Note: Large images and tables on this page may necessitate printing in landscape mode.

The Circulatory System: Introduction

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.

It is customary to divide the circulatory system into the **macrovasculature,** vessels that are more than 0.1 mm in diameter (large arterioles, muscular and elastic arteries, and muscular veins), and the **microvasculature** (arterioles, capillaries, and postcapillary venules), visible only with a microscope (Figure 11â€“1). The microvasculature is particularly important as the site of interchanges between the blood and surrounding tissues under normal conditions and in the event of inflammatory processes.

Figure 11â€“ 1.

Small blood vessels from the microvasculature (arterioles and venules) surrounded by components of connective tissue. The arrowheads point to fibroblasts. Hematoxylin and eosin (H&E) stain. Low magnification. (Courtesy of TMT Zorn.)

Tissue Components of the Vascular Wall

The vascular wall is composed of three basic structural constituents: **the endothelium,** the **muscular tissue,** and the **connective tissue,** which includes elastic elements (Figure 11â€“2). The amount and arrangement of these tissues within the blood circulatory system are influenced by **mechanical factors,** represented primarily by blood pressure, and **metabolic factors,** which reflect the local needs of the tissues. These tissues are all present in different proportions in the vascular wall, except for capillaries and postcapillary venules, in which the only structural elements represented are the endothelium, its basal lamina, and **pericytes.**

Figure 11â€“ 2.

Diagrams of a muscular artery prepared by H&E staining (**left**) and an elastic artery stained by Weigert's method (**right**). The tunica media of a muscular artery contains predominantly smooth muscle, whereas the tunica media of an elastic artery is formed by layers of smooth muscle intercalated by elastic laminas. The adventitia and the outer part of the media have small blood vessels (vasa vasorum) and elastic and collagenous fibers.

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 (Gr. *angeion,* vessel, + *tendere,* to stretch) to angiotensin II (see Chapter 19: The Urinary System).
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.

Growth factors such as vascular endothelial growth factors (VEGFs) play pivotal roles in the formation of the vascular system during embryonic development, in the regulation of capillary growth under normal and pathological conditions in adults, and in the maintenance of the normal vasculature.

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

MEDICAL APPLICATION

The endothelium also has an antithrombogenic action, preventing blood coagulation. When endothelial cells are damaged by atherosclerotic lesions, for example, the uncovered subendothelial connective tissue induces the aggregation of blood platelets. This aggregation initiates a cascade of events that produces fibrin from blood fibrinogen. An intravascular coagulum, or **thrombus** (plural, thrombi), is formed that may grow until there is complete obstruction of the local blood flow. From this thrombus, solid masses called **emboli** (singular, embolus) may detach and be carried by the blood to obstruct distant blood vessels. In both cases, the vascular flow may stop, a potentially life-threatening condition. Thus, the integrity of the endothelial layer, which prevents contact between platelets and the subendothelial connective tissue, is an important antithrombogenic mechanism (see Chapter 12: Blood Cells).

Vascular Smooth Muscle

Vascular smooth muscle tissue is present in all vessels except capillaries and pericytic venules. **Smooth muscle cells** are frequent and are arranged in helical layers in the tunica media of the blood vessels. Each muscle cell is enclosed by a basal lamina and by variable amounts of connective tissue both secreted by it. Vascular smooth muscle cells, mainly of arterioles and small arteries, are frequently connected by communicating (gap) junctions.

Vascular Connective Tissue

Components of **connective tissue** are present in the walls of blood vessels in amounts and proportions that vary based on local functional requirements. **Collagen fibers,** a ubiquitous element in the vascular system wall, are found between muscle cells, in adventitia, and in some subendothelial layers. Collagen types IV, III, and I are present in the basement membranes, tunica media, and adventitia, respectively. **Elastic fibers** guarantee the resilient shrinkage of the expanded vascular wall. These fibers predominate in large arteries where they are organized in parallel lamellae regularly distributed between the muscle cells throughout the entire media. **Ground substance** forms a heterogeneous gel in the extracellular spaces of the vessel wall. It contributes to the physical properties of the walls of the vessels and probably affects the diffusion and permeability across the wall. The concentration of glycosaminoglycans is higher in arterial than in venous tissue.

