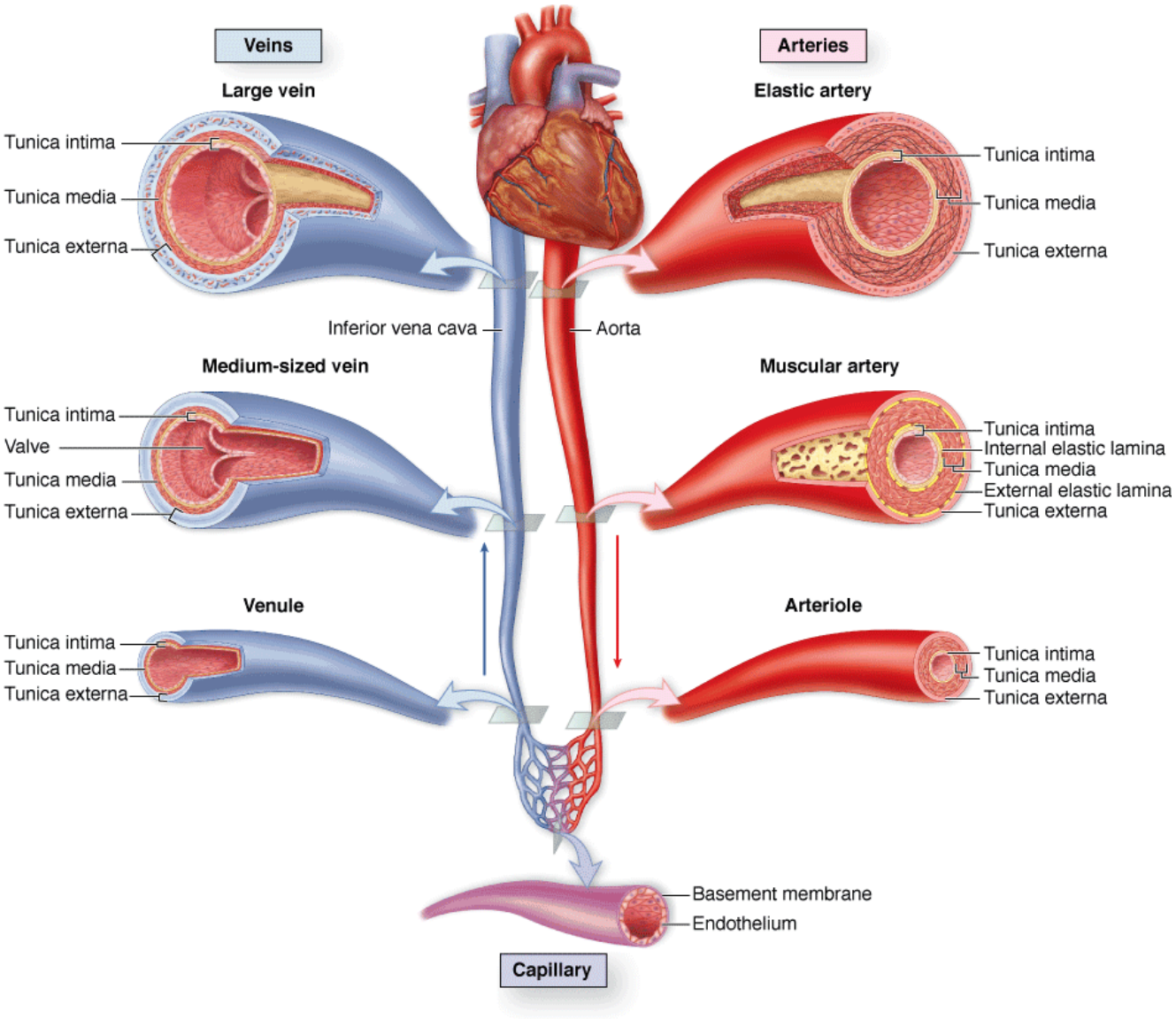
Note: Large images and tables on this page may necessitate printing in landscape mode.

THE CIRCULATORY SYSTEM: INTRODUCTION

The circulatory system includes both the blood and lymphatic vascular systems. The **blood vascular system** (Figure 11–1) 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 its nutrients and oxygen, to the tissues.
- The **capillaries,** the smallest blood vessels, constituting a complex network of thin tubules that branch profusely in almost every organ and through whose walls the interchange between blood and tissues takes place.
- The **veins,** which result from the convergence of capillaries into a system of larger channels that continue enlarging as they approach the heart, toward which they convey the blood to be pumped again.

Figure 11–1.



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Vessels of the blood circulatory system.

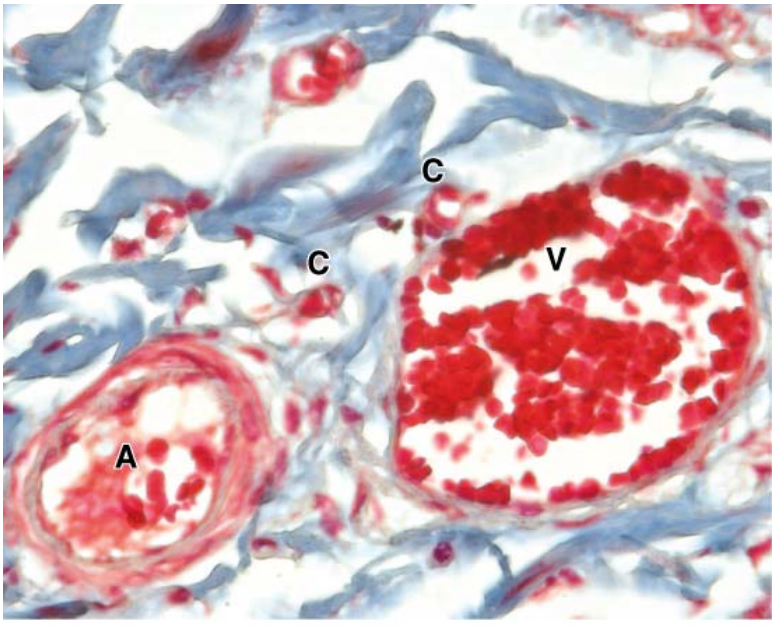
The heart is the principal organ of the blood circulatory system, pumping blood throughout the body and providing the force by which nutrients leave the capillaries and enter tissues. Large elastic arteries leave the heart and branch to form muscular arteries. These arteries branch further and enter organs, where they branch much further to form arterioles. These arterioles branch into the smallest vessels, the capillaries, the site of exchange between blood and surrounding tissue. Capillaries then merge to form venules, which merge further into small and then medium-sized veins. These veins leave organs, form larger veins which eventually bring blood back to the heart.

The **lymphatic vascular system**, introduced with the discussion of interstitial fluid in Chapter 5, begins with the **lymphatic capillaries,** which are

closed-ended tubules that merge 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 circulatory system is considered to consist of 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 11–2). The microvasculature is particularly important functionally, being the site of interchanges between blood and the surrounding tissues both under normal conditions and during inflammatory processes.

Figure 11–2.



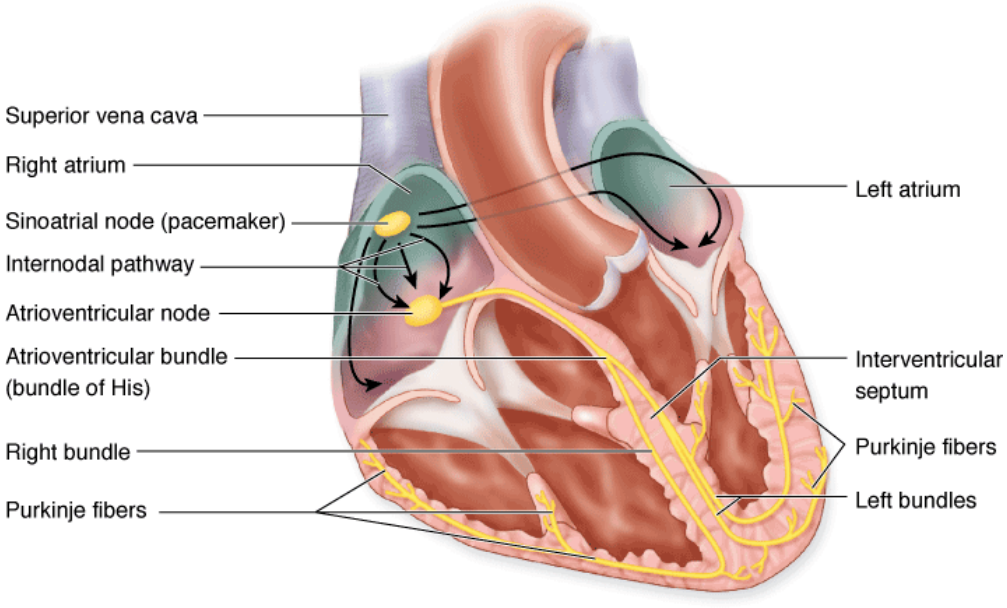
Vessels of the microvasculature.

Arterioles (A), small capillaries (C) and venules (V) make up the microvasculature where, in almost every organ, exchange takes place between blood and the interstitial fluid of the tissues. X200. Masson trichrome.

HEART

The heart is a muscular organ that contracts rhythmically, pumping the blood through the circulatory system (Figure 11–3). The right and left **ventricles** pump blood to the lungs and the rest of the body respectively; right and left **atria** receive blood from the body and the pulmonary veins respectively. The walls of all four heart chambers consist of three major layers or tunics: the internal endocardium; the middle myocardium; and the external epicardium.

Figure 11–3.



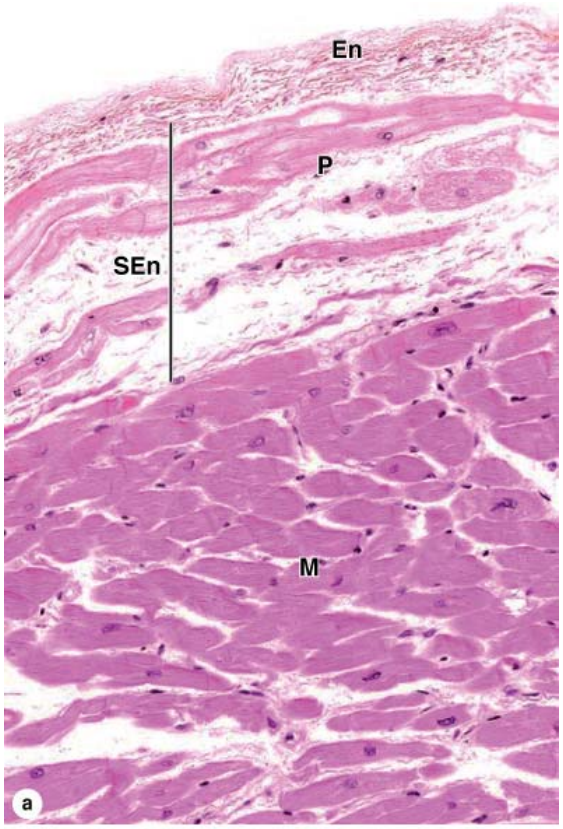
Major histological features of the heart.

