Blood

Blood (about 5.5 L in a man) consists of the cells and fluid that flow in a regular unidirectional movement within the closed circulatory system. Blood is made up of two parts:***blood cells****, and* ***plasma***. The ***blood cells***are **erythrocytes** (red blood cells), **platelets,** and **leukocytes** (white blood cells).

Blood that is collected and kept from coagulating by the addition of anticoagulants (eg, heparin, citrate) separates, when centrifuged, into layers that reflect its heterogeneity. The **hematocrit** is an estimate of the volume of packed erythrocytes per unit volume of blood. The normal value is 40–50% in men and 35–45% in women.

The translucent, yellowish, somewhat viscous supernatant obtained when whole blood is centrifuged is the **plasma**. The formed elements of the blood separate into two easily distinguishable layers. The lower layer represents 42–47% of the entire volume of blood in the hematocrit tube. It is red and is made up of erythrocytes. The layer immediately above (1% of the blood volume), which is white or grayish in color, is called the **buffy coat** and consists of leukocytes. These elements separate because the leukocytes are less dense than the erythrocytes. Covering the leukocytes is a fine layer of platelets not distinguishable by the naked eye.

Leukocytes, which have diversified functions, are one of the body's chief defenses against infection. They circulate throughout the body via the blood vascular system, but while suspended in the blood they are round and inactive. Crossing the wall of venules and capillaries, these cells penetrate the tissues, where they display their defensive capabilities. The blood is a distributing vehicle, transporting oxygen, carbon dioxide (CO_2), metabolites, and hormones, among other substances. O_2 is bound mainly to the hemoglobin of the erythrocytes, whereas CO_2, in addition to being bound to the proteins of the erythrocytes (mainly hemoglobin), is carried in solution in the plasma as CO_2 or HCO_3^-.

The plasma transports nutrients from their site of absorption or synthesis, distributing them to various areas of the organism. It also transports metabolic residues, which are removed from the blood by the excretory organs. Blood, as the distributing vehicle for the hormones, permits the exchange of chemical messages between distant organs for normal cellular function. It further participates in the regulation of body temperature and in acid–base and osmotic balance.

Composition of Plasma

Plasma is an aqueous solution containing substances of low or high molecular weight that make up 10% of its volume. The plasma proteins account for 7% of the volume and the inorganic salts for 0.9%; the remainder of the 10% consists of several organic compounds ,eg, amino acids, vitamins, hormones, lipoproteins of various origins.

The composition of plasma is usually an indicator of the mean composition of the extracellular fluids in general.

The main plasma proteins are **albumin** and **globulins; lipoproteins,** and proteins that participate in blood coagulation, such as **prothrombin** and **fibrinogen.** Albumin, the most abundant component, has a fundamental role in maintaining the osmotic pressure of the blood.

Products and Functions of the Blood Cells.		
Cell Type	***Main Products***	***Main Functions***
Erythrocyte	Hemoglobin	CO_2 and O_2 transport
Leukocytes	Specific granules and modified lysosomes(azurophilic granules)	Phagocytosis of bacteria
Neutrophil (terminal cell)		
Eosinophil (terminal cell)	Specific granules, pharmacologically active substances	Defense against parasitic helminths; modulation of inflammatory processes
Basophil (terminal cell)	Specific granules containing histamine and heparin	Release of histamine and other inflammation mediators
Monocyte (not terminal cell)	Granules with lysosomal enzymes	Generation of mononuclear-phagocyte system cells in tissues; phagocytosis and digestion of protozoa and virus and senescent cells
B lymphocyte	Immunoglobulins	Generation of antibody-producing terminal cells (plasma cells)
T lymphocyte	Substances that kill cells. Substances that control the activity of other leukocytes (interleukins)	Killing of virus-infected cells
Natural killer cell (lacks T and B cell markers)	Attacks virus-infected cells and cancer cells without previous stimulation	Killing of some tumor and virus-infected cells
Platelet	Blood-clotting factors	Clotting of blood

Staining of Blood Cells

Blood cells are generally studied in ***smears or films*** prepared by spreading a drop of blood in a thin layer on a microscope slide. The blood should be evenly distributed over the slide and allowed to dry rapidly in air. In such films the cells are clearly visible and distinct from one another. Their cytoplasm is spread out, facilitating observation of their nuclei and cytoplasmic organization.

Blood smears are routinely stained with special mixtures of red (acidic) and blue (basic) dyes. These mixtures also contain **azures,** dyes that are useful in staining some structures of blood cells known as **azurophilics** (azure + Gr. *philein*, to love). Some of these special mixtures ***(eg, Giemsa, Wright's, Leishman's)*** are named for the investigators who introduced their own modifications into the original mixture.

Erythrocytes

Erythrocytes (red blood cells), which are anucleate, are packed with the O_2-carrying protein hemoglobin. Under normal conditions, these corpuscles never leave the circulatory system.

Most mammalian erythrocytes are biconcave disks without nuclei. When suspended in an isotonic medium, human erythrocytes are 7.5 mμ in diameter, 2.6 mμ thick at the rim, and 0.8 mμ thick in the center. *The biconcave shape provides erythrocytes with a large surface-to-volume ratio, thus facilitating gas exchange.*

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.

Leukocytes

Leukocytes (white blood cells) migrate to the tissues, where they perform multiple functions and most die by apoptosis. According to the type of granules in their cytoplasm and the shape of their nuclei, leukocytes are divided into two groups: **granulocytes** (polymorphonuclear leukocytes) and **agranulocytes** (mononuclear leukocytes). Both granulocytes and agranulocytes are spherical while suspended in blood plasma, but some become ameboid after leaving the blood vessels and invading the tissues. Their estimated sizes mentioned below refer to blood smears, in which the cells are spread and appear larger than they actually are in the blood.

Granulocytes possess two types of granules: 1-the **specific** granules that bind neutral, basic, or acidic components of the dye mixture and have specific functions and 2-the **azurophilic granules.**Azurophilic granules stain purple and are lysosomes. Granulocytes have nuclei with two or more lobes and include the **neutrophils, eosinophils,** and **basophils**. All granulocytes are nondividing terminal cells with a life span of a few days, dying by apoptosis in the connective tissue. The resulting cellular debris is removed by macrophages and does not elicit an inflammatory response. Being nondividing terminal cells, granulocytes do not synthesize much protein. Their Golgi complex and rough endoplasmic reticulum are poorly developed. They have few mitochondria (low energy metabolism) and depend more on glycolysis; they contain glycogen and can function in regions scarce in oxygen, such as inflamed areas.

Agranulocytes do not have specific granules, but they do contain azurophilic granules (lysosomes) that bind the azure dyes of the stain. The nucleus is round or indented. This group includes **lymphocytes** and **monocytes**.

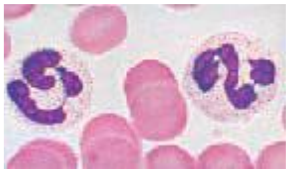
Number and Percentage of Blood Corpuscles (Blood Count).		
Corpuscle Type	**Approximate Number per μL[a]**	**Approximate Percentage**
Erythrocyte	Female: 3.9–5.5 x 10^6/μL	
	Male: 4.1–6 x 10^6/μL	
Reticulocyte		1% of the erythrocyte count
Leukocyte	6000–10,000	
Neutrophil	5000	60–70%
Eosinophil	150	2–4%
Basophil	30	0.5%
Lymphocyte	2400	28%
Monocyte	350	5%
Platelet	300,000	

Leukocytes are involved in the cellular and humoral defense of the organism against foreign material. In suspension in the circulating blood, they are spherical, nonmotile cells, but they are capable of becoming flattened and motile on encountering a solid substrate. Leukocytes leave the venules and capillaries by passing between endothelial cells and penetrating the connective tissue by **diapedesis**, a process that accounts for the unidirectional flow of granulocytes and monocytes from the blood to the tissues. Diapedesis is increased in individuals infected by microorganisms. Inflamed areas release chemicals originating mainly from cells and microorganisms, which increase diapedesis. The attraction of specific cells by chemical mediators is called **chemotaxis,** a significant event in inflammation through which leukocytes rapidly concentrate in places where their defensive properties are needed.

The number of leukocytes in the blood varies according to age, sex, and physiological conditions. In normal adults, there are roughly 6000–10,000 leukocytes per microliter of blood.

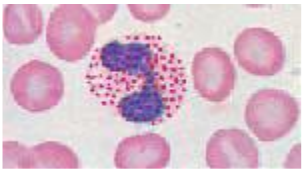
Neutrophils (Polymorphonuclear Leukocytes)

Neutrophils constitute 60–70% of circulating leukocytes. They are 12–15 mμ in diameter (in blood smears), with a nucleus consisting of two to five (usually three) lobes linked by fine threads of chromatin.



Eosinophils

Eosinophils are far less numerous than neutrophils, constituting only 2–4% of leukocytes in normal blood. In blood smears, this cell is about the same size as a neutrophil and contains a characteristic bilobednucleus. The main identifying characteristic is the presence of many large and elongated refractile specific granules (about 200 per cell) that are stained by eosin.It contains a protein—called the **major basic protein**—with a large number of arginine residues. This protein constitutes 50% of the total granule protein and accounts for the eosinophilia of these granules. *The major basic protein also seems to function in the killing of parasitic worms such as schistosomes.*

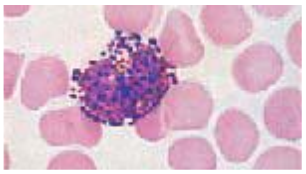


Basophils

Basophils make up less than 1% of blood leukocytes and are therefore difficult to find in smears of normal blood. They are about 12–15 mμ in diameter. The nucleus is divided into irregular lobes, but the overlying specific granules usually obscure the division.

The specific granules (0.5 mμ in diameter) stain metachromatically (change the color of the stain used) with the basic dye of the usual blood stains. This metachromasia is due to the presence of heparin. Specific granules in basophils are fewer and more irregular in size and shape than the granules of the other granulocytes. Basophilic specific granules contain heparin and histamine. Basophils may supplement the functions of mast cells in immediate hypersensitivity reactions by migrating into connective tissues.

There is some similarity between granules of basophils and those of mast cells. Both are metachromatic and contain heparin and histamine. Despite the similarities they present, mast cells and basophils are not the same, for even in the same species they have different structures, and they originate from different stem cells in the bone marrow.



Lymphocytes

Lymphocytes constitute a family of spherical cells with similar morphological characteristics. They can be classified into several groups according to distinctive surface molecules (markers), which can be distinguished by immunocytochemical methods. They also have diverse functional roles, all related to immune reactions in defending against invading microorganisms, foreign macromolecules, and cancer cells.

Lymphocytes with diameters of 6–8 mμ are known as **small lymphocytes.** A small number of **medium-sized lymphocytes** and **large lymphocytes** with diameters up to 18 mμ are present in the circulating blood. This difference has functional significance in that some larger lymphocytes are believed to be cells activated by specific antigens. The small lymphocyte, which is predominant in the blood, has a spherical nucleus, sometimes with an indentation. Its chromatin is condensed and appears as coarse clumps, so that the nucleus is intensely stained in the usual preparations, a characteristic that facilitates identification of the lymphocyte. In blood smears, the nucleolus of the lymphocyte is not visible, but it can be demonstrated by special staining techniques and with the electron microscope. The cytoplasm of the small lymphocyte is scanty, and in blood smears it appears as a thin rim around the nucleus. It is slightly basophilic, assuming a light blue color in stained smears. It may contain a few azurophilic granules. The cytoplasm of the small lymphocyte has a few mitochondria and a small Golgi complex; it contains free polyribosomes.

Lymphocytes vary in life span; some live only a few days, and others survive in the circulating blood for

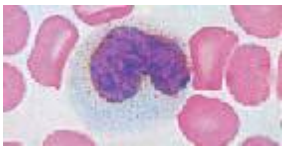
many years. Lymphocytes are the only type of leukocytes that return from the tissues back to the blood, after diapedesis.

Monocytes

Monocytes are bone marrow-derived agranulocytes with diameters varying from 12 to 20 mμ. The nucleus is oval, horseshoe, or kidney shaped and is generally eccentrically placed. The chromatin is less condensed than that in lymphocytes. Because of their delicate chromatin distribution, the nuclei of monocytes stain lighter than do those of large lymphocytes.

The cytoplasm of the monocyte is basophilic and frequently contains very fine azurophilic granules (lysosomes), some of which are at the limit of the light microscope's resolution. These granules are distributed through the cytoplasm, giving it a bluish-gray color in stained smears. In the electron microscope, one or two nucleoli are seen in the nucleus, and a small quantity of rough endoplasmic reticulum, polyribosomes, and many small mitochondria is observed. A Golgi complex involved in the formation of the lysosomal granules is present in the cytoplasm. Many microvilli and pinocytotic vesicles are found at the cell surface.

Blood monocytes are not terminal cells; rather, they are precursor cells of the mononuclear phagocyte system. After crossing venule or capillary walls and entering connective tissues, monocytes differentiate into macrophages.



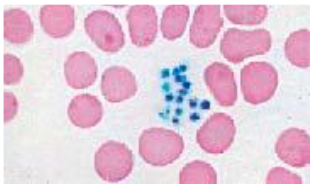
Platelets

Blood platelets (**thrombocytes**) are nonnucleated, disklike cell fragments 2–4 mμ in diameter. Platelets originate from the fragmentation of giant polyploid**megakaryocytes** that reside in the bone marrow. Platelets promote blood clotting and help repair gaps in the walls of blood vessels, preventing loss of blood. Normal platelet counts range from 200,000 to 400,000 per microliter of blood. Platelets have a life span of about 10 days.

In stained blood smears, platelets often appear in clumps. Each platelet has a peripheral light blue-

stained transparent zone, the **hyalomere,** and a central zone containing purple granules, called the **granulomere.**

Platelets contain a system of channels, the **open canalicularsystem,** that connects to invaginations of the platelet plasma membrane. This arrangement is probably of functional significance in facilitating the liberation of active molecules stored in platelets. Around the periphery of the platelet lies a **marginal bundle** of microtubules; this bundle helps to maintain the platelet's ovoid shape. In the hyalomere, there are also a number of electron-dense irregular tubes known as the **dense tubular system.** Actin and myosin molecules in the hyalomere can assemble to form a contractile system that functions in platelet movement and aggregation. A cell coat rich in glycosaminoglycans and glycoproteins, 15–20 nm thick, lies outside the plasmalemma and is involved in platelet adhesion.The central granulomere possesses a variety of membrane-bound granules and a sparse population of mitochondria and glycogen particles.



Platelet Functions

The role of platelets in controlling hemorrhage can be summarized as follows.

1-Primary aggregation—Discontinuities in the endothelium, produced by injuries, are followed by platelet aggregation to the exposed collagen, via collagen-binding protein in platelet membrane. Thus, a **platelet plug** is formed as a first step to stop bleeding.
2-Secondary aggregation—Platelets in the plug release an adhesive glycoprotein and ADP. Both are potent inducers of platelet aggregation, increasing the size of the platelet plug.
3-Blood coagulation—During platelet aggregation, factors from the blood plasma, damaged blood vessels, **fibrin,** that forms a three-dimensional network of fibers trapping red cells, leukocytes, and platelets to form a **blood clot,** or **thrombus.**
4-Clot retraction—The clot that initially bulges into the blood vessel lumen contracts because of the interaction of platelet actin, myosin, and ATP.
5-Clot removal—Protected by the clot, the vessel wall is restored by new tissue formation. The clot is then removed, mainly by the proteolytic enzyme.

Hematopoiesis

Mature blood cells have a relatively short life span (Gr. *haima,* blood, + *poiesis,* a making) organs. In the earliest stages of embryogenesis, blood cells arise from the *yolk sac* mesoderm. Sometime later, the *liver and spleen* serve as temporary hematopoietic tissues, but by the second month the clavicle has begun to ossify and begins to develop bone marrow in its core. As the prenatal ossification of the rest of the skeleton accelerates, the *bone marrow* becomes an increasingly important hematopoietic tissue.

At last 1/3 of intrauterine life, after birth and on into childhood, erythrocytes, granular leukocytes, monocytes, and platelets are derived from stem cells located in bone marrow. The origin and maturation of these cells are termed, respectively, erythropoiesis (Gr. *erythros,* red, + *poiesis*), granulopoiesis, monocytopoiesis, and megakaryocytopoiesis. The bone marrow also produces cells that migrate to the lymphoid organs, producing the various types of lymphocytes.

Before attaining maturity and being released into the circulation, blood cells go through specific stages of differentiation and maturation. Because these processes are continuous, cells with characteristics that lie between the various stages are frequently encountered in smears of blood or bone marrow.

Pluripotential Hematopoietic Stem Cells

It is believed that all blood cells arise from a single type of stem cell in the bone marrow. Because this cell can produce all blood cell types, it is called a *pluripotential stem cell*. These cells proliferate and form one cell lineage that will become *lymphocytes* (lymphoid cells) and another lineage that will form the *myeloid cells* that develop in bone marrow (granulocytes, monocytes, erythrocytes, and megakaryocytes). Early in their development, lymphoid cells migrate from the bone marrow to the thymus, lymph nodes, spleen, and other lymphoid structures, where they proliferate.

Progenitor & Precursor Cells

Hematopoiesis is therefore the result of simultaneous, continuous proliferation and differentiation of cells derived from stem cells whose potentiality is reduced as differentiation progresses. This process can be observed in both *in vivo* and *in vitro* studies, in which colonies of cells derived from stem cells with various potentialities appear. Colonies derived from a myeloid stem cell can produce erythrocytes, granulocytes, monocytes, and megakaryocytes, all in the same colony.

In these experiments, however, some colonies produce only red blood cells (erythrocytes). Other colonies produce granulocytes and monocytes. Cells forming colonies are called colony-forming cells (CFC) or colony-forming units (CFU). The

convention in naming these various cell colonies is to use the initial letter of the cell each colony produces. Thus, MCFC denotes a monocyte-forming colony, ECFC forms erythrocytes, MGCFC forms monocytes and granulocytes, and so on.

Once the necessary environmental conditions are present, the development of blood cells depends on factors that affect cell proliferation and differentiation. These substances are called growth factors, colony-stimulating factors (CSF).

Under normal conditions, the production of blood cells by the bone marrow is adjusted to the body's needs, increasing its activity several-fold in a very short time. Bone marrow is found in the medullary canals of long bones and in the cavities of cancellous bones. Two types of bone marrow have been described based on their appearance on gross examination: *red, or hematogenous*, bone marrow, whose color is produced by the presence of blood and blood-forming cells; and *yellow bone marrow*, whose color is produced by the presence of a great number of adipose cells. In newborns, all bone marrow is red and is therefore active in the production of blood cells. As the child grows, most of the bone marrow changes gradually into the yellow variety. *Under certain conditions, such as severe bleeding or hypoxia, yellow bone marrow is replaced by red bone marrow.*

Red Bone Marrow

Red bone marrow is composed of a **1-*stroma*,2- *hematopoietic cords*, and 3-*sinusoidal capillaries*.** The stroma is a three-dimensional meshwork of reticular cells and a delicate web of reticular fibers containing hematopoietic cells and macrophages. The stroma of bone marrow contains collagen types I and III, fibronectin, laminin, and proteoglycans. The sinusoids are formed by a discontinuous layer of endothelial cells.

An external discontinuous layer of reticular cells and a loose net of reticular fibers reinforce the sinusoidal capillaries.

The main functions of red bone marrow are the production of blood cells, destruction of worn-out red blood cells, and storage (in macrophages) of iron derived from the breakdown of hemoglobin.

Maturation of Erythrocytes

A mature cell is one that has differentiated to the stage at which it has the capability of carrying out all its specific functions. The basic process in maturation is *the synthesis of hemoglobin* and *the formation of an enucleated*, biconcave, small corpuscle, the erythrocyte. During maturation of the erythrocyte, several major changes. Cell volume decreases, and the nucleoli diminish in size until they become invisible in the light microscope. The nuclear diameter decreases, and the chromatin becomes

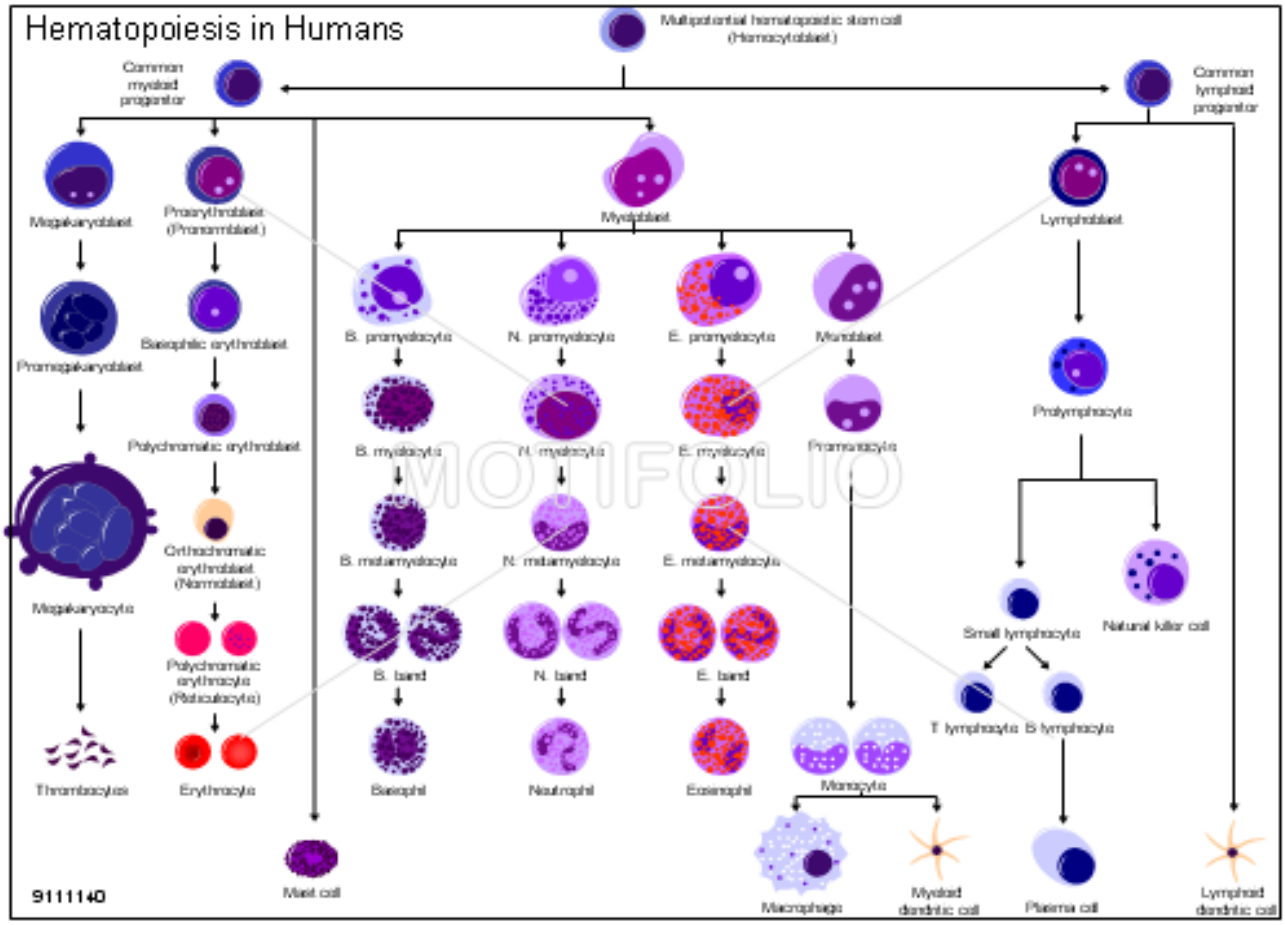
increasingly more dense until the nucleus presents a pyknotic appearance and is finally extruded from the cell. There is a gradual decrease in the number of polyribosomes (basophilia decreases), with a simultaneous increase in the amount of hemoglobin (an acidophilic protein) 5 Mitochondria and other organelles gradually disappear.

There are three to five intervening cell divisions between the proerythroblast and the mature erythrocyte. The development of an erythrocyte from the first recognizable cell of the series to the release of reticulocytes into the blood takes approximately 7 days. ***The hormone erythropoietin and substances such as iron, folic acid, and cyanocobalamin (vitamin B_{12}) are essential for the production of erythrocytes*.** Erythropoietin is a glycoprotein produced mainly in the kidneys that stimulates the production of mRNA for globin, the protein component of the hemoglobin molecule.

Differentiation

The differentiation and maturation of erythrocytes involve the formation (in order) of proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, orthochromatophilic erythroblasts (normoblasts), reticulocytes, and erythrocytes.

The first recognizable cell in the erythroid series is the *proerythroblast*. It is a large cell with loose, lacy chromatin and clearly visible nucleoli; its cytoplasm is basophilic. The next stage is represented by *the basophilic erythroblast*, with a strongly basophilic cytoplasm and a condensed nucleus that has no visible nucleolus. The basophilia of these two cell types is caused by the large number of polyribosomes involved in the synthesis of hemoglobin. During the next stage, polyribosomes decrease, and areas of the cytoplasm begin to be filled with hemoglobin. At this stage, staining causes several colors to appear in the cell *the polychromatophilic erythroblast*. In the next stage, the nucleus continues to condense and no cytoplasmic basophilia is evident, resulting in a uniformly acidophilic cytoplasm *the orthochromatophilic erythroblast*. At a given moment, this cell puts forth a series of cytoplasmic protrusions and expels its nucleus, encased in a thin layer of cytoplasm. The expelled nucleus is engulfed by macrophages. The remaining cell still has a small number of polyribosomes that, when treated with the dye brilliant cresyl blue, aggregate to form a stained network. This cell is *the reticulocyte*, which soon loses its polyribosomes and becomes a *mature erythrocyte.*



Granulopoiesis.

The maturation process of granulocytes takes place with cytoplasmic changes characterized by the synthesis of a number of proteins that are packed in two organelles: the azurophilic and specific granules. These proteins are produced in the rough endoplasmic reticulum and the Golgi complex in two successive stages. The first stage results in the production of the azurophilic granules, which stain with basic dyes in the Wright or Giemsa methods and contain enzymes of the lysosomal system. In the second stage, a change in synthetic activity takes place with the production of several proteins that are packed in the specific granules. These granules contain different proteins in each of the three types of granulocytes and are utilized for the various activities of each type of granulocyte. Evidently, a shift in gene expression occurs in this process, permitting neutrophils to specialize in bacterial destruction and eosinophils and basophils to become involved in the regulation of inflammation.

Maturation of Granulocytes

The *myeloblast* is the most immature recognizable cell in the myeloid series. It has a finely dispersed chromatin, and nucleoli can be seen. In the next stage, the *promyelocyte*(*pro,* before, + Gr. *myelos,* marrow, + *kytos,* cell) is characterized by its

basophilic cytoplasm and azurophilic granules. These granules contain lysosomal enzymes and myeloperoxidase. The promyelocyte gives rise to the three known types of granulocyte. The first sign of differentiation appears in the *myelocytes*, in which specific granules gradually increase in quantity and eventually occupy most of the cytoplasm. These *neutrophilic*, *basophilic*, *and eosinophilicmyelocytes* mature with further condensation of the nucleus and a considerable increase in their specific granule content. Before its complete maturation, the neutrophilic granulocyte passes through an intermediate stage in which its nucleus has the form of a curved rod (band cell). This cell appears in quantity in the blood after strong stimulation of hematopoiesis.

Maturation of Lymphocytes & Monocytes

Study of the precursor cells of lymphocytes and monocytes is difficult, because these cells do not contain specific cytoplasmic granules or nuclear lobulation, both of which facilitate the distinction between young and mature forms of granulocytes. Lymphocytes and monocytes are distinguished mainly on the basis of size, chromatin structure, and the presence of nucleoli in smear preparations. As lymphocyte cells mature, their chromatin becomes more compact, nucleoli become less visible, and the cells decrease in size. In addition, subsets of the lymphocyte series acquire distinctive cell-surface receptors during differentiation that can be detected by immunocytochemical techniques.

Lymphocytes

Circulating lymphocytes originate mainly in the thymus and the peripheral lymphoid organs (eg, spleen, lymph nodes, tonsils). However, all lymphocyte progenitor cells originate in the bone marrow. Some of these lymphocytes migrate to the thymus, where they acquire the full attributes of T lymphocytes. Subsequently, T lymphocytes populate specific regions of peripheral lymphoid organs.

Other bone marrow lymphocytes differentiate into B lymphocytes in the bone marrow and then migrate to peripheral lymphoid organs, where they inhabit and multiply in their own special compartments.

The first identifiable progenitor of lymphoid cells is the *lymphoblast*, a large cell capable of incorporating and dividing two or three times to form *prolymphocytes*. Prolymphocytes are smaller and have relatively more condensed chromatin but none of the cell-surface antigens that mark prolymphocytes as *T or B lymphocytes*. In the bone marrow and in the thymus, these cells synthesize cell-surface receptors characteristic of their lineage, but they are not recognizable as distinct B or T lymphocytes in routine histological procedures. Using immunocytochemical techniques makes the distinction.

Monocytes

The *monoblast* is a committed progenitor cell that is almost identical to the myeloblast in its morphological characteristics. Further differentiation leads to *the promonocyte*, a large cell (up to 18 mμ in diameter) with a basophilic cytoplasm and a large, slightly indented nucleus. The chromatin is lacy, and nucleoli are evident. Promonocytes divide twice in the course of their development into *monocytes*. A large amount of rough endoplasmic reticulum is present, as is an extensive Golgi complex in which granule condensation can be seen to be taking place. These granules are primary lysosomes, which are observed as fine azurophilic granules in blood monocytes. Mature monocytes enter the blood stream, circulate for about 8 h, and then enter the connective tissues, where they mature into macrophages and function for several months.

Origin of Platelets

In adults, platelets originate in the red bone marrow by fragmentation of the cytoplasm of mature megakaryocytes (Gr. megas, big, + karyon, nucleus, + kytos), which, in turn, arise by differentiation of megakaryoblasts.

*Megakaryoblasts :*The megakaryoblast is 15–50 μm in diameter and has a large ovoid or kidney-shaped nucleus with numerous nucleoli. The nucleus becomes highly polyploid (ie, it contains up to 30 times as much DNA as a normal cell) before platelets begin to form. The cytoplasm of this cell is homogeneous and intensely basophilic.

