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Handout of:

Animal Biology and Physiology

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Preface

This handout is designed to provide accessible information on animal biology and physiology includes the essential concepts. This document is intended for students of the 1st year bachelor professional degree, in Agri-Food Processes (COFFEE 1). It complies with the programs established by the Ministry of Higher Education and Scientific Research.

The aim of this handout is to provide the student with the essential bases and it consists of introducing students to the particularities of the developmental biology of certain animal species.

It provides the basic principles of animal biology and physiology in a simple and easy language, where the handout is devided into three parts, covering a major aspect of animal biology and physiology. The first which is the embroyology section which deals with gametogenesis, fertilization, segmentation, gastrulation, neurulation, the extraembryonic membranes in birds and also with the particularities of human embryology (Cycle, implantation, evolution annexes, placenta). As well as histological part, which covers connective tissues, blood tissues, cartilaginous tissues, muscle tissue and nervous tissues.

While the third part, it review the animal physiology: physiology of respiration, nervous system, cardiovascular system, circulatory system, and finally elimination and secretion.

A very simple, yet hopefully clear, figures and tables are provided throughout the handout. Although my principle of simplicity in informations and diagrams for students use and memorization remains paramount.

I will be particularly grateful to the readers who are kind enough to share their comments and criticisms inspired by reading this handout and hopes that it will help students with the information necessary for studying the animal biology and physiology.

Dr. Bouteldja Meryem

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General definitions

Embryology : Embryology is the study of the development of living beings. It is limited to the period of life that begins from the fertilization (zygote) and ends at birth (viviparous animals) or hatching (oviparous animals).

Ontology: Corresponds to a series of transformations undergone by the individual from the fertilized egg to the perfect being ; **ontology** is the study of being.

Grec, Ontos = Ontos = être (being)

Logia = Logia = discours (langage)

Embryogenesis : Embryogenesis is a part of ONTOGENESIS (formation of the living being). It is the study of development.

Embryo grec ; embruon = fetus or embryo.

The early stages of ontogenesis constitute embryonic development or embryogenesis.

1. Introduction

Every living being tends to conserve itself as an individual and to perpetuate itself as a member of a species. These two tendencies are both based on a fundamental faculty of living matter, the faculty of reproduction.

Reproduction is the creation of new individuals, the ways in which life is maintained, propagated and diversified are many and varied. There are two modes of reproduction.

• Sexual reproduction • Asexual reproduction

- **Sexual reproduction:**

It requires a male (sperm) and a female (ovum) belonging to the same species. Sex cells are specialized cells called gametes.

- **In hermaphrodite species,** in which the individual exhibits both male and female organs, either simultaneously or alternately (successive hermaphroditism). **Example:** invertebrates
- **In gonochoric species,** gonochorism "separation", Characteristic of animal species (vertebrates) with separate sexes, in which the male gametes (spermatozoa) and the female gametes (ovules) are produced by different individuals.

  Heterogametic: two categories of gametes: the male (XY) in mammals and the female (ZW) in birds.

  Homogametic: The other sex is homogametic and forms only one category of gametes: the female (XX) in mammals and the male (ZZ) in birds.

- **Asexual reproduction:**

This mode of reproduction exists in bacteria and single-celled organisms in the form of binary division; multiple division or budding.

Exp; As in the hydra and some jellyfish, It may be the budding of new individuals from the parent organism,

Asexual reproduction can also result from the splitting of the organism into several parts, as in certain worms and in the sea anemone,

- Offspring are genetically identical, both to each other and to their only parent; this mode of reproduction is less widespread in animals than in plants but it is found in various groups where it most often coexists with a mode of sexual reproduction.
- Freshwater hydras, corals, some jellyfish and sea anemones, some worms and some insects

Parthenogenesis:

Parthenogenesis is a mode of reproduction independent of any sexuality, allowing the development of an individual from an unfertilized ovum. Although asexual, it requires reproductive cells. It was studied for the first time in 1740 (in aphids) by Charles Bonnet but it exists in a large number of animal species, is found in particular in the phylum of the Arthropods (Insects in particular), but also in certain Lizards and in the Turkey.

- **In Metazoa**, the most typical form of development is that seen in sexual reproduction.

2. Gametogenesis

2.1. Introduction

Haploid reproductive cells differentiate: - sperm and - the ovum (called gametes), there were produced via gametogenesis process, so it is the production of reproductive cells, female and male germinal. Spermatogenesis, takes place in a specialized organ, the male gonad: testicles and oogenesis takes place in specialized organs, the female gonad: ovaries.

Ovogenes and spermogenesis differ greatly in their chronology and physiology, however a fundamental point is the meiosis, which allows the chromosomal maturation. Mixing genes and obtaining a reproductive cell whose genetic material has been reduced by half compared to the mother cell. It takes place in several phases:

- **Multiplication phase:** In this phase the primordial germ cells multiply thanks to normal mitosis and give rise to gonia (oogonia in the female, spermatogonia in the male).
- **Growth phase:** Then the gonia increase in volume by accumulating reserves (oogonia). At the end of this period, the gonia take the name of oocytes I or spermatocytes I.
- **Ripening phase:** During which the oocytes or spermatocytes undergo meiosis comprising two successive mitoses. The first mitosis is said to be reductional or reductive, the second equational normal.

2.2. Spermatogenesis

Is a biological process whose purpose is to produce the male gametes, the spermatozoa, these latter only contain 23 chromosomes because they are the product of a sexual stem cell (the spermatogonia) having undergone.

2.2.1. Spermatogenesis phases

The complex process of spermatogenesis occurs in three steps (**Figure 1. 1)**.

- **Multiplication phase**

It concerns spermatogonia, diploid stem cells, these cells undergo a succession of mitoses, and resulted in the formation of spermatocytes, also diploid (one spermatogonia gives 4 primary spermatocytes). They develop from primordial germ cells that migrate into the testes early in embryogenesis.

- **Growth phase**

Preceded by a phase of growth and corresponds to meiosis and concerns the two generations of spermatocytes (primary 1 or secondary 2), the spermatocyctes I to 2 n undergoes the 1st devision and gives 2 spermatocytes II to n chromosomes, each spermatocytes II

undergoes the 2nd division of meiosis (equational) and gives spermaditis with n chromosomes, therefore a spermatocyte I therefore gave 4 spermatids at the end of the meiosis.

Spermatids: are the product of the second equational division of meiosis and lack the ability to divide. Spermatids undergo an additional stage of differentiation (spermiogenesis) to produce motile sperm.

- **Differentiation phase**

Differentiation phase, also called spermiogenesis phase, here there is no devision but only a differentiation of spermadites into spermatozoa (undergoes the formation of structures that give them mobility and the ability to penetrate the ovum. The process of releasing sperm from the Sertoli cell is called spermiation.

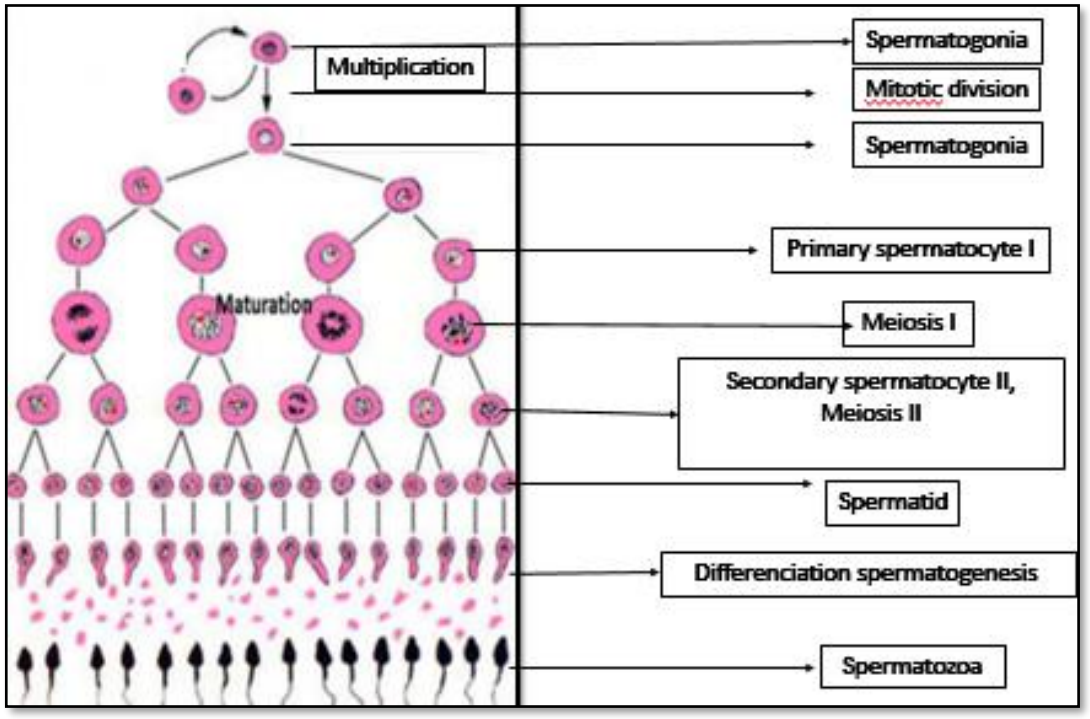

Figure 1. 1. Diagram of spermatogenesis process.

2.2.2. Phases of spermatogenisis or differenciation

Structure du spermatozoïde: In most animal species, the spermatozoon is made up of three parts: During the phase of spermatogenesis or the differentiation of spermatids into spermatozoa, several stages take place: Briefly, there are:

- **Core condensation**

Compaction and condensation of kernel contents to minimum volume.

- **Acrosome formation**

Formation of a head cap (acrosome) containing enzymes which play an important role in the penetration of the zona pellucida of the oocyte. The acrosome thusformed contains many enzymes allowing, during fertilization, the progress of the acrosomal reaction.

- **Flagellum formation and cytoplasm reduction.**

Note:

The head: Its shape varies according to the species. It is essentially composed of the nucleus which contains genetic information. The acrosome located at the anterior end of the head is full of proteolytic enzymes necessary for fertilization **(Figure 1. 2).**

Midpiece: Formed of 9 bundles of dense fibersand mitochondria contrary to the tail which do not contains mitochondria.

In some species, the spermatozoa are immobile and move by amoeboid movements (some crustaceans and insects and in nematodes).

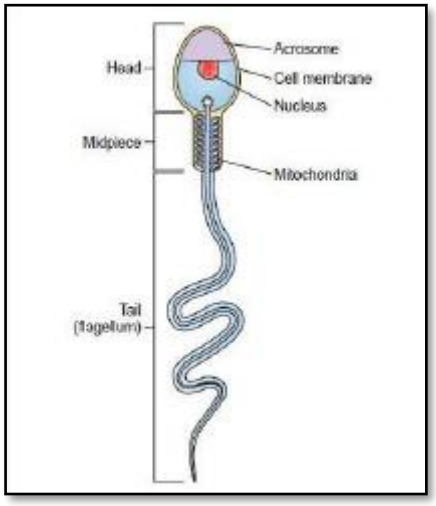

Figure 1. 2. Normal spermatozoa structure.

2.2.3. Capacity

The gametes are all modified along their journey in the genital tract, in the majority of mammals, the spermatozoa are not fertilizing immediately afterwards ejaculation. They require a short stay in the female genital tract during which they acquire their fertilizing power, where a set of membrane and intracellular modifications of the sperm take place in the female genital tract and which cause its maturation to be able to attach to the zona pellucida and operate its acrosomic reaction to fertilize the oocyte.

All these modifications allow the spermatozoa:

- **To activate their motor skills:** sperm movements (increased frequency and amplitude of the flagellar movement).
- **To attach to the zona pellucida of the oocyte**, which will cause the acrosome reaction.
- **To enter to the cumulus cells.**

1/ First, capacitation begins with the removal of all superficial proteins that cover the surface of the sperm cell membrane and allow its stabilization.

2/ Capacitating removes cholesterol inserted into the lipid bilayer of the spermatozoa membrane by binding to albumin and HDL lipoprotein. This phenomenon causes a modification of the membrane fluidity.

3/ The unmasking of sperm receptors is due to the redistribution of phospholipids and the entry of Ca++ ions which modify the oligosaccharide chains of surface proteins, thus making them visible: through these sperm receptors, sperm will attach to the zona pellucida.

2.3. Oogenesis

Oogenesis is the type of gametogenesis through which ova, also called the female gametes are formed and the produced female gamete is known as an ovum **(Figure 1. 3)**. So, is the process of formation of female gametes. This process begins inside the fetus before birth. In mammals this process is called folliculogenesis; which designates a process of maturation of the primordial follicles until ovulation or atresia.

The follicles are located in the ovarian cortex, that is, peripherally in the ovary, and are the structures that contain the oocytes. As the follicular development process progresses, the follicles are named differently, which determines the different phases of folliculogenesis.

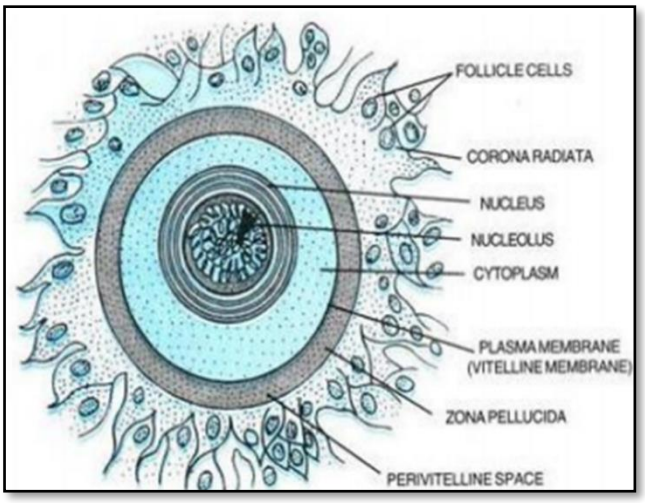

Figure 1. 3. Structure of ovum.

2.3.1. **Stages of folliculogenesis**

- **Primordial follicle**

The primordial follicle constitutes the first stage of follicular development. It is afollicle formed by an oocyte that is surrounded by a single layer of flattened pre-granulosa cells.

- **Primary follicle**

Primary follicle **i**s characterized by an increased size, oocyte I blocked in prophase I, a single layer of cuboidal follicular cells, an undifferentiated theca.

- **Secondary follicle**

The number of layers of follicular cells is greater, the set of follicular cells is dir granulosa. Cette étape se caractérise par une accumulation de réserves cytoplasmiques et un début de constitution de la thèque interne.

- **Tertiary (cavitary) follicle**

The follicle has almost reached its size and becomes oval, the theca interna cells are capable of excreting estrogen **(Figure 1. 4)**.

- **Follicle wall**

The Graafian or pre-ovulatory follicle is the fully developed follicle, which will lead to ovulation of the oocyte it contains.

- **Corpus luteum**

The dehiscent follicle heals, forming a temporary gland called the corpus luteum. the granulosa cells of the corpus luteum become luteal, capable of synthesizing progestrone. cells in the internal theca are still synthesizing estrogens. In the absence of fertilization the yellow body is called progestogen, its lifespan is 14 days. In case of fertilization is said to be gestative,

its lifespan is 3 months, then it degenerates and the relay of the synthesis of steroids is taken by the cells of the placenta.

- **Albicans corpus**

In the ovary, the degeneration of the yellow body gives the white body, which will be phagocytosed.

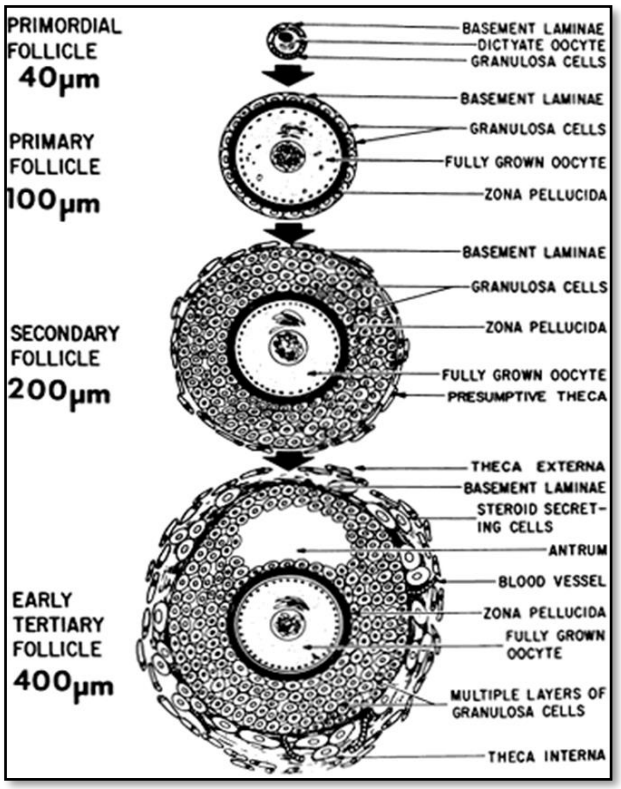

Figure 1. 4. Follicle growth and development, or diagram illustrating the size and histologic organization of early developing human follicles during the gonadotropin-independent period of folliculogenesis.

2.3.2. **Oogenesis phases**

- As with sperm production, oogenesis starts with a germ cell, called an oogonium (plural: oogonia), During the embryonic phase this cell undergoes mitosis to increase in number, eventually resulting in up to one to two million cells in the embryo, in both ovaries.
- The cell starting meiosis is called a primary oocyte. This cell will begin the first meiotic division, but at birth be arrested in its progress in the first prophase stage. Those who escape atresia (500,000 to 700,000) remain in reservein this form until puberty. A few rare follicles begin to develop before puberty but do not reach maturity.
- From puberty (sexual maturity), in each cycle (28 days), 5 to 15 primordial follicles enter the growth and maturation phase. Anterior pituitary hormones cause the development of a number of follicles in an ovary. This results in the primary oocyte

finishing the first meiotic division. The cell divides unequally, with most of the cellular material and organelles going to one cell, called a secondary oocyte, and only one set of chromosomes and a small amount of cytoplasm going to the other cell.

- This second cell is called a polar body and usually dies. A secondary meiotic arrest occurs, this time at the metaphase II stage. At ovulation, this secondary oocyte will be released and travel toward the uterus through the oviduct. If the secondary oocyte is fertilized, the cell continues through the meiosis II, completing meiosis, producing a second polar body and a fertilized egg **(Figure 1. 5).**

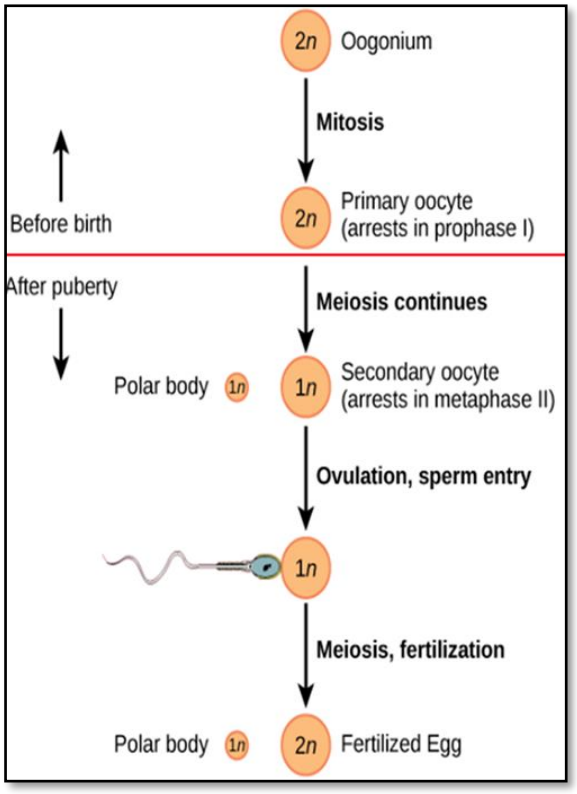

Figure 1. 5. The process of oovogenesis occurs in the ovary's outermost layer.

3. Fertilization

3.1. Introduction

Fertilization, reproductive process in which a male sex cell (sperm) unites with a female sex cell (egg), where an union of a sperm nucleus, of paternal origin, with an egg nucleus, of maternal origin (Amphimixis), to form the primary nucleus of an embryo.

In all organisms the essence of fertilization is, in fact, the fusion of the hereditary material of two different sex cells, or gametes, each of which carries half the number of chromosomes typical of the species.

The most primitive form of fertilization, found in microorganisms and protozoans, consists of an exchange of genetic material between two cells.

In species with external fertilization (e.g. sea urchin), a peptide of 14 amino acids, resact, secreted by the gelatinous gangue of the egg is responsible for the attraction of spermatozoa (chemotaxis). In animals with internal fertilization, the mechanism of attraction of spermatozoa to ova is poorly understood

1.1.1 Fertilization steps

In mammals, during ovulation, the oocyte, which is in metaphase II, is surrounded by the zona pellucida and the corona radiata. The oviduct secretes enzymes that weaken the connections between the cells of the corona radiata, thus facilitating the passage of spermatozoa through this first cellular barrier.

Step 1. Preparation of the sperm

Ejaculated sperm are not ready to fertilize an egg when they enter the vagina. In response to the dilution of semen in the vagina, they undergo several changes, which are collectively known as capacitation.

Step 2. Sperm-egg binding

In sea urchins, the sperm head binds directly to the egg outer surface and this triggers the acrosome reaction that allow fusion of the sperm and egg plasma membranes. In humans the process of sperm-egg binding is not so simple. It was found that the spermatozoon-zona pellucida interaction is of the ligand-receptor type and showing that ZPGP III is the sperm receptor than ZPGP II. The ZPGP I protein is not required for fertilization but is important for the structural integrity of the zona pellucida **(Figure 1. 6).**

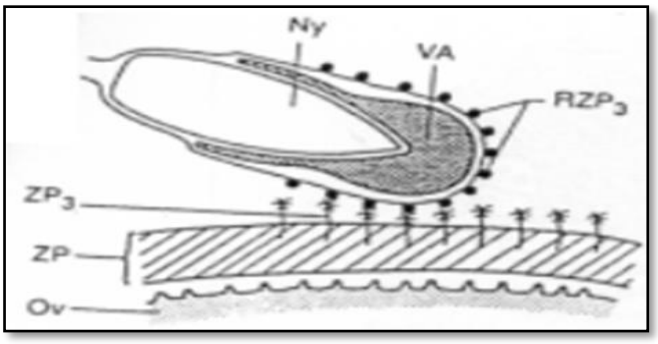

Figure 1. 6. Sperm-Egg Binding.

Step 3. Acrosome reaction

As a result of irreversible binding of the sperm to the egg, the zona pellucida triggers the acrosome reaction. The outer plasma membrane of the acrosome fuses at multiple sites with the plasma membrane and the contents of the acrosome are released, Two of the important components are acrosin, a serine protease, and N-acetylglucoaminidase. Acrosin bores a hole in the zona pellucida so that the sperm can reach the egg itself. N-acetylglucoaminidase hydrolyzes the O-linked oligosaccharides in ZPGP III to allow the sperm to detach which thought to contain new binding sites for ZPGP II **(Figure 1. 7).**

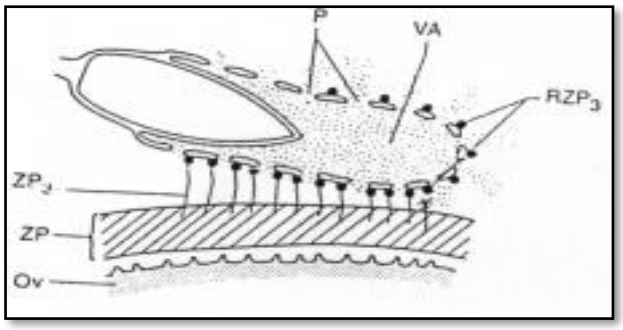

Figure 1. 7. Acrosome reaction.

Step 4. Fusion of plasma membranes and fusion of nuclei, or amphimixis

In mammals, fertilins (β-fertilin), proteins of the inner membrane of the acrosome, bind to the integrins of the oocyte membrane and are directly involved in the fusion process. The fusion takes place between the lateral membrane of the sperm and that of the villi of the oocyte **(Figure 1. 8).** The oocyte cytoplasm surrounds the sperm nucleus, membrane fusion induce specially the formation of fertilization membrane via Ca++ release and which is involved in the formation of a first barrier to **polyspermy** and in the activation of the egg. Then introduction to cleavage.

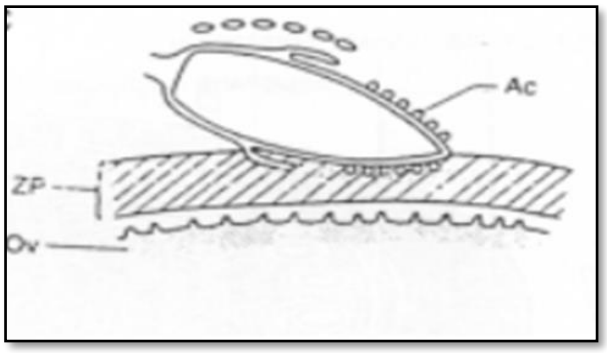

Figure 1. 8. Fusion of plasma membranes and fusion of nuclei.

Note: Polyspermy refers to the fertilization of the egg by more than one sperm, resulting in zygotes with greater than a diploid amount of DNA. This causes early embryonic defects and arrest of development.

4. Cleavage

4.1. Introduction

Cleavage can be defined as the process of progressive subdivision of the zygote of mitotic cell divisions into an increasing number of cells of progressively decreasing size. Is a period after fertilization, when a 1-cell embryo starts developing into a multicellular organism. Due to a series of mitotic divisions, the large volume of a fertilized egg is divided into numerous smaller, nucleated cells—blastomeres **(Figure 1. 9)**. So, the process consists of a series of divisions breaking up the zygote into smaller and smaller ones called blastomeres. The embryo that divides is a blastula, within the blastula appears a cleavage cavity or blastocoel.

The cleavage also establishes the fundamental conditions for the initiation of next developmental stage —Gastrulation. Cleavage begins immediately after the nuclear fusion of the sperm and ovum. Where the egg provide sufficient energy itself within needed for cell division and the resultant cell are called blastomeres and the unicellular fertilized egg is transformed by consecutive division into help of cells called morula.

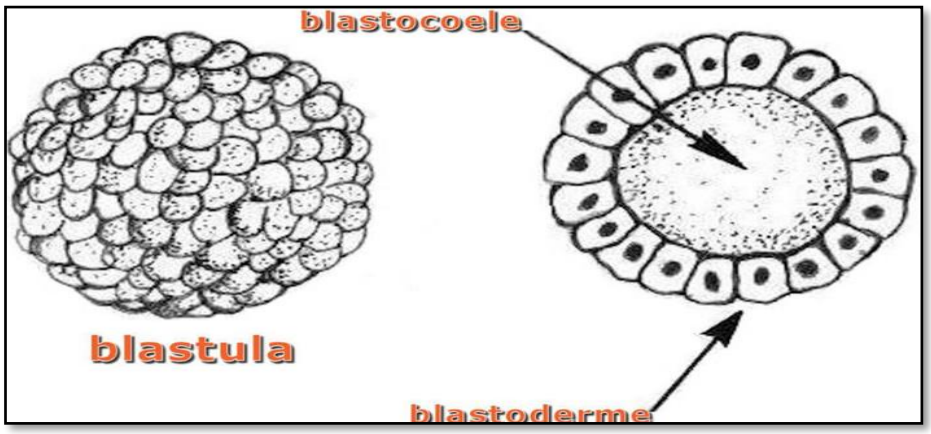

Figure 1. 9. Blastula structure.

Cleavage is affected by different factors:

- The point of entry of the sperm into the egg;
- Cytoplasmic factors;
- The amount and distribution of yolk.

4.2. Different types of eggs

Alecithal Egg

When the egg contains no yolk, it is called alecithal egg. Eg. The eggs of superior mammals.

Microlecithal Egg

When the egg contain. Small or negligible amount of yolk named also as **oligolecithal** eggs Eg'. Amphioxus, Tunicates

Heterolecithic eggs, (Mesolecithal)

The amount of yolk present is moderate and is not high, example, in amphibian, Dipnoi and Petromyzon

Macrolecithal or Megalecithal or Polylecithal Egg

When the egg contains large amount of yolk. Example. Reptiles, Birds, Prototheria (Monotremata). Instead of the amount of the yolk and based on the distribution other nominations can exists:

- **Isolecithal or Homolecithal Egg :** In isolecithal eggs, the very little amount of yolk present is uniformly distributed throughout the ooplasm (Eg. Echinoderms).
- **Telolecithe eggs:** with a moderate or large quantity of yolk,, the nucleus being pushed back into a reduced cytoplasmic area: the embryonic disc (Eg. numerous Fishes, Cephalopod).
- **Centrolecithal Egg:** Egg of many arthropods and some coelenterates are described as centrolecithal. They are relatively large and elongate and have a very great amount of yolk. Here the nucleus lies at the geometric centre of the yolk mass, surrounded by a small amount of cytoplasm.

4.3. The different types of cleavage.

Depending the amount and distribution of yolk in the egg cleavage can be of two main types :

- **Holoblastic or Total or Complete cleavage:**
  - Equal holoblastic cleavage.
  - Unequal cleavage holoblastic.
- **Meroblastic or Partial or Incomplete cleavage:**
  - Discoidal cleavage.
  - Superficial meroblastic cleavage.

Holoblastic cleavage, eggs (aleciths, oligoleciths and heteroleciths)

Holoblastic cleavage involves the division of the entire egg into blastomeres. The size of the blastomeres differs in this kind of cleavage. Holoblastic cleavage is common in mammals, nematodes, echinoderms, flatworms, and annelids. Holoblastic cleavage is also known as complete cleavage. Holobalstic cleavage can be:

- **Equal cleavage**

Gives blastomeres of the same size at the end of the cleavage, eg. : Echinoderm which has an alecith egg.

- **Unequal cleavage**

Producing blastomeres of unequal size. It means that, the region with a higher amount of yolk (vegetal hemisphere) has larger blastomeres than the region with low yolk concentration (animal hemisphere). Larger blastomeres are called macromeres, while the smaller ones are called micromeres. Example: Amphibians.

Concerning the planes of holoblastic division, it can be:

- **Meridional plane of cleavage**

When a furrow bisect both the poles of the egg passing through the median axis or centre of egg it is called meridional plane of cleavage. The median axis runs between the centre of animal pole and vegetal pole **(Figure 1. 10 (a)).**

- **Vertical plane of cleavage**

When a furrow passes in any direction (does not pass through the median axis) from the animal pole towards the opposite pole **(Figure 1. 10 (b)).**

- **Equatorial plane of cleavage**

This type of cleavage plane divides the egg halfway between the animal and vegetal poles and the line of division runs at right angle to the median axis **(Figure 1. 10 (c)).**

- **Latitudinal plane of cleavage**

This is almost similar to the equatorial plane of cleavage, but the furrow runs through the cytoplasm on either side of the equatorial plane. During early cleavage, distinct geome-trical relationships exist between the blastomeres, i.e., each plane of cell-division bears a definite relationship with each other **(Figure 1. 10 (d)).**

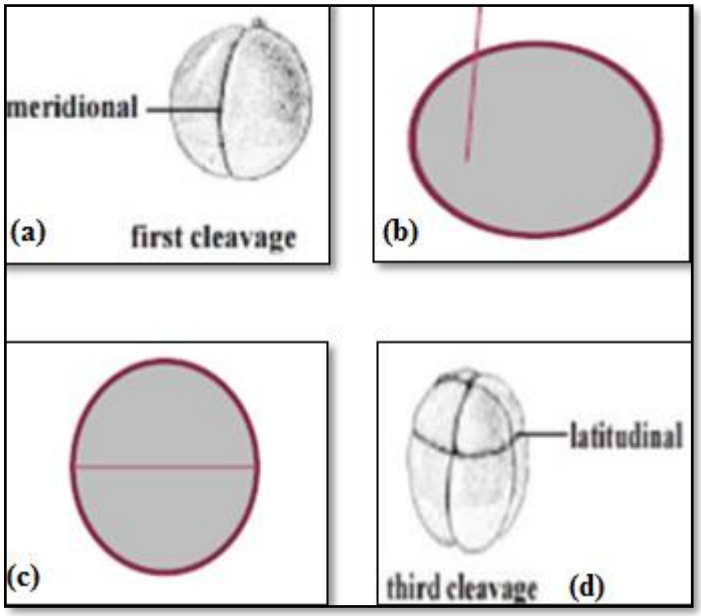

Figure 1. 10. Planes of holoblastic division **(a)**; Meridional plane; **(b)** Vertical plane; **(c)** Equatorial plane; (d) Latitudinal plane.

4.4. Patterns of cleavage

Patterns of holoblastic cleavage

Depending on the arrangement of the daughter blastomeres, we distinguish: Four major cleavage types can be observed in isolecithal cells (cells with a small even distribution of yolk) or in mesolecithal cells (moderate amount of yolk in a gradient) – **Spiral holoblastic, radial holoblastic, bilateral holoblastic, and rotational holoblastic (Figure 1.11).**

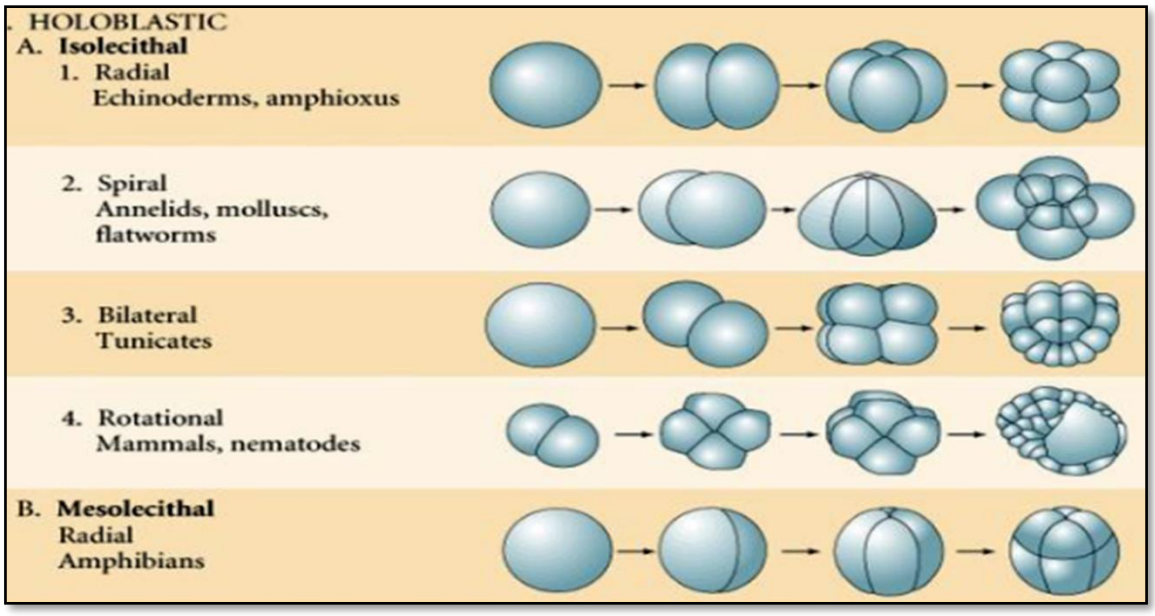

Figure 1. 11. Major cleavage types.

- **Radial cleavage**

It is one of the simplest cleavage patterns in which the successful division planes are at 90° relative to each other. Thus this cleavage results in daughter cells that are located exactly on top of one another. This type of cleavage is seen in deuterostomes like echinoderms and some vertebrates.

- **Spiral cleavage**

Protostomes, especially in a clade called spiralia. Here, the resulting daughter cells are not located exactly on top of each other. Instead, the blastomeres are organised spirally around the embryo's pole-to-pole axis. Each blastomere produces one micrometer in the animal hemisphere and one macromer in the vegetative hemisphere.

- **Bilateral cleavage**

The first cleavage results in bisection of the zygote into left and right halves. defined by the first meridian division. The second meridian division does not pass through the center of the egg and produces two large anterior blastomeres (A and a) and two smaller posterior blastomeres (B and b). In bilateral holoblastic cleavage, the divisions of the blastomeres are complete and separate; compared with bilateral meroblastic cleavage, in which the blastomeres stay partially connected.

- **Rotational cleavage**

Rotational cleavage involves a normal first division along the meridional axis, giving rise to two daughter cells. The way in which this cleavage differs is that one of the daughter cells divides meridionally, whilst the other divides equatorially.

Meroblastic cleavage (teloleciths, centroleciths)

Some eggs with a high concentration of yolk only cleave or divide in the animal pole. This is due to the high concentration of cytoplasm in this region. The yolk remains undivided. This type of cleavage is known as meroblastic cleavage. Meroblastic cleavage is of two types: discoidal (In the telolecithal eggs of birds) and superficial (In the centrolecithal eggs of insects).

