CHAPTER

# 11 The Circulatory System



The circulatory system pumps and directs blood cells and substances carried in blood to all tissues of the body. It includes both the blood and lymphatic vascular systems, and in an adult the total length of its vessels is estimated at between 100,000 and 150,000 km. The **blood vascular system**, or **cardiovascular system** (Figure 11–1), consists of the following structures:

- The **heart** propels blood through the system.
- **Arteries**, a series of vessels efferent from the heart that become smaller as they branch into the various organs, carry blood to the tissues.
- **Capillaries**, the smallest vessels, are the sites of $O_2$, $CO_2$, nutrient, and waste product exchange between blood and tissues. Together with the smallest arterial and venous branches carrying blood to and from them, capillaries in almost every organ form a complex network of thin, anastomosing tubules called the **microvasculature** or microvascular bed.
- **Veins** result from the convergence of venules into a system of larger channels which continue enlarging as they approach the heart, toward which they carry the blood to be pumped again.

As shown in Figure 11–1, two major divisions of arteries, microvasculature, and veins make up the **pulmonary circulation**, where blood is oxygenated in the lungs, and the **systemic circulation**, where blood brings nutrients and removes wastes in tissues throughout the body.

The **lymphatic vascular system**, introduced with the discussion of interstitial fluid in Chapter 5, begins with the **lymphatic capillaries**, which are thin-walled, closed-ended tubules carrying lymph which merge to form vessels of steadily increasing size. The largest lymph vessels connect with the blood vascular system and empty into the large veins near the heart. This returns fluid from tissue spaces all over the body to the blood.

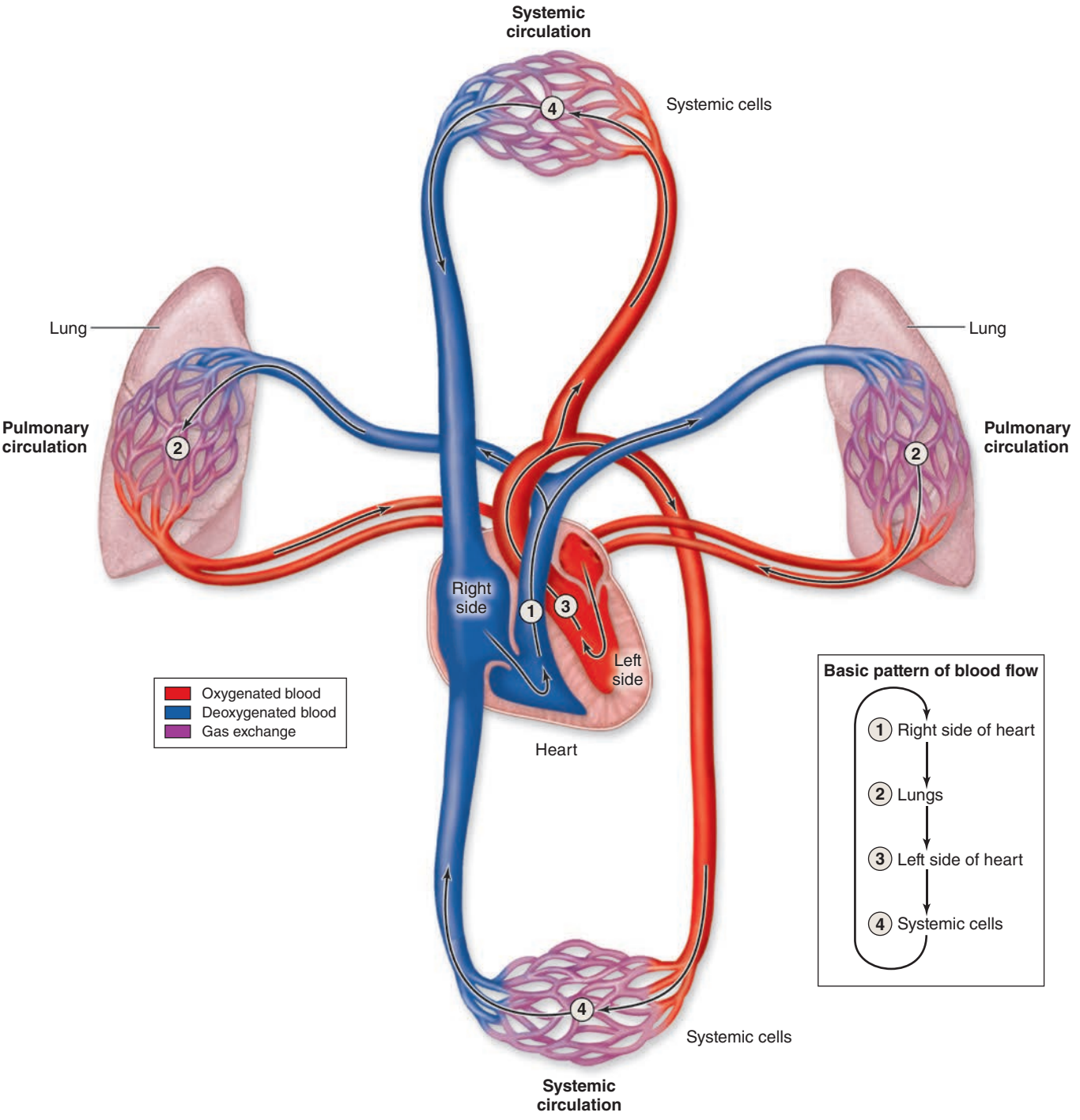
The internal surface of all components of the blood and lymphatic systems is lined by a simple squamous epithelium called **endothelium**. As the interface between blood and the organs, cardiovascular endothelial cells have crucial physiologic and medical importance. Not only must endothelial cells maintain a selectively permeable, antithrombogenic (inhibitory to clot formation) barrier, they also determine when and where white blood cells leave the circulation for the interstitial space of tissues and secrete a variety of paracrine factors for vessel dilation, constriction, and growth of adjacent cells.