Megakaryocytes :The megakaryocyte is a giant cell (35–150μm in diameter) with an irregularly lobulated nucleus, coarse chromatin, and no visible nucleoli. The cytoplasm contains numerous mitochondria, a well-developed rough endoplasmic reticulum, and an extensive Golgi complex. Platelets have conspicuous granules, originating from the Golgi complex, that contain biologically active substances, such as platelet-derived growth factor, fibroblast growth factor, von Willebrand's factor (which promotes adhesion of platelets to endothelial cells), and platelet factor IV (which stimulates blood coagulation). With maturation of the megakaryocyte, numerous invaginations of the plasma membrane ramify throughout the cytoplasm, forming the demarcation membranes. This system defines areas of a megakaryocyte's cytoplasm that shed platelets, extruding them into the circulation.

The Circulatory System

The circulatory system comprises both the blood and lymphatic vascular systems. The blood vascular system is composed of the following structures:

The **heart,** an organ whose function is to pump the blood.

The **arteries,** a series of efferent vessels that become smaller as they branch, and whose function is to carry the blood, with nutrients and oxygen, to the tissues.

The **capillaries,** the smallest blood vessels, constituting a complex network of thin tubules that anastomose profusely and through whose walls the interchange between blood and tissues takes place.

The **veins,** which result from the convergence of the capillaries into a system of channels. These channels become larger as they approach the heart, toward which they convey the blood to be pumped again.

The **lymphatic vascular system** begins in the **lymphatic capillaries,** closed-ended tubules that anastomose to form vessels of steadily increasing size; these vessels terminate in the **blood vascular system** emptying into the large veins near the heart. One of the functions of the lymphatic system is to return the fluid of the tissue spaces to the blood. The internal surface of all components of the blood and lymphatic systems is lined by a single layer of a squamous epithelium, called ***endothelium.***

The endothelium is a special type of epithelium interposed as a semipermeable barrier between two compartments of the internal medium, the blood plasma and the interstitial fluid. Endothelium is highly differentiated to actively mediate and monitor the extensive bidirectional exchange of small molecules and to restrict the transport of some macromolecules.

In addition to their role in interchanges between blood and surrounding tissues, endothelial cells perform several other functions:

1. **Conversion** of angiotensin I to angiotensin II.
2. Conversion of bradykinin, serotonin, prostaglandins, norepinephrine, thrombin, etc, to biologically inert compounds.
3. **Lipolysis** of lipoproteins by enzymes located on the surface of endothelial cells, to yield triglycerides and cholesterol (substrates for steroid-hormone synthesis and membrane structure).
4. **Production of vasoactive factors** that affect the vascular tone, such as endothelins, vasoconstrictive agents, and nitric oxide, a relaxing factor.

Note that endothelial cells are functionally diverse based on the vessel they line.

Structural Plan of Blood Vessels

All blood vessels above a certain diameter have a number of structural features in common and present a general plan of construction. However, the same type of vessel can exhibit remarkable structural variations. On the other hand, the distinction between different types of vessels is often not clear-cut because the transition from one type of vessel to another is gradual.

Blood vessels are usually composed of the following layers, or tunics.

Tunica Intima; The intima consists of one layer of endothelial cells supported by a subendothelial layer of loose connective tissue containing occasional smooth muscle cells. In arteries, the intima is separated from the media by an **internal elastic lamina,** the most external component of the intima. This lamina, composed of elastin, has gaps (fenestrae) that allow the diffusion of substances to nourish cells deep in the vessel wall. As a result of the absence of blood pressure and the contraction of the vessel at death, the tunica intima of the arteries generally has an undulating appearance in tissue sections.

Tunica Media The media consists primarily of concentric layers of helically arranged smooth muscle cells. Interposed among these cells are variable amounts of elastic fibers and lamellae, reticular fibers (collagen type III), proteoglycans, and glycoproteins. Smooth muscle cells are the cellular source of this extracellular matrix. In arteries, the media has a thinner **external elastica lamina,** which separates it from the tunica adventitia.

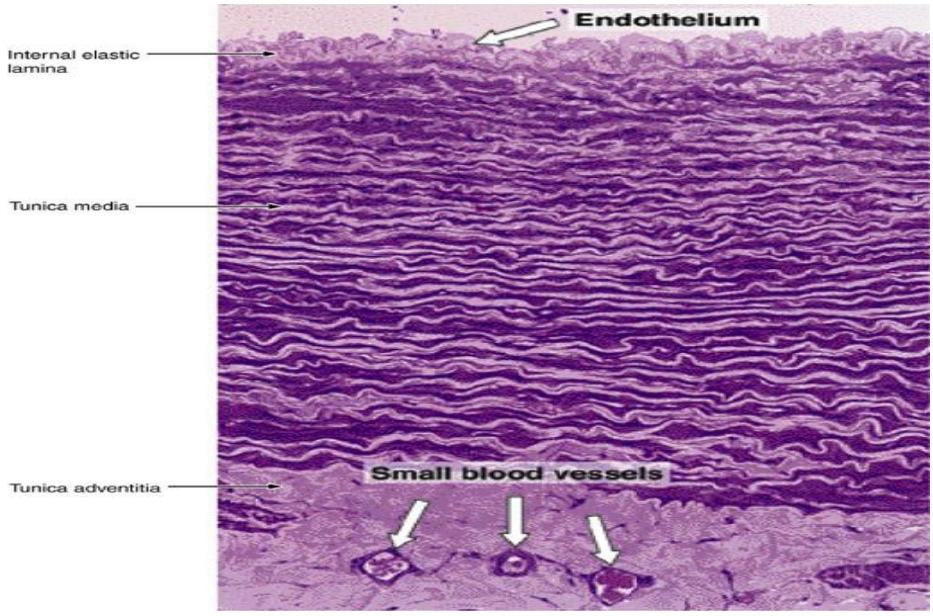
Tunica Adventitia The adventitia consists principally of collagen and elastic fibers. Collagen in the adventitia is type I. The adventitial layer gradually becomes continuous with the connective tissue of the organ through which the vessel runs.

Vasa Vasorum

Large vessels usually have vasa vasorum (vessels of the vessel), which are arterioles, capillaries, and venules that branch profusely in the adventitia and the outer part of the media. The vasa vasorum provide metabolites to the adventitia and the media, since in larger vessels the layers are too thick to be nourished solely by diffusion from the blood in the lumen. Vasa vasorum are more frequent in veins than in arteries. In arteries of intermediate and large diameter, the intima and the most internal region of the media are devoid of vasa vasorum. These layers receive oxygen and nutrition by diffusion from the blood that circulates into the lumen of the vessel.

Large Elastic Arteries:

Large elastic arteries help to stabilize the blood flow. In arteries, the intima is separated from the media by an **internal elastic lamina,** the most external component of the intima. The intima is thicker than the corresponding tunic of a muscular artery. An internal elastic lamina, although present, may not be easily discerned, since it is similar to the elastic laminae of the next layer. The media consists of elastic fibers and a series of concentrically arranged, perforated elastic laminae whose number increases with age (there are 40 in the newborn and 70 in the adult). Between the elastic laminae are smooth muscle cells, reticular fibers, proteoglycans, and glycoproteins. The tunica adventitia is relatively underdeveloped. The several elastic laminae contribute to the important function of making the blood flux more uniform. During ventricular contraction (**systole**), the elastic laminae of large arteries are stretched and reduce the pressure change. During ventricular relaxation (**diastole**), ventricular pressure drops to a low level, but the elastic rebound of large arteries helps to maintain arterial pressure. As a consequence, arterial pressure and blood velocity decrease and become less variable as the distance from the heart increases.



Atherosclerotic lesions: are characterized by focal thickening of the intima, proliferation of smooth muscle cells and increased deposition of extracellular connective tissue elements, and lipoproteins in the subendothelial layer. Monocytes are attracted to these areas where they differentiate into macrophages characterized by the extensive uptake of atherogenic lipoproteins by receptor-mediated endocytosis. When heavily loaded with lipid, these cells are referred to as **foam cells** and form the macroscopically visible fatty streaks and plaques that characterize **atherosclerosis.** These changes may extend to the inner part of the tunica media, and the thickening

may become so great as to occlude the vessel. Coronary arteries are among those most predisposed to atherosclerosis. Uniform thickening of the intima is believed to be a normal phenomenon of aging.

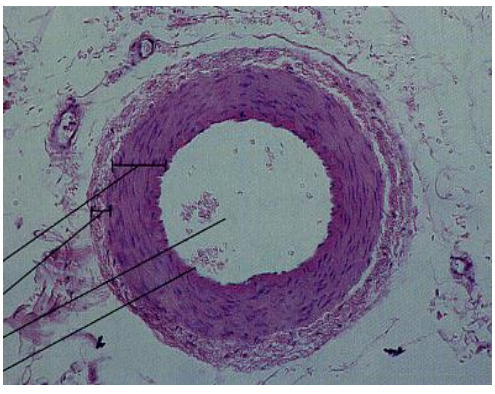
Some arteries irrigate only specific areas of certain organs, and obstruction of the blood supply results in **necrosis** (death of tissues from a lack of metabolites). These **infarcts** commonly occur in the heart, kidneys, cerebrum, and certain other organs. In other regions (such as the skin), arteries anastomose frequently, and the obstruction of one artery does not lead to tissue necrosis, because the blood flow is maintained.

When the media of an artery is weakened by an embryonic defect, disease, or lesion, the wall of the artery may dilate extensively. Progression of this process of dilatation leads to the development of an **aneurysm.** Rupture of the aneurysm brings severe consequences and may cause death.

Arteriovenous Anastomoses

Arteriovenous anastomoses participate in the regulation of blood flow in certain regions of the body by allowing direct communication between arterioles and venules. The luminal diameters of anastomotic vessels vary with the physiological condition of the organ. Changes in diameter of these vessels regulate blood pressure, flow, and temperature and the conservation of heat in particular areas. In addition to these direct connections, there are more complex structures, the **glomera** mainly in fingerpads, fingernail beds, and ears. When the arteriole penetrates the connective tissue capsule of the glomus, it loses an internal elastic membrane and develops a thick muscular wall and small lumen. All arteriovenous anastomoses are richly innervated by the sympathetic and parasympathetic nervous systems.

Medium (Muscular) Arteries



The muscular arteries may control the affluence of blood to the organs by contracting or relaxing the smooth muscle cells of the tunica media. The intima have a subendothelial layer that is somewhat thicker than that of the arterioles. The internal elastic lamina, the most external component of the intima, is prominent, and the tunica

media may contain up to 40 layers of smooth muscle cells. These cells are intermingled with various numbers of elastic lamellae (depending on the size of the vessel) as well as reticular fibers and proteoglycans, all synthesized by the smooth muscle fibers. An external elastic lamina, the last component of the media, is present only in the larger muscular arteries. The adventitia consists of connective tissue. Lymphatic capillaries, vasa vasorum, and nerves are also found in the adventitia, and these structures may penetrate to the outer part of the media

Arterioles

The arterioles are generally less than 0.5 mm in diameter and have relatively narrow lumens. The subendothelial layer is very thin. In the very small arterioles, the internal elastic lamina is absent, and the media is generally composed of one or two circularly arranged layers of smooth muscle cells; it shows no external elastic lamina. Above the arterioles are small arteries in which the tunica media is more developed, and the lumens are larger than those of the arterioles. In both arterioles and small arteries, the tunica adventitia is very thin.

Capillaries

Capillaries have structural variations to permit different levels of metabolic exchange between blood and surrounding tissues. They are composed of a single layer of **endothelial cells** rolled up in the form of a tube. The average diameter of capillaries varies from 7 to 9mμ, and their length is usually not more than 50 mμ. The total length of capillaries in the human body has been estimated at 96,000 km (60,000 miles). When cut transversely, their walls are observed to consist of portions of one to three cells. The external surfaces of these cells usually rest on a basal lamina, a product of endothelial origin.

In general, endothelial cells are polygonal and elongated in the direction of blood flow. The nucleus causes the cell to bulge into the capillary lumen. Its cytoplasm contains few organelles, including a small Golgi complex, mitochondria, free ribosomes, and a few cisternae of rough endoplasmic reticulum. Junctions of the zonula occludentes type are present between most endothelial cells and are of physiologic importance. Such junctions offer variable permeability to the macromolecules that play a significant role in both normal and pathological conditions.

Junctions between endothelial cells of venules are the loosest. At these locations there is a characteristic loss of fluid from the circulatory system during the inflammatory response, leading to edema.

At various locations along capillaries and postcapillary venules are cells of mesenchymal origin with long cytoplasmic processes that partly surround the

endothelial cells. These cells, called **pericytes**, are enclosed in their own basal lamina, which may fuse with that of the endothelial cells. The presence of myosin, actin, and tropomyosin in pericytes strongly suggests that these cells also have a contractile function. After tissue injuries, pericytes proliferate and differentiate to form new blood vessels and connective tissue cells, thus participating in the repair process.

Capillaries have structural variations to permit different levels of metabolic exchange between blood and surrounding tissues. They can be grouped into three types, depending on the continuity of both the endothelial sheet and the basal lamina.

1. The **continuous,** or **somatic, capillaries** are characterized by the absence of fenestrae in their wall. They are found in all types of muscle tissue, connective tissue, exocrine glands, and nervous tissue. In some places, but not in the nervous system, numerous pinocytotic vesicles are present on both surfaces of endothelial cells. Pinocytotic vesicles appear as isolated vesicles in the cytoplasm of these cells. They can also fuse forming transendothelial channels, responsible for the transport of macromolecules in both directions across the endothelial cytoplasm.

2. The **fenestrated,** or **visceral,capillaries** are characterized by the presence of several circular transcellular openings in the endothelium membrane called **fenestrae.** Fenestrae are limited by the cell membrane, resulting in a continuous cell membrane channel from the blood front to the tissue front. Each fenestra is obliterated by a **diaphragm** that is thinner than a cell membrane. The diaphragm does not have the trilaminar structure of a unit membrane. The exact chemical nature of the diaphragm is still unknown. The hydrophobic barrier may be absent in these diaphragms. The basal lamina of the fenestrated capillaries is continuous.

3. The **discontinuous sinusoidal capillaries,** the third type, have the following characteristics:

a. The capillaries have a tortuous path and greatly enlarged diameter (30-40m), which slows the circulation of blood.

b. The endothelial cells form a discontinuous layer and are separated from one another by wide spaces.

c. The cytoplasm of the endothelial cells has multiple fenestrations without diaphragms.

d. The basal lamina is discontinuous.

Sinusoidal capillaries are found mainly in the liver and in hematopoietic organs such as the bone marrow and spleen. The interchange between blood and tissues is greatly facilitated by the structure of the capillary wall.

Capillaries anastomose freely, forming a rich network that interconnects the small arteries and veins. The arterioles branch into small vessels surrounded by a discontinuous layer of smooth muscle, the **metarterioles**, which branch into capillaries. Constriction of metarterioles helps to regulate the circulation in capillaries when it is not necessary for the tissue to have blood flow throughout the entire capillary network. In some tissues, there are arteriovenous anastomoses that enable the arterioles to empty directly into venules. This is an additional mechanism that contributes to regulation of the capillary circulation. These interconnections are abundant in skeletal muscle and in the skin of the hands and feet. When vessels of the arteriovenous anastomosis contract, all the blood must pass through the capillary network. When they relax, some blood flows directly to a vein instead of circulating in the capillaries. Capillary circulation is controlled by neural and hormonal stimulation. The richness of the capillary network is related to the metabolic activity of the tissues. Tissues with high metabolic rates, such as the kidney, liver, and cardiac and skeletal muscle, have an abundant capillary network; the opposite is true for tissues with low metabolic rates, such as smooth muscle and dense connective tissue.

Small molecules, both hydrophobic and hydrophilic (eg, oxygen, carbon dioxide, and glucose), can diffuse or be actively transported across the plasmalemma of capillary endothelial cells. These substances are then transported by diffusion through the endothelial cytoplasm to the opposite cell surface, where they are discharged into the extracellular space. Water and some other hydrophilic molecules, less than 1.5 nm in diameter and below 10 kDa in molecular mass, can cross the capillary wall by diffusing through the intercellular junctions (paracellular pathway). The pores of fenestrated capillaries, the spaces among endothelial cells of sinusoid capillaries, and the pinocytotic vesicles are other pathways for the passage of large molecules.

Postcapillary Venules

The transition from capillaries to venules occurs gradually. The immediate postcapillary venules (pericytic venules), ranging in diameter from 0.1 to 0.5 mm and in length from 0.5 to 70 mm, are characterized by the presence of pericytes. The tunica intima of these vessels is composed of endothelium and a very thin subendothelial layer. It has the loosest endothelial junctions along the entire vascular system. The media of these venules may contain only contractile pericytes. Postcapillary venules have several features in common with capillaries, eg, participation in inflammatory processes and exchange of cells and molecules between blood and tissues.

Muscular Veins

Most venules are muscular, with at least a few smooth muscle cells in their walls. These vessels usually accompany artherioles from which they are easily distinguished in sectioned tissues because their thinner wall and irregular and collapsed lumen.

These venules may also influence blood flow in the arterioles by producing and secreting diffusible vasoactive substances.

From venules, the blood is collected in veins of increased size, arbitrary classified as small, medium, and large. The majority of veins are small or medium-sized, with a diameter of 1 mm. The intima usually has a thin subendothelial layer, which may be absent at times. The media consists of small bundles of smooth muscle cells intermixed with reticular fibers and a delicate network of elastic fibers. The collagenous adventitial layer is well developed.

The big venous trunks, close to the heart, are large veins. Large veins have a well-developed tunica intima, but the media is much thinner, with few layers of smooth muscle cells and abundant connective tissue. The adventitial layer is the thickest and best-developed tunic in veins; it frequently contains longitudinal bundles of smooth muscle. These veins, particularly the largest ones, have valves in their interior. The valves consist of 2 semilunar folds of the tunica intima that project into the lumen. They are composed of connective tissue rich in elastic fibers and are lined on both sides by endothelium. The valves, which are especially numerous in veins of the limbs, direct the venous blood toward the heart. The propulsive force of the heart is reinforced by contraction of skeletal muscles that surround these veins.

Heart

The heart is a muscular organ that contracts rhythmically, pumping the blood through the circulatory system. It is also responsible for producing a hormone called atrial natriuretic factor. Its walls consist of three tunics: the internal, or endocardium; the middle, or myocardium; and the external, or pericardium (peri + Gr. kardia, heart). The fibrous central region of the heart, called, rather inappropriately, the fibrous skeleton, serves as the base of the valves as well as the site of origin and insertion of the cardiac muscle cells.

The endocardium is homologous with the intima of blood vessels. It consists of a single layer of squamous endothelial cells resting on a thin subendothelial layer of loose connective tissue that contains elastic and collagen fibers as well as some smooth muscle cells. Connecting the myocardium to the subendothelial layer is a layer of connective tissue (often called the subendocardial layer) that contains veins, nerves, and branches of the impulse-conducting system of the heart (Purkinje cells).

The myocardium is the thickest of the tunics of the heart and consists of cardiac muscle cells arranged in layers that surround the heart chambers in a complex spiral. A large number of these layers insert themselves into the fibrous cardiac skeleton. The arrangement of these muscle cells is extremely varied, so that in histological preparations of a small area, cells are seen to be oriented in many directions.

The heart is covered externally by simple squamous epithelium (mesothelium) supported by a thin layer of connective tissue that constitutes the epicardium. A subepicardial layer of loose connective tissue contains veins, nerves, and nerve ganglia. The adipose tissue that generally surrounds the heart accumulates in this layer. ***The epicardium*** corresponds to the visceral layer of the pericardium, the serous membrane in which the heart lies. Between the visceral layer (epicardium) and the parietal layer is a small amount of fluid that facilitates the heart's movements.

The cardiac fibrous skeleton is composed of dense connective tissue. Its principal components are the **septum membranaceum**, **the trigona fibrosa, and the annuli fibrosi.** These structures consist of dense connective tissue, with thick collagen fibers oriented in various directions. Certain regions contain nodules of fibrous cartilage.

The cardiac valves consist of a central core of dense fibrous connective tissue (containing both collagen and elastic fibers), lined on both sides by endothelial layers. The bases of the valves are attached to the annuli fibrosi of the fibrous skeleton.

impulse-conducting system: The heart has a specialized system to generate a rhythmic stimulus that is spread to the entire myocardium. This system consists of two nodes located in the atrium- **the sinoatrial node** and the atrioventricular node and **the atrioventricular bundle**. The atrioventricular bundle originates from the node of the same name and branches to both ventricles. The cells of the ***impulse-conducting system*** are functionally integrated by gap junctions. The sinoatrial node is a mass of modified cardiac muscle cells that is fusiform, is smaller than atrial muscle cells, and has fewer myofibrils. The cells of the atrioventricular node are similar to those of the sinoatrial node, but their cytoplasmic projections branch in various directions, forming a network.

The atrioventricular bundle is formed by cells similar to those of the atrioventricular node. Distally, however, these cells become larger than ordinary cardiac muscle cells and acquire a distinctive appearance. These so-called **Purkinje cells** have one or two central nuclei, and their cytoplasm is rich in mitochondria and glycogen. The myofibrils are sparse and are restricted to the periphery of the cytoplasm. After traveling in the subendocardic layer, they penetrate the ventricle and became intramyocardic. This arrangement is important because it allows the stimulus to get into the innermost layers of the ventricular musculature.

Lymphatic Vascular System

The lymphatic vascular system returns the extracellular liquid to the bloodstream. In addition to blood vessels, the human body has a system of endothelium-lined thin-walled channels that collects fluid from the tissue spaces and returns it to the blood. This fluid is called lymph; unlike blood, it circulates in only one direction, toward the heart. The lymphatic capillaries originate in the various tissues as thin, closed-ended

vessels that consist of a single layer of endothelium and an incomplete basal lamina. Lymphatic capillaries are held open by numerous microfibrils of the elastic fiber system, which also bind them firmly to the surrounding connective tissue. The thin lymphatic vessels gradually converge and ultimately end up as two large trunks the thoracic duct and the right lymphatic duct that empty into the junction of the left internal jugular vein with the left subclavian vein and into the confluence of the right subclavian vein and the right internal jugular vein. Interposed in the path of the lymphatic vessels are lymph nodes, Lymphoid Organs. With rare exceptions, such as the central nervous system and the bone marrow, a lymphatic system is found in almost all organs.

The lymphatic vessels have a structure similar to that of veins except that they have thinner walls and lack a clear-cut separation between layers (intima, media, adventitia). They also have more numerous internal valves. The lymphatic vessels are dilated and assume a nodular, or beaded, appearance between the valves.

As in veins, lymphatic circulation is aided by the action of external forces (eg, contraction of the surrounding skeletal muscle) on their walls. These forces act discontinuously, and unidirectional lymph flow is mainly a result of the presence of many valves in these vessels. Contraction of smooth muscle in the walls of larger lymphatic vessels also helps to propel lymph toward the heart.

The structure of the large lymphatic ducts (thoracic duct and right lymphatic duct) is similar to that of veins, with reinforced smooth muscle in the middle layer. In this layer, the muscle bundles are longitudinally and circularly arranged, with longitudinal fibers predominating. The adventitia is relatively underdeveloped. Like arteries and veins, large lymphatic ducts contain vasa vasorum and a rich neural network.

The function of the lymphatic system is to return the fluid of the tissue spaces to the blood. Upon entering the lymphatic capillaries, this fluid contributes to the formation of the liquid part of the lymph; by passing through the lymphoid organs, it contributes to the circulation of lymphocytes and other immunological factors.

Lymphoid Organs

The body has a system of cells **the immune system** that has the ability to distinguish "self" (the organism's own molecules) from "nonself" (foreign substances). This system has the ability to neutralize or inactivate foreign molecules (such as soluble molecules as well as molecules present in viruses, bacteria, and parasites) and to destroy microorganisms or other cells (such as virus-infected cells, cells of transplanted organs, and cancer cells). On occasion, the immune system of an individual reacts against its own normal body tissues or molecules, causing **autoimmune diseases.**

The cells of the immune system (1) are distributed throughout the body in the blood, lymph, and epithelial and connective tissues; (2) are arranged in small spherical nodules called **lymphoid nodules** found in connective tissues and inside several organs; and (3) are organized as differently sized organs called **lymphoid organs**—the lymph nodes, the spleen, the thymus, and the bone marrow. Lymphoid nodules and isolated cells of the immune system found in the mucosa of the digestive system (tonsils, Peyer's patches, and appendix), the respiratory system, the reproductive system, and the urinary system are collectively known as mucosa-associated lymphoid tissue **(MALT)** and may be considered a lymphoid organ. The wide distribution of immune system cells and the constant traffic of lymphocytes through the blood, lymph, connective tissues, and lymphoid organs provide the body with an elaborate and efficient system of surveillance and defense.

Cells of the Immune System

The primary cells that participate in the immune response are lymphocytes, plasma cells, mast cells, neutrophils, eosinophils, and cells of the mononuclear phagocyte system. Antigen-presenting cells, a group of very diverse cell types, assist other cells in the immune response. This group includes, among other cells, lymphocytes, macrophages, and dendritic cells.

Lymphocytes

Lymphocytes are classified as **B,T,** or **natural killer (NK) cells.** The B and T cells are the only cells that have the ability to selectively recognize a specific epitope among a vast number of different epitopes. B and T cells differ based on their life history, surface receptors, and behavior during an immune response. Although B and T cells are morphologically indistinguishable in either the light or electron microscope, they can be distinguished by immunocytochemical methods because they have different surface proteins (markers). The precursors of all lymphocyte types originate in the bone marrow; some lymphocytes mature and become functional in the bone marrow, and after leaving the bone marrow enter the blood circulation to colonize connective tissues, epithelia, lymphoid nodules, and lymphoid organs. These are the **B lymphocytes**. **T**

lymphocyte precursors, on the other hand, leave the bone marrow, and through the blood circulation reach the thymus where they undergo intense proliferation and differentiation or die by apoptosis. After their final maturation, T cells leave the thymus and are distributed throughout the body in connective tissues and lymphoid organs. Because of their function in lymphocyte production and maturation, the bone marrow and the thymus are called the **primary** or **central lymphoid organs.** The other lymphoid structures are the **secondary** or **peripheral lymphoid** organs (spleen, lymph nodes, solitary lymphoid nodules, tonsils, appendix, and Peyer's patches of the ileum). B and T cells are not anchored in the lymphoid organs; instead, they continuously move from one location to another, a process known as **lymphocyte recirculation.**

B and T cells are not uniformly distributed in the lymphoid system but occupy preferential sites in these organs.

Approximate Percentage of B and T Lymphocytes in Lymphoid Organs.

Lymphoid Organ	**T Lymphocytes, (%)**	**B Lymphocytes, (%)**
Thymus	100	0
Bone marrow	10	90
Spleen	45	55
Lymph nodes	60	40
Blood	65	35

B Lymphocytes

In B lymphocytes, the surface receptors able to recognize antigens are monomeric molecules of IgM; each B cell is covered by about 150,000 molecules of IgM. The encounter of a B lymphocyte with the epitope it recognizes leads to several cycles of cell proliferation, followed by a redifferentiation of most of these lymphocytes into **plasma cells.** This population of plasma cells secretes antibodies against the same epitope as that of the B cell that originated them. In most cases, the activation of B cells requires the assistance of a subclass of T lymphocytes known as **T-helper lymphocytes.** Not all activated B cells, however, become plasma cells; some remain **B memory lymphocytes,** which react rapidly to a second exposure to the same epitope.

T Lymphocytes

T cells constitute 65–75% of blood lymphocytes. To recognize epitopes, all T cells have on their surfaces a molecule called a **T cell receptor (TCR).** In contrast to B cells, which recognize soluble antigens or antigens present on cell surfaces, T lymphocytes recognize only epitopes (mostly small peptides) that form complexes with special proteins of the cell surface of other cells (proteins of the major histocompatibility complex, see below).

Natural Killer Cells

The **natural killer** lymphocytes lack the marker molecules characteristic of B and T cells. They comprise about 10–15% of the lymphocytes of circulating blood. Their name derives from the fact that they attack virus-infected cells, transplanted cells, and cancer cells without previous stimulation; for this reason they are involved in what is called an **innate immune response.**

Lymphoid Tissue

Lymphoid tissue is a type of connective tissue characterized by a rich supply of lymphocytes. It exists free within the regular connective tissue or is surrounded by capsules, forming the lymphoid organs. Because lymphocytes have very little cytoplasm, lymphoid tissue stains dark blue in hematoxylin and eosin-stained sections. Lymphoid tissues are basically made up of free cells; as a result, they typically have a rich network of reticular fibrils (made principally of type III collagen) that supports the cells. In most lymphoid organs, the fibrils are produced by a fibroblastic cell called a **reticular cell,** whose many processes rest on the reticular fibrils. The thymus is an exception in so far as its cells are supported by a reticulum of epithelial cells of endodermic origin.

The network of reticular fibrils of the lymphoid tissue may be relatively closed (**dense lymphoid tissue**) and is, thus, able to hold many free cells (mostly lymphocytes, macrophages, and plasma cells). Another type is **loose lymphoid** tissue, whose network has fewer but larger spaces, providing means for easy movement of the free cells.

In the **nodular lymphoid tissue,** groups of lymphocytes are arranged as spheres, called **lymphoid nodules** or **lymphoid follicles,** that primarily contain B lymphocytes. When lymphoid nodules become activated as a result of the arrival of antigen-carrying APCs and recognition of the antigens by B lymphocytes, these lymphocytes proliferate in the central portion of the nodule, which then stains lighter and is called a **germinative center.** After completion of the immune response, the germinative center may disappear. The germinative centers contain a special cell, the **follicular dendritic cell**, that has many processes that bind antigen on their surfaces, to be presented to B lymphocytes.

Lymphoid nodules vary widely in size, typically measuring a few hundred micrometers to 1 mm in diameter. They are found free in connective tissues anywhere in the body or within lymphoid organs (lymph nodes, spleen, tonsils, but not in the thymus). They are,

however, never covered by a capsule. Free lymphoid nodules are commonly present in the lamina propria of several mucosal linings, where, together with free lymphocytes, they constitute the mucosa-associated lymphoid tissue (MALT).

