clonal expansion. Normal cells are subject to signals that regulate their proliferation and behaviour. All cancers disrupt normal controls of cell proliferation & for each cell there is a finite number of ways this disruption can occur. Cancer cells develop a degree of autonomy from external regulatory signals that are responsible for normal cellular homeostasis. Multiple mutations lead to a tumour mass. Subsequent mutations lead to malignant tumour which break through the basal membrane and spread to distant locations.





**Figure 42**. Example showing cancers are clonal in origin. Genetic analysis of myeloid cells in some patients with Chronic Myeloid Leukaemia (CML, a blood cancer) contain only one type of the enzyme, G6PD, either type A or B, but never both. Since normal tissues on the other hand, are a mosaic of cells with both type A & B, this clearly demonstrates the clonal origins of cancer.




### Identification and histopathology of cancers

Why do we need to identify and classify cancers? There are several benefits to identifying and classifying cancers using histological sections and staining methodology.

**1-Diagnosis:** Microscopic observation helps determine whether the tumour tissue is benign (harmless) or malignant (potentially fatal). Gross cellular morphology and tissue specific markers are used to classify cancerous cells.

**2-Therapy:** Pathology can be used as a confirmation or in prognosis E.g: has the surgeon removed the entire tumour? Or was the treatment effective in eliminating tumours'? Or what is the rate of progression of the cancer'? Progression can be predicted by histotyping. E.g. Patients with simple hyperplasia in the uterine epithelium have <1% chance of developing cancer compared 82% risk in patients with atypical hyperplasia.

**3-Cellular origin (histogenesis):** Determining the origins of the tumour by histopathological classification of tissue is useliji in a) identifying whether the tumour is a primary or secondary tumour e.g. a liver tumour may have metastasized from elsewhere or b) source of origin of the tumour e.g. lung cancer due to smoking is epithelial (lung carcinoma) but due to asbestos exposure is mesothelial (***mesothelioma*** or asbestos cancer)





What are mesotheliomas? The mesothelium is a layer of cells which cover various organs in the body protecting them and allowing organs to move against each other as the lungs expand and contract or the heart beats. The mesothelium surrounding the lungs and lining the chest cavity is called the pleura, so mesotheliomas affecting the cells lining the sacs surrounding the chest or lungs are referred to as pleural mesothelioma, whereas a cancer in the abdominal lining, or peritoneum, is called peritoneal mesothelioma.

### The 6 hallmarks of cancer

DNA mutations result in defects in the regulatory circuits of a cell, which disrupt normal cell proliferation behaviour. However the complexity of this disease is not as simple at the cellular and molecular level. Individual cell behaviour is not autonomous, and it usually relies on external signals from surrounding cells in the tissue or microenvironment. There are more than 100 distinct types of cancers and any specific organ can contain tumours of more than one subtype. This provokes several questions. I low many of these regulatory circuits need to be broken to transform a normal cell into a cancerous one? is there a common regulatory circuit that is broken among different types of cancers? Which of these circuits are broken inside a cell and which of these are linked to external signals from neighbouring cells in the tissue'?

The answer to these questions can be summarised in a heterotypic model, manifested as the six common changes in cell physiology that results in cancer (proposed by Douglas Hanahan and Robert Weinberg in 2000). This model looks at tumours as complex tissues, in which cancer cells recruit and use normal cells in order to enhance their own survival and proliferation. The 6 hallmarks of this currently accepted model can be described using a traffic light analogy (Figure 43).

**1-Immortality:** Continuous cell division and limitless replication
**2-Produce 'Go' signals** (growth factors from oncogenes)
**3-Override 'Stop'** signals (anti-growth signals from tumour suppressor genes)
**4-Resistance to cell death** (apoptosis)
**5-Angiogcncsis:** Induction of new blood vessel growth
**6-Metastasis**: Spread to other sites.





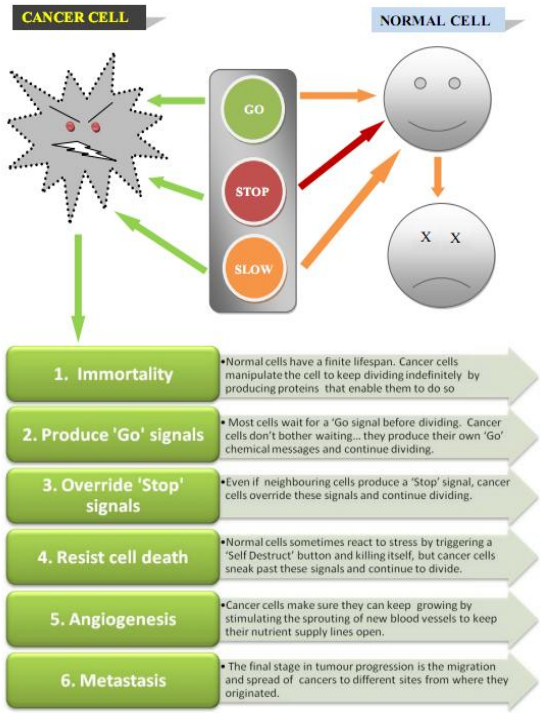



**Figure 43**.The six hallmarks of cancer. Almost all cancers share some or all of the 6 traits described below, depending on the tumour. Some tumours may show all these changes because of mutations in one key gene (e.g. the p53 gene controls at least 4 of the traits) whereas other tumours may need more than 1 mutation for progression. Arrows on the right (orange and red) show signals that regulate normal cell behaviour. The green arrows on the left indicate abnormal growth triggered by cancer cells. The green boxes outline the *6* key characteristics of cancer cells.

**Cellular principles of invasion and metastasis**

The spread of cancer cells to distant sites in the body via the blood stream/lymphatics is known as metastasis and is the most lethal form of the disease (Figure 44). Metastatic cells are less adhesive than normal cells and are able to degrade and penetrate tissue barriers such as the extracellular matrix (ECM) of surrounding connective tissue and the basement membrane of blood vessels. After gaining access to the systemic circulation they can invade normal tissue at various sites in the body forming secondary colonies. The invasion- metastasis cascade involves:

1- Acquisition of local invasiveness

2- Invasion of the cell into blood/ lymph vessels (intravasation)

3-Transport through the blood/lymph vessels to distant tissue sites

4-Escape of the cancer cells from circulation (extravasation)

5-Ability to adapt to the local tissue environment and to proliferate

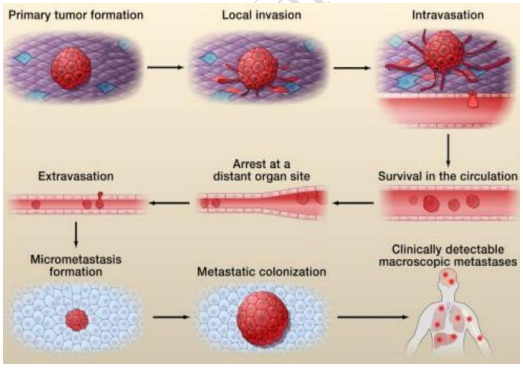



**Figure 44:** Steps involved in the metastatic cascade. During metastatic progression, tumour cells exit their primary sites of growth (local invasion, intravasation; 1 & 2), translocate systemically (survival in the circulation, arrest at a distant organ site, extravasation; 3 & 4), and adapt to survive and thrive in foreign microenvironments (5). Adapted from Valastyan S and Weinberg RA, Cell 147, 275-292, 2011.





**Causes of cancer (aetiology of cancer)**

In addition to the actions of the three main gene groups related to developing cancers, encogenes, tumer suppressor genes and DNA repair genes, there is a an environmental related actions as well as life style patterns. The exposure to mutagens or radiation greatly increases the mutation rate and thus the probability of developing cancer. Fore example;

**1-**Chemical mutagens comprise a quite disparate group of chemicals that modify DNA through a range of mechanisms, such as alkylation or deamination of DNA bases, or through intercalation between base pairs and formation of DNA adducts (e.g. aromatic hydrocarbons). Oxidative damage may also affect DNA integrity.

2- X-rays and radioactive radiation tend to induce DNA double-strand breaks, whereas UV radiation results in the formation of pyrimidine dimers, by cross-linking of adjacent pyrimidine bases.

**Treatment Modalities Arising from Cancer Cell Biology**

**1-Tumour immunology and immunotherapy**

The immune system is able to launch attacks not only against foreign invaders, but also against body cells that may display 'foreign' antigens, such as cancer cells. The 'immune surveillance theory' is supported by the observation that the incidence of certain cancers is drastically increased in immune-compromised patients. Tumour cells may be recognised by the immune system through the expression of tumour-associated antigens, but the antigenicity varies considerably between different types of antigens. In order to avoid an attack by the immune system, tumour cells use a range of strategies, such as suppression of expression of tumour-associated antigens or of MHC class 1 molecules, or even counterattack against immune cells.

Research into immunotherapy of cancers aims to devise novel strategies to support the anti-cancer immune response; principal approaches include:

*Antigen-independent cytokine therapy (e.g. interleukins or interferons)





*Stimulating cell-mediated immune responses (adoptive T-cell transfer, vaccines)

*Passive immunotherapy using monoclonal antibodies (e.g. Herceptin, Rituxan).

**2-Novel approaches arising from cancer cell biology**

The progress in our knowledge about gene mutations frequently occurring in cancers, combined with the development of modern molecular biology methods has led to both new diagnostic tools and new treatment modalities that have shown some success in the management of selected types of cancers. The knowledge about cancer–associated genes and their role in cellular growth signalling pathways has led to the development of a considerable number of anti-cancer drugs targeting such signalling pathways:

1) monoclonal antibodies that target the extracellular domains of growth factor receptors and 2) small-molecule inhibitors, targeting either receptor tyrosine kinases or other components of growth signalling pathways, such as Ras, b-Raf or mTOR.