MEDICAL APPLICATION

In aging, the extracellular matrix is disordered by an increased secretion of collagen types I and III and of some glycosaminoglycans. Changes in the molecular conformation of elastin and other glycoproteins also occur and may facilitate deposition of **lipoproteins** and calcium ions in the tissue with subsequent calcification. Modifications of the components of the extracellular matrix associated with other more complex factors may lead to the formation of an **atherosclerotic plaque.**
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 (L. *tunica*, coat), as shown in Figures 11â€“2 and 11â€“3.

Figure 11â€“ 3.

Drawing of a medium-sized muscular artery, showing its layers. Although the usual histological preparations cause the layers to appear thicker than those shown here, the drawing is actually similar to the in vivo architecture of the vessel. At the moment of death, the artery experiences an intense contraction; consequently, the lumen is reduced, the internal elastic membrane undulates, and the muscular tunica thickens.

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 (Figures 11â€“2 and 11â€“11).

Figure 11â€“ 11.

Cross sections of small arteries. **A:** The elastic lamina is not stained and is seen as a pallid lamina of scalloped appearance just below the endothelium (arrowhead). Medium magnification. **B:** A small artery with a distinctly stained internal elastic lamina (arrowhead). Low magnification. (From a preparation of the late G Gomori.)

Tunica Media

The media consists primarily of concentric layers of helically arranged smooth muscle cells (Figure 11â€“3). 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 (Figures 11â€“2 and 11â€“3). 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 (Figures 11â€“2 and 11â€“7). 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.

Figure 11â€“ 7.

Transverse section showing part of a muscular (medium caliber) artery. Small blood vessels (vasa vasorum) are observed in the tunica adventitia.

Innervation

Most blood vessels that contain smooth muscle in their walls are supplied with a profuse network of unmyelinated sympathetic nerve fibers (vasomotor nerves) whose neurotransmitter is norepinephrine. Discharge of norepinephrine from these nerves results in vasoconstriction. Because these efferent nerves generally do not enter the media of arteries, the neurotransmitter must diffuse for several micrometers to affect smooth muscle cells of the media. Gap junctions between smooth muscle cells of the

media propagate the response to the neurotransmitter to the inner layers of muscle cells. In veins, nerve endings are found in both the adventitia and the media, but the overall density of innervation is less than that encountered in arteries. Arteries in skeletal muscle also receive a cholinergic vasodilator nerve supply. Acetylcholine released by these vasodilator nerves acts on the endothelium to produce nitric oxide, which diffuses into the smooth muscle cells, activating a cyclic GMP system of intracellular messengers. The muscle cells then relax, and the vessel lumen is dilated.

For didactic purposes, the arterial blood vessels are classified, based on their diameter, into arterioles, arteries of medium diameter (muscular arteries), and larger (elastic) arteries.
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 (Figures 11â€“2 and 11â€“4). 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.

Figure 11â€“ 4.
Transverse section showing part of a large elastic artery showing a well-developed tunica media containing several elastic laminas. Pararosanilineâ€“toluidine blue (PT) stain. Medium magnification.

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 (Figure 11â€“5).

Figure 11â€“ 5.

Graph showing the relationship between the characteristics of blood circulation (**left**) and the structure of the blood vessels (**bottom**). The arterial blood pressure and speed of flow decrease and become more constant as the distance from the heart increases. This decrease coincides with a reduction in the number of elastic fibers and an increase in the number of smooth muscle cells in the arteries. The graph illustrates the gradual changes in the structure of vessels and their biophysical properties. (Reproduced, with permission, from Cowdry EV: *Textbook of Histology.* Lea & Febiger, 1944.)