Mucosa-Associated Lymphoid Tissue & Tonsils

The digestive, respiratory, and genitourinary tracts are common sites of microbial invasion because their lumens are open to the external environment. To protect the organism, the mucosa and submucosa of these tracts contain a large amount of diffuse collections of lymphocytes, IgA-secreting plasma cells, APCs, and lymphoid nodules. Most of the lymphocytes are B cells; among T cells, $CD4^+$ helper cells predominate. In some places, these aggregates form conspicuous structures such as the tonsils and the Peyer's patches in the ileum. Similar aggregates are found in the appendix.

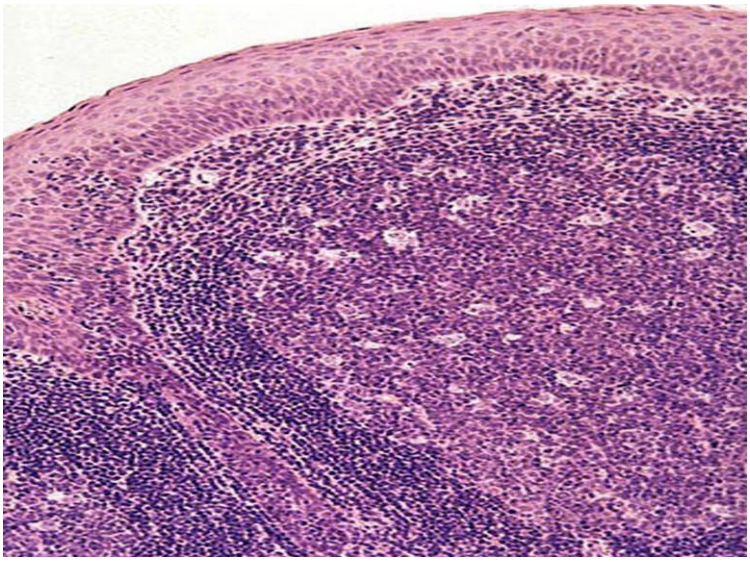
In the Peyer's patches, some of the regular surface epithelial cells may be replaced by special **M cells**. The M cells do not have microvilli as do the regular cells that line the intestine. By pinocytosis they actively capture and transport antigens from the intestinal lumen to the connective tissues where APCs and B lymphocytes are usually present. The plasma cells derived from these lymphocytes secrete mostly IgA, which is transported through the epithelium toward the intestinal cavity.

Tonsils

Tonsils belong to the MALT, but because they are incompletely encapsulated, they are considered organs and will be studied apart from the MALT. The tonsils constitute a lymphoid tissue that lies beneath, and in contact with, the epithelium of the initial portion of the digestive tract. Depending on their location, tonsils in the mouth and pharynx are called **palatine, pharyngeal,** or **lingual.**

Palatine Tonsils

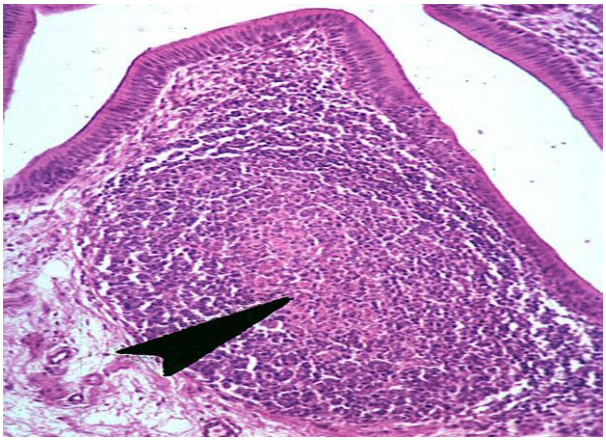
The two palatine tonsils are located in the lateral walls of the oral part of the pharynx. They are lined with a squamous stratified epithelium that often becomes so densely infiltrated by lymphocytes that it may be difficult to recognize. The lymphoid tissue in these tonsils forms a band that contains free lymphocytes and lymphoid nodules, generally with germinal centers. Each tonsil has 10–20 epithelial invaginations that penetrate the tonsil deeply, forming **crypts,** whose lumens contain desquamated epithelial cells, live and dead lymphocytes, and bacteria. Crypts may appear as purulent spots in tonsillitis. Separating the lymphoid tissue from subjacent structures is a band of dense connective tissue, the **capsule** of the tonsil . This capsule usually acts as a barrier against spreading tonsillar infections.



Pharyngeal Tonsil

The pharyngeal tonsil is a single tonsil situated in the superior— posterior portion of the pharynx. It is covered by ciliated pseudostratified columnar epithelium typical of the respiratory tract, although areas of stratified epithelium can also be observed.

The pharyngeal tonsil is composed of pleats of mucosa and contains diffuse lymphoid tissue and lymphoid nodules. It has no crypts, and its capsule is thinner than the capsule of the palatine tonsils. Hypertrophied pharyngeal tonsils resulting from chronic inflammation are called **adenoids.**



Lingual Tonsils

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

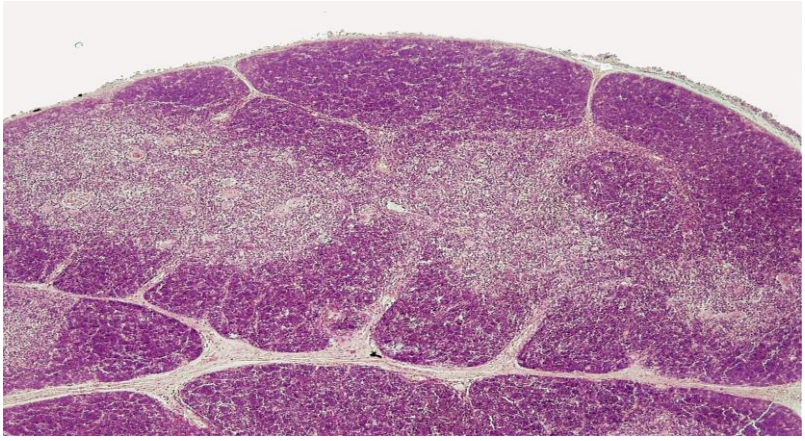
Thymus

The thymus is a lymphoepithelial organ located in the mediastinum; it attains its peak development during youth. Whereas the other lymphoid organs originate exclusively from mesenchyme (mesoderm), the thymus has a dual embryonic origin. Its lymphocytes arise in the bone marrow from cells of mesenchymal origin that invade an epithelial primordium that has developed from the endoderm of the third and fourth pharyngeal pouches.

The thymus has a connective tissue capsule that penetrates the parenchyma and divides it into incomplete lobules, so that there is continuity between the cortex and medulla of adjoining lobules. Each lobule has a peripheral dark zone known as the **cortex** and a central light zone called the **medulla**.

The **cortex** is composed of an extensive population of T cell precursors (also called **thymocytes**), dispersed epithelial reticular cells, and macrophages. Because the cortex is richer in small lymphocytes than the medulla, it stains more darkly. The epithelial reticular cells are stellate cells with light-staining oval nuclei. They are usually joined to similar adjacent cells by desmosomes.

The **medulla** contains epithelial reticular cells, many differentiated T lymphocytes, and structures called **thymic corpuscles** or **Hassall corpuscles,** which are characteristic of this region, although their function is unknown. These corpuscles contain flattened epithelial reticular cells that are arranged concentrically and are filled with keratin filaments. They sometimes calcify.



Vascularization of the Thymus

Arterioles and capillaries in the thymus are surrounded by processes of epithelial reticular cells. Thymus capillaries have a nonfenestrated endothelium and a very thick basal lamina, making these blood vessels particularly impermeable to proteins. This

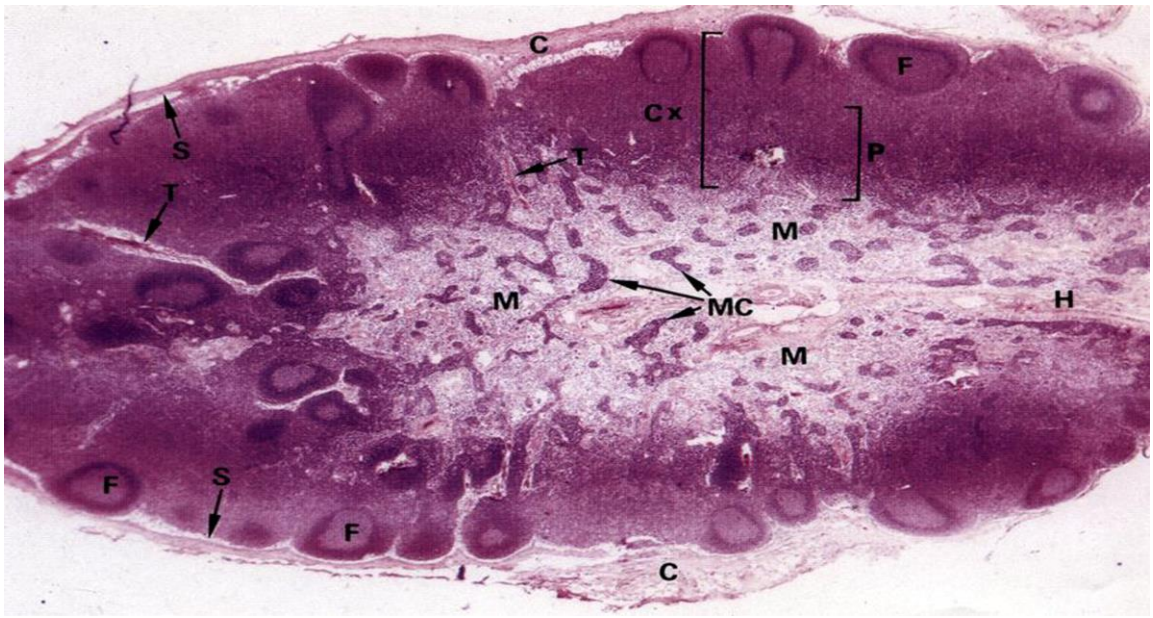
prevents most circulating antigens from reaching the thymus cortex, thus creating the so-called **thymic–blood barrier.**

The thymus has no afferent lymphatic vessels and does not constitute a filter for the lymph, as do lymph nodes. The few lymphatic vessels encountered in the thymus are all efferent; they are located in the walls of blood vessels and in the connective tissue of the septa and the capsule.

Lymph Nodes

Lymph nodes are distributed throughout the body along the course of the lymphatic vessels. The nodes are found in the axilla and the groin, along the great vessels of the neck, and in large numbers in the thorax and abdomen, especially in mesenteries. Lymph nodes constitute a series of in-line filters that are important in the body's defense against microorganisms and the spread of tumor cells. All this lymph, derived from tissue fluid, is filtered by at least one node before returning to the circulation. Lymph nodes are elongated or kidney-shaped organs that have a convex surface that is the entrance site of lymphatic vessels and a concave depression, the **hilum**, through which arteries and nerves enter and veins and lymphatic vessels leave the organ. A connective tissue **capsule** surrounds the lymph node, sending trabeculae into its interior.

The most common cells of lymph nodes are lymphocytes, macrophages and other APCs, plasma cells, and reticular cells; follicular dendritic cells are present within the lymphoid nodules. The different arrangement of the cells and of the reticular fibril skeleton that supports the cells creates two regions, a cortex and a **medulla**. The cortex can be subdivided into an **outer cortex** and an **inner cortex** or **paracortical region.**



Cortex

The outer cortex, situated under the capsule, consists of the following components:

1. A diffuse population of cells composed mainly of T lymphocytes and reticular cells; macrophages and APCs are also present in this area.
2. Lymphoid nodules, with or without germinative centers, formed mainly by B lymphocytes, embedded in the diffuse population of cortical cells.
3. Areas of loose lymphoid tissue (whose reticular fibril meshes are wide) situated immediately beneath the capsule, called the **subcapsular sinuses**. They are composed of a loose network of reticular cells and fibers. Lymph, containing antigens, lymphocytes, and APCs, circulates around the wide spaces of these sinuses after being delivered into these channels by the afferent lymphatic vessels.
4. **Intermediate** or **radial sinuses** that run between lymphoid nodules. These sinuses arise from and share the same structure with the subcapsular sinuses. They communicate with the subcapsular sinuses through spaces similar to those present in the medulla.

The inner cortex or paracortical region does not have precise boundaries with the outer cortex and contains few, if any, nodules but many T lymphocytes.

Medulla

The medulla has two components:

1. The **medullary cords** are branched cordlike extensions of dense lymphoid tissue that arise in the inner cortex. They contain primarily B lymphocytes and often plasma cells and macrophages.
2. The medullary cords are separated by dilated spaces, frequently bridged by reticular cells and fibers, called the **medullary sinuses**. They contain lymph, lymphocytes, often many macrophages, and sometimes even granulocytes if the lymph node is draining an infected region. These sinuses (which arise from the intermediate sinuses) join at the hilum delivering the lymph to the efferent lymph vessel of the lymph node.

Lymph Circulation

Afferent lymphatic vessels cross the capsule and pour lymph into the subcapsular sinus . From there, lymph passes through the intermediate sinuses and, finally, into the medullary sinuses. During this passage, the lymph infiltrates the cortex and the medullary cords. The lymph is finally collected by efferent lymphatic vessels at the hilum. Valves in both the afferent and efferent vessels aid the unidirectional flow of lymph.

Spleen

The spleen is the largest accumulation of lymphoid tissue in the body and the only one interposed in the blood circulation. Because of its abundance of phagocytic cells, the spleen is an important defense against antigens that reach the blood circulation. It is also the site of destruction of aged erythrocytes. As is true of all other lymphoid organs, the spleen is a production site of activated lymphocytes, which are delivered to the blood. The spleen reacts promptly to antigens carried in the blood and is, thus, an important blood filter and antibody-forming organ.

General Structure

The spleen is surrounded by a **capsule** of dense connective tissue from which emerge **trabeculae**, which divide the parenchyma, or **splenic pulp**, into incomplete compartments. Large trabeculae originate at the hilum, on the medial surface of the spleen; these trabeculae carry nerves and arteries into the splenic pulp as well as veins that bring blood back into the circulation. Lymphatic vessels that arise in the splenic pulp also leave through the hilum via the trabeculae.

In humans, the connective tissue of the capsule and trabeculae contains only a few smooth muscle cells.

Splenic Pulp

The spleen is composed of a network of reticular tissue that contains reticular cells, many lymphocytes and other blood cells, macrophages, and APCs. The splenic pulp has two components, the **white pulp** and the **red pulp**. These names derive from the fact that on the surface of a cut through an unfixed spleen, white spots (lymphoid nodules) are observed within a dark red tissue that is rich in blood. The white pulp consists of the **periarterial lymphatic sheath** and the **lymphoid nodules,** whereas the red pulp consists of **splenic cords (Billroth's cords)** and blood **sinusoids.**

White Pulp

The splenic artery divides as it penetrates the hilum, branching into **trabecular arteries** of various sizes that follow the course of the connective tissue trabeculae. When they leave the trabeculae to enter the parenchyma, the arteries are immediately enveloped by a sheath of T lymphocytes, the periarterial lymphatic sheath **(PALS)**, which is part of the white pulp. These vessels are known as **central arteries** or **white pulp arteries.** After coursing through the parenchyma for variable stretches, the PALS receive large collections of lymphocytes —mostly B cells—forming lymphoid nodules. In these nodules the artery, which has now turned into an arteriole, occupies an eccentric position but is still called the central artery. During its passage through the white pulp, the artery also divides into numerous radial branches that supply the surrounding lymphoid tissue.

Surrounding the lymphoid nodules is a **marginal zone** consisting of many blood sinuses and loose lymphoid tissue. A few lymphocytes but many active macrophages can be found there. The marginal zone contains an abundance of blood antigens and thus plays a major role in the immunological activities of the spleen.

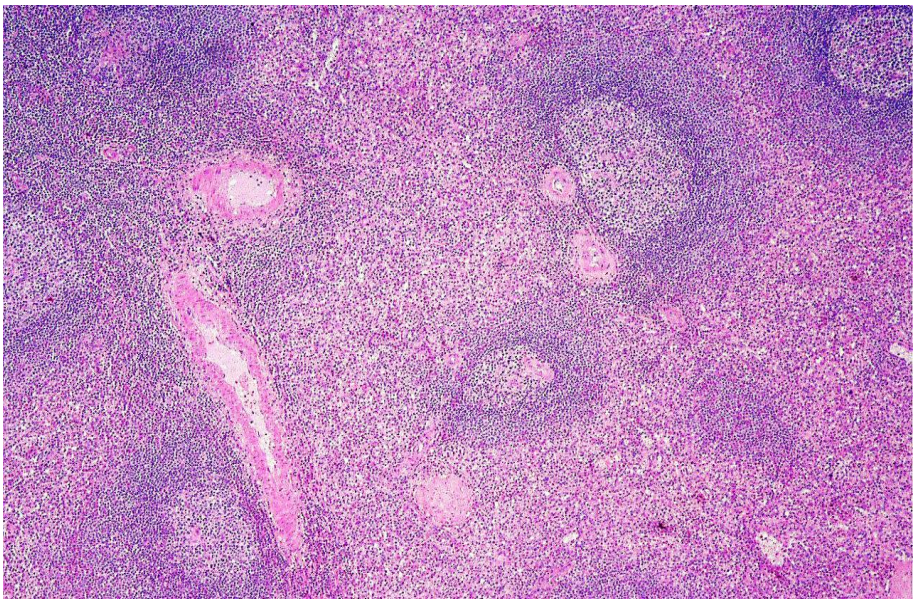
After leaving the white pulp, the sheath of lymphocytes slowly thins and the central artery (arteriole) subdivides to form straight **penicillar arterioles**. Near their termination, some of the penicillar arterioles are surrounded by a thick sheath of reticular cells, lymphoid cells, and macrophages. How the blood is delivered to the trabecular veins is not exactly known and will be discussed later.

Red Pulp

The red pulp is composed of splenic cords and sinusoids. The splenic cords contain a network of reticular cells supported by reticular fibers. The splenic cords contain T and B lymphocytes, macrophages, plasma cells, and many blood cells (erythrocytes, platelets, and granulocytes).

The splenic cords are separated by irregularly shaped wide sinusoids. Elongated endothelial cells line the sinusoids of the spleen with the long axes parallel to the long axes of the sinusoids. These cells are enveloped in reticular fibers set primarily in a transverse direction, much like the hoops on a barrel.

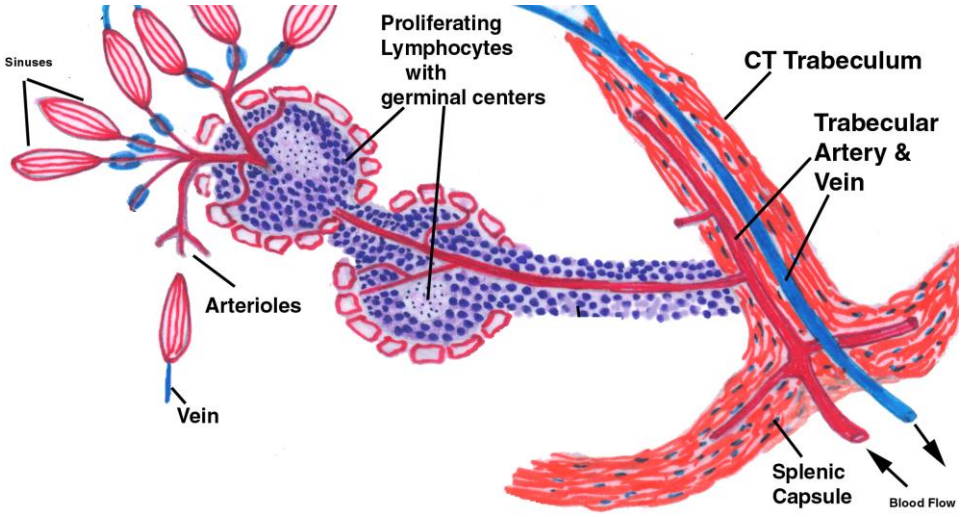
Surrounding the sinusoid is an incomplete basal lamina. Because the spaces between the endothelial cells of the splenic sinusoids are smaller, only flexible cells are able to pass easily from the red pulp cords to the lumen of the sinusoids. Unfortunately, because the lumen of sinusoids in the red pulp may be very narrow and the splenic cords are infiltrated with red blood cells, microscopic observation of a spleen section is not always easy; observation of PALS may also be difficult.



Closed and Open Blood Circulation in the Spleen

The manner in which blood flows from the arterial capillaries of the red pulp to the interior of the sinusoids has not yet been completely explained. Some investigators suggest that the capillaries open directly into the sinusoids, forming a **closed circulation** in which the blood always remains inside the vessels. Others maintain that the prolongations of the penicillar arteries open into the splenic cords, and the blood passes through the space between the cells to reach the sinusoids **(open circulation)**.

From the sinusoids, blood proceeds to the red pulp veins that join together and enter the trabeculae, forming the **trabecular veins**. The splenic vein originates from these vessels and emerges from the hilum of the spleen. The trabecular veins do not have individual muscle walls. They can be considered channels hollowed out in the trabecular connective tissue and lined by endothelium.



Functions of the Spleen

Phagocytosis and Immunological Defense

Because of its strategic position in the blood circulation, the spleen is able to filter, phagocytose, and mount immunological responses against blood-borne antigens. The spleen contains all the components (B and T lymphocytes, APCs, and phagocytic cells) necessary for this function.

The white pulp of the spleen is an important production site of lymphocytes, which then migrate to the red pulp and reach the lumen of the sinusoids, where they enter the blood circulation. Inert particles are also intensely phagocytosed by spleen macrophages.

Destruction of Erythrocytes

Erythrocytes have an average life span of around 120 days, after which they are destroyed, mainly in the spleen. A reduction in their flexibility and changes in their membrane seem to be the signals for their destruction. Degenerating erythrocytes are also removed in the bone marrow.

Macrophages in the splenic cords engulf and digest the erythrocytes that frequently fragment in the extracellular space. The hemoglobin they contain is broken down into several parts. The protein, globin, is hydrolyzed to amino acids that are reused in protein synthesis. Iron is released from heme and, joined to transferrin, is transported in the blood to the bone marrow, where it is reused in erythropoiesis. Iron-free heme is metabolized to **bilirubin,** which is excreted in the bile by liver cells. After surgical removal of the spleen (splenectomy), there is an increase in abnormal erythrocytes, seen to have deformed shapes in blood smears. There is also an increase in the number of blood platelets, indicating that the spleen normally removes aged platelets.

The Nervous System

The human nervous system, by far the most complex system in the human body, is formed by a network of more than ***100 million*** nerve cells (**neurons**), assisted by many ***more*** **glial cells**. Each neuron has, on average, at least 1000 interconnections with other neurons, forming a very complex system for communication.

Neurons are grouped as **circuits.** Like electronic circuits, neural circuits are highly specific combinations of elements that make up systems of various sizes and complexities. Although a neural circuit may be single, in most cases it is a combination of two or more circuits that interacts to generate a function. A neural function is a set of coordinated processes intended to produce a definite result. A number of elementary circuits may be combined to form higher-order systems.

Nerve tissue is distributed throughout the body as an integrated communications network. Anatomically, the nervous system is divided into the **central nervous system,** consisting of the brain and the spinal cord, and the **peripheral nervous system,** composed of nerve fibers and small aggregates of nerve cells called **nerve ganglia** Structurally, nerve tissue consists of two cell types: **nerve cells,** or **neurons,** which usually show numerous long processes, and several types of **glial cells** (Gr. *glia,* glue), which have short processes, support and protect neurons, and participate in neural activity, neural nutrition, and the defense processes of the central nervous system.

Neurons

Nerve cells, or neurons, are responsible for the reception, transmission, and processing of stimuli; the triggering of certain cell activities; and the release of neurotransmitters and other informational molecules.

Most neurons consist of three parts: the **dendrites,** which are multiple elongated processes specialized in receiving stimuli from the environment, sensory epithelial cells, or other neurons; the **cell body,** or **perikaryon** (Gr. *peri,* around, + *karyon,* nucleus), which is the trophic center for the whole nerve cell and is also receptive to stimuli; and the **axon** (from Greek, meaning axis), which is a single process specialized in generating or conducting nerve impulses to other cells (nerve, muscle, and gland cells). Axons may also receive information from other neurons; this information mainly modifies the transmission of action potentials to other neurons. The distal portion of the axon is usually branched and constitutes the **terminal arborization.** Each branch of this arborization terminates on the next cell in dilatations called **end bulbs** (**boutons**), which interact with other neurons or nonnerve cells, forming structures called **synapses.** Synapses transmit information to the next cell in the circuit. Neurons and their processes are extremely variable in size and shape. Cell bodies can be spherical, ovoid, or angular; some are very large, measuring up to 150 µm in diameter—large enough to be visible to

the naked eye. Other nerve cells are among the smallest cells in the body; for example, the cell bodies of granule cells of the cerebellum are only 4–5 µm in diameter.

Based on the size and shape of their processes, most neurons can be placed in one of the following categories: **multipolar neurons,** which have more than two cell processes, one process being the axon and the others dendrites; **bipolar neurons,** with one dendrite and one axon; and **pseudounipolar neurons,** which have a single process that is close to the perikaryon and divides into two branches. The process then forms a **T shape**, with one branch extending to a peripheral ending and the other toward the central nervous system. In pseudounipolar neurons, stimuli that are picked up by the dendrites travel directly to the axon terminal without passing through the perikaryon.

During the maturation process of pseudounipolar neurons, the central (axon) and the peripheral (dendrite) fibers fuse, becoming one single fiber. In these neurons, the cell body does not seem to be involved in the conduction of impulses, although it does synthesize many molecules, including neurotransmitters that migrate to the peripheral fibers.

Most neurons of the body are multipolar. Bipolar neurons are found in the cochlear and vestibular ganglia as well as in the retina and the olfactory mucosa. Pseudounipolar neurons are found in the spinal ganglia (the sensory ganglia located in the dorsal roots of the spinal nerves). They are also found in most cranial ganglia.

Neurons can also be classified according to their functional roles. **Motor** (**efferent**) **neurons** control effector organs such as muscle fibers and exocrine and endocrine glands. **Sensory** (**afferent**) **neurons** are involved in the reception of sensory stimuli from the environment and from within the body. **Interneurons** establish relationships among other neurons, forming complex functional networks or circuits (as in the retina).

During mammalian evolution a great increase in the number and complexity of interneurons has occurred. Highly developed functions of the nervous system cannot be ascribed to simple neuron circuits; rather, they depend on complex interactions established by the integrated functions of many neurons.

In the central nervous system, nerve cell bodies are present only in the gray matter. White matter contains neuronal processes but no nerve cell bodies. In the peripheral nervous system, cell bodies are found in ganglia and in some sensory regions (eg, olfactory)

*Cell Body (***perikaryon***)*

The cell body, also called **perikaryon,** is the part of the neuron that contains the nucleus and surrounding cytoplasm, exclusive of the cell processes. It is primarily a trophic center, although it also has receptive capabilities. The perikaryon of most neurons

receives a great number of nerve endings that convey excitatory or inhibitory stimuli generated in other nerve cells.

Most nerve cells have a spherical, unusually large, euchromatic (pale-staining) nucleus with a prominent nucleolus. Binuclear nerve cells are seen in sympathetic and sensory ganglia. The chromatin is finely dispersed, reflecting the intense synthetic activity of these cells.

The cell body contains a highly developed rough endoplasmic reticulum organized into aggregates of parallel cisternae. In the cytoplasm between the cisternae are numerous polyribosomes, suggesting that these cells synthesize both structural proteins and proteins for transport. When appropriate stains are used, rough endoplasmic reticulum and free ribosomes appear under the light microscope as basophilic granular areas called **Nissl bodies**. The number of Nissl bodies varies according to neuronal type and functional state. They are particularly abundant in large nerve cells such as motor neurons. The **Golgi complex** is located only in the cell body and consists of multiple parallel arrays of smooth cisternae arranged around the periphery of the nucleus. Mitochondria are especially abundant in the axon terminals. They are scattered throughout the cytoplasm of the cell body.

Neurofilaments are abundant in perikaryons and cell processes. Neurofilaments bundle together as a result of the action of certain fixatives. When impregnated with silver, they form **neurofibrils** that are visible with the light microscope. The neurons also contain microtubules that are identical to those found in many other cells. Nerve cells occasionally contain inclusions of pigments, such as **lipofuscin,** which is a residue of undigested material by lysosomes.

Dendrites

Dendrites (Gr. *dendron,* tree) are usually short and divide like the branches of a tree. They receive many synapses and are the principal signal reception and processing sites on neurons. Most nerve cells have numerous dendrites, which considerably increase the receptive area of the cell. The arborization of dendrites allows one neuron to receive and integrate a great number of axon terminals from other nerve cells. It has been estimated that up to 200,000 axonal terminations establish functional contact with the dendrites of a Purkinje cell of the cerebellum. That number may be even higher in other nerve cells. Bipolar neurons, with only one dendrite, are uncommon and are found only in special sites. Unlike axons, which maintain a constant diameter from one end to the other, dendrites become thinner as they subdivide into branches. The cytoplasmic composition of the dendrite base, close to the neuron body, is similar to that of the perikaryon but is devoid of Golgi complexes. Most synapses impinging on neurons are located in **dendrite spines,** which are usually mushroom-shaped structures (an expanded head connected to the dendrite shaft by a narrower neck) measuring 1–3 µm long and less than 1 µm in diameter. These spines, which play relevant functions, occur in vast numbers, estimated

to be on the order of 10^{14} for the human cerebral cortex. Dendrite spines are the first processing locale for synaptic signals arriving on a neuron. The processing apparatus is contained in a complex of proteins attached to the cytosolic surface of the postsynaptic membrane, which is visible under the electron microscope and received the name postsynaptic membrane long before its function was disclosed. Dendritic spines participate in the plastic changes that underlie adaptation, learning, and memory. They are dynamic structures with a morphological plasticity based on the cytoskeletal protein actin, which is related to the development of the synapses and their functional adaptation in adults.