In discoidal cleavage, the division does not touch the yolk. Instead, however, disc-like cells known as blastodiscs form on top of the yolk. Discoidal cleavage is common in birds, reptiles, and fish **(Figure 1. 12).** On the other hand, **superficial cleavage** occurs in arthropods (insects and crustaceans). Their yolk is located at the center, and only their nucleus divides by mitosis, forming a polynuclear cell. The nuclei then move to one side of the egg, and a plasma membrane then forms and separates the nuclei into two daughter cells. This type of segmentation is called superficial or even peripheral which results in the formation of a blastula called periblastula which does not contain a blastocoel **(Figure 1. 13)**.

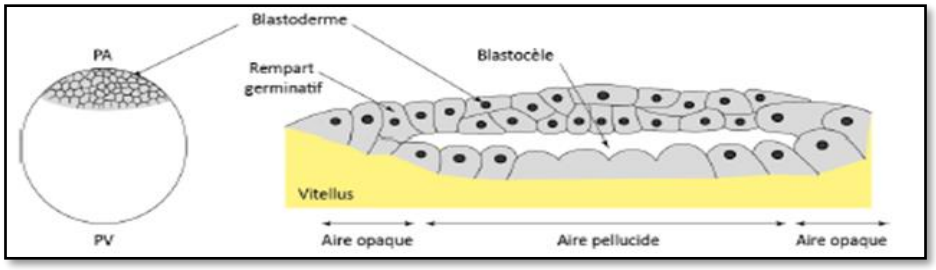

Figure 1. 12. Discoidal cleavage.

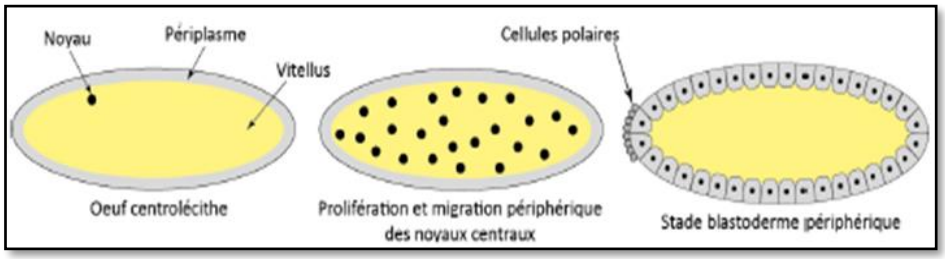

Figure 1. 13. Superficial cleavage.

5. Gastrulation

5.1. Introduction

Gastrulation is defined as an early developmental process in which an embryo transforms from a one-dimensional layer of epithelial cells (blastula) and reorganizes into a multilayered and multidimensional structure called the gastrula, also, it is defined as all the morphogenetic movements which result in the establishment of the three fundamental germ layers called triploblastic Metazoa (ectoderm, mesoderm, and endoderm) **(Figure 1.14).**

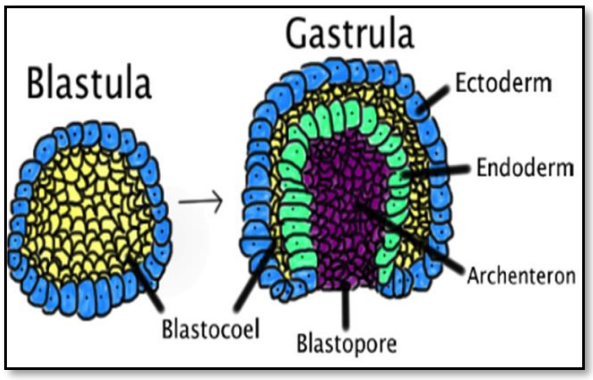

Figure 1. 14. Gastrulation.

5.2. The different modalities of gastrulation

Although gastrulation patterns exhibit enormous variation throughout the animal kingdom, they are unified by the five basic types of movements that occur during gastrulation, It have been recognized:

Epiboly

When the vegetative blastomeres are too large to burrow inside the blastocoel, the cells of the vegetative hemisphere become internal in a way passive, by multiplication and covering of the cells of the animal hemisphere forming a layer which envelops them progressively **(Figure 1. 15).** In simpler words it may be said as the expansion of one cell sheet over other cells, eg, formation of ectoderm in sea urchin, tunicates and amphibian.

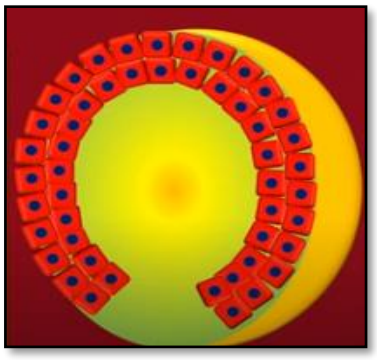

Figure 1. 15. Epiboly gastrulation.

Emboly

The inward movement of cells is classified into different types depending on the behaviour of migrating cells. This inward movement of cells is due to innate forces within various cell groups. **Embolic movement involves the following types of cell behaviour:**

Invagination: A small depression is formed in the region occupied by the grey crescent area. This depression grows inwards and forms the archenteron or gastrocoel or secondary body cavity **(Figure 1. 16).** The outer opening of the gastrocoel is called the gastropole. The blastopore meanwhile becomes expanded and becomes ring shaped. (eg: Endodermis of sea urchins).

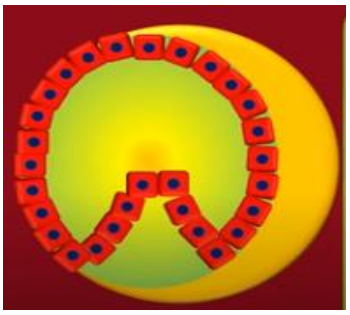

Figure 1. 16. Invagination.

Involution: From one end near the edge of the blastoderm, the cells begin to move inwards to form the inner lining of the blastoderm **(Figure 1. 17).** Eg Amphibian mesoderm.

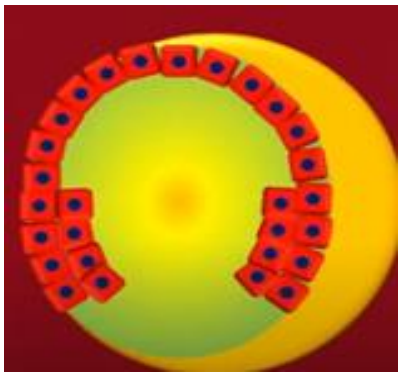

Figure 1. 17. Involution.

Ingression (poly-invagination): When a cell or small groups of cells separate itself from other layers and migrate into the segmentation cavity within the developing body **(Figure 1. 18)**. This is seen in the case of reptiles, birds and mammals where the mesodermal cells detach themselves from the primitive streak and migrate into the space between the epiblast and hypoblast. In simple its is the movement of cell from surface to interior of embryo separately to become mesenchyme cells, mesoderm of sea urchin and neuroblast of drosophila.

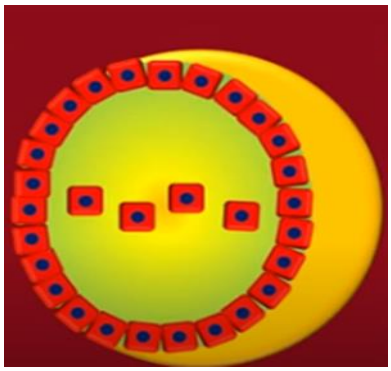

Figure 1. 18. Ingression (poly-invagination).

Delamination: Splitting of one layer of cells to form two or more parallel new layers internally **(Figure 1. 19),** eg: Formation of hypoblast in birds and mammals.

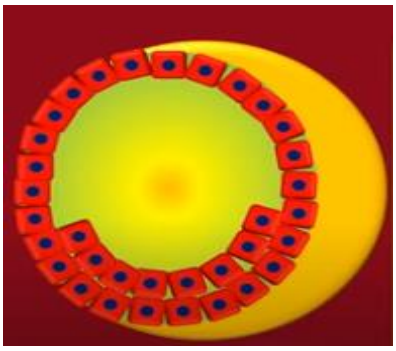

Figure 1. 19. Delamination.

5.3. Gastrulation in mammals (Human)

In the human embryo, gastrulation occurs by embolism. Invagination is the process by which the MCI (inner cell mass) cells of the blastocyst are folded inward and introduced into the blastocoel. Thus, the first two embryonic layers appear: the ectoderm and the endoderm.

Morphogenetic movements and the placement of germ layers in mammals are similar to those in birds. Gastrulation begins with the formation of the primitive streak. This is the first phase of morphogenesis - in humans, from the 15th day. Around the 15th day of embryonic development, the primitive streak appears, is a linear band of thickened epiblast that first appears at the caudal end of the embryo and grows cranially. At the cranial end its cells proliferate to form the primitive knot (Primitive node) **(Figure 1. 20).**

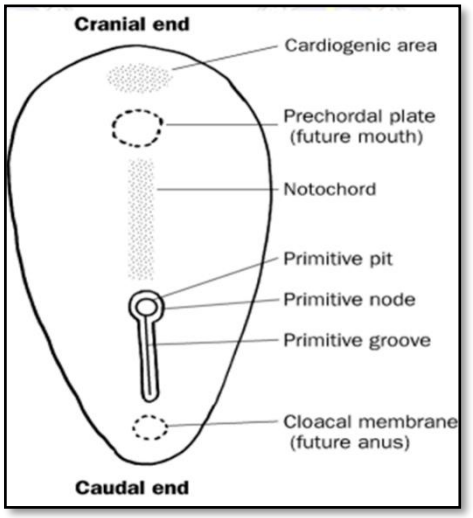

Figure 1. 20. The primitive streak.

The primitive streak is made up of several parts **(Figure 1. 21):**

- **Raised edges (epiblastic cellular thickenings) surrounding the primitive groove.**
- **A primitive knot (Hensen's knot), epiblastic elevation, surrounding a primitive depression (or primitive pit) (fosse primitive in french).** With the appearance of the primitive streak it is possible to distinguish cranial **(primitive knot**) and caudal (**primitive streak)** ends of the embryo. Epiblast cells migrate to the primitive streak. Upon arrival in the line region, the first cells that detach from the epiblast slide below and replace the hypoblast to give rise to the definitive **endoderm**. The following cells migrate between the epiblast and the endoderm to form the **mesoderm.** The remaining epiblast cells on the surface form the **ectoderm.**The primitive streak gradually regresses caudally to disappear, around one month, giving rise to the caudal region.

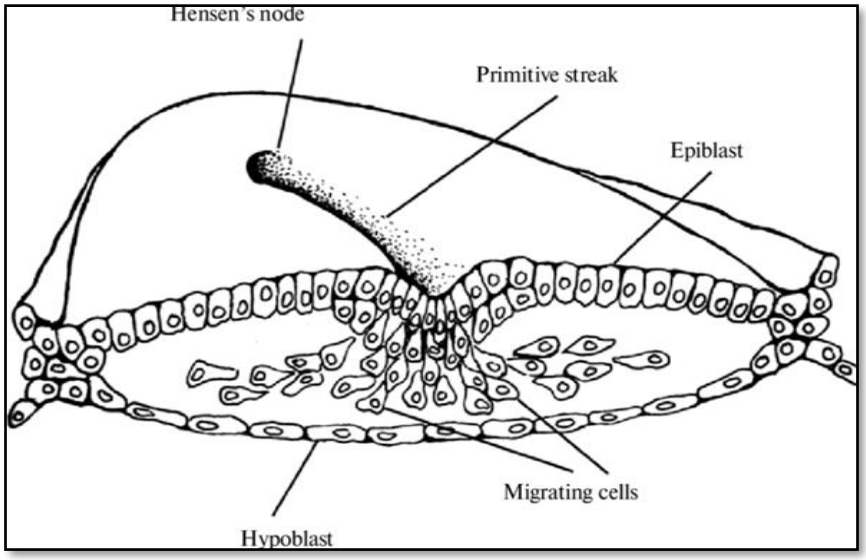

Figure 1. 21. Cell migration over the primitive streak during gastrulation in higher vertebrates.

6. Neurulation

6.1. What is neurulation?

Neurulation is one stage of embryogenesis, neurulation takes place in the endometrium between the 14th to the 17th day from fertilization. This process is the first step to the formation of the central nervous system that includes the brain and the spinal cord. The ectoderm of the embryo signals the formation of the neural tube. Upon evolution, the neural tube differentiated into more mature structures; brain and spinal cord.

6.2. Formation of the neural tube

There are two major ways of forming a neural tube:

Primary neurulation

In primary neurulation, the cells surrounding the neural plate direct proliferate, invaginate, and pinch off from the surface to form a hollow tube.

Secondary neurulation

In secondary neurulation, the neural tube arises from a solid cord of cells that sinks into the embryo and subsequently hollows out (cavitates) to form a hollow tube.

Some examples:

- Neurulation in fishes is exclusively secondary.
- In birds, the anterior portions of the neural tube are constructed by primary neurulation, while the neural tube caudal to the twenty-seventh somite pair (i.e., everything posterior to the hindlimbs) is made by secondary neurulation.
- In amphibians, such as Xenopus, most of the tadpole neural tube is made by primary neurulation, but the tail neural tube is derived from secondary neurulation.
- In mice (and probably humans, too), secondary neurulation begins at or around the level of somite 35.

6.3. Neurulation stages

During the neural plate stage, the ectoderm on the dorsal side of the embryo overlying the notochord thickens to form the neural plate.

At the neural fold stage, the thickened ectoderm folds, leaving an elevated area along the neural groove. The neural fold is wider in the anterior portion of the vertebrate embryo, which is the region that will form the brain.

During the neural tube stage, the neural folds move closer together and fuse - the neural groove becomes the cavity within the neural tube, which will later be capable of circulating cerebrospinal fluid that aids in the function of the central nervous system **(Figure 1. 22).**

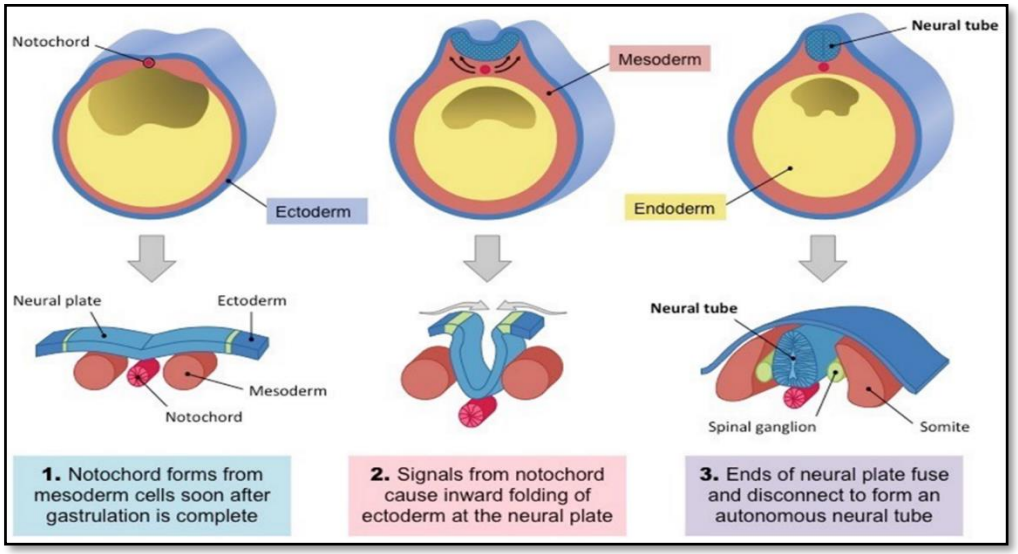

Figure 1. 22. Overview of the neurulation.

6.4. Germ layers evolution and their derivatives

The ectoderm

During neurulation, ectoderm differentiates into two parts:

The first is the surface ectoderm, which gives rise to tissues on the outer surface of the body like: Epidermis and skin appendages: In higher vertebrates, the appendages appear in the form of various structures: hairs, feathers, nails and claws, etc. Sensory placodes: eg: the olfactory placodes…

The second is the neuroectoderm, which forms the nervous system of the embryo. The neuroectoderm further divides into the neural tube, which acts as the precursor for the embryo's central nervous system, and into the neural crest, a collection of mobile cells shed from the junction between the neural tube and the epidermis after the neural tube forms. The neural crest helps form many of the bones and connective tissues of the head and face, as

well as parts of the peripheral nervous system. Eg: In fishes, the neural crest helps form dorsal fins, and in turtles is helps from the carapace.

The mesoderm

As the notochord and neural tube form, the intraembryonic mesoderm on each side forms longitudinal columns, the paraxial mesoderm, each in turn being continuous laterally with the intermediate mesoderm, and the latter gradually thinning out further laterally into the lateral mesoderm **(Figure 1. 23).**

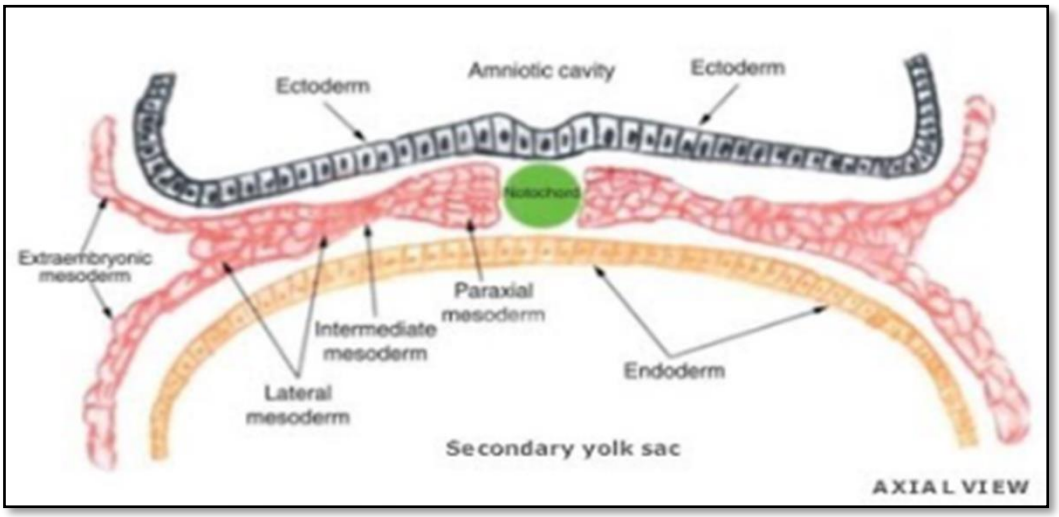

Figure 1. 23. Intermembranic mesoderm differenciation.

Paraxial mesoderm and somite formation: somite development begins about day 20 and is the result of segmentation of the paraxial mesoderm

a/The paraxial mesoderm thickens and fragments metamerically, dividing into paired cuboid bodies called somites which give rise to most of the axial skeleton and associated musculature as well as much of the dermis of the skin.

b/ The first pair of somites develops just caudal to the cranial end of the notochord (future occipital area), and subsequent pairs form in a craniocaudal sequence after the appearance of the first somites.

c/ About 38 somite pairs form during days 20-30, the so-called somite period. Eventually about 42-44 somite pairs develop by the end of week 5.

Somites give origin to the sclerotome, whose cells condense around the notochord and give rise to the vertebral primordia and the myotome, which gives rise to the vertebral muscles, where the myotome with the somatopleure gives origin to the muscles of the limbs and the anterior lateral body wall.

Intermediate and lateral plate mesoderm

Intermediate mesoderm gives rise to the nephrogenic cord from which the excretory apparatus originates (This mesodermal cell aggregation undergoes metameric segmentation parallel to the somites and forms nephrotomes. Then, lateral plate mesoderm splits into two layers: The intraembryonic splanchnopleure, applied against the endoderm, it is which gives rise to myocardium and endocardium, smooth muscles of the digestive tract, endothelium of blood vessels, and the intraembryonic somatopleure, applied against the ectoderm , it gives rise to the visceral musculature of the head, the pericardium, the connective and skeletal structures of the limbs.

The endoderm

It gives rise to the epithelial lining of the gastrointestinal and respiratory tracts; the parenchyma of the tonsils, the liver, the thymus, the thyroid, the parathyroids, and the pancreas; the epithelial lining of the urinary bladder and urethra; and the epithelial lining of the tympanic cavity, tympanic antrum, and auditory tube.

6.5. What are the similarities between neurulation and gastrulation?

- Both neurulation and gastrulation take place during embryogenesis.
- Both take place in the endometrium.
- Both lead to differentiation of the embryo.

7. The extraembryonic membranes in birds

7.1. Introduction

During embryological development, there are four extraembryonic membranes that are formed and which are ultimately discarded by the organism following birth.

These membranes include the chorion (placenta) in mammals, amnion, allantois and the umbilical sac (also called the yolk sac) **(Figure 1. 24).** These are formations of ectodermal, mesodermal and endodermal origin which develop outside the body of the embryo and they do not form any part of the embryo but performs various which assist in the development of embryo, these formations provide various functions:

- Protection;
- Breathing;
- Waste disposal;
- Storage;
- Uptake of reserves.

The amnion, along with the chorion, the yolk sac and the allantois protect the embryo. In birds, reptiles and monotremes, the protective sac is enclosed in a shell. In marsupials and placental mammals, it is enclosed in a uterus.

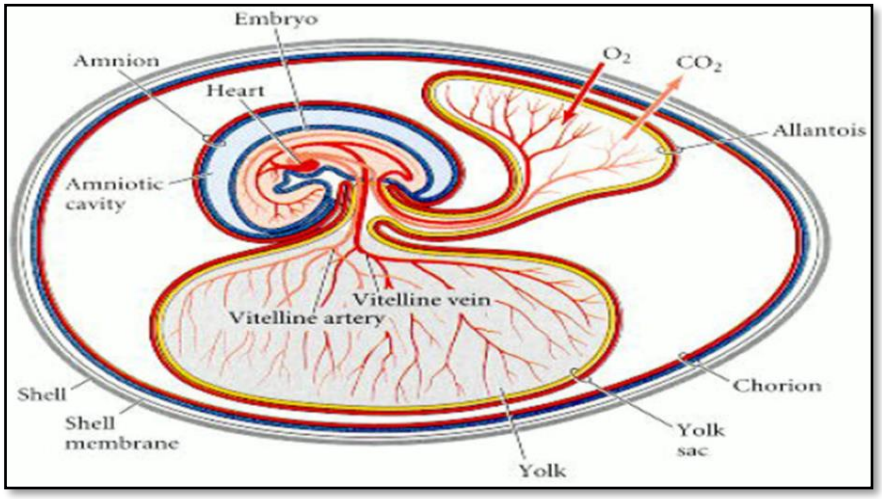

Figure 1. 24. Seven day chick embryo.

7.2. The different extraembryonic membranes in birds

7.2.1. The chorion

The chorion develops from the trophoblast and also contains parts of the mesodermal germ layer. It encloses the entire embryo along with the other three extraembryonic membranes. Besides, the chorionic cavity contains a fluid. Its function includes protecting the embryo from damage by absorbing some of the shock, While, the chorion lines the inner surface of the shell (which is permeable to gases) and participates in the exchange of O_2 and CO_2 between the embryo and the outside air.

7.2.2. The amnion

The amnion a thin ectodermal membrane lined with mesoderm grows to enclose the embryo like a balloon. The amnion is the outer membrane, created by bilateral folding of the extraembryonic somatopleure and fusion of the chorioamniotic folds dorsal to the embryo in domestic animals. It appears after 30 hours of incubation. The amnion is the membranous sac that contains a fluid-filled cavity that helps in the protection of the embryo from the mechanical injury and desiccation (absorbs shock but also keeps the embryo from drying out supports hydration and allows some degree of movement). Also, protect from sudden temperature changes

7.2.3. The yolk sac

The yolk sac is a ventral, endodermally lined structure, constituted by the endoderm lined externally by the extra-embryonic splanchnopleure communicating with the primitive digestive tract by the vitelline duct. It is formed completely on the 9^{th} day of incubation. The yolk sac is the sole source of food until hatching, it contains a nutritious substance called the yolk (made predominately of glycoproteins) which is used to nourish the developing embryo. The yolk sac is a multifunctional extraembryonic organ that serves not only as a site of nutrient (yolk) absorption, but also for early hemopoiesis, and formation of blood vessels.

Although the yolk sac membrane being specialized to function as an extraembryonic absorptive organ, it is neither morphologically nor functionally part of the embryonic gut. Yolk absorption is by the phagocytic activity of the extraembryonic endoderm. In mammalian embryos does not serve a nutritive function

7.2.4. The allantois

The allantois is a small, endodermally lined diverticulum off the ventral side of the hindgut. Where about the 3rd day of incubation the region of the future floor of endodermal hindgut begins to bulgeas precocious urinary bladder called allantois. In birds , the allantois stores metabolic wastes (chiefly uric acid) of the embryo and, as it grows larger, also participates in gas exchange (facilitates respiration) via the vascular chorioallantonic membranes of allantois and chorion that acts as an extraembryonic lung which supply oxygen to the developing embryo. In addition, the allantois is used for storage of waste byproducts such as ammonia. But, it should be noted that allantois does not serve a direct function of respiration or storage of wastes in humans, these functions are carried out through the placenta and the umbilical vessels that arise in conjunction with the allantois.

7.2.5. Fate of appendages after hatching

Amnios, allantois are eliminated along with the shell. The albumen has been completely used1/3 to 1/5 of the yolk remains. It retracts inside the abdominal cavity of the embryo and is incorporated into the midgut; it will be used in the first two days of free life. So, with these four membranes, the developing embryo is able to carry on essential metabolism while sealed within the egg. Surrounded by amniotic fluid, the embryo is kept as moist as a fish embryo in a pond.

7.2.6. Placental mammal

Placental mammal, (infraclass Eutheria), any member of the mammalian group characterized by the presence of a placenta, a vascular organ that develops during gestation, which facilitates exchange of nutrients and wastes between the blood of the mother and that of the fetus. So, the primary function of the placenta is to act as an interface between the dam and fetus. The fetus and placenta are connected by the umbilical cord. It is constituted by extra embryonic annexes, interfaced with the uterine mucosa of the mother. The placental types in eutherian mammals are classified from various standpoints based on the gross shape, the histological structure of the materno-fetal interface, the type of materno-fetal interdigitation, etc. Particularly, the histological structure is generally considered one of the most useful and instructive classifications for functionally describing placental type.

- **The placental types**

Three main types are recognized according to the histologic relationship established between the chorion and uterine wall **(Figure 1. 25).**

- **Epitheliochorial type**

This type is the most superficial placenta and lacks significant invasion of the uterine lining. Pockets of columnar trophoblasts are loosely applied to the maternal endometrial epithelium. No destruction or invasion of the maternal tissues occurs and no layers are removed. **The epitheliochorial type is found in horses, pigs and ruminants.** Although there is some controversy over the evolution of the placenta, it is considered that the common ancestor of living placental mammals had a moderately invasive placenta of **the endotheliochorial type**. **The syndesmochorial** type is a placenta from which the endometrial epithelium is removed after implantation and was added to the placental classification list for a while. However, electron microscopic examination eliminated this type from the classification. On the other hand, some reports have described that the syndesmochorial placenta is an unusual type of placenta for ruminants, eg. Sheep & Cow.

- **Endotheliochorial type**

The maternal uterine epithelium and connective tissue disappear after implantation, and the trophoblasts come into direct contact with the maternal endometrial. The endotheliochorial type occurs in orders from all four major clades of eutherian mammals (Euarchontoglires, Laurasiatheria, Xenarthra and Afrotheria), including carnivores**.**

- **Hemochorial type**

This type is the most invasive placenta. All maternal tissue layers disappear through erosion, leading to direct connection between the chorion and maternal blood. There are hemomonochorial (primates), hemodichorial (rabbits), and hemotrichorial (rats and mice) placentas, with one, two and three trophoblast layers, respectively.

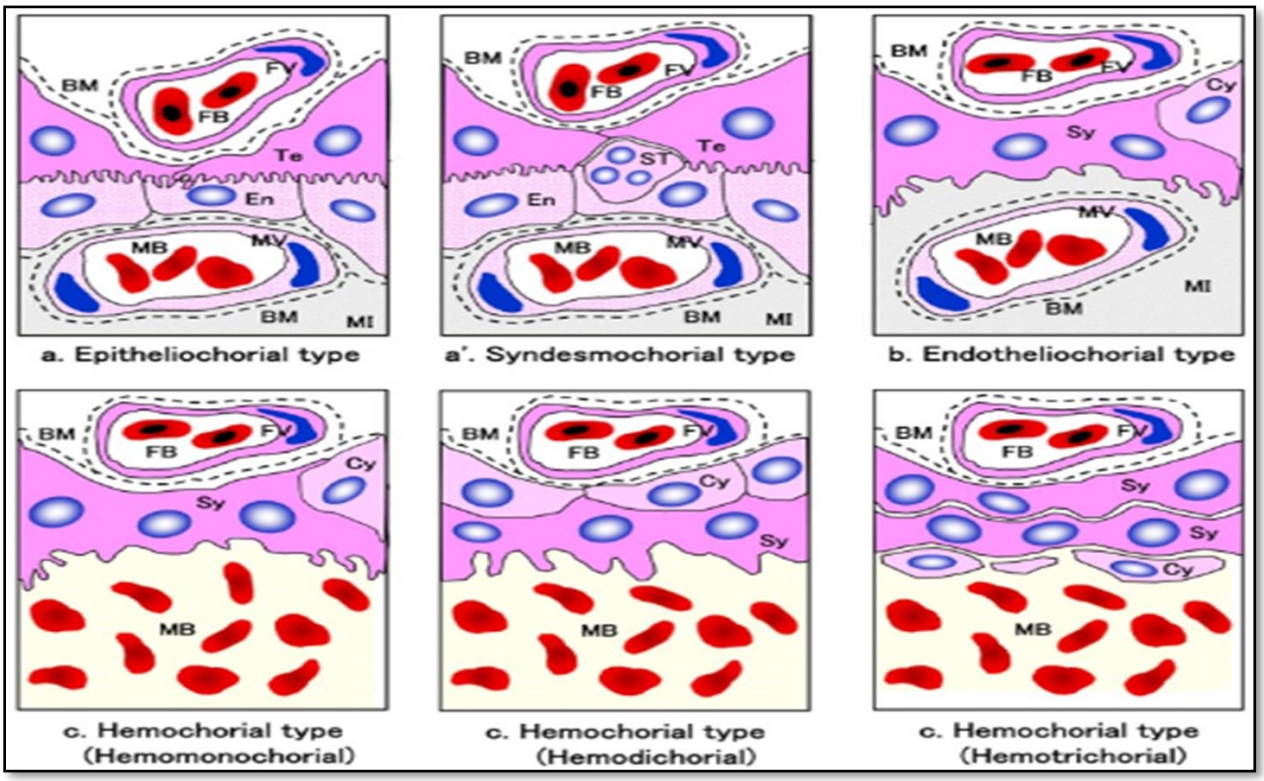

Figure 1. 25. Placental types based on the classification by relationship between the chorion and uterine wall.

BM, basement membrane; Te, trophectoderm; Cy, cytotrophoblast; En, endometrium; FB, fetal blood; FV, fetal vessel; MB, maternal blood; MI, maternal interstitium; MV, maternal vessel; ST, specific trophoblast; Sy, syncytiotrophoblast.

Placental mammals functions

- The placenta passes oxygen, nutrients, and other useful substances from the mother to the fetus;
- It also passes carbon dioxide and other wastes from the fetus to the mother;
- The placenta lets blood from the fetus and mother exchange substances without actually mixing;
- Thus, it protects the fetus from being attacked by the mother's immune system as a "foreign parasite";
- Helps protect fetus;
- Passes immunity;
- Produces hormones that help fetus to grow.

8. Particularities of human embryology (cycle, implantation, evolution annexes, placenta)

8.1. The menstrual cycle

The menstrual cycle has four main phases **(Figure 1.26):**

8.1.1. The menstrual phase

This is the first phase of the menstrual cycle, during which the lining of the uterus (endometrium) is shed through the vagina. This phase is also called menstruation or your period. It usually lasts 3-7 days.

8.1.2. The follicular phase

This is the second phase of the menstrual cycle. It begins after menstruation and ends just before ovulation. During this phase, the ovaries begin to mature a group of eggs (follicles) in preparation for ovulation. The hormone estrogen is produced and causes the endometrium to thicken.

8.1.3. The ovulatory phase

This is the third phase of the menstrual cycle. It occurs when an egg is released from the ovary (ovulation). Ovulation typically occurs around day 14 of a 28-day menstrual cycle, but this can vary widely from person to person.

8.1.4. The luteal phase

This is the final phase of the menstrual cycle. It begins after ovulation and ends when the next period starts. During this phase, the hormone progesterone is produced by the corpus luteum (a structure that forms in the ovary after ovulation). Progesterone helps to prepare the endometrium for pregnancy and prevents the uterus from contracting to expel the fertilized egg. If pregnancy does not occur, the corpus luteum will break down and the production of progesterone will decrease, causing the endometrium to shed and initiating menstruation. The luteal phase usually lasts about 14 days.

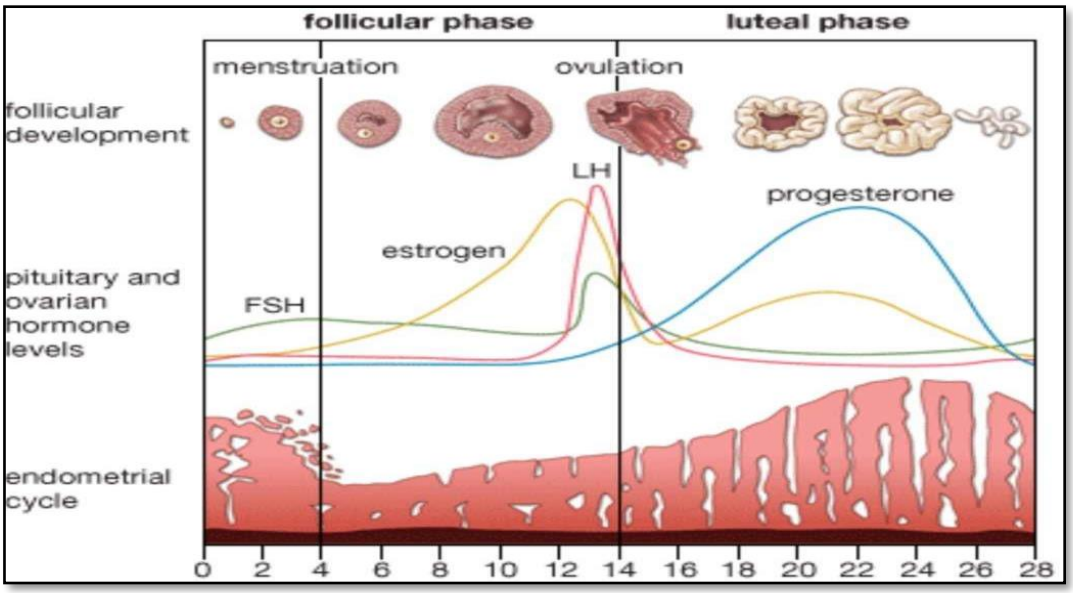

Figure 1. 26. The menstrual cycle.

8.2. Implantation

Implantation is a process in which a developing embryo, moving as a blastocyst through a uterus, makes contact with the uterine wall and remains attached to it until birth.

The lining of the uterus (endometrium) prepares for the developing blastocyst to attach to it via many internal changes. Without these changes, implantation will not occur, and the embryo sloughs off during menstruation. So, implantation is defined as the process by which the embryo attaches to the endometrial surface of the uterus and invades the epithelium and then the maternal circulation to form the placenta. Implantation consists of three stages:

(a) The blastocyst contacts the implantation site of the endometrium (apposition);

(b) Trophoblast cells of the blastocyst attach to the receptive endometrial epithelium (adhesion);

(c) Invasive trophoblast cells cross the endometrial epithelial basement membrane and invade the endometrial stroma (invasion).

8.3. Evolution annexes

8.3.1. The amnion

Amniotic membrane or amnion is the innermost layer of the placenta and consists of a thick basement membrane and an avascular stromal matrix.The Human Amniotic Membrane (HAM) contains two cell types, from different embryological origins, which display some

characteristic properties of stem cells. Human amnion epithelial cells (hAECs) are derived from the embryonic ectoderm, whereas human amnion mesenchymal stromal cells (hAMSCs) are derived from the embryonic mesoderm.

The amniotic cavity—opens up between it and the trophoblast. Cells from the upper layer of the disc (the epiblast) extend around the amniotic cavity, creating a membranous sac that forms into the amnion by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

8.3.2. The yolk sac

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the hypoblast) extend into the blastocyst cavity and form a yolk sac. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development.

It helps circulate gasses between you and the embryo. The yolk sac also produces cells that turn into important structures, such as the umbilical cord, blood cells and reproductive organs, in humans, the yolk sac begins to develop during the second week of gestation (pregnancy).