## HEART

Cardiac muscle in the four chambers of the **heart** wall contracts rhythmically, pumping the blood through the circulatory system (Figure 11–2). The right and left **ventricles** propel blood to the pulmonary and systemic circulations, 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: the internal endocardium, the middle myocardium, and the external epicardium.

- The **endocardium** consists of the lining endothelium, its supporting layer of fibroelastic connective tissue with scattered fibers of smooth muscle, and a deeper layer of connective tissue (continuous with that of the myocardium and often called the **subendocardial layer**) surrounding variable numbers of modified cardiac muscle fibers which comprise the heart's impulse conducting system (Figure 11–3).
- The **myocardium** consists mainly of typically contractile cardiac muscle fibers arranged spirally around each heart chamber. Because strong force is required to

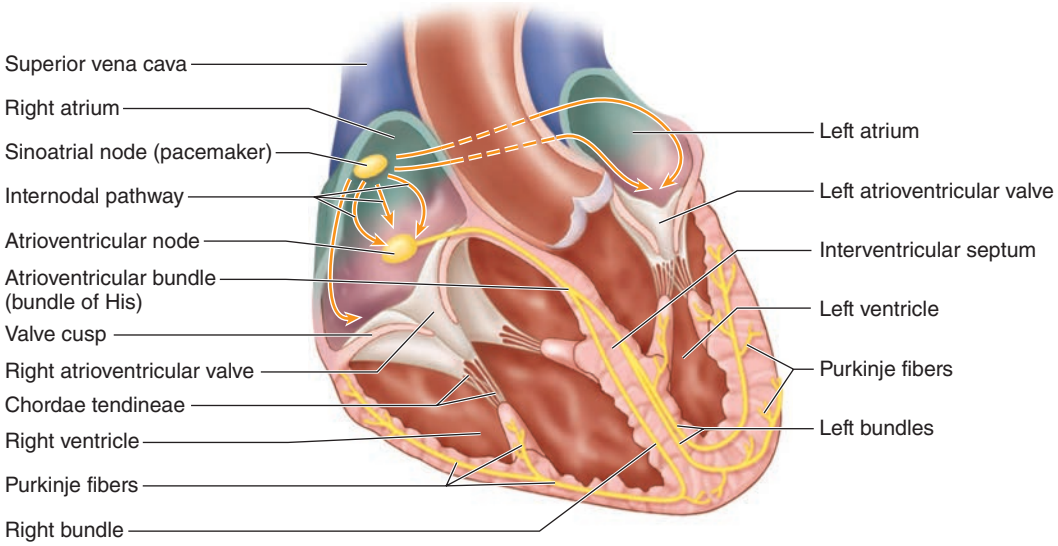
## FIGURE 11–1 Diagram of the cardiovascular system.




The system consisting of the **heart, arteries, veins**, and **microvascular beds** is organized as the **pulmonary circulation** and the **systemic circulation**. In the pulmonary circulation the right side of the heart pumps blood through pulmonary vessels, through the lungs for oxygenation, and back to the left side of the heart. The larger systemic circulation pumps blood from the left side of the heart through vessels supplying either the head and arms or the lower body, and back to the right side of the heart.

When the body is at rest, approximately 70% of the blood moves through the systemic circulation, about 18% through the pulmonary circulation, and 12% through the heart.

## FIGURE 11–2 Overview of the heart.




As seen in the diagram, the human heart has two **atria** and two **ventricles**. The myocardium of the ventricular walls is thicker than that of the atria. The **valves** are basically flaps of connective tissue anchored in the heart's dense connective tissue, or **cardiac skeleton**, concentrated in the regions shown in white. This fibrous tissue includes the chordae tendineae, cords which extend from the cusps of both atrioventricular valves and attach to papillary muscles, preventing the valves from turning inside-out during ventricular contraction. Valves and cords are covered by the nonthrombogenic endothelium.

Shown in yellow are parts of the cardiac **conducting system**, which initiates the electrical impulse for contraction (heartbeat) and spreads it through the ventricular myocardium. Both the **sinoatrial (SA) node (pacemaker)**, in the right atrial wall, 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 a specialized bundle of cardiac muscle fibers, the **AV bundle** (of His), which gives rise to right and left bundle branches that run along the interventricular septum to the apex of the heart. At the apex the bundle branches subdivide further as **conducting (Purkinje) fibers** which extend into myocardium of the ventricles.

pump blood through the systemic and pulmonary circulations, the myocardium is much thicker in the walls of the ventricles, particularly the left, than in the atrial walls (Figure 11–3).

- The **epicardium** is a simple squamous **mesothelium** supported by a layer of loose connective tissue containing blood vessels and nerves (Figure 11–4). The epicardium corresponds to the **visceral layer of the pericardium**, the membrane surrounding the heart. Where the large vessels enter and leave the heart, the epicardium is reflected back as the **parietal layer** lining the pericardium. During heart movements, underlying structures are cushioned by deposits of adipose tissue in the epicardium and friction within the pericardium is prevented by lubricant fluid produced by both layers of serous mesothelial cells.