Axons

Most neurons have only one axon; a very few have no axon at all. An axon is a cylindrical process that varies in length and diameter according to the type of neuron. Although some neurons have short axons, axons are usually very long processes. For example, axons of the motor cells of the spinal cord that innervate the foot muscles may be up to 100 cm (about 40 inches) in length. All axons originate from a short pyramid-shaped region, the **axon hillock,** that usually arises from the perikaryon. The plasma membrane of the axon is called the **axolemma** (*axon* + Gr. *eilema,* sheath); its contents are known as **axoplasm**.

In neurons that give rise to a myelinated axon, the portion of the axon between the axon hillock and the point at which myelination begins is called the **initial segment.** This is the site at which various excitatory and inhibitory stimuli impinging on the neuron are algebraically summed, resulting in the decision to propagate—or not to propagate—an action potential, or nerve impulse. It is known that several types of ion channels are localized in the initial segment and that these channels are important in generating the change in electrical potential that constitutes the action potential. In contrast to dendrites, axons have a constant diameter and do not branch profusely. Occasionally, the axon, shortly after its departure from the cell body, gives rise to a branch that returns to the area of the nerve cell body. All axon branches are known as **collateral branches**. Axonal cytoplasm (axoplasm) possesses mitochondria, microtubules, neurofilaments, and some cisternae of smooth endoplasmic reticulum. The absence of polyribosomes and rough endoplasmic reticulum emphasizes the dependence of the axon on the perikaryon for its maintenance. If an axon is severed, its peripheral parts degenerate and die.

There is a lively bidirectional transport of small and large molecules along the axon.

Macromolecules and organelles that are synthesized in the cell body are transported continuously by an **anterograde flow** along the axon to its terminals.

Anterograde flow occurs at three distinct speeds. A slow stream (a few millimeters per day) transports proteins and actin filaments. A flow of intermediate speed transports

mitochondria, and a fast stream (100 times more rapid) transports the substances contained in vesicles that are needed at the axon terminal during neurotransmission.

Simultaneously with anterograde flow, a **retrograde flow** in the opposite direction transports several molecules, including material taken up by endocytosis (including viruses and toxins), to the cell body. This process is used to study the pathways of neurons; peroxidase or another marker is injected in regions with axon terminals, and its distribution is followed after a certain period of time.

Motor proteins related to axon flow include **dynein,** a protein with ATPase activity present in microtubules (related to retrograde flow), and **kinesin,** a microtubule-activated ATPase that, when attached to vesicles, promotes anterograde flow in the axon.

Synaptic Communication

The synapse (Gr. *synapsis,* union) is responsible for the unidirectional transmission of nerve impulses. Synapses are sites of functional contact between neurons or between neurons and other effector cells (eg, muscle and gland cells). The function of the synapse is to convert an electrical signal (impulse) from the presynaptic cell into a chemical signal that acts on the **postsynaptic** cell. Most synapses transmit information by releasing **neurotransmitters** during the signaling process. Neurotransmitters are chemicals that, when combined with a receptor protein, either open or close ion channels or initiate second-messenger cascades. **Neuromodulators** are chemical messengers that do not act directly on synapses but modify neuron sensitivity to synaptic stimulation or inhibition. Some neuromodulators are neuropeptides or steroids produced in the nerve tissue; others are circulating steroids. The synapse itself is formed by an axon terminal (**presynaptic terminal**) that delivers the signal, a region on the surface of another cell at which a new signal is generated (**postsynaptic terminal**), and a thin intercellular space called the **synaptic cleft**. If an axon forms a synapse with a cell body, the synapse is called **axosomatic;** if it forms a synapse with a dendrite, it is called **axodendritic;** and if it forms a synapse with an axon, it is called **axoaxonic**.

Although most synapses are **chemical synapses** and use chemical messengers, a few synapses transmit ionic signals through gap junctions that cross the pre- and postsynaptic membranes, thereby conducting neuronal signals directly. These synapses are called **electrical synapses.**

The presynaptic terminal always contains **synaptic vesicles** with neurotransmitters and numerous **mitochondria**.

Neurotransmitters are generally synthesized in the cell body; they are then stored in vesicles in the presynaptic region of a synapse. During transmission of a nerve impulse, they are released into the synaptic cleft by **exocytosis.** The extra membrane that collects at the presynaptic region as a result of exocytosis of the synaptic vesicles is recycled by

endocytosis. Retrieved membrane fuses with the smooth endoplasmic reticulum of the presynaptic compartment to be reused in the formation of new synaptic vesicles. Some neurotransmitters are synthesized in the presynaptic compartment, using enzymes and precursors brought by axonal transport.

The first neurotransmitters to be described were acetylcholine and norepinephrine. Most neurotransmitters are amines, amino acids, or small peptides (neuropeptides). Inorganic substances such as nitric oxide have also been shown to act as neurotransmitters. Several peptides that act as neurotransmitters are used elsewhere in the body, eg, as hormones in the digestive tract. Neuropeptides are important in regulating feelings and drives, such as pain, pleasure, hunger, thirst, and sex.

Glial Cells & Neuronal Activity

Glial cells are 10 times more abundant in the mammalian brain than neurons; they surround both cell bodies and their axonal and dendritic processes that occupy the interneuronal spaces.

Nerve tissue has only a very small amount of extracellular matrix, and glial cells furnish a microenvironment suitable for neuronal activity.

Origin and Principal Functions of Neuroglial Cells.

Glial Cell	**Origin**	**Location**	**Main Functions**
Oligodendroc	Neural tube	Central nervous system	Myelin production, electric insulation
Schwann cell	Neural tube	Peripheral nerves	Myelin production, electric insulation
Astrocyte	Neural tube	Central nervous system	Structural support, repair processes
			Blood–brain barrier, metabolic exchanges
Ependymal	Neural tube	Central nervous system	Lining cavities of central nervous system
Microglia	Bone marrow	Central nervous system	Macrophagic activity

Oligodendrocytes

Oligodendrocytes (Gr. *oligos,* small, + *dendron* + *kytos,* cell) produce the myelin sheath that provides the electrical insulation of neurons in the central nervous system. These cells have processes that wrap around axons.

Schwann Cells

Schwann cells have the same function as oligodendrocytes but are located around axons in the peripheral nervous system. One Schwann cell forms myelin around a segment of one axon, in contrast to the ability of oligodendrocytes to branch and serve more than one neuron and its processes.

Astrocytes

Astrocytes (Gr. *astron*, star, + *kytos*) are star-shaped cells with multiple radiating processes. These cells have bundles of intermediate filaments made of **glial fibrillary acid protein** that reinforce their structure. Astrocytes bind neurons to capillaries and to the pia mater (a thin connective tissue that covers the central nervous system). Astrocytes with few long processes are called **fibrous astrocytes** and are located in the white matter; **protoplasmic astrocytes,** with many short-branched processes, are found in the gray matter. Astrocytes are by far the most numerous glial cells and exhibit an exceptional morphological and functional diversity.

In addition to their supporting function, astrocytes participate in controlling the ionic and chemical environment of neurons. Some astrocytes develop processes with expanded **end feet** that are linked to endothelial cells. It is believed that through the end feet, astrocytes transfer molecules and ions from the blood to the neurons. Expanded processes are also present at the external surface of the central nervous system, where they make a continuous layer. Furthermore, when the central nervous system is damaged, astrocytes proliferate to form cellular scar tissue.

Astrocytes also play a role in regulating the numerous functions of the central nervous system.

Astrocytes can influence neuronal survival and activity through their ability to regulate constituents of the extracellular environment, absorb local excess of neurotransmitters, and release metabolic and neuroactive molecules. The latter molecules include peptides of the angiotensinogen family, vasoactive endothelins, opioid precursors called **enkephalins,** and the potentially neurotrophic somatostatin. On the other hand, there is some evidence that astrocytes transport energy-rich compounds from the blood to the neurons and also metabolize glucose to lactate, which is then supplied to the neurons.

Finally, astrocytes are in direct communication with one another via gap junctions, forming a network through which information can flow from one point to another, reaching distant sites. For example, by means of gap junctions and the release of various cytokines, astrocytes can interact with oligodendrocytes to influence myelin turnover in both normal and abnormal conditions.

Ependymal Cells

Ependymal cells are low columnar epithelial cells lining the ventricles of the brain and central canal of the spinal cord. In some locations, ependymal cells are ciliated, which facilitates the movement of cerebrospinal fluid.

Microglia

Microglia (Gr. *micros,* small, + *glia*) are small elongated cells with short irregular processes. They can be recognized in routine hematoxylin and eosin (H&E) preparations by their dense elongated nuclei, which contrast with the spherical nuclei of other glial cells. Microglia, phagocytic cells that represent the mononuclear phagocytic system in nerve tissue, are derived from precursor cells in the bone marrow. They are involved with inflammation and repair in the adult central nervous system, and they produce and release neutral proteases and oxidative radicals. When activated, microglia retract their processes and assume the morphological characteristics of macrophages, becoming phagocytic and acting as antigen-presenting cells. Microglia secrete a number of immunoregulatory cytokines and dispose of unwanted cellular debris caused by central nervous system lesions.

The Central Nervous System

The central nervous system consists of the **cerebrum, cerebellum,** and **spinal cord.** It has almost no connective tissue and is therefore a relatively soft, gel-like organ.

When sectioned, the cerebrum, cerebellum, and spinal cord show regions that are white (**white matter**) and that are gray (**gray matter**). The differential distribution of myelin in the central nervous system is responsible for these differences: The main component of white matter is myelinated axons and the myelin-producing oligodendrocytes. White matter does not contain neuronal cell bodies.

Gray matter contains neuronal cell bodies, dendrites, and the initial unmyelinated portions of axons and glial cells. This is the region at which synapses occur. Gray matter is prevalent at the surface of the cerebrum and cerebellum, forming the **cerebral and cerebellar cortex**, whereas white matter is present in more central regions. Aggregates of neuronal cell bodies forming islands of gray matter embedded in the white matter are called **nuclei.** In the **cerebral cortex,** the gray matter has six layers of cells with different forms and sizes. Neurons of some regions of the cerebral cortex register **afferent** (**sensory**) impulses; in other regions, **efferent** (**motor**) neurons generate motor impulses that control voluntary movements. Cells of the cerebral cortex are related to the integration of sensory information and the initiation of voluntary motor responses.

The **cerebellar cortex** has three layers: an outer molecular layer, a central layer of large Purkinje cells, and an inner granule layer. The Purkinje cells have a conspicuous cell body and their dendrites are highly developed, assuming the aspect of a fan. These dendrites occupy most of the molecular layer and are the reason for the sparseness of nuclei. The granule layer is formed by very small neurons (the smallest in the body), which are compactly disposed, in contrast to the less cell-dense molecular layer.

In cross sections of the **spinal cord,** white matter is peripheral and gray matter is central, assuming the shape of an **H**. In the horizontal bar of this **H** is an opening, the **central canal,** which is a remnant of the lumen of the embryonic neural tube. It is lined with ependymal cells. The gray matter of the legs of the **H** forms the **anterior horns.** These contain motor neurons whose axons make up the ventral roots of the spinal nerves. Gray matter also forms the posterior horns (the arms of the **H**), which receive sensory fibers from neurons in the spinal ganglia (dorsal roots).

Meninges

The skull and the vertebral column protect the central nervous system. It is also encased in membranes of connective tissue called the **meninges**. Starting with the outermost layer, the meninges are the **dura mater, arachnoid,** and **pia mater.** The arachnoid and the pia mater are linked together and are often considered a single membrane called the **pia-arachnoid.**

The dura mater is always separated from the arachnoid by the thin subdural space. The internal surface of all dura mater, as well as its external surface in the spinal cord, is covered by simple squamous epithelium of mesenchymal in origin.

1- Dura Mater

The dura mater is the external layer and is composed of dense connective tissue continuous with the periosteum of the skull. The dura mater that envelops the spinal cord is separated from the periosteum of the vertebrae by the epidural space, which contains thin-walled veins, loose connective tissue, and adipose tissue.

2- Arachnoid

The arachnoid (Gr. *arachnoeides*, cobweblike) has two components: a layer in contact with the dura mater and a system of trabeculae connecting the layer with the pia mater. The cavities between the trabeculae form the **subarachnoid space,** which is filled with cerebrospinal fluid and is completely separated from the **subdural space.** This space forms a hydraulic cushion that protects the central nervous system from trauma. The subarachnoid space communicates with the ventricles of the brain. The arachnoid is composed of connective tissue devoid of blood vessels. The same type of simple squamous epithelium that covers the dura mater covers its surfaces. Because the

arachnoid has fewer trabeculae in the spinal cord, it can be more clearly distinguished from the pia mater in that area. In some areas, the arachnoid perforates the dura mater, forming protrusions that terminate in venous sinuses in the dura mater. These protrusions, which are covered by endothelial cells of the veins, are called **arachnoid villi.** Their function is to reabsorb cerebrospinal fluid into the blood of the venous sinuses.

3- Pia Mater

The pia mater is a loose connective tissue containing many blood vessels. Although it is located quite close to the nerve tissue, it is not in contact with nerve cells or fibers. Between the pia mater and the neural elements is a thin layer of neuroglial processes, adhering firmly to the pia mater and forming a physical barrier at the periphery of the central nervous system. This barrier separates the central nervous system from the cerebrospinal fluid.

The pia mater follows all the irregularities of the surface of the central nervous system and penetrates it to some extent along with the blood vessels. Squamous cells of mesenchymal origin cover pia mater.

Blood vessels penetrate the central nervous system through tunnels covered by pia mater—the **perivascular spaces.** The pia mater disappears before the blood vessels are transformed into capillaries. In the central nervous system, the blood capillaries are completely covered by expansions of the neuroglial cell processes.

Blood–brain Barrier

The blood–brain barrier results from the reduced permeability that is characteristic of blood capillaries of nerve tissue. Occluding junctions, which provide continuity between the endothelial cells of these capillaries, represent the main structural component of the barrier. The cytoplasm of these endothelial cells does not have the fenestrations found in many other locations, and very few pinocytotic vesicles are observed. The expansions of neuroglial cell processes that envelop the capillaries are partly responsible for their low permeability. The blood–brain barrier is a functional barrier that prevents the passage of some substances, such as antibiotics and chemical and bacterial toxic matter, from the blood to nerve tissue.

Choroid Plexus & Cerebrospinal Fluid

The choroid plexus consists of invaginated folds of pia mater, rich in dilated fenestrated capillaries, that penetrate the interior of the brain ventricles. It is found in the roofs of the third and fourth ventricles and in part in the walls of the lateral ventricles. The choroid plexus is composed of loose connective tissue of the pia mater, covered by a simple cuboidal or low columnar epithelium made of ion-transporting cells.

Peripheral Nervous System

The main components of the peripheral nervous system are the **nerves, ganglia,** and **nerve endings.** Nerves are bundles of nerve fibers surrounded by connective tissue sheaths.

Nerve Fibers

Nerve fibers consist of axons enveloped by a special sheath derived from cells of ectodermal origin. Groups of nerve fibers constitute the tracts of the brain, spinal cord, and peripheral nerves. Nerve fibers exhibit differences in their enveloping sheaths, related to whether the fibers are part of the central or the peripheral nervous system.

Single or multiple folds of a sheath cell cover most axons in adult nerve tissue. In peripheral nerve fibers, the sheath cell is the **Schwann cell,** and in central nerve fibers it is the **oligodendrocyte.** Axons of small diameter are usually **unmyelinated nerve fibers**. Progressively thicker axons are generally sheathed by increasingly numerous concentric wrappings of the enveloping cell, forming the **myelin sheaths.** These fibers are known as **myelinated nerve fibers**.

Myelinated Fibers

In myelinated fibers of the peripheral nervous system, the plasmalemma of the covering Schwann cell winds and wraps around the axon. The layers of membranes of the sheath cell unite and form **myelin,** a whitish lipoprotein complex whose lipid component can be partly removed by standard histological procedures.

Myelin consists of many layers of modified cell membranes. These membranes have a higher proportion of lipids than do other cell membranes. The myelin sheath shows gaps along its path called the **nodes of Ranvier**; these represent the spaces between adjacent Schwann cells along the length of the axon. Interdigitating processes of Schwann cells partially cover the node. The distance between two nodes is called an **internode** and consists of one Schwann cell. The length of the internode varies between 1 and 2 mm. There are no Schwann cells in the central nervous system; there, the processes of the oligodendrocytes form the myelin sheath. Oligodendrocytes differ from Schwann cells in that different branches of one cell can envelop segments of several axons.

Unmyelinated Fibers

In both the central and peripheral nervous systems, not all axons are sheathed in myelin. In the peripheral system, all unmyelinated axons are enveloped within simple clefts of the Schwann cells (Figure 9–26). Unlike their association with individual myelinated axons, each Schwann cell can sheathe many unmyelinated axons.

Unmyelinated nerve fibers do not have nodes of Ranvier, because abutting Schwann cells are united to form a continuous sheath. The central nervous system is rich in unmyelinated axons; unlike those in the peripheral system, these axons are not sheathed. In the brain and spinal cord, unmyelinated axonal processes run free among the other neuronal and glial processes.

Nerves

In the peripheral nervous system, the nerve fibers are grouped in bundles to form the nerves. Except for a few very thin nerves made up of unmyelinated fibers, nerves have a whitish, homogeneous, glistening appearance because of their myelin and collagen content. Nerves have an external fibrous coat of dense connective tissue called **epineurium,** which also fills the space between the bundles of nerve fibers. Each bundle is surrounded by the **perineurium,** a sleeve formed by layers of flattened epitheliumlike cells. The cells of each layer of the perineurial sleeve are joined at their edges by tight junctions, an arrangement that makes the perineurium a barrier to the passage of most macromolecules and has the important function of protecting the nerve fibers from aggression. Within the perineurial sheath run the Schwann cell-sheathed axons and their enveloping connective tissue, the **endoneurium**. The endoneurium consists of a thin layer of reticular fibers, produced by Schwann cells. The nerves establish communication between brain and spinal cord centers and the sense organs and effectors (muscles, glands, etc). They possess afferent and efferent fibers to and from the central nervous system. **Afferent** fibers carry the information obtained from the interior of the body and the environment to the central nervous system. **Efferent** fibers carry impulses from the central nervous system to the effector organs commanded by these centers. Nerves possessing only sensory fibers are called **sensory nerves;** those composed only of fibers carrying impulses to the effectors are called **motor nerves.** Most nerves have both sensory and motor fibers and are called **mixed nerves;** these nerves have both myelinated and unmyelinated axons.

Ganglia

Ganglia are ovoid structures containing neuronal cell bodies and glial cells supported by connective tissue. Because they serve as relay stations to transmit nerve impulses, one nerve enters and another exits from each ganglion. The direction of the nerve impulse determines whether the ganglion will be a **sensory** or an **autonomic** ganglion.

Sensory Ganglia

Sensory ganglia receive afferent impulses that go to the central nervous system. Two types of sensory ganglia exist. Some are associated with cranial nerves (**cranial ganglia**); others are associated with the dorsal root of the spinal nerves and are called

spinal ganglia. The latter comprise large neuronal cell bodies with prominent fine Nissl bodies surrounded by abundant small glial cells called **satellite cells.**

A connective tissue framework and capsule support the ganglion cells. The neurons of these ganglia are pseudounipolar and relay information from the ganglion's nerve endings to the gray matter of the spinal cord via synapses with local neurons.

Autonomic Ganglia

Autonomic ganglia appear as bulbous dilatations in autonomic nerves. Some are located within certain organs, especially in the walls of the digestive tract, where they constitute the **intramural ganglia.** These ganglia are devoid of connective tissue capsules, and their cells are supported by the stroma of the organ in which they are found.

Autonomic ganglia usually have multipolar neurons. As with craniospinal ganglia, autonomic ganglia have neuronal perikaryons with fine Nissl bodies.

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

Autonomic Nervous System

The autonomic (Gr. *autos,* self, + *nomos,* law) nervous system is related to the control of smooth muscle, the secretion of some glands, and the modulation of cardiac rhythm. Its function is to make adjustments in certain activities of the body to maintain a constant internal environment (**homeostasis**). Although the autonomic nervous system is by definition a motor system, fibers that receive sensation originating in the interior of the organism accompany the motor fibers of the autonomic system. The term "autonomic" is not correct—although it is widely used—inasmuch as most of the functions of the autonomic nervous system are not autonomous; they are organized and regulated in the central nervous system. The concept of the autonomic nervous system is mainly functional. Anatomically, it is composed of collections of nerve cells located in the central nervous system, fibers that leave the central nervous system through cranial or spinal nerves, and nerve ganglia situated in the paths of these fibers. The term "autonomic" covers all the neural elements concerned with visceral function. In fact, the so-called autonomic functions are as dependent on the central nervous system as are the motor neurons that trigger muscle contractions.

The autonomic nervous system is a two-neuron network. The first neuron of the autonomic chain is located in the central nervous system. Its axon forms a synapse with the second multipolar neuron in the chain, located in a ganglion of the peripheral nervous system. The nerve fibers (axons) of the first neuron are called **preganglionic fibers;** the

axons of the second neuron to the effectors—muscle or gland—are called **postganglionic fibers.** The chemical mediator present in the synaptic vesicles of all preganglionic endings and at anatomically parasympathetic postganglionic endings is **acetylcholine,** which is released from the terminals by nerve impulses.

The adrenal medulla is the only organ that receives preganglionic fibers, because the majority of the cells, after migration into the gland, differentiate into secretory cells rather than ganglion cells. The autonomic nervous system is composed of two parts that differ both anatomically and functionally: the sympathetic system and the parasympathetic system. Nerve fibers that release acetylcholine are called **cholinergic.** Cholinergic fibers include all the preganglionic autonomic fibers (sympathetic as well as parasympathetic) and postganglionic parasympathetic fibers to smooth muscles, heart, and exocrine glands.

Sympathetic System

The nuclei (formed by a collection of nerve cell bodies) of the sympathetic system are located in the thoracic and lumbar segments of the spinal cord. Therefore, the sympathetic system is also called the **thoracolumbar division** of the autonomic nervous system. The axons of these neurons—preganglionic fibers—leave the central nervous system by way of the ventral roots and white communicating rami of the thoracic and lumbar nerves. The chemical mediator of the postganglionic fibers of the sympathetic system is **norepinephrine,** which is also produced by the adrenal medulla. Nerve fibers that release norepinephrine are called **adrenergic** (a word derived from noradrenalin, another term for norepinephrine). Adrenergic fibers innervate sweat glands and blood vessels of skeletal muscle. Cells of the adrenal medulla release epinephrine and norepinephrine in response to preganglionic sympathetic stimulation.

Parasympathetic System

The parasympathetic system has its nuclei in the medulla and midbrain and in the sacral portion of the spinal cord. The preganglionic fibers of these neurons leave through four of the cranial nerves (III, VII, IX, and X) and also through the second, third, and fourth sacral spinal nerves. The parasympathetic system is therefore also called the craniosacral division of the autonomic system. The second neuron of the parasympathetic series is found in ganglia smaller than those of the sympathetic system; it is always located near or within the effector organs. These neurons are usually located in the walls of organs (eg, stomach, intestines), in which case the preganglionic fibers enter the organs and form a synapse there with the second neuron in the chain.

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

Degeneration & Regeneration of Nerve Tissue

Although it has been shown that neurons can divide in the brain of adult birds, mammalian neurons usually do not divide, and their degeneration represents a permanent loss. Neuronal processes in the central nervous system are, within very narrow limits, replaceable by growth through the synthetic activity of their perikaryons. Peripheral nerve fibers can also regenerate if their perikaryons are not destroyed.

Death of a nerve cell is limited to its perikaryon and processes. The neurons functionally connected to the dead neuron do not die, except for those with only one link. In this latter instance, the isolated neuron undergoes **transneuronal degeneration.** In contrast to nerve cells, neuroglia of the central nervous system—and Schwann cells and ganglionic satellite cells of the peripheral nervous system—are able to divide by mitosis. Spaces in the central nervous system left by nerve cells lost by disease or injury are invaded by neuroglia.

Skin Sensorial Receptors

One of the most important functions of the skin, with its great extension and abundant sensory innervation, is to receive stimuli from the environment. The skin is the most extensive sensory receptor. In addition to numerous free nerve endings in the epidermis, hair follicles, and cutaneous glands, encapsulated and expanded receptors are present in the dermis and subcutaneous tissue; they are more frequently found in the dermal papillae. Free nerve endings are sensitive to touch-pressure (pressure is sustained touch), tactile reception, high and low temperatures, pain, itching, and other sensations. The expanded ending includes the Ruffini endings, and the encapsulated ending includes the Pacini, Meissner, and Krause corpuscles. There is evidence that the expanded and encapsulated corpuscles are not necessary for cutaneous sensation. Their distribution is irregular, with many areas of skin containing only free nerve endings. However, when present, the expanded and encapsulated receptors respond to tactile stimuli, functioning as mechanoreceptors. Pacini corpuscles and Ruffini endings are also found in the connective tissue of organs located deep in the body, where they probably are sensitive to movements of internal organs and to pressure of one organ over another.

Skin

The skin is the heaviest single organ of the body, accounting for about 16% of total body weight and, in adults, presenting 1.2-2.3 m^2 of surface to the external environment. It is composed of the **epidermis,** an epithelial layer of ectodermal origin, and the **dermis,** a layer of connective tissue of mesodermal origin. Based on the comparative thickness of the epidermis, **thick** and **thin** skin can be distinguished. The junction of dermis and epidermis is irregular, and projections of the dermis called **papillae** interdigitate with evaginations of the epidermis known as **epidermal ridges.** In three dimensions, these interdigitations may be of the peg-and-socket variety (thin skin) or formed of ridges and grooves (thick skin). Epidermal derivatives include hairs, nails, and sebaceous and sweat glands. Beneath the dermis lies the **hypodermis** (Gr. *hypo,* under, + *derma,* skin), or **subcutaneous tissue,** a loose connective tissue that may contain a pad of adipose cells, the **panniculus adiposus.** The hypodermis, which is not considered part of the skin, binds skin loosely to the subjacent tissues and corresponds to the superficial fascia of gross anatomy.

The external layer of the skin is relatively impermeable to water; this prevents water loss by evaporation and allows for terrestrial life. The skin functions as a receptor organ in continuous communication with the environment and protects the organism from impact and friction injuries. **Melanin,** a pigment produced and stored in the cells of the epidermis, provides further protective action against the sun's ultraviolet (UV) rays. Glands of the skin, blood vessels, and adipose tissue participate in thermoregulation, body metabolism, and the excretion of various substances. Under the action of solar radiation received by skin, active vitamin D_3 is formed from precursors synthesized by the organism through the modification of molecules introduced with foodstuff. Because skin is elastic, it can expand to cover large areas in conditions associated with swelling, such as edema and pregnancy.

Upon close observation, certain portions of human skin show ridges and grooves arranged in distinctive patterns. These ridges first appear during intrauterine life: at 13 weeks in the tips of the fingers and later in the volar surfaces of the hands and feet (palm and sole). The patterns assumed by ridges and intervening sulci are known as **dermatoglyphics.** They are unique for each individual, appearing as loops, arches, whorls, or combinations of these forms. These configurations, which are used for personal identification (fingerprints), are probably determined by multiple genes; the field of dermatoglyphics has come to be of considerable medical and anthropological as well as legal interest.

Epidermis

The epidermis consists mainly of a stratified squamous keratinized epithelium, but it also contains three less abundant cell types: **melanocytes, Langerhans cells,** and

Merkel's cells. The keratinizing epidermal cells are called keratinocytes. It is customary to distinguish between the **thick skin** (**glabrous,** or smooth and nonhairy) found on the palms and soles and the **thin skin** (hairy) found elsewhere on the body. The designations "thick" and "thin" refer to the thickness of the epidermal layer, which varies between 75 and 150 m for thin skin and 400 and 600 m for thick skin. Total skin thickness (epidermis plus dermis) also varies according to site. For example, skin on the back is about 4 mm thick, whereas that of the scalp is about 1.5 mm thick.

From the dermis outward, the epidermis consists of five layers of keratin-producing cells (keratinocytes).

1- Stratum Basale (Stratum Germinativum)

The stratum basale consists of a single layer of basophilic columnar or cuboidal cells resting on the basement membrane at the dermalâ€“epidermal junction (Figure 18â€“1). Desmosomes bind the cells of this layer together in their lateral and upper surfaces. Hemidesmosomes, found in the basal plasmalemma, help bind these cells to the basal lamina. The stratum basale, containing stem cells, is characterized by intense mitotic activity and is responsible, in conjunction with the initial portion of the next layer, for constant renewal of epidermal cells. The human epidermis is renewed about every 15-30 days, depending on age, the region of the body, and other factors. All cells in the stratum basale contain intermediate keratin filaments about 10 nm in diameter. As the cells progress upward, the number of filaments increases until they represent half the total protein in the stratum corneum.

2- Stratum Spinosum

The stratum spinosum consists of cuboidal, or slightly flattened, cells with a central nucleus and a cytoplasm whose processes are filled with bundles of keratin filaments. These bundles converge into many small cellular extensions, terminating with desmosomes located at the tips of these spiny projections . The cells of this layer are firmly bound together by the filament-filled cytoplasmic spines and desmosomes that punctuate the cell surface, providing a spine-studded appearance. These keratin bundles, visible under the light microscope, are called **tonofilaments;** they end at and insert into the cytoplasmic densities of the desmosomes. The filaments play an important role in maintaining cohesion among cells and resisting the effects of abrasion. The epidermis of areas subjected to continuous friction and pressure (such as the soles of the feet) has a thicker stratum spinosum with more abundant tonofilaments and desmosomes. All mitoses are confined to what is termed the **malpighian layer,** which consists of both the stratum basale and the stratum spinosum. Only the malpighian layer contains epidermal stem cells.

3- Stratum Granulosum

The stratum granulosum consists of three to five layers of flattened polygonal cells whose cytoplasm is filled with coarse basophilic granules called **keratohyalin granules.** The proteins of these granules contain a phosphorylated histidine-rich protein as well as proteins containing cystine. The numerous phosphate groups account for the intense basophilia of keratohyalin granules, which are not surrounded by a membrane.