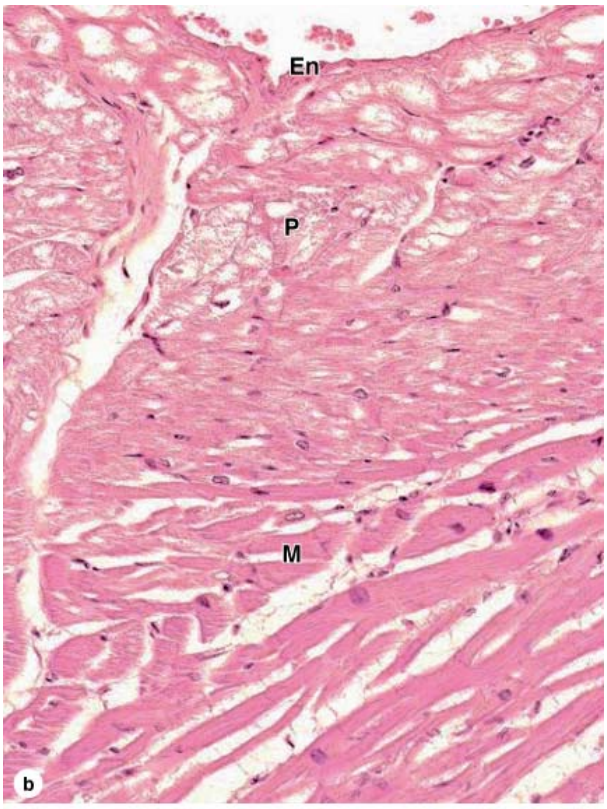
Longitudinal view of human heart showing the two atria and two ventricles. The ventricular walls are thicker than those of the atria, principally because of the much

thicker myocardium. The **valves** are basically flaps of connective tissue anchored in the heart's dense **fibrous skeleton** region, shown in white. Other parts of the fibrous skeleton are the chordae tendinae, cords of dense connective tissue extending from the valves and attached to papillary muscles that help prevent valves from turning inside-out during ventricular contraction. All these parts of the fibrous skeleton are covered by endothelium. Shown in yellow are parts of the cardiac **conducting system**, which initiates the electrical impulse for heart's contraction (heartbeat) and spreads it through the ventricular myocardium. Both the sinoatrial (SA) node (pacemaker), in the posterior wall of the right atrium, and the atrioventricular (AV) node in the floor of the right atrium consist of myocardial tissue that is difficult to distinguish histologically from surrounding cardiac muscle. The AV node is continuous with specialized bundles of cardiac muscle fibers, the **AV bundle** (of His) which run along the interventricular septum to the apex of the heart, where they branch further as **conducting (Purkinje) fibers** which extend into myocardium of both ventricles.

The **endocardium** consists of a single layer of squamous endothelial cells on a thin layer of loose connective tissue containing elastic and collagen fibers as well as some smooth muscle cells. Connecting this subendothelial layer to the myocardium is additional connective tissue (often called the **subendocardial layer**) containing veins, nerves, and branches of the impulse-conducting system of the heart (Figure 11–4).

Figure 11–4.





Endocardium & subendocardial conducting network.

The endocardium (En) is a thin layer of connective tissue lined by simple squamous endothelium. Between the endocardium and myocardium is a layer of variable thickness called the subendocardial layer (SEn) containing small nerves and in the ventricles the conducting (Purkinje) fibers (P) of the subendocardial conducting network. These fibers are cardiac muscle cells joined by intercalated disks but specialized for impulse conduction rather than contraction. Purkinje fibers are usually larger than contractile cardiac muscle fibers with large amounts of lightly stained glycogen filling most of the cytoplasm and displacing sparse myofibrils to the periphery. **(a):** Purkinje fibers running separately within the subendocardial layer. **(b):** Purkinje fibers intermingling with contractile fibers within the myocardium (M). Along with the nodes of specialized cardiac muscle in the right atrium which generate the electrical impulse, the network of conducting fibers comprises the conducting system of the heart. Both X200. H&E.

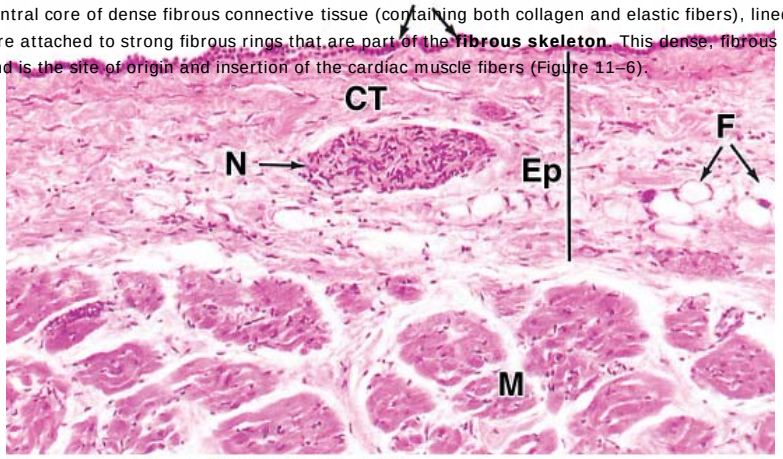
The **myocardium** is the thickest of the tunics and consists of cardiac muscle cells (see Chapter 10) arranged in layers that surround the heart chambers in a complex spiral. The myocardium is much thicker in the ventricles than in the atria. The arrangement of these muscle cells is extremely varied, so that in sections 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 many adipocytes (Figure 11–5). The epicardium corresponds to the visceral layer of the **pericardium,** the serous membrane in which the heart lies. In the space between the pericardium's visceral layer (epicardium) and its parietal layer is a small amount of lubricant fluid that facilitates the heart's movements.

Figure 11–5.

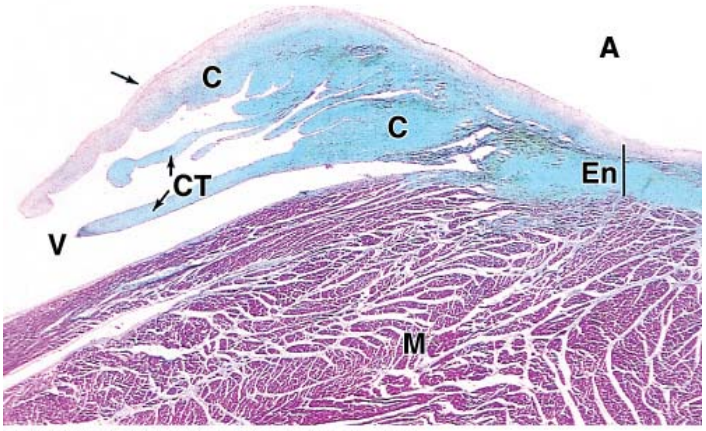
The cardiac valves consist of a central core of dense fibrous connective tissue (containing both collagen and elastic fibers), lined on both sides by endothelial layers. The bases of the valves are attached to strong fibrous rings that are part of the **fibrous skeleton.** This dense, fibrous region around the heart valves anchors the base of the valves and is the site of origin and insertion of the cardiac muscle fibers (Figure 11–6).

Figure 11–6.



Epicardium or visceral pericardium.

The external tunic of the heart, the epicardium, is the site of the coronary vessels and contains considerable adipose tissue. This section of atrium shows part of the myocardium (M) and epicardium (Ep). The epicardium consists of loose connective tissue (CT) containing both autonomic nerves (N) and fat (F). The epicardium is the visceral layer of the pericardium and is covered by the simple squamous-to-cuboidal epithelium (arrows) that also lines the pericardial space. These mesothelial cells secrete a lubricate fluid that prevents friction as the beating heart contacts the parietal pericardium on the other side of the pericardial cavity. X100. H&E.



Valve leaflet and fibrous skeleton.

The fibrous skeleton of the heart consists of masses of dense connective tissue in the endocardium which anchors the valves and surrounds the two atrioventricular canals, maintaining their proper shape. Section through a leaflet of the left atrioventricular valve (arrows) shows that valves are largely dense connective tissue (C) covered with a thin layer of endothelium. The collagen-rich connective tissue of the valves is stained pale green here and is continuous with the fibrous ring of connective tissue at the base of the valves, which fills the endocardium (En) of this area between the atrium (A) and ventricle (V). The **chordae tendinae** (CT), small strands of connective tissue which bind distal parts of valve leaflets, can also be seen here. The interwoven nature of the cardiac muscle fibers, with many small fascicles, in the myocardium (M) is also shown. X20. Masson trichrome.

The heart has a specialized system to generate a rhythmic stimulus for contraction that is spread to the entire myocardium. This system (Figure 11–3) consists of two nodes located in the right atrium—the **sinoatrial (SA) node** (pacemaker) and the **atrioventricular (AV) node**—and the **atrioventricular bundle** (of His). The SA node is a small mass of modified cardiac muscle cells that are fusiform, smaller and with fewer myofibrils than neighboring muscle cells. The cells of the AV node are similar to those of the SA node but their cytoplasmic projections branch in various directions, forming a network. The AV bundle originates from the node of the same name, passes along the interventricular septum and splits into left and right bundles, and then branches further to both ventricles. The cells/fibers of the impulse-conducting system are modified cardiac muscle cells functionally integrated by gap junctions.

Distally fibers of the AV bundle become larger than ordinary cardiac muscle fibers and acquire a distinctive appearance. These **conducting myofibers** or **Purkinje fibers** have one or two central nuclei and their cytoplasm is rich in mitochondria and glycogen. Myofibrils are sparse and restricted to the periphery of the cytoplasm (Figure 11–4). After forming the subendocardial conducting network, these fibers penetrate the myocardial layer of both ventricles, an important arrangement that allows the stimulus for contraction to reach the innermost layers of the ventricular musculature.

Both parasympathetic and sympathetic neural components innervate the heart. Ganglionic nerve cells and nerve fibers are present in the regions close to the SA and AV nodes, where they affect heart rate and 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 afferent free nerve endings related to sensibility and pain. Partial obstruction of the coronary arteries reduces the supply of oxygen to the myocardium and causes pain (angina pectoris).

TISSUES OF THE VASCULAR WALL

Walls of larger blood vessels contain three basic structural components: a simple squamous **endothelium**, **smooth muscle**, and **connective tissue** with elastic elements in addition to collagen. The amount and arrangement of these tissues in vessels are influenced by **mechanical factors**, primarily blood pressure, and **metabolic factors** reflecting local needs of tissues.

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

Besides their role in the exchanges between blood and tissues, endothelial cells perform several other functions, including production of vasoactive factors that affect the vascular tone, such as nitric oxide, endothelins, and vasoconstrictive agents, and conversion of circulating angiotensin I to angiotensin II (see Chapter 19). Although morphologically similar, the endothelial cells of different blood vessels exert their various functional properties differently. Endothelial cells, especially those of arteries, contain unique very small, elongated vesicles called Weibel-Palade bodies, which contain selectin and von Willebrand factor involved in blood coagulation.

Growth factors such as vascular endothelial growth factor (VEGF) help maintain the vasculature, regulate the formation of the vascular system from embryonic mesenchyme (vasculogenesis) and promote capillary outgrowth from existing vessels (angiogenesis) under normal and pathologic conditions in adults.

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 produce fibrin from circulating fibrinogen. An intravascular clot, or **thrombus** (plural, thrombi), is formed that may grow until there is complete obstruction of the local vascular 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 preventing the contact between platelets and the subendothelial connective tissue is an important antithrombogenic mechanism.

Smooth muscle cells or fibers occur in the walls of all vessels larger than capillaries and are arranged helically in layers. Each muscle cell is enclosed by an external lamina and by various amounts of other extracellular material, all of which these cells produce. In arterioles and small arteries the smooth muscle cells are frequently connected by communicating gap junctions.