8.3.3. The allantois

The allantois is derived from splanchnopleure (endoderm and splanchnic mesoderm). It arises as a diverticulum of the hindgut and gradually fills the entire extraembryonic coelom (exocoelom) in most species. During week 3, a finger-like outpocketing of the yolk sac develops into the allantois, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and allantois establish the outer structure of the umbilical cord **(Figure 1. 27).** That's why in humans, the allantois is vestigial, but in a functional sense, the human placenta is a chorioallantoic type.

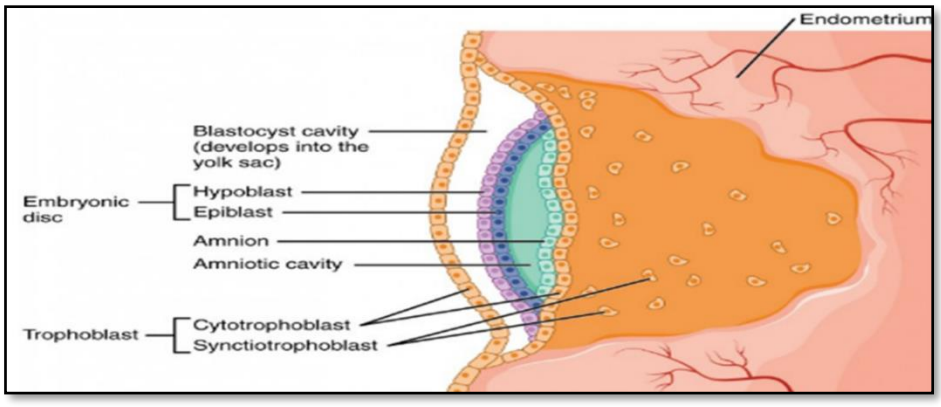

Figure 1. 27. Formation of the embryonic disc leaves spaces on either side that develop into the amniotic cavity and the yolk sac.

Amnion vs chorion

- Amnion and chorion, both are part of the extraembryonic membranes, which function in an embryo's overall development. They also play important roles in the embryo's nourishment, breathing, and seepage.
- The amnion is a thin but tough sac of membrane that covers an embryo. It is present in the embryonic development of reptiles, birds, and mammals. However, it is not present in the development for amphibians and fish offspring.
- Amnion is an inner membrane that surrounds the embryo whereas the chorion surrounds the embryo, amnion, and other membranes.
- The amnion is filled with amniotic fluid, which holds the embryo in suspension while chorion acts as a protective barrier during the embryo's development
- The amnion comprises of tresodeum and ectoderm while the chorion includes the trophoblast and the mesoderm.
- The chorion has a special feature called chorion villi, which acts as a barrier between the maternal blood and fetal blood. It absorbs maternal blood for the embryo's necessities whereas the amnion plays a part during the delivery stage.

The last of the extra-embryonic membranes is the chorion, which is the one membrane that surrounds all others. It relates to the growth and development of the placenta.

8.3.4. Development of the placenta

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and

the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells.

These form the chorionic membrane, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called chorionic villi that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The cytotrophoblast cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi.

Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta **(Figure 1. 28).**

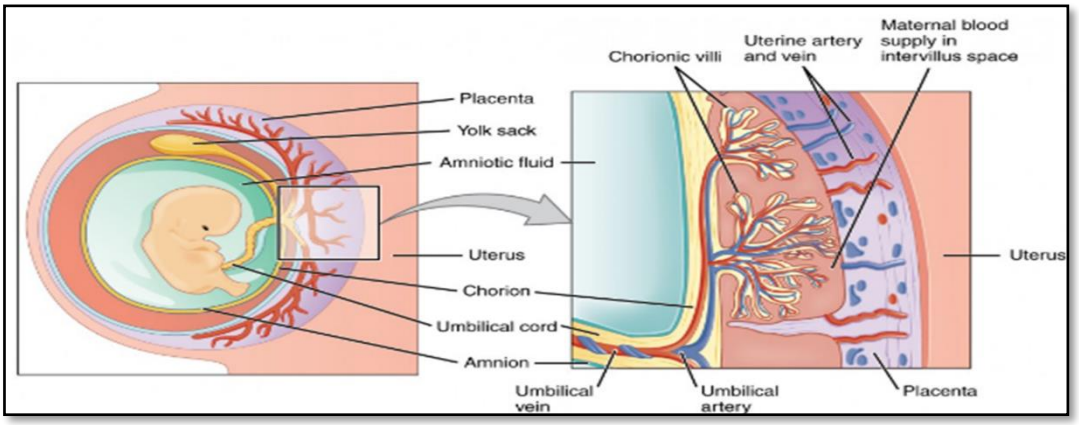

Figure 1. 28. The placenta.

Placenta functions

The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; placentation is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function. It receives blood from the fetus through the umbilical arteries. Besides, capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. On the other hand, some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other lipid-soluble substances take this route, and other substances move across by facilitated diffusion. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

Second part: Histology

Definitions

Histology: The word "histology" came from the Greek "**histo-**" meaning tissue + "logos", treatise.

Histology is the study of the microanatomy of cells, tissues, and organs as seen through a microscope. It examines the correlation between structure and function.

Tissue: Tissues are groups of cells that have a similar structure and act together to perform a specific function. The word tissue comes from a form of an old French verb meaning “to weave”. There are four different types of tissues in animals: connective, muscle, nervous, and epithelial.

1. Covering epithelium

1.1. Definition

The covering epithelia are sheets of tissue that cover the external surfaces (skin, lungs, gut) and line the internal cavities, (blood and lymphatic vessels, pleura) of the body.

1.2. Classification

A. Depending on the number of cell layers, several types are defined:

- **Simple epithelium:**
  - Consists of a single layer;
  - Typically found where absorption, secretion, and filtration occur.
- ***Stratified epithelium:***
  - Composed of ≥ 2 layers;
  - Found in high-abrasion areas (skin and lining of the mouth);
  - Name of cells in stratified epithelia based on shape of cells in apical layer.
- **Pseudostratified epithelium:**
  - All cells are attached to the basement membrane, but not all cells extend to the free surface;
  - The nuclei, being at different levels, give the epithelia a stratified appearance.

B. Depending on the shape of the cells, several types are characterized:

- **The squamous epithelia** are made up of flattened cells, wider than they are tall, with a prominent nucleus
- **Cubic epithelia,** as their name suggests, are formed of cubic cells, as wide as they are tall, with a rounded nucleus.
- **Columnar, or cylindrical (prismatic)** epithelia have cells that are taller than they are wide, with an ovoid nucleus located in the middle or lower third of the cell. Seen from the front, they form a polygonal surface.
- **Transitional:** shape of cells "goes through a transition": When the organ (e.g., bladder) is relaxed, cells appear cuboidal. While, when the organ is distended, cells flatten.

B.1. Cell shape and characteristics

The cell shape of the upper cell layer of a type of epithelium determines the name for the whole epithelium.

- **Flat (squamous epithelium)**

Appearance: Upper cells have a squamous (flat) shape (width > height).

Examples: Skin, esophagus, cervix.

- **Cube-shaped (cuboidal epithelium)**

Appearance: Upper cells have a cube-like shape (width = height).

Examples: Bile ducts, renal tubules.

- **Column-shaped (columnar epithelium)**

Appearance: Upper cells have a rectangular or cylindrical shape (width < height).

Examples: Intestine, respiratory tract (respiratory epithelium).

So, based on the different classifications we can observe the different next epitheliums:

- **Simple Epithelium**

a) Simple squamous epithelium (Figure 2.1):

- Single layer of flattened cells;
- Disc-shaped nuclei (most prominent structure);
- Sparse cytoplasm ;
- Typically found in lining of vessels, regulating passing substances to the tissue(s);
- Located in: (Air sacs/ Alveoli of lungs, Lining of the heart, Blood vessels and lymphatic vessels, Renal loops of Henle, Cornea).

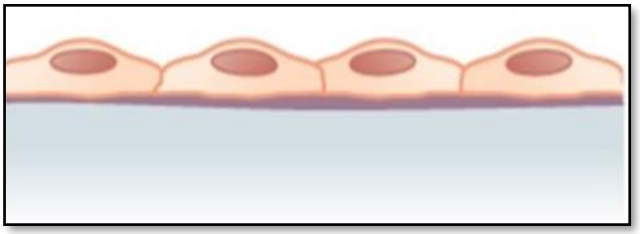

Figure 2. 1. Simple squamous epithelium.

b) Simple cuboidal epithelium (Figure 2.2):

- Single layer of cube-like cells;
- Cuboidal shape allows increased mitochondria and other organelles needed for functions such as active transport, secretion, and absorption;
- Found in: (Ducts and secretory portions of glands Kidney tubules).

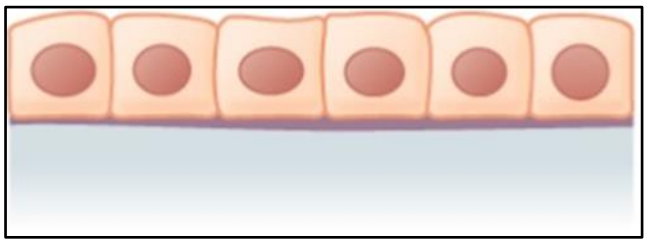

Figure 2. 2. Simple cuboidal epithelium.

c) Simple columnar epithelium (Figure 2.3):

- Single-layer tall cells;
- Often with cilia or microvilli;
- Mostly involved in absorption and secretion;
- Found in:Ciliated epithelium in the bronchi, fallopian tubes, and Uterus ;
- Smooth (nonciliated) epithelium in the digestive tract ;
- Lining of the gallbladder.

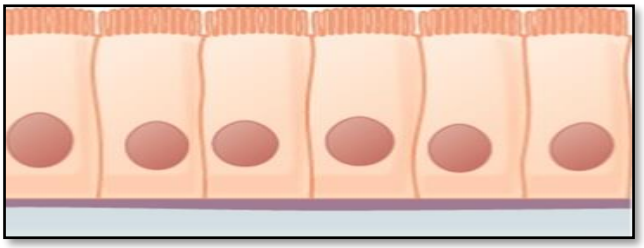

Figure 2. 3. Simple columnar epithelium.

➢ **Pseudostratified, Stratified, and transitional epithelia**

a) **Pseudostratified columnar epithelium (Figure 2.4):**

- Cells vary in height, with all cells resting on the basement membrane but only some reaching all the way to the apical surface;
- Nuclei placed at different heights;
- Some have cilia;

- Functions in secretion and absorption;
- Found in ciliated epithelium of the trachea and part of the upper digestive tract.

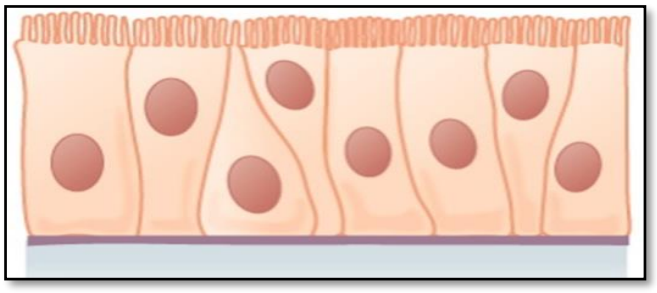

Figure 2. 4. Pseudostratified columnar epithelium.

b) **Stratified squamous epithelium (Figure 2.5):**

- Most widespread of the stratified epithelia;
- Composed of several layers, providing protective function;
- Free surface cells are squamous;
- Deeper layer cells are cuboidal or columnar;
- Found in areas subjected to wear and tear;
- Found in: Skin, which is keratinized or filled with keratin;
- These cells will lose the organelles and nuclei as they flatten and accumulate keratin;
- Cells move toward the surface, becoming metabolically inactive and are sloughed off; Esophagus, mouth, vagina, which have nonkeratinized cells (retain the nuclei).

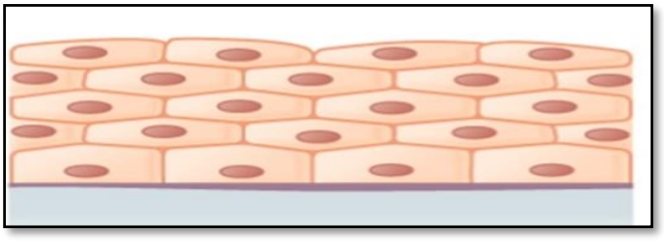

Figure 2. 5. Pseudostratified columnar epithelium.

c) **Stratified columnar epithelium and stratified cuboidal epithelium (Figure 2.6):**

- Both are rare and have limited distribution;
- Stratified columnar epithelium;
- Secretory and protective function
- Found in male urethra, some glandular ducts, stratified cuboidal epithelium is found in ducts of large glands (e.g., sweat glands, mammary glands).

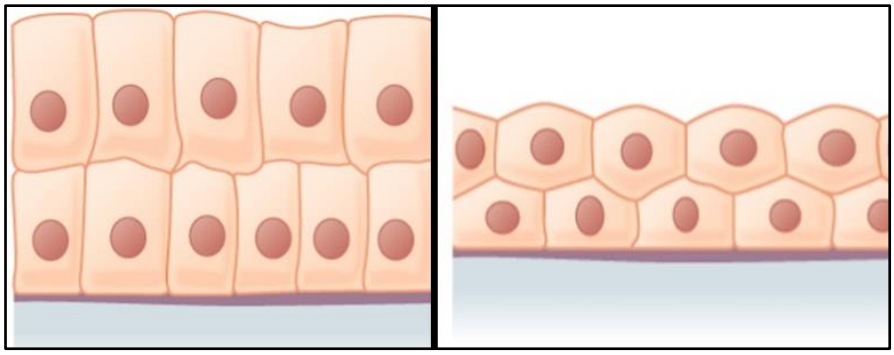

Figure 2. 6. Stratified columnar epithelium and stratified cuboidal epithelium**.**

d) **Transitional epithelium (Figure 2.7):**

- Surface layer of umbrella cells (dome-like cells);
- Allows for stretching of the organs as they distend;
- Urothelium: transitional epithelium in the urinary tract ;
- Found in urinary bladder, urethra, ureters.

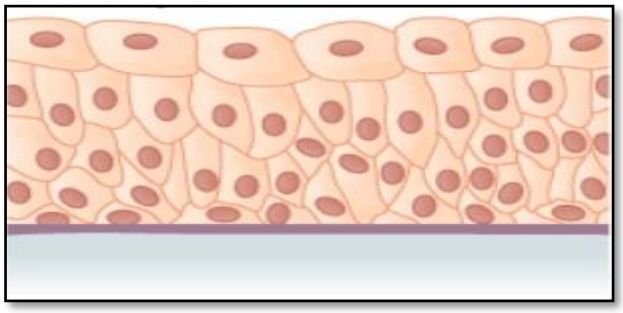

Figure 2. 7. Transitional epithelium.

➢ **Special surface epithelia**

a) Keratinized stratified squamous epithelium

Keratinized stratified squamous epithelium is only found in the epidermis.

b) Nonkeratinized squamous epithelium

Definition: epithelium that does not show keratinization and is composed of multiple cell layers upon a basement membrane

Structure: There are three different cell layers:

Basal layer: a layer of cuboidal to columnar cells that lie on the basement membrane

Intermediate layer: multiple layers of polygonal cells

Surface layer: multiple layers of squamous cells

Properties: especially resistant to mechanical stress (e.g., through food passage)

Distribution: Mucous membranes of the oral cavity, pharynx, esophagus, anal canal, navicular fossa of the urethra, vagina.

c) Urothelium (transitional epithelium)

Definition: stratified epithelium with cells of variable height and shape

Structure: There are three cell layers (stratum basale, stratum intermedium, superficial layer) between the basement membrane and the surface.

Empty bladder: 5–7 cell layers; cells in the superficial layer (multinucleated umbrella cells) are hemispherical

Full bladder: 3–4 cell layers; umbrella cells are flattened

Properties: adapts to variations in pressure/volumetric load; permeability barrier for urine and substances dissolved in urine

Distribution: Throughout the urinary tract: renal pelvis, ureter, bladder, proximal urethra

Exceptions: Parts of the male urethra.

d) Respiratory epithelium

Definition: Ciliated columnar epithelium (pseudostratified columnar epithelium with kinocilia) and numerous interspersed goblet cells.

Structure: ***Basal :*** basal cells (stem cell reserves of goblet and ciliated cells); ***Luminal :*** goblet cells (mucogenic), ciliated cells (bear kinocilia)Properties: cleans the airways through mucus secretion and orally directed cilia motion (= mucociliary clearance)

Distribution: Throughout the respiratory tract: nasal cavity, nasopharynx, larynx, trachea, main bronchi to the terminal bronchioli.

1.3. Covering epithielium functions

The covering epithelia play important roles that can be as a:

- **Protection** (provides covering surface or lining), For example, your skin is made up of epithelial tissue and protects the tissues deeper in your body, such as blood vessels, muscle and internal organs. The cilia on the epithelial cells that line your intestines protect the rest of your body from intestinal bacteria.
- **Secretion** (release of hormones, sweat, mucus, and enzymes) as found in glands
- Absorption (substance intake as seen in the intestinal lining, the internal epithelial lining of your intestines absorbs nutrients from the food you eat.)
- **Exchange of substances**: Epithelial tissue regulates the exchange of substances between body and external environment as well as the internal exchange between different parts of the body. Everything that enters the body or enters the bloodstream by absorption has to cross the epithelial barrier
- **Excretion and filtration of substances**: The epithelial tissue in your kidneys excrete waste, and the epithelial tissue in your sweat glands excrete sweat. The epithelium of your respiratory tract filters out dirt and particles and cleans the air that you breathe in. Epithelial tissue in your kidneys filters your blood.
- **Sensory reception** (detection of sensation) as found in olfactory epithelium.
- **Diffusion:** In biology, diffusion is the passive movement of molecules or particles from regions of higher concentrations to regions of lower concentration. Simple squamous epithelial cells form a membrane that allows selective diffusion of materials to pass through. Diffusion helps with filtration, absorption and secretion functions.

2.Glandular epithelium

2. 1. Definition

Glandular epithelium, also known as glandular tissue, refers to a type of epithelial tissue involved in the production and release of different secretory products, such as sweat, saliva, breast milk, digestive enzymes, and hormones, among many other substances. Glandular epithelium is arranged into structures known as glands, which can either be a single cell or a group of cells specialized in producing and releasing a specific substance.

2.2. .How is glandular epithelium formed?

Glandular epithelium is formed during fetal life by the development of epithelial cells into the connective tissue underlying the epithelium. Initially, all glands are connected to the surface epithelium by a channel called a duct. However, later on, each gland will differentiate into exocrine or endocrine according to the presence or absence of ducts, respectively.

2.3. Structure of the glandular epithelium

Glands develop from covering epithelia in the fetus by cell proliferation and growth into the underlying connective tissue, followed by further differentiation. The shape of the cells of the glandular epithelium can range from cuboidal to columnar as the squamous cells quite rare in the secretory epithelium. The glandular epithelium of the endocrine glands is rich in vascularization as well as innervation. Besides, the secretory cells in the glandular epithelium may synthesize, store, and release proteins (e.g., in the pancreas), lipids (e.g., adrenal, sebaceous glands), or complexes of carbohydrates and proteins. The cells of some glands (e.g., sweat glands) have little synthetic activity and secrete mostly water and electrolytes (ions) transferred from the blood.

The glands can be classified according to several criteria but depending on the environment in which these glands discharge their products of secretion there are:

Exocrine glands

Exocrine glands have a secretory portion and a duct that releases the secretory products into an epithelial surface, such as the skin or the digestive and respiratory tracts.

Endocrine glands

Endocrine glands do not have ducts, and instead release their secretory products, also known as hormones, into nearby blood vessels, where they then travel to other parts of the body.

The **table 2. 1** and the **figure 2. 8** represents a comparison between the endocrine and exocrine glands.

Table 2. 1. A Comparison between endocrine and exocrine glands.

Endocrine Glands	**Exocrine Glands**
No duct system	Ducts to release products
Secretions directed into the extracellular fluid (basal side), move into vascular system	Secretions released to the apical cell surface, move out of ducts to outside environment

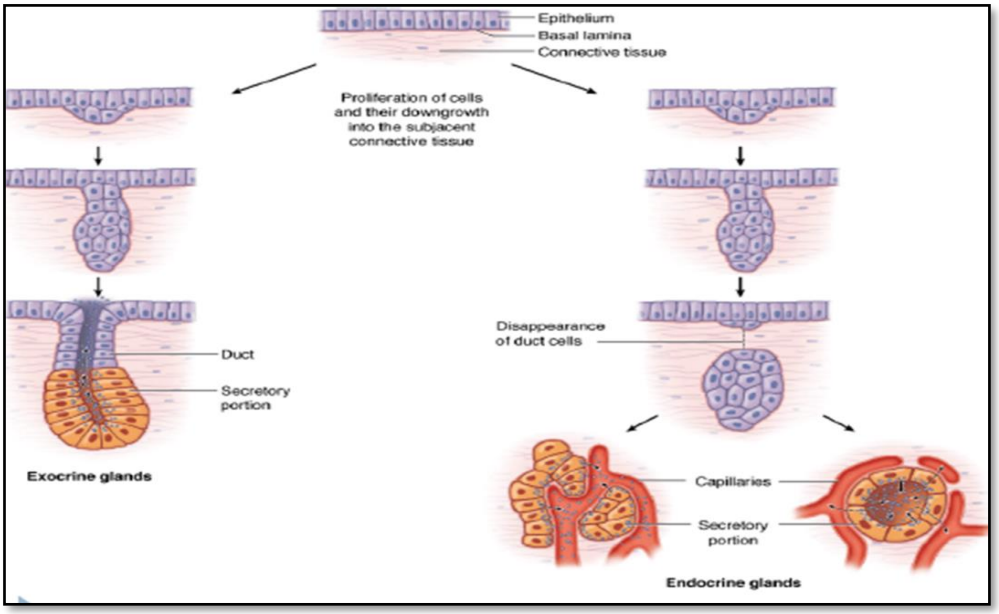

Figure 2. 8. Endocrine and exocrine glands.

2.4. Classification of exocrine glands

Exocrine glands are composed of a secreting part, known as adenomere, and an excretory duct, whose function is to expel the substance outside the gland. Those glands are often the only glands associated with the term "glandular epithelium." These glands are classified by the following morphological characteristics:

a) Number of cells constituting the adenomere:

The next table **(Table 2. 2)** represent the Classification of exocrine glands based on the number of cells constituting the adenomere.

Table 2. 2. Classification of exocrine glands based on the number of cells constituting the adenomere.

Unicellular Glands	Multicellular Glands
Made of only one glandular epithelium cell; called **intraepithelial cells**	Multiple cells make up one gland; called **extraepithelial cells** (Sheet glands "juxtaposed", Intra-epithelial glands in clusters. Simple glands and composed glands.
Goblet cells are the only human example	Many examples, including secretory sheets in the human stomach

b) Depending on the number and branchings of the excretory ducts:

Based on the number and branchings of the excretory ducts, the exocrine glands can be classified into three types **(Table 2. 3)**

Table 2. 3. Classification of exocrine glands based on the number and branchings of the excretory ducts

Simple gland	Branched gland	Compound gland
An adenomere presents only one excretory duct	Several adenomeres present only one excretory duct	Several draining excretory ducts firstly converge in each other and then towards a common excretory duct

c) Depending on the shape of the adenomere:

Shapes include tubular, coiled tubular, acinar or alveolar, or a combination of these (**Figure 2. 9)**.

- The adenomere has an elongated shape and presents a quite prominent lumen= Glands are called **tubular glands**;
- If the shape of the adenomere is round, small and, therefore, hardly visible, the gland is **acinar**
- In case the adenomere is round, large and clearly visible, the gland is called **alveolar**.
- In branched glands, there might be a combination of tubular adenomeres and either acinar **(tubuloacinar glands)** or alveolar adenomeres **(tubuloalveolar glands).**

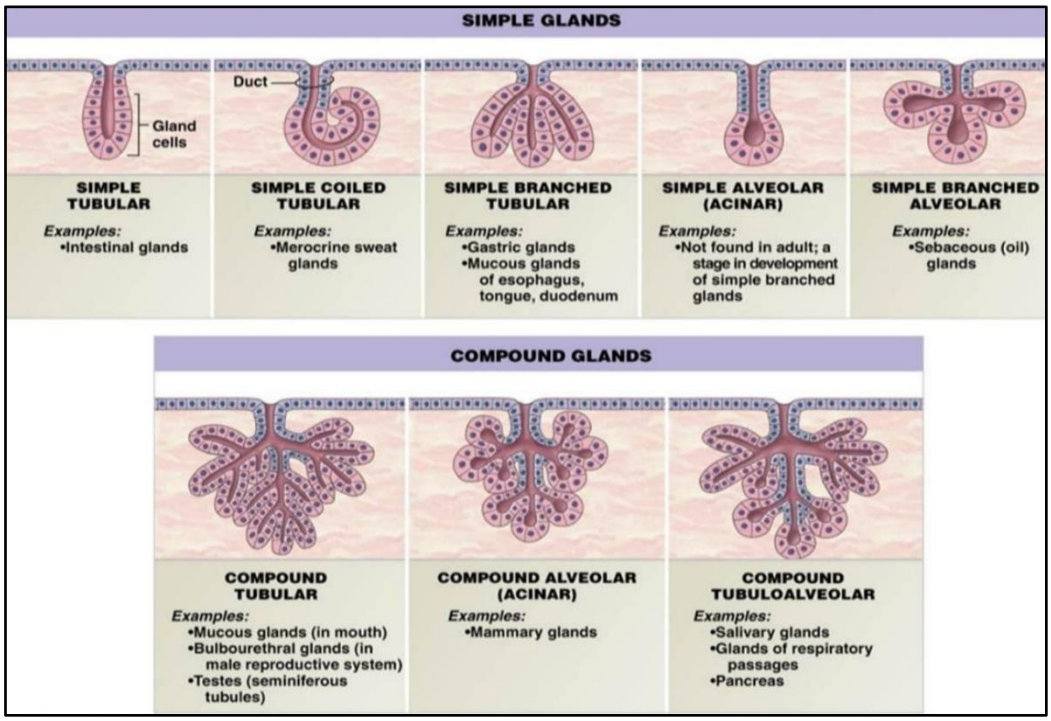

Figure 2. 9. Representation of various shapes and arrangements of exocrine glands.

d) Depending on the mechanism of secretion:

The next table **(Table 2. 4)** showed the different types of of exocrine glands based on the mechanism of secretion.

Table 2. 4. Classification of exocrine glands based on the mechanism of secretion.

Merocrine (or eccrine) secretion	The secretory product is released through the cytoplasmic membrane (exocytocis). In this way, the cell remains intact, e.g. parotid, exocrine pancreas and salivary glands.
Apocrine secretion	The substance is expelled in the excretory duct due to the disintegration of the cell itself, eg: sebaceous cells.
Holocrine secretion	Part of the cytoplasm, surrounded by the cytoplasmic membrane, is lost during the secretory phase and becomes part of the secreted substance; here are some examples: mammary glands (limited to lipid secretion), sweat glands with a wide lumen.

e) Depending on the type of secretion (only in merocrine glands):

Merocrine is considered the most common type of secretion. It releases secretory vesicles into the extracellular space, it can be classified into three types based on the type of secretion.

Table 2. 5. Classification of merocrine glands based on the mechanism of secretion.

Serous	**Mucous**	**Mixed Serous-Mucous**
Thin, watery protein-rich secretion	Viscous secretion with lubricating or protective function	Serous demilunes (cells) secrete into space between mucous cells

f) Depending on their topographical location:

Depending on the topographical location of the glands, we distinguish two types: intraepithelial glands and extraepithelial glands, themselves divided into parietal glands and extraparietal glands.

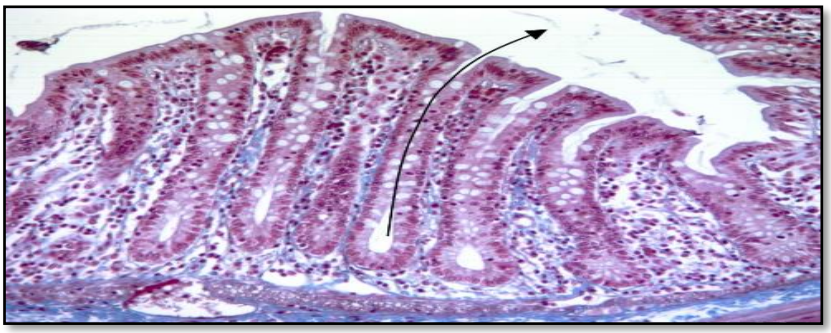

Figure 2. 10. Rat colon intestinal glands**.**

The previous figure **(Figure 2.10)** represents exocrine simple tubular glands that open onto the luminal surface (the arrow shows the glandular lumen and the direction of the secrete). In this manner, the secretion product is directly poured into the lumen.

2.5. Classification of endocrine glands

These glands produce a specific type of molecules, generally known as hormones, whose aim is to regulate the function of the specific organs they are produced for (known as target organs). Hormones can be either amino acid or lipid derived. For endocrine glands there are:

- **Endocrine glands:** composed exclusively of endocrine tissue;
- **Amphicrine glands:** composed of both endocrine and exocrine tissue (for example: the parenchyma of pancreas, generally marked by exocrine secretion, presents cell conglomerates with endocrine activity: the pancreatic islets – or islets of Langerhans).

Endocrine glands are classified in in the next table **(Table 2 .6)**:

Table 2. 6. Classification of endocrine glands based on the mechanism of secretion.

Endocrine glands with solid epithelial cords	**Follicular endocrine gland**	**Islets endocrine glands**	**Interstitital endocrine gland**
Secretory cells form cell cords which are variably located in space. Most of endocrine glands belong to this type: hypophysis, parathyroids, adrenal glands, epiphysis, placenta, corpus luteum;	Here the secretory part is represented by follicles lined by cells that produce a precursor of thyroid hormones (thyroglobulin), the only example of which is the thyroid gland;	The pancreatic islets of Langerhans;	These glands can be found in ovaries and in the interstitial space between the seminiferous tubules of testicles, in groups of six, eight or more cells surrounding a capillary in which they release the secretory substance (testosterone).

Concerning amphicrine glands morphologically we can distinguish are classified as:

- When the same cells have these two functions, the gland is said to be "homotypic amphicrine". as is the case for liver hepatocytes.
- When different types of cells each have one of these two functions, the gland is called **"heterotypic amphicrine":** this is the case of the pancreas, whose cells of the islets of Langerhans are endocrine, while the acinar cells are exocrine.

2.6. Glands functions

The major function of epithelial tissue is secretion; some other functions are listed below:

- They help in regulating body temperature and maintaining homeostasis with watery mucus released by the exocrine glands.
- They provide protection against microbial invasion and inhibit water loss with oily secretions from the sebaceous glands and the ceruminous glands by lubricating the epithelium covering.
- Helps in digestion by producing digestive enzymes from salivary glands and the digestive glands.
- Helps in regulating overall growth and development of the body with the help of thyroid gland and pituitary glands.
- Helps in regulating the immune system, blood pressure and metabolism with the help of adrenaline glands.
- Production of gametes from ovary and testes that are necessary for sexual reproduction.

3. Connective tissues

3.1. Definition

Connective tissue, group of tissues that connects or separates. It also provides metabolic support by creating a hydrophilic environment that mediates the exchange of substances between the blood and tissue. Connective tissue is of mesodermal origin and consists of a mixture of cells, fibers, and ground substance. Fibers (collagen, elastic, and reticular) and the ground substances constitute the extracellular matrix of connective tissue. However, connective tissue differs from other types in that its cells are loosely, rather than tightly, packed within the ECM **(Figure 2.28).** The classification and function of connective tissue are based on the differences in the composition and amounts of cells, fibers, and ground substance.

Based on the cells present and the ECM structure, we differ two types of connective tissue:

- **Connective tissue proper**; further divided into loose and dense connective tissues;
- **Specialized connective tissue;** reticular, blood, bone, cartilage and adipose tissues.

The three components of connective tissue are **cells**, **ground substance and fibers**. Ground substance and fibers make up the extracellular matrix (ECM).

3.2. Constituants of connective tissues

Connective tissue cells

The cells of the connective tissue are divided into two main groups: Some cells differentiate from mesenchymal cells, such as fibroblasts which are responsible for synthesis and maintenance of the extracellular material, these cells and others are formed and reside in the connective tissue and are **called fixed cells (Resident cell populations).**

Free, wandering or visitant cells of connective tissue, which arise from hematopoietic stem cells, differentiate in the bone marrow and migrate from the blood circulation into connective tissue where they perform their functions, these cells have a part in immune surveillance and responses, cells include **plasma cells, and leukocytes**...

A. Fixed or permanent cell

A.1. Mesenchymal cells

They have an irregular stellate shape with delicate branching cytoplasmic processes that form an interlacing network throughout the tissue **(Figure 2.11).** The nucleus is oval with dispersed chromatin and prominent nucleoli. Mesenchymal cells are relatively unspecialized

and are capable of differentiation into all types of connective tissue cells including that of the skeleton and smooth muscles.

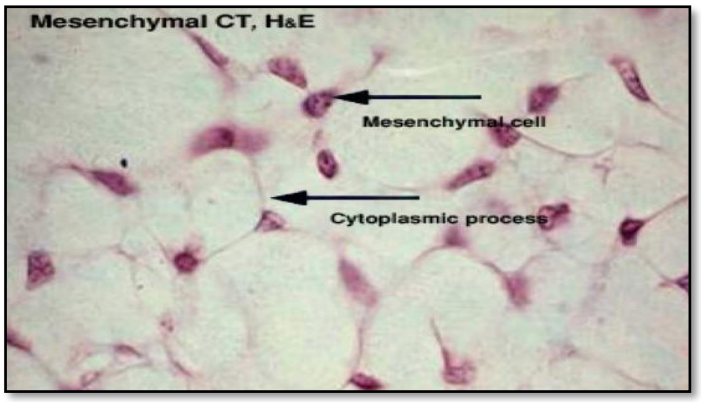

Figure 2. 11. Mesenchymal cells.

A.2. Macrophages (histiocytes)

The macrophages are present practically in all organs, constituting a diffuse system called mononuclear phagocyte system. They may have other names such as: osteoclasts in bone; monocytes in blood; dust cells or heart failure cells in lung alveoli; Kupffer cells in liver, and microglia in the central nervous system. Many macrophages can fuse with each other forming large multinucleated cells called foreign body giant cells that can engulf large foreign bodies.

Macrophages are involved in synthesis and secret many substances such as lysozyme (antibacterial agent), interferon (antiviral), interleukin that are essential for the proliferation of T and B-lymphocytes. Also, in the Antigen processing and antigen presentation.

The macrophage can be:

a. Fixed macrophages or histiocytes

- The cells are stellate or fusiform that are difficult to distinguish from fibroblasts;
- They could be differentiated from fibroblasts;
- They have smaller and darker nuclei;
- They give a strong positive reaction when stained for lysosomal enzymes such as acid phosphatase.

b. Stimulated or active macrophages

- They are large ovoid or spherical cells with eccentric kidney-shaped nuclei and foamy cytoplasm;
- Actively phagocytic cells exhibit irregular cytoplasmic projections or pseudopodia;

- The cytoplasm shows well-developed Golgi apparatus, abundant lysosomes, many phagosomes and residual bodies, a few mitochondria and variable amount of free ribosomes.

A.3. Pericytes

Pericytes are elongated connective tissue cells with long cytoplasmic processes located external to the endothelium of blood capillaries and small venules. They share a common basal lamina with the adjacent endothelial cells and they have a fusiform nucleus and scanty cytoplasm that contains many mitochondria, free ribosomes, and small Golgi complex**.**

A.4. Fibroblasts and fibrocytes

Fibroblasts and fibrocytes represents the most common cells in connective tissue, their nuclei are ovoid or spindle shaped and can be large or small in size depending on their stage of cellular activity. While, the cytoplasm is extensive and strongly basophilic with numerous interconnected cytoplasmic extensions. The inactive fibroblasts (fibrocytes) are smaller and appear spindle in shape with fewer processes. Fibroblasts synthesis and secret the precursors of collagen (tropocollagen), elastin (tropoelastin), the glycosaminoglycans, and all other extracellular components.

B. Free, wandering or visitant cells

B.1. Adipose cells (Adipocytes or fat cells)

There are two types of fat cells; white (monolocular) and brown (multilocular):

- **The white adipocytes** are polygonal or spherical in shape, occupied by a single large lipid surrounded by a thin rim of cytoplasm.
- **The brown adipocytes** are smaller than white one, the nuclei are oval, surrounded by a significant amount of strongly acidophilic cytoplasm. They could be differentiated from the white adipose tissue on the basis of Lipid which is stored as multiple, small droplets (multilocular fat cells) that give the cytoplasm a vacuolated appearance. Brown adipocytes have relatively large amount of cytoplasm contains abundant mitochondria that are rich in cytochromes, which give the brown color of this tissue.
- **B.2. Mast cells**

Mast cells are bone marrow origin. They are large polymorphic, spherical or ovoid cells with spherical centrally located nuclei. Mast cells contain Fc membrane receptors, which bind to immunoglobulin (Ig) E antibodies, an important cellular interaction involved in anaphylactic

shock. The granules of the mast cells contain histamine, heparin, ECF-A (Eosinophil Chemotactic Factor for Anaphylaxis) **(Figure 2.12)** and serotonin in rat and mouse.