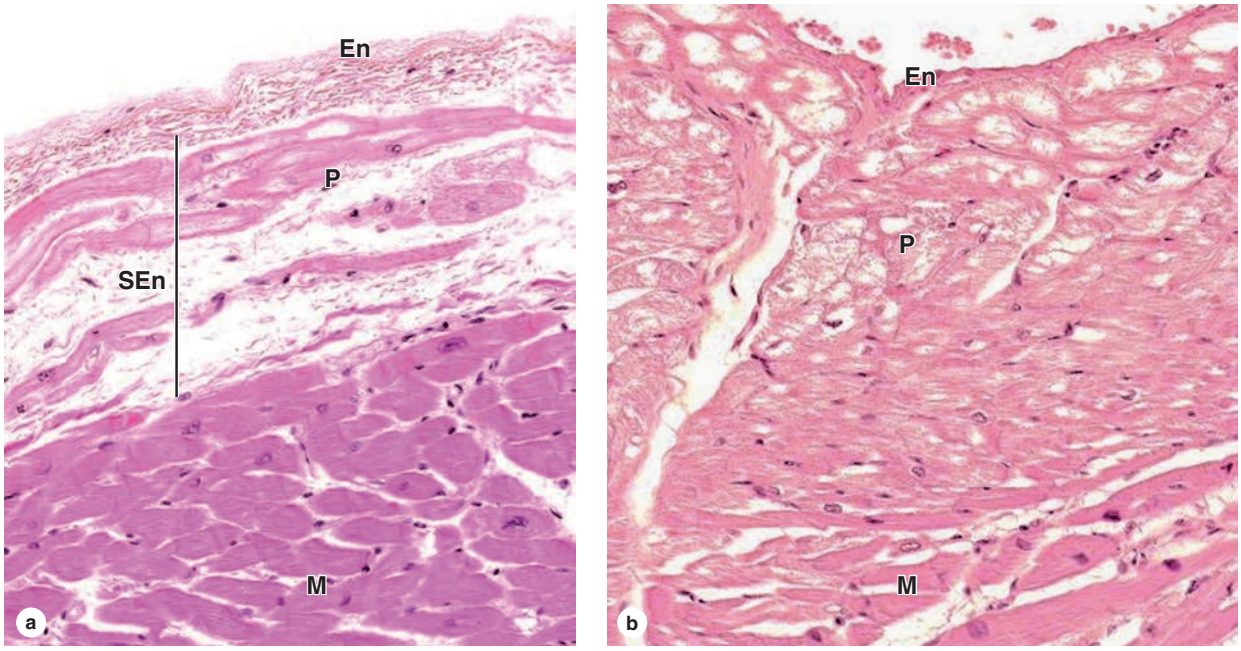
Within these major layers the heart contains other structures important for its overall function of moving blood. Prominent dense irregular connective tissue comprising the fibrous **cardiac skeleton** separates the musculature of the atria from that of the ventricles, forms part of the interventricular and interatrial septa, and extends into the valve cusps and the chordae tendineae to which they are attached (Figures 11–2 and 11–5). Various regions of the cardiac skeleton have the following functions:

- Surrounding, anchoring, and supporting all heart valves;
- providing firm points of insertion for cardiac muscle in the atria and ventricles; and
- helping coordinate the heartbeat by acting as electrical insulation between atria and ventricles.

In both the subendocardial layer and the adjacent myocardium, modified cardiac muscle cells make up the impulse **conducting system of the heart**, specialized to generate and conduct waves of depolarization which stimulate rhythmic contractions in adjacent myocardial fibers. This system (Figure 11–2) consists of two nodes of specialized myocardial tissue in the right atrial wall: the **sinoatrial (SA) node** (or **pacemaker**) and the **atrioventricular (AV) node**, from which the **AV bundle** (bundle of His) emerges.

Located in the right atrial wall near the superior vena cava, the SA node is a 6- to 7-$mm^3$ region of less well-stained cardiac muscle cells with smaller size, fewer myofibrils, and fewer typical intercalated disks than the neighboring contractile fibers.

## FIGURE 11–3 Endocardium, myocardium, and fibers of the subendocardial conducting network.




The lining layer of the heart, the **endocardium**, includes the surface endothelium (**En**), a supporting layer of fibroelastic connective tissue, and a deeper layer of connective tissue surrounding variable amounts of cardiac muscle specialized for impulse conduction, which is often called the **subendocardial layer** and is continuous with connective tissue of the myocardium.

**(a)** The subendocardial layer of connective tissue (**SEn**) in the ventricles surrounds Purkinje fibers (**P**) of the heart's impulse conducting network. These are modified cardiac muscle fibers joined by intercalated disks but specialized for impulse conduction rather than contraction. Containing glycogen but relatively few organelles and peripheral myofibrils, Purkinje fibers typically are paler staining than contractile muscle fibers (**M**).

**(b)** In the atrial walls conducting Purkinje-like fibers (P) often occupy most of the subendocardial layer, lying close to the endothelium (**En**), and merging with the contractile fibers of the myocardium (**M**), which is organized into many partially separated bundles and muscles. (Both X200; H&E)

Impulses initiated by these cells move along myocardial fibers of both atria, stimulating their contraction. When the impulses reach the slightly smaller AV node, located in the floor of the right atrium near the AV valve and composed of cells similar to those of the SA node, they stimulate depolarization myocytes there. From the AV node conducting myocytes are grouped into the AV bundle, which passes through an opening in the cardiac skeleton into the interventricular septum where it bifurcates into left and right bundles of myocytes located within the myocardium and subendocardial layer.

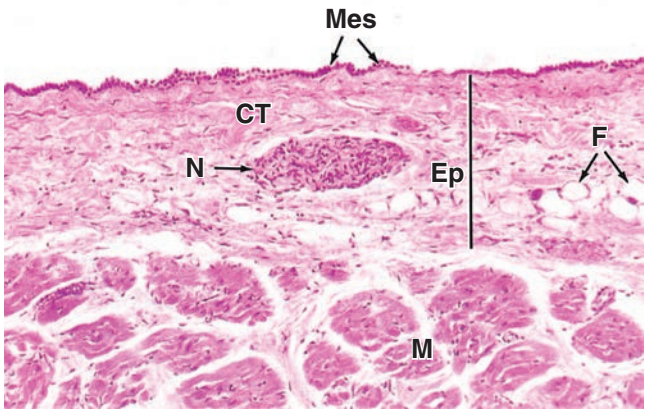
At the apex of the heart, these bundles subdivide further into a subendocardial conducting network of cardiac muscle fibers, usually called **Purkinje fibers**. These are pale-staining fibers, larger than the adjacent contractile fibers, with sparse, peripheral myofibrils, and much glycogen (Figure 11–3). Purkinje fibers mingle distally with contractile muscle fibers of each ventricle and trigger waves of contraction through both ventricles simultaneously.