There are two examples of such successful anti-cancer agents are the monoclonal antibody Herceptin for the treatment of a specific subtype of breast cancer, and the small-molecule inhibitor Gleevec targeting the fusion protein Bcr-abl, a mutant tyrosine kinase, involved in the development of chronic myeloic leukaemia (CML). A third group of potential drug targets are some anti-apoptotic proteins that are frequently over expressed in cancer cells.





## HISTOLOGY

**Histology**

The name "Histology" is derived from the Greek word for a tissue "Histos", and "-logos" = "the study of". Today the concept of Histology as a subject includes far more than just the study of tissues. It includes understanding of the structure and function of cells, tissues, organs and organ systems, which can better be described as "Microscopic Anatomy"

In addition to understanding the histology and ultrastructure of cells, tissues and organs, it is also necessary to complement the morphological observations with an understanding of the biochemistry, physiology and biophysics of these structures

**The study of tissue biology (Histology) focusing on the** structure and function of each tissue type, how these tissues are combined to form the organs and systems of the body, and how these combinations function together.

According to the **cell concept,** cell is defined as the smallest basic structure of an organism capable of independent existence. Therefore, **t**issues are groups of cells of similar structure, function and origin that form functional units within the multicellular organism.

Tissues are made of cells and extracellular matrix, these two components are intimately related functionally. Each organ represent greater measure of complexity and are composed of an orderly combination of several tissues

At an even higher level of organization there are the organ systems composed of several organs. Thus the body can be seen to be formed of different levels of organization, with increasing levels of complexity and each of which plays important roles in the physiological homeostasis of the body

**Level of Organsiation.**

The cells in complex multicellular organisms like people are organized into tissues, groups of similar cells that work together on a specific task. Organs are structures made up of two or more tissues organized to carry out a particular function, and groups of organs with related functions make up the different organ systems. This is illustrated (Figure ) by **Cells -Tissues - Organs - Organ Systems –Organism**.

Thus a tissue is as a group of cells with similar structure and embryonic origin working together to perform a particular function in the body. Therefore study of tissues structure and function is helpful for understanding the body biology.

**The Four Primary Tissue Types**

There are four primary tissue types (Figure 1 ), these are: 1) the Epithelial tissue, 2) the Connective tissue, 3) the Mussel tissue, and 4) the Nervous tissue. Every cell in the body belongs to one of these four tissue types that is specialized to perform specific functions, as the anatomical characteristics of each are adapted to effectively carry out these functions.

1-The EPITHELIAL TISSUE covers the body surfaces, lines hollow organs, ventral body cavities and ducts and forms glands.

2-The CONNECTIVE TISSUE protects and supports the body and its organs, binds organs together, stores energy and provides immunity.

3-The MUSCLE TISSUE is responsible for movement and the generation of force.

4-The NERVOUS TISSUE carries information very quickly from one side of the body to the other.

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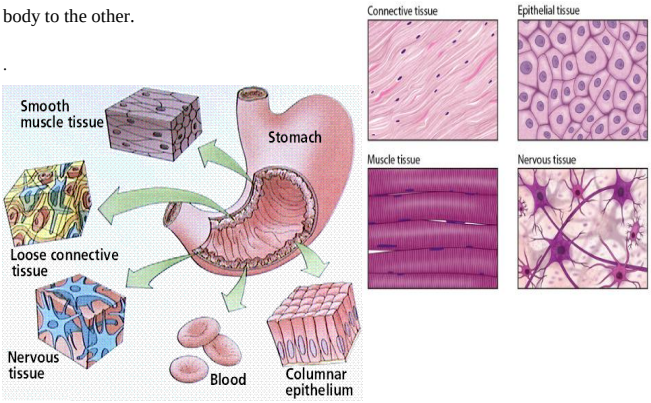


**Figure 1. The Four Primary Tissue Types**

**The comparisons between the four tissues types:**





Microscopic observation reveals that the cells in a tissue share morphological features and are arranged in an orderly pattern that achieves the tissue's functions. From the evolutionary perspective, tissues appear in more complex organisms. For example, multicellular protists, ancient eukaryotes, do not have cells organized into tissues. Although there are many types of cells in the human body, they are organized into four broad categories of tissues: epithelial, connective, muscle, and nervous. Each of these categories is characterized by specific functions that contribute to the overall health and maintenance of the body as shown in Figure 2. For instance, the cells in the small intestine that absorb nutrients look very different from the muscle cells needed for body movement. The structure of the heart reflects its job of pumping blood throughout the body, while the structure of the lungs maximizes the efficiency with which they can take up oxygen and release carbon dioxide.

**Epithelial Tissues 'Epithelia'**
**The features and function of Epithelial tissues**

There are two basic types of epithelial tissues as following:

**1-Covering and lining epithelia**.

The Lining epithelial cells form a continuous layer over all the free surfaces of the body (see **Figure 3**) such as the outer layer of the skin; the inner surface of the digestive and respiratory cavities; the inner surface of the heart and blood vessels; the walls and the organs of the closed ventral body cavities; and the ducts of the exocrine glands.

**2-Glandular epithelia:** These make up most of the glands in the body forming their secreting surfaces





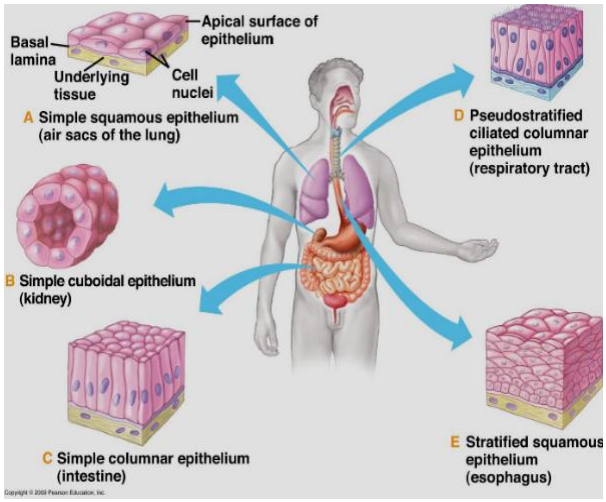


**Figure 3. Covering and lining epithelia over all the free surfaces of the body.**

**Common Histological characteristics of epithelial tissues**

1-They are made of many cells close to each other (there is little extracellular material between epithelial cells, see figure 4).

2-Several types of junctional specializations unite adjacent epithelial cells (tight junctions, desmosomes and gap junctions).

3-With the exception of endocrine glands, all epithelia have one free surface, called the apical surface, which is exposed at the body surface or at the lumen (space) of the body cavity, duct, tube or vessel.

4-The lower surface of an epithelium (or basal surface) rests on a basement membrane: a non-living adhesive material secreted by the epithelium and the underlying connective tissue.





5-There are no blood vessels within the epithelial layer.

6-These cells are often characterized by frequent cell division because they are exposed to wear and tear and injury, necessitating replacement.

**Functions of epithelial tissues:**

The covering epithelia perform and serve several important functions, these are:

1-Epithelia protect underlying tissues against physical damage, drying out, chemical injury and infection.

2-Epithelia allow and regulate the passage of materials (diffusion, absorption, filtration, secretion, excretion) into and out of the deeper tissues of the body which they cover or line. Oxygen, water, food, and waste must pass through one or more epithelial layers.

3-Specialized epithelia form sensory parts of organs such as the eye, ear, mouth (taste buds), and nose (olfactory epithelium).

The glands which are derived from epithelial cells specialized for producing secretions. The material secreted is usually a watery fluid containing substances such as salts, enzymes, hormones, mucus, fats, etc. The functions of glandular secretions are exceedingly diverse. Milk, insulin, sweat, saliva, calcitonin, tears and bile are all products of glands.

**The classification of covering and lining epithelia**

Epithelia is classified based on following characteristic features:

1) Based on the number of cell layers where:

* If the tissue is composed from one layer is known as **simple epithelium**

*If tissue is composed from Several layers is known as **stratified epithelium.**

2)-Based on the shape of the cells

* **Flat**: squamous epithelium,

* **Square:** cuboidal epithelium,

* **Rectangular:** columnar epithelium,

In some tissue, if cell shape changes depending of the degree of stretching of the tissue, this called a **transitional epithelium**.

Importantly, most often, it is very hard to distinguish the cell's boundary on a light photomicrograph. However, to figure out what type of cells you are dealing with, look at the shape and position of the nuclei:

*If the nuclei are flat and parallel to the free surface: squamous epithelium,

*If the nuclei are oval and parallel to the axis of the cell and situated at its base: columnar epithelium,

*If the nuclei are round and situated in the middle of the cell: cuboidal epithelium.

3- Based on the specializations of their cell surfaces (e.g cilia, microvilli, etc).

There are two subtypes of epithelia:

**1-The simple epithelia**

Being composed of one layer of cells only, they are very thin. They are found in areas of minimum wear and tear. Their main function is to allow passage of substances between the lumen and the surrounding tissues.

**2-The stratified epithelia:**

Being composed of several layers of cells, they are very thick. Their main function is to protect the tissues that they cover. The shape of the cells closest to the basement membrane is quite different from that of the cells at the top, near the lumen. Thus, the problem is: how can you further classify the stratified epithelia? By convention, stratified epithelia are further classified according to the shape of the cells at the free surface.