Connective tissue components are present in vascular walls in amounts and proportions that vary based on local functional requirements. **Collagen fibers** are found throughout the wall: in the subendothelial layer, between muscle layers, and in the outer layers. **Elastic material** provides the resiliency for the vascular wall expanded under pressure. Elastin predominates in large arteries where it forms parallel lamellae regularly distributed between the muscle

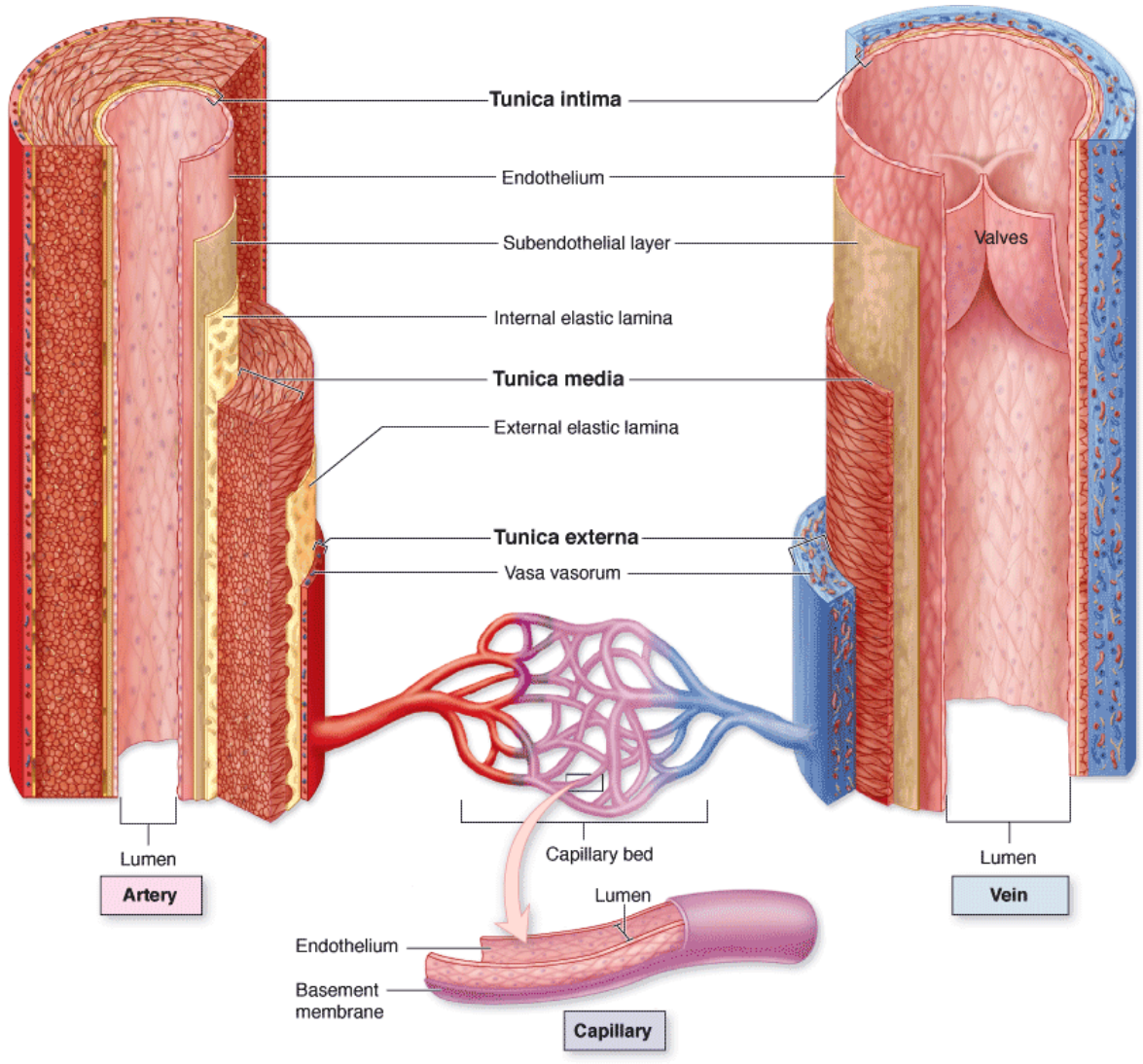
layers. **Ground substance** forms a heterogeneous gel in the extracellular spaces of the wall, contributing to the wall's physical properties and affecting permeability and diffusion of substances through the wall. Concentrations of glycosaminoglycans are higher in arterial than in venous tissues.

STRUCTURAL PLAN OF BLOOD VESSELS

All blood vessels greater than a certain diameter have many structural features in common and present a similar plan of construction. The distinction between different types of vessels often is not clear-cut because the transition from one type to another is gradual. Blood vessels are usually composed of the following layers, or tunics (L. *tunica,* coat), as shown in Figures 11–1 and 11–7.

- The **tunica intima** has one layer of endothelial cells supported by a thin subendothelial layer of loose connective tissue with 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 holes (fenestrae) that allow the diffusion of substances to nourish cells deep in the vessel wall. As a result of the loss of blood pressure and contraction of the vessel at death, the tunica intima of arteries may have a slightly folded appearance in tissue sections (Figure 11–8).
- The **tunica media**, the middle layer, consists chiefly of concentric layers of helically arranged smooth muscle cells (Figures 11–7 and 11-8). Interposed among the smooth muscle cells are variable amounts of elastic fibers and lamellae, reticular fibers of collagen type III, proteoglycans, and glycoproteins, all of which is produced by these cells. In arteries, the media has a thinner **external elastic lamina,** which separates it from the tunica adventitia.
- The **tunica adventitia** or tunica externa consists principally of type I collagen and elastic fibers (Figures 11–7 and 11-8). This adventitial layer is gradually continuous with the stromal connective tissue of the organ through which the blood vessel runs.

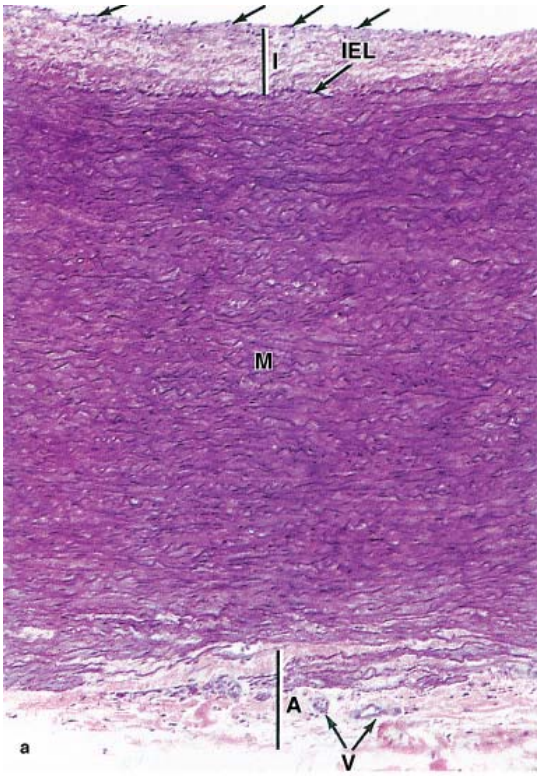
Figure 11–7.

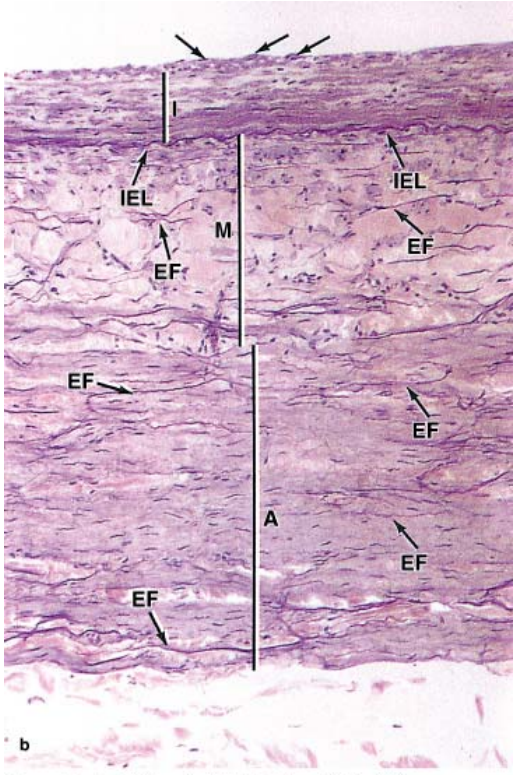


Walls of arteries, veins, and capillaries.

Walls of both arteries and veins have a tunica intima, tunica media, and tunica externa (or adventitia), which correspond roughly to the heart's endocardium, myocardium and epicardium. An artery has a thicker tunica media and relatively narrow lumen. A vein has a larger lumen and its tunica externa is the thickest layer. The tunica intima of veins is often folded to form valves. Capillaries have only an endothelium, with no subendothelial layer or other tunics.

Figure 11–8.



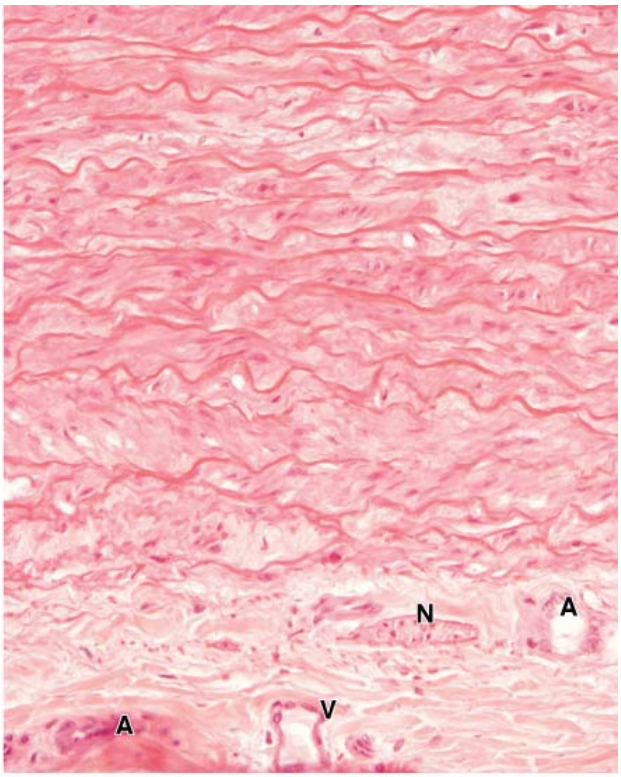


Tunics of the vascular wall.

Comparison of the three major layers or **tunics** in the largest artery and vein. **(a):** aorta **(b):** vena cava. Simple squamous endothelial cells (arrows) line the tunica intima (I) which has subendothelial loose connective tissue and is separated from the tunica media by the internal elastic lamina (IEL), a prominent sheet of elastin. The media (M) contains elastic lamellae and fibers (EF) and multiple layers of smooth muscle not seen well here. The tunica media is much thicker in large arteries than veins, with relatively more elastin. Elastic fibers are also present in the outer tunica adventitia (A), which is relatively thicker in large veins. Vasa vasorum (V) are seen in the adventitia of the aorta. The connective tissue of the adventitia always merges with the less dense connective tissue around it. Both X122. Elastic.

Large vessels usually have **vasa vasorum** ("vessels of the vessel"), which consist of arterioles, capillaries, and venules in the tunica adventitia and the outer part of the media (Figure 11–9). The vasa vasorum provide metabolites to cells of those layers, since in larger vessels the wall is too thick to be nourished solely by diffusion from the blood in the lumen. Luminal blood alone does provide nutrients and oxygen for cells of the tunica intima. Since they carry deoxygenated blood, large veins typically have more vasa vasorum than arteries.

Figure 11–9.



Vasa vasorum.

Walls of the larger vessels, as the aorta, contain in the tunica adventitia a supply of microvasculature to bring O_2 and nutrients to local cells too far from the lumen to be nourished by blood there. These arterioles (A), capillaries and venules (V) constitute the vasa vasorum (vessels of vessels). The adventitia of large arteries is also supplied more sparsely with small sympathetic nerves (N) for control of vasoconstriction. X100. H&E.