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 activity of the pacemaker. Between fibers of the myocardium are afferent free nerve endings that register pain, such as the discomfort called angina pectoris that occurs when partially occluded coronary arteries cause local oxygen deprivation.

### ›› MEDICAL APPLICATION

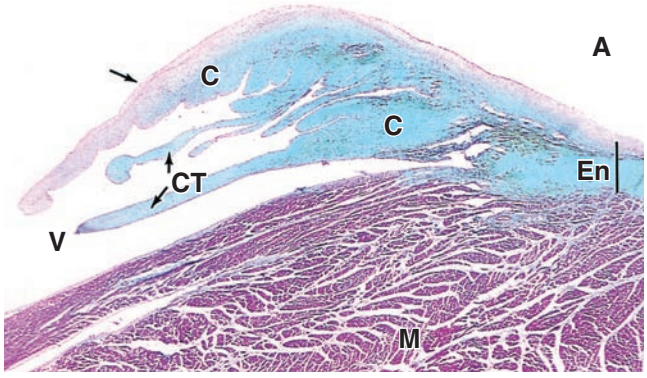
Abnormalities in the structure of heart valves can be produced by developmental defects, scarring after certain infections, or cardiovascular problems such as hypertension. Such abnormal valves may not close tightly, allowing slight regurgitation and backflow of blood. This produces an abnormal heart sound referred to as a **heart murmur**. If the valve defect is severe, the heart will have to work harder to circulate the normal amount of blood, eventually enlarging to accommodate the increased workload. Defective heart valves often may be repaired surgically or replaced by an artificial valve or one from a large animal donor. Because such valve replacements lack a complete endothelial covering, the patients require exogenous anticoagulant agents to prevent thrombus formation at these sites.

**FIGURE 11–4 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 autonomic nerves (**N**) and variable amounts of fat (**F**). The epicardium is the visceral layer of the pericardium and is covered by the simple mesothelium (**Mes**) which also lines the pericardial space. The mesothelial cells secrete a lubricant fluid which prevents friction as the beating heart contacts the parietal pericardium on the other side of the pericardial cavity. (X100; H&E)

**FIGURE 11–5 Valve leaflet and cardiac skeleton.**




The fibrous **cardiac skeleton** consists of dense irregular connective tissue, primarily in the endocardium (**En**), which anchors the valves and surrounds the two atrioventricular canals, maintaining their proper shape. The micrograph shows a section through a cusp of an **atrioventricular valve** (arrow) and attached chordae tendineae (**CT**). These structures are largely dense connective tissue (**C**) covered with a thin layer of endothelium. The collagen-rich connective tissue of the valves is stained pale blue here and is continuous with the fibrous ring of connective tissue at the base of the valves, which fills the endocardium between the atrium (**A**) and ventricle (**V**). The thick ventricular myocardium (**M**) is also shown. (X20; Masson trichrome)

## TISSUES OF THE VASCULAR WALL

Walls of all blood vessels except capillaries contain smooth muscle and connective tissue in addition to the endothelial lining. The amount and arrangement of these tissues in vessels are influenced by **mechanical factors**, primarily blood pressure, and **metabolic factors** reflecting the local needs of tissues.

The **endothelium** is a specialized epithelium that acts as a semipermeable barrier between two major internal compartments: the blood and the interstitial tissue fluid. Vascular endothelial cells are squamous, polygonal, and elongated with the long axis in the direction of blood flow. Endothelium with its basal lamina is highly differentiated to mediate and actively monitor the bidirectional exchange of molecules by simple and active diffusion, receptor-mediated endocytosis, transcytosis, and other mechanisms discussed in Chapter 4.

Besides their key role in metabolite exchanges between blood and tissues, endothelial cells have several other functions:

- The endothelium presents a **nonthrombogenic surface** on which blood will not clot and actively secretes agents that control local clot formation (such as heparin, tissue plasminogen activator, and von Willebrand factor).
- The cells regulate local **vascular tone and blood flow** by secreting various factors that stimulate smooth muscle contraction (such as endothelin-1 and angiotensin-converting enzyme [ACE]) or relaxation (including nitric oxide [NO] and prostacyclin).
- Endothelium has several roles in **inflammation and local immune responses**. In venules endothelial cells induce specific white blood cells to stop and undergo transendothelial migration at sites of injury or infection. Under those conditions **P-selectin** is expressed rapidly on the luminal surface when unique elongated granules, called **Weibel–Palade bodies**, fuse with the cell membrane. As described further in Chapter 12, adhesion to selectins is the first step in the activation of white blood cells specifically where they are needed. Endothelial cells also secrete various factors called **interleukins** that affect the activity of local white blood cells during inflammation.
- Under various conditions endothelial cells secrete various **growth factors**, including proteins promoting proliferation of specific white blood cell lineages and cells that make up the vascular wall.

Growth factors such as vascular endothelial growth factor (VEGF) stimulate formation of the vascular system from embryonic mesenchyme (**vasculogenesis**), help maintain the vasculature in adults, and promote capillary sprouting and outgrowth from small existing vessels (**angiogenesis**) during normal growth, during tissue repair and regeneration, and in tumors and other pathological conditions. In both processes other growth factors, called **angiopoietins**, stimulate endothelial cells to recruit smooth muscle cells and fibroblasts to form the other tissues of the vascular wall.