Arterial Degenerative Alterations

MEDICAL APPLICATION

Arteries undergo progressive and gradual changes from birth to death, and it is difficult to say where the normal growth processes end and the processes of involution begin. Each artery exhibits its own aging pattern.

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.

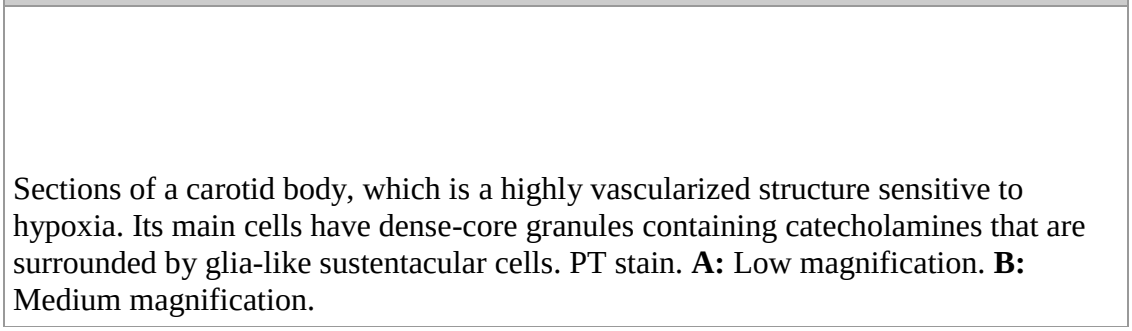
When the media of an artery is weakened by an embryonic defect, disease, or lesion, the wall of the artery may dilate extensively. Progression of this process of dilatation leads to the development of an **aneurysm.** Rupture of the aneurysm brings severe consequences and may cause death.

Carotid Bodies

The carotid bodies, encountered near the bifurcation of the common carotid artery, are chemoreceptors sensitive to carbon dioxide and oxygen concentrations in the blood. These structures are richly irrigated by fenestrated capillaries that surround type I and type II cells. The type II cells are supporting cells, whereas type I cells contain numerous dense-core vesicles that store dopamine, serotonin, and adrenaline (Figure 11â€“6). Most of the nerves of the carotid body are afferent fibers (they carry impulses

to the central nervous system). The carotid bodies are sensitive to low oxygen tension, high carbon dioxide concentration, and low arterial blood pH. Whether the afferent nerve endings or type I cells are the principal chemoreceptor elements is controversial. Aortic bodies located on the arch of the aorta are similar in structure to carotid bodies and are believed to have a similar function.

Figure 11â€“ 6.



Sections of a carotid body, which is a highly vascularized structure sensitive to hypoxia. Its main cells have dense-core granules containing catecholamines that are surrounded by glia-like sustentacular cells. PT stain. **A:** Low magnification. **B:** Medium magnification.

Carotid Sinuses

Carotid sinuses are slight dilatations of the internal carotid arteries. These sinuses contain baroreceptors that detect changes in blood pressure and relay the information to the central nervous system. The arterial media layer of the sinus is thinner to allow it to respond to changes in blood pressure. The intima and the adventitia are very rich in nerve endings. The afferent nerve impulses are processed in the brain to control vasoconstriction and maintain normal blood pressure.

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** (singular, **glomus**), 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 (Figures 11â€“3 and 11â€“7). The internal elastic lamina, the most external component of the intima, is prominent (Figure 11â€“7), 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 (Figures 11â€“8 and 11â€“18). 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 (Figures 11â€“8 and 11â€“18). Above the arterioles are small arteries in which the tunica media is more developed, and the lumens are larger than those of the arterioles (Figures 11â€“9, 11â€“10, and 11â€“11). In both arterioles and small arteries, the tunica adventitia is very thin.

Figure 11â€“ 8.