Larger vessels are supplied with a network of unmyelinated sympathetic nerve fibers (**vasomotor nerves**) whose neurotransmitter is norepinephrine (Figure 11–9). Discharge of norepinephrine from these nerves produces 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, where gap junctions propagate the response to the inner layers of muscle cells. In thinner-walled 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. In skeletal muscle, arteries also receive a cholinergic vasodilator nerve supply. Acetylcholine released by these nerves acts on the endothelium to produce nitric oxide, which diffuses into the smooth muscle cells. The muscle cells then relax and the vessel lumen is dilated.

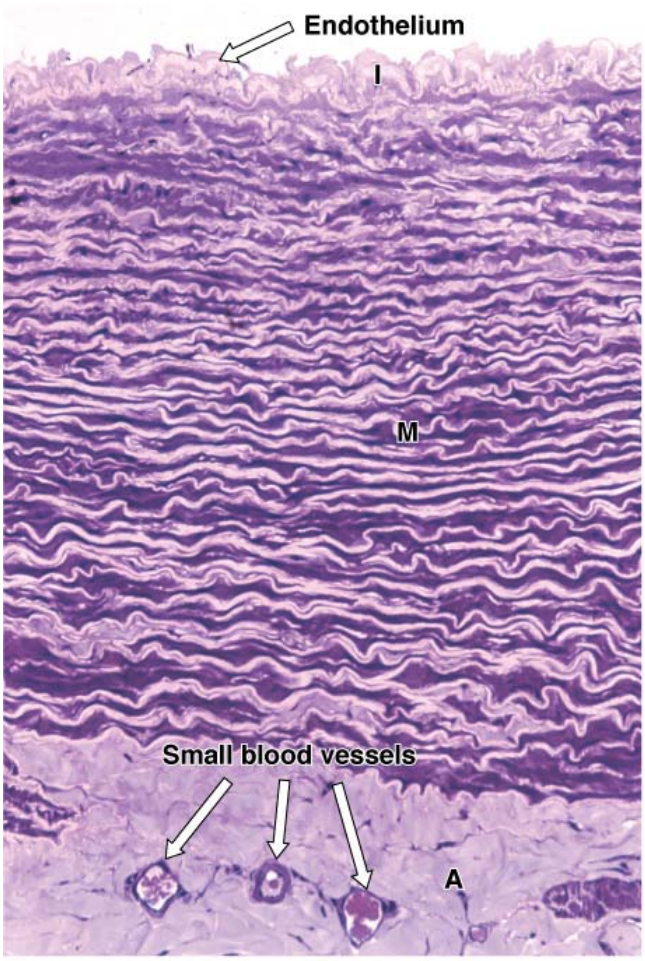
VASCULATURE

For didactic purposes vessels of the macrovasculature are classified arbitrarily as the types indicated in the following discussion.

Large Elastic Arteries

Large elastic arteries help to stabilize the blood flow. The elastic arteries include the aorta and its large branches. Freshly dissected, they have a yellowish color from the 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 (Figures 11–8 and 11–10). The media consists of elastic fibers and a series of concentrically arranged, perforated elastic laminae whose number increases with age (there are about 40 in the newborn, 70 in the adult). Between the elastic laminae are smooth muscle cells, reticular fibers, proteoglycans, and glycoproteins. The tunica adventitia is relatively underdeveloped.

Figure 11–10.



Elastic artery.

The largest arteries contain considerable elastic material and expand with blood when the heart contracts. A transverse section through part of a large elastic artery shows a thick tunica media (M) consisting largely of many well-developed elastic lamellae. Strong pressure of blood pulsating into such arteries during systole expands the arterial wall, reducing the pressure and allowing strong blood flow to continue during diastole. The intima (I) of the empty aorta is typically folded and the adventitia (A) contains vasa vasorum. X200. PT.

The several elastic laminae contribute to the important function of making blood flow more uniform. During ventricular contraction (**systole**), the elastic laminae of large arteries are stretched, reducing the force of the pressure somewhat. 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.

MEDICAL APPLICATION

Arterial Degenerative Alterations

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 connective tissue elements, and the deposit of cholesterol in smooth muscle cells and macrophages. When heavily loaded with lipid, these cells may be 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.

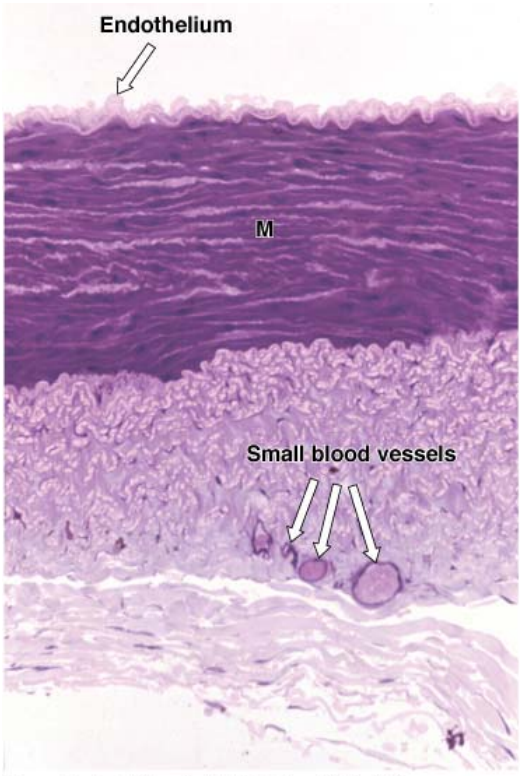
Certain arteries irrigate only specific areas of specific organs and obstruction of this blood supply results in **necrosis** (death of tissues from a lack of metabolites). These **infarcts** occur commonly in the heart, kidneys, cerebrum, and certain other organs. In other regions (such as the skin),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

When the tunica media of an artery is weakened by an embryonic defect, disease, or lesion, the wall of the artery may dilate extensively. As this process of dilatation progresses, it becomes an **aneurysm**. Rupture of the aneurysm brings severe consequences and may cause death.

Muscular Arteries

The muscular arteries can control blood flow to organs by contracting or relaxing the smooth muscle cells of the tunica media. The intima has a very thin subendothelial layer and the internal elastic lamina, the most external component of the intima, is prominent (Figure 11–11). The tunica media may contain up to 40 layers of more prominent smooth muscle cells which are intermingled with a variable number of elastic lamellae (depending on the size of the vessel) as well as reticular fibers and proteoglycans. 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.

Figure 11–11.



Muscular artery.

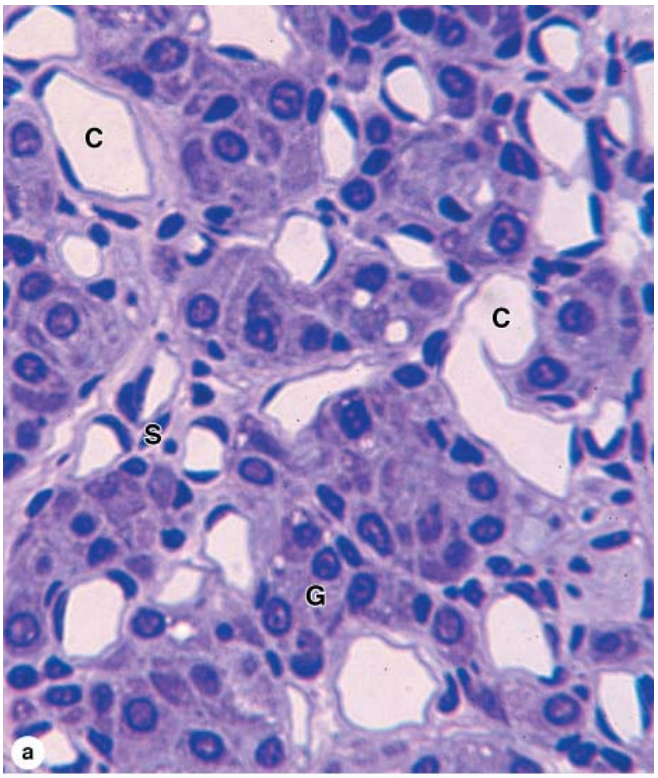
With distance from the heart arteries gradually have relatively less elastin and more smooth muscle in their walls. Most arteries large enough to have names are of this muscular type. A transverse section through a muscular (medium caliber) artery shows multiple layers of smooth muscle in the media (M). The smooth muscle layers are more prominent than the elastic lamellae and fibers with which they intersperse. Vasa vasorum are seen in the tunica adventitia. X200. PT.

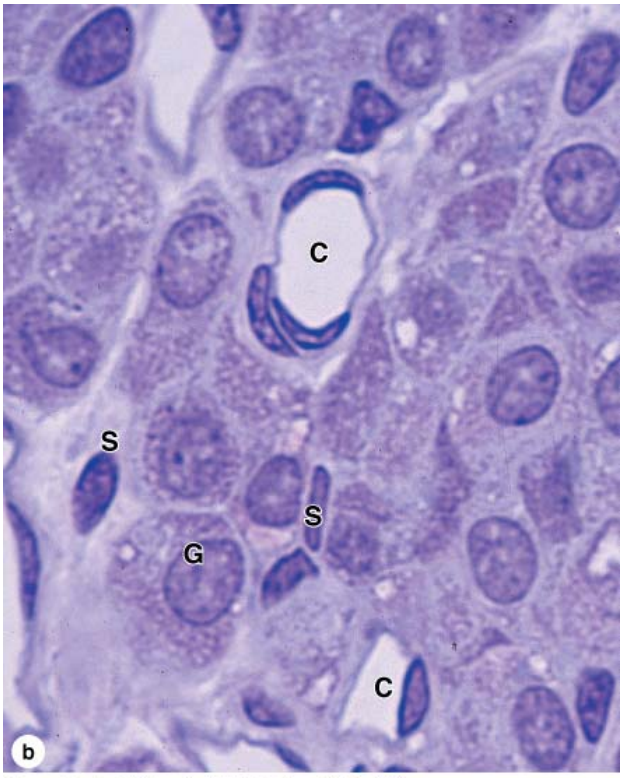
Arterial Sensory Structures

Carotid sinuses are slight dilatations of the internal carotid arteries which contain **baroreceptors** detecting increases in blood pressure. The tunica media of each carotid sinus is thinner, allowing greater distension when blood pressure rises, and the intima and adventitia are rich in sensory nerve endings from cranial nerve IX, the glossopharyngeal nerve. The afferent nerve impulses are processed in the brain to trigger adjustments in vasoconstriction that return pressure to normal. Similar baroreceptors occur in aortic arches and other large arteries.

The **carotid bodies** are small, ganglia-like structures (paraganglia) near the bifurcation of the common carotid arteries that contain **chemoreceptors** sensitive to blood CO_2 and O_2 concentrations. A network of sinusoidal capillaries is intermixed with **glomus (type I) cells** containing numerous dense-core vesicles with dopamine, serotonin, and adrenaline (Figure 11–12). Dendritic fibers of cranial nerve IX, the glossopharyngeal nerve, synapse with the glomus cells. The sensory nerve is activated by neurotransmitter release from glomus cells in response to changes in the sinusoidal blood: increased CO_2, decreased O_2, or increased H^+ levels. **Aortic bodies** located on the arch of the aorta are similar in structure and function to carotid bodies.

Figure 11–12.





Glomus body.