Each subtype of epithelia is subdivided into 4 classes (**Figures 5, 6 and 7**) giving a total of 8 classes of epithelia that we have to learn to identify:

**Simple squamous epithelium**

It is composed of one layer of flat cells (having one flat nucleus). It is found in the alveoli of the lungs, in the kidney glomeruli, in the lining of the heart, blood vessels and lymphatic vessels and in the lining of the ventral body cavities. Because this epithelium is the thinnest of all, it is well adapted for diffusion (for example gas exchange between alveoli and blood in the lung or exchange of waste and nutrients between blood and surrounding tissues), filtration (of plasma in the





kidney glomeruli to produce urine), secretion (of a lubricating substance in the lining of the body cavities).

**Simple cuboidal epithelium**

It is composed of one layer of cuboidal cells (having one round nucleus). It is found in small glands, kidney tubules and ovary surface. It is adapted for secretion and absorption of substances (for example to give urine its final composition, it moves substances in and out of the kidney tubule).

**Simple columnar epithelium**

It is composed of one layer of columnar cells (having one oval nucleus). They can be ciliated or non-ciliated:

The non-ciliated, simple columnar epithelium contains microvilli on the apical surface of its cells. Microvilli increase the surface area of the epithelium, and thus, the non-ciliated type is found mainly lining the digestive tract and is involved in absorption of digested food products and in secretion of mucus, enzymes and other substances. It is also found lining the ducts of some glands.

The ciliated simple columnar epithelium contains, of course, cilia on its apical surface. It is found in the small bronchi, the uterine tubes and part of the uterus. It is involved in the secretion of mucus and other substances and in moving mucus or female reproductive cells.

**Simple pseudostratified epithelium**

This epithelium has only one layer of cells: all its cells rest on the basement membrane, but it appears stratified because the cells are of different heights and their nuclei are at different levels. They can be ciliated or non-ciliated:

The non-ciliated pseudostratified epithelium is found lining part of the male urethra and ducts of large glands.

The ciliated pseudostratified epithelium contains cilia on its apical surface. It is found in the trachea, primary bronchi and in most of the upper respiratory tract and is involved in secretion and propulsion of mucus.





**Stratified squamous epithelium**

This epithelium has several layers of epithelial cells, but the surface layer of this epithelium is composed of flat cells. It is the thickest of all the epithelia and its function is protection.

The cells of the surface layer may or may not contain keratin, a tough protective protein which prevents water loss, is resistant to friction and repels bacteria.

Keratinized, stratified squamous epithelium forms the epidermis of the skin.

Non-keratinized stratified squamous epithelium lines wet surfaces subjected to abrasion, such as the lining of the mouth, oesophagus, tongue

**Stratified cuboidal epithelium**

This epithelium has several layers of epithelial cells, but the surface layer of this epithelium is composed of cuboidal cells.

It is found in the largest ducts of sweat glands, mammary glands, salivary glands and in parts of the male urethra. Its role is protection.

**Stratified columnar epithelium**

This epithelium has several layers of epithelial cells, but the surface layer of this epithelium is composed of columnar cells. Rarely, it lines part of the urethra, large ducts of some glands, portion of the conjunctiva of the eye. Its roles are protection and secretion.

**Stratified transitional epithelium**

This epithelium has several layers of epithelial cells. It is found lining surfaces of organs subjected to stretch, such as the bladder, the ureters and part of the urethra. Its allows for distension of the urinary organ. Because the shape of the cells at the surface layer is transitory (changes depending on the degree of stretching of the organ), this epithelium is called transitional. It will look like a stratified squamous epithelium if it is stretched or a stratified cuboidal epithelium if it is unstretched.

**The Glandular Epithelia**

A gland may consist of one cell or a group of specialised cells that make and secrete substances. Glands are classified as **Endocrine** or **Exocrine** depending on their route of secretion.





**Endocrine Glands:** Their products, called hormones, are secreted directly into the blood and circulate throughout the body to their target areas. Hormones act as chemical messengers to regulate specific body functions. Most of the endocrine gland are epithelial derivatives.

The endocrine glands are formed by invagination from an epithelial sheet and initially have ducts connecting them to the free surface of the epithelial sheet. During embryonic development, they will lose their ducts and thus are called ductless glands (No ducts). Under the microscope, they look like any stratified epithelial tissues with one big difference: They do not have a free surface and are surrounded directly by other tissues.

**Exocrine Glands:** They release their products onto the free surface of the skin or of the open cavities of the body such as the digestive, respiratory or reproductive tracts. Their products are NOT released into the blood. They are also classified on the basis of their structure (**see figure 8**)

*** Unicellular glands**

They are consist of single cells specialized for secretion scattered amongst other non-secretory epithelial cells of a surface membrane. They have no ducts, of course, but they secrete their products directly on the free surface of open body cavities and thus, are considered exocrine. The most common unicellular exocrine glands are the goblet cells (mucus secreting cells) found in the epithelium of the trachea and the digestive tube.

*** Multicellular glands**

They are multicelled glands. They are formed by invagination from an epithelial sheet (like the endocrine glands) but will never lose the duct connecting them to the free surface of the epithelial sheet (surface of the skin or lumen of the open body cavities). Exocrine multicellular glands occur in several forms.

**Lateral and apical surface modifications of epithelia cells**

As shown in figure 9 below there are modification of epithelial cells at lateral and apical surfaces such as desmosomes, gap junctions, microvillie,..etc.

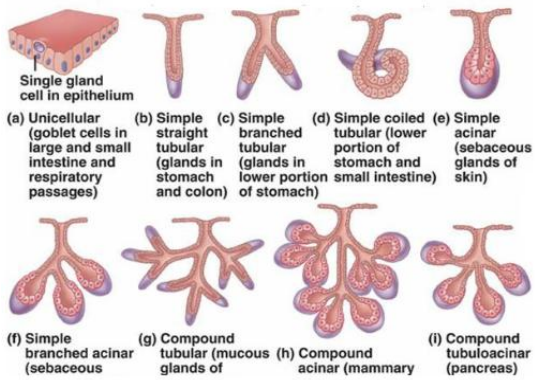


**Figure 8. Glandular Epithelia**

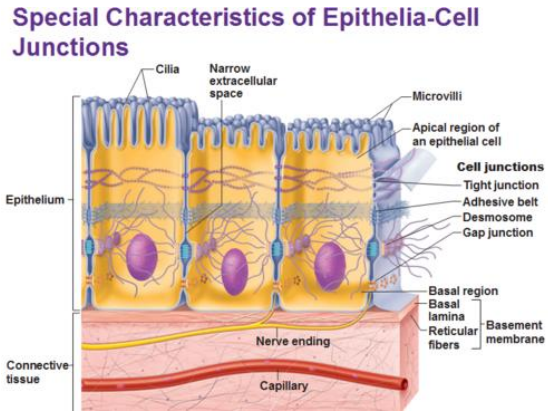


**Figure 9 Special characteristics of epithelial cells**





## Connective Tissues

**General features and functions of the connective tissues**

Connective tissues ( see **figure 10**) are the most abundant of the primary tissues and is found everywhere in the body. They are very different from the epithelial, muscle and nervous tissues as cells of these tissues are close together, but the cells of the connective tissues are far apart, separated by an abundant amount of extracellular material that is called extracellular matrix. Due to cells properties and the composition/arrangement of the extracellular matrix elements vary tremendously, an amazing diversity of connective tissues found, each uniquely adapted to perform its specific function in the body.

**Functions of the connective tissues include the followings:**

1-Binding, support and packaging: Other tissues (epithelia, muscles, nerves) are supported, surrounded and held in place by connective tissues. Connective tissue fibers form capsules and membranes which surround organs, and form ligaments and tendons which bind bones to each other or to muscles. They also form the 3-dimensional fibrous mesh which supports cells inside large soft organs such as the liver and spleen. Bone and cartilage support body organs. The delicate and fragile areolar connective tissue forms a soft packing around organs.

**2-Protection, defense and repair:** Some connective tissues have great regenerative ability and are important in repair following injury. Scar tissue is formed of connective tissue which fills in spaces where the original tissue does not regenerate. Several cellular and molecular components of connective tissue function in defense against invading bacteria or chemical substances. Inflammation is a defensive response of connective tissue at the site of infection or injury. The skull is a bony chamber which protects the soft brain tissue.

**3-Insulation:**

Fat cells or adipose tissue, is a connective tissue which not only cushions body organs but also insulates them and provides reserve energy fuel.





**4-Transportation:**

Blood is a connective tissue and it carries and delivers oxygen and nutrient to tissues.

## The classification of connective tissues

There are four classes of connective tissues, these are Blood, Bone, Cartilage, and the connective tissue proper based on their identification by three criteria: 1) cell types, 2) kinds, density and arrangement of their fibers, and 3) Amount and nature of the amorphous ground substances which is present between its cells.

**I-Types of cells** found in connective tissues can be placed in two categories:

**1**-The cells of the connective tissue ***per see*** which secrete the matrix or maintain it. Each of the major classes of connective tissue contains an undifferentiated cell type whose name ends ***in -blast***. This cell retains its capacity for division and secretes the matrix that is characteristic of the tissue. In most connective tissues, once the matrix is produced, the undifferentiated cells lose their capacity for cell division and become mature cells whose name ends **in -cyste**. These mature cells are less active and in general are responsible for maintaining the matrix in a healthy state. **Fibroblasts** are the primary blast cells of the connective tissue proper; **hemocytoblasts** are the primary blast cells of the blood; **chondroblasts** and **osteoblasts** are the primary blast cells of cartilage and bone, respectively.

2-The accessory cells which are supported by the connective tissue.