Another characteristic structure in the cells of the granular layer of epidermis that can be seen with the electron microscope is the membrane-coated **lamellar granule,** a small (0.1- 0.3 µm) ovoid or rodlike structure containing lamellar disks that are formed by lipid bilayers. These granules fuse with the cell membrane and discharge their contents into the intercellular spaces of the stratum granulosum, where they are deposited in the form of sheets containing lipid. The function of this extruded material is similar to that of intercellular cement in that it acts as a barrier to penetration by foreign materials and provides a very important sealing effect in the skin. Formation of this barrier, which appeared first in reptiles, was one of the important evolutionary events that permitted development of terrestrial life.

4- Stratum Lucidum

More apparent in thick skin, the stratum lucidum is a translucent, thin layer of extremely flattened eosinophilic epidermal cells. The organelles and nuclei are no longer evident, and the cytoplasm consists primarily of densely packed keratin filaments embedded in an electron-dense matrix. Desmosomes are still evident between adjacent cells.

5- Stratum Corneum

The stratum corneum consists of 15-20 layers of flattened nonnucleated keratinized cells whose cytoplasm is filled with a birefringent filamentous scleroprotein, **keratin.** The composition of tonofilaments changes as epidermal cells differentiate. Basal cells contain polypeptides of lower molecular weight, whereas more differentiated cells synthesize higher-molecular-weight polypeptides. Tonofilaments are packed together in a matrix contributed by the keratohyalin granules.

After keratinization, the cells consist of only fibrillar and amorphous proteins and thickened plasma membranes; they are called **horny cells.** During keratinization, lysosomal hydrolytic enzymes play a role in the disappearance of the cytoplasmic organelles. These cells are continuously shed at the surface of the stratum corneum.

This description of the epidermis corresponds to its most complex structure in areas where it is very thick, as on the soles of the feet.

In thin skin, the stratum granulosum and the stratum lucidum are often less well developed, and the stratum corneum may be quite thin .

Nonkeratogenic cells of the epidermis

1- Melanocytes

The color of the skin is the result of several factors, the most important of which are its content of **melanin** and **carotene,** the number of blood vessels in the dermis, and the color of the blood flowing in them. **Eumelanin** is a dark brown pigment produced by the **melanocyte**, a specialized cell of the epidermis found beneath or between the cells of the stratum basale and in the hair follicles. The pigment found in red hair is called **pheomelanin** (Gr. *phaios,* dusky, + *melas,* black) and contains **cysteine** as part of its structure. Melanocytes are derived from neural crest cells. They have rounded cell bodies from which long irregular extensions branch into the epidermis, running between the cells of the strata basale and spinosum. Tips of these extensions terminate in invaginations of the cells present in the two layers. The electron microscope reveals a pale-staining cell containing numerous small mitochondria, a well-developed Golgi complex, and short cisternae of rough endoplasmic reticulum. Although melanocytes are not attached to the adjacent keratinocytes by desmosomes, they are bound to the basal lamina by hemidesmosomes.

Melanin is synthesized in the melanocyte, with tyrosinase playing an important role in the process.

2- Langerhans Cells

Langerhans cells, star-shaped cells found mainly in the stratum spinosum of the epidermis, represent 2-8% of the epidermal cells. They are bone marrow derived, carried to the skin by the blood, and capable of binding, processing, and presenting antigens to T lymphocytes, thus participating in the stimulation of these cells. Consequently, they have a significant role in immunological skin reactions. Langerhans cells are **antigen-presenting** cells.

3- Merkel's Cells

Merkel's cells, generally present in the thick skin of palms and soles, somewhat resemble the epidermal epithelial cells but have small dense granules in their cytoplasm. The composition of these granules is not known. Free nerve endings that form an expanded terminal disk are present at the base of Merkel's cells. These cells may serve as sensory mechanoreceptors, although other evidence suggests that they have functions related to the diffuse neuroendocrine system.

Immunological Activity in the Skin

Because of its large size, the skin has an impressive number of lymphocytes and antigen-presenting cells (Langerhans cells), and because of its location it is in close contact with many antigenic molecules. For these reasons, the epidermis has an important role in some types of immune responses. Most lymphocytes found in the skin are "homed" in the epidermis.

Dermis

The dermis is the connective tissue that supports the epidermis and binds it to the subcutaneous tissue (hypodermis). The thickness of the dermis varies according to the region of the body and reaches its maximum of 4 mm on the back. The surface of the dermis is very irregular and has many projections (dermal papillae) that interdigitate with projections (epidermal pegs or ridges) of the epidermis. Dermal papillae are more numerous in skin that is subjected to frequent pressure; they increase and reinforce the dermalâ€“epidermal junction. During embryonic development, the dermis determines the developmental pattern of the overlying epidermis. Dermis obtained from the sole always induces the formation of a heavily keratinized epidermis irrespective of the site of origin of the epithelial cells. A **basal lamina** is always found between the stratum germinativum and the papillary layer of the dermis and follows the contour of the interdigitations between these layers. Underlying the basal lamina is a delicate net of reticular fibers, the **lamina reticularis.** This composite structure is called the **basement membrane** and can be seen with the light microscope The dermis contains two layers with rather indistinct boundaries the outermost papillary layer and the deeper reticular layer. The thin **papillary layer** is composed of loose connective tissue; fibroblasts and other connective tissue cells, such as mast cells and macrophages, are present. Extravasated leukocytes are also seen. The papillary layer is so called because it constitutes the major part of the dermal papillae. From this layer, special collagen fibrils insert into the basal lamina and extend into the dermis. They bind the dermis to the epidermis and are called **anchoring fibrils.** The **reticular layer** is thicker, composed of irregular dense connective tissue (mainly type I collagen), and therefore has more fibers and fewer cells than does the papillary layer. The principal glycosaminoglycan is dermatan sulfate. The dermis contains a network of fibers of the elastic system, with the thicker fibers characteristically found in the reticular layer. From this region emerge fibers that become gradually thinner and end by inserting into the basal lamina. As these fibers progress toward the basal lamina, they gradually lose their amorphous elastin component , and only the microfibrillar component inserts into the basal lamina. This elastic network is responsible for the elasticity of the skin. The dermis also contains epidermal derivatives such as the hair follicles and sweat and sebaceous glands. There is a rich supply of nerves in the dermis, and the effector nerves to the skin are postganglionic fibers of sympathetic ganglia of the paravertebral chain. No parasympathetic innervation is present. The afferent nerve endings form a superficial

dermal network with free nerve endings, a hair follicle network, and the innervation of encapsulated sensory organs.

Subcutaneous Tissue

The subcutaneous tissue layer consists of loose connective tissue that binds the skin loosely to the subjacent organs, making it possible for the skin to slide over them. The hypodermis often contains fat cells that vary in number according to the area of the body and vary in size according to nutritional state. This layer is also referred to as the superficial fascia and, where thick enough, the panniculus adiposus.

Vessels & Skin Sensorial Receptors

The connective tissue of the skin contains a rich network of blood and lymphatic vessels. The arterial vessels that nourish the skin form two plexuses. One is located between the papillary and reticular layers; the other is located between the dermis and the subcutaneous tissue. Thin branches leave these plexuses and vascularize the dermal papillae. Each papilla has only one arterial ascending branch and one venous descending branch. Veins are disposed in three plexuses, two in the position described for arterial vessels and the third in the middle of the dermis. Arteriovenous anastomoses with glomera are frequent in the skin, participating in the regulation of body temperature. Lymphatic vessels begin as closed sacs in the papillae of the dermis and converge to form two plexuses, as described for the arterial vessels. One of the most important functions of the skin, with its great extension and abundant sensory innervation, is to receive stimuli from the environment. The skin is the most extensive sensory receptor. In addition to numerous free nerve endings in the epidermis, hair follicles, and cutaneous glands, encapsulated and expanded receptors are present in the dermis and subcutaneous tissue; they are more frequently found in the dermal papillae. Free nerve endings are sensitive to touch-pressure (pressure is sustained touch), tactile reception, high and low temperatures, pain, itching, and other sensations. The expanded ending includes the **Ruffini endings,** and the encapsulated ending includes the **Vater-Pacini, Meissner,** and **Krause** corpuscles. There is evidence that the expanded and encapsulated corpuscles are not necessary for cutaneous sensation. Their distribution is irregular, with many areas of skin containing only free nerve endings. However, when present, the expanded and encapsulated receptors respond to tactile stimuli, functioning as mechanoreceptors. Vater Pacini corpuscles and Ruffini endings are also found in the connective tissue of organs located deep in the body, where they probably are sensitive to movements of internal organs and to pressure of one organ over another.

Hairs

Hairs are elongated keratinized structures derived from invaginations of epidermal epithelium. Their color, size, and disposition vary according to race, age, sex, and region of

the body. Hairs are found everywhere on the body except on the palms, soles, lips, glans penis, clitoris, and labia minora. The face has about 600 hairs/cm^2, and the remainder of the body has about 60/cm^2. Hairs grow discontinuously and have periods of growth followed by periods of rest. This growth does not occur synchronously in all regions of the body or even in the same area; rather, it tends to occur in patches. The duration of the growth and rest periods also varies according to the region of the body. Thus, in the scalp, the growth periods (anagen) may last for several years, whereas the rest periods (catagen and telogen) average 3 months. Hair growth in such regions of the body as the scalp, face, and pubis is strongly influenced not only by sex hormones especially androgens but also by adrenal and thyroid hormones.

Each hair arises from an epidermal invagination, the **hair follicle**, that during its growth period has a terminal dilatation called a **hair bulb.** At the base of the hair bulb, a **dermal papilla** can be observed. The dermal papilla contains a capillary network that is vital in sustaining the hair follicle. Loss of blood flow or loss of the vitality of the dermal papilla will result in death of the follicle. The epidermal cells covering this dermal papilla form the hair root that produces and is continuous with the hair shaft, which protrudes beyond the skin.

During periods of growth, the epithelial cells that make up the hair bulb are equivalent to those in the stratum germinativum of the skin. They divide constantly and differentiate into specific cell types. In certain types of thick hairs, the cells of the central region of the root at the apex of the dermal papilla produce large, vacuolated, and moderately keratinized cells that form the **medulla** of the hair. Root cells multiply and differentiate into heavily keratinized, compactly grouped fusiform cells that form the **hair cortex.** Farther toward the periphery are the cells that produce the **hair cuticle,** a layer of cells that is cuboidal midway up the bulb, then becomes tall and columnar. Higher up, these cells change from horizontal to vertical, at which point they form a layer of flattened, heavily keratinized, shinglelike cells covering the cortex. These cuticle cells are the last cell type in the hair follicle to differentiate.

The outermost cells give rise to the **internal root sheath,** which completely surrounds the initial part of the hair shaft. The internal sheath is a transient structure whose cells degenerate and disappear above the level of the sebaceous glands. The **external root sheath** is continuous with epidermal cells and, near the surface, shows all the layers of epidermis. Near the dermal papilla, the external root sheath is thinner and is composed of cells corresponding to the stratum germinativum of the epidermis.

Separating the hair follicle from the dermis is a noncellular hyaline layer, the **glassy membrane**, which results from a thickening of the basal lamina. The dermis that surrounds the follicle is denser, forming a sheath of connective tissue. Bound to this sheath and connecting it to the papillary layer of the dermis are bundles of smooth muscle cells, the **arrector pili** muscles. They are disposed in an oblique direction, and their contraction

results in the erection of the hair shaft to a more upright position. Contraction of arrector pili muscles also causes a depression in the skin where the muscles attach to the dermis. This contraction produces the "gooseflesh" of common parlance.

Hair color is created by the activity of melanocytes located between the papilla and the epithelial cells of the hair root. The epithelial cells produce the pigment found in the medullary and cortical cells of the hair shaft. The melanocytes produce and transfer melanin to the epithelial cells by a mechanism similar to that described for the epidermis.

Although the keratinization processes in the epidermis and hair appear to be similar, they differ in several ways:

1. The epidermis produces relatively ***soft*** keratinized outer layers of dead cells that adhere slightly to the skin and desquamate continuously. The opposite occurs in the hair, which has a ***hard*** and compact keratinized structure.

2. Although keratinization in the epidermis ***occurs continuously and over the entire surface***, it is intermittent in the hair and occurs ***only in the hair root***. The connective tissue of the hair papilla has an inductive action on the covering epithelial cells, promoting their proliferation and differentiation. Injuries to the dermal papillae thus result in the loss of hair.

3. Contrary to what happens in the epidermis, where the differentiation of all cells ***in the same direction*** gives rise to the final keratinized layer, cells in the hair root differentiate into ***various cell types*** that differ in ultrastructure, histochemical characteristics, and function.

Mitotic activity in hair follicles is influenced by androgens.

Nails

Nails are plates of keratinized epithelial cells on the dorsal surface of each distal phalanx. The proximal part of the nail, hidden in the nail groove, is the **nail root.** The epithelium of the fold of skin covering the nail root consists of the usual layers of cells. The stratum corneum of this epithelium forms the **eponychium,** or **cuticle.** The **nail plate,** which corresponds to the stratum corneum of the skin, rests on a bed of epidermis called the **nail bed.** Only the stratum basale and the stratum spinosum are present in the nail bed. Nail plate epithelium arises from the **nail matrix.** The proximal end of the matrix extends deep to the nail root. Cells of the matrix divide, move distally, and eventually cornify, forming the proximal part of the nail plate. The nail plate then slides forward over the nail bed (which makes no contribution to the formation of the plate). The distal end of the plate becomes free of the nail bed and is worn away or cut off. The nearly transparent nail plate and the thin epithelium of the nail bed provide a useful window on the amount of oxygen in the blood by showing the color of blood in the dermal vessels.

Glands of the Skin

Sebaceous Glands

Sebaceous glands are embedded in the dermis over most of the body surface. There are about 100 of these glands per square centimeter over most of the body, but the frequency increases to 400 - 900/cm^2 in the face, forehead, and scalp. Sebaceous glands, which are not found in the glabrous skin of the palms and soles, are acinar glands that usually have several acini opening into a short duct. This duct usually ends in the upper portion of a hair follicle; ***in certain regions, such as the glans penis, glans clitoridis, and lips, it opens directly onto the epidermal surface.*** The acini consist of a basal layer of undifferentiated flattened epithelial cells that rests on the basal lamina. These cells proliferate and differentiate, filling the acini with rounded cells containing increasing amounts of fat droplets in their cytoplasm. Their nuclei gradually shrink, and the cells simultaneously become filled with fat droplets and burst. The product of this process is **sebum,** the secretion of the sebaceous gland, which is gradually moved to the surface of the skin.

The sebaceous gland is an example of a **holocrine** gland, because its product of secretion is released with remnants of dead cells. This product comprises a complex mixture of lipids that includes triglycerides, waxes, squalene, and cholesterol and its esters. Sebaceous glands begin to function at puberty. The primary controlling factor of sebaceous gland secretion in men is testosterone; in women it is a combination of ovarian and adrenal androgens.

The functions of sebum in humans are largely unknown. It may have weak antibacterial and antifungal properties. Sebum does not have any importance in preventing water loss.

Sweat Glands

Sweat glands are widely distributed in the skin ***except for certain regions, such as the glans penis.***

The **merocrine** sweat glands are simple, coiled tubular glands whose ducts open at the skin surface . Their ducts do not divide, and their diameter is thinner than that of the secretory portion. The secretory part of the gland is embedded in the dermis; it measures approximately 0.4 mm in diameter and is surrounded by myoepithelial cells. Contraction of these cells helps to discharge the secretion. Two types of cells have been described in the secretory portion of sweat glands. **Dark cells** are pyramidal cells that line most of the luminal surface of this portion of the gland. Their basal surface does not touch the basal lamina. Secretory granules containing glycoproteins are abundant in their apical cytoplasm. **Clear cells** are devoid of secretory granules. Their basal plasmalemma has the numerous

invaginations characteristic of cells involved in transepithelial salt and fluid transport. The ducts of these glands are lined with stratified cuboidal epithelium.

The fluid secreted by sweat glands is not viscous and contains little protein. Its main components are water, sodium chloride, urea, ammonia, and uric acid. Its sodium content of 85 mEq/L is distinctly below that of blood (144 mEq/L), and the cells present in the sweat ducts are responsible for sodium absorption, to prevent excessive loss of this ion. The fluid in the lumen of the secretory portion of the gland is an ultrafiltrate of the blood plasma. This ultrafiltrate is derived from a network of capillaries that intimately envelops the secretory region of each gland. After its release on the surface of the skin, sweat evaporates, cooling the surface. In addition to its important cooling role, sweat glands also function as an auxiliary excretory organ, eliminating several substances not necessary for the organism.

In addition to the merocrine sweat glands just described, another type of sweat gland the **apocrine** gland is present in the axillary, areolar, and anal regions. Apocrine glands are much larger (3-5 mm in diameter) than merocrine sweat glands. They are embedded in the dermis and hypodermis, and their ducts open into hair follicles. These glands produce a viscous secretion that is initially odorless but may acquire a distinctive odor as a result of bacterial decomposition.

Apocrine glands are innervated by adrenergic nerve endings, whereas merocrine glands receive cholinergic fibers.

The glands of Moll in the margins of the eyelids and the ceruminous glands of the ear are modified sweat glands.

The Respiratory System

The respiratory system includes the lungs and a system of tubes that links the sites of gas exchange with the external environment. A ventilation mechanism, consisting of the thoracic cage, intercostal muscles, diaphragm, and elastic and collagen components of the lungs, is important in the movement of air through the lungs. The respiratory system is customarily divided into two principal regions: ***a conducting portion***, consisting of the nasal cavity, nasopharynx, larynx, trachea, bronchi (Gr. *bronchos,* windpipe), bronchioles, and terminal bronchioles; ***and a respiratory portion*** (where gas exchange takes place), consisting of respiratory bronchioles, alveolar ducts, and alveoli. Alveoli are specialized saclike structures that make up the greater part of the lungs. They are the main sites for the principal function of the lungsâ€"the exchange of O_2 and CO_2 between inspired air and blood.

The conducting portion serves two main functions: to provide a conduit through which air can travel to and from the lungs and to condition the inspired air. To ensure an uninterrupted supply of air, a combination of cartilage, elastic and collagen fibers, and smooth muscle provides the conducting portion with rigid structural support and the necessary flexibility and extensibility.

Respiratory Epithelium

Most of the conducting portion is lined with ciliated pseudostratified columnar epithelium that contains a rich population of goblet cells and is known as respiratory epithelium. Typical respiratory epithelium consists of ***five cell types*** (as seen in the electron microscope). ***1- Ciliated columnar*** cells constitute the most abundant type. Each cell has about 300 cilia on its apical surface; beneath the cilia, in addition to basal bodies, are numerous small mitochondria that supply adenosine triphosphate (ATP) for ciliary beating.

The next most abundant cells in the respiratory epithelium are ***2- the mucous goblet cells***. The apical portion of these cells contains the mucous droplets composed of glycoproteins. The remaining columnar cells are known as ***3- brush cells*** because of the numerous microvilli on their apical surface. Brush cells have afferent nerve endings on their basal surfaces and are considered to be sensory receptors. ***4- Basal (short) cells*** are small rounded cells that lie on the basal lamina but do not extend to the luminal surface of the epithelium. These cells are believed to be generative stem cells that undergo mitosis and subsequently differentiate into the other cell types. The last cell type is ***5- the small granule cell***, which resembles a basal cell except that it possesses numerous granules 100 - 300 nm in diameter with dense cores. Histochemical studies reveal that these cells constitute a population of cells of the diffuse neuroendocrine system. All cells of the ciliated pseudostratified columnar epithelium touch the basement membrane.

Nasal Cavity

The nasal cavity consists of two structures: the external vestibule and the internal nasal fossae.

Vestibule

The vestibule is the most anterior and dilated portion of the nasal cavity. The outer integument of the nose enters the nares (nostrils) and continues partway up the vestibule. Around the inner surface of the nares are numerous sebaceous and sweat glands, in addition to the thick short hairs, or vibrissae, that filter out large particles from the inspired air. Within the vestibule, the epithelium loses its keratinized nature and undergoes a transition into typical respiratory epithelium before entering the nasal fossae.

Nasal Fossae

Within the skull lie two cavernous chambers separated by the osseous nasal septum. Extending from each lateral wall are three bony shelf like projections known as conchae. Of the superior, middle, and inferior conchae, only the middle and inferior projections are covered with respiratory epithelium. The superior conchae are covered with a specialized olfactory epithelium. The narrow, ribbonlike passages created by the conchae improve the conditioning of the inspired air by increasing the surface area of respiratory epithelium and by creating turbulence in the airflow. The result is increased contact between air streams and the mucous layer. Within the lamina propria of the conchae are large venous plexuses known as swell bodies. Every 20 - 30 min, the swell bodies on one side of the nasal fossae become engorged with blood, resulting in distention of the conchal mucosa and a concomitant decrease in the flow of air. During this time, most of the air is directed through the other nasal fossa. These periodic intervals of occlusion reduce airflow, allowing the respiratory epithelium to recover from desiccation.

In addition to swell bodies, the nasal cavity has a rich vascular system with a complex organization. Large vessels form a close-meshed latticework next to the periosteum, from which arcading branches lead toward the surface. Blood in arcading vessels flows forward from the rear region in a direction counter to the flow of inspired air. As a result, the incoming air is efficiently warmed by a countercurrent system.

Smell (Olfaction)

The olfactory chemoreceptors are located in the olfactory epithelium, a specialized area of the mucous membrane in the superior conchae, located in the roof of the nasal

cavity. In humans, it is about 10 cm^2 in area. It is a pseudostratified columnar epithelium composed of three types of cells.

1-The supporting cells have broad, cylindrical apexes and narrower bases. On their free surface are microvilli submerged in a fluid layer. Well-developed junctional complexes bind the supporting cells to the adjacent olfactory cells. The supporting cells contain a light yellow pigment that is responsible for the color of the olfactory mucosa.

2-The basal cells are small; they are spherical or cone shaped and form a single layer at the base of the epithelium.

Between the basal cells and the supporting cells are the olfactory cells

3-bipolar neurons distinguished from the supporting cells by the position of their nuclei, which lie below the nuclei of the supporting cells. Their apexes (dendrites) possess elevated and dilated areas from which arise six to eight cilia. These cilia are very long and nonmotile, and respond to odoriferous substances by generating a receptor potential. The cilia increase the receptor surface considerably. The afferent axons of these bipolar neurons unite in small bundles directed toward the brain, where they synapse with neurons of the brain olfactory lobe.

The lamina propria of the olfactory epithelium possesses the **glands of Bowman**, which of pure serous glands and also named olfactory glands. Their secretion produces a watery fluid environment around the olfactory cilia that may clear the cilia, facilitating the access of new odoriferous substances.

Conditioning of Air

A major function of the conducting portion is to condition the inspired air. Before it enters the lungs, inspired air is cleansed, moistened, and warmed. To carry out these functions, the mucosa of the conducting portion is lined with a specialized respiratory epithelium, and there are numerous mucous and serous glands as well as a rich superficial vascular network in the lamina propria.

As the air enters the nose, large vibrissae (***specialized hairs***) remove coarse particles of dust. Once the air reaches the nasal fossae, particulate and gaseous impurities are trapped in a layer of mucus. ***This mucus***, in conjunction with serous secretions, also serves to moisten the incoming air, protecting the delicate alveolar lining from desiccation. ***A rich superficial vascular network*** also warms the incoming air.

Paranasal Sinuses

The paranasal sinuses are closed cavities in the frontal, maxillary, ethmoid, and sphenoid bones. They are lined with a thinner respiratory epithelium that contains few goblet cells. The lamina propria contains only a few small glands and is continuous with the underlying periosteum. The paranasal sinuses communicate with the nasal cavity through small openings. The mucus produced in these cavities drains into the nasal passages as a result of the activity of its ciliated epithelial cells.

Nasopharynx

The nasopharynx is the first part of the pharynx, continuing caudally with the oropharynx, the oral portion of this organ. It is lined with respiratory epithelium in the portion that is in contact with the soft palate.

Larynx

The larynx is an irregular tube that connects the pharynx to the trachea. Within the lamina propria lie a number of laryngeal cartilages. ***The larger cartilages (thyroid, cricoid, and most of the arytenoids) are hyaline. The smaller cartilages (epiglottis, cuneiform, corniculate, and the tips of the arytenoids) are elastic cartilages*****.** In addition to their supporting role (maintenance of an open airway), these cartilages serve as a valve to prevent swallowed food or fluid from entering the trachea. They also participate in producing sounds for phonation.

The epiglottis, which projects from the rim of the larynx, extends into the pharynx and has both a lingual and a laryngeal surface. The entire lingual surface and the apical portion of the laryngeal surface are covered with stratified squamous epithelium. Toward the base of the epiglottis on the laryngeal surface, the epithelium undergoes a transition into ciliated pseudostratified columnar epithelium. Mixed mucous and serous glands are found beneath the epithelium.

Below the epiglottis, the mucosa forms two pairs of folds that extend into the lumen of the larynx. The upper pair constitutes the false vocal cords (vestibular folds), covered with typical respiratory epithelium beneath which lie numerous serous glands within the lamina propria. The lower pair of folds constitutes the true vocal cords. Large bundles of parallel elastic fibers that compose the vocal ligament lie within the vocal folds, which are covered with a stratified squamous epithelium. Parallel to the ligaments are bundles of skeletal muscle, the vocalis muscles, which regulate the tension of the fold and its ligaments. As air is forced between the folds,

these muscles provide the means for sounds of different frequencies to be produced.

Trachea

The trachea is lined with a typical respiratory mucosa. In the lamina propria are 16 - 20 C-shaped rings of hyaline cartilage that keep the tracheal lumen open and numerous seromucous glands that produce a more fluid mucus. The open ends of these cartilage rings are located on the posterior surface of the trachea. A fibroelastic ligament and bundle of smooth muscle bind to the perichondrium and bridge the open ends of these C-shaped cartilages. The ligament prevents overdistention of the lumen, and the muscle allows regulation of the lumen (the inner space delimited by a tissue wall is the lumen of the organ).
Contraction of the muscle and the resultant narrowing of the tracheal lumen are involved in the cough reflex. The smaller bore of the trachea after contraction provides for increased velocity of expired air, which aids in clearing the air passage.

Bronchial Tree

The trachea divides into two **primary bronchi** that enter the lungs at the hilum. At each hilum, arteries enter and veins and lymphatic vessels leave. These structures are surrounded by dense connective tissue and form a unit called the pulmonary root.

After entering the lungs, the primary bronchi course downward and outward, giving rise to three bronchi in the right lung and two in the left lung, each of which supplies a pulmonary lobe. These lobar bronchi divide repeatedly, giving rise to smaller bronchi, whose terminal branches are called bronchioles. Each bronchiole enters a pulmonary lobule, where it branches to form five to seven terminal bronchioles.

The pulmonary lobules are pyramid shaped, with the apex directed toward the pulmonary hilum. Each lobule is delineated by a thin connective tissue septum, best seen in the fetus. In adults, these septa are frequently incomplete, resulting in a poor delineation of the lobules.

The primary bronchi generally have the same histological appearance as the trachea. Proceeding toward the respiratory portion, the histological organization of both the epithelium and the underlying lamina propria becomes simplified. It must be stressed that this simplification is gradual; no abrupt transition can be observed between the bronchi and bronchioles. For this reason, the division of the bronchial tree into bronchi, bronchioles, etc, is to some extent artificial, although this division has both pedagogical and practical value.

Bronchi

Each primary bronchus branches dichotomously 9 - 12 times, with each branch becoming progressively smaller until it reaches a diameter of about 5 mm. *Except for the organization of cartilage and smooth muscle*, the mucosa of the bronchi is structurally similar to the mucosa of the trachea. The bronchial cartilages are more irregular in shape than those found in the trachea; in the larger portions of the bronchi, the cartilage rings completely encircle the lumen. As bronchial diameter decreases, the cartilage rings are replaced with isolated plates, or islands, of hyaline cartilage. Beneath the epithelium, in the bronchial lamina propria, is a smooth muscle layer consisting of crisscrossing bundles of spirally arranged smooth muscle. Bundles of smooth muscle become more prominent near the respiratory zone. Contraction of this muscle layer after death is responsible for the folded appearance of the bronchial mucosa observed in histological section. The lamina propria is rich in elastic fibers and contains an abundance of mucous and serous glands whose ducts open into the bronchial lumen. Numerous lymphocytes are found both within the lamina propria and among the epithelial cells. Lymphatic nodules are present and are particularly numerous at the branching points of the bronchial tree.

Bronchioles

Bronchioles, intralobular airways with diameters of 5 mm or less, have neither cartilage nor glands in their mucosa; there are only scattered goblet cells within the epithelium of the initial segments. In the larger bronchioles, the epithelium is ciliated pseudostratified columnar, which decreases in height and complexity to become ciliated simple columnar or cuboidal epithelium in the smaller terminal bronchioles. The epithelium of terminal bronchioles also contains **Clara cells**, which are devoid of cilia, have secretory granules in their apex, and are known to secrete proteins that protect the bronchiolar lining against oxidative pollutants and inflammation.

Bronchioles also exhibit specialized regions called neuroepithelial bodies. These are formed by groups of 80 - 100 cells that contain secretory granules and receive cholinergic nerve endings. Their function is poorly understood, but they are probably chemoreceptors that react to changes in gas composition within the airway. They also seem involved in the reparative process of airway epithelial cell renewal after injury.

Bronchiolar lamina propria is composed largely of smooth muscle and elastic fibers. The musculature of both the bronchi and the bronchioles is under the control of the vagus nerve and the sympathetic nervous system. Stimulation of the vagus nerve decreases the diameter of these structures; sympathetic stimulation produces the opposite effect.

Respiratory Bronchioles

Each terminal bronchiole subdivides into two or more respiratory bronchioles that serve as regions of transition between the conducting and respiratory portions of the respiratory system. The respiratory bronchiolar mucosa is structurally identical to that of the terminal bronchioles, except that their walls are interrupted by numerous saclike alveoli where gas exchange occurs. Portions of the respiratory bronchioles are lined with ciliated cuboidal epithelial cells and Clara cells, but at the rim of the alveolar openings the bronchiolar epithelium becomes continuous with the squamous alveolar lining cells (type I alveolar cells; see below). Proceeding distally along these bronchioles, the alveoli increase greatly in number, and the distance between them is markedly reduced. Between alveoli, the bronchiolar epithelium consists of ciliated cuboidal epithelium; however, the cilia may be absent in more distal portions. Smooth muscle and elastic connective tissue lie beneath the epithelium of respiratory bronchioles.