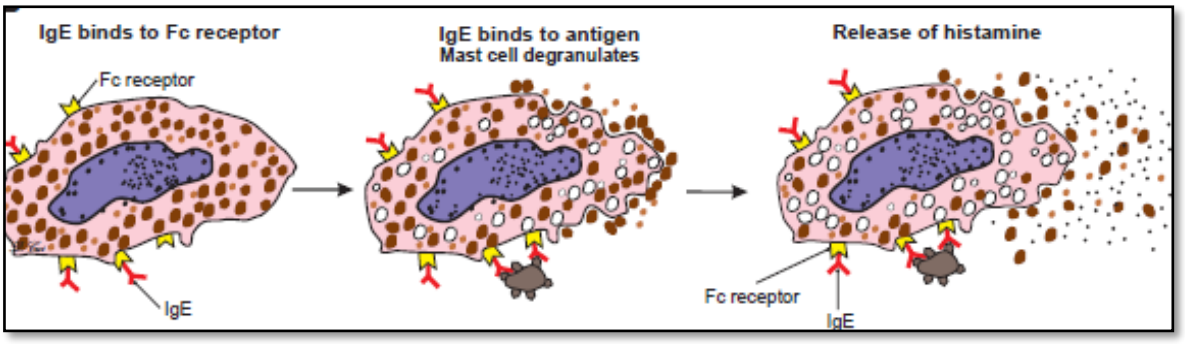

Figure 2. 12. A representation of a mast cell in an allergic reaction (anaphylaxis).

B.3. Plasma cells

Plasma cells are spherical, oval or pear-shaped cells with spherical, eccentric nucleus. They have the ability to secrete antibodies that are antigen specific, most plasma cells reside in connective tissues, especially in the gastrointestinal and respiratory tracts**.** They are also abundant in the salivary glands, lymph nodes, spleen, and red bone marrow.

B.4. Melanocytes

All melanocytes, whether resident in the basal epidermis or in the matrix of the hair, have migrated there during embryonic life from a region known as the neural crest. They are large pigmented cells with numerous long branching processes.

B.5. Other connective tissue cells

They include lymphocytes, monocytes and granulocytes (especially eosinophils and neutrophils) **(Figure 2.13).**

Leukocytes: White blood cells are considered the transient cells of connective tissue. They migrate from the blood vessels into connective tissue by the process of diapedesis. After entering connective tissue, leukocytes, with the exception of lymphocytes, do not return to the blood. The following leukocytes are commonly found in connective tissue:

(1) Lymphocytes: These cells have a round or bean-shaped nucleus and are often located in the subepithelial connective tissue.

(2) Neutrophils (polymorphs): Each cell has a multilobed nucleus and functions in the defense against infection.

(3) Eosinophils: Each cell has a bilobed nucleus and reddish granules in the cytoplasm, They have antiparasitic activity and moderate the allergic reaction function.

(4) Basophils: These cells are not easy to find in normal tissues. Their primary function is similar to that of mast cells.

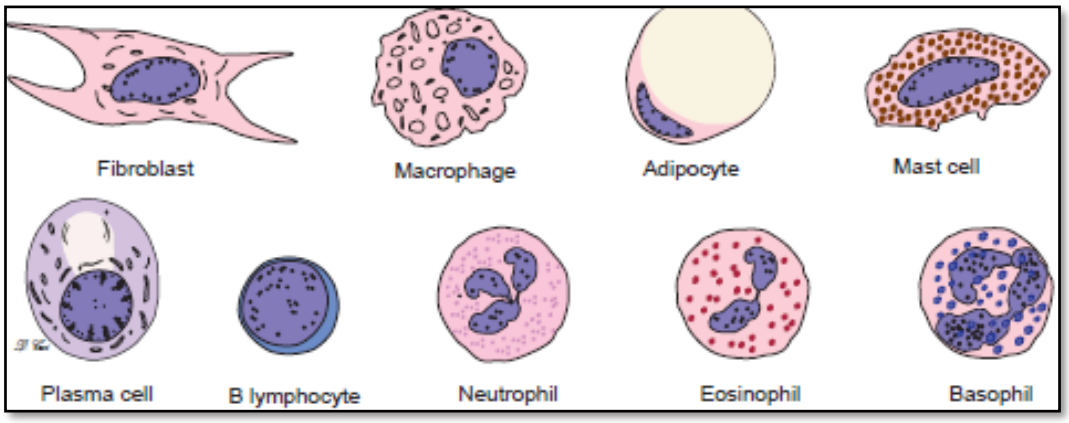

Figure 2. 13. Representation of the main types of connective tissue cells.

Connective tissue fibers

Three types of fibers are found in connective tissue: collagen, elastic, and reticular (Structural fibrous proteins). Three fibers all consist of proteins that form elongated structures, which, although produced primarily by fibroblasts, may be produced by other cell types in certain locations.

A. Collagen fibers

Collagen is a biomolecule produced by fibroblasts and forms the collagen fiber **(Figure 2.14).** The collagen, in turn, is an aggregate of tropocollagens. The tropocollagen is made up of three polypeptide strands (referred to as alpha peptides) that are twisted together into a superhelix or a right-handed triple helix. Where the amino acids in each chain are arranged in a regular pattern. There are various types of collagen (e.g. type I, type II, type III….).

Collagens are composed primarily of type I collagen . These are the most abundant protein fiber type, providing varying degrees of strength and rigidity to tissues. There are over 20 different types.

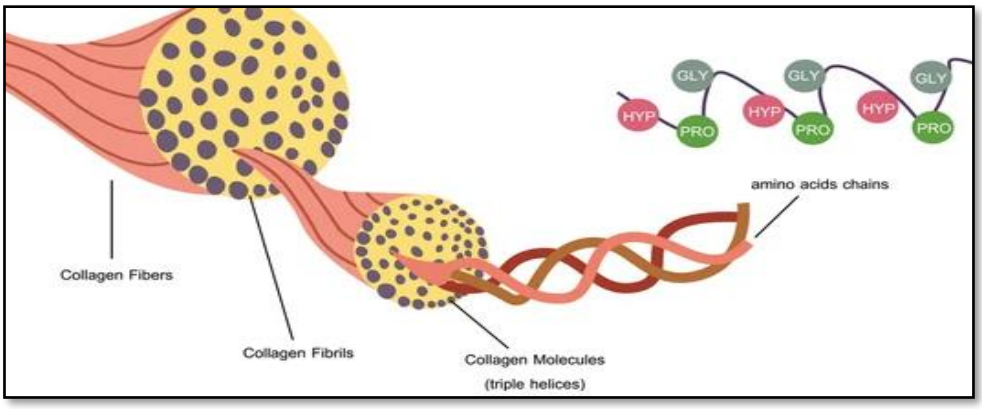

Figure 2. 14. Representation of the collagen fibers structure.

B. Elastic fibers

Elastic fibers have a very resilient nature (stretch and recoil), which is important in areas like the lungs, aorta, and skin. They are composed of two proteins, elastin and fibrillin, and do not have a banding pattern **(Figure 2.15).** These fibers are primarily produced by the fibroblasts but can also be produced by smooth muscle cells and chondrocytes**.** Eastic fibers **c**an stretch up to150 times its relaxed size

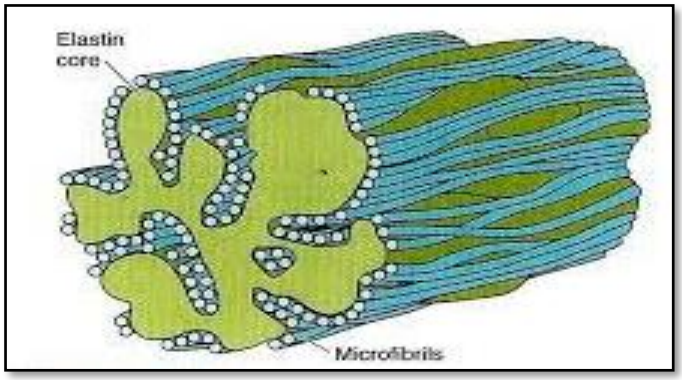

Figure 2. 15. Shematic diagram of elastic fiber.

C. Reticular fibers

Reticular fibers are small-diameter fibers, meshlike framework for organs that are composed mostly of cells (such as the liver, spleen, pancreas, lymphatic tissue, etc.).They are called argyrophilic fibers because they appear black after exposure to silver salts, made up of collagen but are thinner as compared to collagen fibers. They are produced by modified fibroblasts (reticular cells) and are composed of type III collagen.

Ground substance of connective tissue

The ground substance maybe viscou (as in blood), semi solid (as in cartilage, or solid (as in bone). Its major component is glycosaminoglycans (GAGs), which are long, unbranched chains of polysaccharides with repeating disaccharide units. Most GAGs are covalently bonded to a large central protein to form larger molecules called proteoglycans. Both GAGs and proteoglycans have negative charges and attract water.

Glycosaminoglycans

GAGs are unbranched polysaccharide chains composed of repeating disaccharide units, a sulfated amino sugar (N-acetylglucosamine orN-acetylgalactosamine), and uronic acid (glucuronic or iduronic). Highly negatively charged. Four types of GAGs exist: hyaluronan, chondroitin sulfate and dermatan sulfate, heparan sulfate, and keratan sulfate. GAGs in connective tissue usually constitute less than 10% of the weight of fibrous proteins. Hyaluronan is the simplest GAG. In contrast to the other GAGs, hyaluronan is not covalently attached to any protein and is synthesized directly from the cell surface by an enzyme complex embedded in the plasma membrane.

A. Proteoglycan

Proteoglycans are a diverse group of glycoproteins with functions mediated by their core proteins and GAG chains. Proteoglycans provide hydrated space around and between cells.. Proteoglycans also can bind other secreted proteins, such as proteases and protease inhibitors. This binding allows proteoglycans to regulate proteins by immobilizing the protein and restricting its range of action, providing a reservoir of the protein for delayed release, altering the protein to allow more effective presentation to cell surface receptors, and prolonging the action of the protein by protecting it from degradation, or blocking the activity of the protein.

B. The fibrous adhesion proteins

- **Laminins**

Laminins are large molecular weight glycoproteins constituted by the assembly of three disulfide-linked polypeptides, the α, β and γ chains **(Figure 2.16).** Structurally, laminin chains differ by the number, size and organization of a few constitutive domains. The human genome encodes 11 genetically distinct laminin chains.

Laminins are indispensable building blocks for cellular networks physically bridging the intracellular and extracellular compartments.

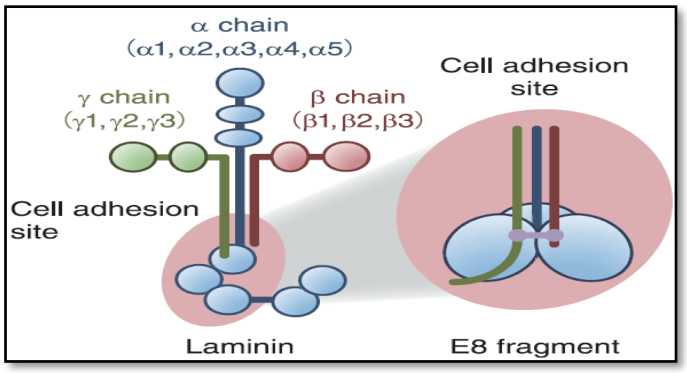

Figure 2. 16. Structure de la laminine.

- **Fibronectin**

Fibronectin is secreted as a soluble, covalently bound dimer of ~440 kD molecular weight. Fibronectins are involved in cell adhesion, cell motility, opsonization, wound healing, and maintenance of cell shape. It exists in a soluble protomeric form in micromolar concentration in blood plasma and in an insoluble multimeric form in the ECM. Two types of fibronectin are present in vertebrates: (soluble plasma and insoluble cellular). It is binds to other extracellular matrix proteins such as collagen, fibrin, and heparan sulfate proteoglycans (e.g. syndecans). Fibronectin is a critically important ECM protein that mediates cell: ECM interaction during fundamental events such as development, wound healing, fibrosis, and tumor progression.

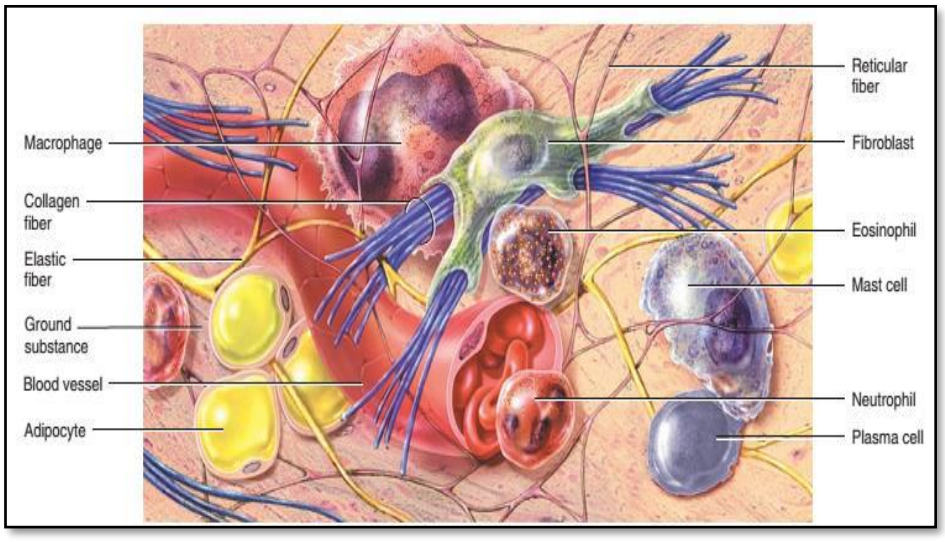

Figure 2. 17. The different constituents of connective tissues.

3.3. Types of connective tissues

There are three different types of connective tissues.

Connective tissue proper

A. Dense connective tissue

A.1. Dense irregular connective tissue:

This type consists of few connective tissue cells and many connective tissue fibers, the majority being type I collagen fibers, interlaced with a few elastic and reticular fibers **(Figure 2.29).** These fibers are arranged in bundles without a definite orientation. Exp: The dermis of the skin and capsules of many organs.

A.2. Dense regular connective tissue:

Dense regular connective tissue also consists of fewer cells and more fibers, with a predominance of type I collagen fibers **(Figure 2.18)**. Here, the fibers are arranged into a definite linear pattern. Fibroblasts are arranged linearly in the same orientation. Exp: Tendons and ligaments are the most common examples.

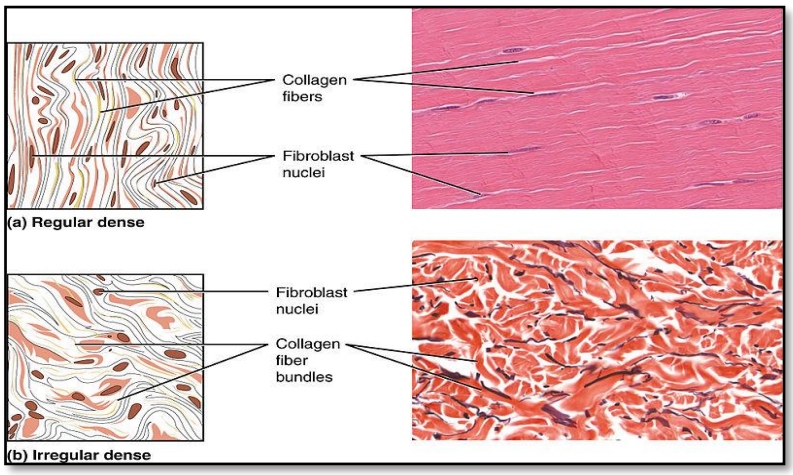

Figure 2. 18. Dense connective tissue.

B. Loose connective tissue

Also called areolar connective tissue, is characterized by abundant ground substance **(Figure 2.19)**, with numerous connective tissue cells and fewer fibers compared to dense connective tissue. It is richly vascularized, flexible, and not highly resistant to stress. It provides protection, suspension, and support for the tissue.

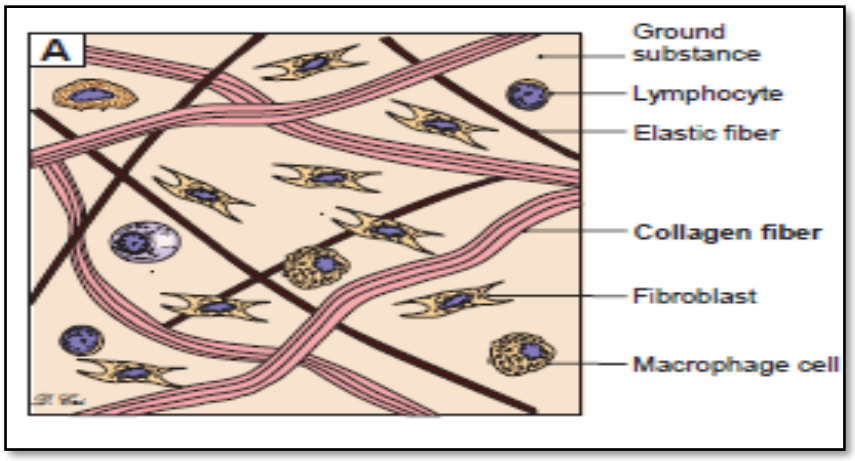

Figure 2. 19. A representation of collagen fibers in loose connective tissue.

Specialized connective tissues

A. Adipose tissue

A special form of connective tissue, consisting predominantly of adipocytes that are the primary site for fat storage and are specialized for heat production. It has a rich neurovascular supply. Adipose tissue can be divided into white adipose tissue and brown adipose tissue.

A.1. White adipose tissue

White adipose tissue is composed of unilocular adipose cells. The typical appearance of cells in white adipose tissue is lipid stored in the form of a single, large droplet in the cytoplasm of the cell. The flattened nucleus of each adipocyte is displaced to the periphery of the cell. White adipose tissue is found throughout the adult human body.

A.2. Brown adipose tissue:

Brown adipose tissue, in contrast, is composed of multilocular adipose cells. The lipid is stored in multiple droplets in the cytoplasm. Cells have a central nucleus and a relatively large amount of cytoplasm. Brown adipose tissue is more abundant in hibernating animals and is also found in the human embryo, in infants, and in the perirenal region in adults.

B. Reticular tissue

The reticular tissue is a specialized loose connective tissue that contains a network of branched reticular fibers, reticulocytes (specialized fibroblasts), macrophages, and parenchymal cells, such as pancreatic cells **(Figure 2.20)** and hepatocytes. Reticular fibers are actually type III collagen fibrils and are very fine and much smaller than collagen type I and elastic fibers. As maturity or repair continues, the majority of them are replaced by the stronger type I collagen.

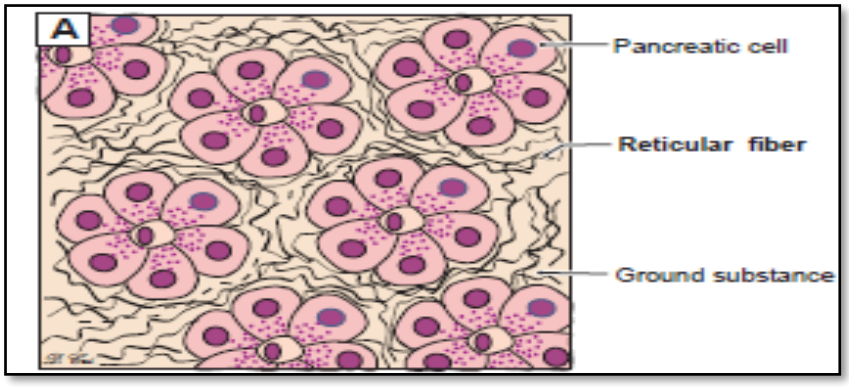

Figure 2. 20. A representation of reticular fibers in the pancreas.

C. Elastic tissue

Elastic tissue is a dense connective tissue **(Figure 2. 21)**, which contains predominantly elastic fibers rather than collagen and fibroblasts filling the interstitial space. In certain locations, such as in elastic arteries, elastic material and collagen fibers can be produced by smooth muscle cells. This tissue provides flexible support for other tissues. Elastic tissue is usually found in the vertebral ligaments, lungs, large arteries, and the dermis of the skin.

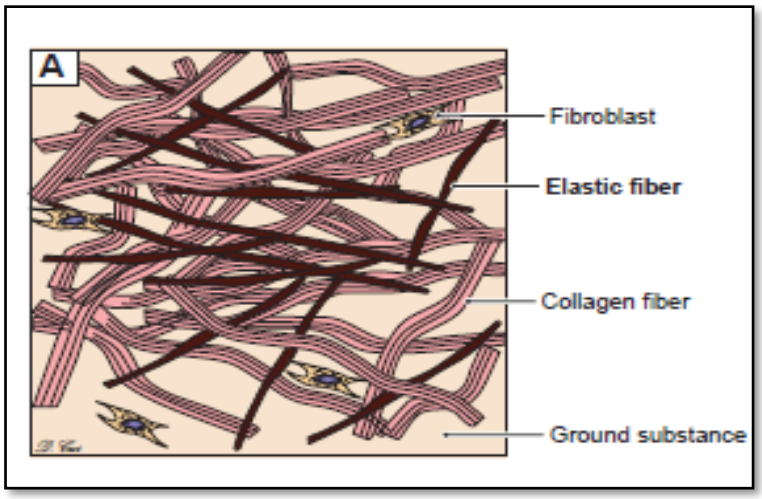

Figure 2. 21. *A representation of the elastic fibers in dense connective tissue.*

Embryonic connective tissues

This tissue type is subdivided into two groups:

A. Mesenchymal connective tissue

Embryonic connective tissues is formed during the development of the embryo. Is contains considerable ground substance, scattered reticular fibers and star-shaped mesenchymal cells that have pale-staining cytoplasm with small processes. Capable of differentiating into different types of connective tissues.

B. Mucous connective tissue:

Mucous connective tissue exhibits a jellylike matrix with some collagen fibers and stellate-shaped fibroblasts. Mucous tissue is the main constituent of the umbilical cord and is called Wharton jelly. In adults, it is found in omasal laminae and in the comb and wattles of the chickens. It consists of large stellate, fibroblasts with branching and anastomosed cytoplasmic processes. Few macrophages and lymphoid cells are also present. The intercellular substance is rich in mucin and contains thin collagenous fibers, which increase with age.

4. Blood tissues

4.1. Definition

Blood is a fluid connective tissue. It circulate continually around the body, consists of cells and cell fragments (formed elements) suspended in an intercellular matrix (plasma).

Blood is the only liquid tissue in the body that measures about 5 liters in the adult human and accounts for 8 percent of the body weight. The body consists of metabolically active cells that need a continuous supply of nutrients and oxygen. Metabolic waste products need to be removed from the cells to maintain a stable cellular environment. Blood is the primary transport medium that is responsible for meeting these cellular demands.

4.2. Functions of the blood

The main function of the blood is to maintain intracellular homeostasis by:

- Carries O_2 and nutrients (glucose, amino acids, lipids, and vitamins) to the cells.
- Carries CO_2 and other wastes (nitrates, creatine, nucleic acid) away from the cell.
- Providing intercellular communication in the body: carries hormones (secreted by endocrine glands) to the target organs.
- Protection and defense: it allows cells and immunological proteins to transport from place to place where need them.
- Self repair mechanism: clotting cascade.

4.3. Blood components

Blood is composed from two fractions **(Figure 2. 22):**

1. Plasma: Non living extracellular matrix composes about 55% of total blood volume.

2. Formed elements (living cells): Composes about 45% of total blood volume. Where the fractions of blood can be separated by spinning.

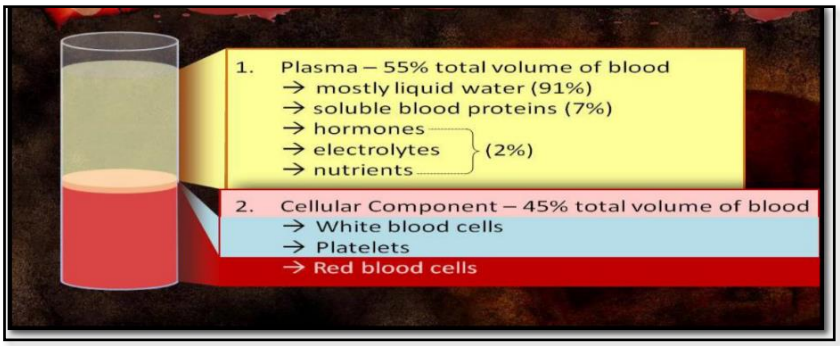

Figure 2. 22. Blood components.

4.4. **Specific components and their function**

A/ Plasma: Plasma performs several functions: transporting blood cells and nutrients; regulating the body's water and mineral salts; irrigating tissues; providing a defense against infections; and coagulating blood. The constituents of plasma are:

A.1. Water (90-92%)

A. 2. Plasma proteins: Plasma proteins are the most abundant substances in the plasma and are present in three major types, namely, albumin, globulins, and fibrinogen. They play specialized roles as follows:

A.2.1. Albumin: (Produced by the liver): It is the smallest among the plasma proteins but makes up the largest percentage (about 60% of total plasma protein). They are responsible for maintain normal plasma osmotic pressure. Albumins also act as carrier molecules free fatty acids, some drugs and steroid hormones.

A.2.2. Globulins (36%): Globulins are of three types, alpha, beta (produced by the liver), and gamma (released by plasma cells), from smallest to largest. Gamma-globulins are called antibodies. The alpha globulins include the high-density lipoproteins (HDL) which are important in carrying fats to the cells for building various substances as well as for energy metabolism. HDL is best known for its role in preventing plaque formation by keeping cholesterol in transport within the blood. Low-density lipoproteins (LDL) are beta globulins which transport fat to the cells for steroid and cell membrane synthesis. It also promotes cholesterol plaque formation which is a risk factor for arterial and heart disease. Antibodies or gamma globulins are also called immunoglobulins. They are produced by the B lymphocytes, a subset of the immune cells. Antibodies are responsible for the body's humoral immune

function, recognizing pathogens via specific receptors and neutralizing them by various mechanisms.

A.2.3. Fibrinogen (4%) (Produced by the liver): Fibrinogen is an important soluble plasma clotting factor precursor, which is converted to a threadlike protein called fibrin on contact with a sticky surface. The fibrin threads formed in this way trap platelets to form the primary platelet clot on which a stable blood clot is formed by the process of coagulation.

A.2.4. Clotting factors and inhibitors: The clotting factors in plasma cause a blood clot to form at the site of any break in the smooth endothelial lining of the blood vessels. This not only prevents blood loss but also protects the body against invading microbes. Coagulation inhibitor proteins prevent the clotting of blood at unwanted locations or times.

A.2.5. Complement proteins: The complement system is another important set of plasma proteins, which are involved in immune and inflammatory reactions in response to many different infectious particles.

As other functions, plasma proteins keep the blood pH slightly alkaline by binding excess hydrogen ions in the blood; also, they can supply amino acids if required by being broken down by macrophages. In addition, they often carriers for small molecules, each binding after absorption from the gut with its own specific protein carrier for transport to the tissue or organ that uses it.

A.3. Inorganic salts (electrolytes): like Ca, Na, PO_4 that are responsible for muscle contraction, transmission of nerve impulses…ect.

A.4. Nutrients: glucose, amino acid, fatty acids and glycerol.

A.5. Waste products: like urea, creatinine and uric acid they are carried in the blood to the kidney for excretion.

A.6. Hormones and gases: (Exp CO_2, steroid and thyroid hormones are carried by plasma proteins).

Note: The buffy coat (< 1%) is the fraction of an anticoagulated blood sample that contains most of the white blood cells and platelets following centrifugation. It is rich in a number of immune cells including leukocytes, granulocytes.

A.7. Formed elements of the Blood - 45% (Cellular content of Blood) :

There are three types of blood cell:

- **Erythrocytes (Red Blood Cells =RBC);**
- **Leukocytes (white blood cells = WBC):** they include monocytes, lymphocytes, neutrophils, eosinophils, and basophils.
- **Platelets (thrombocytes);**

4.5. Blood cells carachteristics

Source of blood cells could comes from different sources:

- Mature blood cells have a relatively short life spine;
- Blood cells are synthesised mainly in the red bone marrow;
- Some lymphocytes, additionally are produced in lymphoid tissue;
- The organ or system responsible for synthesis blood cells are called hematopoietic system and the process of blood cell formation is called hematopoiesis.

Erythrocytes (Red Blood Cell)

Red blood cells are biconcave discs, they have no nucleus, mitochondria. They contain a red coloured protein called hemoglobin (Small size and biconcave shape increase the surface area-to-volume ratio, improving gas exchange, while lack of a nucleus makes additional space for hemoglobin, a key protein used in oxygen transport. Lack of mitochondria keeps red blood cells from using any of the oxygen they are carrying, maximizing the amount delivered to tissues of the body). Their main function is in gas transport, mainly of O_2 but they also carry some CO_2. The biconcave shape increases their surface area for gas exchange, and the thinness of the central portion allows fast entry and exit of gases. Human erythrocytes are 7.5 μm in diameter, 2.6 μm thick at the rim and 0.8 μm thick in the center.

The cells are flexible so they can squeeze through narrow capillaries. The normal concentration of erythrocytes in blood is approximately 3.9- 5.5 million per microliter in women and 4.1-6 million per microliter in men.

Erythrocyte have an average life span of 120 days. Old or damaged red blood cells are broken down in the liver and spleen, and new ones are produced in the bone marrow and which is controlled by the hormone erythropoietin. The process of RBC development from stem cells takes about 7 days and is called erythropoiesis. The immature cells are released into the blood stream as reticulocytes and then mature into erythrocytes over 1-2 days within circulation. During this time, they lose their nucleus and therefore become incapable of division. The

hormone erythropoietin and substances such as iron, folic acid, and vitamin B12 are essential for the production of erythrocytes. Erythropoietin hormone is a glycoprotein hormone produced in the kidneys and stimulates the production of globin (the protein component of Hb), enhances the release reticulocytes in the circulation and enhances reticulocytes maturation to mature RBC.

Hb is the most important constituent of red blood cells. It is responsible for transport of O_2 from lungs to tissues and CO_2 from tissues to lungs. Molecules of hemoglobin is large and complex. They are made up of heme and globin. Heme is made up of iron (in ferrous form) and porphyrin. While globin is a protein that has 4 polypeptides chains (2 alpha and 2 beta). • Each unit of Hb contains 4 units of heme that are united together by the alpha and beta chains of globin. Each unit of heme can combine with one molecule of O_2. So one molecule of Hb can carry four molecule of O_2. Hb with O_2 is called oxyhemoglobin, and Hb without O_2 called deoxyhemoglobin. Hemoglobin does not exist free in the plasma in order to protect hemoglobin from breaking into fragments that would leak out of the bloodstream (through porous capillary walls), and to prevent hemoglobin from making blood more viscous and raising osmotic pressure.

The plasma membrane of erythrocytes are composed of lipids and proteins. Several types of proteins are present including A, B proteins (antigens) and Rh (D) factor responsible for person's blood group **(Figure 2. 23).**

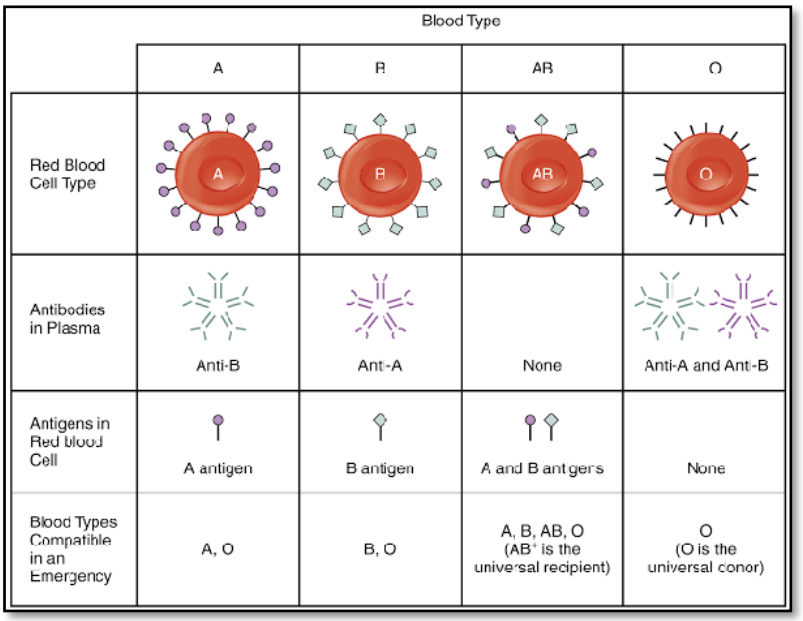

Figure 2. 23. Blood groups.

Leukocytes (White Blood Cells)

Leucocytes are the largest blood cells. They account for only about 1% of the blood volume. Their role is also very different from that of red blood cells: they are primarily involved in immune responses, recognizing and neutralizing invaders such as bacteria and viruses.

Neutrophils represent 60-70% of total WBC. And about 20-30% lymphocytes. While eosinophils are about 3%, basophils 1% and monocytes about 5%. Leucocytes are different from erythrocytes in several ways:

- They are true cells, each leucocyte having a nucleus, mitochondria, and other organelles;
- They do not contain Hb;
- Leucocytes can actively move while erythrocytes do not have mobility of their own;
- Normally erythrocytes do not leave the vascular system but leucocytes can leave vessels and enter the surrounding tissue;
- Most leucocytes have a relatively short life span.

➢ **The granulocyte**

- **Neutrophils**

Also known as polymorphonuclear (PMN) leukocytes, are the most abundant cell type in human blood. Represent about 70% of all leukocytes, they are produced in the bone marrow in large numbers, ~1011 cell per day. Neutrophil development in the marrow takes about 14 days. They are 12-15 μm in diameter with nucleus consisting of 2-5 lobes. The cytoplasm of the neutrophil contains two main types of granules (specific granules and azurophilic granules). The distribution of one enzyme, alkaline phosphatase, corresponded to that of specific granules, while the distribution of peroxidase and six lysosomal enzymes (acid phosphatase, arylsulfatase, beta-galactosidase, beta-glucuronidase, esterase, and 5'-nucleotidase) corresponded to that of azurophil granules. Three main antimicrobial functions are recognized for neutrophils: phagocytosis, degranulation, and the release of nuclear material in the form of neutrophil extracellular traps (NETs).

- **Eosinophils**

The eosinophil is a specialized cell of the immune system. One of the immune system components responsible for combating multicellular parasites and certain infections in vertebrates. This pro inflammatory white blood cell generally has a nucleus with two lobes (bilobed) and cytoplasm filled with approximately 200 large granules containing enzymes and

proteins with different (known and unknown) functions, which contain many chemical mediators, such as eosinophil peroxidase, ribonuclease (RNase), deoxyribonucleases (DNase), lipase, plasminogen, and major basic protein. This protein has ability to kill parasitic worm.

- **Basophils**

Basophils are the least common type of granulocyte. There are about 12-15 μm, contain large cytoplasmic granules which obscure the cell nucleus under the microscope when stained.

The nucleus is divided into irregular lobes or S shaped. Besides, Basophils contain anticoagulant heparin, which prevents blood from clotting too quickly. They also contain the vasodilator histamine, which promotes blood flow to tissues. They are responsible for inflammatory reactions during immune response, as well as in the formation of acute and chronic allergic diseases, including anaphylaxis, asthma, atopic dermatitis and hay fever.

- **The agranulocytes**
- **Lymphocyte**

Lymphocytes are spherical cells, there are small lymphocytes with diameter of 6-8 μm and large lymphocytes with diameter up to 18 μm. The nucleus of lymphocyte are large and rounded. A lymphocyte is a type of white blood cell that is part of the immune system. There are two main types of lymphocytes: B cells and T and natural killer (NK) cells. The B cells produce antibodies that are used to attack invading bacteria, viruses, and toxins. The T cells destroy the body's own cells that have themselves been taken over by viruses or become cancerous. While, NK cells are a part of the innate immune system and play a major role in defending the host from tumors and virally infected cells. NK cells modulate the functions of other cells, including macrophages and T cells, and distinguish infected cells and tumors from normal and uninfected cells.

- **Monocyte**

Monocytes are amoeboid in appearance, and have nongranulated cytoplasm. Although they might occasionally display some azurophil granules and/or vacuoles. With a diameter of 15–22 μm, monocytes are the largest cell type in peripheral blood. Monocytes are mononuclear cells and the ellipsoidal nucleus is often lobulated/indented, causing a bean-shaped or kidney-shaped appearance. They are produced by the bone marrow from precursors called monoblasts, bipotent cells that differentiated from hematopoietic stem cells and they circulate in the

bloodstream for about one to three days and then typically migrate into tissues throughout the body where they differentiate into macrophages and dendritic cells. The life span in the circulation is few days but 60-120 days in the tissues.