Connective tissue (especially one of the proper connective tissues: the loose connective tissue) is also home to an assortment of other cell types such as:

***Fat storing cells** that provide reserve energy fuel

***White blood cells**; **mast cells; macrophages; antibody-producing plasma cells** that are mobile and migrate into the connective tissue matrix from the blood stream. They are involved in the body defence and in the elimination of dying or dead tissue cells.

### Components of the extra cellular matrix

The extracellular matrix is composed of ground substance and fibers





**The ground substance**

It is the amorphous substance that fills the space between the cells and contains the fibers. It is composed of interstitial fluid, cell adhesion proteins and proteoglycans. Cells adhesion proteins allow the connective tissue cells to attach themselves to matrix elements. The proteoglycans are proteins to which polysaccharides are attached. These polysaccharides can trap more or less water depending their nature and form a substance that varies from a fluid to a semi-stiff hydrated gel. The relative amounts and kinds of polysaccharides help determine the properties of the matrix. For example, the more polysaccharides, the stiffer the ground substance is. The ground substance supports cells, binds them together and functions as a medium through which nutrients and other dissolved substances can diffuse between capillaries and cells.

**Fibers**

Fibers in the matrix provide strength. Three types of fibers are found in the connective tissue matrix: collagen, elastic and reticular.

**1-Collagen fibers (white fibers):** are extremely tough. They are stronger than steel fibers of the same size. They provide high tensile strength, which is the ability to resist longitudinal stress. Since fresh collagen fibers have a glistening white appearance they are sometime called "white fibers".

**2-Elastic fibers (yellow fibers):** can be stretched to one and one-half times their length, but recoil to their initial length when released. They are found where greater elasticity is needed such as the lungs and the blood vessel walls. Fresh elastic fibers appear yellow and are also called yellow fibers.

**3-Reticular fibers:** are fine collagenous fibers. They form a delicate branching network supporting soft organs such as the liver and spleen.

There are four classes of connective tissues further subdivided into subclasses and types as shown in figure 12.

**A] CONNECTIVE TISSUE PROPER LOOSE (Figure 13)**

The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix). The fibers are loosely woven and thus the ground substance is highly visible. A great number of accessory cells (blood cells, fat cells) can be

found in these tissues. The connective tissue proper loose serves as a general packaging material. It can be subdivided into three types: **aerolar; adipose and reticular.**

**I-Connective Tissue Proper Loose areolar (Figure 14)** with the following characters:

**1**-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The fibers are loosely woven and thus the ground substance is highly visible.

**3**-The three types of fibers (collagen, elastic and reticular) are present in roughly the same amount.

**4**-Many accessory cells (macrophages, mast cells, ...) can be found in these tissues.

**5**-It is the most widely distributed connective tissue in the body.

**6**-Connective tissue proper loose areolar is a soft pliable tissue that serves as a general packaging material. It packages organs, wraps small blood vessels and nerves, surrounds glands, forms the superficial part of the dermis as well as the hypodermis which attaches the skin to underlying structures. It is present in all mucous membranes as the lamina propria

**II-Connective Tissue Proper Loose adipose (Figure 15)** with the following characters:

**1**-This tissue is basically an aerolar connective tissue invaded by fat cells (adipocytes). Seen through the light microscope, the adipocytes look like big white blobs: an oil droplet occupies most of the cell volume, pushing the cell's nucleus to the periphery. The adipocytes are packed closely together and account for about 90% of the tissue mass.

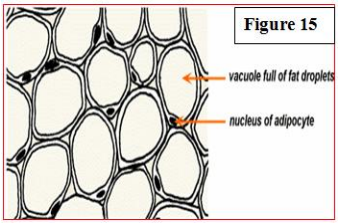

Figure 15

**2**-Adipose tissue provides reserve fuel for cells in the body. Since fat is a poor heat conductor it insulates the body against heat loss. It also supports and protects organs by acting as shock absorber.





**3**-Adipose tissue may develop almost anywhere areolar tissue is plentiful, but it usually accumulates in subcutaneous tissue, around kidneys and eyeballs, in bones, in breasts and within the abdomen.

4-Adipose tissue is richly vascularized, indicating its high metabolic activity.

III-**Connective Tissue Proper Loose reticular (figure 16)** with the following characters:

**1**-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The ground substance is highly visible. It is loosely packed with fibers mostly reticular, which form a fine network supporting accessory cells.

**3**-Reticular tissue forms the delicate framework (or stroma) that supports blood cells in lymph nodes, the spleen and bone marrow.

**Connective Tissue Proper dense (Figure 17)** with the following characters:

**1**-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The fibers are densely packed and thus the ground substance is barely visible. Fibers are the predominant element of this connective tissue and, for this reason, dense connective tissue proper is often referred to as fibrous connective tissue.

**3**-In contrast with loose connective tissue proper, most of the cells found here are fibroblasts: there are virtually no accessory cells.

**4**-Connective tissue proper dense can be subdivided into three types **regular**, **irregular elastic** and are found in organs that have to withstand great tensile stress (stretch).

**I- Connective Tissue Proper dense regular (Figure.18)** with the following characters:

**1**-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The fibers are densely packed and thus the ground substance is barely visible. The fibers are primary collagenous fibers and are arranged parallel to each other (a few elastic fibers are also present in the matrix). This results in a white flexible





tissue with great resistance to forces pulling in one direction. The collagen fibers are slightly wavy: this allows the tissue to stretch a little until the fibers are straightened out but not more.

**3**-It is found in areas where tension is always exerted in a single direction, such as: tendons (cords attaching muscles to bones), aponeuroses (flat sheets attaching muscles to bones or to other muscles) and ligaments (attaching bones together at joints). Ligaments contain more elastic fibers than do tendons and thus are slightly more stretchy.

II-**Connective Tissue Proper dense irregular (Figure 19)** with the following characters:

1-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The fibers are densely packed and thus the ground substance is barely visible. The fibers are primary collagenous fibers and are interwoven without a regular orientation (a few elastic fibers are also present in the matrix). This results in a white flexible tissue with great resistance to forces pulling in several directions. The collagen fibers are slightly wavy: this allows the tissue to stretch a little until the fibers are straightened out but not more.

**3**-It usually forms sheets in area where tension is exerted in many directions such as: the skin (in the deeper layer of the dermis), the wall of the digestive tract (it forms the submucosa), heart valves, fibrous pericardium, perichondrium (membrane around the surface of cartilage), periosteum (membrane around the surface of the bone), fibrous capsules of organs and of joints

III- **Connective Tissue Proper dense elastic (Figure 20)** with the following characters:

**1**-The fibroblasts are embedded in the matrix: they do not lie in lacunae (chambers within the matrix).

**2**-The fibers are densely packed and thus the ground substance is barely visible. The fibers are primary elastic fibers and they give the tissue a yellowish color. Dense elastic connective tissue combines strength with elasticity: it can be stretched very easily and then recoils to its original length as soon as the tension is





released. It confers elastic properties which enable recovery of tissue shape following normal physiological deformation or stretching.

**3**-It is found in the vocal cords, in some ligaments (such as the ligamenta flava that connect adjacent vertebrae and the suspensory ligament of penis), in the walls of elastic arteries, in parts of the trachea and bronchi, and in the lung tissue.

**B] Cartilage:**

1-Cartilage is a tough but flexible tissue which provides a resilient rigidity to the structures it supports.

2-The matrix of cartilage consists of elastic and collagenous fibers embedded in chondroitin sulfate (a jellylike component of the ground substance).The chondroitin sulfate gives resilience to cartilage, and collagen fibers gives it its strength.

3-The cells of mature cartilage **(Figure 21)** are called chondrocytes. They are easy to spot on photomicrographs because they lie singly or in groups within chambers in the matrix called lacunae. Unlike other connective tissues, cartilage has no blood vessels or nerves. There are three types of cartilage: hyaline cartilage, fibrocartilage and elastic cartilage

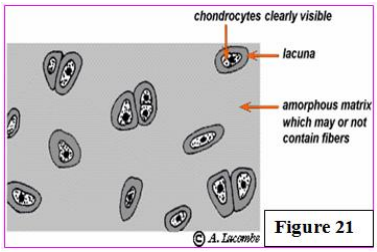

Figure 21

**I-Hyaline Cartilage (Figure 22).** It is characterised by:

1-The chondrocytes lie within chambers in the matrix called lacunae.

2-The hyaline cartilage contains a gel-like amorphous matrix. Fine collagen fibers are present in the matrix, but they are not visible with ordinary staining techniques.

3-Hyaline cartilage affords firm support with some pliability. It has resilient cushioning properties and resists compressive stress. It reduces friction and absorbs shocks in joints.

Hyaline Cartilage is the most abundant type of cartilage: It is found at the ends of long bones (as articular cartilage). It supports the tip of the nose, the trachea and the bronchi. It forms most of the larynx and connects the ribs to the sternum. It is also found in epiphyseal plates of children.

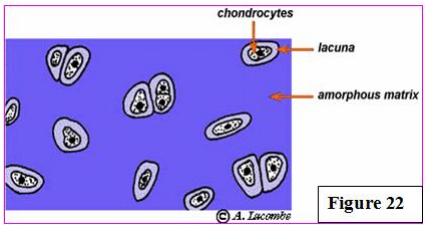

Figure 22

**II-Fibrocartilage (Figure 23).** It is characterised by

1-The chondrocytes lie within chambers in the matrix called lacunae. Fibrocartilage is quite similar to hyaline cartilage but its matrix contains many coarse collagen fibers running parallel to each other.

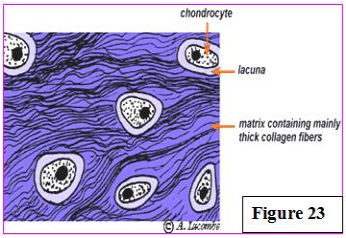

Figure 23

2-Because of the presence of these extra collagen fibers, not only can fibrocartilage resist compression but it can also resist pulling.