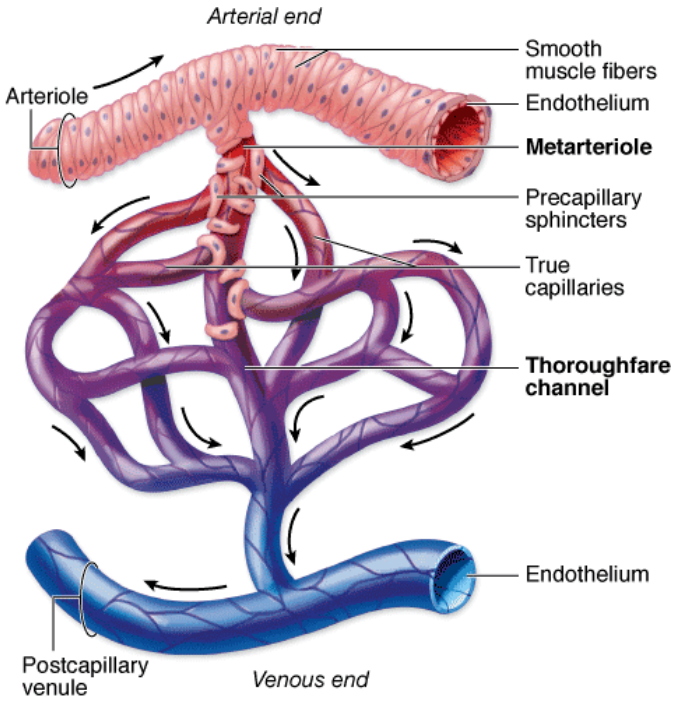
(a) and **(b):** Specialized regions in the walls of specific arteries contain cells that act of chemoreceptors providing information to the brain regarding blood chemistry. The glomus bodies are two small (0.5–5 mm diameter) ganglion-like structures found near the bifurcations of the common carotid arteries. They contain many large sinusoidal capillaries (C) intermingled with clusters of large glomus cells (G) with round nuclei and cytoplasm filled with vesicles of various neurotransmitters that are clearly seen in (b). Supportive sheath cells (S) with elongated nuclei are associated with the groups of glomus cells. Glomus cells form synaptic connections with dendritic fibers of the glossopharyngeal nerve. Changes in the CO_2, O_2 and H^+ concentrations in the sinusoidal blood are detected by the chemoreceptive glomus cells, which then release neurotransmitter that activates the sensory nerve to relay this information to the brain. a: X200; b: X400. Both PT.

Arterioles

Muscular arteries branch repeatedly into smaller and smaller arteries, until reaching a size with only two or three medial layers of muscle. The smallest arteries branch as **arterioles**, which have one or two smooth muscle layers and indicate the beginning of an organ's **microvasculature** (Figure 11–13) where exchanges between blood and tissue fluid occur. Arterioles are generally less than 0.5 mm in diameter, with lumens approximately as wide as the wall is thick

(Figures 11–2 and 11–14). The subendothelial layer is very thin, the elastic laminae are absent and the media is generally composed of circularly arranged smooth muscle cells. In both small arteries and arterioles, the tunica adventitia is very thin and inconspicuous.

Figure 11–13.

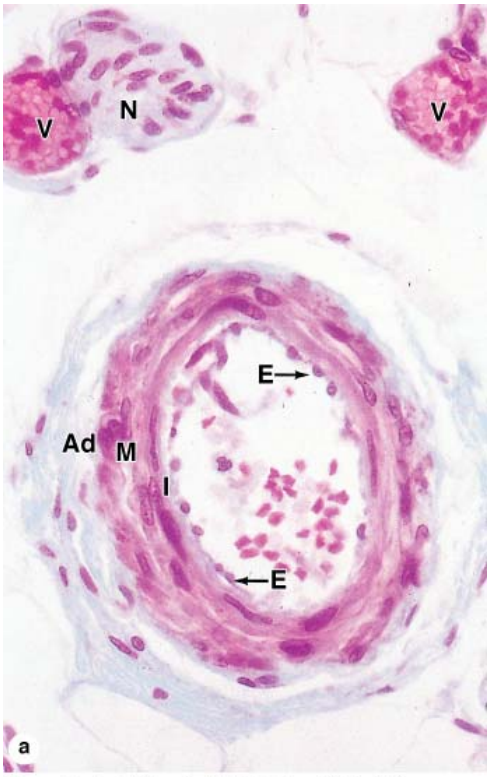


Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

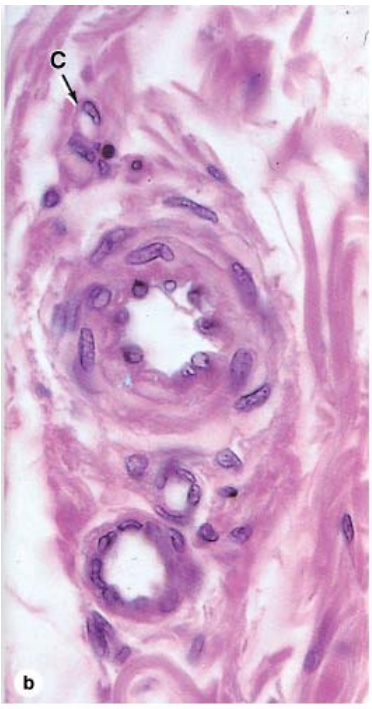
Structure of microvasculature.

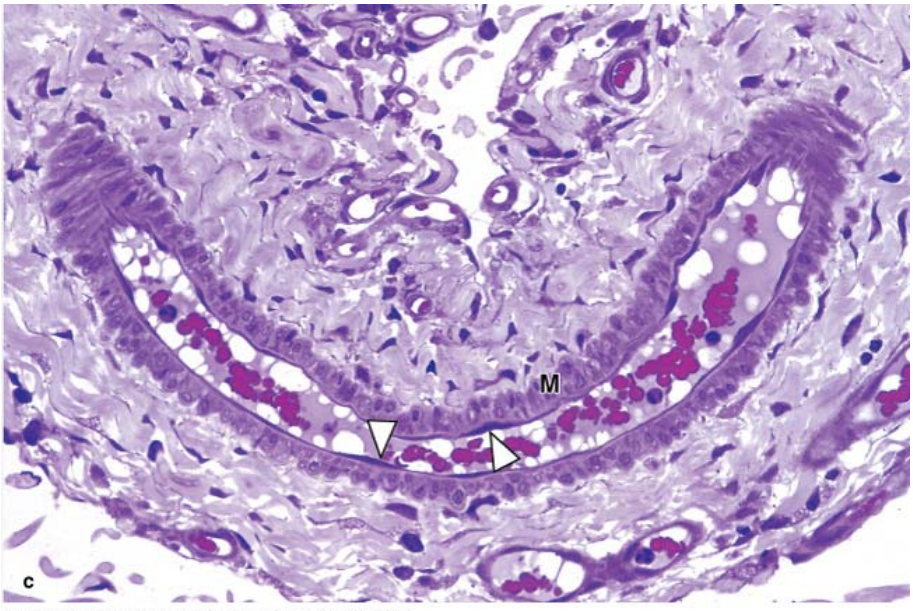
Microvasculature arises to meet nutritional needs of one organ or parts of one organ and consists of blood vessels of less than 0.5 mm diameter. Microvessels include **arterioles** and their smaller branches called **metarterioles** in which the layer of smooth muscle cells is dispersed as bands of cells that act as **precapillary sphincters**. The distal portion of the metarteriole, sometimes called a **thoroughfare channel**, lacks any smooth muscle cells. The wall of capillaries lacks smooth muscle cells altogether. The precapillary sphincters allow blood to enter the bed of capillaries in a pulsatile manner for maximally efficient exchange of nutrients, wastes, O_2, and CO_2 across the capillary wall. Capillaries and the metarteriole converge as **postcapillary venules**, the last component of the microvasculature. Blood enters microvasculature well-oxygenated and leaves poorly oxygenated.

Figure 11–14.



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com





Arterioles.

(a): Arterioles are microvessels with a tunica intima (I) that consists only of the endothelium (E), in which the cells may have rounded nuclei. They have tunica media (M) with only one or two layers of smooth muscle, and usually thin, inconspicuous adventitia (Ad). X350. Masson trichrome. **(b):** Three arterioles of various sizes are shown here and a capillary. X400. H&E. **(c):** A large mesenteric arteriole is cut obliquely and longitudinally and clearly shows the endothelial cells (arrow heads) and one or two layers of smooth muscle cells (M) cut transversely. Adventitia merges imperceptibly with neighboring connective tissue. X300. PT.

In certain tissues and organs **arteriovenous shunts** or **anastomoses** regulate blood flow by allowing direct communication between arterioles and venules. Arterioles in such shunts have a relatively thick, capsule-like adventitia and a thick smooth muscle layer. Arteriovenous shunts are richly innervated by the sympathetic and parasympathetic nervous systems. 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 venule instead of circulating in the capillaries. Their luminal diameters vary with the physiologic condition of the organ. Changes in diameter of these vessels regulate blood pressure, blood flow, temperature and heat conservation in affected areas.

Capillaries

Capillaries 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 5 to 10 μm and their individual length is usually not more than 50 μm. Altogether capillaries comprise over 90% of all blood vessels in the body, with a total length of nearly 96,000 km (60,000 miles). 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, but in capillaries blood flows only 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.

Endothelial cells are functionally diverse according to the vessel they line. The capillaries are often referred to as exchange vessels, since it is at these sites that O_2, CO_2, 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 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 between endothelial cells of sinusoidal capillaries, and the pinocytotic vesicles are other pathways for the passage of large molecules.

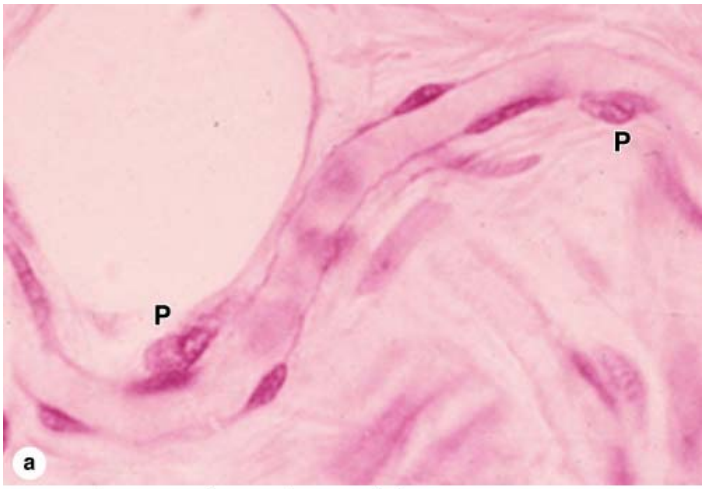
In general, endothelial cells are polygonal and elongated in the direction of blood flow (Figure 11–7). The nucleus causes that part of the cell to bulge into the capillary lumen. The cytoplasm contains a small Golgi appraratus, mitochondria, free ribosomes, and sparse cisternae of RER. Junctions of the tight zonula occludentes type are present between most endothelial cells, conferring the wall with variable permeability to macromolecules that plays significant roles in both normal and pathologic conditions.