In general, monocytes and their macrophage and dendritic cell progeny serve three main functions in the immune system. These are phagocytosis, antigen presentation, and cytokine production.

Platelets

The platelets also called thrombocytes, they are not cells in the strict sense, they are cytoplasmic fragments (2-4 μm in diameter) of extraordinarily large cells called megakaryocytes that reside in the red bone marrow. Each platelet has a peripheral light blue stain transparent zone the hyalomere and a central zone containing granules called the granulomere which contain lots of chemicals that act in the clotting process, (including serotonin, Ca^{2+}, a variety of enzymes, ADP, and platelet derived growth factor (PDGF)).

Platelets are very sticky so appear under light microscope as clumps of cells. Platelets promote blood clotting and help repair gaps in the walls of blood vessels, preventing loss of blood. Platelets, or thrombocytes, are smaller than the red and white blood cells.

When the lining of a blood vessel is damaged (for instance, if you cut your finger deeply enough for it to bleed), platelets are attracted to the wound site, where they form a sticky plug.

The platelets release signals, which not only attract other platelets and make them, become sticky, but also activate a signaling cascade that ultimately converts fibrinogen, a water-soluble protein present in blood plasma, into fibrin (a non-water soluble protein). The fibrin forms threads that reinforce the platelet plug, making a clot that prevents further loss of blood.

- **What happens during red blood cell production (erythropoiesis)?**

Red blood cell production occurs in your bone marrow. An HSC matures into a precursor cell called an erythroblast. An erythroblast becomes an immature red blood cell called a reticulocyte. Finally, a reticulocyte develops into a mature red blood cell.

- **What happens during white blood cell production (leukopoiesis)?**

Although they’re all white blood cells, granulocytes (basophils, eosinophils and neutrophils) have slightly different origins from monocytes and lymphocytes.

- **Granulocyte production**

An HSC follows a development path called the myeloid cell line for granulocyte production. Whene an HSC becomes a precursor cell called a myeloblast then a myeloblast forms a myelocyte, which later becomes a basophil, eosinophil or neutrophil

- **Mononuclear cell production**

Monocytes get made in your bone marrow, while lymphocytes (B-cells, T-cells and natural killer cells) get made in your bone marrow and other lymph tissue like thymus. Monocytes, which means that they're part of the myeloid cell line. They become a precursor cell called a monoblast before maturing into a fully developed monocyte. HSCs that eventually become lymphocytes develop along the lymphoid cell line. HSCs become precursor cells called lymphoblasts. They eventually differentiate into T-cells, B-cells or natural killer cells.

- **Platelet production (thrombopoiesis)**

The process platelet production start with an HSC whichmatures into a precursor cell called a megakaryoblast, then the megakaryoblast becomes a megakaryocyte and in his turn the fragments of the megakaryocyte break off, becoming platelets.

4.6. Coagulation (blood clotting)

Coagulation is the process by which a blood clot is formed in order to stop bleeding, so it is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion and aggregation of platelets, as well as deposition and maturation of fibrin. The process of coagulation is complex and involves many steps and many factors (most of which is proteins). The factors are identified by roman numerals (I – XIII), and given names as shown in the next slide. It involves two main pathways – extrinsic and intrinsic pathways. The extrinsic pathway is initiated by tissue factor produced as a result of damaged blood vessels. The intrinsic pathway is initiated by contact activation.

4.7. Haemostasis: hemostasis

Haemostasis is a complex process involving adhesion of platelets to damaged endothelium, formation of a platelet plug (aggregation), formation of a fibrin network to stabilise the plug, clot retraction and finally fibrinolysis. This involves coagulation, which changes blood from a liquid to a gel, but not always, involves formation of a blood clot. Hemostasis is maintained in the body via three mechanisms.

Vascular spasm

Is produced by vascular smooth muscle cells, and is the blood vessel's first response to injury. The smooth muscle cells are controlled by vascular endothelium, which releases intravascular signals to control the contracting properties. The damaged vessels will constrict (vasoconstrict) which reduces the amount of blood flow through the area and limits the amount of blood loss. Collagen is exposed at the site of injury, the collagen promotes platelets to adhere to the injury site. Platelets release cytoplasmic granules which increase the effect of vasoconstriction.

Platelet plug formation

Platelets adhere to damaged endothelium to form a platelet plug (primary hemostasis) and then degranulate.

- **Primary aggregation:** When platelets come across the injured endothelium cells, they change shape, release granules and ultimately become 'sticky'. Platelets express certain receptors, some of which are used for the adhesion of platelets to collagen.
- **Secondary aggregation:** Platelets release cytoplasmic granules such as adenosine diphosphate (ADP), serotonin and thromboxane A2 and which are potent platelet aggregation, increasing the size of the platelets plug.

Clot formation (coagulation)

Is the actual formation of a blood clot. It results from a chemical "cascade" which begins with the prothrombin activators released by platelets. In the final common pathway, the prothrombin activator converts prothrombin (present in the plasma) to thrombin (an enzyme). Thrombin acts on the plasma protein fibrinogen and converts it into insoluble fibers of fibrin these fibers form a meshwork in which blood get entangled to form a sold clot. The final common pathway (Prothrombin Activator) can be initiated by two processes (pathways). Coagulation may be initiated by either the intrinsic or the extrinsic pathway. Coagulation consists of three pathways, the **extrinsic, intrinsic, and common pathways**, that interact together to form a stable blood clot. The extrinsic and intrinsic coagulation pathways both lead into the final common pathway by independently activating factor X. The extrinsic pathway involves initiation by factor III (i.e., tissue factor) and its interaction with factor VII. Whereas, factors XII, XI, IX, and VIII are utilized in the intrinsic pathway. Then, the common pathway uses factors X, V, II, I, and XIII.

The extrinsic pathway begins when there is injury to the endothelial tissue (i.e., skin tissue), exposing tissue factor **(factor III)** to the blood. Tissue factor then becomes bound with calcium and factor **VIIa to activate factor X**. **Factor VII** is present in the blood and requires vitamin K to be activated.

Meanwhile, **the intrinsic pathway** begins when factor **XII** or the Hageman factor is exposed to collagen, kallikrein, and high molecular weight kininogen (HMWK) and is subsequently activated. **Factor XIIa activates factor XI into XIa**. With a calcium ion, **factor XIa activates factor IX**. Then, factor **IXa, factor VIIIa, and calcium form a complex to activate factor X**. **Factor VIII is found in the blood and is often activated by thrombin (factor IIa).**

The common pathway may result after the activation of factor X at the end of either pathway. The common pathway begins **when factor Xa, Va**, and calcium bind together, forming a prothrombinase complex. **The prothrombinase** complex then activates **prothrombin (factor II)** into **thrombin (factor IIa).** Next, **thrombin cleaves fibrinogen (factor I) into fibrin (factor Ia).** Afterwards, thrombin cleaves the **stabilizing factor (factor XIII) into XIIIa**. **Factor XIIIa binds** with calcium to then create fibrin crosslinks to stabilize the clot. Thrombin has several functions, including activating platelets (cell fragments involved in clot formation) and **activating factors V, VIII, and IX (Figure 2. 24)** .

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium Ions
Factor V	Labile Factor
Factor VII	Stable Factor
Factor VIII	Antihemophilic Factor
Factor IX	Christmas Factor, or Plasma Thromboplastin Component (PTC)
Factor X	Stuart-Prower Factor
Factor XI	Plasma Thromboplastin Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor

Figure 2. 24. The different clotting factors.

4.8. Fibrinolysis

Fibrinolysis is a normal body process. It prevents blood clots that occur naturally from growing and causing problems. Fibrinolysis is tightly controlled by the actions of various cofactors, inhibitors, and receptors, where the plasmin is the main protein that activates fibrinolysis. **Plasmin** is converted from **plasminogen** by tissue plasminogen activator (tPA) and urokinase (up A).

Hematopoiesis

Hematopoiesis is blood cell production. Your body continually makes new blood cells to replace old ones. Hematopoiesis ensures you have a healthy supply of blood cells to supply oxygen to your tissue (red blood cells), fight infection (white blood cells) and clot your blood when you're injured (platelets). Most blood cells get made in your bone marrow is called **medullary hematopoiesis**. Less often, hematopoiesis takes place in other parts of your body, like your liver and spleen. Hematopoiesis that occurs outside of your bone marrow is called **extramedullary hematopoiesis.** Hematopoiesis starts before birth and continues as a cycle throughout life.

Before birth:

- Blood cell production starts when you're still in the uterus. It begins in the yolk sac, a structure that surrounds an embryo at the beginning of pregnancy.
- Toward the end of pregnancy, most blood cell production happens in your bone marrow.
- **Week 3:** A type of red blood cell slightly less developed than the red blood cells that get made during adulthood is made in the yolk sac.
- **Months 2 & 3:** Red blood cells and platelets get made in your liver and spleen. White blood cells get made in your liver, spleen and thymus.
- **Month 5:** Most blood cell production happens in your bone marrow. The thymus, spleen and other lymph tissue also make some types of white blood cells.

After birth:

- Most blood cell production happens in your bone marrow from infancy and into adulthood. Certain types of white blood cells called lymphocytes develop in your thymus, too.

- Disease creates the exception. If you have a condition that prevents your bone marrow from making enough blood cells, hematopoiesis may shift to your blood cell production sites before birth. Blood cell production may shift to your liver, spleen or lymph nodes.
- Hematopoiesis begins with an originator cell common to all blood cell types. It's called a hematopoietic stem cell (HSC).
- An HSC develops into a precursor cell, or "blast" cell. A precursor cell is on track to become a specific type of blood cell, but it's still in the early stages.
- A precursor cell goes through several cell divisions and changes before it becomes a fully mature blood cell.

5. Cartilaginous tissues

5.1. Definition

Cartilage and Bone are specialised forms of connective tissue. Cartilage is thin, avascular, flexible and resistant to compressive forces. Its is made up of cells embedded in an extracellular matrix.

5.2. Functions of cartilage tissue

Several functions of cartilage tissue exists:

- Allows the tissue to bear mechanical;
- Stresses without permanent distortion;
- Supports soft tissues;
- Shock-absorbing because it is resilient;
- Smooth surface allows sliding against it;
- Essential for growth, development of bone.

5.3. Constituents of cartilage

Cartilage is a strong, flexible and semi-rigid supporting tissue. It can withstand compression forces, and yet it can bend. It is made up of cells called chondroblasts and chondrocytes, (chondro - cartilage) and extracellular matrix, made up about 10% aggrecan, 75% water, and a mix of collagen fibres and other constituents **(Figure 2. 25).**

Chondrocytes synthesize and maintain all ECM components and are located in matrix cavities called lacunae. Cartilage does not receive a blood supply and is therefore avascular.

The cells receive nutrition by diffusion from nearby capillaries in the perichondrium. This means that cartilage can never become too thick and the growth/turnover of cells in the cartilage is very slow. Cartilage is aneural, it does not contain any nerves. Therefore, any pain associated with pathology is typically due to irritation of surrounding tissues.

5.4. Types of cartilage

There are three types of cartilage, which differ mostly in the type of fibres they contain:

Hyaline: Most common - has a glassy appearance (hyalos - is greek for glass).

Fibrocartilage: tendon insertions and invertebral discs: reinforced with parallel bundles of collagen fibres.

Elastic cartilage: external ear and epiglottis: flexible and resilient - has elastic fibres as well as collagen fibres.

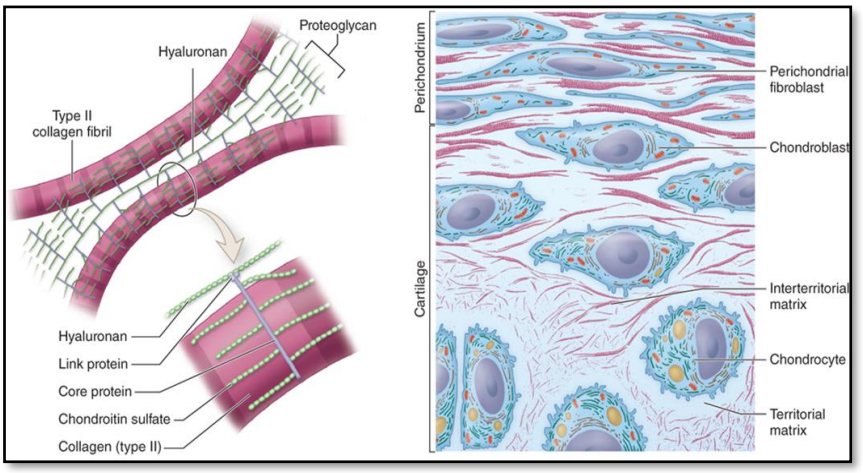

Figure 2. 25. *The structure of cartilage matrix and cells.*

Hyaline cartilage

The word hyaline means "glass-like", and hyaline cartilage is a glossy, greyish-white tissue with a uniform appearance. The most common of the three types, is homogeneous and semitransparent in the fresh state. In adults hyaline cartilage is located in the articular surfaces of movable joints, in the walls of larger respiratory passages (nose, larynx, trachea, bronchi), in the ventral ends of ribs, where they articulate with the sternum, and in the epiphyseal plates of long bones, where it makes possible longitudinal bone growth. In the embryo, hyaline cartilage forms the temporary skeleton that is gradually replaced by bone. It is mostly made up of collagen (type II) with relatively few elastic fibres and is surrounded by a perichondrium **(Figure 2. 26).**

- **Function of hyaline cartilage**

- Hyaline cartilage provides support and flexibility to different parts of the body;
- It is found in structures like the nose, ears, and areas where the ends of the ribs attach to the sternum, and in parts of the respiratory system like the trachea and larynx, where it helps give these parts their form but also gives them some flexibility;

- When hyaline cartilage is on the articular surfaces of bones (the surfaces at joints), it is called articular cartilage. Articular cartilage functions as a shock absorber and reduces friction between bones where they meet at joints.

➢ **Structure of hyaline cartilage.**

- **Matrix**

The dry weight of hyaline cartilage is nearly 40% collagen embedded in a firm, hydrated gel of proteoglycans and structural glycoproteins. In routine histology preparations, the proteoglycans make the matrix generally basophilic and the thin collagen fibrils are barely discernible. Most of the collagen in hyaline cartilage is type II, although small amounts of minor collagens are also present.

- **Aggrecan**

Aggrecan (250 kDa), with approximately 150 GAG side chains of chondroitin sulfate and keratan sulfate, is the most abundant proteoglycan of hyaline cartilage. Hundreds of these proteoglycans are bound noncovalently by link proteins to long polymers of hyaluronan. These proteoglycan complexes bind further to the surface of type II collagen fibrils. Water bound to GAGs in the proteoglycans constitutes up to 60%-80% of the weight of fresh hyaline cartilage.

Another important component of cartilage matrix is the structural multiadhesive glycoprotein chondronectin. Like fibronectin in other connective tissues, chondronectin binds specifically to GAGs, collagen, and integrins, mediating the adherence of chondrocytes to the ECM. Immediately surrounding each chondrocyte, the ECM is relatively richer in GAGs than collagen, often causing these areas of territorial matrix to stain differently from the intervening areas of interterritorial matrix.

- **Chondrocytes**

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

oxygen tension. Hyaline cartilage cells metabolize glucose mainly by anaerobic glycolysis. Nutrients from the blood diffuse to all the chondrocytes from the cartilage surface, with movements of water and solutes in the cartilage matrix promoted by intermittent tissue compression and decompression during body movements.

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

- **Perichondrium**

Except in the articular cartilage of joints, a layer of dense connective tissue, the perichondrium, covers all hyaline cartilage, which is essential for the growth and maintenance of cartilage.

The outer region of the perichondrium consists largely of collagen type I fibers and fibroblasts, but an inner layer adjoining the cartilage matrix also contains mesenchymal stem cells which provide a source for new chondroblasts that divide and differentiate into chondrocytes.

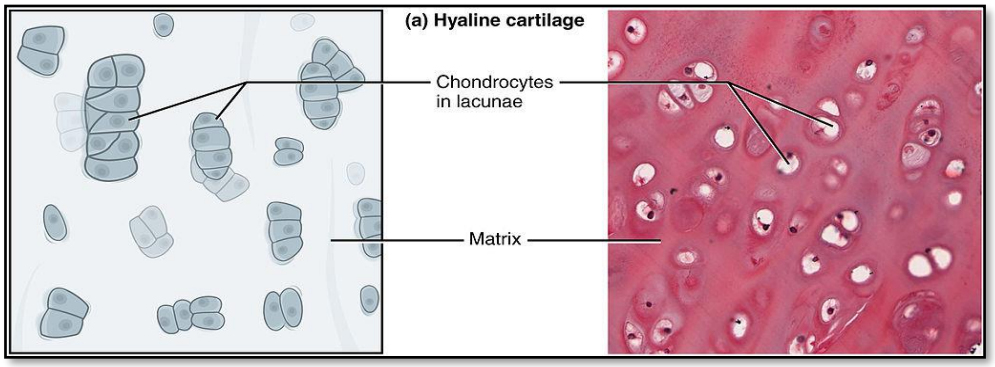

Figure 2. 26. Structure of hyaline cartilage.

Fibrocartilage

Fibrocartilage does not have a perichondrium. It has type II collagen, as do the other two types of cartilage. It is characterized by thick, coarse bundles of type I collagen fi bers that alternate with parallel groups of columns (or rows) of chondrocytes within the matrix **(Figure 2. 27).** The chondrocytes of fibrocartilage are smaller and much less numerous than in the other two types of cartilage and are often arranged in columns or rows. Because fibrocartilage has no

perichondrium, its growth depends on interstitial growth. Fibrocartilage is resistant to tearing and compression, can accommodate great pressure. It is found in areas where support and tensile strength are required, such as intervertebral disks, the pubic symphysis, and the insertions of tendons and ligaments.

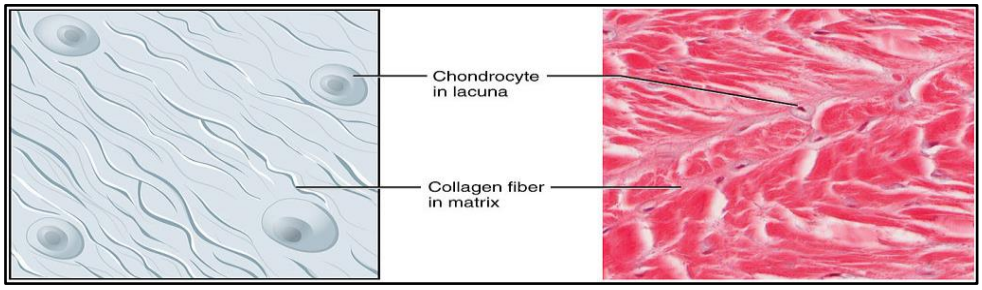

Figure 2. 27. Diagram showing the structure of fibrocartilage.

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Elastic cartilage

Elastic cartilage is similar to hyaline cartilage except for its rich network of elastic fi bers, arranged in thick bundles in the matrix. This type of cartilage has a perichondrium, as does hyaline cartilage, and it also contains type II collagen in the matrix. The chondrocytes of elastic cartilage are more abundant and larger than those of hyaline cartilage. Elastic cartilage is located in areas where elasticity and fi rm support are required, such as the epiglottis and larynx, auditory canal and tube, and the pinna of the ear, which is able to recover its shape after deformation (**Figure 2. 28).**

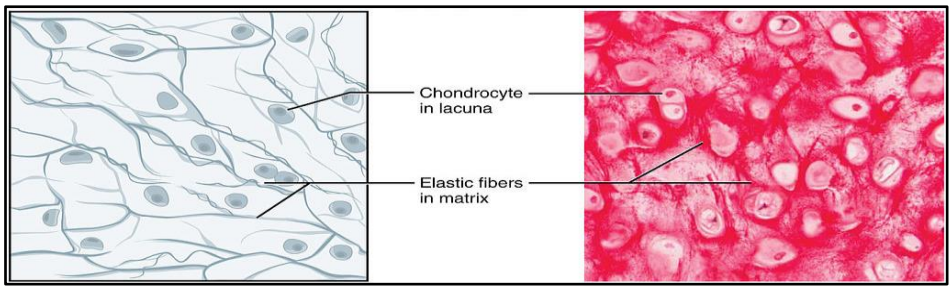

Figure 2. 28. Diagram showing the structure of elastic cartilage.

5.5. Cartilage formation and growth

In general the terms “chondroblasts” and “chondrocytes” respectively refer to the cartilage cells during and after the period of rapid proliferation. During embryonic development, the cartilage differentiation takes place primarily from the center outward;

therefore the more central cells have the characteristics of chondrocytes, whereas the peripheral cells are typical chondroblasts.

The superficial mesenchyme develops as the perichondrium. Once formed, the cartilage tissue enlarges both by interstitial growth, involving mitotic division of preexisting chondrocytes, and by appositional growth, which involves chondroblast differentiation from progenitor cells in the perichondrium. In both cases, the synthesis of matrix contributes greatly to the growth of the cartilage. Appositional growth of cartilage is more important during postnatal development, while, interstitial growth in cartilaginous regions within long bones is important in increasing the length of these structures. So**,** cartilage can expand by producing new cartilaginous tissue both from inside and outside the formed cartilage:

Appositional growth – Chondroblasts, found along the surface of the inner cellular layer of the perichondrium, continuously produce new matrix.

Interstitial growth – During childhood and adolescence, new cartilaginous tissue is formed from within the cartilage as the chondrocytes divide and produce new matrix.

6. Bone tissue

6.1. Definition

Bone tissue is a mineralized and viscous-elastic connective tissue, which exerts crucial functions in our body such as support and protection of other tissues and mineral storage. Bone can adapt itself through a remodeling process, which is controlled by its cells, various local and systemic factors.

Bone is made up of compact tissue (the hard, outer layer) and cancellous tissue (the spongy, inner layer that contains red marrow). Bone tissue is maintained by bone-forming cells called osteoblasts and cells that break down bone called osteoclasts. Bones also contain blood vessels, nerves, proteins, vitamins, and minerals. Also called osseous tissue. Bone tissue makes up the individual bones of the human skeletal system and the skeletons of other vertebrates and, among modern vertebrates, it is found only in bony fish and higher classes.

6.2. Functions of bone tissue

The functions of bone includs:

- Structural support for the mechanical action of soft tissues, such as the contraction of muscles and the expansion of lungs;
- Protection of soft organs and tissues, as by the skull;
- Provision of a protective site for specialized tissues such as the blood-forming system (bone marrow);
- A mineral reservoir, whereby the endocrine system regulates the level of calcium and phosphate in the circulating body fluids.

6.3. Bone morphology

Grossly, bone tissue is organized into a variety of shapes and configurations adapted to the function of each bone.

Broad, flat plates, such as the scapula (a), serve as anchors for large muscle masses.

Hollow, thick-walled tubes, such as the femur (b), the radius, and the ulna, support weight or serve as a lever arm. Their external shape than by their basic structure distinguishes these different types of bone more. All bones have an exterior layer called cortex that is smooth, compact, continuous, and of varying thickness. In its interior, bony tissue is arranged in a network of intersecting plates and spicules called trabeculae, which vary in amount in different bones and enclose spaces filled with blood vessels and marrow.

6.4. Macroscopic bone structure

Long bones are composed of both cortical and cancellous bone tissue. They consist of several areas. The epiphysis is located at the end of the long bone and is the parts of the bone that participate in joint surfaces. The diaphysis is the shaft of the bone and has walls of cortical bone and an underlying network of trabecular bone. The epiphyseal growth plate lies at the interface between the shaft and the epiphysis and is the region in which cartilage proliferates to cause the elongation of the bone. The metaphysis is the area in which the shaft of the bone joins the epiphyseal growth plate **(Figure 2.29).**

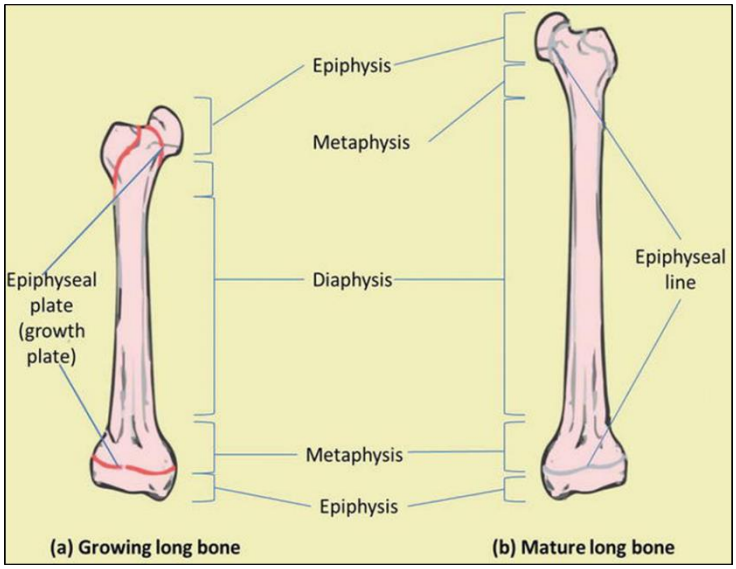

Figure 2. 29. Bone macrostructure.

(a) Growing long bone showing epiphyses, epiphyseal plates, metaphysis and diaphysis.

(b) Mature long bone showing epiphyseal lines

6.5. Bone cells

Microscopically, bone consists of hard, apparently homogeneous intercellular material, within or upon which can be found four characteristic cell types **(Figure 2. 30):**

Osteoblasts

Osteoblasts are cuboidal cells that are located along the bone surface comprising 4–6% of the total resident bone cells and are largely known for their bone forming function. Some of these osteoblasts show cytoplasmic processes towards the bone matrix and reach the osteocyte processes, At this stage, the mature osteoblasts can undergo apoptosis or become osteocytes or bone lining cells. These cells show morphological characteristics of protein synthesizing cells, including abundant rough endoplasmic reticulum and prominent Golgi apparatus, as well as

various secretory vesicles. So, are responsible for the synthesis and deposition on bone surfaces of the protein matrix of new intercellular material. The osteoblasts secrete the osteoid toward the bone matrix. Osteoblasts are derived from mesenchymal stem cells. The transition of preosteoblasts to mature osteoblasts is characterized by an and the fibrillar phases.

These findings suggest that besides professional phagocytes, osteoblasts are also able to engulf and degrade apoptotic bodies during alveolar bone formation

- **Function**

The synthesis of bone matrix and which occurs in two main steps: deposition of organic matrix and its subsequent mineralization.

- **Produce**

In the 1st phase of bone matrix synthesis : collagen type I - noncollagen proteins (osteocalcin « OCN », osteonectin, sialoprotein « BSP» II, and osteopontin), and proteoglycan including decorin and biglycan, which form the organic matrix. While in the 2nd phase, there is production of matrix vesicles, and which are released from the apical membrane domain of the osteoblasts into the newly formed bone matrix rich in phosphatases (alkaline phosphatase, pyrophosphatase).

Bone lining cells

Bone lining cells are quiescent flat shaped osteoblasts that cover the bone surfaces,where neither bone resorption nor bone formation occurs. These cells exhibit a thin and flat nuclear profile; its cytoplasm extends along the bone surface and displays few cytoplasmic organelles such as profiles of rough endoplasmic reticulum and Golgi apparatus. Some of these cells show processes extending into canaliculi, and gap junctions are observed between adjacent bone lining cells and between these cells and osteocytes. The secretory activity of bone lining cells depends on the bone physiological status, whereby these cells can reacquire their secretory activity, enhancing their size and adopting a cuboidal appearance.

- **Functions**

Bone lining cells functions are not completely understood, but it has been shown that these cells prevent the direct interaction between osteoclasts and bone matrix, when bone resorption should not occur, and participate in osteoclast differentiation. Moreover, the bone

lining cells, together with other bone cells, are an important component of the BMU (Bone Remodeling Unit), an anatomical structure that is present during the bone remodeling cycle

Osteocytes

Comprise 90–95% of the total bone cells, are the most abundant and long-lived cells, with a lifespan of up to 25 years. Osteocytes are osteoblasts that have been trapped within intercellular material, residing in a cavity (lacuna) and communicating with other osteocytes as well as with free bone surfaces by means of extensive filamentous protoplasmic extensions that occupy long, meandering channels (canaliculi) through the bone substance. With the exception of certain higher orders of modern fish, all bone, including primitive vertebrate fossil bone, exhibits an osteocytic structure.

Osteocytes are derived from Mesenchymal stem cells (MSCs) lineage through osteoblast differentiation. In this process, four recognizable stages have been proposed: osteoid-osteocyte, preosteocyte, young osteocyte, and mature osteocyte, At the end of a bone formation cycle, a subpopulation of osteoblasts becomes osteocytes, where the number of organelles such as rough endoplasmic reticulum and Golgi apparatus decreases, and the nucleus-to cytoplasm ratio increases, which correspond to a decrease in the protein synthesis and secretion.

During osteoblast/osteocyte transition, cytoplasmic process starts to emerge before the osteocytes have been encased into the bone matrix but the process is not well understood. Once the stage of mature osteocyte totally entrapped within mineralized bone matrix is accomplished, several of the previously expressed osteoblast markers such as OCN, BSPII, collagen type I, and ALP are downregulated. Whereas the osteocyte cell body is located inside the lacuna, its cytoplasmic processes (up to 50 per each cell) cross tiny tunnels that originate from the lacuna space called canaliculi, forming the osteocyte lacunocanalicular system. These cytoplasmic processes are connected to other neighboring osteocytes processes by gap junctions, as well as to cytoplasmic processes of osteoblasts and bone lining cells on the bone surface, facilitating the intercellular transport of small signaling molecules such as prostaglandins and nitric oxide among these cells.

In addition, the osteocyte lacunocanalicular system is in close proximity to the vascular supply, whereby oxygen and nutrients achieve osteocytes. The osteocytes act as mechanosensors as their interconnected network has the capacity to detect mechanical pressures and loads, thereby helping the adaptation of bone to daily mechanical forces.

By this way, the osteocytes seem to act as orchestrators of bone remodeling, through regulation of osteoblast and osteoclast activities. Moreover, osteocyte apoptosis has been recognized as a chemotactic signal to osteoclastic bone resorption. Thus, the shape and spatial arrangement of the osteocytes are in agreement with their sensing and signal transport functions, promoting the translation of mechanical stimuli into biochemical signals, a phenomenon that is called piezoelectric effect.

Osteoclasts

Osteoclasts are terminally differentiated multinucleated cells. Originate from mononuclear cells of the hematopoietic stem cell lineage, under the influence of several factors, among these factors the macrophage colony-stimulating factor (M-CSF), secreted by osteoprogenitor mesenchymal cells and osteoblasts, and RANK ligand, secreted by osteoblasts, osteocytes, and stromal cells, are included, these factors promote the activation of transcription factors and gene expression in osteoclasts.

Osteoclasts have an abundant mitochondria acidophilic cytoplasm and great number of lysosomes. It is working from bone surfaces; resorb bone by direct chemical and enzymatic attack.

There are two distinct features of an osteoclast: a ruffled border and a sealing zone. The ruffled border is composed of a convoluted membrane that develops by the merging of secretory lysosomes with the plasma membrane. The sealing zone contains an actin filament ring, which surrounds the ruffled border, isolating the acidified microenvironment inside the cell from the general extracellular space. Protons and enzymes, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, and matrix metalloproteinase-9 (MMP-9) are transported into a compartment called Howship lacuna leading to bone degradation (a ruffled border region).

Abnormal increase in osteoclast formation and activity leads to some bone diseases such as osteoporosis, where resorption exceeds formation causing decreased bone density and increased bone fractures. Findings indicate that osteoclasts are not only bone resorbing cells, but also a source of cytokines that influence the activity of other cells

- **Functions**

Osteoclasts they indirectly respond to calcium-regulating hormones into the bone matrix, which affects the coupling of bone resorption to bone formation. Also, they retain features of

other myeloid cells, including cytokine production and antigen regulation. This ability gives osteoclasts the potential to affect the immune response to several conditions.

Besides those roles, osteoclasts have a function in bone resorption, where there are a few factors that initiate the process of bone resorption. The main determining factor is the body's calcium level. When the blood calcium levels decrease, the parathyroid gland (located in the neck) initiates the secretion of parathyroid hormone (PTH.) PTH accelerated the resorption process to replenish the blood's calcium levels. Other initiating factors include conditions such as psoriatic arthritis, disuse, lack of stimuli, and old age. The bone resorption process begins with the polarization of osteoclasts, which leads to the formation of the bone-apposed ruffled membrane. The osteoclast then attaches itself to the surface of the bone, with the sealing zone forming an isolated microenvironment. The ruffled membrane then secretes hydrochloric acid to dissolve the bone material, and the demineralized bone matrix is broken down by enzymes cathepsin K and matrix metalloprotease. Calcium and phosphate are produced in this process, and they find their way into the blood. In order to regulate this process, the parathyroid gland reduces the amount of parathyroid hormone when it detects that the calcium levels in the blood are too high, leading to the inactivation of osteoclasts.

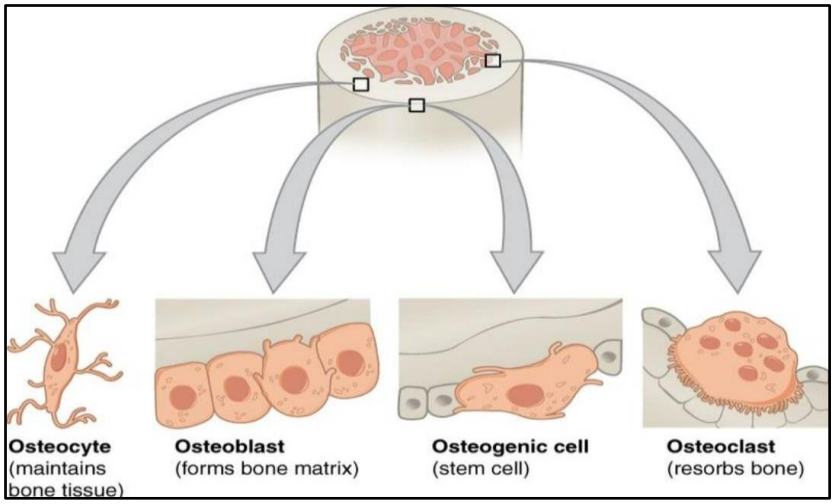

Figure 2. 30. *Bone cells.*

6.6. Extracellular bone matrix

Bone is composed by inorganic salts and organic matrix. The inorganic material of bone consists predominantly of phosphate and calcium ions; however, significant amounts of bicarbonate, sodium, potassium, citrate, magnesium, carbonate, fluorite, zinc, barium, and strontium are also present. Calcium and phosphate ions nucleate to form the hydroxyapatite crystals, together with collagen, the noncollagenous matrix proteins form a scaffold for

hydroxyapatite deposition and such association is responsible for the typical stiffness and resistance of bone tissue.

The organic matrix contains collagenous proteins (90%), predominantly type I collagen, and noncollagenous proteins including osteocalcin, osteonectin, osteopontin, fibronectin and bone sialoprotein II, bone morphogenetic proteins (BMPs), and growth factors.

There are also small leucine-rich proteoglycans including decorin, biglycan, lumican, osteoaderin, and seric proteins.

Besides, it has been demonstrated that there is a variation in the concentration of bone matrix proteins with age, nutrition, disease, and antiosteoporotic treatments which may contribute to postyield deformation.

6.7. The bone remodeling cycle

The remodeling cycle consists of three consecutive phases: resorption, during which osteoclasts digest old bone; reversal, when mononuclear cells appear on the bone surface; and formation, when osteoblasts lay down new bone until the resorbed bone is completely replaced. Bone remodeling serves to adjust bone architecture to meet changing mechanical needs and it helps to repair microdamages in bone matrix preventing the accumulation of old bone.

6.8. Types of bone tissue

There are two types of bone tissue: compact and spongy. The names imply that the two types differ in density, or how tightly the tissue is packed together.

Compact bone

Compact bone consists of closely packed osteons or haversian systems; The osteon consists of a central canal called the osteonic (haversian) canal, which is surrounded by concentric rings (lamellae) of matrix. Between the rings of matrix, the bone cells (osteocytes) are located. In compact bone, the haversian systems are packed tightly together to form what appears to be a solid mass.

Spongy (Cancellous) bone

Spongy (cancellous) bone is lighter and less dense than compact bone. Spongy bone consists of plates (trabeculae) and bars of bone adjacent to small, irregular cavities that contain red bone marrow. The canaliculi connect to the adjacent cavities, instead of a central haversian canal, to receive their blood supply.

6.9. Classification of bones

Long Bones

They consist of a long shaft with two bulky ends or extremities. They are primarily compact bone but may have a large amount of spongy bone at the ends or extremities. Long bones include bones of the thigh, leg, arm, and forearm.

Short Bones

Short bones are roughly cube shaped with vertical and horizontal dimensions approximately equal. They consist primarily of spongy bone, which is covered by a thin layer of compact bone. Short bones include the bones of the wrist and ankle.

Flat Bones

Flat bones are thin, flattened, and usually curved. Most of the bones of the cranium are flat bones.