3-It will be found where strong support and the ability to withstand heavy pressure is required, such as the pubic symphysis (point where hipbones join anteriorly), intervertebral discs (discs between vertebrae) and the menisci of knees (disc of knee joint).

**III-Elastic Cartilage (Figure 24)**. It is characterised by

**1-**The chondrocytes lie within chambers in the matrix called lacunae. Elastic cartilage is quite similar to hyaline cartilage but its matrix contains many elastic fibers.





**2-**Elastic cartilage provides strength and elasticity: it allows flexibility while maintaining the shape of the structure.

**3-**It is found in the epiglottis of the larynx, the external ear and the (Eustachian) auditory tubes.

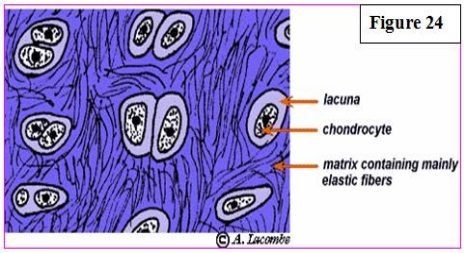

Figure 24

**C] Bone:**

**1-**Bone is one of the hardest tissues in the body. The hardness of the bone, its ability to resist compression, is due to the inorganic calcium phosphate (calcium hydroxyapatite) deposited within the matrix. Numerous collagen fibers embedded within the matrix give the bone its ability to resist twisting and stretching.

**2-**The mature bone cells are called osteocytes. They are connected together by very fine tentacle-like cytoplasmic processes. Osteocytes lie within chambers in the matrix called lacunae. Radiating in all direction from the lacunae are minute canals called canaliculi. They connect the lacunae with each other. Canaliculi are filled with extracellular fluid and contain the slender cytoplasmic processes of the osteocytes. There are two types of bone tissue: **compact bone** and **spongy bone**





**I-Compact Bone (Figure 25a,b).**

1-Compact (dense) bone tissue consists of precise arrangements of microscopic cylindrical structures called osteons. The matrix and osteocytes of osteon are laid down in concentric rings around a central (Haversian) canal.

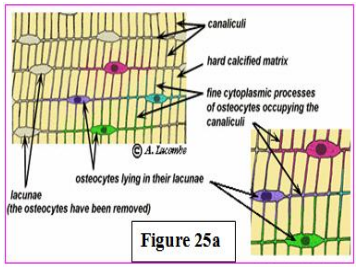

Figure 25a

2-Compact bone tissue forms the external layer of all bones and the bulk of the diaphyses (shaft) of the long bones.

3-The matrix is the whitish background substanceIt provides protection and support and helps the long bones resist the stress of weight placed on them.

**II-Spongy Bone: (Figure 26)**

1-In contrast to compact bone tissue, spongy (cancellous) bone consists of an irregular latticework of thin blades of bone called trabeculae.

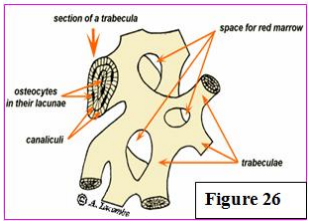

Figure 26

2-The space between the trabeculae are filled with red marrow which produces blood cells. 3-Spongy bone makes up most of the bone tissue of short, flat and irregularly shaped bones and most of the heads (epiphyses) of long bones.

**D] Blood:**

1-Blood (**Figure 27**) is considered a connective tissue, because it consists of blood cells surrounded by a nonliving fluid matrix called blood plasma. It is the most atypical connective tissue: the fibers of blood are soluble protein molecules that become visible during blood clotting and found in in blood vessels.

The Blood has three functions:

**1-Transportation**





Blood delivers oxygen from the lungs and nutrient from the digestive tract to all body cells; it transports carbon dioxide to the lungs and nitrogenous waste to the kidney for removal from the body; it transports hormones from their endocrine glands to their target organs.

**2-Regulation**

Blood helps regulate body temperature and pH in body tissues.

**3-Protection**

Platelets and plasma proteins prevent blood loss by forming clots when blood vessels are damaged. Antibodies, complement proteins and white blood cells fight infection.

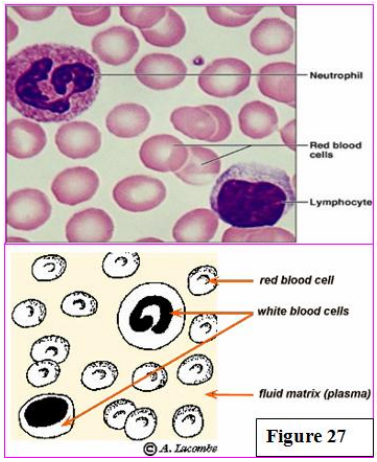

Figure 27

**Muscle Tissues**

**General features and functions**

Muscle tissue consists of cells that are highly specialized for the active generation of force for contraction. These cells are elongated and can change their shape by becoming shorter and thicker. By contracting, the muscle cells pull at their attached ends and cause body parts to move.

**Histological characteristics** of muscle tissues. These characteristic are common to all muscle tissues as follows:

**1**-They are made of many cells close together (there is little extracellular material between muscle cells).

**2**-They are well vascularized (lots of blood vessels).

**3**-The cells are elongated.

**4**-The cells contain myofilaments (contractile proteins).

**Functional Characteristics of Muscles**: Muscle tissue has four characteristics that play a role in maintaining homeostasis.

**1-Excitability:** The ability to receive and respond to stimuli. Stimuli initiate nerve impulses which are interpreted by the brain and spinal cord and transmitted back to the muscles, causing them to respond.

**2-Contractility:** the ability to shorten and thicken, or contract, when a sufficient stimulus is received. This characteristic distinguishes muscle tissue from other types of tissue.

**3-Extensibility:** the ability to stretch or extend.

**5-Elasticity:** the ability of muscle to return to its original shape after contraction or extension

M**uscles perform four function:**

**1-Movement or motion:** Skeletal muscles provide movements of the body by muscle contraction, such as walking, and running. Cardiac muscle contraction maintains the beating of the heart. Smooth muscle contraction in the intestines, urinary bladder, and blood vessels moves substances through the body.

**2-Maintenance of posture:** Skeletal muscles contract and make small adjustments almost continuously to hold the body in stationary positions, such as sitting or standing.

**3-Stabilize joints:** Skeletal muscles add stability to joints that have poor reinforcement and articular surfaces that do not fit well, such as in the shoulder and knee joints¯





**4**-Heat production: Skeletal muscle constitutes 40% of body mass. Contractions produce heat and are important in maintaining normal body temperature.

**Types of Muscle Tissues**

Three kinds of muscle tissues (**Figure 28**) found in different organs of the body:

**1-Skeletal muscle**

Skeletal muscle is found attached to and covering bones. They are classified as skeletal, striated, voluntary muscles. The muscle fibers are multinucleated (contain many nuclei), have band-like striations, and contraction is by conscious control.

**2-Cardiac muscle**

Cardiac muscle is located in the walls of the heart and is classified as cardiac, striated, involuntary muscle. The muscle fibers are branched, contain a single nucleus, have band-like striations, and are not under conscious control. They have thicker striations, called intercalated discs, where muscle fiber joins the next fiber.

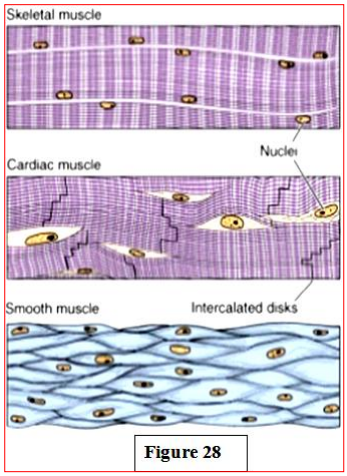

**Figure 28**

**3-Smooth muscle**

Smooth muscle is located in the walls of hollow visceral (internal) organs such as the intestines, stomach, urinary bladder, respiratory passages, and blood vessels. They are classified as visceral, nonstriated, involuntary muscles. The muscle fibers contain a single nucleus, no striations, and are not under conscious control.

**The Skeletal Muscle Structure**

Muscle tissues differ in structure. Skeletal muscle fibres (Figures 29) are packed into regular parallel bundles. Smooth muscle has bundles of thin and thick filaments. Cardiac muscle bundles are branched but connected.





Unlike other tissue, skeletal muscle cells contain myofibrils – these are shaped like long cylinders and extend along the full length of the muscle fibre/cell. Each myofibril consists of two types of protein filaments called thick filaments and thin filaments. The thick filaments and the thin filaments within *myofibrils* overlap, and the sections where they overlap and occur together are called sarcomeres. When muscle contraction occurs, the thin filaments and the thick filaments slide past each other. Muscle varies in thickness and is attached to bones via strong bands of connective tissue called tendons. The skeletal muscle is organized into bundles of muscle cells or fibres that are held together by a sheath of connective tissue that enables muscle cells to function together as a unit.

Each muscle fiber is a single cell with many nuclei. Around each cell is plasma membrane called the sarcolemma which contains sarcoplasm (cytoplasm). Each cell/fibre is comprised of many smaller myofibrils arranged lengthwise. Myofibrils appear as banded units called Sarcomeres.