Alveolar Ducts

Proceeding distally along the respiratory bronchioles, the number of alveolar openings into the bronchiolar wall becomes ever greater until the wall consists of nothing else, and the tube is now called an alveolar duct. Both the alveolar ducts and the alveoli are lined with extremely attenuated squamous alveolar cells. In the lamina propria surrounding the rim of the alveoli is a network of smooth muscle cells. These sphincterlike smooth muscle bundles appear as knobs between adjacent alveoli. Smooth muscle disappears at the distal ends of alveolar ducts. A rich matrix of elastic and reticular fibers provides the only support of the duct and its alveoli.

Alveolar ducts open into atria that communicate with **alveolar sacs**, two or more of which arise from each atrium. Elastic and reticular fibers form a complex network encircling the openings of atria, alveolar sacs, and alveoli. The elastic fibers enable the alveoli to expand with inspiration and to contract passively with expiration. The reticular fibers serve as a support that prevents overdistention and damage to the delicate capillaries and thin alveolar septa.

Alveoli

Alveoli are saclike evaginations (about 200 µm in diameter) of the respiratory bronchioles, alveolar ducts, and alveolar sacs. Alveoli are responsible for the spongy structure of the lungs. Structurally, alveoli resemble small pockets that are open on one side, similar to the honeycombs of a beehive. Within these cuplike structures, O_2 and CO_2 are exchanged between the air and the blood. The structure of the alveolar walls is specialized for enhancing diffusion between the external and internal environments. Generally, each wall lies between two neighboring alveoli and is therefore called an interalveolar septum, or wall. An interalveolar septum consists of two thin squamous epithelial layers between which lie capillaries, elastic and reticular fibers, and connective tissue matrix and cells. The capillaries and connective

tissue constitute the interstitium. Within the interstitium of the interalveolar septum is found the richest capillary network in the body.

Air in the alveoli is separated from capillary blood by three components referred to collectively as the blood-air barrier: the surface lining and cytoplasm of the alveolar cells, the fused basal laminae of the closely apposed alveolar and endothelial cells, and the cytoplasm of the endothelial cells. The total thickness of these layers varies from 0.1 to 1.5 µm. Within the interalveolar septum, anastomosing pulmonary capillaries are supported by a meshwork of reticular and elastic fibers. These fibers, which are arranged to permit expansion and contraction of the interalveolar septum, are the primary means of structural support of the alveoli. The basement membrane, leukocytes, macrophages, and fibroblasts can also be found within the interstitium of the septum. The fusion of two basal laminae produced by the endothelial cells and the epithelial (alveolar) cells of the interalveolar septum forms the basement membrane.

O_2 from the alveolar air passes into the capillary blood through the blood-air barrier; CO_2 diffuses in the opposite direction. Liberation of CO_2 from H_2CO_3 is catalyzed by the enzyme carbonic anhydrase present in erythrocytes. The approximately 300 million alveoli in the lungs considerably increase their internal exchange surface, which has been calculated to be approximately 140 m^2.

Capillary endothelial cells are extremely thin and can be easily confused with type I alveolar epithelial cells. The endothelial lining of the capillaries is continuous and not fenestrated. Clustering of the nuclei and other organelles allows the remaining areas of the cell to become extremely thin, increasing the efficiency of gas exchange. The most prominent feature of the cytoplasm in the flattened portions of the cell is numerous pinocytotic vesicles.

alveolar epithelial cells are:

1- Type I cells, or squamous alveolar cells, are extremely attenuated cells that line the alveolar surfaces. Type I cells make up 97% of the alveolar surfaces (type II cells make up the remaining 3%). These cells are so thin (sometimes only 25 nm) that the electron microscope was needed to prove that all alveoli are covered with an epithelial lining. Organelles such as the Golgi complex, endoplasmic reticulum, and mitochondria are grouped around the nucleus, reducing the thickness of the blood-air barrier and leaving large areas of cytoplasm virtually free of organelles. The cytoplasm in the thin portion contains abundant pinocytotic vesicles, which may play a role in the turnover of surfactant (described below) and the removal of small particulate contaminants from the outer surface. In addition to desmosomes, all type I epithelial cells have occluding junctions that prevent the leakage of tissue fluid into the alveolar air space. The main role of these cells is to provide a barrier of minimal thickness that is readily permeable to gases.

2-Type II cells are interspersed among the type I alveolar cells with which they have occluding and desmosomal junctions. Type II cells are rounded cells that are usually found in groups of two or three along the alveolar surface at points at which the alveolar walls unite and form angles. These cells, which rest on the basement membrane, are part of the epithelium, with the same origin as the type I cells that line the alveolar walls. They divide by mitosis to replace their own population and also the type I population. In histological sections, they exhibit a characteristic vesicular or foamy cytoplasm. These vesicles are caused by the presence of lamellar bodies that are preserved and evident in tissue prepared for electron microscopy. Lamellar bodies, which average 1-2 µm in diameter, contain concentric or parallel lamellae limited by a unit membrane. Histochemical studies show that these bodies, which contain phospholipids, glycosaminoglycans, and proteins, are continuously synthesized and released at the apical surface of the cells. The lamellar bodies give rise to a material that spreads over the alveolar surfaces, providing an extracellular alveolar coating, pulmonary surfactant, that lowers alveolar surface tension.

The surfactant layer consists of an aqueous, proteinaceous hypophase covered with a monomolecular phospholipid film that is primarily composed of dipalmitoyl phosphatidylcholine and phosphatidylglycerol. Surfactant also contains several types of proteins. Pulmonary surfactant serves several major functions in the economy of the lung, but it primarily aids in reducing the surface tension of the alveolar cells. The reduction of surface tension means that less inspiratory force is needed to inflate the alveoli, and thus the work of breathing is reduced. In addition, without surfactant, alveoli would tend to collapse during expiration. In fetal development, surfactant appears in the last weeks of gestation and coincides with the appearance of lamellar bodies in the type II cells.

The surfactant layer is not static but is constantly being turned over. The lipoproteins are gradually removed from the surface by the pinocytotic vesicles of the squamous epithelial cells, by macrophages, and by type II alveolar cells.

Alveolar lining fluids are also removed via the conducting passages as a result of ciliary activity. As the secretions pass up through the airways, they combine with bronchial mucus, forming a bronchoalveolar fluid, which aids in the removal of particulate and noxious components from the inspired air.

3- Lung Macrophages: Alveolar macrophages, also called dust cells, are found in the interior of the interalveolar septum and are often seen on the surface of the alveolus. Numerous carbon- and dust-laden macrophages in the connective tissue around major blood vessels or in the pleura probably are cells that have never passed through the epithelial lining. The phagocytosed debris within these cells was most likely passed from the alveolar lumen into the interstitium by the pinocytotic activity of type I alveolar cells. The alveolar macrophages that scavenge the outer surface of the

epithelium within the surfactant layer are carried to the pharynx, where they are swallowed.

Pulmonary Blood Vessels

Circulation in the lungs includes both nutrient (systemic) and functional (pulmonary) vessels. Pulmonary arteries and veins represent the functional circulation. Pulmonary arteries are thin walled as a result of the low pressures (25 mm Hg systolic, 5 mm Hg diastolic) encountered in the pulmonary circuit. Within the lung the pulmonary artery branches, accompanying the bronchial tree. Its branches are surrounded by adventitia of the bronchi and bronchioles. At the level of the alveolar duct, the branches of this artery form a capillary network in the interalveolar septum and in close contact with the alveolar epithelium. The lung has the best-developed capillary network in the body, with capillaries between all alveoli, including those in the respiratory bronchioles.

Pleura

The pleura is the serous membrane covering the lung. It consists of two layers, parietal and visceral, that are continuous in the region of the hilum. Both membranes are composed of mesothelial cells resting on a fine connective tissue layer that contains collagen and elastic fibers. The elastic fibers of the visceral pleura are continuous with those of the pulmonary parenchyma.

The parietal and visceral layers define a cavity entirely lined with squamous mesothelial cells. Under normal conditions, this pleural cavity contains only a film of liquid that acts as a lubricant, facilitating the smooth sliding of one surface over the other during respiratory movements.

In certain pathological states, the pleural cavity can become a real cavity, containing liquid or air. The walls of the pleural cavity, like all serosal cavities (peritoneal and pericardial), are quite permeable to water and other substances hence the high frequency of fluid accumulation (pleural effusion) in this cavity in pathological conditions. This fluid is derived from the blood plasma by exudation. Conversely, under certain conditions, liquids or gases in the pleural cavity can be rapidly absorbed.

Organs Associated with the Digestive Tract

The organs associated with the digestive tract include the ***salivary glands, the pancreas, the liver, and the gallbladder.*** The main functions of the saliva produced by salivary glands are to wet and lubricate the oral mucosa and the ingested food, to initiate the digestion of carbohydrates and lipids (by means of amylase and lingual lipase activities, respectively), and to secrete germicidal protective substances such as immunoglobulin A (IgA), lysozyme, and lactoferrin. The saliva also has a very important buffering function and forms a protective pellicle on the teeth by means of calcium-binding proline-rich salivary proteins. In some species (but not in humans), saliva is very important for evaporative cooling.

The main functions of the pancreas are to produce digestive enzymes that act in the small intestine and to secrete hormones such as insulin and glucagon into the bloodstream. Both are very important for the metabolism of the absorbed nutrients. The liver produces bile, an important fluid in the digestion of fats. It plays a major role in lipid, carbohydrate, and protein metabolism and inactivates and metabolizes many toxic substances and drugs. It also participates in iron metabolism and the synthesis of blood proteins and the factors necessary for blood coagulation. The gallbladder absorbs water from the bile and stores the bile in a concentrated form.

Salivary Glands

Saliva is a complex fluid that has digestive, lubricating, and protective functions. In addition to the small salivary glands scattered throughout the oral cavity, there are three pairs of large salivary glands: the **parotid, submandibular,** and **sublingual glands.** In humans, the minor salivary glands secrete 10% of the total volume of saliva, but they account for approximately 70% of the mucus secreted.

A capsule of connective tissue, rich in collagen fibers, surrounds the large salivary glands. The parenchyma of the glands consists of secretory end pieces and a branching duct system arranged in lobules, separated by septae of connective tissue originating from the capsule. The secretory end pieces present two types of secretory cells serous and mucous as well as the nonsecretory myoepithelial cells. This secretory portion is followed by a duct system whose components modify and conduct the saliva to the oral cavity.

Serous cells are usually pyramidal in shape, with a broad base resting on the basal lamina and a narrow apical surface with short, irregular microvilli facing the lumen. They exhibit characteristics of polarized protein-secreting cells. Adjacent secretory cells are joined together by junctional complexes and usually form a spherical mass of cells called **acinus,** with a small lumen in the center. This structure can be thought of as a grape attached to its stem; the stem corresponds to the duct system.

Mucous cells are usually cuboidal to columnar in shape; their nuclei are oval and pressed toward the bases of the cells. They exhibit the characteristics of mucus-secreting cells, containing glycoproteins important for the moistening and lubricating functions of the saliva. Most of these glycoproteins are called mucins and contain 70-80% carbohydrate moieties in their structure. Mucous cells are most often organized as **tubules,** consisting of cylindrical arrays of secretory cells surrounding a lumen. In the human **submandibular and sublingual glands,** serous and mucous cells are arranged in a characteristic pattern. The mucous cells form tubules, but their ends are capped by serous cells, which constitute the **serous demilunes**.

Myoepithelial cells, Epithelial Tissue, are found between the basal lamina and the basal plasma membrane of the cells forming secretory end pieces and intercalated ducts, which form the initial portion of the duct system. Myoepithelial cells surrounding each secretory portion, usually two to three cells per secretory unit, are well developed and branched (and are sometimes called **basket cells**), whereas those associated with intercalated ducts are spindle shaped and lie parallel to the length of the duct. These cells show several characteristics that resemble smooth muscle cells, including contractility. However, they also establish intercellular junctions among themselves and with secretory cells, such as desmosomes. Although the contraction of myoepithelial cells accelerates the secretion of saliva, their main function seems to be the prevention of end piece distention during secretion due to the increase in intraluminal pressure.

In the **duct system,** secretory end pieces empty into the **intercalated ducts,** lined by cuboidal epithelial cells. These cells have the ability to divide and differentiate into secretory or ductal cells. Several of these short intercalated ducts join to form **striated ducts**, characterized by radial striations that extend from the bases of the cells to the level of the central nuclei. When viewed in the electron microscope, the striations are seen to consist of infoldings of the basal plasma membrane with numerous elongated mitochondria that are aligned parallel to the infolded membranes; this structure is characteristic of ion-transporting cells. Intercalated and striated ducts are also called intralobular ducts because of their location within the lobule.

The striated ducts of each lobule converge and drain into ducts located in the connective tissue septae separating the lobules, where they become **interlobular,** or **excretory, ducts.** They are initially lined with pseudostratified or stratified cuboidal epithelium, but more distal parts of the excretory ducts are lined with stratified columnar epithelium containing a few mucus-secreting cells. The main duct of each major salivary gland ultimately empties into the oral cavity and is lined with nonkeratinized-stratified squamous epithelium.

Vessels and nerves enter the large salivary glands at the hilum and gradually branch into the lobules. A rich vascular and nerve plexus surrounds the secretory and ductal components of each lobule. The capillaries surrounding the secretory end pieces are very important for the secretion of saliva, stimulated by the autonomic nervous system.

Parasympathetic stimulation, usually through the smell or taste of food, promotes vasodilation and a copious watery secretion content. Sympathetic stimulation produces small amounts of viscous saliva, rich in organic material

Parotid Gland

The parotid gland is a branched acinar gland; its secretory portion is composed exclusively of serous cells containing secretory granules that are rich in proteins and have a high amylase activity. This activity is responsible for most of the hydrolysis of ingested carbohydrates. The digestion begins in the mouth and continues for a short time in the stomach, before the gastric juice acidifies the food and thus decreases amylase activity considerably. Intercalated and striated ducts are easily observed within the lobules, due to their length.

As in other large salivary glands, the connective tissue contains many plasma cells and lymphocytes. The plasma cells secrete IgA, which forms a complex with a **secretory component** synthesized by the serous acinar, intercalated duct, and striated duct cells. The IgA-rich secretory complex released into the saliva is resistant to enzymatic digestion and constitutes an immunological defense mechanism against pathogens in the oral cavity.

Submandibular Gland

The submandibular gland is a branched tubuloacinar gland its secretory portion contains both mucous and serous cells. The serous cells are the main component of this gland and are easily distinguished from mucous cells by their rounded nuclei and basophilic cytoplasm. In humans, 90% of the end pieces of the submandibular gland are serous acinar, whereas 10% consist of mucous tubules with serous demilunes. The presence of extensive lateral and basal membrane infoldings toward the vascular bed increases the ion-transporting surface area 60 times, facilitating electrolyte and water transport. Because of these folds, the cell boundaries are indistinct. Serous cells are responsible for the weak amylolytic activity present in this gland and its saliva. The cells that form the demilunes in the submandibular gland secrete the enzyme **lysozyme,** whose main activity is to hydrolyze the walls of certain bacteria. Some acinar and intercalated duct cells in large salivary glands also secrete lactoferrin, which binds iron, a nutrient necessary for bacterial growth. Striated ducts are easily observed in the human submandibular gland, but intercalated ducts are very short.

Sublingual Gland

The sublingual gland, like the submandibular gland, is a branched tubuloacinar gland formed of serous and mucous cells. Mucous cells predominate in this gland; serous cells are present almost exclusively on demilunes of mucous tubules. As in the submandibular

gland, cells that form the demilunes in this gland secrete lysozyme. Intralobular ducts are not as well developed as in other major salivary glands.

Minor Salivary Glands

These nonencapsulated glands are distributed throughout the oral mucosa and submucosa. Saliva is produced by small groups of secretory units and is conducted to the oral cavity by short ducts, with little modification of its content. Although variations exist, minor salivary glands are usually mucous. The small serous glands present in the posterior region of the tongue (von Ebner's glands) are the only exception . Lymphocyte agregates are commonly observed within minor salivary glands, associated with IgA secretion

Pancreas

The pancreas is a mixed exocrine and endocrine gland that produces digestive enzymes and hormones. The enzymes are stored and released by cells of the exocrine portion, arranged in acini. The hormones are synthesized in clusters of endocrine epithelial cells known as islets of Langerhans. The exocrine portion of the pancreas is a compound acinar gland, similar in structure to the parotid gland. In histological sections, a distinction between the two glands can be made based on the absence of striated ducts and the presence of the islets of Langerhans in the pancreas. Another characteristic detail is that in the pancreas the initial portions of intercalated ducts penetrate the lumens of the acini. Nuclei, surrounded by a pale cytoplasm, belong to **centroacinar cells** that constitute the intraacinar portion of the intercalated duct. These cells are found only in pancreatic acini. Intercalated ducts are tributaries of larger intralobular ducts that, in turn, form larger interlobular ducts lined by columnar epithelium, located within the connective tissue septa. There are no striated ducts in the pancreatic duct system.

The exocrine pancreatic acinus is composed of several serous cells surrounding a lumen. These cells are highly polarized, with a spherical nucleus, and are typical protein-secreting cells. The number of zymogen granules present in each cell varies according to the digestive phase and attains its maximum in animals that have fasted.

A thin capsule of connective tissue covers the pancreas and sends septa into it, separating the pancreatic lobules. The acini are surrounded by a basal lamina that is supported by a delicate sheath of reticular fibers. The pancreas also has a rich capillary network, essential for the secretory process.

The exocrine pancreas secretes 1500-3000 mL of isosmotic alkaline fluid per day containing water, ions, and several proteases (**trypsinogens 1, 2,** and **3, chymotrypsinogen, proelastases 1** and **2, protease E, kallikreinogen, procarboxypeptidases A1, A2, B1,** and **B2),amylase, lipases** (**triglyceride lipase, colipase,** and **carboxyl ester hydrolase**), **phospholipase** A_2**,** and **nucleases**

(**deoxyribonuclease** and **ribonuclease**). The majority of the enzymes are stored as proenzymes in the secretory granules of acinar cells, being activated in the lumen of the small intestine after secretion. Enterokinase, an intestinal enzyme, cleaves trypsinogen to form trypsin, which then activates the other proteolytic enzymes in a cascade. This is very important for the protection of the pancreas as well as the synthesis of protease inhibitors by the acinar cells.

Pancreatic secretion is controlled mainly through two hormones **secretin** and **cholecystokinin** that are produced by enteroendocrine cells of the intestinal mucosa (duodenum and jejunum). Stimulation of the vagus nerve (parasympathetic stimulation) will also produce pancreatic secretion. Actually, the hormonal and neural systems act in concert to control pancreatic secretion.

Gastric acid (or pH < 4.5) in the intestinal lumen is a strong stimulus for secretin release. Secretin causes acinar and duct cells to add water and bicarbonate to the fluid, promoting the secretion of an abundant alkaline fluid rich in electrolytes and poor in enzyme activity. This fluid neutralizes the acidic **chyme** (partially digested food) so that pancreatic enzymes can function at their optimal neutral pH range. The release of cholecystokinin is triggered by the presence of long-chain fatty acids, gastric acid, and certain essential amino acids in the intestinal lumen. Cholecystokinin promotes secretion of a less abundant but enzyme-rich fluid acting mainly in the extrusion of zymogen granules. The integrated action of both these hormones provides for a heavy secretion of enzyme-rich pancreatic juice.

Liver

The liver is the second-largest organ of the body (the largest is the skin) and the largest gland, weighing about 1-1.5 kg. It is situated in the abdominal cavity beneath the diaphragm. The liver is the organ in which nutrients absorbed in the digestive tract are processed and stored for use by other parts of the body. It is thus an interface between the digestive system and the blood. Most of its blood (70-80%) comes from the portal vein, arising from the stomach, intestines, and spleen; the smaller percentage (20-30%) is supplied by the hepatic artery. All the materials absorbed via the intestines reach the liver through the portal vein, except the complex lipids (**chylomicrons**), which are transported mainly by lymph vessels. The position of the liver in the circulatory system is optimal for gathering, transforming, and accumulating metabolites and for neutralizing and eliminating toxic substances. Elimination occurs in the bile, an exocrine secretion of the liver that is important for lipid digestion. The liver also has the very important function of producing plasma proteins, such as albumin, other carrier proteins, coagulation factors, and growth factors.

Stroma

The liver is covered by a thin connective tissue capsule (**Glisson's capsule**) that becomes thicker at the **hilum,** *where the portal vein and the hepatic artery enter the organ and where the right and left hepatic ducts and lymphatics exit*. These vessels and ducts are surrounded by connective tissue all the way to their termination (or origin) in the **portal spaces** between the liver lobules. At this point, a delicate reticular fiber network that supports the hepatocytes and sinusoidal endothelial cells of the liver lobules is formed.

The Liver Lobule

The basic structural component of the liver is the liver cell, or **hepatocyte**. These epithelial cells are grouped in interconnected plates and constitute two-thirds of the mass of the liver. In light-microscope sections, structural units called **liver lobules** can be seen. The liver lobule is formed of a polygonal mass of tissue about 0.7 x 2 mm in size, with **portal spaces** at the periphery and a vein, called the **central or centrolobular vein,** in the center. Portal spaces, regions located in the corners of the lobules, contain connective tissue, bile ducts, lymphatics, nerves, and blood vessels. The human liver contains three to six portal spaces per lobule, each with a venule (a branch of the portal vein), an arteriole (a branch of the hepatic artery), a duct (part of the bile duct system), and lymphatic vessels. The venule contains blood coming from the superior and inferior mesenteric and splenic veins. The arteriole contains oxygen-rich blood coming from the celiac trunk of the abdominal aorta. The duct, lined by cuboidal epithelium, carries bile synthesized by the hepatocytes and eventually empties into the hepatic duct. One or more lymphatics carry lymph, which eventually enters the blood circulation. In certain animals (eg, pigs), the lobules are separated by a layer of connective tissue. This is not the case in humans, where the lobules are in close contact along most of their length, making it difficult to establish the exact limits between different lobules.

The hepatocytes in the liver lobule are radially disposed and are arranged like the bricks of a wall. These cellular plates are directed from the periphery of the lobule to its center and anastomose freely, forming a labyrinthine and spongelike structure. The space between these plates contains capillaries, the **liver sinusoids**. The Circulatory System, sinusoidal capillaries are irregularly dilated vessels composed solely of a discontinuous layer of fenestrated endothelial cells. The fenestrae are about 100 nm in diameter, have no diaphragm, and are grouped in clusters. There are also spaces between the endothelial cells, which, together with the cellular fenestrae and a discontinuous basal lamina (depending on the species), give these vessels great permeability.

A subendothelial space known as the **space of Disse** separates the endothelial cells from the hepatocytes. The fenestrae and discontinuity of the endothelium allow the free flow of plasma but not of cellular elements into the space of Disse, permitting an easy exchange of molecules (including macromolecules) from the sinusoidal lumen to the hepatocytes and vice versa. This exchange is physiologically important not only because of the large

number of macromolecules (eg, lipoproteins, albumin, fibrinogen) secreted into the blood by hepatocytes but also because the liver takes up and catabolizes many of these large molecules. The basolateral side of the hepatocyte, which lines the space of Disse, contains many microvilli and demonstrates endocytic and pinocytic activity. The sinusoid is surrounded and supported by a delicate sheath of reticular fibers. In addition to the endothelial cells, the sinusoids contain macrophages known as **Kupffer cells**. These cells are found on the luminal surface of the endothelial cells, within the sinusoids. Their main functions are to metabolize aged erythrocytes, digest hemoglobin, secrete proteins related to immunological processes, and destroy bacteria that eventually enter the portal blood through the large intestine. Kupffer cells account for 15% of the liver cell population. Most of them are located in the periportal region of the liver lobule, where they are very active in phagocytosis. In the space of Disse (perisinusoidal space), **fat-storing cells,** also called stellate or Ito's cells, contain vitamin and rich lipid inclusions. In the healthy liver, these cells have several functions, such as uptake, storage, and release of retinoids, synthesis and secretion of several extracellular matrix proteins and proteoglycans, secretion of growth factors and cytokines, and the regulation of the sinusoidal lumen diameter in response to different regulators (eg, prostaglandins, thromboxane A_2). Blood Supply

Portal Vein System

The portal vein branches repeatedly and sends small **portal venules** to the portal spaces. The portal venules branch into the **distributing veins** that run around the periphery of the lobule. From the distributing veins, small **inlet venules** empty into the **sinusoids.** The sinusoids run radially, converging in the center of the lobule to form the **central vein**. This vessel has thin walls consisting only of endothelial cells supported by a sparse population of collagen fibers. As the central vein progresses along the lobule, it receives more and more sinusoids and gradually increases in diameter. At its end, it leaves the lobule at its base by merging with the larger **sublobular vein**. The sublobular veins gradually converge and fuse, forming the two or more large **hepatic veins** that empty into the inferior vena cava.

Arterial System

The hepatic artery branches repeatedly and forms the **interlobular arteries.** Some of these arteries irrigate the structures of the portal spaces, and others form arterioles that end directly in the sinusoids at various distances from the portal spaces, thus providing a mixture of arterial and portal venous blood in the sinusoids. The main function of the arterial system is to supply an adequate amount of oxygen to hepatocytes.

Blood flows from the periphery to the center of the **liver lobule.** Consequently, oxygen and metabolites, as well as all other toxic or nontoxic substances absorbed in the intestines, reach the peripheral cells first and then reach the central cells of the lobule. This direction of blood flow partly explains why the behavior of the perilobular cells differs from that of the centrolobular cells. This duality of behavior of the hepatocyte is particularly evident in

pathological specimens, where changes are seen in either the central cells or the peripheral cells of the lobule.

The Hepatocyte

Hepatocytes are polyhedral, with six or more surfaces, and have a diameter of 20-30 m. In sections stained with hematoxylin and eosin (H&E), the cytoplasm of the hepatocyte is eosinophilic, mainly because of the large number of mitochondria and some smooth endoplasmic reticulum. Hepatocytes located at different distances from the portal spaces show differences in structural, histochemical, and biochemical characteristics. The surface of each hepatocyte is in contact with the wall of the sinusoids, through the space of Disse, and with the surfaces of other hepatocytes. *Wherever two hepatocytes abut, they delimit a tubular space between them known as the* **bile canaliculus**.

The canaliculi, the first portions of the bile duct system, are tubular spaces 1-2 m in diameter. They are limited only by the plasma membranes of two hepatocytes and have a small number of microvilli in their interiors. The cell membranes near these canaliculi are firmly joined by tight junctions. Gap junctions are frequent between hepatocytes and are sites of intercellular communication, an important process in the coordination of these cells' physiological activities. The bile canaliculi form a complex anastomosing network progressing along the plates of the liver lobule and terminating in the region of the portal spaces. The bile flow therefore progresses in a direction opposite to that of the blood, ie, from the center of the lobule to its periphery. At the periphery, bile enters the **bile ductules,** or **Hering's canals**, composed of cuboidal cells. After a short distance, the ductules cross the limiting hepatocytes of the lobule and end in the **bile ducts** in the portal spaces. Bile ducts are lined by cuboidal or columnar epithelium and have a distinct connective tissue sheath. They gradually enlarge and fuse, forming right and left **hepatic ducts,** which subsequently leave the liver.

The surface of the hepatocyte that faces the space of Disse contains many microvilli that protrude into that space, but there is always a space between them and the cells of the sinusoidal wall. The hepatocyte has one or two rounded nuclei with one or two nucleoli. Some of the nuclei are polyploid, ie, they contain some even multiples of the haploid number of chromosomes. Polyploid nuclei are characterized by their greater size, which is proportional to their ploidy. The hepatocyte has an abundant endoplasmic reticulumâ both smooth and rough. In the hepatocyte, the rough endoplasmic reticulum forms aggregates dispersed in the cytoplasm; these are often called **basophilic bodies.** Several proteins (eg, blood albumin, fibrinogen) are synthesized on polyribosomes in these structures. Various important processes take place in the smooth endoplasmic reticulum, which is distributed diffusely throughout the cytoplasm. This organelle is responsible for the processes of oxidation, methylation, and conjugation required for inactivation or detoxification of various substances before their excretion from the body. The smooth endoplasmic

reticulum is a labile system that reacts promptly to the molecules received by the hepatocyte.

The hepatocyte frequently contains glycogen. This polysaccharide appears in the electron microscope as coarse, electron-dense granules that frequently collect in the cytosol close to the smooth endoplasmic reticulum. The amount of glycogen present in the liver conforms to a diurnal rhythm; it also depends on the nutritional state of the individual. Liver glycogen is a depot for glucose and is mobilized if the blood glucose level falls below normal. In this way, hepatocytes maintain a steady level of blood glucose, one of the main sources of energy for use by the body.

Each hepatocyte has approximately 2000 mitochondria. Another common cellular component is the lipid droplet, whose numbers vary greatly. Hepatocyte lysosomes are important in the turnover and degradation of intracellular organelles. Like lysosomes, peroxisomes are enzyme-containing organelles abundant in hepatocytes. Some of their functions are the oxidation of excess fatty acids, breakdown of the hydrogen peroxide generated by this oxidation (by means of catalase activity), breakdown of excess purines (AMP, GMP) to uric acid, and participation in the synthesis of cholesterol, bile acids, and some lipids used to make myelin. Golgi complexes in the hepatocyte are also numerous up to 50 per cell. The functions of this organelle include the formation of lysosomes and the secretion of plasma proteins (eg, albumin, proteins of the complement system), glycoproteins (eg, transferrin), and lipoproteins (eg, very low-density lipoproteins).

Bile secretion is an exocrine function in the sense that hepatocytes promote the uptake, transformation, and excretion of blood components into the bile canaliculi. Bile has several other essential components in addition to water and electrolytes: bile acids, phospholipids, cholesterol, lecithin, and bilirubin. About 90% of these substances are derived by absorption from the distal intestinal epithelium and are transported by the hepatocyte from the blood to bile canaliculi (enterohepatic recirculation). About 10% of bile acids are synthesized in the smooth endoplasmic reticulum of the hepatocyte by conjugation of cholic acid (synthesized by the liver from cholesterol) with the amino acid glycine or taurine, producing glycocholic and taurocholic acids. Bile acids have an important function in emulsifying the lipids in the digestive tract, promoting easier digestion by lipases and subsequent absorption.