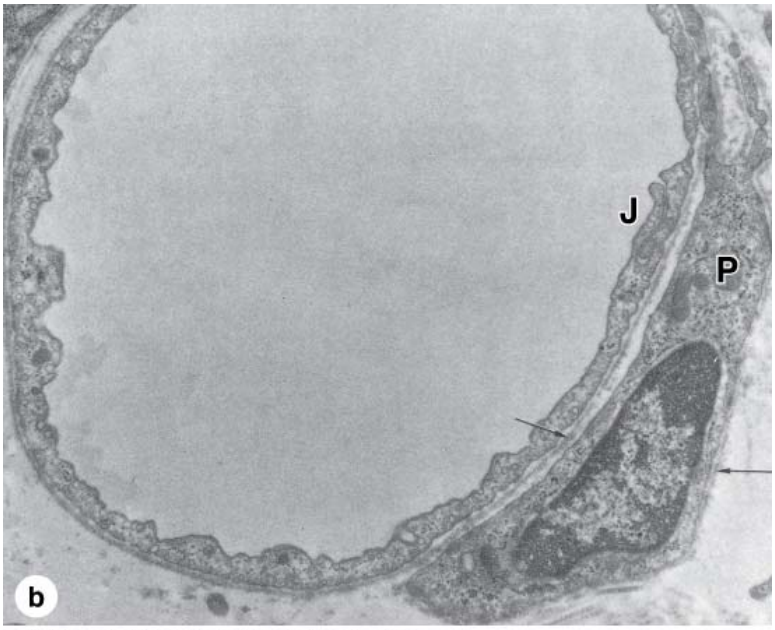
MEDICAL APPLICATION

Junctions between endothelial cells of postcapillary venules are the loosest of the microvasculature. 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 partly surrounding the endothelial layer. These cells are called **pericytes** (Gr. *peri,* around, + *kytos,* cell). They are enclosed in their own basal lamina, which may fuse with that of the endothelial cells (Figure 11–15). Well-developed networks of myosin, actin, and tropomyosin in pericytes indicate these cells' primary contractile function. After tissue injuries, pericytes proliferate and differentiate to form both tunica media of new blood vessels and cells with various other functions in re-establishing the microvasculature and its ECM.

Figure 11–15.





Capillary with pericyte.

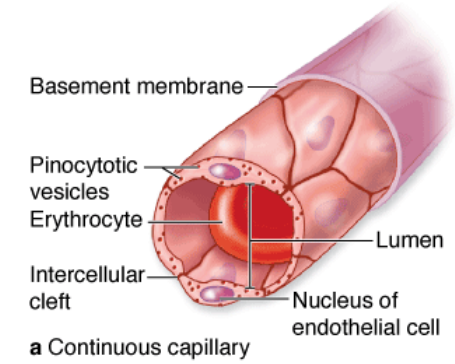
Capillaries consist only of an endothelium rolled as a tube, across which molecular exchange occurs between blood and tissue fluid. **(a):** Capillaries are normally associated with perivascular contractile cells called pericytes (P) which have a variety of functions. The more flattened nuclei belong to endothelial cells. X400. H&E. **(b):** TEM of a capillary cut transversely, showing the thin wall of one endothelial cell covered by an external lamina (arrows). Endothelial cells have numerous transcytotic vesicles and their edges overlap and are bound tightly together with occluding junctions (J). One pericyte (P) is shown, surrounded by its own external

lamina. Pericytes can proliferate to form smooth muscle cells when a capillary is transformed into an arteriole or venule after tissue injury and repair. X13,000. (Figure 11–15b, reproduced, with permission, from Kelly DE, Wood RL, Enders AC (eds): *Bailey's Textbook of Microscopic Anatomy,* 18th ed. Williams & Wilkins, 1984. Reproduced, with permission, from Kelly D. E., Wood R.L., and Enders AC (eds): Bailey's Textbook of Microscopic Anatomy, 18th ed. Williams & Wilkins, 1984.)

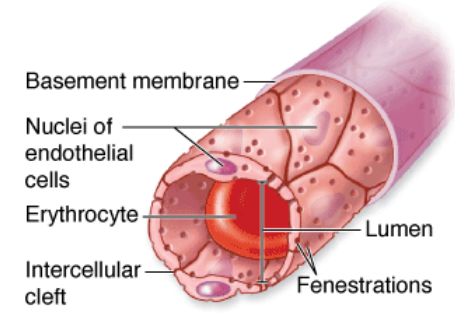
Capillaries have structural variations which permit different levels of metabolic exchange between blood and surrounding tissue. They can be grouped into three types, depending on the continuity of the endothelial cells and the external lamina (Figure 11–16).

1. The **continuous,** or tight, **capillary** (Figure 11–17) allows regulated exchange of material and is characterized by the distinct continuity of the endothelial cells in its wall. This is the most common type of capillary and is found in all kinds 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 endothelial cell surfaces. Vesicles also appear as isolated vesicles in the cytoplasm of these cells and are responsible for transcytosis of macromolecules in both directions across the endothelial cytoplasm.
2. The **fenestrated capillary** allows more extensive molecular exchange across the endothelium and is characterized by the presence of small circular fenestrae (L, *fenestra*, perforation) through the very thin squamous endothelial cells. Each fenestra is usually covered by a very thin diaphragm containing heparan proteoglycans but no lipid bilayer (Figure 11–18). The basal lamina of the fenestrated capillaries is continuous, covering the fenestrae. Fenestrated capillaries are found in tissues where rapid interchange of substances occurs between the tissues and the blood, as in the kidney, the intestine, the choroid plexus and the endocrine glands. Macromolecules experimentally injected into the bloodstream can cross the capillary wall through the fenestrae to enter tissue spaces.
3. The **sinusoid** or **discontinuous capillary** permits maximal exchange of macromolecules as well as cells between tissues and blood and has the following characteristics: endothelial cells have large fenestrae without diaphragms; the cells form a discontinuous layer and are separated from one another by wide spaces; the basal lamina is also discontinuous. Sinusoids are irregularly shaped and have diameters as large as 30–40 μm, much greater than those of other capillaries, properties which further slow blood flow at this site. Sinusoidal capillaries are found in the liver, spleen, some endocrine organs, and bone marrow (Figure 11–19).

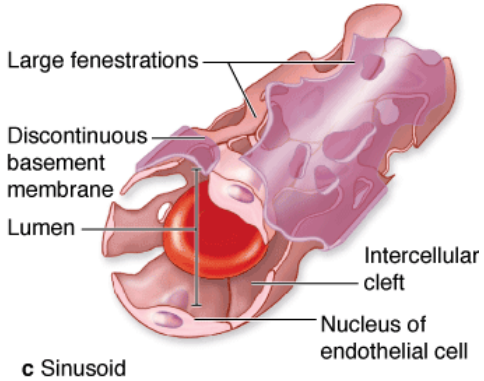
Figure 11–16.



a Continuous capillary



b Fenestrated capillary

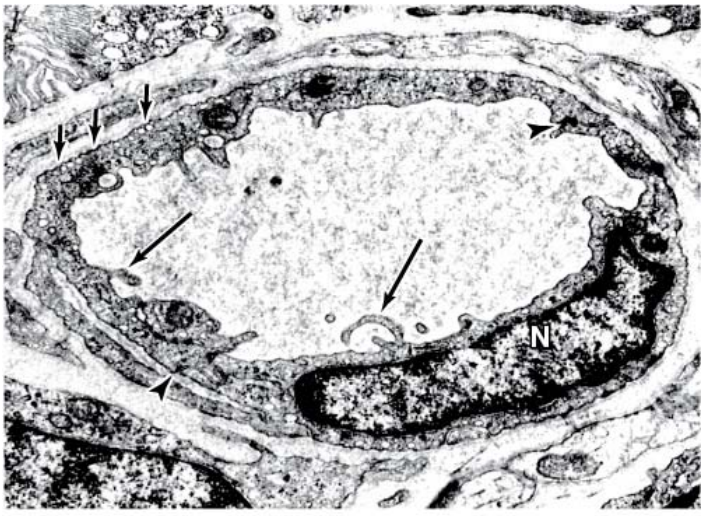


c Sinusoid

Types of capillaries.

The vessels between arterioles and venules can be any of three types. **(a): Continuous capillaries**, the most common type, have tight, occluding junctions sealing the intercellular clefts between all the endothelial cells to produce minimal fluid leakage. All molecules exchanged across the endothelium must cross the cells by diffusion or transcytosis. **(b): Fenestrated capillaries** also have tight junctions, but perforations (fenestrae) through the endothelial cells allow greater exchange across the endothelium. The external lamina is continuous in both these capillary types. Fenestrated capillaries are found in organs where molecular exchange with the blood is important, such as endocrine organs, intestinal walls, and choroid plexus. **(c): Sinusoids** usually have a wider diameter than the other types of capillaries and have discontinuities between the endothelial cells, large fenestrae through the cells, and a partial, discontinuous basement membrane. Sinusoids are found in organs where exchange of macromolecules and cells occurs readily between tissue and blood, such as in bone marrow, liver, and spleen.

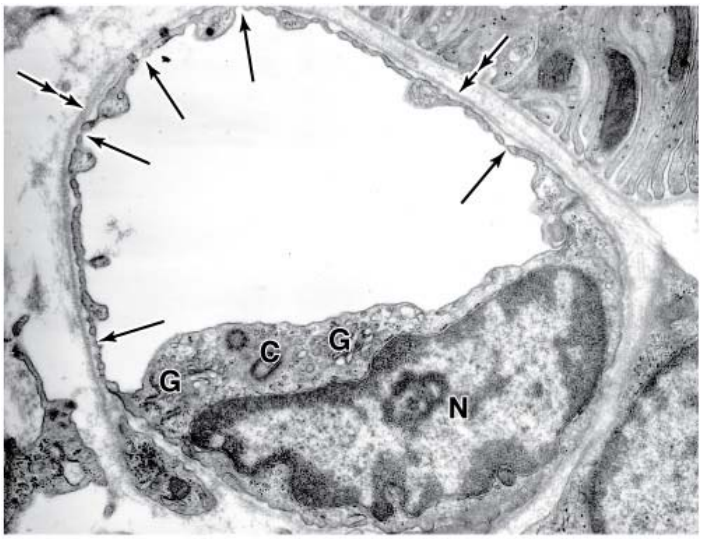
Figure 11–17.



Continuous capillary.

Continuous capillaries exert the tightest control over what molecules leave across their walls. TEM shows a continuous capillary in transverse section. A nucleus (N) is prominent, but tight or occluding junctions along overlapping folds between two cells can also be seen (arrowheads). Numerous transcytotic vesicles are evident (small arrows). The long arrows show extensions of broad cytoplasmic sheets suggesting phagocytosis, which is consistent with the presence of vacuoles and electron-dense lysosomes. All material that crosses continuous capillary endothelium must pass *through* the cells, usually by diffusion or transcytosis. X10,000.

Figure 11–18.



Fenestrated capillary.

Fenestrated capillaries are specialized for uptake of molecules such as hormones in endocrine glands or for outflow of molecules such as in the kidney's filtration system. TEM of a transversely sectioned fenestrated capillary in the peritubular region of the kidney shows many typical fenestrae closed by diaphragms (arrows), with a continuous external lamina on the outer surface of the endothelial cell (double arrows). The diaphragms contain heparan sulfate proteoglycans, but their functional role is poorly understood at the molecular level. In this cell the Golgi apparatus (G), nucleus (N), and centrioles (C) can be seen. Fenestrated capillaries allow a freer exchange of molecules than continuous capillaries and are found in the intestinal wall, kidneys and endocrine glands. X10,000. (With permission, from Johannes Rhodin, Department of Cell Biology, New York University School of Medicine.)

Figure 11–19.

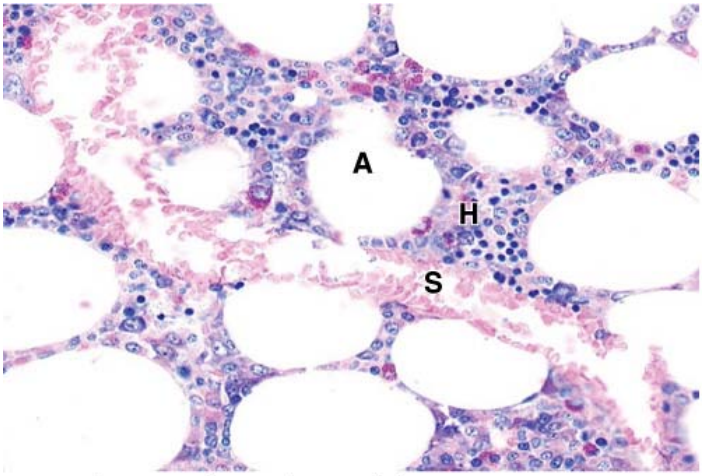


Figure 11-19. Sinusoidal capillary.