## ›› MEDICAL APPLICATION

The normal vascular endothelium is antithrombogenic, allowing adhesion of no blood cells or platelets and preventing blood clot formation. When endothelial cells of the microvasculature are damaged by tissue injury, collagen is exposed in the subendothelial tissues and induces the aggregation of blood platelets. These platelets release factors which initiate a cascade of events that produce fibrin from circulating plasma fibrinogen. An intravascular clot, or **thrombus** (plural, thrombi), with a fibrin framework quickly forms to stop blood loss from the damaged vessels.

From large thrombi, solid masses called **emboli** (singular, embolus) may detach and be carried by the blood to obstruct distant vessels. In both cases vascular flow may be blocked, producing a potentially life-threatening condition. Thus, the integrity of the endothelial layer preventing contact between platelets and the subendothelial connective tissue is an important antithrombogenic mechanism.

Individuals in the initial stages of medical conditions involving thrombus formation, such as myocardial infarct, stroke, or pulmonary embolism, are treated intravenously with tissue plasminogen activator, commonly abbreviated as tPA. This is a serine protease that breaks down fibrin and quickly dissolves the clot.

**Smooth muscle** fibers occur in the walls of all vessels larger than capillaries and are arranged helically in layers. In arterioles and small arteries, the smooth muscle cells are connected by many more gap junctions and permit vasoconstriction and vasodilation that are of key importance in regulating the overall blood pressure.

**Connective tissue** components are present in vascular walls in variable amounts and proportions based on local functional requirements. Collagen fibers are found in the subendothelial layer, between the smooth muscle layers, and in the outer covering. Elastic fibers provide the resiliency required for the vascular wall to expand under pressure. Elastin is a major component in large arteries where it forms parallel lamellae, regularly distributed between the muscle layers. Variations in the amount and composition of ground substance components such as proteoglycans and hyaluronate also contribute to the physical and metabolic properties of the wall in different vessels, especially affecting their permeability.

The walls of all blood vessels larger than the microvasculature have many components in common and similar organization. Branching of the vessels helps produce reductions in their size that are accompanied by gradual changes in the composition of the vascular wall. Transitions such as those from "small arteries" to "arterioles" are not clear-cut. However, all of these larger vessels have walls with three concentric layers, or tunics (L. *tunica*, coat), as shown in the diagram of Figure 11–6 and in the micrographs of Figures 11–7 through 11–9.

- The innermost tunica **intima** consists of the endothelium and a thin subendothelial layer of loose connective tissue sometimes containing smooth muscle fibers (Figure 11–7). In arteries the intima includes a thin layer, the **internal elastic lamina**, composed of elastin, with holes allowing better diffusion of substances from blood deeper into the wall.
- The tunica **media**, the middle layer, consists chiefly of concentric layers of helically arranged smooth muscle cells (Figures 11–6 and 11–7). Interposed among the muscle fibers are variable amounts of elastic fibers and elastic lamellae, reticular fibers, and proteoglycans, all of which are produced by the smooth muscle cells. In arteries the media may also have an external elastic lamina separating it from the outermost tunic.
- The outer **adventitia**, or tunica externa, is connective tissue consisting principally of type I collagen and elastic fibers (Figures 11–7 and 11–8). The adventitia is continuous with and bound to the stroma of the organ through which the blood vessel runs.

Just as the heart wall is supplied with its own coronary vasculature for nutrients and $O_2$, large vessels usually have **vasa vasorum** ("vessels of the vessel"): arterioles, capillaries, and venules in the adventitia and outer part of the media (Figure 11–8). The vasa vasorum are required to provide metabolites to cells in those tunics in larger vessels because the wall is too thick to be nourished solely by diffusion from the blood in the lumen. Luminal blood alone does provide the needs of cells in the intima. Because they carry deoxygenated blood, large veins commonly have more vasa vasorum than arteries.

The adventitia of larger vessels also contains a network of unmyelinated autonomic nerve fibers, the vasomotor nerves (Figure 11–8), which release the vasoconstrictor norepinephrine. The density of this innervation is greater in arteries than in veins.