Lipids and carbohydrates are stored in the liver in the form of triglycerides and glycogen. This capacity to store metabolites is important, because it supplies the body with energy between meals. The liver also serves as the major storage compartment for vitamins, especially vitamin A. Vitamin A originates in the diet, reaching the liver along with other dietary lipids in the form of chylomicrons. In the liver, vitamin A is stored in Ito's cells.

The hepatocyte is also responsible for the synthesis of glucose from other metabolites such as lipids and amino acids by means of a complex enzymatic process called **gluconeogenesis**. It is also the main site of amino acid deamination, resulting in the

production of urea. Urea is transported through the blood to the kidney and is excreted by that organ.

Various drugs and substances can be inactivated by oxidation, methylation, or conjugation. The enzymes participating in these processes are located mainly in the smooth endoplasmic reticulum. Glucuronyltransferase, the enzyme that conjugates glucuronic acid to bilirubin, also causes conjugation of several other compounds such as steroids, barbiturates, antihistamines, and anticonvulsants. Under certain conditions, drugs that are inactivated in the liver can induce an increase in the hepatocyte's smooth endoplasmic reticulum, thus improving the detoxification capacity of the organ.

Biliary Tract

The daily basal secretion of bile is approximately 500 mL. The bile produced by the hepatocyte flows through the **bile canaliculi, bile ductules,** and **bile ducts.** These structures gradually merge, forming a network that converges to form the right and left hepatic ducts, which unite to form the common **hepatic duct.** The common hepatic duct, after receiving the **cystic duct** from the gallbladder, continues to the duodenum as the **common bile duct** (ductus choledochus).

The hepatic, cystic, and common bile ducts are lined with a mucous membrane of simple columnar epithelium. The lamina propria is thin and is surrounded by an inconspicuous layer of smooth muscle. This muscle layer becomes thicker near the duodenum and finally, in the intramural portion, forms a sphincter that regulates bile flow (sphincter of Oddi).

Gallbladder

The gallbladder is a hollow, pear-shaped organ attached to the lower surface of the liver. It can store 30-50 mL of bile. The wall of the gallbladder consists of a mucosa composed of simple columnar epithelium and lamina propria, a layer of smooth muscle, a perimuscular connective tissue layer, and a serous membrane.

The mucosa has abundant folds that are particularly evident when the gallbladder is empty. The epithelial cells are rich in mitochondria. All these cells are capable of secreting small amounts of mucus. Tubuloacinar mucous glands near the cystic duct are responsible for the production of most of the mucus present in bile. The main function of the gallbladder is to store bile, concentrate it by absorbing its water, and release it when necessary into the digestive tract. This process depends on an active sodium-transporting mechanism in the gallbladder's epithelium. Water absorption is an osmotic consequence of the sodium pump. Contraction of the smooth muscle of the gallbladder is induced by **cholecystokinin,** a hormone produced by enteroendocrine cells located in the epithelial lining of the small intestine. Release of cholecystokinin is, in turn, stimulated by the presence of dietary fats in the small intestine.

The Urinary System

The urinary system consists of the paired kidneys and ureters and the unpaired bladder and urethra. This system contributes to the maintenance of homeostasis by a complex process that involves filtration, active absorption, passive absorption, and secretion. The result is the production of urine, in which various metabolic waste products are eliminated. Urine produced in the kidneys passes through the ureters to the bladder, where it is temporarily stored and then released to the exterior through the urethra. The two kidneys produce about 125 mL of filtrate per minute; of this amount, 124 mL is absorbed in the organ, and only 1 mL is released into the ureters as urine. About 1500 mL of urine is formed every 24 h. The kidneys also regulate the fluid and electrolyte balance of the body and are the site of production of renin, a substance that participates in the regulation of blood pressure. Erythropoietin, a growth factor that stimulates the production of erythrocytes, is also produced in the kidneys. Erythropoietin also hydroxylates vitamin D3, a steroid prohormone, to its active form.

Kidneys

Each kidney has a concave medial border, the hilum where nerves enter, blood and lymph vessels enter and exit, and the ureter exits and a convex lateral surface . The renal pelvis, the expanded upper end of the ureter, is divided into two or three major calyces. Several small branches, the minor calyces, arise from each major calyx.

The kidney can be divided into an outer cortex and an inner medulla. In humans, the renal medulla consists of 10-18 conical or pyramidal structures, the medullary pyramids. From the base of each medullary pyramid, parallel arrays of tubules, the medullary rays, penetrate the cortex.

Each kidney is composed of 1-4 million nephrons . Each nephron consists of a dilated portion, the renal corpuscle; the proximal convoluted tubule; the thin and thick limbs of Henle's loop; the distal convoluted tubule; and the collecting tubules and ducts. Some investigators do not consider the collecting tubules and ducts to be part of the nephron. The nephron is the functional unit of the kidney.

Renal Corpuscles & Blood Filtration

Each renal corpuscle is about 200 m in diameter and consists of a tuft of capillaries, the glomerulus, surrounded by a double-walled epithelial capsule called glomerular (Bowman's) capsule. The internal layer (the visceral layer) of the capsule envelops the capillaries of the glomerulus. The external layer forms the outer limit of the renal corpuscle and is called the parietal layer of Bowman's capsule. Between the

two layers of Bowman's capsule is the urinary space, which receives the fluid filtered through the capillary wall and the visceral layer. Each renal corpuscle has a vascular pole, where the afferent arteriole enters and the efferent arteriole leaves, and a urinary pole, where the proximal convoluted tubule begins. After entering the renal corpuscle, the afferent arteriole usually divides into two to five primary branches, each subdividing into capillaries and forming the renal glomerulus.

The parietal layer of Bowman's capsule consists of a simple squamous epithelium supported by a basal lamina and a thin layer of reticular fibers. At the urinary pole, the epithelium changes to the simple cuboidal, or low columnar, epithelium characteristic of the proximal tubule.

During embryonic development, the epithelium of the parietal layer remains relatively unchanged, whereas the internal, or visceral, layer is greatly modified. The cells of this internal layer, the podocytes, have a cell body from which arise several primary processes. Each primary process gives rise to numerous secondary processes, called pedicels, that embrace the capillaries of the glomerulus. At a periodic distance of 25 nm, the secondary processes are in direct contact with the basal lamina. However, the cell bodies of podocytes and their primary processes do not touch the basement membrane.

The secondary processes of podocytes interdigitate, defining elongated spaces about 25 nm wide the filtration slits. Spanning adjacent processes (and thus bridging the filtration slits) is a diaphragm about 6 nm thick. Podocytes have bundles of actin filaments in their cytoplasm that give them a contractile capacity. Between the fenestrated endothelial cells of the glomerular capillaries and the podocytes that cover their external surfaces is a thick basement membrane. This membrane is believed to be the filtration barrier that separates the urinary space and the blood in the capillaries. The basement membrane is derived from the fusion of capillary- and podocyte-produced basal laminae. With the aid of the electron microscope, a central electron-dense layer (lamina densa) and, on each side, a more electron-lucent layer can be distinguished. The two electron-lucent laminae rarae contain fibronectin, which may serve to bind them to the cells. The lamina densa is a meshwork of type IV collagen and laminin in a matrix containing the negatively charged proteoglycan heparan sulfate that restricts the passage of cationic molecules. Thus, the glomerular basement membrane is a selective macromolecular filter in which the lamina densa acts as a physical filter, whereas the anionic sites in the laminae rarae act as a charge barrier. Particles greater than 10 nm in diameter do not readily cross the basal lamina, and negatively charged proteins with a molecular mass greater than that of albumin (69 kDa) pass across only sparingly.

The blood flow in the two kidneys of an adult amounts to 1.2-1.3 L of blood per minute. This means that all the circulating blood in the body passes through the

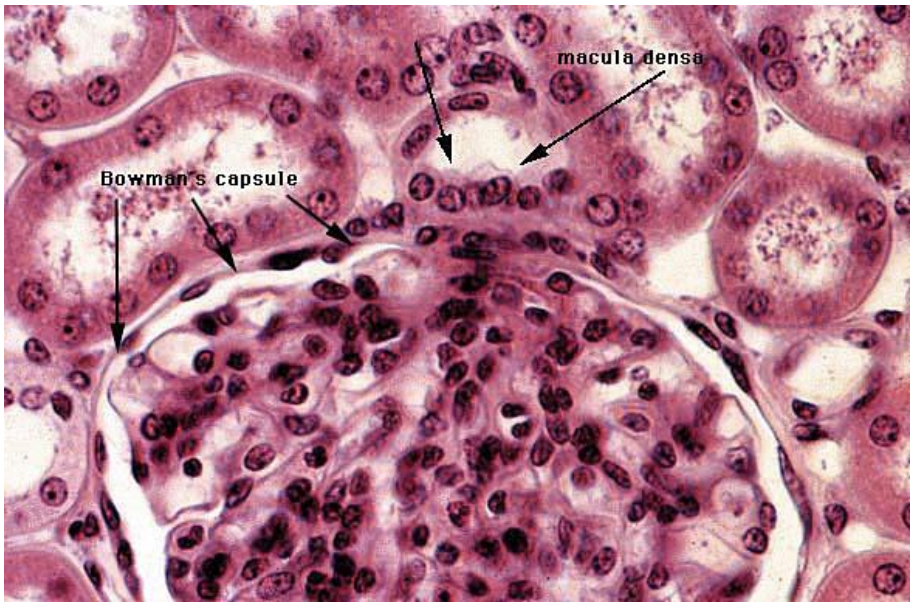
kidneys every 4-5 min. The glomeruli are composed of arterial capillaries in which the hydrostatic pressure about 45 mm Hg is higher than that found in other capillaries.

The glomerular filtrate is formed in response to the hydrostatic pressure of blood, which is opposed by the osmotic (oncotic) pressure of plasma colloids (20 mm Hg), and the hydrostatic pressure of the fluids in Bowman's capsule (10 mm Hg). The net filtration pressure at the afferent end of glomerular capillaries is 15 mm Hg.

The glomerular filtrate has a chemical composition similar to that of blood plasma but contains almost no protein, because macromolecules do not readily cross the glomerular filter. The largest protein molecules that succeed in crossing the glomerular filter have a molecular mass of about 70 kDa, and small amounts of plasma albumin appear in the filtrate.

The endothelial cells of glomerular capillaries are of the fenestrated variety, but they lack the thin diaphragm that spans the openings of other fenestrated capillaries.

In addition to endothelial cells and podocytes, the glomerular capillaries have mesangial cells adhering to their walls. Mesangial cells are contractile and have receptors for angiotensin II. When these receptors are activated, the glomerular flow is reduced. Mesangial cells also have receptors for the natriuretic factor produced by cardiac atria cells. This factor is a vasodilator and relaxes the mesangial cells, probably increasing the blood flow and the effective surface area available for filtration. Mesangial cells also have several other functions: they give structural support to the glomerulus, synthesize extracellular matrix, endocytose and dispose of normal and pathological (immune complex) molecules trapped by the glomerular basement membrane, and probably produce chemical mediators such as cytokines and prostaglandins. In the vascular pole but outside the glomerulus, there are the so-called extraglomerular mesangial cells that form part of the juxtaglomerular apparatus.



Proximal Convoluted Tubule

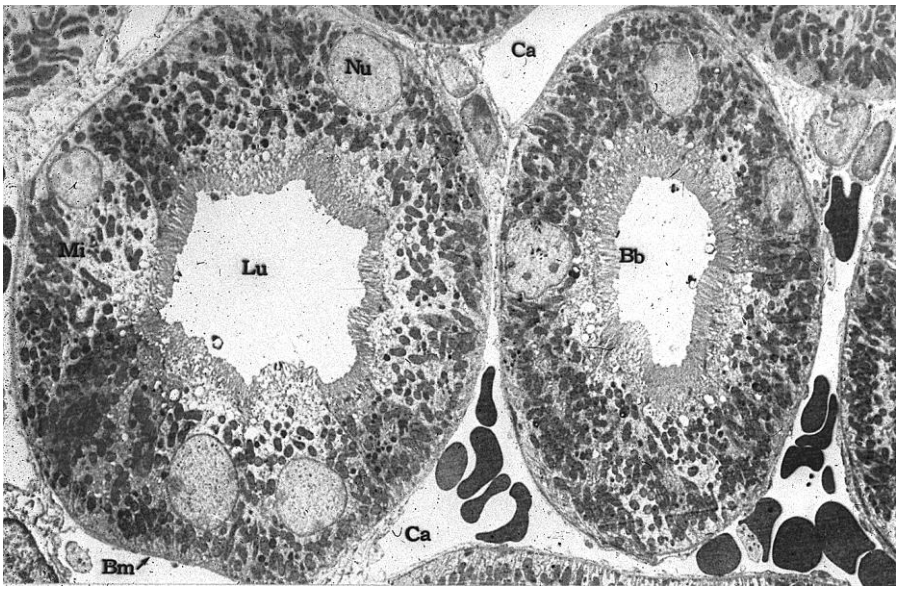
At the urinary pole of the renal corpuscle, the squamous epithelium of the parietal layer of Bowman's capsule is continuous with the cuboidal, or low columnar, epithelium of the proximal convoluted tubule. This tubule is longer than the distal convoluted tubule and is therefore more frequently seen near renal corpuscles in the renal cortex.

The cells of this cuboidal epithelium have an acidophilic cytoplasm because of the presence of numerous elongated mitochondria. The cell apex has abundant microvilli about 1 m in length, which form a brush border. Because the cells are large, each transverse section of a proximal tubule contains only three to five spherical nuclei.

In the living animal, proximal convoluted tubules have a wide lumen and are surrounded by peritubular capillaries. In routine histological preparations, the brush border is usually disorganized and the peritubular capillary lumens are greatly reduced in size or collapsed.

The apical cytoplasm of these cells has numerous canaliculi between the bases of the microvilli; these canaliculi increase the capacity of the proximal tubule cells to absorb macromolecules. Pinocytotic vesicles are formed by evaginations of the apical membranes and contain macromolecules (mainly proteins with a molecular mass less than 70 kDa) that have passed across the glomerular filter. The pinocytotic vesicles fuse with lysosomes, where macromolecules are degraded, and monomers are returned to the circulation. The basal portions of these cells have abundant membrane invaginations and lateral interdigitations with neighboring cells. The Na+/K+-ATPase (sodium pump) responsible for actively transporting sodium ions out of the cells is localized in these basolateral membranes. Mitochondria are concentrated at the base of the cell and arranged parallel to the long axis of the cell. This mitochondrial location and the increase in the area of the cell membrane at the base of the cell are characteristic of cells engaged in active ion transport. Because of the extensive interdigitations of the lateral membranes, no discrete limits can be observed (in the light microscope) between cells of the proximal tubule. The glomerular filtrate formed in the renal corpuscle passes into the proximal convoluted tubule, where the processes of absorption and excretion begin. The proximal convoluted tubule absorbs all the glucose and amino acids and about 85% of the sodium chloride and water contained in the filtrate, in addition to phosphate and calcium. Glucose, amino acids, and sodium are absorbed by these tubular cells through an active process involving Na+/K+-ATPase (sodium pump) located in the basolateral cell membranes. Water diffuses passively, following the osmotic gradient. When the amount of glucose in the filtrate exceeds the absorbing capacity of the proximal tubule, urine becomes more abundant and contains glucose.

In addition to these activities, the proximal convoluted tubule secretes creatinine and substances foreign to the organism, such as para-aminohippuric acid and penicillin, from the interstitial plasma into the filtrate. This is an active process referred to as tubular secretion.



Henle's Loop

Henle's loop is a U-shaped structure consisting of a thick descending limb, a thin descending limb, a thin ascending limb, and a thick ascending limb. The thick limbs are very similar in structure to the distal convoluted tubule. In the outer medulla, the thick descending limb, suddenly narrows and continues as the thin descending limb. The lumen of this segment of the nephron is wide because the wall consists of squamous epithelial cells whose nuclei protrude only slightly into the lumen.

Approximately one-seventh of all nephrons are located near the corticomedullary junction and are therefore called juxtamedullary nephrons. The other nephrons are called cortical nephrons. All nephrons participate in the processes of filtration, absorption, and secretion. Juxtamedullary nephrons, however, are of prime importance in establishing the gradient of hypertonicity in the medullary interstitium the basis of the kidneys' ability to produce hypertonic urine. Juxtamedullary nephrons have very long Henle's loops, extending deep into the medulla. These loops consist of a short thick descending limb, long thin descending and ascending limbs, and a thick ascending limb. Cortical nephrons, on the other hand, have very short thin descending limbs and no thin ascending limbs.

Henle's loop is involved in water retention; only animals with such loops in their kidneys are capable of producing hypertonic urine and thus maintaining body water. Henle's loop creates a gradient of hypertonicity in the medullary interstitium that influences the concentration of the urine as it flows through the collecting ducts.

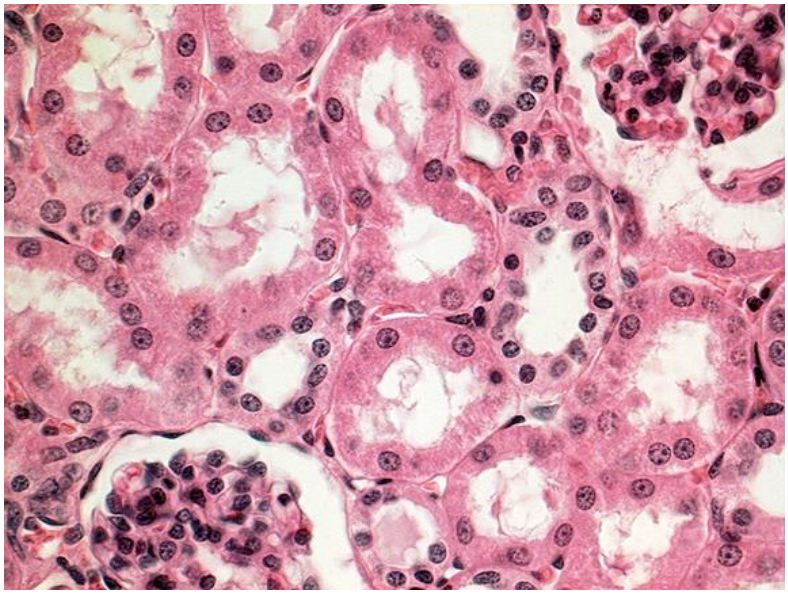
Although the thin descending limb of the loop is freely permeable to water, the entire ascending limb is impermeable to water. In the thick ascending limb, sodium chloride is actively transported out of the tubule to establish the gradient of hypertonicity in the medullary interstitium that is necessary for urine concentration. The osmolarity of the interstitium at the tips of the medullary pyramids is about four times that of blood.

Distal Convoluted Tubule

The thick ascending limb of Henle's loop penetrates the cortex; after describing a certain trajectory, it becomes tortuous and is called the distal convoluted tubule. This tubule, like the ascending limb, is lined with simple cuboidal epithelium.

The distal convoluted tubules differ from the proximal convoluted tubules (both found in the cortex) because they have no brush border, no apical canaliculi, and smaller cells. Because distal tubule cells are flatter and smaller than those of the proximal tubule, more nuclei are seen in the distal tubule than in the proximal tubule. Cells of the distal convoluted tubule have elaborate basal membrane invaginations and associated mitochondria indicative of their ion-transporting function.

The distal convoluted tubule establishes contact with the vascular pole of the renal corpuscle of its parent nephron. At this point of close contact, the distal tubule is modified, as is the afferent arteriole. In this juxtaglomerular region, cells of the distal convoluted tubule usually become columnar, and their nuclei are closely packed together. Most of the cells have a Golgi complex in the basal region. This modified segment of the wall of the distal tubule, which appears darker in microscopic preparations because of the close proximity of its nuclei, is called the **macula densa**. The cells of the macula densa are sensitive to the ionic content and water volume of the tubular fluid, producing molecular signals that promote the liberation of the enzyme renin in the circulation.



In the distal convoluted tubule, there is ion exchange if aldosterone is present in high enough concentration: Sodium is absorbed, and potassium ions are secreted. This mechanism influences the total salt and water content of the body. The distal tubule also secretes hydrogen and ammonium ions into tubular urine. This activity is essential for maintenance of the acid base balance in the blood.

Collecting Tubules & Ducts

Urine passes from the distal convoluted tubules to collecting tubules that join each other to form larger, straight collecting ducts, which widen gradually as they approach the tips of the medullary pyramids.

The smaller collecting tubules are lined with cuboidal epithelium and have a diameter of approximately 40 m. As they penetrate deeper into the medulla, their cells increase in height until they become columnar. The diameter of the collecting duct reaches 200 m near the tips of the medullary pyramids.

Along their entire extent, collecting tubules and ducts are composed of cells that stain weakly with the usual stains. They have an electron-lucent cytoplasm with few organelles. In collecting tubules and cortical collecting ducts, a dark-staining intercalated cell is also seen; its significance is not understood. The intercellular limits of the collecting tubule and duct cells are clearly visible in the light microscope. Cortical collecting ducts are joined at right angles by several generations of smaller collecting tubules that drain each medullary ray. In the medulla, collecting ducts are a major component of the urine-concentrating mechanism.

The epithelium of collecting ducts is responsive to argininevasopressin, or antidiuretic hormone, secreted by the posterior pituitary. If water intake is limited, antidiuretic hormone is secreted and the epithelium of the collecting ducts becomes permeable to water, which is absorbed from the glomerular filtrate, transferred to blood capillaries, and thus retained in the body. In the presence of antidiuretic hormone, intramembrane particles in the luminal membrane aggregate to form what may be channels for water absorption.

Juxtaglomerular Apparatus

Adjacent to the renal corpuscle, the tunica media of the afferent arteriole has modified smooth muscle cells. These cells are called juxtaglomerular (JG) cells and have a cytoplasm full of secretory granules. Secretions of JG cells play a role in the maintenance of blood pressure. The macula densa of the distal convoluted tubule is usually located near the region of the afferent arteriole that contains the JG cells; together, this portion of the arteriole and the macula densa form the JG apparatus. Also a part of the JG apparatus are some light-staining cells whose functions are not well

understood. They are called extraglomerular mesangial cells or lacis cells. The internal elastic membrane of the afferent arteriole disappears in the area of the JG cells.

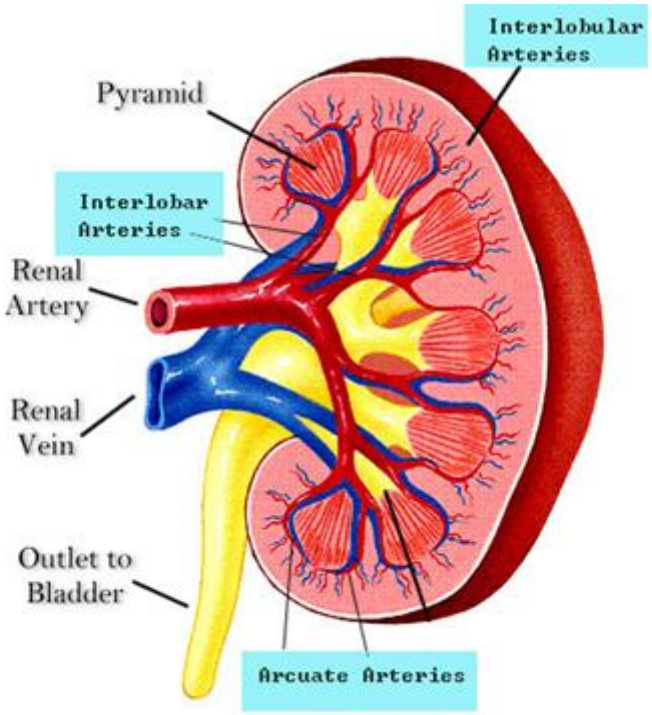
When examined with the electron microscope, JG cells show characteristics of protein-secreting cells, including an abundant rough endoplasmic reticulum, a highly developed Golgi complex, and secretory granules measuring approximately 10-40 nm in diameter. JG cells produce the enzyme renin, which acts on a plasma protein angiotensinogen to produce an inactive decapeptide, angiotensin I. As a result of the action of a converting enzyme present in high concentration in lung endothelial cells, this substance loses two amino acids and becomes an active vasopressive octapeptide, angiotensin II.

Blood Circulation

Each kidney receives blood from its renal artery, which usually divides into two branches before entering the organ. One branch goes to the anterior part of the kidney and the other to the posterior part. While still in the hilum, these branches give rise to arteries that branch again to form the interlobar arteries located between the renal pyramids. At the level of the corticomedullary junction, the interlobar arteries form the arcuate arteries. Interlobular arteries branch off at right angles from the arcuate arteries and follow a course in the cortex perpendicular to the renal capsule. Interlobular arteries form the boundaries of the renal lobules, which consist of a medullary ray and the adjacent cortical labyrinth. From the interlobular arteries arise the afferent arterioles, which supply blood to the capillaries of the glomeruli. Blood passes from these capillaries into the efferent arterioles, which at once branch again to form a peritubular capillary network that will nourish the proximal and distal tubules and carry away absorbed ions and low-molecular-weight materials. The efferent arterioles that are associated with juxtamedullary nephrons form long, thin capillary vessels. These vessels, which follow a straight path into the medulla and then loop back toward the corticomedullary boundary, are called vasa recta (straight vessels). The descending vessel is a continuous-type capillary, whereas the ascending vessel has a fenestrated endothelium. These vessels, containing blood that has been filtered through the glomeruli, provide nourishment and oxygen to the medulla. Because of their looped structure, they do not carry away the high osmotic gradient set up in the interstitium by Henle's loop.

The capillaries of the outer cortex and the capsule of the kidney converge to form the stellate veins (so called because of their configuration when seen from the surface of the kidney), which empty into the interlobular veins.

Veins follow the same course as arteries. Blood from interlobular veins flows into arcuate veins and from there to the interlobar veins. Interlobar veins converge to form the renal vein through which blood leaves the kidney.



Renal Interstitium

The space between uriniferous tubules and blood and lymph vessels is called the renal interstitium. It occupies a very small volume in the cortex but increases in the medulla. The renal interstitium contains a small amount of connective tissue with fibroblasts, some collagen fibers, and, mainly in the medulla, a highly hydrated ground substance rich in proteoglycan. In the medulla the secreting cells called interstitial cells are found. They contain cytoplasmic lipid droplets and are implicated in the synthesis of prostaglandins and prostacyclin.

Bladder & Urinary Passages

The bladder and the urinary passages store the urine formed in the kidneys and conduct it to the exterior. *The calyces, renal pelvis, ureter, and bladder* have the same basic histological structure, with the walls of the ureters becoming gradually thicker as proximity to the bladder increases.

The mucosa of these organs consists of transitional epithelium and a lamina propria of loose-to-dense connective tissue. Surrounding the lamina propria of these organs is a dense woven sheath of smooth muscle.

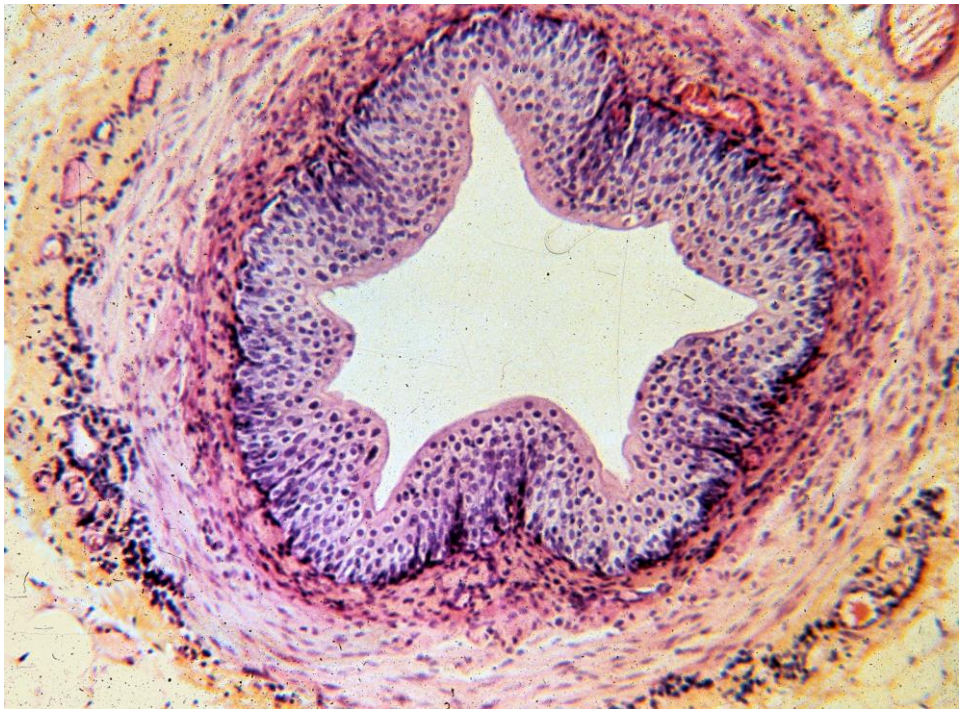
The transitional epithelium of the bladder in the undistended state is five or six cells in thickness; the superficial cells are rounded and bulge into the lumen. These cells are frequently polyploid or binucleate. When the epithelium is stretched, as when the bladder is full of urine, the epithelium is only three or four cells in thickness, and the superficial cells become squamous.

The superficial cells of the transitional epithelium have a special membrane of thick plates separated by narrow bands of thinner membrane that are responsible for the osmotic barrier between urine and tissue fluids. When the bladder contracts, the membrane folds along the thinner regions, and the thicker plates invaginate to form fusiform cytoplasmic vesicles. These vesicles represent a reservoir of these thick plates that can be stored in the cytoplasm of the cells of the empty bladder and used to cover the increased cell surface in the full bladder. This luminal membrane is assembled in the Golgi complex and has an unusual chemical composition; cerebroside is the major component of the polar lipid fraction.