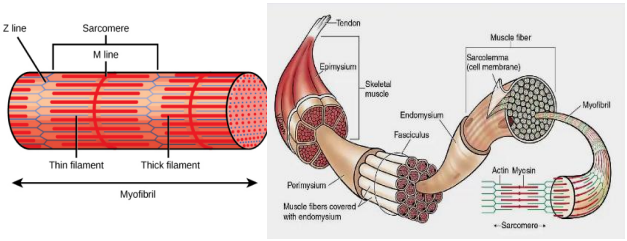


**Figure 29**. Skeletal muscle cell showing thick and thin protein filaments and the sarcomere where they overlap. Source: Science Learning Hub, University of Waikato, www.sciencelearn.org.nz

Each sarcomere is comprised of two kinds of myofilaments, a thin protein called actin and a thicker one called myosin . These are the units that cause muscle contraction. They overlap to form light and dark bands and it is this banding that gives skeletal muscle its striated appearance. A sarcomere has two distinct bands – an 'I' band and an 'A' band. The 'I' band corresponds to a light area. This is where the actin proteins are located. The 'A' band is dark and corresponds to the area in





which actin and myosin overlap. An 'H' zone marks the location of myosin proteins only. The boundary of each sarcomere is marked by 'Z' lines.

Nervous tissue is one of four major classes of tissues. It is specialized tissue found in the central nervous system and the peripheral nervous system. The nervous system can be organized by anatomical or functional divisions.

**1-Nervous system** is divided anatomically into the central nervous system **(CNS),** which includes the brain and spinal cord, and the peripheral nervous system **(PNS),** which includes the nerves outside the CNS and their associated ganglia.

**2-Nervous system** is divided functionally into a sensory component, which transmits electrical impulses (signals) to the CNS, and a motor component, which transmits impulses from the CNS to various structures of the body. The motor component is further divided into the somatic and autonomic systems.

**3-Nervous tissue** contains two types of cells: nerve cells (neurons), which conduct electrical impulses, and glial (neuroglial) cells, which support, nurture, and protect the neurons.

**Cells of Nervous System**

**1]-Neurons** consist of a **cell body** and its processes, which usually include multiple **dendrites** and a single **axon.** Neurons comprise the smallest and largest cells of the body, ranging from 5 to 150 m in diameter.

**1-Morphologically,** Neurons are classified as shown in **figure 31** into:

**a-A Unipolar neurons** possess a single process but are rare in vertebrates.

**b-**Bipolar neurons possess a single axon and a single dendrite. These neurons are present in some sense organs (e.g., the vestibular–cochlear mechanism).

**c-Multipolar neurons** possess a single axon and more than one dendrite. These neurons are the **most common type** of neuron in vertebrates.

**d-**Pseudounipolar neurons possess a single process that extends from the cell body and subsequently branches into an axon and dendrite

**2-Functionally,** Neurons are classified into:

**a-Sensory neurons** receive stimuli from the internal and external environments. They conduct impulses to the CNS for processing and analysis.

**b-Interneurons** connect other neurons in a chain or sequence. They commonly connect sensory and motor neurons; they also regulate signals transmitted to neurons.

**c-Motor neurons** conduct impulses **from the CNS** to other neurons, muscles, and glands.

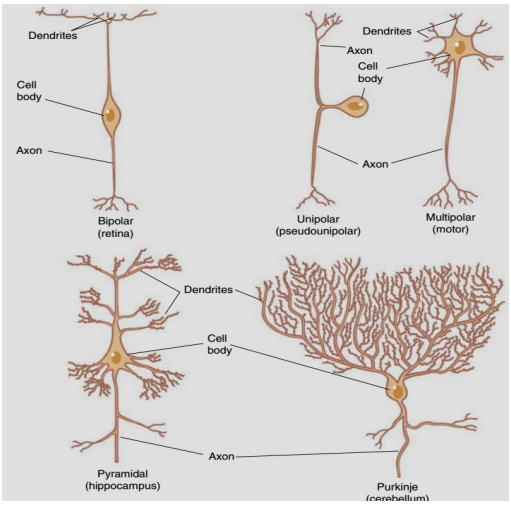


**Figure 31** . Various types of neurons. (Reprinted with permission from Gartner LP, Hiatt JL: Color Textbook of Histology, 2nd ed. Philadelphia, Saunders, 2001, p 187.)

**Neuron Structure**

Neurons are highly specialized nerve cells that generate and conduct nerve impulses **(Figure 32)**.A typical neuron consists of dendrites, the cell body, and an axon.

Dendrites are responsible for responding to stimuli; they receive incoming signals towards the cell body. The axons are responsible for transmitting impulses over





long distances from cell body. The cell body is like a factory for the neuron. It produces all the proteins and contains specialized organelles such as nucleus, granules and Nissl bodies. The axon is surrounded by a whitish, fatty layer called the myelin sheath. Outside the myelin sheath there is a cellular layer called the neurilemma. Axons conduct impulses away from the soma to the axon terminals without any diminution in their strength.

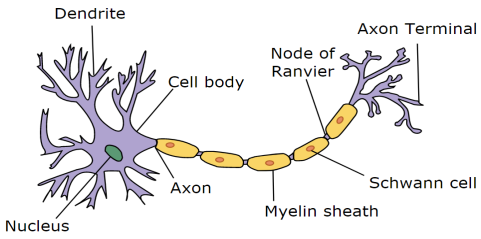


**Figure 32. the structure of a Neuron**

**2] Neuroglial cells** are located only in the CNS (Schwann cells are the PNS equivalent). They function to support and protect neurons, but they do not conduct impulses or form synapses with other cells. Neuroglial cells possess the capacity to undergo cell division. Neuroglia are revealed in histologic sections of the CNS only with special gold and silver stains. There are six types of neuroglia; **4** in the central nervous system and **2** in the PNS. These glial cells are involved in many specialized functions apart from support of the neurons. Neuroglia in the CNS include astrocytes, microglial cells, ependymal cells and oligodendrocytes. In the PNS, satellite cells and Schwann cells are the two kinds of neuroglia.

**Synapses**

Synapses are sites of **functional apposition** where signals are transmitted from one neuron to another or from a neuron to another type of cell (e.g., muscle cell). Synapses are classified according to the site of synaptic contact and the method of signal transmission.





**1-Site of synaptic contact**

**a-Axodendritic synapses** are located between an axon and a dendrite. **b-Axosomatic synapses** are located between an axon and a soma. The CNS primarily contains axodendritic and axosomatic synapses.

**c-Axoaxonic synapses** are located between axons.

**d-Dendrodendritic synapses** are located between dendrites.

**2. Method of signal transmission**

**a) Chemical synapses**

**(1)** These synapses involve the release of a chemical substance (**neurotransmitter** or **neuromodulator**) by the presynaptic cell, which acts on the postsynaptic cell to generate an action potential.

**(2)** Chemical synapses are the most common neuron–neuron synapse and the only neuron–muscle synapse.

**(3)** Signal transmission across these synapses is **delayed** by about 0.5 ms, the time required for secretion and diffusion of neurotransmitter from the presynaptic membrane of the first cell into the synaptic cleft and then to the postsynaptic membrane of the receiving cell.

**(4)** Neurotransmitters do not effect the change, they only activate a response in the receiving cell.

**b) Electrical synapses**

(1) These synapses involve movement of ions from one neuron to another via gap junctions, which transmit the action potential of the presynaptic cell directly to the postsynaptic cell.

(2)Electrical synapses are much less numerous than chemical synapses.

(3)Signal transmission across these synapses is nearly instantaneous.

**Clinical Considerations**

**Alzheimer disease** is the most common cause of dementia. The disease is characterized by the loss of neurons and synapses mainly within the cerebral cortex followed by atrophy of the individual cerebral lobes. Patients with Alzheimer





disease develop ß-amyloid plaques and neurofibrillary tangles that render the neurons non-functional.

**Huntington chorea**

Huntington chorea is a fatal hereditary disease that becomes evident during the third and fourth decades of life, first presenting as painful joints and progressing to uncontrolled flicking of joints, motor disfunction, dementia, and death. The cause is thought to be the loss of neurons that produce the neurotransmitter -aminobutyric acid (GABA). The symptoms of dementia are thought to be related to the loss of the cells secreting acetylcholine.

**Multiple sclerosis**

Multiple sclerosis (MS) is an immune-mediated disease characterized by chronic and progressive dysfunction of the nervous system due to demyelination of the CNS, especially in the brain, spinal cord, and optic nerves. MS afflicts about 1 in 700 in this country, mos

## Skeletal System

**Types of bone Cells (Figure 33)**

**There are** four types of cells: osteoblasts, osteoclasts, osteocytes, and osteoprogenitor (or osteogenic) cells.

**1-Osteoblast** is responsible for forming new bone and found in the growing portions of bone, including the periosteum and endosteum.

**2-The Osteocyte** is formed when the osteoblast becomes trapped within the calcified secreted matrix produced. It is the primary cell of mature bone and the most common type of bone cell.

**3-Osteoprogenitor** are undifferentiated cells with high mitotic activity and are the only bone cells that divide. Immature osteogenic cells are found in the deep layers of the periosteum and the marrow. When they differentiate, they develop into osteoblasts.

**4-Osteoclast** is responsible for bone resorption, or breakdown and found on bone surfaces, is multinucleated, and originates from monocytes and macrophages (two types of white blood cells) rather than from osteogenic cells.

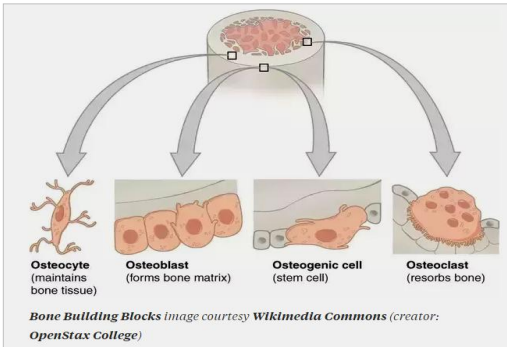


**Figure 33. Types of Bone cells**

**Bone Histogenesis**

Bone Histogenesis occurs by two processes, intramembranous and endochondral bone formation. Both processes produce bone that appears histologically identical. Bone histogenesis is accompanied by bone resorption. The combination of bone formation and resorption, termed remodeling, occurs throughout life, although it is slower in secondary than in primary bone.