# › VASCULATURE

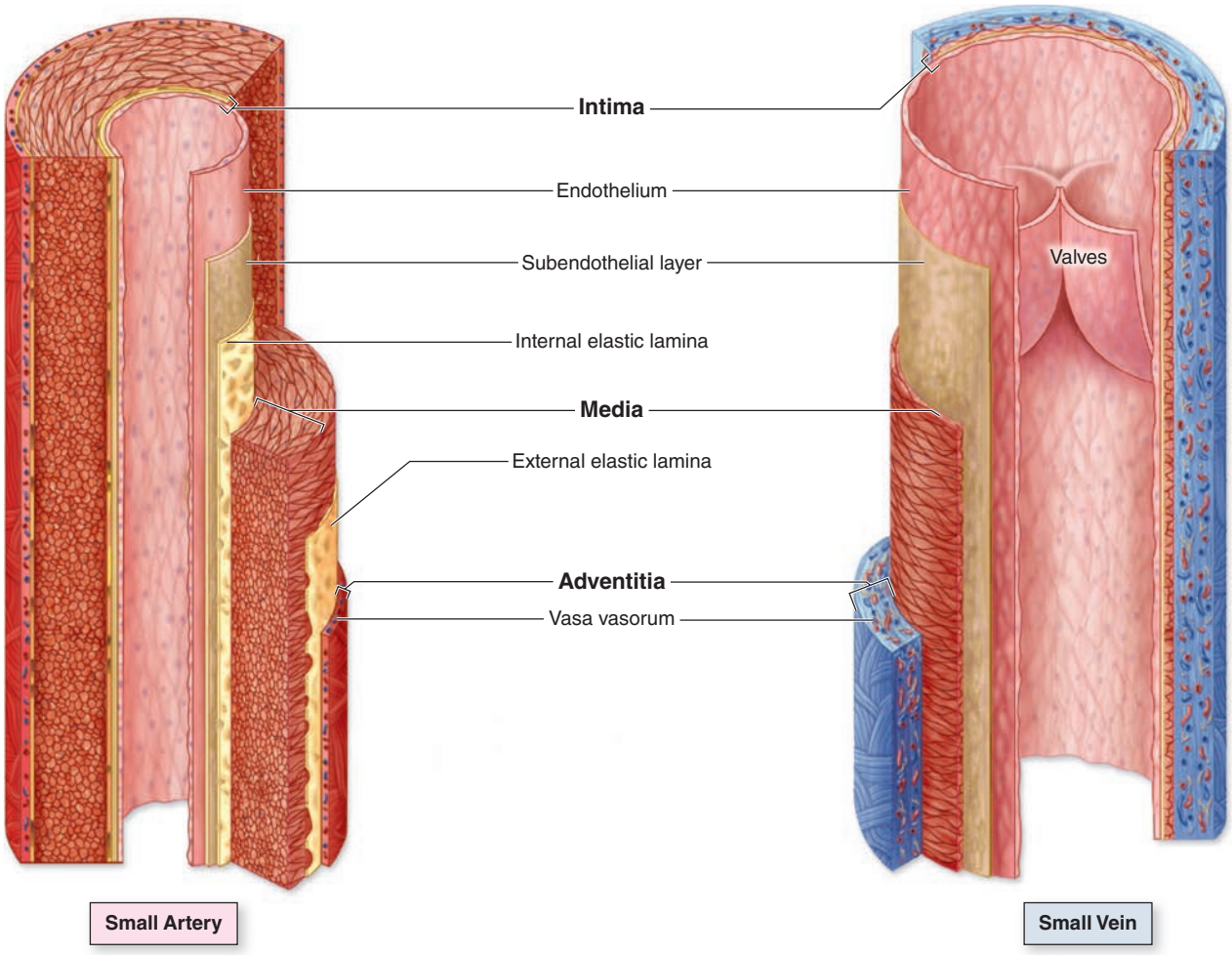
Large blood vessels and those of the microvasculature branch frequently and undergo gradual transitions into structures with different histologic features and functions. For didactic purposes vessels can be classified arbitrarily as the types discussed here and listed in Table 11–1.

## Elastic Arteries

**Elastic arteries** are the aorta, the pulmonary artery, and their largest branches; these large vessels are also called **conducting arteries** because their major role is to carry blood to smaller arteries. As shown in Figure 11–7a, the most prominent feature of elastic arteries is the thick tunica media in which elastic lamellae alternate with layers of smooth muscle fibers. The adult aorta has about 50 elastic lamellae (more if the individual is hypertensive).

The tunica intima is well developed, with many smooth muscle cells in the subendothelial connective tissue, and often shows folds in cross section as a result of the loss of blood pressure and contraction of the vessel at death (Figure 11–8). Between the intima and the media is the internal elastic

FIGURE **11–6** **Walls of arteries and veins.**




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

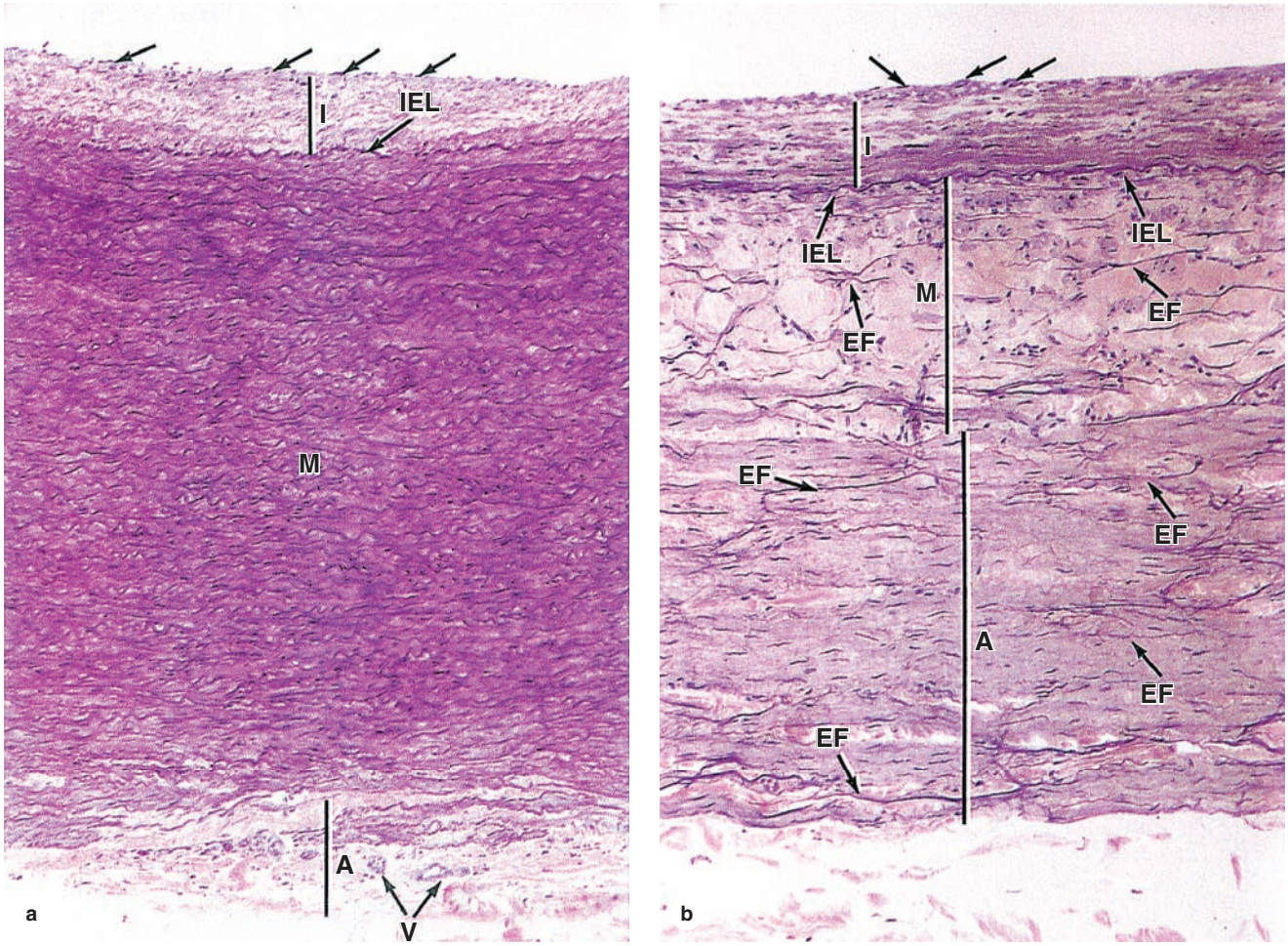
lamina, which is more well-defined than the elastic laminae of the media (Figures 11–7a and 11–9). The adventitia is much thinner than the media.