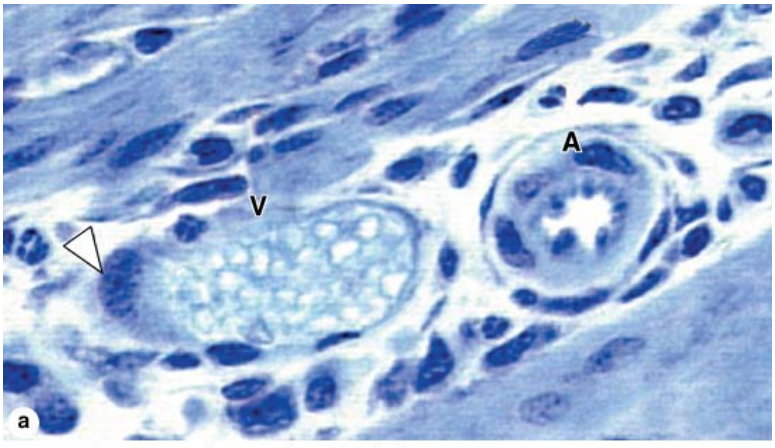
Sinusoidal capillaries or sinusoids generally have much greater diameters than most capillaries and are specialized not only for maximal molecular exchange between blood and surrounding tissue, but also for easy movement of blood cells across the endothelium. The sinusoid (S) shown here is in bone marrow and is surrounded by tissue containing adipocytes (A) and masses of hematopoietic cells (H). The endothelium is very thin and cell nuclei are more difficult to find than in smaller capillaries. Ultrastructurally sinusoidal capillaries are seen to have large fenestrae through the cells and large discontinuities between the cells and through the basal lamina. X200. H&E.

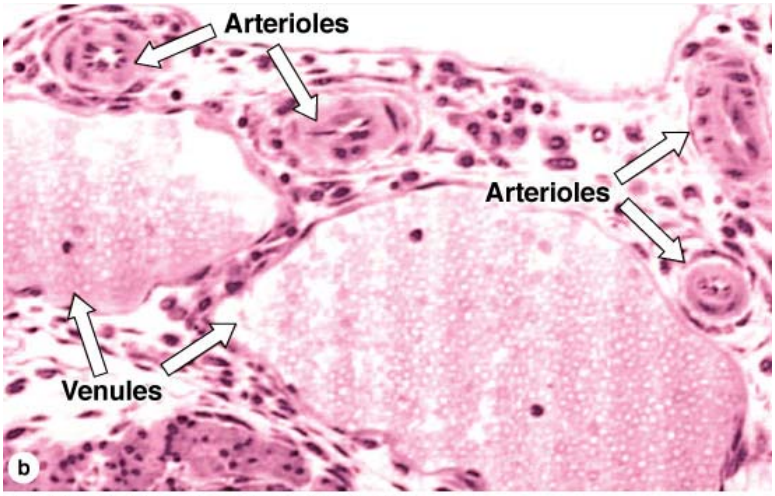
Capillaries anastomose freely, forming a rich network or bed that interconnects the arterioles and venules (Figure 11–13). The arterioles may first branch into smaller vessels with a sparse layer of smooth muscle called **metarterioles**, which branch further into capillaries. Metarterioles often form a preferential channel for blood flow though a microcirculatory bed and help to regulate the circulation in capillaries. 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 of tissues with low metabolic rates, such as smooth muscle and dense connective tissue.

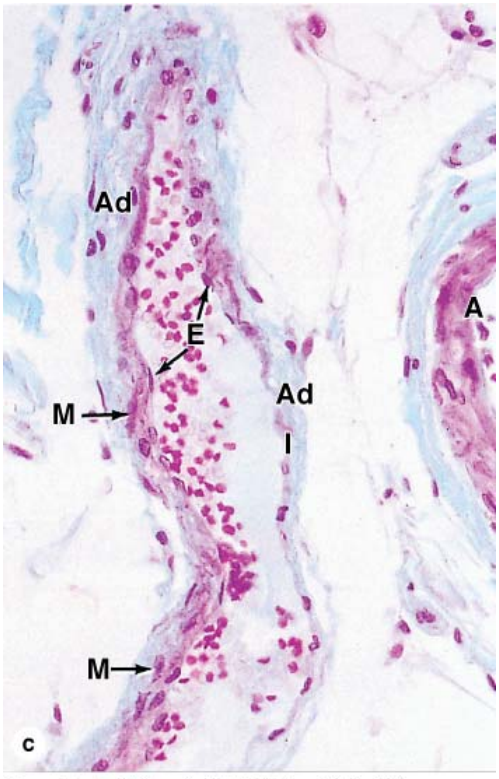
Venules

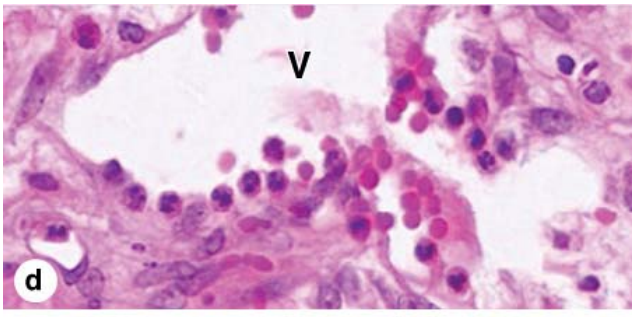
The transition from capillaries to venules occurs gradually. The immediate **postcapillary venules** are similar structurally to capillaries, with pericytes, but range in diameter from 15 to 20 μm. Postcapillary venules participate in the exchanges between the blood and the tissues and, as described in Chapter 12, are the primary site at which white blood cells leave the circulation at sites of infection or tissue damage. These venules converge into larger **collecting venules** which have more contractile cells. With greater size the venules become surrounded by recognizable tunica media with two or three smooth muscle layers and are called **muscular venules**. A characteristic feature of all venules is the large diameter of the lumen compared to the overall thinness of the wall (Figure 11–20).

Figure 11–20









Venules.

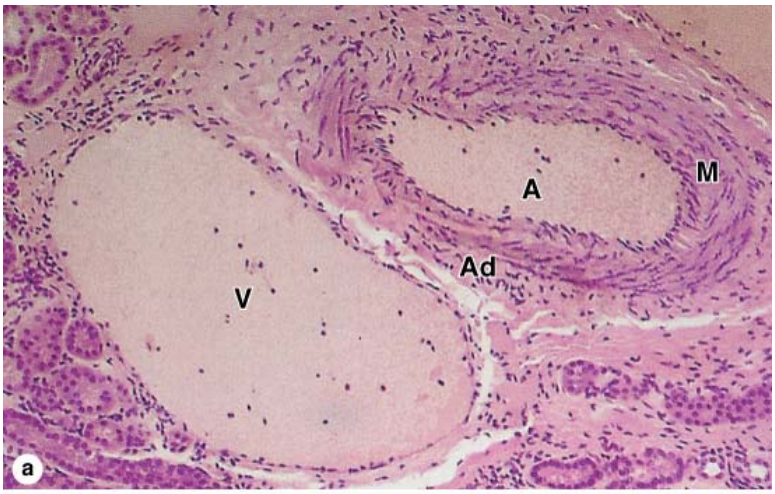
A series of increasingly larger and more organized venules lie between capillaries and veins. **(a): Postcapillary venules** resemble large capillaries, having only an endothelium with occasional pericytes (arrowhead). Their lumens and overall diameters are greater than those of nearby arterioles. X400. TB. **(b):** Large **collecting venules** have much greater diameters than arterioles but the wall is still very thin, consisting of an endothelium with more numerous pericytes or smooth muscle cells. X200. TB. **(c): Muscular venule** has a better defined tunica media, with as many as three layers of smooth muscle (M) in some areas, a very thin intima (I) of endothelial cells (E), and a more distinct tunica adventitia (Ad). Part of an arteriole (A) is included for comparison. Venules are the site in the vasculature where white blood cells leave the circulation to become functional in the interstitial space of surrounding tissues when such tissues are inflamed or infected. Such conditions cause endothelial cells of venules to loosen intercellular junctions and express new protein receptors on their luminal surface. Surface proteins on passing leukocytes bind these receptors, causing the cells to stick to the endothelial cells in a process termed margination. This adhesion is quickly followed by emigration from the venule between endothelial cells. X200. Masson trichrome. **(d):** Venule (V) from an infected small intestine shows several leukocytes adhering to and

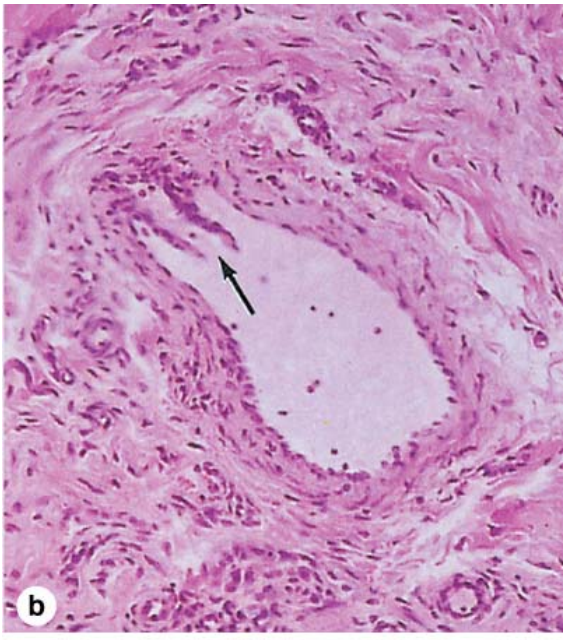
migrating across the endothelium. X200. H&E. (Figure 11–20a, with permission, from Telma M.T. Zorn, Department of Cell and Developmental Biology, University of São Paulo, Brazil.)

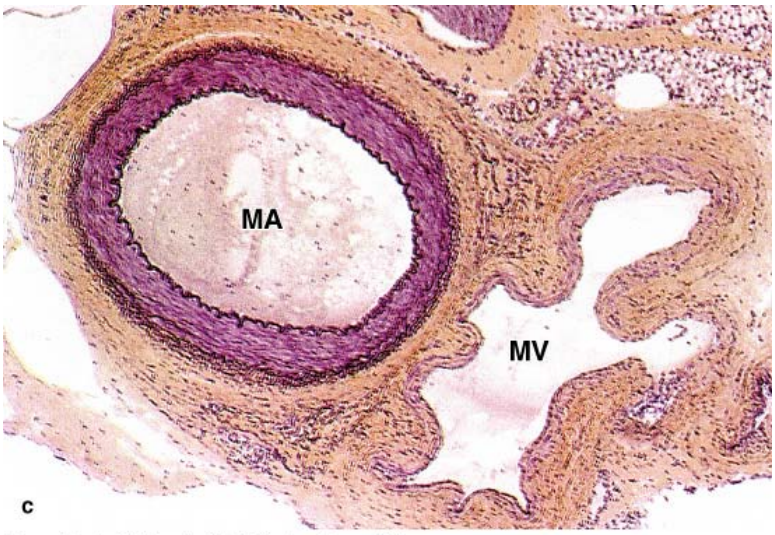
Veins

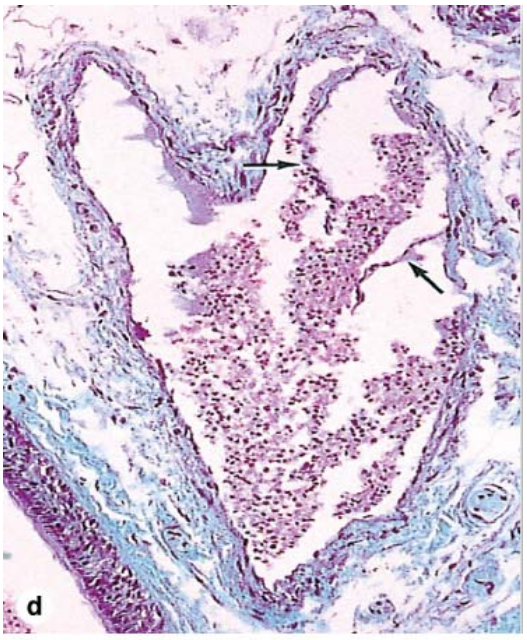
Blood entering veins is under very low pressure and moves toward the heart by contraction of the tunica media and external compressions from surrounding muscles and other organs. Valves project from the tunica intima to prevent back-flow of blood. Most veins are **small** or **medium veins** (Figure 11–21), with diameters less than one centimeter. Such veins are usually located in parallel with corresponding muscular arteries. The intima usually has a thin subendothelial layer and 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.