**Intramembranous Ossification**

Intramembranous ossification is the process of bone development from fibrous membranes. It is involved in the formation of the flat bones of the skull, the mandible, and the clavicles. Ossification begins as mesenchymal cells form a template of the future bone. They then differentiate into osteoblasts at the ossification center. Osteoblasts secrete the extracellular matrix and deposit calcium, which hardens the matrix. The non-mineralized portion of the bone or osteoid continues to form around blood vessels, forming spongy bone. Connective tissue in the matrix differentiates into red bone marrow in the fetus. The spongy





bone is remodeled into a thin layer of compact bone on the surface of the spongy bone.

**Endochondral Ossification**

Endochondral ossification is the process of bone development from hyaline cartilage (Figure 34). All of the bones of the body, except for the flat bones of the skull, mandible, and clavicles, are formed through endochondral ossification.

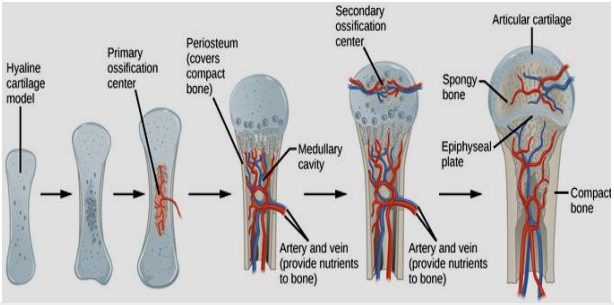


**Figure 34.** Process of endochondral ossification: Endochondral ossification is the process of bone development from hyaline cartilage. The periosteum is the connective tissue on the outside of bone that acts as the interface between bone, blood vessels, tendons, and ligaments.

## Blood and Hemopoiesis

Blood is a specialized connective tissue that consists of formed elements (erythrocytes, leukocytes, and platelets) and a fluid component called plasma. The volume of blood in an average human adult is approximately 5 L. Blood circulates in a closed system of vessels and transports nutrients, waste products, hormones, proteins, ions, oxygen (O2), carbon dioxide (CO2), and formed elements. It also regulates body temperature and assists in regulation of osmotic and acid–base balance. Blood cells have short life spans and are continuously replaced by a process called hemopoiesis.





**BONE MARROW**

The bone marrow includes: A) **Yellow marrow** is located in the long bones of adults and is highly infiltrated with fat. It is not hemopoietic, but it has the potential to become so if necessary. B) In adults, **red marrow** is located in the epiphyses of long bones and in flat, irregular, and short bones. It is highly vascular and composed of a stroma, irregular sinusoids, and islands of hemopoietic cells. ***Red marrow is the site of blood cell differentiation and maturation***. The largest cells of bone marrow are the megakaryocytes, precursors of platelets.

**PRENATAL HEMOPOIESIS**

This process occurs successively in the yolk sac, liver, spleen, and bone marrow.

1-The bone marrow first participates in hemopoiesis at about 6 months' gestation and assumes an increasingly large role thereafter.

2-The liver and spleen cease hemopoiesis at about the time of birth

**POSTNATAL HEMOPOIESIS**

This process involves three classes of cells: stem, progenitor, and precursor cells.

**A. Comparison of stem, progenitor, and precursor cells**

**1-Stem cells** are capable of self-renewal and can undergo enormous proliferation.

a-These cells can differentiate into multiple cell lineages.

b-They are present in circulation (as null cells) and in bone marrow.

**2-Progenitor cells** have reduced potentiality and are committed to a single cell lineage.

a-They proliferate and differentiate into precursor cells in the presence of appropriate growth factors.

b-They are morphologically indistinguishable from stem cells, and both appear similar to small lymphocytes.

**3-Precursor cells** are all the cells in each lineage that display distinct morphological characteristics.

**BLOOD CONSTITUENTS**

**A-Plasma** consists of 90% water; 9% organic compounds (such as proteins, amino acids, and hormones); and 1% inorganic salts, dissolved gases, and nutrients.

**1.Main plasma proteins**





**a. Albumin**, a small protein (60,000 molecular weight), preserves osmotic pressure in the vascular system and helps transport some metabolites.

**b. Globulins** are antibodies (immunoglobulins).

**c. Globulins** and -globulins transport metal ions (e.g., iron and copper) and lipids (in the form of lipoproteins).

**d.Clotting** proteins, including fibrinogen, a soluble protein that is converted into fibrin during blood clotting.

**e.Complement proteins** (C1–C9) are part of the innate immune system, and they function in nonspecific host defense and initiate the inflammatory process.

**2-Serum** is the yellowish fluid that remains after blood has clotted. It is similar to plasma but lacks fibrinogen and clotting factors.

**B. Formed elements of blood**

**1-Erythrocytes (red blood cells** [RBCs]) with the following characters.

a-RBCs are round, anucleate, biconcave cells that stain light salmon pink with either Wright or Giemsa stains.

**(2)**The average life span of an RBC is 120 days. Aged RBCs are fragile and express membrane surface oligosaccharides that are recognized by splenic, hepatic, and bone marrow macrophages, which destroy those erythrocytes.

**(3)** Carbohydrate determinants for the **A, B,** and **O blood groups** are located on the external surface of the erythrocyte's plasmalemma.

**(4)** Several **cytoskeletal proteins** (ankyrin, band 4.1 and band 3 proteins, spectrin, and actin) maintain the shape of RBCs.

**(5)** Mature erythrocytes possess no organelles but are filled with **hemoglobin (Hb)**.

**6)** Erythrocytes also contain **soluble enzymes** that are responsible for glycolysis, the hexose monophosphate pathway, and the production of adenosine triphosphate (ATP). The hematocrit is an estimation of the volume of packed erythrocytes per unit volume of blood and is expressed as a percentage.

**Clinical Considerations**

As the abnormal forms include **HbS,** which occurs as a result of a point mutation in the ß-chain (substitution of the amino acid **valine** for **glutamate**). Erythrocytes containing HbS are sickle shaped and fragile, and they cause **sickle cell anemia.**

**Sickle cell anemia** is caused by a point mutation in the deoxyribonucleic acid (DNA) encoding the Hb molecule, leading to production of an abnormal Hb (HbS). Although this disease occurs almost exclusively among people of African descent (1 in 500 is affected in the United States); among the US Hispanic population, 1 in 1,000 to 1,400 people is affected with sickle cell anemia

**2. Leukocytes, or white blood cells (**WBCs)

They possess varying numbers of azurophilic granules. These are lysosomes containing various hydrolytic enzymes.

**1) Granulocytes** include neutrophils, eosinophils, and basophils.

(1) Granulocytes possess specific granules with type-specific contents.

(2) These cells generate ATP via the glycolytic pathway, Krebs cycle (basophils), and anaerobic pathways (neutrophils).

(3) Destruction of phagocytosed microorganisms by neutrophils occurs in 2 ways.

(a) Azurophilic granules release hydrolytic enzymes into phagosomes to destroy microorganisms. (b) Reactive O2 compounds superoxide (O2), hydrogen peroxide (H2O2), and hypochlorous acid (HOCl) formed within phagosomes (catalyzed by myeloperoxidase) destroy microorganisms.

**2) Agranulocytes** lack specific granules.

(1) They include lymphocytes and monocytes.

**(2)** There are three categories of lymphocytes: B lymphocytes, T lymphocytes, and null cells. B lymphocytes are responsible for the humoral immune response, and T lymphocytes are responsible for the cellular immune response. Null cells constitute approximately 5% of the circulating lymphocytes and are of two types, pluripotential hemopoietic stem cells (PHSCs) and natural killer (NK) cells. Null cells resemble lymphocytes but lack their characteristic surface determinants.





**Clinical Considerations**

**Leukemias** are characterized by the replacement of normal hemopoietic cells of the bone marrow by neoplastic cells and are classified according to the **type** and **maturity** of the cells involved.

**a. Acute leukemias** occur mostly in children.

**(1)** These leukemias involve **immature cells.**

**(2) Rapid onset** of the following signs and symptoms occur: anemia; high WBC count and/or many circulating immature WBCs; low platelet count; tenderness in bones; enlarged lymph nodes, spleen, and liver; vomiting; and headache.

**b. Chronic leukemias** occur mainly in adults.

**(1)** These leukemias initially involve relatively **mature cells.**

**(2)** Early signs include **slow onset** of a mild leukocytosis and enlarged lymph nodes; later, signs and symptoms include anemia, weakness, enlarged spleen and liver, and reduced platelet count.