The muscular layers in the calyces, renal pelvis, and ureters have a helical arrangement. As the ureteral muscle cells reach the bladder, they become longitudinal. The muscle fibers of the bladder run in every direction (without distinct layers) until they approach the bladder neck, where three distinct layers can be identified: The internal longitudinal layer, distal to the bladder neck, becomes circular around the prostatic urethra and the prostatic parenchyma in men. It extends to the external meatus in women. Its fibers form the true involuntary urethral sphincter. The middle layer ends at the bladder neck, and the outer longitudinal layer continues to the end of the prostate in men and to the external urethral meatus in women.

The ureters pass through the wall of the bladder obliquely, forming a valve that prevents the backflow of urine. The intravesical ureter has only longitudinal muscle fibers.

The urinary passages are covered externally by an adventitial membrane, except for the upper part of the bladder, which is covered by serous peritoneum.



Urethra

The urethra is a tube that carries the urine from the bladder to the exterior. In men, sperm also pass through it during ejaculation. In women, the urethra is exclusively a urinary organ.

Male Urethra

The male urethra consists of four parts: **prostatic, membranous, bulbous, and pendulous.** The initial part of the urethra passes through the prostate , which is situated very close to the bladder, and the ducts that transport the secretions of the prostate open into the ***prostatic urethra***.

In the dorsal and distal part of the prostatic urethra, there is an elevation, the verumontanum (from Latin, meaning mountain ridge), that protrudes into its interior. A closed tube called the prostatic utricle opens into the tip of the verumontanum; this tube has no known function. The ejaculatory ducts open on the sides of the verumontanum. The seminal fluid enters the proximal urethra through these ducts to be stored just before ejaculation. The prostatic urethra is lined with transitional epithelium.

The membranous urethra extends for only 1 cm and is lined with stratified or pseudostratified columnar epithelium. Surrounding this part of the urethra is a sphincter of striated muscle, the external sphincter of the urethra. The voluntary external striated sphincter adds further closing pressure to that exerted by the involuntary urethral sphincter. The latter is formed by the continuation of the internal longitudinal muscle of the bladder.

The bulbous and pendulous parts of the urethra are located in the corpus spongiosum of the penis. The urethral lumen dilates distally, forming the fossa navicularis. The epithelium of this portion of the urethra is mostly pseudostratified and columnar, with stratified and squamous areas.

Littre's glands are mucous glands found along the entire length of the urethra but mostly in the pendulous part. The secretory portions of some of these glands are directly linked to the epithelial lining of the urethra; others have excretory ducts.

Female Urethra

The female urethra is a tube 4-5 cm long, lined with stratified squamous epithelium and areas of pseudostratified columnar epithelium. The mid part of the female urethra is surrounded by an external striated voluntary sphincter.

Endocrine System

Hormones

Hormones are molecules that function as chemical signals. Endocrine cells usually aggregate as endocrine glands, where they typically arrange themselves as cords of cells. A notable exception is the thyroid gland, in which the cells are organized as microspheres called follicles. In addition to the glands, there are many isolated endocrine cells in the body, such as the endocrine cells of the digestive tract, the cells of the placenta, the cells of the heart that produce the atrial natriuretic factor, and the juxtaglomerular cells of the kidney. Most hormones act at a distance from the site of their secretion. Therefore, the endocrine cells are always very close to blood capillaries, which receive the secreted hormones and distribute them throughout the organism.

Endocrine glands are also target organs providing a way for the body to control hormone secretion through a mechanism of feedback and to keep blood hormonal levels within strict limits.

The endocrine system, however, does not act alone in the control of body functions. It interacts closely with the nervous system (mainly through the connection between the adenohypophysis and the central nervous system) and the immune system. Endocrine disfunctions may affect the immune response and vice versa.

Hypophysis (pituitary gland)

The **hypophysis** (Gr. *hypo,* under, + *physis,* growth), or **pituitary gland,** weighs about 0.5 g, and its normal dimensions in humans are about 10 x 13 x 6 mm. It lies in a cavity of the sphenoid bone—**the sella turcica**—an important radiological landmark. During embryogenesis, the hypophysis develops partly from oral ectoderm and partly from nerve tissue. The neural component arises as an evagination from the floor of the diencephalon and grows caudally as a stalk without detaching itself from the brain. The oral component arises as an outpocketing of ectoderm from the roof of the primitive mouth of the embryo and grows cranially, forming a structure called **Rathke's pouch.** Later, a constriction at the base of this pouch separates it from the oral cavity. At the same time, its anterior wall thickens, reducing the lumen of Rathke's pouch to a small fissure.

Because of its dual origin, the hypophysis actually consists of two glands—the **neurohypophysis** and the **adenohypophysis**—that are united anatomically but that have different functions. The **neurohypophysis,** the part of the hypophysis that develops from nerve tissue, consists of a large portion, the **pars nervosa,** and the

smaller **infundibulum,** or **neural stalk**. The neural stalk is composed of the stem and median eminence. The part of the hypophysis that arises from oral ectoderm is known as the **adenohypophysis** and is subdivided into three portions: a large **pars distalis,** or **anterior lobe;** a cranial part, the **pars tuberalis,** which surrounds the neural stalk; and the **pars intermedia**.

The Hypothalamo-Hypophyseal System

Because of its embryological origin, the hypophysis is connected to the hypothalamus, with which it has important anatomic and functional relationships.

In the hypothalamo-hypophyseal system there are three known sites of production of hormones that liberate three groups of hormones:

1. The first group consists of peptides produced by aggregates (nuclei) of secretory neurons in the hypothalamus: the supraoptic and the paraventricular nuclei. The hormones are transported along the axons of these neurons and accumulate in the ends of these axons, which are situated in the neurohypophysis. These hormones are released by exocytosis, enter capillaries of the neurohypophysis, and are distributed by the blood.
2. The second group of peptide hormones is produced by neurons of the dorsal medial, ventral medial, and infundibular nuclei of the hypothalamus. These hormones are carried along axons that end in the median eminence where the hormones are stored. After being released these hormones enter the blood capillaries of the median eminence and are transported to the adenohypophysis through the first stretch of the hypophyseal portal system.
3. The third group of hormones consists of proteins and glycoproteins produced by cells of the pars distalis and liberated into blood capillaries of the second stretch of the portal system. These capillaries surround the secretory cells and distribute the hormones to the general circulation.

Adenohypophysis

Pars Distalis The main components of the pars distalis are cords of epithelial cells interspersed with capillaries. The hormones produced by these cells are stored as secretory granules. The few fibroblasts that are present produce reticular fibers that support the cords of hormone-secreting cells. The pars distalis accounts for 75% of the mass of the hypophysis. Common stains allow the recognition of three cell types in the pars distalis: **chromophobes** (Gr. *chroma,* color, + *phobos,* fear) and two types of **chromophils** (Gr. *chroma* + *philein,* to love) called **basophils** and **acidophils** according to their affinity for basic and acid dyes, respectively. The subtypes of basophil and acidophil cells are named for the hormones they produce. Chromophobes do not stain

intensely and, when observed with an electron microscope, show two populations of cells. One has few secretory granules and the other has none. The group with no secretory granules probably contains undifferentiated cells and follicular cells. With the exception of the gonadotropic cell, which produces two hormones, the other cells produce only a single hormone. Many dyes have been used in attempts to distinguish the five types of hormone-secreting cells, but with little success. Immunocytochemical methods and electron microscopy are currently the only reliable techniques to distinguish these cell types. The hormones produced by the hypophysis have widespread physiological activity; they regulate almost all other endocrine glands, the secretion of milk, and the metabolism of muscle, bone, and adipose tissue.

Secretory Cells of the Pars Distalis.

Cell Type	**Stain Affinity**	**HormoneProduced**	**Main Physiological Activities**
Somatotropic cell	Acidophilic	Growth hormone (GH, somatotropin)	Anabolic activity: increased protein, DNA, RNA synthesis, increased blood glucose, increased use of fat in fat cells (some of these effects via insulin-like growth factor [IGF]-1, produced mainly in the liver)
			Stimulates growth of long bones via IGF-1 produced locally acting on differentiation of chondrocytes
Mammotropic cell	Acidophilic	Prolactin (PRL)	Promotes milk secretion (depends on earlier action of estrogen, progesterone, and placental hormones)
Gonadotropic cell	Basophilic	Follicle-stimulating hormone (FSH)	Promotes ovarian follicle development and estrogen secretion in women
			Stimulates spermatogenesis in men
		Luteinizing hormone (LH)	Promotes ovarian follicle maturation and progesterone secretion in women
			Leydig cell stimulation and androgen secretion in men
Thyrotropic cell	Basophilic	Thyrotropin (TSH)	Stimulates thyroid hormone synthesis, storage, and liberation
Corticotropic cell	Basophilic	Corticotropin (ACTH)	Stimulates secretion of adrenal cortex hormones
Melanotropes?	Basophilic	-Melanocyte-stimulating hormone? (-MSH)	Darkening of skin, inhibition of appetite in the hypothalamus, other actions

Pars Tuberalis The pars tuberalis is a funnel-shaped region surrounding the infundibulum of the neurohypophysis. Most of the cells of the pars tuberalis secrete gonadotropins (follicle-stimulating hormone and luteinizing hormone) and are arranged in cords alongside the blood vessels.

Pars Intermedia The pars intermedia, which develops from the dorsal portion of Rathke's pouch, is, in humans, a rudimentary region made up of cords and follicles of weakly basophilic cells that contain small secretory granules. -Melanocyte-stimulating hormone (-MSH) is probably produced in the intermediate zone, and probably also by basophils of the pars distalis.

Neurohypophysis:

The neurohypophysis consists of the pars nervosa and the neural stalk. The pars nervosa, unlike the adenohypophysis, does not contain secretory cells. It is composed of some 100,000 unmyelinated axons of secretory neurons situated in the supraoptic and paraventricular nuclei. The secretory neurons have all the characteristics of typical neurons, including the ability to conduct an action potential, but have well-developed Nissl bodies related to the production of the neurosecretory material. The neurosecretions are transported along the axons and accumulate at their endings in the pars nervosa. Here they form structures known as **Herring bodies,** which are visible in the light microscope. The electron microscope reveals that the Herring bodies contain many neurosecretory granules that have a diameter of 100–200 nm and are surrounded by a membrane. The granules are released and their content enters the fenestrated capillaries that exist in large numbers in the pars nervosa; the hormones are then distributed to the general c circulation.

The **neurosecretory material** consists of two hormones, both cyclic peptides made up of nine amino acids. The hormones have a slightly different amino acid composition, which results in different primary actions with some overlapping functions. They are **argininevasopressin**—also called **antidiuretic hormone** (**ADH**)—and **oxytocin.** Each hormone is joined to a binding protein (**neurophysin**). The hormone-neurophysin complex is synthesized as a single protein and is transported to the neurohypophysis where it is stored. Proteolysis of this protein yields the hormone and its specific binding protein. Vasopressin and oxytocin are released into the blood because of impulses in the nerve fibers from the hypothalamus. Although there is some overlap, the fibers from supraoptic nuclei are mainly concerned with vasopressin secretion, whereas most of the fibers from the paraventricular nuclei are concerned with oxytocin secretion.

Cells of the Neurohypophysis

Although the neurohypophysis consists mainly of *axons from hypothalamic neurons,* about 25% of its volume consists of a specific type of highly branched *glial cell called a* ***pituicyte***.

Actions of the Hormones of the Neurohypophysis

Argininevasopressin or ADH is released in response to increased tonicity of the blood, usually resulting from water loss or intake of salt, which is recognized by osmoreceptor cells present in the hypothalamus. The main effect of ADH is to increase the permeability of collecting tubules of the kidney to water. As a result, more water is resorbed instead of being eliminated in the urine. Thus, vasopressin helps to regulate the osmotic balance of the internal milieu. In large doses, vasopressin may induce the contraction of smooth muscle of small arteries and arterioles. It is doubtful, however, if the amount of endogenous vasopressin is sufficient to exert any appreciable effect on blood pressure.

Oxytocin stimulates contraction of the myoepithelial cells that surround the alveoli and ducts of the mammary glands during nursing and of the smooth muscle of the uterine wall during copulation and childbirth. The secretion of oxytocin is stimulated by nursing or by distention of the vagina or the uterine cervix. This occurs via nerve tracts that act on the hypothalamus. The neurohormonal reflex triggered by nursing is called the **milk-ejection reflex**.

Adrenal (Suprarenal) Glands

The adrenal glands are paired organs that lie near the superior poles of the kidneys, embedded in adipose tissue. They are flattened structures with a half-moon shape; in the human, they are about 4–6 cm long, 1–2 cm wide, and 4–6 mm thick. Together they weigh about 8 g, but their weight and size vary with the age and physiological condition of the individual. Examination of a fresh section of adrenal gland shows that it is formed by two concentric layers: a yellow peripheral layer, the **adrenal cortex;** and a reddish-brown central layer, the **adrenal medulla**.

The layer immediately beneath the connective tissue capsule is the ***zona glomerulosa***, in which columnar or pyramidal cells are arranged in closely packed, rounded, or arched cords surrounded by capillaries.

The next layer of cells is known as the ***zona fasciculata*** because of the arrangement of the cells in one- or two-cell thick straight cords that run at right angles to the surface of

the organ and have capillaries between them . The cells of the zona fasciculata are polyhedral, with a great number of lipid droplets in their cytoplasm. As a result of the dissolution of the lipids during tissue preparation, the fasciculata cells appear vacuolated in common histological preparations. Because of their vacuolization, the cells of the fasciculata are also called **spongyocytes.**

The ***zona reticularis***, the innermost layer of the cortex, lies between the zona fasciculata and the medulla; it contains cells disposed in irregular cords that form an anastomosing network. These cells are smaller than those of the other two layers. Lipofuscin pigment granules in the cells are large and quite numerous. Irregularly shaped cells with pyknotic nuclei—suggesting cell death—are often found in this layer.

Cortical Hormones & Their Actions

Adrenal steroids originate from modifications of the molecule of cholesterol. Cholesterol is obtained by the cortical cells from the blood (mainly as low-density lipoproteins [LDL] and, secondarily, can be synthesized from acetate (in the form of acetyl coenzyme A) in the smooth endoplasmic reticulum. Cholesterol is converted to the final hormones partly in the mitochondria and partly in the smooth endoplasmic reticulum—a clear example of collaboration between two cell organelles.

The steroids secreted by the cortex can be divided into three groups, according to their main physiological action: **mineralocorticoids, glucocorticoids,** and **androgens**. The main product of the zona glomerulosa is a mineralocorticoid called **aldosterone;** the zona fasciculata and possibly the zona reticularis secrete glucocorticoids, especially **cortisol;** the zona reticularis produces **dehydroepiandrosterone,** a weak androgen.

The adrenal cortex and the adrenal medulla can be considered two organs with distinct origins, functions, and morphological characteristics that became united during embryonic development. They arise from different germ layers. The cortex arises from the coelomic epithelium, whereas the cells of the medulla derive from the neural crest, from which sympathetic ganglion cells also originate.

The general histological appearance of the adrenal gland is typical of an endocrine gland in which cells of both cortex and medulla are grouped in cords along capillaries.

The dense connective tissue capsule that covers the adrenal gland sends thin septa to the interior of the gland as trabeculae. The stroma consists mainly of a rich network of reticular fibers that supports the secretory cells.

Adrenal Cortex

The cells of the adrenal cortex, which have the typical ultrastructure of steroid-secreting cells, do not store their secretory products in granules; rather, they synthesize and

secrete steroid hormones upon demand. Steroids, being low-molecular-weight lipid-soluble molecules, diffuse through the plasma membrane and do not require the specialized process of exocytosis for their release.

The layer immediately beneath the connective tissue capsule is the zona glomerulosa, in which columnar or pyramidal cells are arranged in closely packed, rounded, or arched cords surrounded by capillaries.

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The **mineralocorticoids** act mainly on the distal renal tubules as well as on the gastric mucosa, colon, and salivary and sweat glands, stimulating the reabsorption of sodium by epithelial cells.

The **glucocorticoids** affect the metabolism of carbohydrates by stimulating both the production of glucose from amino acids or fatty acids (gluconeogenesis) and the conversion of glucose into glycogen. Cortisol may decrease the uptake of glucose by

cells, which together with the increased production of glucose may lead to hyperglycemia or to the maintenance of adequate levels of glucose in the blood during hunger and stress reactions. In the skin, muscle and adipose tissue, glucocorticoids not only decrease synthetic activity but also promote protein and lipid degradation. The by-products of degradation, amino acids and fatty acids, are removed from the blood and used by the hepatocytes for gluconeogenesis and protein synthesis.

Glucocorticoids also suppress the immune response by destroying circulating lymphocytes, inhibiting mitotic activity in lymphocyte-forming organs, and controlling secretion of cytokines.

The separation of steroids produced by the adrenal cortex into glucocorticoids and mineralocorticoids is, however, somewhat arbitrary, because most glucocorticoids also act on ion transport.

Dehydroepiandrosterone (DHEA) is the only sex hormone that is secreted in significant physiological quantities by the adrenal cortex. DHEA is a weak androgen that circulates in the blood as a sulfate and exerts its actions after being converted into testosterone in several tissues.

Adrenal Medulla

The adrenal medulla is composed of polyhedral cells arranged in cords or clumps and supported by a reticular fiber network. A profuse capillary supply intervenes between adjacent cords, and there are a few parasympathetic ganglion cells. The medullary cells arise from neural crest cells, as do the postganglionic neurons of sympathetic and parasympathetic ganglia. Thus, the cells of the adrenal medulla can be considered modified sympathetic postganglionic neurons that have lost their axons and dendrites during embryonic development and have become secretory cells.

Medullary cells have abundant membrane-limited electron-dense secretory granules, 150–350 nm in diameter. These granules contain one or the other of the catecholamines, **epinephrine** or **norepinephrine.** The secretory granules also contain adenosine triphosphate (ATP), proteins called **chromogranins** (which may serve as binding proteins for catecholamines), dopamine -hydroxylase (which converts dopamine to norepinephrine), and opiatelike peptides (enkephalins) .

A large body of evidence shows that epinephrine and norepinephrine are secreted by two different types of cells in the medulla. When observed with the transmission electron microscope epinephrine-secreting cells show smaller and less electron-dense granules, whose contents fill the granule. Norepinephrine-secreting cells have larger, more electron-dense granules. Their content is irregular in shape, and there is an electron-

lucent layer beneath the surrounding membrane. About 80% of the catecholamine output of the adrenal vein is epinephrine.

Unlike the cortex, which does not store steroids, cells of the medulla accumulate and store their hormones in granules. The adrenal medullary cells are innervated by cholinergic endings of preganglionic sympathetic neurons. Glucocorticoids produced in the cortex, which reach the medulla through capillaries that bathe cells of the cortex, constitute another mechanism of control.

Islets of Langerhans

The islets of Langerhans are multihormonal endocrine microorgans; they appear as rounded clusters of cells embedded within the exocrine pancreatic tissue.

Although most islets are 100–200 μm in diameter and contain several hundred cells, small groups of endocrine cells are also found interspersed among the pancreatic exocrine cells. There may be more than 1 million islets in the human pancreas, with a slight tendency for islets to be more abundant in the tail of the pancreas. A fine capsule of reticular fibers surrounds each islet, separating it from the adjacent pancreatic tissue.

Each islet consists of lightly stained polygonal or rounded cells, arranged in cords separated by a network of blood capillaries.

Routine stains or trichrome stains allow the recognition of acidophils (α) and basophils (β) . Using immunocytochemical methods, four types of cells—A, B, D, and F—have been recognized in the islets.. The ultrastructure of these cells resembles that of cells synthesizing polypeptides. The secretory granules of cells of the islets vary according to the species studied. In humans, the A cells have regular granules with a dense core surrounded by a clear region bounded by a membrane. The B (insulin-producing) cells have irregular granules with a core formed of irregular crystals of insulin in complex with zinc.

The relative quantities of the four cell types found in islets are not uniform; they vary considerably with the islet's location in the pancreas. Table 20–3 summarizes the types, quantities, and functions of the hormones produced by the islet cells.

Table 20-3. Cell Types in Human Islets of Langerhans.

Cell Type	Quantity	Position	Hormone Produced	Hormonal Function
A	20%	Usually in periphery	Glucagon	Acts on several tissues to make energy stored in glycogen and fat available through glycogenolysis and lipolysis; increases blood glucose content
B		Central region	Insulin	Acts on several tissues to cause entry of glucose into cells and promotes decrease of blood glucose content

	70%			
D	<5%	Variable	Somatostatin	Inhibits release of other islet cell hormones through local paracrine action
F	Rare	Variable	Pancreatic polypeptide	Control of gastric secretion? Control of secretion of the exocrine

Both the endocrine cells and the blood vessels of the islets are innervated by autonomic nerve fibers. Sympathetic and parasympathetic nerve endings have been found in close association with about 10% of the A, B, and D cells. These nerves function as part of the insulin and glucagon control system. Gap junctions presumably transfer the ionic changes associated with autonomic discharge to the other cells.

Thyroid

The thyroid gland, located in the cervical region anterior to the larynx, consists of two lobes united by an isthmus. It originates in early embryonic life from the endoderm of the initial portion of the primitive gut. Its function is to synthesize the hormones thyroxine (T_4) and triiodothyronine (T_3), which are important for growth, for cell differentiation, and for the control of oxygen consumption and the basal metabolic rate in the body. Thyroid hormones affect the metabolism of proteins, lipids, and carbohydrates. Thyroid tissue is composed of 20–30 million microscopic spheres called **thyroid follicles.** The follicles are lined by a simple epithelium and their central cavity contains a gelatinous substance called **colloid**. The thyroid is the only endocrine gland whose secretory product is stored in great quantity. This accumulation is also unusual in that it occurs in the extracellular colloid. In humans, there is sufficient hormone within the follicles to supply the organism for up to 3 months. Thyroid colloid is composed of a glycoprotein of high molecular mass (660 kDa) called **thyroglobulin.** In sections, follicular cells range from squamous to columnar and the follicles have an extremely variable diameter. The gland is covered by a loose connective tissue capsule that sends septa into the parenchyma. As these septa gradually become thinner they reach all the follicles, separating them from one another by fine, irregular connective tissue composed mainly of reticular fibers. The thyroid is an extremely vascularized organ, with an extensive blood and lymphatic capillary network surrounding the follicles. Endothelial cells of these capillaries are fenestrated, as they are in other endocrine glands. This configuration facilitates the transport of molecules between the gland cells and the blood capillaries.

The morphological appearance of thyroid follicles varies according to the region of the gland and its functional activity. In the same gland, larger follicles that are full of colloid and have a cuboidal or squamous epithelium are found alongside follicles that are lined

by columnar epithelium. Despite this variation, the gland is considered hypoactive when the average composition of these follicles is squamous.

The thyroid epithelium rests on a basal lamina. Its cells exhibit the characteristics of a cell that simultaneously synthesizes, secretes, absorbs, and digests proteins (Figures 20–27 and 20–28). The basal part of these cells is rich in rough endoplasmic reticulum. The nucleus is generally round and situated in the center of the cell. The apical pole has a discrete Golgi complex and small secretory granules whose content is similar to that of the follicular colloid. Abundant lysosomes, 0.5–0.6 µm in diameter, and some large phagosomes are found in this region. The cell membrane of the apical pole has a moderate number of microvilli. Mitochondria and cisternae of rough endoplasmic reticulum are dispersed throughout the cytoplasm.

Another type of cell present in the thyroid, the **parafollicular,** or **C, cell,** is found as part of the follicular epithelium or as isolated clusters between thyroid follicles (Figures 20–26 and 20–28). Parafollicular cells are larger than thyroid follicular cells and with the light microscope appear less stained. They have a small amount of rough endoplasmic reticulum, long mitochondria, and a large Golgi complex. The most striking feature of these cells is their numerous small (100–180 nm in diameter) granules containing hormone. These cells are responsible for the synthesis and secretion of **calcitonin,** a hormone whose main effect is to lower blood calcium levels by inhibiting bone resorption. Secretion of calcitonin is triggered by an elevation in blood calcium concentration.

Control of the Thyroid

The major regulator of the anatomic and functional state of the thyroid is thyroid-stimulating hormone (TSH; thyrotropin), secreted by the anterior pituitary. TSH stimulates all stages of production and release of thyroid hormones. Thyroid hormones inhibit the synthesis of TSH maintaining an adequate quantity of T_4 and T_3 in the organism. TSH increases the height of the follicular epithelium and decreases the quantity of the colloid and the size of the follicles. The cell membrane of the basal portion of follicular cells is rich in receptors for thyrotropin. Secretion of thyrotropin is also increased by exposure to cold and decreased by heat and stressful stimuli.

Synthesis & Accumulation of Hormones by Follicular Cells

Synthesis and accumulation of hormones take place in four stages: synthesis of thyroglobulin, uptake of iodide from the blood, activation of iodide, and iodination of the tyrosine residues of thyroglobulin.

1. **Synthesis of thyroglobulin** is similar to that in other protein-exporting cells. Briefly, the secretory pathway consists of the synthesis of protein in

the rough endoplasmic reticulum, the addition of carbohydrate in the endoplasmic reticulum and the Golgi complex, and the release of thyroglobulin from formed vesicles at the apical surface of the cell into the lumen of the follicle.

2. The **uptake of circulating iodide** is accomplished in the thyroid follicular cells by a membrane transport protein. This protein, called the Na/I symporter (NIS), is located in the basolateral membrane of the follicular cells and simultaneously carries two molecules, sodium and iodide. Serum iodine plays an important role in regulating thyroid function because low iodine levels increase the amount of NIS and thus increase the uptake, compensating for the lower serum concentration.

3. Iodide is **oxidized** by thyroid peroxidase and is transported into the follicle cavity by an anion transporter called pendrin.

4. Within the colloid occurs the **iodination of tyrosine residues** of thyroglobulin, also catalyzed by thyroid peroxidase, resulting in the formation of monoiodotyrosine and diiodotyrosine. The coupling of these molecules produces the hormones T_3 and T_4, which become part of the much larger thyroglobulin molecule.

Liberation of T_3 & T_4

When stimulated by TSH, thyroid follicular cells take up colloid by endocytosis. The colloid within the endocytic vesicles is then digested by lysosomal enzymes. Hydrolysis of thyroglobulin results in T_4, T_3, diiodotyrosine, and monoiodotyrosine, which are liberated into the cytoplasm. The free T_4 and T_3 cross the basolateral cell membrane and are discharged into the capillaries. Monoiodotyrosine and diiodotyrosine are not secreted into the blood, and their iodine is removed by a deiodinase. The products of this enzymatic reaction, iodine and tyrosine, are reused by the follicular cells. T_4 is the more abundant compound, constituting 90% of the circulating thyroid hormone, although T_3 acts more rapidly and is more potent.

Parathyroid Glands

The parathyroids are four small glands—3 x 6 mm—with a total weight of about 0.4 g. They are located behind the thyroid gland, one at each end of the upper and lower poles, usually in the capsule that covers the lobes of the thyroid. Sometimes they are embedded in the thyroid gland. The parathyroid glands are derived from the pharyngeal pouches—the superior glands from the fourth pouch and the inferior glands from the third pouch. They can also be found in the mediastinum, lying beside the thymus, which originates from the same pharyngeal pouches.

Each parathyroid gland is contained within a connective tissue capsule. These capsules send septa into the gland, where they merge with the reticular fibers that support elongated cordlike clusters of secretory cells.

The endocrine cells of the parathyroid are arranged in cords. There are two types of cells: the chief, or principal, cells and the oxyphil cells.

The **chief cells** are small polygonal cells with a vesicular nucleus and a pale-staining, slightly acidophilic cytoplasm. Electron microscopy shows irregularly shaped granules (200–400 nm in diameter) in their cytoplasm. They are the secretory granules containing **parathyroid hormone,** which is a polypeptide in its active form. **Oxyphil cells** constitute a smaller population. They are larger polygonal cells, and their cytoplasm contains many acidophilic mitochondria with abundant cristae. The function of the oxyphil cells is not known.

Action of Parathyroid Hormone & Its Interrelation with Calcitonin

Parathyroid hormone binds to receptors in osteoblasts. This is a signal for these cells to produce an osteoclast-stimulating factor, which increases the number and activity of osteoclasts and thus promotes the absorption of the calcified bone matrix and the release of Ca^{2+} into the blood. The resulting increase in the concentration of Ca^{2+} in the blood suppresses the production of parathyroid hormone. Calcitonin from the thyroid gland also influences osteoclasts by inhibiting both their resorptive action on bone and the liberation of Ca^{2+}. Calcitonin thus lowers blood Ca^{2+} concentration and increases osteogenesis; its effect is opposite to that of parathyroid hormone. These hormones constitute a dual mechanism to regulate blood levels of Ca^{2+}, an important factor in homeostasis.

In addition to increasing the concentration of Ca^{2+}, parathyroid hormone reduces the concentration of phosphate in the blood. This effect is a result of the activity of parathyroid hormone on kidney tubule cells, diminishing the absorption of phosphate and causing an increase of phosphate excretion in urine. Parathyroid hormone indirectly increases the absorption of Ca^{2+} from the gastrointestinal tract by stimulating the synthesis of vitamin D, which is necessary for this absorption. The secretion of parathyroid cells is regulated by blood Ca^{2+} levels.

Pineal Gland

The pineal gland is also known as the **epiphysis cerebri,** or **pineal body.** In the adult, it is a flattened conical organ situated on the roof of the diencephalons, measuring approximately 5–8 mm in length and 3–5 mm at its greatest width and weighing about 120 mg.

The pineal gland is covered by pia mater. Connective tissue septa containing blood vessels and unmyelinated nerve fibers originate in the pia mater and penetrate the pineal tissue. Along with the capillaries, they surround the cellular cords and follicles, forming irregular lobules.

The pineal gland consists of several types of cells, principally **pinealocytes** and astrocytes. Pinealocytes have a slightly basophilic cytoplasm with large irregular or lobate nuclei and sharply defined nucleoli. When impregnated with silver salts, the pinealocytes appear to have long and tortuous branches reaching out to the vascular connective tissue septa, where they end as flattened dilatations. These cells produce **melatonin** and some ill-defined pineal peptides.

The **astrocytes** of the pineal gland are a specific type of cell characterized by elongated nuclei that stain more heavily than do those of parenchymal cells. They are observed between the cords of pinealocytes and in perivascular areas. These cells have long cytoplasmic processes that contain a large number of intermediate filaments 10 nm in diameter.