Cross section through an arteriole and its accompanying venule from the myometrium of mouse uterus. Note the elongated, large nucleus (arrowhead) of a pericyte surrounding the venule wall. Toluidine blue stain. High magnification. (Courtesy of TMT Zorn.)

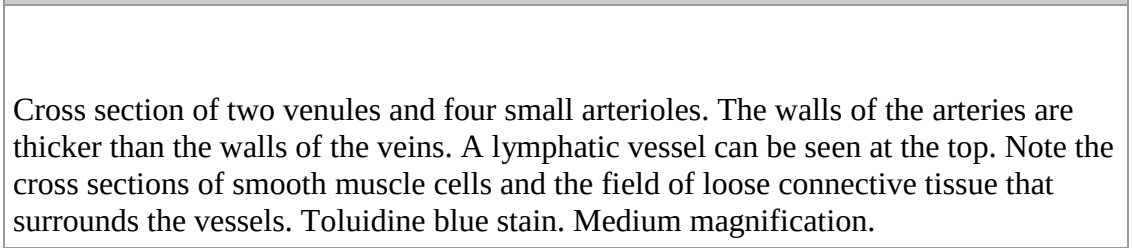
Figure 11â€“ 9.

Cross section through a small artery and its accompanying muscular vein. Because of vasodilatation, the arteriole is unusually filled with blood. At this stage the internal elastic lamina is not distinguished. Many other small arterial branches and capillaries can be seen in the surrounding connective tissue. PT stain. Medium magnification.

Figure 11â€“ 10.

Oblique section of a small artery from the mesentery. Note the transverse section of the smooth muscle cells of the media and the endothelial layer covering the lumen of the vessel (arrowheads). PT stain. Medium magnification.

Figure 11â€“ 18.



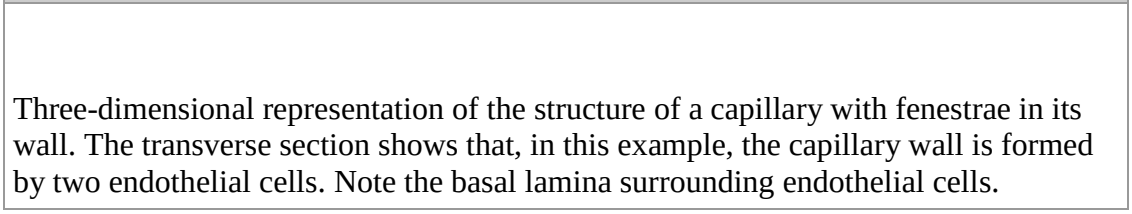
Cross section of two venules and four small arterioles. The walls of the arteries are thicker than the walls of the veins. A lymphatic vessel can be seen at the top. Note the cross sections of smooth muscle cells and the field of loose connective tissue that surrounds the vessels. Toluidine blue stain. Medium magnification.

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 9 m, and their length is usually not more than 50 m. 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 (Figure 11â€“12). The external surfaces of these cells usually rest on a basal lamina, a product of endothelial origin.

Figure 11â€“ 12.



Three-dimensional representation of the structure of a capillary with fenestrae in its wall. The transverse section shows that, in this example, the capillary wall is formed by two endothelial cells. Note the basal lamina surrounding endothelial cells.

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 (Figure 11â€“13). 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.

Figure 11â€“ 13.

Electron micrograph of a section of a continuous capillary. Note the ruffled appearance of its interior surface, the large and small pinocytic vesicles, and numerous microfilaments in the cytoplasm. Arrows show the basal lamina. Medium magnification.

MEDICAL APPLICATION

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** (Gr. *peri,* around, + *kytos,* cell), 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** (Figure 11â€“14) 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 (Figures 11â€“15 and 11â€“16). 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 (30â€“40 m), 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. Macrophages are located either among or outside the cells of the endothelium.
e. The basal lamina is discontinuous.