Figure 11–21.









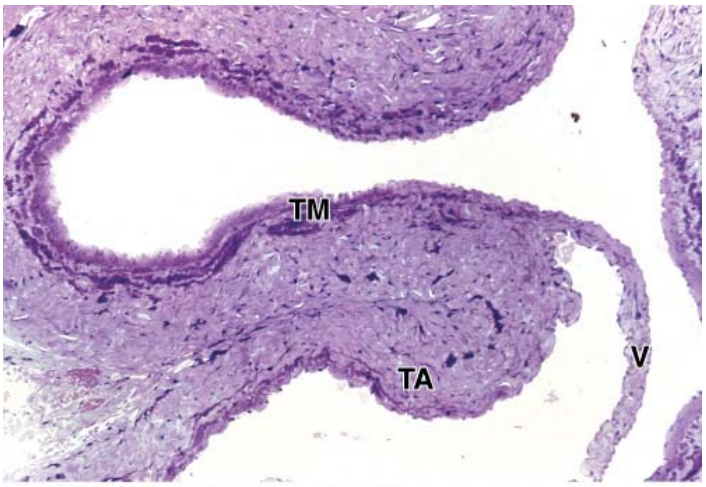
Veins.

Veins usually travel near arteries and are classified as small, medium, or large based on size and development of the tunics. **(a):** Micrograph of small vein (V) shows a relatively large lumen compared to the small muscular artery (A) with its thick media (M) and adventitia (Ad). The wall of a small vein is very thin, containing only two or three layers of smooth muscle. X200. H&E. **(b):** Micrograph of a convergence between two small veins showing valves (arrow). Valves are thin folds of tunica intima projecting well into the lumen which act to prevent backflow of blood. X200. H&E. **(c):** Micrograph of a medium vein (MV) showing a thicker wall, but still less prominent than that of the accompanying muscular artery (MA). Both the media and adventitia are better developed, but the wall is often folded around the relatively large lumen. X100. H&E. **(d):** Micrograph of a medium vein containing blood and showing valve folds (arrows). X200. Masson trichrome.

The big venous trunks, paired with elastic arteries close to the heart, are **large veins** (Figure 11–8). Large veins have a well-developed tunica intima, but the tunica media is relatively thin, with few layers of smooth muscle and abundant connective tissue. The adventitial layer is thick in large veins and frequently contains longitudinal bundles of smooth muscle. Both the media and adventitia contain elastic fibers, but elastic laminae like those of arteries are not present.

Most veins have valves, but these are most prominent in large veins. Valves consist of paired semilunar folds of the tunica intima projecting across part of the lumen (Figures 11–21 and 11–22). They are rich in elastic fibers and are lined on both sides by endothelium. The valves, which are especially numerous in veins of the legs, help keep the flow of venous blood directed toward the heart.

Figure 11–22.



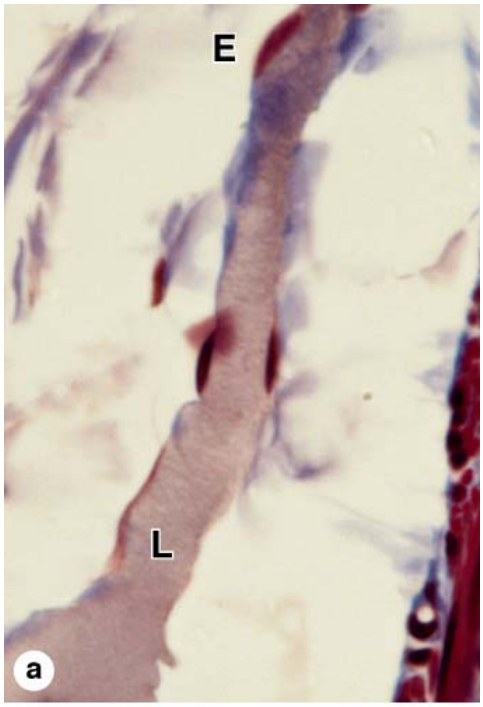
Wall of large vein with valve.

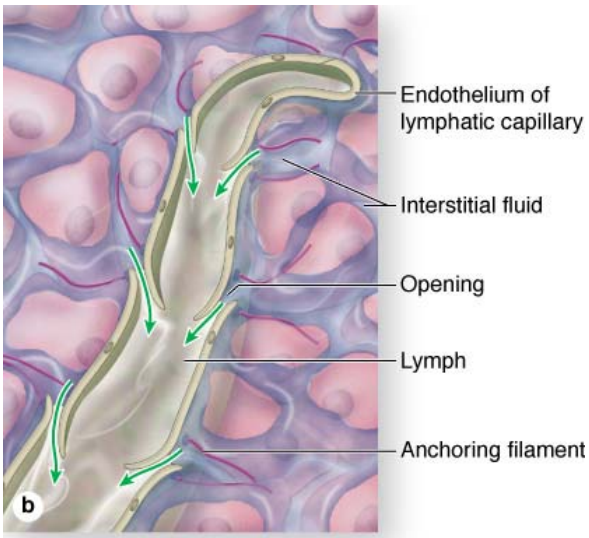
Large veins have a muscular tunica media (TM) that is very thin compared to the tunica adventitia (TA) composed of dense irregular connective tissue. The wall is often folded as shown here. The tunica intima here projects into the lumen as a valve (V), composed of the subendothelial connective tissue with endothelium on both sides. X100, PT.

LYMPHATIC VASCULAR SYSTEM

In addition to blood vessels, the body has a system of thin-walled endothelial channels that collect excess interstitial fluid from the tissue spaces and return it to the blood. This fluid is called lymph; unlike the blood, it flows 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 bundles of anchoring filaments of the elastic fiber system which also bind the vessels firmly to the surrounding connective tissue (Figure 11–23).

Figure 11–23.





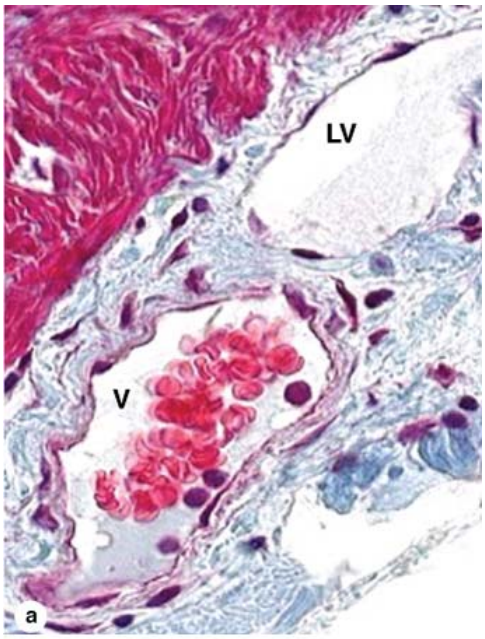
Lymphatic capillary.

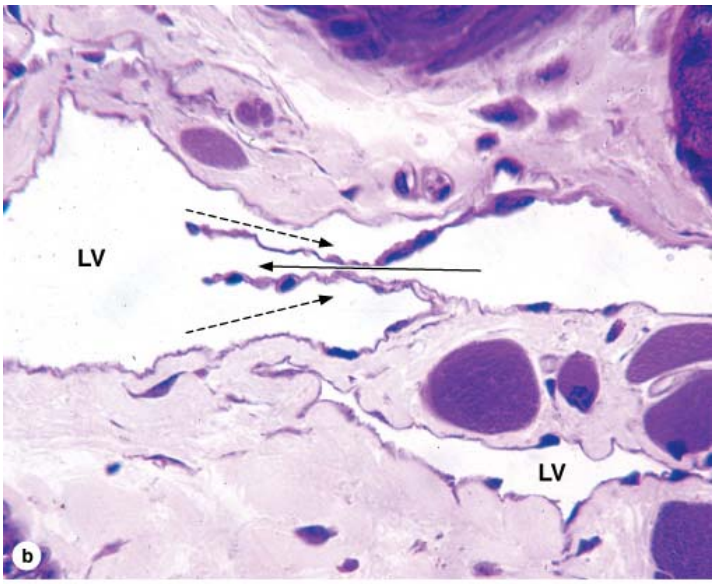
Lymphatic capillaries drain interstitial fluid produced when the plasma forced from the microvasculature by hydrostatic pressure does not all return to blood by the action of osmotic pressure. **(a):** Micrograph showing a lymphatic capillary filled with this fluid called lymph (L). Lymphatics are blind-ended vessels with a wall of very thin endothelial cells (E) and are quite variable in diameter (10-50 μm). Lymph is rich in proteins and other material and often stains somewhat better than the surrounding ground substance, as seen here. X200. Mallory trichrome. **(b):** Diagram indicating details of lymphatics, including the openings between the endothelial cells. The openings are held in place by anchoring filaments containing elastin and are covered by flaps of endothelium. Interstitial fluid enters primarily via these openings and the endothelial folds prevent backflow of lymph into tissue spaces. Lymphatic endothelial cells are typically larger than those of blood vessels.

The thin lymphatic capillaries converge into larger lymphatic vessels. Interposed in the path of these lymphatics are lymph nodes, whose morphologic characteristics and functions are discussed in Chapter 14. With rare exceptions, such as the CNS and the bone marrow, lymphatic are found in almost all organs.

The larger lymphatics have a structure similar to that of veins except that they have thinner walls and lack a clear-cut separation between tunics. They also have more numerous internal valves (Figure 11–24). The lymphatic vessels are often dilated and assume a nodular, or beaded, appearance between the valves. As in veins, lymphatic circulation is aided by external forces (eg, contraction of surrounding skeletal muscle) and unidirectional lymph flow is mainly a result of the many valves. Contraction of smooth muscle in the walls of larger lymphatic vessels also helps to propel lymph toward the heart.

Figure 11–24.





Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Lymphatic vessels and valve.

Lymphatic vessels are formed by the merger of lymphatic capillaries, but their walls remain extremely thin. **(a):** Cross-section showing a lymphatic vessel (LV) near a venule (V), whose wall is thick by comparison. Lymphatic vessels normally do not contain red blood cells, which provides another characteristic distinguishing them from venules. X200. Mallory trichrome. **(b):** Lymphatic vessel (LV) in muscle is cut longitudinally showing 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 lymphatic vessel is a lymphatic capillary with a wall consisting only of endothelium. X200. PT.

Lymphatic vessels ultimately end up as two large trunks: the **thoracic duct** and the **right lymphatic duct**, which respectively empty lymph 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. The structure of these lymphatic ducts is similar to that of large 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, but contains vasa vasorum and a neural network.

Besides gathering interstitial fluid as lymph and returning it to the blood, the lymphatic system of vessels is a major distributor of lymphocytes, antibodies, and other immune components which it picks up at lymph nodes and other lymphoid tissues.