Irregular Bones

Bones that are not in any of the above three categories are classified as irregular bones. They are primarily spongy bone that is covered with a thin layer of compact bone. The vertebrae and some of the bones in the skull are irregular bones.

6.10. Bone growth

Oppositional bone growth (Lengthening of long bones)

Bones continue to grow in length until early adulthood. The lengthening is stopped in the end of adolescence which chondrocytes stop mitosis and plate thins out and replaced by bone, then diaphysis and epiphyses fuse to be one bone. The rate of growth is controlled by hormones. When the chondrocytes in the epiphyseal plate cease their proliferation and bone replaces the cartilage, longitudinal growth stops. The longitudinal growth of long bones continues until early adulthood at which time the chondrocytes in the epiphyseal plate stop proliferating and the epiphyseal plate transforms into the epiphyseal line as bone replaces the cartilage.

The epiphyseal plate is the area of growth in a long bone. It is a layer of hyaline cartilage where ossification occurs in immature bones. On the epiphyseal side of the epiphyseal plate, cartilage is formed. On the diaphyseal side, cartilage is ossified, allowing the diaphysis to grow in length **(Figure 2. 31).**

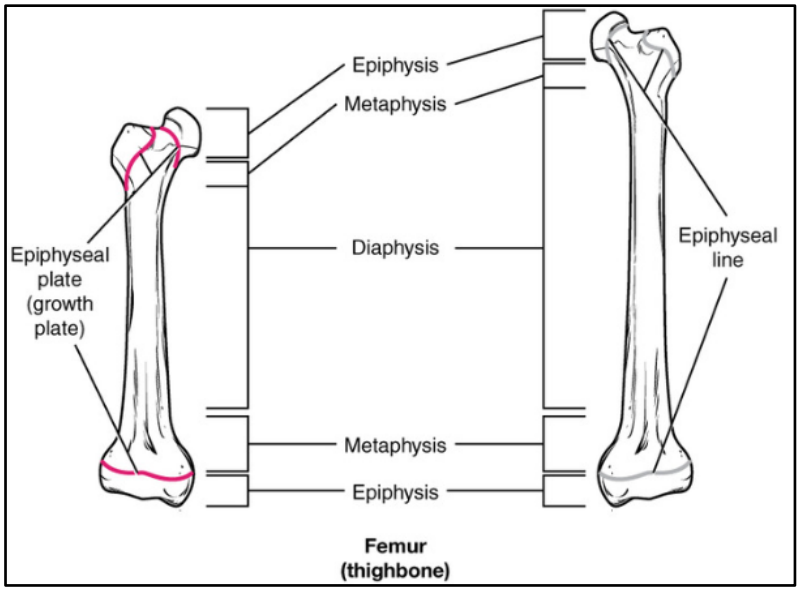

Figure 2. 31. Metaphysis.

Appositional bone growth (Thickening of long bones)

When bones are increasing in length, they are also increasing in diameter; diameter growth can continue even after longitudinal growth stops. Appositional growth is the process by which old bone that lines the medullary cavity is reabsorbed and new bone tissue is grown beneath the periosteum, increasing bone diameter **(Figure 2. 32).**

Osteoclasts, cells that work to break down bone, resorb old bone that lines the medullary cavity. At the same time, osteoblasts via intramembranous ossification, produce new bone tissue beneath the periosteum. The erosion of old bone along the medullary cavity and the deposition of new bone beneath the periosteum not only increase the diameQter of the diaphysis, but also increase the diameter of the medullary cavity. This process is called modeling

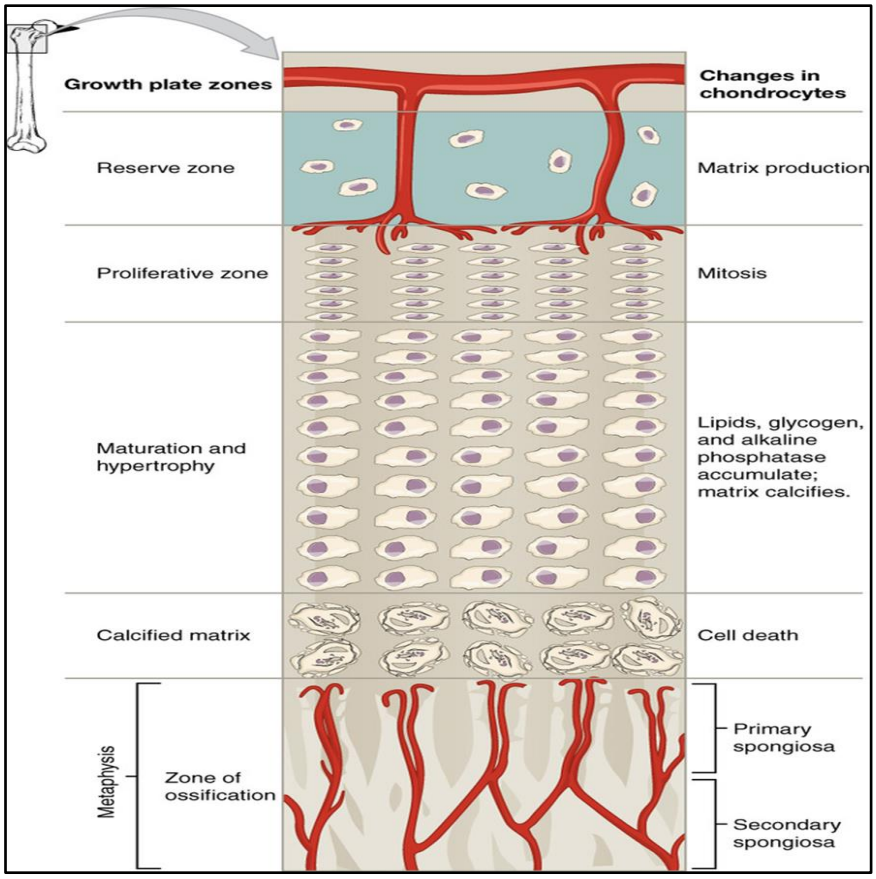

Figure 2. 32. Longitudinal bone growth.

This illustration shows the zones bordering the epiphyseal plate of the epiphysis. The topmost layer of the epiphysis is the reserve zone. The second zone, the proliferative zone, is where chondrocytes are continually undergoing mitosis. The next zone is the zone of maturation and hypertrophy where lipids, glycogen, and alkaline phosphatase accumulate, causing the cartilaginous matrix to calcify. The following zone is the calcified matrix where the chondrocytes have hardened and die as the matrix around them has calcified. The bottom-most row is the zone of ossification which is part of the metaphysis. The newly-deposited bone tissue at the top of the zone of ossification is called the primary spongiosa, while the older bone is labeled the secondary spongiosa.

7. Muscle tissue

7.1. Definition

Muscle is a highly cellular and vascular tissue specialized for contraction via the interaction of myofilaments (between thin and thick filaments); it is responsible for locomotion and movement of the various body parts**.** In addition to movement, muscle contraction also fulfills some other important functions in the body, such as posture, joint stability, and heat production. Muscles make up the bulk of the body and account for 1/3 of its weight. Where, blood vessels and nerves run to every muscle, helping control and regulate each muscle's function.

Muscle cells, which have an elongated shape, are referred to as striated muscle cells or smooth muscle cells, depending on whether or not they have a regular arrangement of myofibrillar contractile proteins, called myofilaments.

Striated muscle cells are characterized by alternating light and dark transverse bands, a feature absent in smooth muscles. There are two types of striated muscles: skeletal muscles, which make up the majority of the body's voluntary muscle mass, and cardiac muscle, which is involuntary and found almost exclusively in the heart. Smooth muscle cells, on the other hand, are located in the walls of blood vessels, visceral organs, and the dermis of the skin.

7.2. Muscle tissue types

Muscle tissue can be categorized into skeletal muscle tissue, cardiac muscle tissue, and smooth muscle tissue.

7.2.1. Skeletal muscle tissue

▪ Skeletal muscle structure

Skeletal muscle is one of the three significant muscle tissues. Each skeletal muscle is considered an organ, and it's made up of connective tissue layers, muscle fibers, blood vessels, and nerves. Skeletal muscles attach to the bones through tendons or through a direct attachment.

Because skeletal muscle cells are long and cylindrical, they are commonly referred to as muscle fibers. Skeletal muscle consists of long, multinucleated, cylindrical cells, measuring between 20 and 130 μm, which contract voluntarily to allow movement of the body or its parts.

Striated skeletal muscle is surrounded by an epimysium, which is an outer layer of connective tissue. The prefix "epi" means upon or over (epidermis is the layer upon your skin),

and "mysium" comes from a Greek word that means "muscle." Therefore, the epimysium is a layer of connective tissue that is over or upon the entire muscle organ.

The muscle fibers are bunched together into something called fascicles, which means "bundles." These fascicles are surrounded by connective tissue called perimysium. "Peri" means "around," and again, "mysium" refers to muscle. So the perimysium is around the fascicles that bundle up these muscle fibers. Perimysium, a dense connective tissue less rich in collagen, derives from the epimysium. Inside the fascicles, another connective tissue layer called the endomysium surrounds individual muscle cells (**Figure 2. 33).**

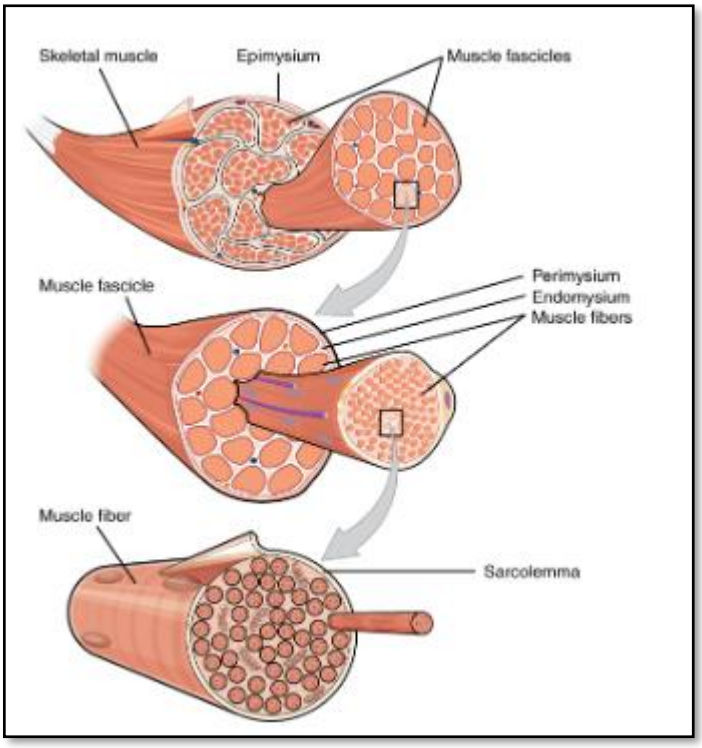

Figure 2. 33. Skeletal muscle structure.

Passing to the individual muscle cells, which are called muscle fibers. These fibers are long and cylindrical, and they contain several nuclei. The nuclei have a peripheral position and are located just below the cell membrane. These muscle fibers are wrapped in a cell membrane called sarcolemma. Within each muscle fiber are myofibrils—long cylindrical structures that lie parallel to the muscle fiber. Myofibrils run the entire length of the muscle fiber, and because they are only approximately 1.2 µm in diameter, hundreds to thousands can be found inside one muscle fiber. They attach to the sarcolemma at their ends, so that as myofibrils shorten, the entire muscle cell contracts.

Satellite cells, small in size and with a single nucleus, play a regenerative role and nestle in slight depressions on the surface of the muscle cell, sharing the outer lamina of the muscle fiber. Their nucleus has a denser and coarser chromatin network than that of the muscle cell. The muscle cells of skeletal striated muscles are also called rhabdomyocytes.

The cytoplasm of muscle fibers is referred to as sarcoplasm, and the specialized smooth endoplasmic reticulum, which stores, releases, and retrieves calcium ions (Ca++) is called the sarcoplasmic reticulum (SR).

For the the structure of a sarcomere, which is the functional unit of a skeletal muscle, it looks like a zigzag sections that mark the end point of each sarcomere. These are called Z discs or Z lines, and they allow for the attachment of the thin (actin) filaments, as well as an elastic protein called titin.

Each sarcomere contains thin (actin) filaments and thick (myosin) filaments. The thin (actin) filaments, anchor to the Z disc. Because the actin and its troponin-tropomyosin complex **(Figure 2. 34),** (projecting from the Z-discs toward the center of the sarcomere) form strands that are thinner than the myosin, it is called the thin filament of the sarcomere. Likewise, because the myosin strands and their multiple heads (projecting from the center of the sarcomere, toward but not all to way to, the Z-discs) have more mass and are thicker, they are called the thick filament of the sarcomere. The thick (myosin) filaments, attach to an elastic, springy protein called titin (**Figure 2. 34),** which then attaches to the Z disc. The actin and myosin filaments engage during muscle contraction. The “M lines” or “M bands” anchor the center of the myosin filaments, holding them together while also acting as a shock absorber.

The sections are devided into bands or zones where the arrangement of filaments within these bands accounts for the striated (striped) appearance of the skeletal muscle fibers **(Figure 2. 35).** That’s an important characteristic.

A band: First, there is an “A band” on each sarcomere, which is a section that contains the entire length of a thick myosin filament, along with overlapping portions of the thin actin filaments. This section makes up the dark part of the striation pattern.

I band: The “I band” is the section of the sarcomere that surrounds the Z disc and contains only thin (actin) filaments. This section makes up the lighter band in the striation pattern.

H zone: The H zone is the section within the A band that consists of the thick myosin filaments and its embedded M lines. There are no thin filaments in this section of the sarcomere when it is relaxed.

Z disc: And again, the Z disc is the zig zag portion that marks the end of each sarcomere and allows for the attachment of actin filaments and titin.

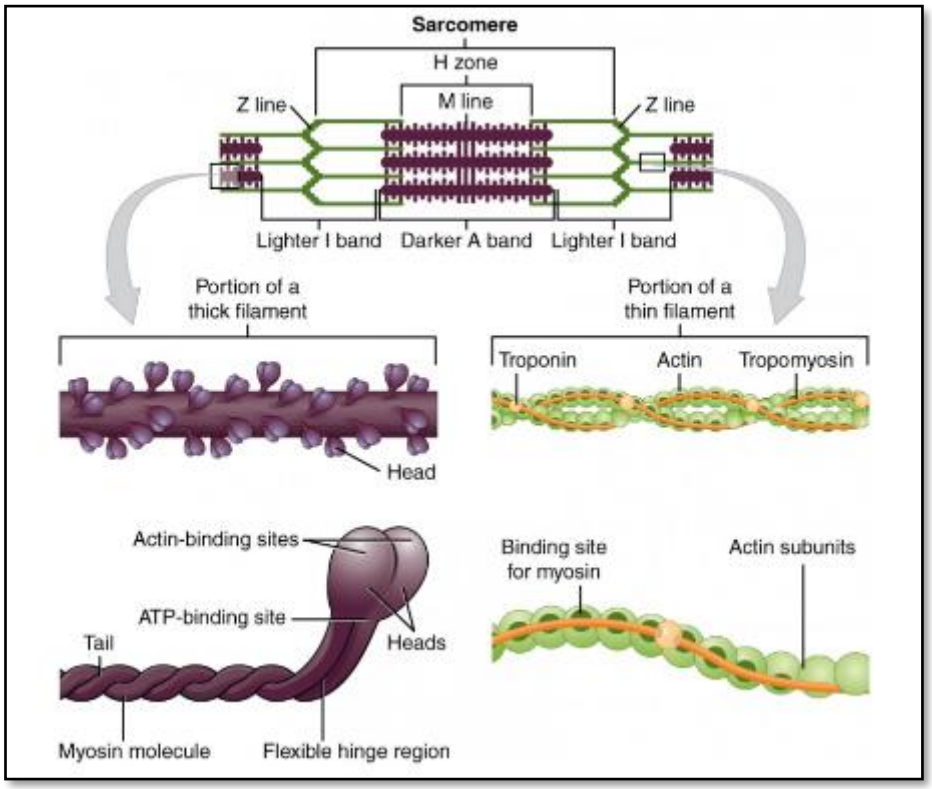

Figure 2. 34. Muscle fiber

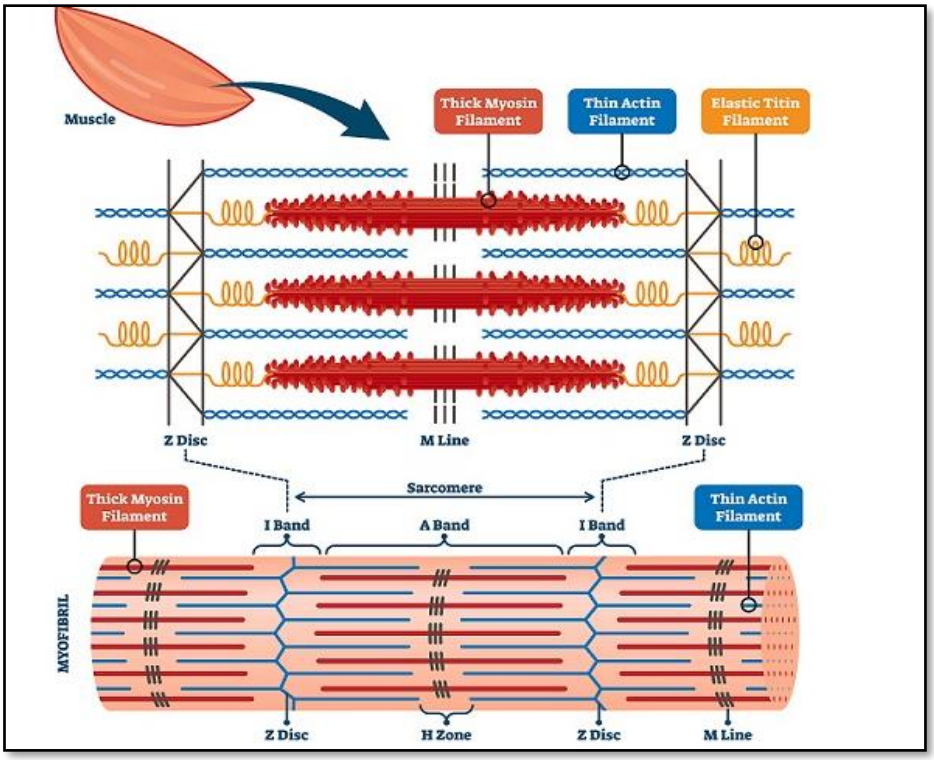

Figure 2. 35. Structure of sarcomere.

The T-system (transverse tubules) is a collection of transverse canaliculi that are tubular invaginations of the plasma membrane surrounding the myofibrils at the A-band I-band junctions. These tubules branch and anastomose but generally remain in a single plane. Each sarcomere has a series of T-tubules at each A- and I-band interface. Thus, the T-tubules extend deep into the fiber and facilitate the conduction of depolarization waves along the sarcolemma.

Striated muscle fibers have numerous mitochondria, elongated and aligned between the myofibrils. Striated muscle fibers are rich in glycogen and lipofuscin granules dispersed in the sarcoplasm.

The cytoplasm (sarcoplasm) of the muscle cell contains longitudinal networks of cylindrical myofibrils, each 1 to 2 μm in diameter. They extend the entire length of the cell and are precisely aligned with neighboring myofibrils. This parallel arrangement of myofibrils is responsible for the transverse striations of light and dark bands characteristic of skeletal muscle observed in longitudinal section.

So, myofibrils are heterogeneous, consisting of a regular succession of dark bands or disks, A-disks (anisotropic with polarized light) and light bands or disks, I-bands (isotropic with

polarized light). The center of each A-band is occupied by a pale area, the H-band, which is divided by the M-striation. Each I-band is bisected by a thin dark line, the Z-disk (Z-line). The region of the myofibril between two successive Z-disks, known as the sarcomere, is 2.5 μm long and is considered the contractile unit of skeletal muscle fibers.

▪ **The neuromuscular junction**

Another specialization of the skeletal muscle is the site where a motor neuron's terminal meets the muscle fiber—called the neuromuscular junction (NMJ). The structure of NMJ can be divided into three main parts: a presynaptic part (nerve terminal), the postsynaptic part (motor endplate), and an area between the nerve terminal and motor endplate (synaptic cleft).

Nerve Terminal: These nerve endings are called nerve terminals or terminal boutons. The nerve terminal membrane has areas of membrane thickening called active zones. Active zones have a family of SNAP proteins (syntaxins and synaptosomal-associated protein 25) and rows of voltage-gated calcium (Ca) channels. A nerve terminal also has potassium channels on its membrane and contains mitochondria, endoplasmic reticulum, and synaptic vesicles (SVs).

Synaptic Cleft / junctional cleft: Synaptic Cleft / Junctional Cleft: The space between the nerve terminal and the plasma membrane of muscle is called synaptic/junctional cleft.

Motor End Plate: forms the postsynaptic part of NMJ. It is the thickened portion of the muscle plasma membrane (sarcolemma). It corresponds to the plasma membrane of the rhabdomyocyte. It is at this level that the receptors for chemical mediators are located.

▪ **Skeletal muscle contraction**

Skeletal muscle contraction initiation and execution occur in the following steps **(Figure 2.36) .**

- An action potential (AP) travels along a motor nerve to its endings on muscle fibers.
- At each motor nerve ending, the nerve secretes acetylcholine (ACh).
- ACh acts locally on the muscle fiber membrane to open ACh-gated cation channels.
- The opening of ACh-gated channels allows large quantities of sodium (Na^+) ions to diffuse to the interior of the muscle fiber membrane.
- This action causes a local depolarization, leading to the opening of voltage-gated sodium (Na^+) channels, which initiates an AP at the membrane.

- The AP depolarizes the muscle membrane, causing the sarcoplasmic reticulum (SR) to release large quantities of Ca^{++} ions stored within the reticulum. The exit of Ca^{++} ions through transmembrane Ca^{++} channels to the cytosol (at the A-I junctions).
- In the resting state, myosin binding sites on actin filaments are partially coated with tropomyosin. In addition, troponin I (TnI) is bound to actin and impedes myosin-actin interaction.
- The Ca^{++} ions produce attractive forces to act between actin and myosin filaments, causing them to slide alongside each other, where this binding of Ca^{++} to troponin C results in a slight displacement of the tropomyosin molecule that breaks the TnI-actin bond; tropomyosin slightly changes its position and uncovers the myosin binding sites (active state), thus leading in an actin-myosin contact.
- The actin-myosin contact triggers the activation of the ATP-ase (actin-dependent) of myosin which catalyzes the hydrolysis of ATP which leads to the fixation of actin on myosin and the conformational change of the myosin head, responsible for the displacement of the actin filament and therefore the contraction of the myofibril. The arrangement of the myosin head on the actin filament makes an angle of approximately 90°.
- The detachment of phosphate from the myosin head is associated with the release of energy resulting in the stronger fixation of myosin on actin and a 45° rotation of the myosin head which results in a displacement of approximately 10 nanometers; the release of ADP leaves the myosin head anchored to actin.
- Relaxation occurs when the Ca^{++} concentration in the cytosol is sufficiently reduced. As a result, tropomyosin returns to its resting position, covering the actin binding sites and restoring the resting state. So, when the Ca^{++} ions are pumped back into the SR by a Ca-membrane pump and remain stored in the SR until a new muscle AP occurs, the removal of Ca^{++} ions from the myofibrils causes muscle contraction to cease.

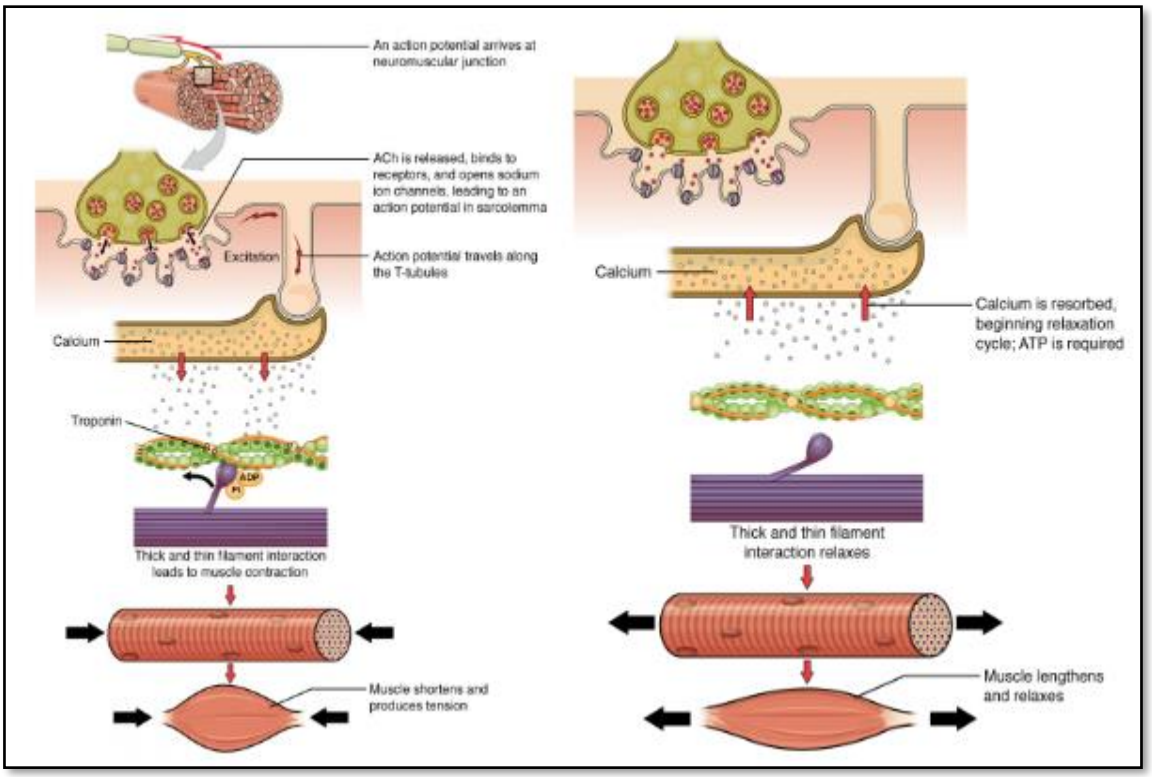

Figure 2. 36. Contraction and relaxation of a muscle fiber.

▪ **Classification of striated muscle fibers**

Skeletal muscle cells (fibers), like other body cells, are soft and fragile. There are three types of skeletal muscle fibers: Type I, Type IIa, and Type IIb. Skeletal muscle fibers can be classified based on two criteria: 1.How fast do fibers contract relative to others. 2 How do fibers regenerate ATP.

Type I - Slow oxidative (SO) fibers contract relatively slowly and use aerobic respiration (oxygen and glucose) to produce ATP. They produce low power contractions over long periods and are slow to fatigue; they appear red because of the high amount of myoglobin;

Type IIa - Fast oxidative (FO) fibers have fast contractions and primarily use aerobic respiration, but because they may switch to anaerobic respiration (glycolysis), can fatigue more quickly than SO fibers; they appear white, have high amount of glycogen; less rich in myoglobin, mitochondria and redox enzymes than the previous ones.

Type IIb- Fast glycolytic (FG) fibers have fast contractions and primarily use anaerobic glycolysis. The FG fibers fatigue more quickly than the others appear pink.

These three types differ from each other in their myoglobin content (a protein that binds O_2), the number of mitochondria, the concentration of various enzymes, and the rate of contraction.

- **Histogenesis and regeneration**

Muscle cells originate from myoblasts, which differentiate from myotome cells, which themselves arise from the somites (paraaxial mesoderm).

Regeneration relies primarily on satellite cells, myogenic progenitors located between the basal lamina and the muscle fiber membrane. However, other cell types located outside the basal lamina, such as pericytes, also possess myogenic potential.

- **Skeletal muscle functions**

The primary functions of the skeletal muscle take place via its intrinsic excitation-contraction coupling process. As the muscle is attached to the bone tendons, the contraction of the muscle leads to movement of that bone that allows for the performance of specific movements.

The skeletal muscle also provides structural support and helps in maintaining the posture of the body. Besides, they acts as a storage source for amino acids that different organs of the body can use for synthesizing organ-specific proteins. The skeletal muscle also plays a central role in maintaining thermostasis and acts as an energy source during starvation.

7.2.2. Cardiac muscle tissue

Cardiac muscle tissue, also known as myocardium, is a structurally and functionally unique subtype of muscle tissue located in the heart, that actually has characteristics from both skeletal and muscle tissues. The myocardium is surrounded by a thin outer layer called the epicardium and an inner endocardium**.** It is capable of strong, continuous, and rhythmic contractions that are automatically generated.

The contractility can be altered by the autonomic nervous system and hormones. In addition, this tissue type has high metabolic, energy, and vascular demands.

- **Cardiac muscle components**

To accomplish this, the structure of cardiac muscle has distinct features that allow it to contract in a coordinated fashion and resist fatigue.

General characteristics of cardiac muscle cells

Cardiomyocytes, also known as cardiac muscle cells, usually have a length varying from 30 to 130 µm and a diameter of 5 to 25 µm, have a cylinder shape with bifurcations at the ends through which they form connections (junctions) with adjacent cells (Eberth's scalariform features), contain one elongated nucleus that lies in the centre. The cytoplasm of cardiomyocytes, called sarcoplasm, is eosinophilic and appears as a 3D network. In fact, cell organelles are also concentrated in this cytoplasmic region around the nucleus. These include mitochondria, Golgi apparatus, lipofuscin filled granules, and glycogen. Lipofuscin is a red-brown pigment.

Cardiac muscle tissue contains additional large and elongated mitochondria located between the myofibrils. In addition, extra glycogen granules are also located between the myofibrils to store the energy.

Therefore, they do not regenerate, heart muscle damage is repaired by the formation of fibrous connective tissue (scar) by fibroblasts.

Besides, cardiac muscle cells, or cardiomyocytes, are contractile cells that make up the heart muscle. There are several types of cardiomyocytes:

- **Contractile cardiomyocytes**, rich in myofibrils. They represent the majority of cardiomyocytes and ensure the contraction of the heart muscle;
- **Cardionector cells**, poor in myofibrils. They allow the initiation and conduction of muscle contraction through the heart tissue;
- **Myoendocrine cells**, poor in myofibrils. They secrete a peptide, called atrial natriuretic factor, which causes an increase in natriuresis (sodium concentration in the urine), which helps lower blood pressure.

Structural components of cardiac muscle cells

Under the electron microscope, myofibrils appear as myofilaments ordered into contractile units, the sarcomeres. Between the myofibrils, we can distinguish cytoplasmic tracts containing mitochondria. The latter use the oxygen supplied to the cells by the blood to produce the energy necessary for contraction.

There are other ultrastructural particularities of the myocardium compared to skeletal striated muscle

-T-tubules in cardiac muscle are larger than those in skeletal muscle and are lined with an external lamina. The sarcolemma invaginates at the Z lines, forming T-tubules—unlike in striated skeletal muscle, where they occur at the A-I junctions. Additionally, these T-tubules may be interconnected by longitudinal tubules that span multiple sarcomeres.

Sarcomeres are the functional subunits of myofibrils and the contractile units of cardiac muscle tissue. They are arranged into a branched pattern, forming a 3D network in the cytoplasm and they are composed of thick and thin filaments. The cytoplasmic regions between the sarcomere branches are filled with mitochondria and smooth endoplasmic reticulum (sER) called sarcoplasmic reticulum, which envelopes each myofibril. Where, the endoplasmic reticulum, is less developed than in the striated skeletal muscle fiber, aand the mitochondria is generally of small size, very numerous.

The end of the myocardial cell has a "stair-step" shape with a succession of segments parallel to its major axis, the length of which is equal to that of a sarcomere and segments, which are perpendicular to it without being straight. The myofibrils end at these ends with a Z striation, which associates, with the sarcolemma in a dense plaque.

To accomplish their attachment roles, nexus-type differentiations, zonula adhaerens and desmosomes (maculae adherentes), are distributed, for the former, on the lateral (horizontal) parts of the cell end, for the latter, on its transverse part (gap junctions) **(Figure 2. 37).**

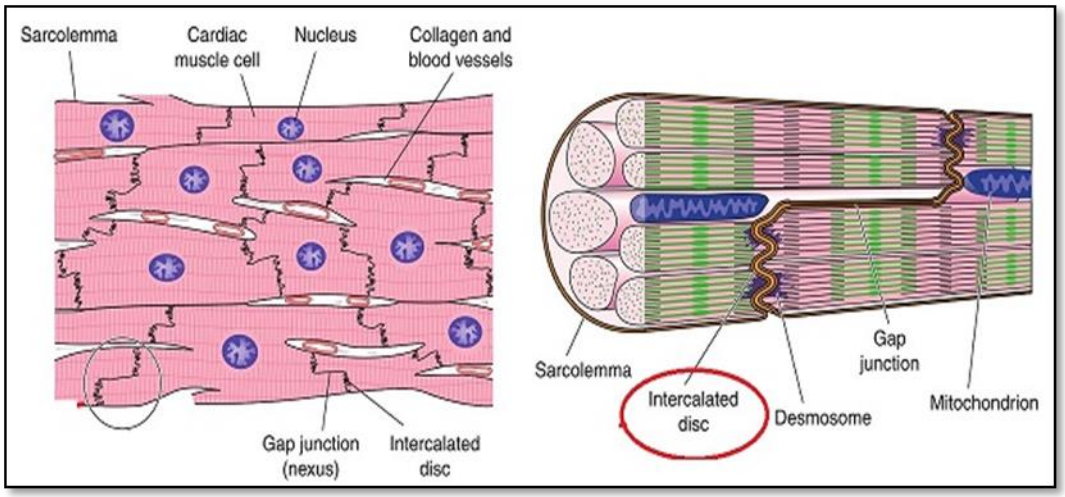

Figure 2. 37. Cardiac muscle tissue.

- **Cardiac muscle function**

The primary function of cardiac muscle is to pump blood into circulation by generating sufficient force. The mechanism behind each coordinated contraction involves the cardiac muscle and electrical impulses. These contractile functions of the heart require ATP, which can be obtained through various substrates, including fatty acids, carbohydrates, proteins, and ketones. Aerobic production is the core utilization process; however, the heart may use anaerobic processes in a limited capacity.

Rapid, involuntary contraction and relaxation of the cardiac muscle are vital for pumping blood throughout the cardiovascular system.

- **Contraction of the myocardium**

The contraction of myocardial fibers has the same molecular mechanism as that of striated skeletal muscle fibers, But, in cardiac muscle, the entire organ contracts as a whole or does not contract at all, whereas in skeletal muscle, only muscle fibers individually stimulated by nerve fibers contract. However, the propagation of the contraction wave throughout the myocardium is ensured by the gap-type junctions of the scalariform lines that realize a true "functional syncitium".

7.2.3. Smooth muscle tissue

Muscle fibers that do not display striations are termed smooth muscle. It is characterized by a slow and involuntary contraction. It is found in particular at the level of hollow organs in muscular tunics (walls of the digestive, respiratory, urinary and genital tracts). The nervous system can use smooth muscle to tightly regulate many of the body's subsystems for life with no thought from the user. Without these vital functions, the body would not be able to maintain even its most basic functions. On the one hand smooth muscle cells contract slower than skeletal muscle cells, on the other hand they are stronger, more sustained and require less energy.

- **Ultrastructure of the smooth muscle cell**

Smooth muscle cells are elongated, fusiform, containing a single central nucleus. It is surrounded by a sarcolemma lined with a basal lamina. Smooth muscle cell is 3-10 µm thick and 20-200 µm long. The cytoplasm is homogeneously eosinophilic and consists mainly of myofilaments. The nucleus is located in the center and takes a cigar-like shape during contraction. In the sarcoplasm, the cellular organelles are organized around the nucleus with numerous mitochondria, some lysosomes, some lipid enclaves, glycogen, poorly developed

sarcoplasmic reticulum, and Golgi apparatus, and which are concentrated near the nucleus and participate in the synthesis of type III collagen, elastin, glycosaminoglycans, external lamina and growth factors **(Figure 2. 38).**

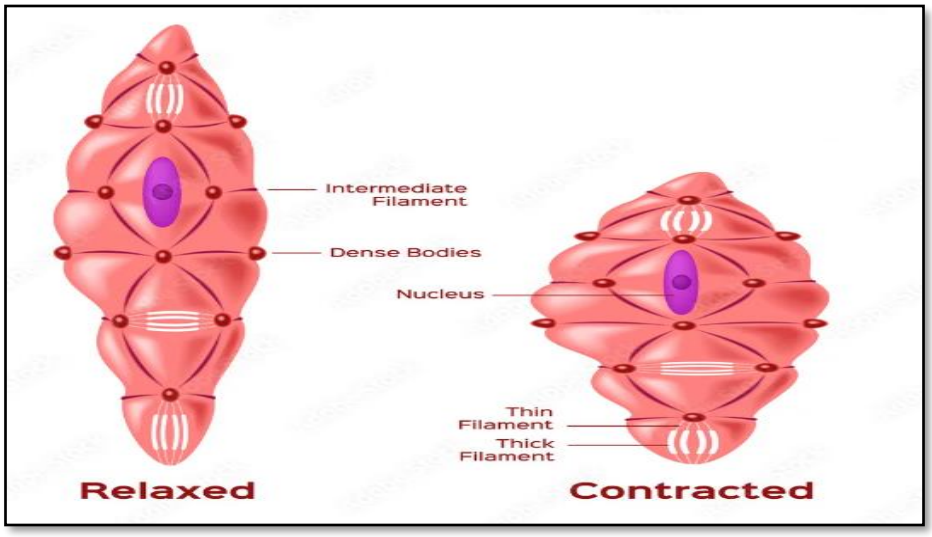

Figure 2. 38. Structure of smooth muscle cell.