Figure 11â€“ 14.

Electron micrograph of a transverse section of a continuous capillary. Note the nucleus (N) and the junctions between neighboring cells (arrowheads). Numerous pinocytotic vesicles are evident (small arrows). The large arrows show large vesicles being formed by infoldings of broad sheets of the endothelial cell cytoplasm. x10,000.

Figure 11â€“ 15.

A fenestrated capillary in the kidney. Arrows indicate fenestrae closed by diaphragms. In this cell the Golgi complex (G), nucleus (N), and centrioles (C) can be seen. Note the continuous basal lamina on the outer surface of the endothelial cell (double arrows). Medium magnification. (Courtesy of J Rhodin.)

Figure 11â€“ 16.

Schematic representation of a longitudinal view of a fenestrated capillary showing its hydrophilic transporting system represented by pinocytotic vesicles **(1)** and fenestrae **(2)**. Observe that fenestrae are obliterated by diaphragms (arrows) whose chemical composition is still unknown. N, nucleus; BM, basement membrane.

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 (Figure 11â€“17). The arterioles branch into small vessels surrounded by a discontinuous layer of smooth muscle, the **metarterioles** (Figure 11â€“17), 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 (Figure 11â€“17) 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.

Figure 11â€“ 17.

Types of microcirculation formed by small blood vessels. **(1)** The usual sequence of

arteriole metarteriole capillary venule and vein. **(2)** An arteriovenous anastomosis. **(3)** An arterial portal system, as is present in the kidney glomerulus. **(4)** A venous portal system, as is present in the liver. (Reproduced, with permission, from KrstÃc RV: *Illustrated Encyclopedia of Human Histology.* Springer-Verlag, 1984.)

The total diameter of the capillaries is approximately 800 times larger than that of the aorta. The velocity of blood in the aorta averages 320 mm/s; in the capillaries it is about 0.3 mm/s. Because of their thin walls and slow blood flow, capillaries are a favorable place for the exchange of water, solutes, and macromolecules between blood and tissues.

The capillaries are often referred to as **exchange vessels,** because it is at these sites that oxygen, carbon dioxide, substrates, and metabolites are transferred from blood to the tissues and from the tissues to blood. The mechanisms responsible for the interchange of materials between blood and tissue are not completely known. They depend on the kind of molecule and also on the structural characteristics and arrangement of endothelial cells in each type of capillary.

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 (Figure 11â€“8). 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 (Figures 11â€“1 and 11â€“18). 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** (Figure 11â€“9), with a diameter of 1â€“9 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 (Figure 11â€“19). These veins, particularly the largest ones, have valves in their interior (Figure 11â€“20). 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.

Figure 11â€“ 19.

Diagram comparing the structure of a muscular artery (**left**) and accompanying vein (**right**). Note that the tunica intima and the tunica media are highly developed in the artery but not in the vein.

Figure 11â€“ 20.

Section showing part of a large vein. The vein has a very thin muscular tunica media that contrasts with the thick adventitia composed of dense connective tissue. Note the presence of a valve. PT stain. Medium magnification.

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 (see Chapter 10: Muscle Tissue) 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.

The heart has a specialized system to generate a rhythmic stimulus that is spread to the entire myocardium. This system (Figures 11â€“21 and 11â€“22) consists of two nodes located in the atriumâ€”the **sinoatrial node** and the **atrioventricular node**â€”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.

Figure 11â€“ 21.

Diagram of the heart, showing the impulse-generating and -conducting system.

Figure 11â€“ 22.

A: Purkinje fibers of the impulse-conducting system. **B:** High magnification showing details of Purkinje cells. They are characterized by a reduced number of myofibrils that are present mainly in the periphery of the muscle cell. The light area around the nuclei of the conducting cells is caused by a local accumulation of glycogen. H&E stain. (Courtesy of TMT Zorn.)