The numerous elastic laminae of these arteries contribute to their important function of making the blood flow more uniform. During ventricular contraction (systole) blood is moved through the arteries forcefully and the elastin is stretched, distending the wall within the limit set by the wall's collagen. When the ventricles relax (diastole) ventricular pressure drops to a low level, but the elastin rebounds passively, helping to maintain arterial pressure. The aortic and pulmonary valves prevent backflow of blood into the heart, so the rebound continues the blood flow away from the heart. Arterial blood pressure and blood velocity decrease and become less variable as the distance from the heart increases.

## ›› MEDICAL APPLICATION

**Atherosclerosis** (Gr. *athero*, gruel or porridge, and *scleros*, hardening) is a disease of elastic arteries and large muscular arteries that may play a role in nearly half of all deaths in developed parts of the world. It is initiated by damaged or dysfunctional endothelial cells oxidizing low-density lipoproteins (LDLs) in the tunica intima, which induces adhesion and intima entry of monocytes/macrophages to remove the modified LDL. Lipid-filled macrophages (called **foam cells**) accumulate and, along with the free LDL, produce a pathologic sign of early atherosclerosis called **fatty streaks**. During disease progression these develop into **fibro-fatty plaques**, or **atheromas**, consisting of a gruel-like mix of smooth muscle cells, collagen fibers, and lymphocytes with necrotic

FIGURE **11–7** **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 intima (**I**) that also has subendothelial connective tissue and in arteries is separated from the media by an internal elastic lamina (**IEL**), a structure absent in all but the largest veins. The media (**M**) contains many elastic lamellae and elastic fibers (**EF**) alternating with layers of smooth muscle. The 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 stain)

regions of lipid, debris, and foam cells. Predisposing factors include dyslipidemia (> 3:1 ratios of LDL to HDL [high-density lipoprotein]), hyperglycemia of diabetes, hypertension, and the presence of toxins introduced by smoking.

In elastic arteries atheromas produce localized destruction within the wall, weakening it and causing arterial bulges or **aneurysms** which can rupture. In muscular arteries such as the coronary arteries, atheromas can occlude blood flow to downstream vessels, leading to ischemic heart disease.

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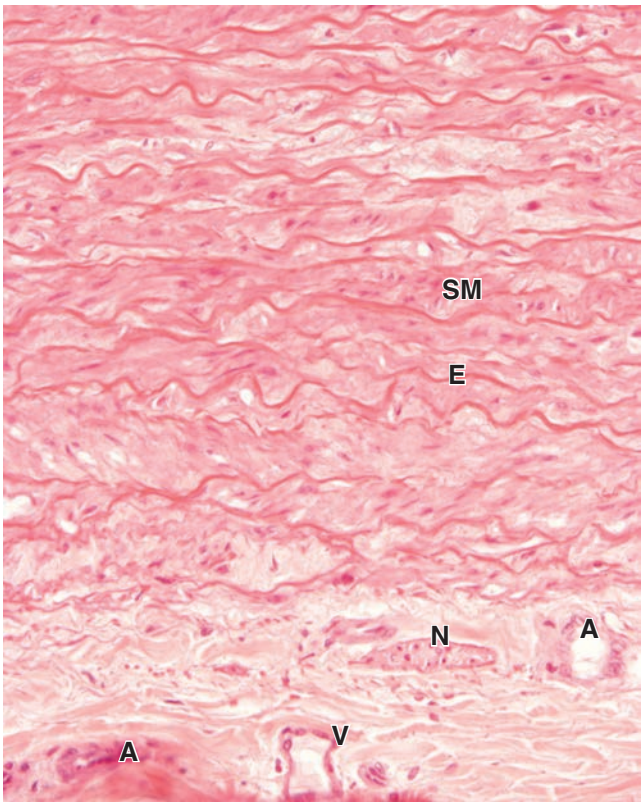
## Arterial Sensory Structures

**Carotid sinuses** are slight dilations of the bilateral internal carotid arteries where they branch from the (elastic) common carotid arteries; they act as important **baroreceptors** monitoring arterial blood pressure. At these sinuses the tunica media is thinner, allowing greater distension when blood pressure rises, and the adventitia contains many sensory nerve endings from cranial nerve IX, the glossopharyngeal nerve. The brain's vasomotor centers process these afferent impulses and adjust vasoconstriction, maintaining normal blood pressure. Functionally similar baroreceptors present in the aortic arch transmit signals pertaining to blood pressure via cranial nerve X, the vagus nerve.