▪ **Myofilaments, cytoskeleton, sarcolemma and sarcoplasmic reticulum in smooth muscle**

Smooth muscle has a less structured organization of its contractile proteins than skeletal and cardiac striated muscles. The sarcoplasm contains parallel myofibrils, composed of thin actin myofilaments and thick myosin myofilaments. Actin myofilaments are stabilized by two structures: anchors, in contact with the plasma membrane, and dense bodies, located in the sarcoplasm, to which these myofilaments attach.

A third type of filament, called intermediate filaments (desmin and vimentin), does not participate in contraction but forms a structural support for the cell. They are present both in the center and at the periphery of the cell. The cytoskeleton nof iintermediate filaments are attached to the sarcoplasmic or sarcolemmal dense bodies (desmin filament in the tunics of the viscera and vimentin in the vessels). In contrast to skeletal muscle, the contractile apparatus in smooth muscle is not organized into myofibrils, and Z lines are lacking. The functional equivalents of the Z lines in smooth muscle cells are ellipsoidal dense bodies in the myoplasm and dense areas that form bands along the sarcolemma, Where the sarcolemma is the seat of numerous invaginations that give rise to vesicles of two kinds: the caveolae, numerous,

arranged in regular rows between the dense sarcolemmal bodies, have a role in the absorption and release of Ca^{++} and pinocytosis vesicles bristling with clathrin. Gap junctions between smooth muscle cells facilitate the propagation of excitation. The sarcolemma also has desmosome-type junctions, zonula occludens **(Figure 2.39).**

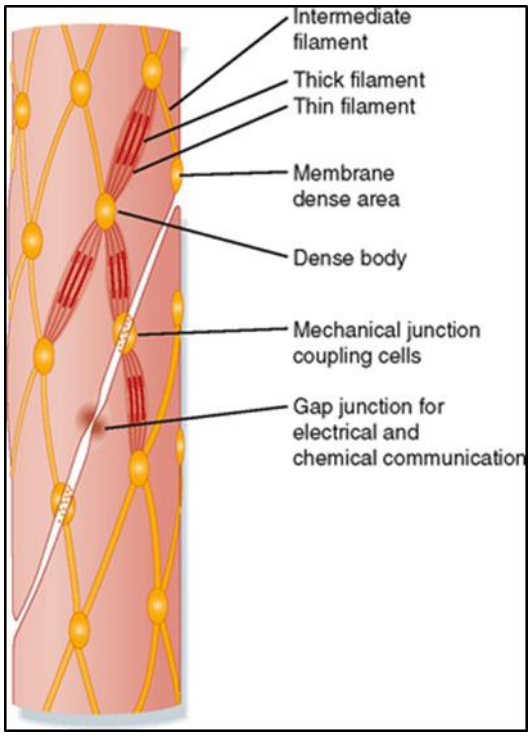

Figure 2. 39. Apparent organization of cell-to-cell contacts, cytoskeleton, and myofilaments in smooth muscle cells.

Smooth muscle consists of two types: single-unit and multi-unit

- **Single-unit**

Single-unit smooth muscle consists of multiple cells connected through connexins that can become stimulated in a synchronous pattern from only one synaptic input.

Connexins allow for cell-to-cell communication between groups of single-unit smooth muscle cells which allows ions and molecules to diffuse between cells giving rise to calcium waves and which in turns allows for synchronous contraction to occur.

- **Multi-unit**

Multi-unit smooth muscle differs from single-unit in that each smooth-muscle cell receives its own synaptic input, allowing the multi-unit smooth muscle to have much finer control.

▪ **Varieties of non-muscle contractile cells**

There are other diffuse contractile cells in various tissues:

• **Pericytes:** surround the capillaries, control and manage vascular flow. Due to their contractile property and the fact that they contain smooth muscle actin, these cells are close to leiomyocytes.

• **Myofibroblasts:** have characteristics of both leiomyocytes (actin, desmin, dense bodies, contractility) and fibroblasts. Play an important role in plasticity and cell migration in connective tissue. They play a vital role in the healing and tissue regeneration process.

• **Myoepithelial cells:** They are generally similar in shape to smooth muscle cells. They contain actin, myosin, and intermediate filaments, as well as dense cytoplasmic and peripheral plaques to which these filaments attach. They participate in mechanical control and facilitate the evacuation of glandular secretion (e.g.: mammary gland, salivary gland).

▪ **Innervation**

The innervation of the smooth musculature is utmost complex. It lies under the influence of the visceral nervous system and works autonomously at the same time.
Furthermore, it is provided by the sympathetic (noradrenergic) nerves and the parasympathetic (cholinergic) nerves of the autonomic nervous system and it is regulated by:

- **Neurotransmitters:** e.g. norepinephrine, acetylcholine;
- **Hormones:** e.g. estrogen, oxytocin;
- **Tissue hormones:** e.g. prostaglandins, histamine.

▪ **Smooth muscle functions**

The functions of smooth muscle in each organ system is an incredibly broad topic and beyond the overall scope, smooth muscle is present in all of the organ systems below:

- Gastrointestinal tract;
- Cardiovascular - blood vessel and lymphatic vessels;
- Renal - urinary bladder;

- Genital - uterus, both male and female reproductive tracts;
- Respiratory tract;
- Integument -Hair Erector Muscle (Arrector Pili Muscle);
- Sensory - the ciliary muscle and iris of the eye.

8. Nervous tissue

8. 1. Definition

The nervous system (NS) specializes in the conduction, transmission, and processing of information. Present in all regions of the body, it represents one of the body's most important means of communication. The nervous system is derived from embryonic neuroectoderm. It is convenient to distinguish, within the nervous system (NS), the central nervous system (CNS) and the peripheral nervous system (PNS).

-Central Nervous System (CNS), consisting of the brain and spinal cord.

-Peripheral Nervous System (PNS), consisting of nerve fibers, aggregates of nerve cells and glia and ganglia.

Nervous tissue consists of two groups of cell types:

-Nerve cells (Neurons)

-Neuroglia.

The brain and spinal cord are composed of gray matter and white matter.

Gray matter contains

-Nerve cell bodies (perikarya)

-Neuroglia

-Neuropil (a complicated network of cell processes)

White matter lacks nerve cell bodies (perikarya), but has many processes of neurons. The white appearance is the result of the myelin that envelops many of the neuronal processes. Neuroglia are also found in the white matter and the nuclei seen in white matter belong to neuroglia. Perikarya in the Peripheral Nervous System (PNS), are found only in ganglia (apart from in some sensory regions such as the retina and olfactory mucosa).

8.2. Neurons

8.2.1. General morphology

Nerve cells (neurons) form the structural and functional units of the central and peripheral nervous systems. Their function is to receive stimuli and transmit nerve impulses to the target organ. Neurons are post-mitotic structures that shortly after birth lose the ability to divide. Further changes involve only reduced number of neurons (neuronal death), or changes in volume or in neuronal connections. Neurons have two special properties:

-Irritability (the ability to respond to a stimulus)

-Propagation of impulses (the ability to conduct impulses).

Most neurons have three main parts:

-**Perikarya (cell bodies).**

-**Dendrites and axon: leave from the extensions.**

Neurons and their processes are very variable in form and size. Some neurons are very large (with perikarya of up to 150µm), whereas others are very small (perikarya of only 4-5µm).

8.2.2. Morphological classification

Neurons are classified according to the size, number and shape of their processes.

-Unipolar neurons (pseudounipolar) have a single process (axon). These are found in sensory ganglia of dorsal roots of spinal nerves.

-Bipolar neurons have two processes (one dendrite and one axon). These are very rare and have a limited distribution in the body. They are present in special sensory structures including the retina, olfactory epithelium, and vestibular and cochlear nerves).

-Multipolar neurons possess several processes (several dendrites and a single axon). Most neurons belong to this category.

-Pseudounipolar neuron is a type of neuron which has one extension from its cell body. This type of neuron contains an axon that has split into two branches. They develop embryologically as bipolar in shape, and are thus termed pseudounipolar instead of unipolar **(Figure 2. 40).**

8.2.3. Physiological classification of neurons

-Sensory neurons: These receive sensory stimuli from the environment (from peripheral or visceral receptors to the CNS) (e.g.unipolar neurons).

-Motor neurons: Transmit motor nerve impulses from the CNS or ganglia to effector cells (smooth muscles). Control the effector organs (muscles, exocrine glands, endocrine glands)

-Interneurons (Intermediate neurons): These are typically found in the CNS and connect between other neurons (often between sensory and motor neurons). It is estimated that over 99.9% of all neurons fall into this category.

-Neurosecretory neurons: These are specialized neurons that synthesize and secrete hormones.

Each neuron has 3 physiological parts or segments:

-Receptive segment (dendrites and perikaryon). The perikaryon also has an additional trophic and synthesizing role.

-Conductive segment (axon).

-Transmissive segment (synapse).

Neurons come in a wide variety of shapes and sizes, neurons are distinguished as stellate, spindle, cone, polyhedral, spherical, and pyramidal (small, medium, large, or giant pyramidal cells).

Depending on the spatial organization of dendritic branches, neurons are distinguished as isodendritic (diverging dendrites in all directions), allodendritic (limited asymmetry of the dendritic tree), or idiodendritic (specific organization of the dendritic tree).

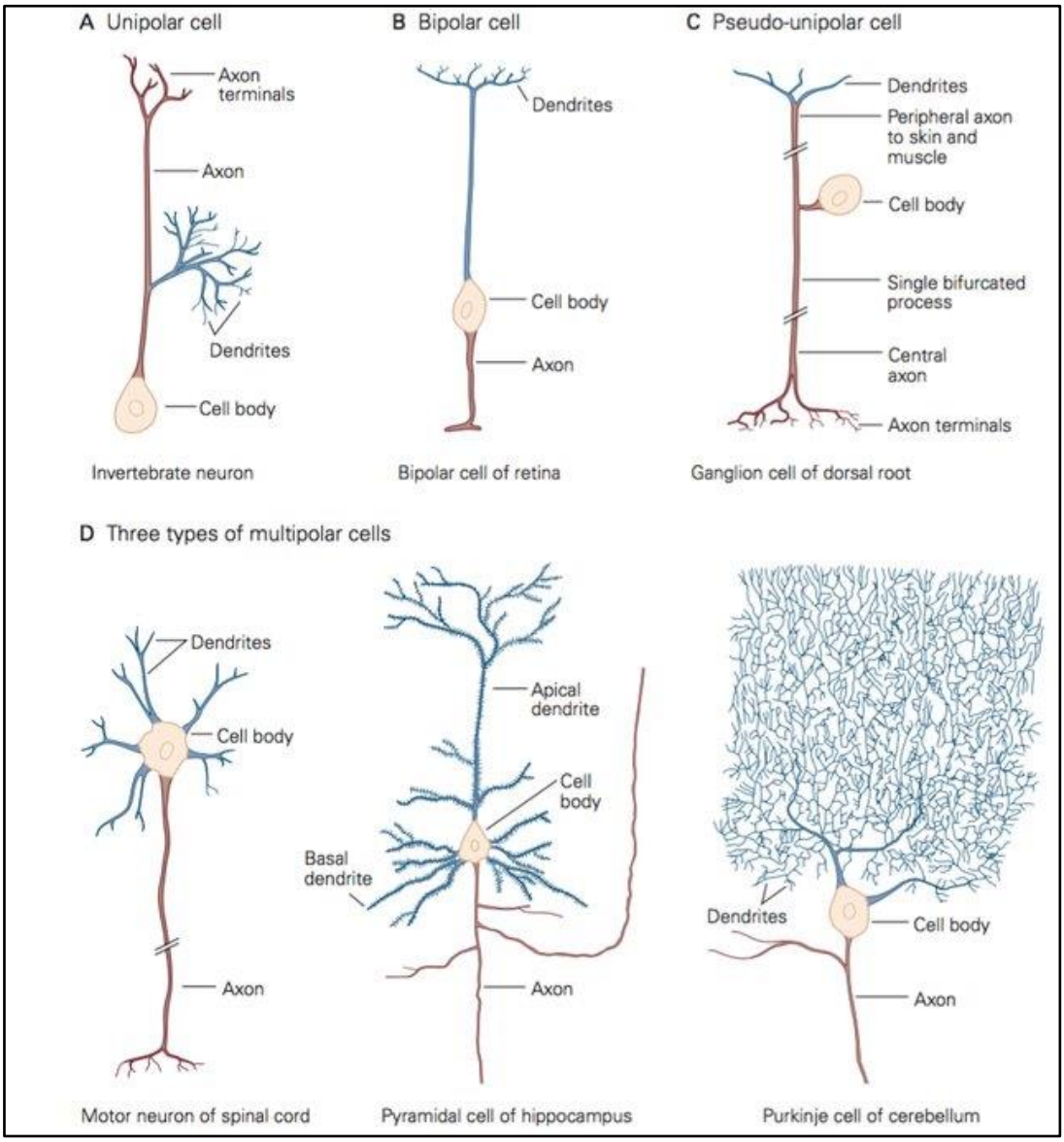

Figure 2. 40. Some representative neurons.

8.2.4. Structure of the neuron

- **Perikaryon**

The perikaryon (neuronal cell body or soma) consists of the nucleus and surrounding cytoplasm. (The term perikaryon implies the area surrounding the nucleus, but the term is used freely today to describe the whole cell body including the nucleus) **(Figure 2. 41)**. The perikaryon is the trophic center of the neuron involved in protein synthesis. The surface of the perikaryon receives nerve impulses and is the site of many synapses, bringing excitatory or inhibitory stimuli. The nuclei of perikarya are large, regular, round or oval. Rough Endoplasmic Reticulum (RER) is abundant in the cytoplasm and is associated with the protein synthetic activities of the neurons. Large well developed Golgi bodies are present in the perikarya, with many large mitochondria are found throughout the perikaryon.

Neurofilaments are abundant and run throughout the cytoplasm of the perikaryon. The neuron cytoskeleton is completed by microtubules and actin microfilaments that are associated with the plasma membrane. Lipofuscin is a brown pigment that is common in perikarya of aged neurons. It is now known to be common to post-mitotic cells and to consist of large secondary lysosomes.

- **Dendrites**

Most nerve cells have several dendrites. These increase the receptive area of the neuron. Dendrites do not maintain a constant diameter (unlike axons) and transmit impulses to the cell body decrementally (unlike axons). The regions of the dendrites closest to the perikaryon are usually larger, than those farther away. Typically dendrites have large numbers of thorny spines, which are now known to be areas of synaptic contact.

The cytoplasm of dendrites is similar to that of the perikaryon, except that it lacks a Golgi apparatus. The number of organelles is reduced or absent near the tips except for mitochondria, which are abundant. Axons arise from the axon hillock (the axon emergence cone), a specialized region of the soma that lacks RERs, ribosomes, Golgi cisternae, and Nissl bodies but contains numerous microtubules and neurofilaments **(Figure 2. 41)**.

- **Axons**

A long process emerging from the cell body. There is only a single axon for each neuron. The axon transmits impulses to other neurons, or to effectors: muscle or gland cells. The distal portion of the axon is usually branched (terminal arborization). The cytoplasm of the axon (axoplasm) lacks a Golgi apparatus but contains a smooth endoplasmic reticulum, an RER, and elongated mitochondria. The plasma membrane surrounding the axon is called the axolemma

and the cytoplasm of the axon is termed the axoplasm. Axons end in numerous small branches (axon terminals) from which impulses are transmitted to another neuron or other cell types **(Figure 2. 41)**.

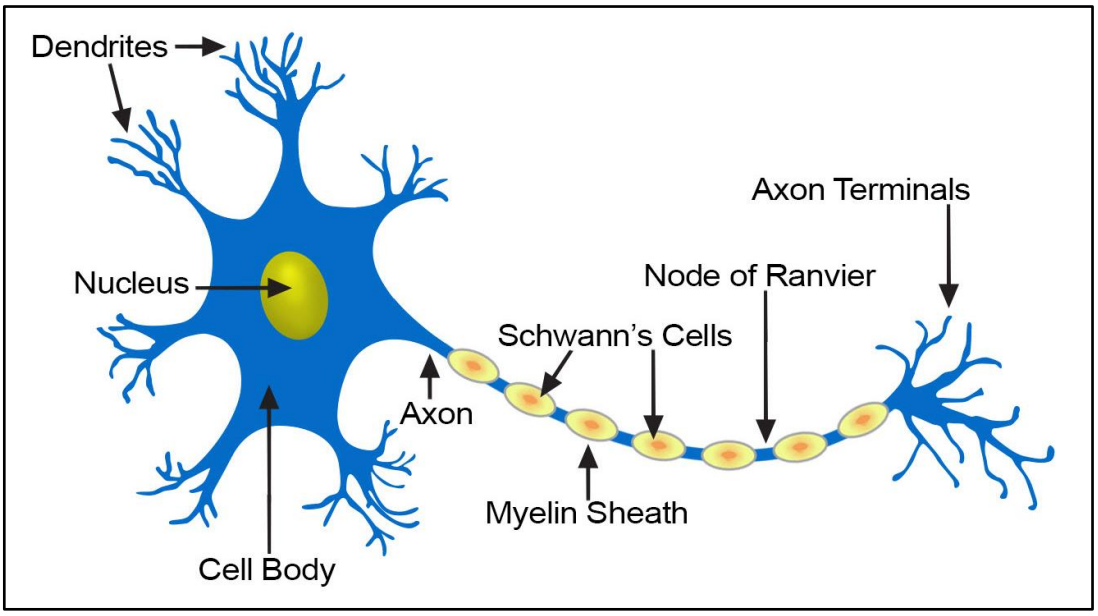

Figure 2. 41. Structure of a typical neuron.

- **Nerve fibers**

On the Basis of presence of myelin sheath There are both myelinated and unmyelinated nerve fibres in the nervous system **(Figure 2. 42)**. Both the types of nerve fibres differ in their relative composition.

-Peripheral nerve fibers: Nerve fibers consist of axons enveloped by special sheaths. In peripheral nerves the sheath cell is the Schwann cell, whereas in the CNS, the sheath-forming cells are the oligodendrocytes, which unite to form a lipoprotein complex. This sheath is interrupted at regular intervals at the level of the Ranvier constrictions, which delimit so-called interannular segments. Each segment is marked by an oblique slit: the Schmidt-Lantermann notch. The myelin sheath is itself surrounded by a Schwann sheath, which is itself surrounded by a basal lamina. The whole is finally enveloped by a thin layer of connective tissue: the Henle sheath.

- Non-myelinated nerve fibers: Non-myelinated nerves are found in both the CNS and PNS. The axons are enclosed in simple clefts of oligodendrocytes or Schwann cells but the myelin is not secreted in such cases, and which are each connected to its plasma membrane by

a mesaxon. Each Schwann cell may enclose several non-myelinated axons. The entire fiber is finally lined with a basal lamina which separates the Schwann cells from the peripheral Henle sheath.

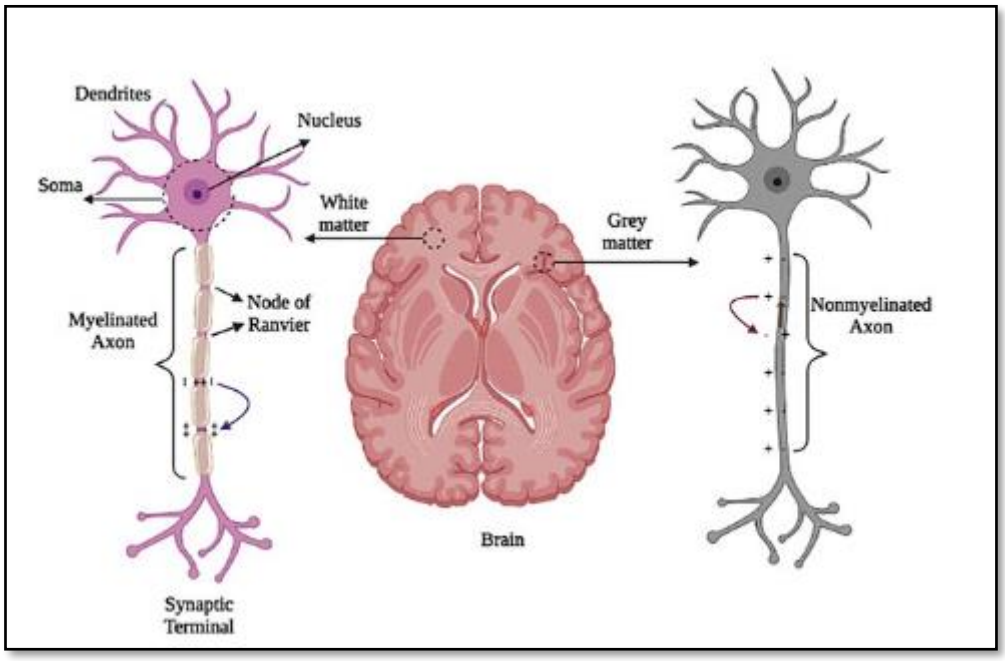

Figure 2. 42. Schematic structure of two different neurons in the brain's white matter and gray matter. (Lefth panel) myelinated (salutatory conduction) and (Right panel) nonmyelinated axons.

8. 3. Neuroglia

Glia or neuroglia get their name from the Greek word for "glue". There is very little connective tissue in the CNS, and the structural support for neurons comes from neuroglia and their processes. It is estimated that for every neuron there are at least 10 neuroglia, they are involved in supporting and protecting neurons. Neurons cannot exist or develop without neuroglia. Neuroglia play several roles like support (especially the astrocytes in the CNS), participation in the blood-brain-barrier (astrocytes), formation of the myelin sheath of axons

(oligodendrocytes), isolation of junctional surfaces of synapses, and repair processes following damage or injury to nerves.

There are 4 basic types of neuroglia, based on morphological and functional features (Astrocytes (Astroglia); Oligodendrocytes (Oligodendroglia); Microglia; and ependymal cells **(Figure 2. 43).**

The astrocytes and oligodendroglia are large cells and are collectively known as macroglia.

• **Astrocytes (Astroglia)**

These are present only in the CNS and are the largest of the neuroglia. They have many long processes, which often terminate in "pedicels" on blood capillaries and contribute to the blood-brain-barrier. There are two categories of astrocytes:

-**Protoplasmic astrocytes:** These are present in the gray matter of the brain and spinal cord. Their processes are relatively thick.

-**Fibrous astrocytes:** These are present in the white matter of the CNS. Their processes are much thinner than those of the protoplasmic astrocytes. Because of their number and their long processes, the astrocytes appear to be the most important supporting elements in the CNS.

• **Oligodendrocytes**

These are smaller than the astrocytes, with fewer and shorter processes. They are found in both the gray and white matter of the CNS and are responsible for the formation of the myelin sheath surrounding axons.

• **The Schwann cells**

Schwann cells are the glial cells that form the myelin sheath on axons outside the brain. Unlike oligodendrocytes, Schwann cells do not have multiple cellular extensions, but instead each cell engulfs a segment of axon and forms a multilayered myelin sheath around it. However, a single Schwann cell can only isolate a single axon, whereas a single oligodendrocyte can isolate multiple axons.

• **Microglia**

These are small cells, with elongated bodies, elongated nuclei with dense chromatin and relatively few processes. They are found in both the gray and white matter of the CNS and are thought to function as macrophages. There is some evidence that they are in fact of mesenchymal origin and derived from blood-borne monocytes.

• **Ependymal cells**

The ependyma is composed of neuroglia that line the internal cavities (ventricles) of the brain and spinal cord (central canal). They are similar in appearance to a stratified columnar

epithelium. The ependymal cells are bathed in **cerebrospinal fluid** (CSF). Modified ependymal cells of the **choroid plexuses** of the brain ventricles are the main source of the CSF.

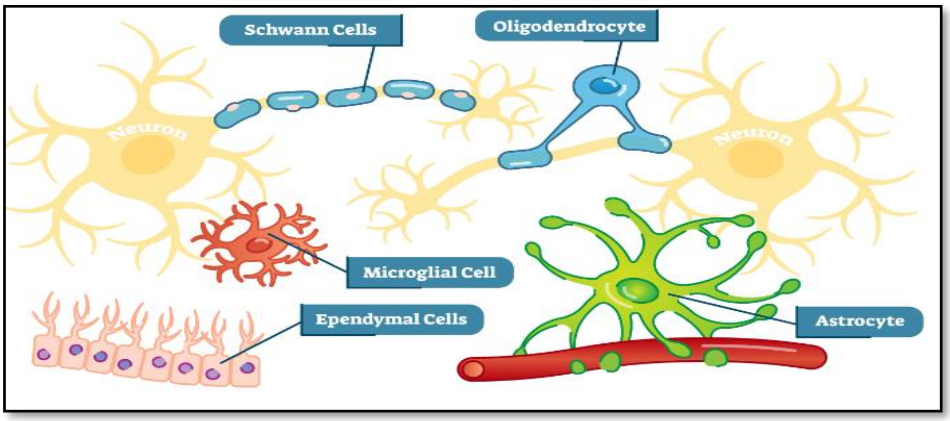

Figure 2. 43. Glial cells types.

8.4. Degeneration and regeneration of nerve fibers

Neurons do not divide, though neuroglia can divide. If neurons are damaged in the CNS, there is permanent loss and no regeneration. In contrast peripheral nerves if crushed or even severed may regenerate provided the perikaryon is not injured.

1. Physiology of breathing

1.1. Introduction

Every cell in an animal requires oxygen to perform cellular respiration. Cellular respiration is the process by which animals take in oxygen and exchange it for carbon dioxide and water as waste products. Animals have specialized systems that help them to do this successfully and efficiently. Where human respiration involves the synchronization of various components, including central neural control (respiratory drive), sensory input systems, respiratory muscles, and lungs. Central neural control and sensory input systems coordinate the timing and rate of ventilation and air volume intake, which is signaled to the respiratory muscles and lungs for the mechanical exchange of inspired gases.

3.2. Gases in the environment

The range of respiratory problems faced by aquatic and terrestrial animals can be seen from the varying composition and physical characteristics of water and air. Air contains about 20 times the amount of oxygen found in air-saturated water, and in order to extract an equivalent amount of oxygen as an air breather, an aquatic animal may find it necessary to pass across the respiratory surfaces a relatively larger volume of the external medium. The diffusion rate of oxygen is much lower in water than in air. The problem is further compounded by the higher density (1,000 times air) and viscosity (100 times air) of water, which impose on the machinery of aquatic respiration a much greater workload. Thus, fish may expend about 20 percent of their total oxygen consumption in running the respiratory pump, as compared with about 1 to 2 percent in mammals, including humans.

3.3. Animal respiratory organs

There are several respiratory organs, trachea, gills, integumentary exchange areas, and lungs.

Trachea

The trachea is a respiratory organ is a hallmark of insects. It is made up of a system of branching tubes that deliver oxygen to, and remove carbon dioxide from the tissues. The pores to the outside, called spiracles, are typically paired structures, two in the thorax and eight in the abdomen. Periodic opening and closing of the spiracles prevents water loss by evaporation. Air containing oxygen enters through spiracles into the tracheal tubes. It then diffuses into the body tissue and reaches every cell in the body. Carbon dioxide released from the cells goes into the tracheal tubes and comes out through spiracles **(Figure 3. 1).**

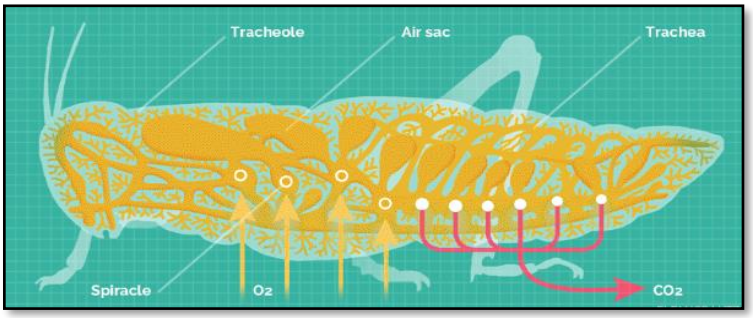

Figure 3. 1. Insects respiration.

The gills

The gills of fishes are supported by a series of gill arches encased within a chamber formed by bony plates (the operculum). A pair of gill filaments projects from each arch, there is a series of secondary folds, the lamellae, where the gas exchange takes place. The blood vessels passing through the gill arches branch into the filaments and then into still smaller vessels (capillaries) in the lamellae. Deoxygenated blood from the heart flows in the lamellae in a direction counter to that of the water flow across the exchange surfaces **(Figure 3. 2).**

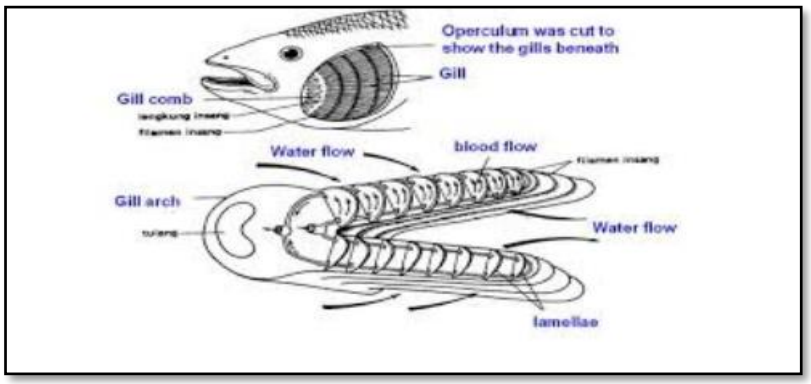

Figure 3. 2. The gill of fish.

Integumentary exchange areas

It is theoretically possible for a skin that is well supplied with blood vessels to serve as a major or even the only respiratory surface. This requires a thin, moist, and heavily vascularized skin.

Through plasma membrane

In unicellular animals, such as amoeba, exchange of gases takes place through cell surface. They absorb oxygen from the surrounding air or water and give out carbon dioxide through plasma membrane by diffusion **(Figure 3. 3).**

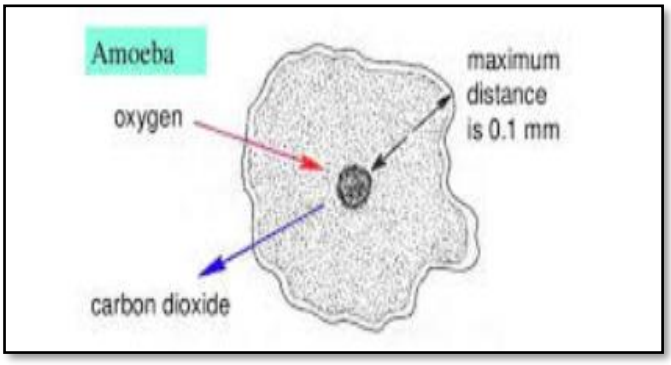

Figure 3. 3. Unicellular organisms respiration.

The lung

The lungs of vertebrates range from simple saclike structures found in the Dipnoi (lungfishes) to the complexly subdivided organs of mammals and birds. The relatively simple lungs of frogs are subdivided by incomplete walls (septa), and between the larger septa are secondary septa that surround the air spaces where gas exchange occurs. While, the diameter of these air spaces (alveoli) in lower vertebrates is larger than in mammals: In mammals, the smaller alveoli are associated with a greater surface for gas exchange: although the respiratory surface of the frog is about 20 square centimetres per cubic centimetre (50.8 square inches per one cubic inch) of air, that of humans is about 300 square centimetres.

3.4. Respiratory mechanisms in mammals

In mammals, pulmonary ventilation occurs via inhalation when air enters the body through the nasal cavity. Inspiration is powered by an aspiration (suction) pump. The chief muscles of inspiration are the diaphragm and the external intercostal muscles, where the diaphragm is a domelike sheet of muscle separating the abdominal and chest cavities that moves downward as it contracts.

When, air passes through the nasal cavity ane as air crosses the surfaces of the mucous membranes, it picks up water. This equilibrates the air to the body, reducing damage that cold, dry air can cause. Particulates in the air are also removed in the nasal passages. These processes are all protective mechanisms that prevent damage to the trachea and lungs. From the nasal cavity, air passes through the pharynx and the larynx to the trachea. The function of the trachea is to funnel the inhaled air to the lungs and the exhaled air out of the body. The human trachea, a cylinder about 10-12 cm long, 2 cm in diameter found in front of the esophagus, extends from the larynx into the chest cavity.

As air enters the lungs, it is diverted through bronchi beginning with the two primary bronchi. Each bronchus divides into secondary, then into tertiary bronchi, which further divide to create smaller diameter bronchioles that split and spread through the lung **(Figure 3. 4).**

Bronchi are innervated by nerves of both the parasympathetic and sympathetic nervous systems that control muscle contraction or relaxation, respectively. In humans, bronchioles with a diameter smaller than 0.5 mm are the respiratory bronchioles. Since they lack cartilage, they rely on inhaled air to support their shape. The terminal bronchioles then subdivide into respiratory bronchioles which subdivide into alveolar ducts. Numerous alveoli (sing. alveolus) and alveolar sacs surround the alveolar ducts. The alveolar ducts are attached to the end of each bronchiole; each duct ends in approximately 100 alveolar sacs. Each sac contains 20-30 alveoli that are 200-300 microns in diameter.

Alveoli are made of thin-walled, parenchymal cells that are in direct contact with capillaries of the circulatory system. This ensures that oxygen will diffuse from alveoli into the blood and that carbon dioxide produced by cells as a waste product will diffuse from the blood into alveoli to be exhaled. As there are so many alveoli (around 300 million per lung) within each alveolar sac and so many sacs at the end of each alveolar duct, the lungs have a sponge-like consistency.

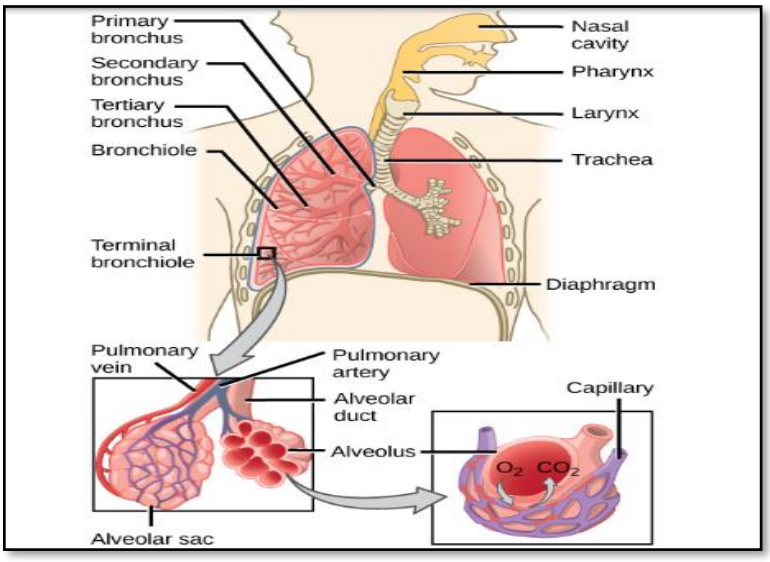

Figure 3. 4. Human respiration: Air enters the respiratory system through the nasal cavity and pharynx. It then passes through the trachea and into the bronchi, which bring air into the lungs.

2. Nervous system

2.1. Introduction

A nervous system is an organism's control center: a network of neurons which send communications between and across different parts of the body; a nervous system collects and processes sensory information from outside (and inside) the body and controls all behaviors, from eating to sleeping to finding a mate.

2.2. Functions of the nervous system

The nervous system plays a role in nearly every aspect. It guides everyday activities such as waking up; automatic activities such as breathing; and complex processes such feeling emotions.

- **Sensory function** -to sense changes (known as stimuli) both outside and within the body. For example the eyes sense changes in light and the ear responds to sound waves.
- **Integrative function -** processing the information received from the sense organs.
- **Motor function -** The third function is the response to the stimuli that causes muscles to contract or glands to secrete.

2.3. Parts of the nervous system

The nervous system has two main parts **(See figure 3. 5):**

The central nervous system (CNS): which consists of the brain and spinal cord.

The peripheral nervous system (PNS): which consists of the nerves that connect to the brain and spinal cord (cranial and spinal nerves) as well as the autonomic (or involuntary) nervous system.