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 (Figure 11â€“22). 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.

Both the parasympathetic and sympathetic divisions of the autonomic system contribute to innervation of the heart and form widespread plexuses at the base of the

heart. Ganglionic nerve cells and nerve fibers are present in the regions close to the sinoatrial and atrioventricular nodes. Although these nerves do not affect generation of the heartbeat, a process attributed to the sinoatrial (pacemaker) node, they do affect heart rhythm, such as during physical exercise and emotional stress. Stimulation of the parasympathetic division (vagus nerve) slows the heartbeat, whereas stimulation of the sympathetic nerve accelerates the rhythm of the pacemaker.

Between the muscular fibers of the myocardium are numerous afferent free nerve endings that are related to sensibility and pain. Partial obstruction of the coronary arteries reduces the supply of oxygen to the myocardium and causes pain (angina pectoris). The same sensorial enervation occurs during a heart attack, which is very painful because many muscular fibers die as a result of the low levels of oxygen.
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 (Figures 11â€“18, 11â€“23, and 11â€“24).

Figure 11â€“ 23.

Structure of a lymphatic capillary at the electron microscope level. Note the overlapping free borders of endothelial cells, the discontinuous basal lamina (arrows), and the attachment of anchoring fibrils (AF). (Courtesy of J James.)

Figure 11â€“ 24.

Two lymphatic vessels (LV). The vessel on top was sectioned longitudinally and shows a valve, the structure responsible for the unidirectional flow of lymph. The solid arrow shows the direction of the lymph flow, and the dotted arrows show how the valves prevent lymph backflow. The lower small vessel presents a very thin wall. PT stain. Medium magnification.

The thin lymphatic vessels gradually converge and ultimately end up as two large trunksâ€”the **thoracic duct** and the **right lymphatic duct**â€”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, whose morphological characteristics and functions are discussed in Chapter 14: 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 (Figure 11â€“24). 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.

References

Boegehold MA: Shear-dependent release of venular nitric oxide: effect on arteriolar tone in rat striated muscle. Am J Physiol 1996;271:H387.

Cantin M et al: Immunocytochemical localization of atrial natriuretic factor in the heart and salivary glands. Histochemistry 1984;80:113. [PMID: 6370928]

Challice CE, Viragh S (editors): *Ultrastructure of the Mammalian Heart.* Academic Press, 1973.

Cliff WJ: *Blood Vessels.* Cambridge University Press, 1976.

Johnson PC: *Peripheral Circulation.* Wiley, 1978.

Joyce NE et al: Contractile proteins in pericytes. J Cell Biol 1985;100:1387. [PMID: 3886666]

Leak LV: Normal anatomy of the lymphatic vascular system. In: *Handbuch der Allgemeine Pathologie.* Meessen H (editor). Springer-Verlag, 1972.

Li X, Erickson U: Novel VEGF family members: VEGF-B, VEGF-C and VEGF-D. Int J Biochem Cell Biol 2001;33:421. [PMID: 12040416]

Masuda H, Kalka C, Asahara T: Endothelial progenitor cells for regeneration. Hum Cell 2000;13:153. [PMID: 11329932]

Rhodin JAG: Architecture of the vessel wall. In: *Handbook of Physiology.* Section 2: *Cardiovascular System.* Vol 2. American Physiological Society, 1980.

Richardson JB, Beaulines A: The cellular site of action of angiotensin. J Cell Biol 1971;51:419. [PMID: 4329616]

Simionescu N: Cellular aspects of transcapillary exchange. Physiol Rev 1983;63:1536. [PMID: 6318239]

Thorgeirsson G, Robertson AL Jr: The vascular endothelium: pathobiologic significance. Am J Pathol 1978;93:802.

Wagner D, Marder J: Biosynthesis of von Willebrand protein by human endothelial cells: processing steps and their intracellular localization. J Cell Biol 1984;99:2123. [PMID: 6334089]