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.

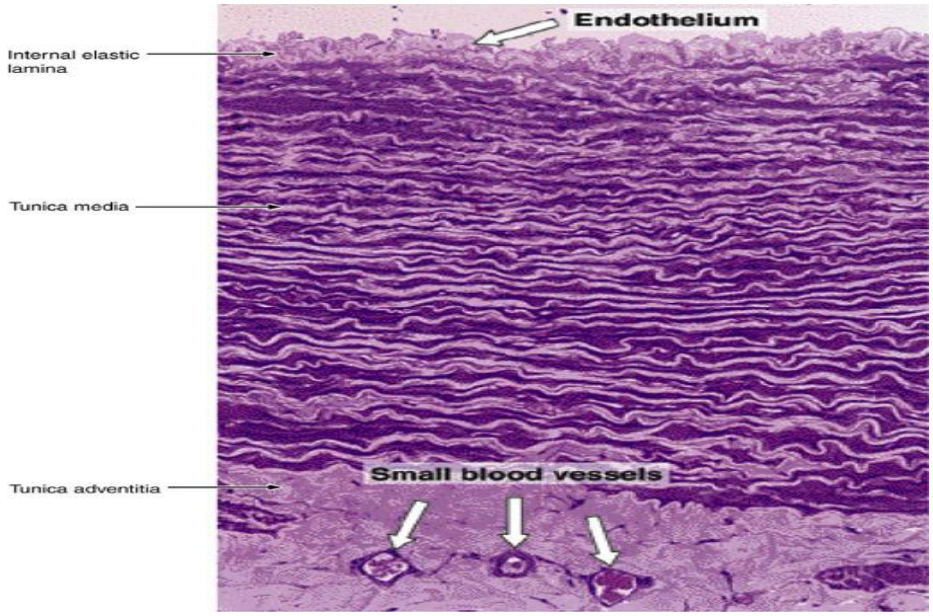
Tunica Adventitia The adventitia consists principally of collagen and elastic fibers. Collagen in the adventitia is type I. The adventitial layer gradually becomes continuous with the connective tissue of the organ through which the vessel runs.

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. The elastic arteries include the aorta and its large branches. They have a yellowish color from the accumulation of elastin in the media. 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.

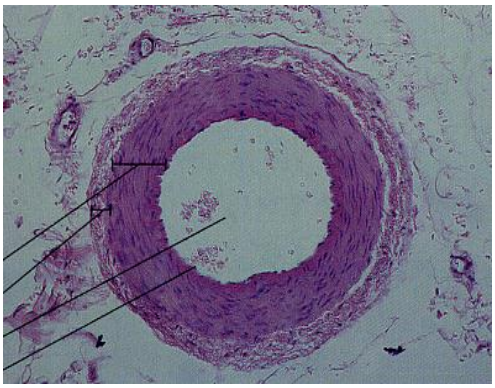
Some arteries irrigate only specific areas of certain organs, and obstruction of the blood supply results in **necrosis** (death of tissues from a lack of metabolites). These **infarcts** commonly occur in the heart, kidneys, cerebrum, and certain other organs. In other regions (such as the skin), arteries 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.