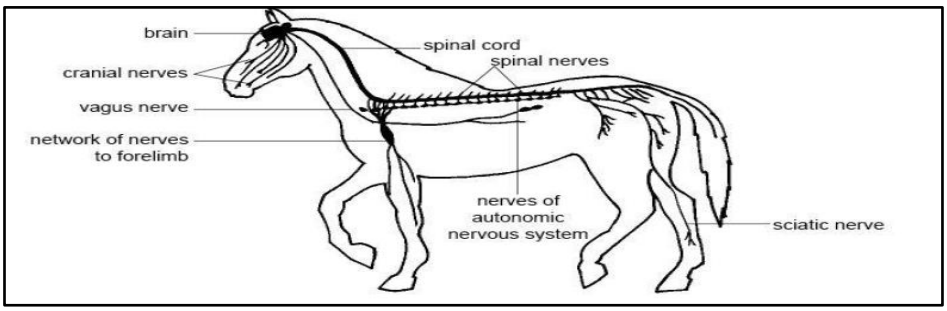

Figure 3. 5. Parts of horse nervous system.

When we look at the brain or spinal cord some regions appear creamy white (white matter) and others appear grey (grey matter). White matter consists of masses of nerve axons

and the grey matter consists of the nerve cells. In the brain the grey matter is on the outside and in the spinal cord it is on the inside.

The major part of the brain lies protected within the sturdy "box" of skull called the cranium, surrounding the fragile brain tissue (and spinal cord) are protective membranes called the meninges **(See figure 3. 6),** and a crystal-clear fluid called cerebrospinal fluid, which protects and nourishes the brain tissue. This fluid also fills four cavities or ventricles that lie within the brain.

The brain consists of three major regions:

1. The fore brain which includes the cerebral hemispheres, hypothalamus and pituitary gland;

2. The hind brain or brain stem, contains the medulla oblongata and pons and the cerebellum or "little brain".

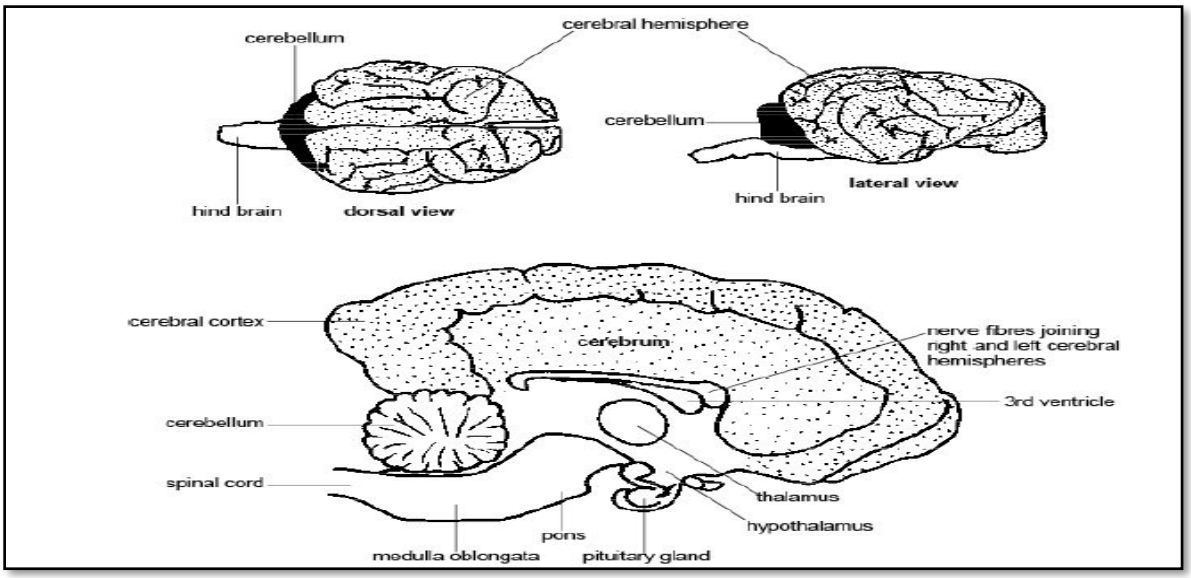

Figure 3. 6. Longitudinal section through the brain of a dog.

The central nervous system

A) The bain

- **The fore brain**

The cerebral hemispheres are the masses of brain tissue that sit on the top of the brain. Where different regions of the cortex are responsible for particular sensory and motor functions, example: Vision, hearing, taste, smell, or moving the fore-limbs, hind-limbs or tail.

The hypothalamus is situated at the base of the brain and is connected by a "stalk" to the **pituitary gland**, the "master" hormone-producing gland. The hypothalamus can be thought of as the bridge between the nervous and endocrine (hormone producing) systems.

- **The hindbrain**

• The medulla oblongata

The medulla oblongata is at the base of the brain and is a continuation of the spinal cord. It carries all signals between the spinal cord and the brain and contains centres that control vital body functions.

• The Cerebellum

The cerebellum (little brain) looks rather like a smaller version of the cerebral hemispheres attached to the back of the brain. It receives impulses from the organ of balance (vestibular organ) in the inner ear and from stretch receptors in the muscles and tendons. By co-ordinating these it regulates muscle contraction during walking and running and helps maintain the posture and balance of the animal.

B) The spinal cord

The spinal cord is a cable of nerve tissue that passes down the channel in the vertebrae from the hindbrain to the end of the tail**.** If we cut across the spinal cord you can see that it consists of white matter on the outside and grey matter in the shape of an H or butterfly on the inside **(Figure 3. 7).**

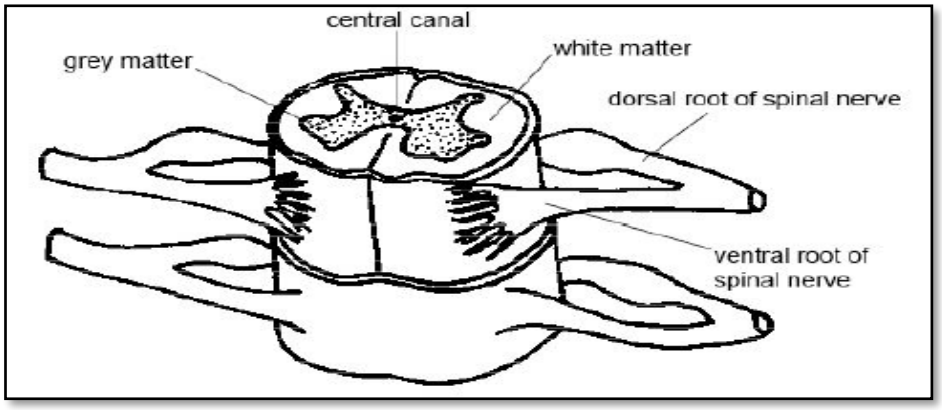

Figure 3. 7. Representation of the spinal cord.

The peripheral nervous system

The peripheral nervous system consists of nerves that are connected to the brain (cranial nerves), and nerves that are connected to the spinal cord (spinal nerves). The autonomic nervous system is also part of the peripheral nervous system.

- **Cranial nerves:** There are twelve pairs of cranial nerves that come from the brain.
- **The olfactory nerves** - (smell) carry impulses from the olfactory organ of the nose to the brain.
- **The optic nerves** - (sight) carry impulses from the retina of the eye to the brain.
- **The auditory (acoustic) nerves** - (hearing) carry impulses from the cochlear of the inner ear to the brain.
- **The vagus nerve** - controls the muscles that bring about swallowing. It also controls the muscles of the heart, airways, lungs, stomach and intestines
- **Spinal nerves:** Spinal nerves connect the spinal cord to sense organs, muscles and glands in the body. The sciatic nerve is the largest spinal nerve in the body.
- **The autonomic nervous system :** The autonomic nervous system controls internal body functions not under conscious control. Where it is divided into 2 parts with 2 different functions: The sympathetic nervous system that is involved in the flight and fight response including increased heart rate, bronchial dilation, dilation of the pupil and decreased gut activity and the parasympathetic nervous system is associated with decreased heart rate, pupil constriction and increased gut activity.

2.4. Action potential

As in all cells in the body, the neuron membrane is polarized, positively on the outside and negatively on the inside. This polarization is due to the existence of a sodium and potassium concentration gradient on either side of the plasma membrane. At rest, this concentration gradient is maintained by the Na-K-ATPase pump and creates a resting potential of -70 mV.

Momentary changes in the permeability of the neuronal membrane to certain ions allow exchanges between the two sides of the membrane and thus cause depolarization. If the depolarization is significant enough to propagate along the axon, it is called an action potential: a propagating wave of depolarization. Depolarization transmitted along the axon is called a nerve impulse.

An action potential, also called a nerve impulse, is an electrical charge that travels along the membrane of a neuron. It can be generated when a neuron's membrane potential is changed by chemical signals from a nearby cell. In an action potential, the cell membrane potential changes quickly from negative to positive as sodium ions flow into the cell through ion channels, while potassium ions flow out of the cell. The action potential is described in four phases **(Figure 3.8)**:

- **Depolarization (rise in AP)**

Following stimulation, voltage-gated sodium channels open rapidly, resulting in an inward sodium current. The membrane potential tends toward the sodium equilibrium potential (+65 mV) but does not reach it.

- **Repolarization**

Na channels close and voltage-gated potassium channels open, resulting in an outward current of K. The membrane potential is restored.

- **Hyperpolarization**

K conductance remains high for some time, resulting in MP hyperpositivity on the outside and hypernegativity on the inside

- **Resting potential**

The Na-K-ATPase pump intervenes to restore the situation by expelling Na from the body and bringing in Na+. The action potential propagates and reaches other voltage-gated channels, thus the depolarization wave travels along the neuron. This depolarization is the physical medium for nerve impulses.d hypernegativity on the inside.

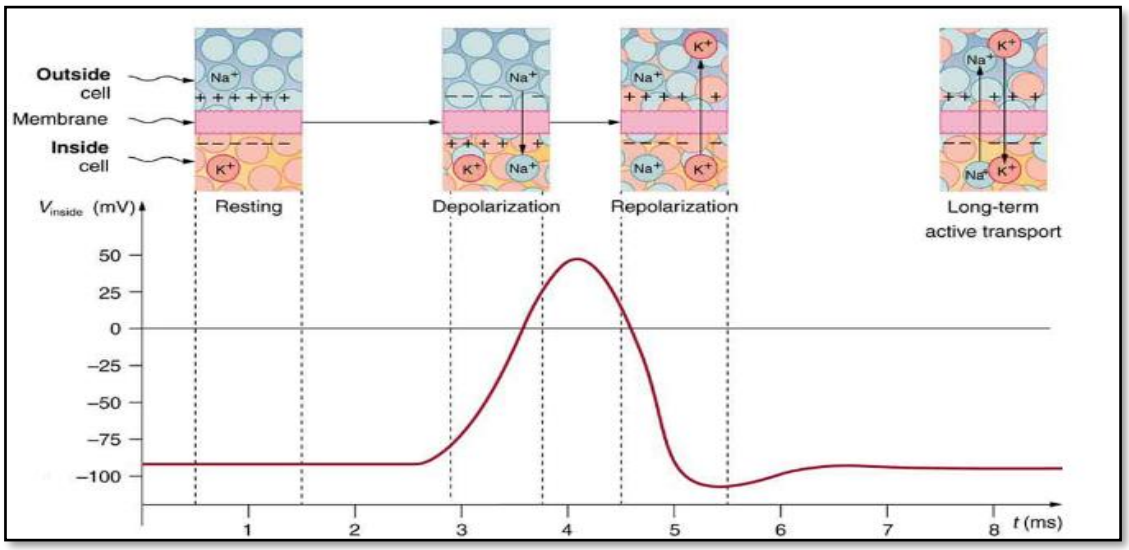

Figure 3. 8. An action potential graph of membrane potential over time.

2.5. Transmitting nerve impulses

The place where an axon terminal meets another cell is called a synapse. This is where the transmission of a nerve impulse to another cell occurs. The synapse is the site of transmission from the pre-synaptic neuron to the post-synaptic neuron. The structures found on either side of the synapse vary depending on the type of synapse. Morphologically various categories of synapses are found including:

• **Axo-dendritic:** A connection formed between the axon of one neuron and the dendrite of another. These tend to be excitatory synapses.

• **Axo-somatic:** A direct connection between the axon of one neuron to the cell body of another neuron. These tend to be inhibitory synapses.

• **Dendro-dendritic:** Located between the dendrites.

• **Axo-axonic:** A connection between the terminal of one axon and another axon. These synapses generate serve a regulatory role; the afferent axon will modulate the release of neurotransmitters from the efferent axon.

Synapses are also classified according to their function: inhibitory synapses and excitatory synapses Some synapses are purely electrical and make direct electrical connections between neurons. However, most synapses are chemical synapses. The transmission of nerve impulses across chemical synapses is more complex (**Figure 3.9).**

2.5.1. Electrical synapses: allow the direct flow of electrical current between the two interconnected cells. Specialized gaps in the cell membranes form a cytoplasmic continuity between the two cells, allowing an ion current to flow through the membrane and thus, a signal to be transmitted. The electrical transmission moves passively and bidirectionally through the pore of the synapse.

2.5.2. Chemical synapses: is a type of synapse which converts electrical signal from presynaptic neuron to the post-synaptic neuron through the neurotransmitters that are released in the synaptic cleft and binds to their corresponding receptors.

A chemical synapse consists of several key components:

The presynaptic terminal: Also known as the synaptic knob, it is located along an axon or at its terminal end. It is densely packed with mitochondria and contains synaptic vesicles—

membrane-bound spheres that store neurotransmitters. This terminal also houses voltage-gated Ca^{2+} channels.

Neurotransmitters: These chemical molecules act as messengers that transmit information between the two cells involved in the chemical synapse.

The synaptic cleft: This is a narrow gap, approximately 20-30 nm wide, between the presynaptic and postsynaptic membranes. It allows neurotransmitters to diffuse across to the postsynaptic neuron, facilitating precise regulation of neurotransmitter concentration.

The postsynaptic membrane: It contains protein receptors that bind to neurotransmitters released from the presynaptic terminal, functioning according to a key-lock mechanism.

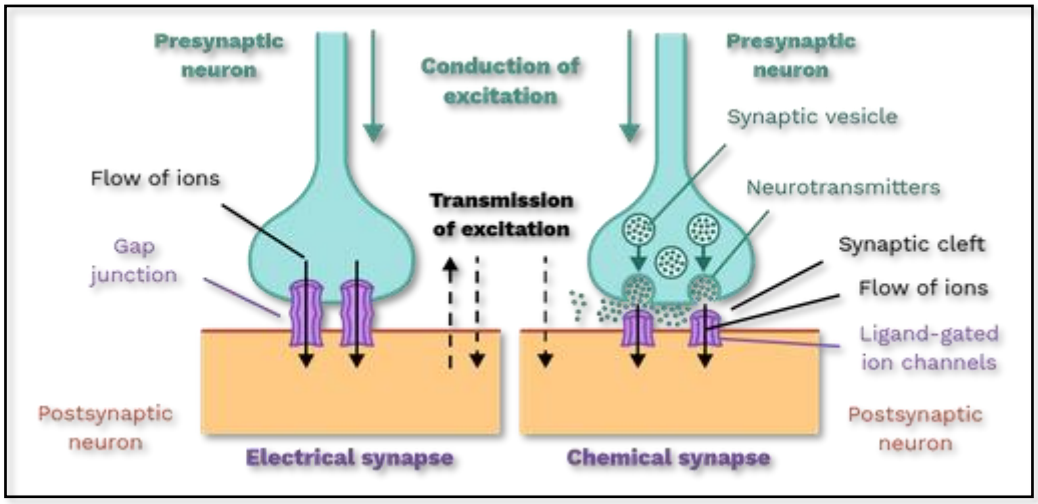

Figure 3. 9. Electrical and chemical synapses.

- **2.6. A reflex arc**

Concerning reflexes, reflex is a rapid automatic response to a stimulus. When you accidentally touch a hot object and automatically jerk your hand away, this is a reflex action. It happens without you having to think about it. The path taken by the nerve impulses in a reflex is called a reflex arc. Most reflex arcs involve only three neurons **(Figure 3. 10)**. The stimulus (a pin in the paw) stimulates the pain receptors of the skin, which initiate an impulse in a sensory neuron. This travels to the spinal cord where it passes, by means of a synapse, to a connecting neuron called the relay neuron situated in the spinal cord. The relay neuron in turn makes a synapse with one or more motor neurons that transmit the impulse to the muscles of the limb causing them to contract and remove the paw from the sharp object. Reflexes do not require

involvement of the brain although you are aware of what is happening and can, in some instances, prevent them happening.

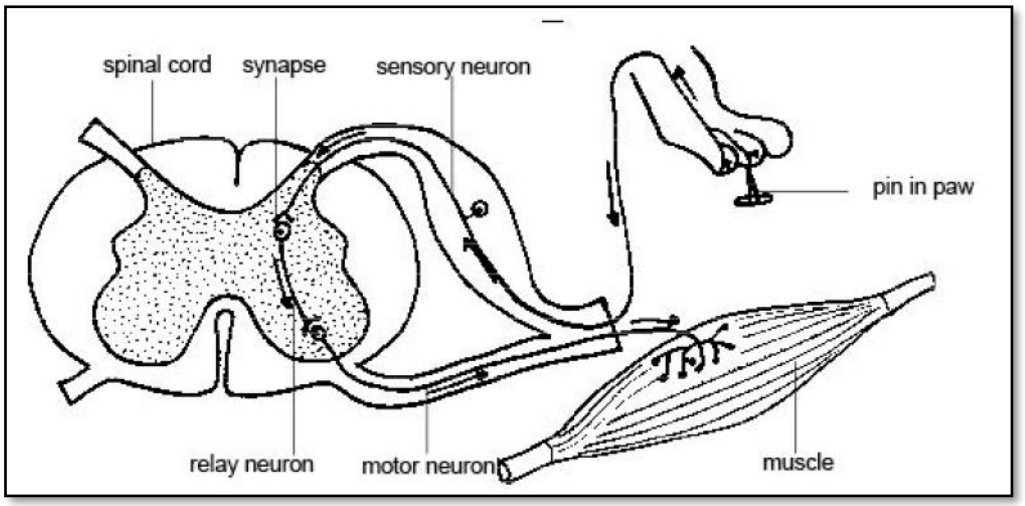

Figure 3. 10. A reflex arc.

3. Circulatory system

3.1. Introduction

Most animals are complex multicellular organisms that require a mechanism for transporting nutrients throughout their bodies and removing waste products. The circulatory system has evolved over time from simple diffusion through cells in the early evolution of animals to a complex network of blood vessels that reach all parts of the human body. Where the cardiovascular and lymphatic are both integral parts of the circulatory system. The cardiovascular system basically moves blood throughout the body. While the lymphatic system is part of the circulatory system, comprising a network of conduits called lymphatic vessels. Rather than blood the lymph systems carries a clear fluid called lymph (from Latin lympha, meaning "water goddess") unidirectionally towards the heart.

3.2. Circulatory system architecture

The circulatory system is effectively a network of cylindrical vessels: the arteries, veins, and capillaries that emanate from a pump, the heart.

3.2.1. Open circulatoty systems

In an open circulatory system, blood vessels transport all fluids into a cavity. When the animal moves, the blood inside the cavity moves freely around the body in all directions. The blood bathes the organs directly, thus supplying oxygen and removing waste from the organs. Most invertebrates (crabs, insects, snails etc.) have an open circulatory system.

3.2.2. Closed circulatory systems

Closed circulatory systems are different to open circulatory systems because blood never leaves the blood vessels. Instead, it is transferred from one blood vessel to another continuously without entering a cavity. Blood is transported in a single direction, delivering oxygen and nutrients to cells and removing waste products. Closed circulatory systems can be further divided into single circulatory systems and double circulatory systems. The two main circulation pathways in invertebrates are the single and double circulation pathways.

A) Single circulatory pathways

Single circulatory pathways consist of a double chambered heart with an atrium and ventricle. Fish possess single circulation pathways. The heart pumps deoxygenated blood to the gills where it gets oxygenated. Oxygenated blood is then supplied to the entire fish body, with deoxygenated blood returned to the heart.

B) Double circulatory systems

Most mammals, including humans, have this type of circulatory system. These circulatory systems are called 'double' circulatory systems because they are made up of two circuits, referred to as the pulmonary and systemic circulatory systems as illustrated in **figure 3. 11**.

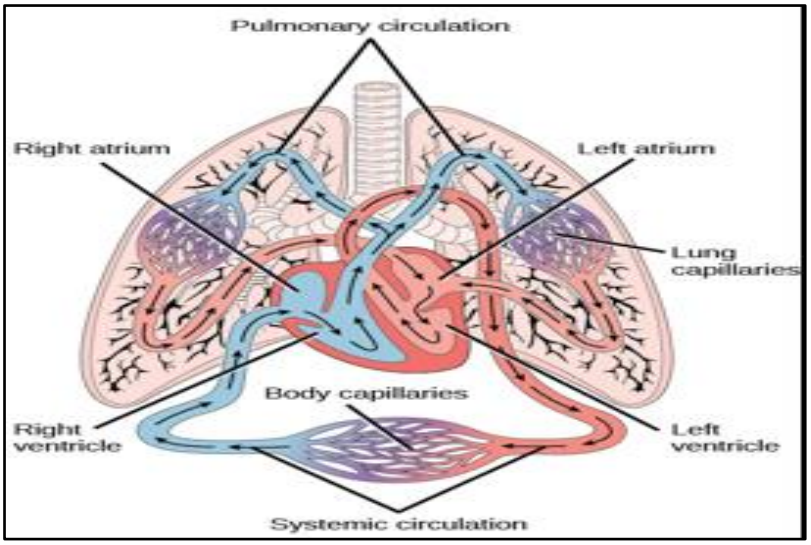

Figure 3. 11. Cardiovascular systems in mammals.

3.3.Cardiovascular system

3.3.1. Anatomic organization of the human cardiovascular system

- The heart has four chambers. The two **atria** serve as reservoirs for blood returning to the heart.
- The two **ventricles** are pumps that propel blood through the circulation.
- A **septum** divides the heart into right and left sides.
- The right atrium is the reservoir serving the right ventricle, which pumps blood to the **pulmonary circulation** via the pulmonary artery. Blood returns from the lungs to the left atrium via the pulmonary veins.
- The left ventricle propels blood, via the aorta, to all other organs in the body through the **systemic circulation (Figure 3. 12).**

Substances transported throughout the cardiovascular system can be categorized as (1) materials entering the body from the external environment (e.g., O_2 and nutrients); (2) materials moving between cells within the body (e.g., hormones and antibodies); and (3) waste products,

from cells, requiring elimination (e.g., heat and CO_2). The exchange of materials between blood and interstitial fluid occurs across capillaries in the microcirculation.

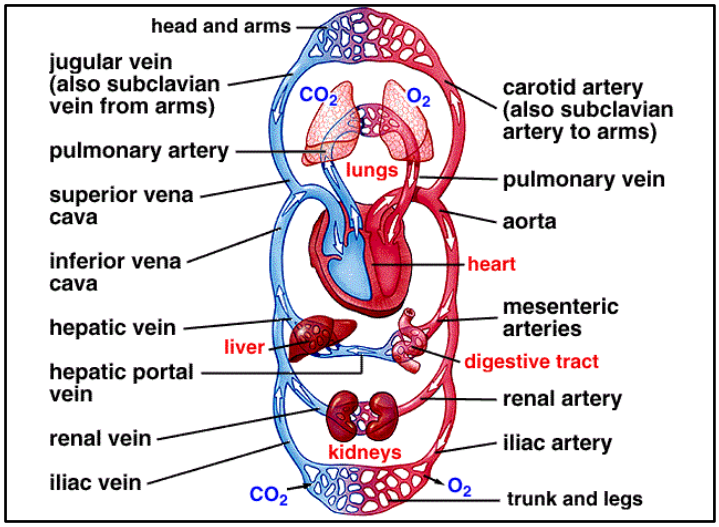

Figure 3. 12. Human cardiovascular system.

3.3.2. Human cardiovascular physiology

Cardiovascular system functions with the help of blood vessels. Some blood vessels (veins) return blood to your heart, while others (arteries) carry blood away from your heart. Blood vessels work with the heart and lungs to continuously move blood through the body. Here's how:

- The heart's right ventricle sends blood that's low in oxygen (oxygen-poor blood) to your lungs. Blood travels through the pulmonary trunk (the main pulmonary artery).

- The blood picks up oxygen in the lungs.

- Pulmonary veins carry the oxygenated blood from the lungs to the heart's left atrium.

- The left atrium sends the oxygenated blood into the left ventricle. This muscular part of the heart pumps blood out to the body through arteries.

-As blood moves through the body and organs, it drops off nutrients, transfers hormones and hauls away waste products.

- The veins carry deoxygenated blood and carbon dioxide back to the heart, which sends the blood to your lungs.

- The lungs exchange oxygen for carbon dioxide, which then exhale.

When blood gets oxygen from the lungs and brings it back to the heart, that's your pulmonary circulation. Systemic circulation describes supplying oxygen-rich blood to the

whole body. In the systemic circuit, oxygenated blood is pumped from the heart's left ventricle to the aorta, the body's largest artery. Blood leaves the aorta to join the systemic arteries, then the arterioles and capillary beds supplying the body's tissues.

3.3.3. The cardiac cycle

The cardiac cycle is described as the repetitive electrical and mechanical events that occur with each beat of the heart. Electrical events precede mechanical events, which result from the entry of Ca^{2+} into the myocytes during cardiac action potentials. Mechanical events of the cardiac cycle occur in five phases **(Figure 3. 13)**:

- **Ventricular diastole.** Throughout most of ventricular diastole, the atria and ventricles are relaxed. The AV valves are open, and the ventricles fill passively;
- **Atrial systole.** During atrial systole, a small amount of additional blood is pumped into the ventricles;
- **Isovolumic ventricular contraction.** Initial contraction increases ventricular pressure, closing the AV valves. Blood is pressurized during isovolumic ventricular contraction;
- **Ventricular ejection**. The semilunar valves open when ventricular pressures exceed pressures in the aorta and pulmonary artery. Ventricular ejection (systole) of blood follows;
- **Isovolumic relaxation**. The semilunar valves close when the ventricles relax and pressure in the ventricles decreases. The AV valves open when pressure in the ventricles decreases below atrial pressure. Atria fill with blood throughout ventricular systole, allowing rapid ventricular filling at the start of the next diastolic period.

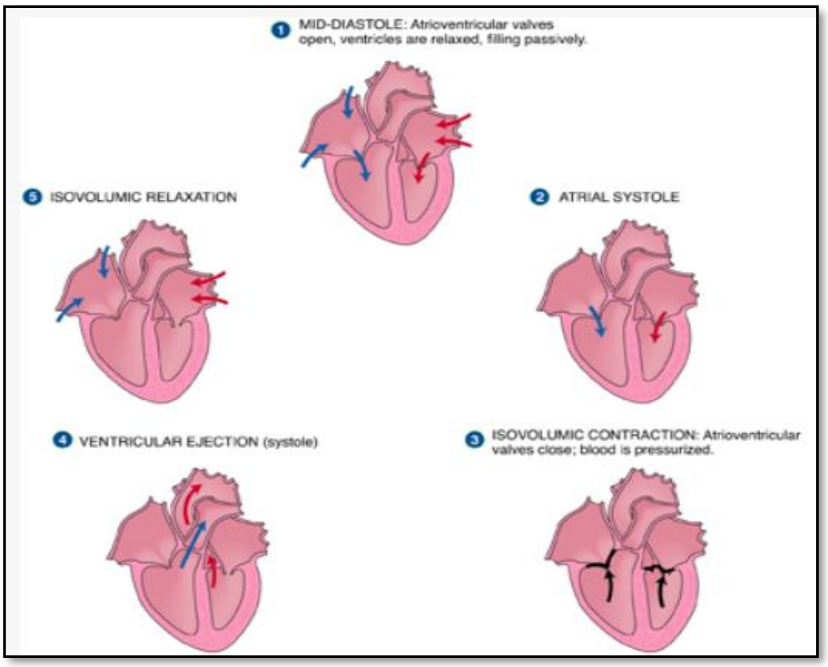

Figure 3. 13. Cardiac cycle.

3.4. Lymphatic system

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck **(Figure 3. 14).**

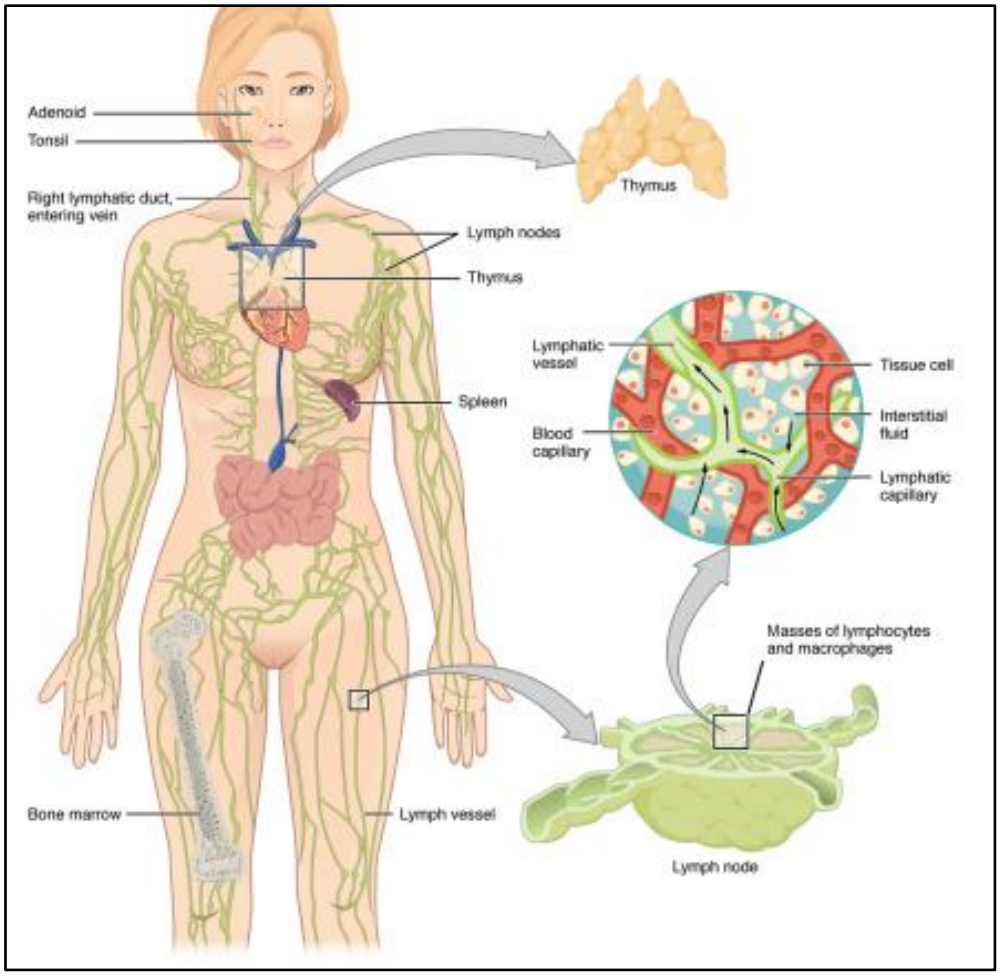

Figure 3. 14. Lymphatic system

4. Elimination and secretion

4.1. Introduction

Organisms consume food for survival, growth and repair. Most of the food is digested and utilised by the body for the production of energy; the rest is expelled from the body by the digestive system in the form of feces. This process is not called excretion, though; it is called egestion (also known as defecation). In another way, excretion means elimination of metabolic waste products and unused materials from an organism's body. Animals accumulate ammonia, urea, uric acid, carbon dioxide, water and ions like Na^+, K^+, Cl^-, phosphate, sulphate, etc., either by metabolic activities or by other means like excess ingestion. These substances have to be removed totally or partially.

4.2. Modes of excretion

The organisms control osmotic pressure – the balance between inorganic ions and water and maintain acid-base balance through this process. It also helps in promoting homeostasis, a process that helps maintain the stability that helps the organs or biological systems to survive.

The excretory system beings expels wastes that are usually toxic when they accumulate in the body. Sweating is also a type of excretion displayed by humans. Depending on the chemical composition, there are two types of excretory waste products: Nitrogenous (Ammonia, urea, and uric acid…) and non-nitrogenous include carbon dioxide, non-metabolised minerals and vitamins, excess of water, pigments, hormones and drugs in the body. Carbon dioxide is eliminated through the lungs in the respiratory system; excess of water is removed by sweating, urination and as moisture in the expired air. Excess of minerals, vitamins and pigments are excreted along with urine, sweat or faecal matter. Based on the excretory product, several modes of excretion are known in animals. They are:

4.2.1. Ammonotelism

The process of eliminating ammonia from the body is known as ammonotelism. Ammonia, as it is readily soluble, is generally excreted by diffusion across body surfaces or through gill surfaces (in fish) as ammonium ions.

4.2.2. Ureotelism

In some mammals, urea is excreted as a metabolic waste product. It is less toxic and comparatively less soluble in water. Such organisms are called ureotelic. In these organisms, ammonia that is produced is converted to urea in the liver of animals and is released back into the blood. The kidneys filter the urea and expel the urea outside the body. Some of the urea is retained

in the matrix of the kidney to maintain a desired osmolarity in the organisms. Humans are ureotelic as we expel the urea through urine. Moreover, urea is comparatively less toxic than ammonia.

4.2.3. Uricotelism

Uricotelic animals remove nitrogenous wastes as uric acid in the form of pellets or paste.

4.2.4. Aminotelism

Some Molluscs and Echinoderms excrete waste products from the body in the form of amino acids. This feature is called aminotelism.

4.2.5. Guanotelism

Spiders convert the ammonia into guanine before excretion. This characteristic is also found in some reptiles, birds and earthworms. It is also insoluble in water; hence no water is required for its excretion.

4.3. Excretory and elimination

Elimination is sometimes used in a broader sense and includes the removal of the absorbed xenobiotic through metabolic pathways as well as through excretion. Diverse mechanisms have evolved that enable the various animal species to inhabit a wide range of environments. In animals whose bodies consist of a single layer of cells, waste disposal is accomplished principally by diffusion from the site of waste production to the outside environment. This method is efficient when the distances over which wastes diffuse are relatively short, when there is a high surface area to volume relationship, and when the rate of waste production is relatively low. In more complex animals, however, waste elimination by diffusion through the body wall to the exterior is less efficient because individual cells are farther removed from the exterior surface of the organism.

The presence of specialized mechanisms of elimination in higher animals enables wastes to be rapidly transported to the exterior surface of the body.

4.3.1. Excretion in human

For example, in humans, the excretory system consists of a pair of kidneys **(Figure 3. 15),** one pair of ureters, a urinary bladder and a urethra.

A human body is an exceptional machine, where different life-processes (respiration, circulation, digestion, etc.) take place simultaneously. As a result, many waste products produced in our body are in various forms that include carbon dioxide, water, and nitrogenous products like urea, ammonia, and uric acid. Blood contains both useful and harmful substances. Hence, we have kidneys which separate useful substances by reabsorption and toxic substances by producing urine.

Kidney has a structural filtration unit called nephron where the blood is filtered. Each kidney contains a million nephrons. Capillaries of kidneys filter the blood and the essential substances like glucose, amino acids, salts, and the required amount of water get reabsorbed and the blood goes into circulation. Excess water and nitrogenous waste in humans are converted to urine. Urine thus produced is passed to the urinary bladder via the ureters. The urinary bladder is under the control of the Central Nervous System. The brain signals the urinary bladder to contract and through the urinary opening called the urethra, we excrete the urine **(Figure 3.15)**.

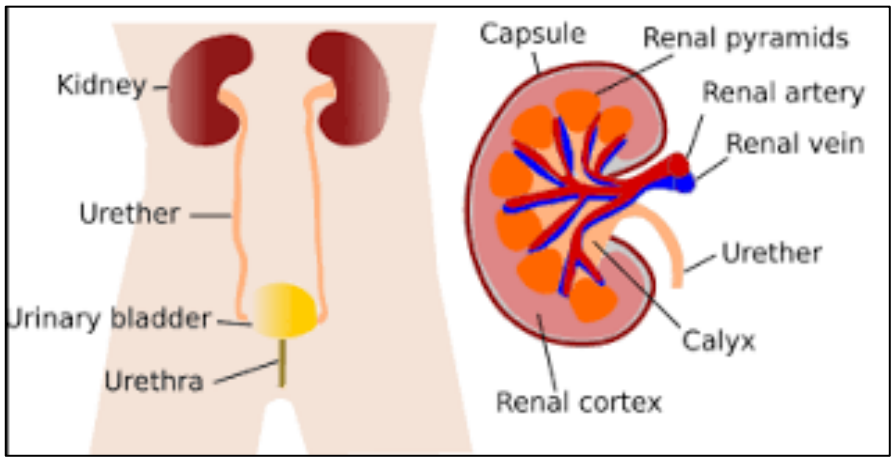

Figure 3. 15. Human urinary system.

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