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تم بحمد الله وفضله
قنـــا 1440هـ/2018 م

## Figure 1. Characters of an eukaryotic cell (animal cell)

-Possess a membrane-bound nucleus
-They are more complex than prokaryotic cells
-Compartmentalize many cellular functions within organelles and the endomembrane system
-Possess a cytoskeleton for support and to maintain cellular structure
-The following can be seen
Plasma membrane, flagellum, nucleolus, nucleolus, chromatin, nuclear envelope, Rough endoplasmic reticulum, smooth endoplasmic reticulum Golgi apparatus, ribosome, microtubules, centriols, mitochonderia, microfilments, Lysosomes, peroxisome

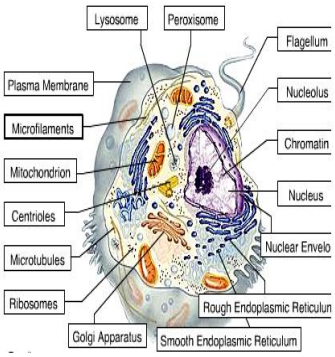
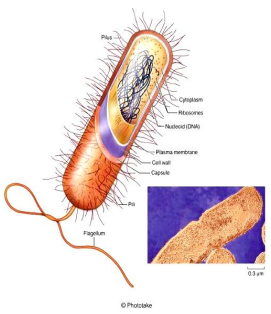



**Figure 2. Characters of a prokaryotic cell (bacterial cell)**

-Prokaryotic cells lack a membrane-bound nucleus
- Genetic material is present in the nucleoid
- Cytoplasm
- Plasma membrane
-Cell wall
-Ribosomes
-Two types of prokaryotes organisms: -archaea and bacteria
-The prokaryotic cell walls protect the cell and maintain cell shape while the bacterial cell walls may be composed of peptidoglycan and -may be Gram positive or Gram negative. The archaean cell walls lack peptidoglycan.
-The Flagella is present in some prokaryotic cells, used for locomotion



## The Cell Membrane

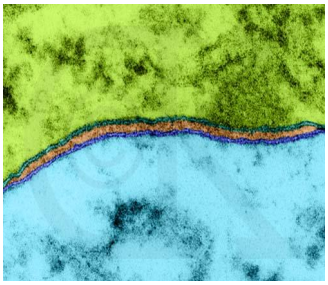


**Figure 3.** Electronic microscope photograph of the plasma membrane

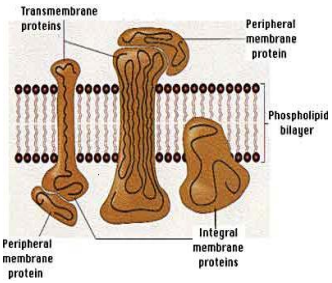



**Figure 4.** Drawing shows Plasma membrane fine structure

## The Golgi apparatus

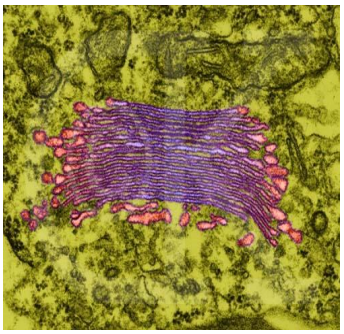


**Figure 5.** An electronic microscope photograph showing Golgi apparatus

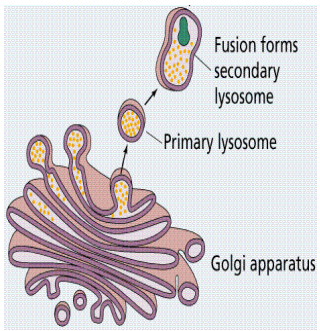



**Figure 6.** Drawing shows the formation of Lysosomes by the Golgi apparatus

## Rough Endoplasmic Reticulum

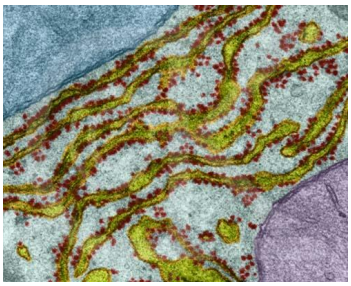


**Figure 7.** Electronic microscope photograph showing Rough Endoplasmic Reticulum

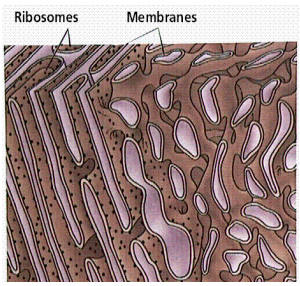



**Figure 8.** Drawing showing membrane sacs of Rough Endoplasmic and associated ribosomes

## The Mitochondria

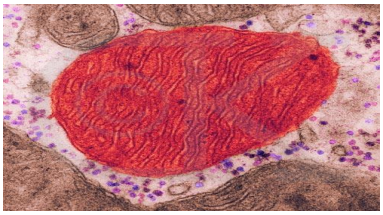


**Figure 9.** Electronic microscope photograph showing Cell mitochondria

## The Nucleolus

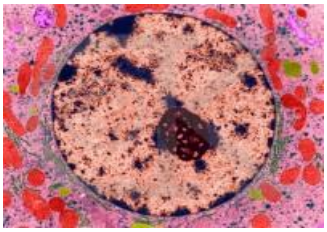


**Figure 11.** An electronic microscope photograph
showing the cell's nucleus

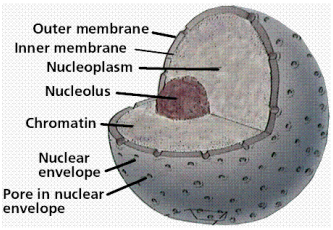
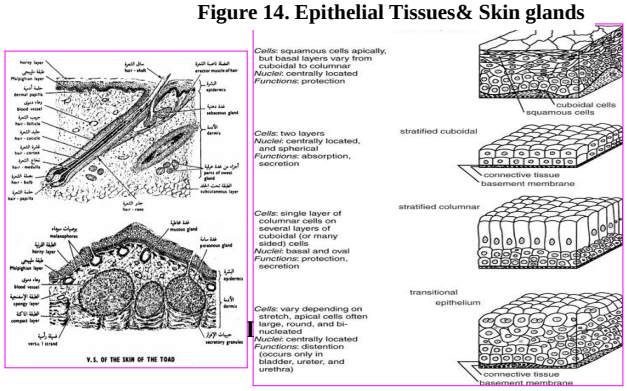
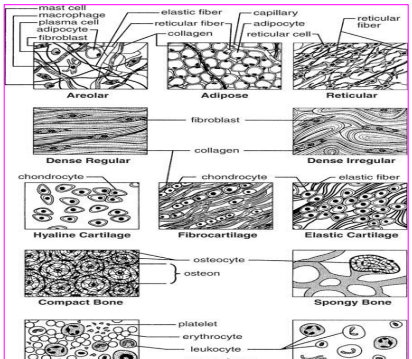



**Figure 12.** Drawing illustrates the Nucleolus fine structure

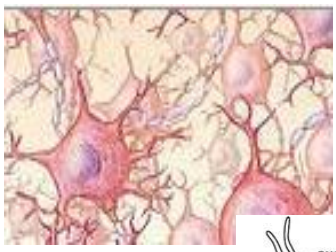
# [2] HISTOLOGY

**Figure 14. Epithelial Tissues& Skin glands**

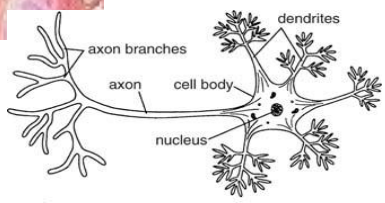



## Figure 16. Nervous Tissues

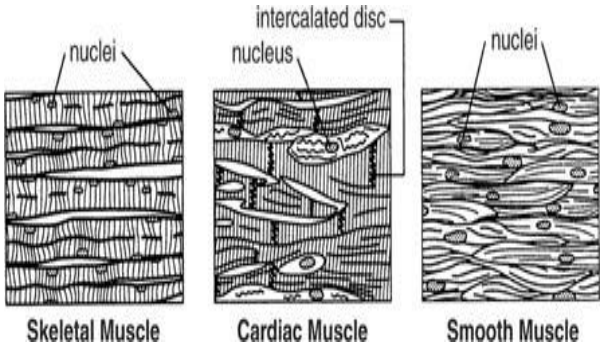


Aneuron is a basic structural unit of the nervous system containing a cell body, dendrites, and an axon.



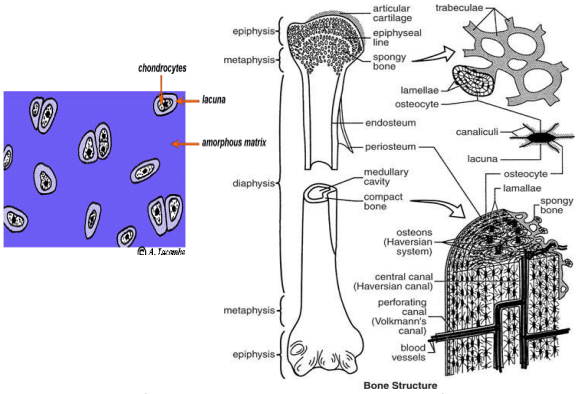

Drawing illustrates the Neuron structure

## Figure 17. Muscular Tissues




**There are three kinds of muscle tissues.**

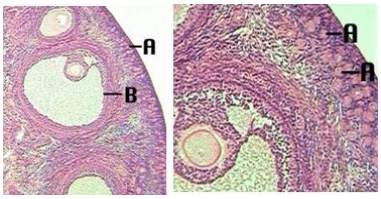
## Figure 17. Cartilage and Bone




There are two kinds of bone tissue, compact bone consists of cylindrical units called osteons (Haversian systems) and spongy bone consists of thin, irregularly shaped plates called trabeculae, while the cartilages constitution is shown (left).

## Figures 20. The Ovary and the Testis

A" marks the primordial or primary follicles in both micrographs. "B" is a Graafian follicle with its oocyte Estrogen and progesterone are produced by the follicles under the influence of FSH and LH from the pituitary gland (hypophysis).




The testis is composed of tightly coiled seminiferous tubules (A). Two are seen here in perfect cross section. Spermatogenesis occurs in the seminiferous tubule resulting in the production of sperm. Between these tubules are interstitial cells (B), the producers of testosterone