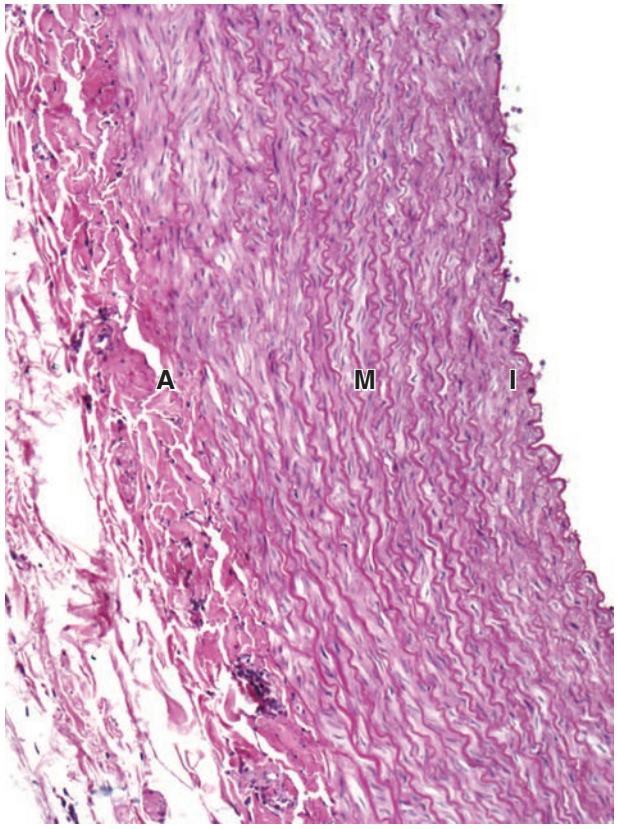
Histologically more complex **chemoreceptors** which monitor blood $CO_2$ and $O_2$ levels, as well as its pH, are found in the

FIGURE **11–8** **Vasa vasorum.**




The adventitia of the larger arteries contains a supply of microvasculature to bring $O_2$ and nutrients to local cells that are 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. Above the adventitia in this section can be seen muscle fibers (**SM**) and elastic lamellae (**E**) in the media. (X100; H&E)

FIGURE **11–9** **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 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 dense irregular connective tissue of the adventitia (**A**) is thinner than the media. (X200; PT)

**carotid bodies** and in the **aortic bodies**, located in the walls of the carotid sinuses and aortic arch, respectively. These structures are parts of the autonomic nervous system called **paraganglia** with rich capillary networks. The capillaries are closely surrounded by large, neural crest-derived **glomus cells** filled with dense-core vesicles containing dopamine, acetylcholine, and other neurotransmitters, which are supported by smaller satellite cells (Figure 11–10). Ion channels in the glomus cell membranes respond to stimuli in the arterial blood, primarily hypoxia (low $O_2$), hypercapnia (excess $CO_2$), or acidosis, by activating release of neurotransmitters. Sensory fibers branching from the glossopharyngeal nerve form synapses with the glomus cells and signal brain centers to initiate cardiovascular and respiratory adjustments that correct the condition.

## Muscular Arteries

The muscular arteries, also called distributing arteries, distribute blood to the organs and help regulate blood pressure by contracting or relaxing the smooth muscle in the media. The intima has a thin subendothelial layer and a prominent internal elastic lamina (Figure 11–11). The media may contain up to 40 layers of large smooth muscle cells interspersed with a variable number of elastic lamellae (depending on the size of the vessel). An external elastic lamina is present only in the larger muscular arteries. The adventitial connective tissue contains lymphatic capillaries, vasa vasorum, and nerves, all of which may penetrate to the outer part of the media.

## Arterioles

Muscular arteries branch repeatedly into smaller and smaller arteries, until reaching a size with three or four layers of medial smooth muscle. The smallest arteries branch as **arterioles**, which have only one or two smooth muscle layers;

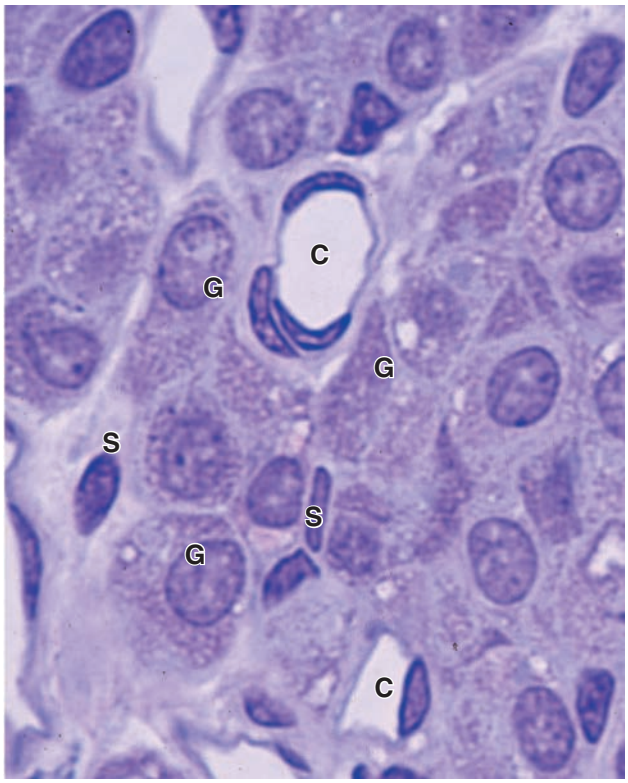
**TABLE 11–1 Size ranges, major features, and important roles of major blood vessel types.**

| Type of Artery | Outer Diameter (Approx. Range) | Intima | Media | Adventitia | Roles in Circulatory System |
|---|---|---|---|---|---|
| **Elastic arteries** | > 10 mm | Endothelium; connective tissue with smooth muscle | Many elastic lamellae alternating with smooth muscle | Connective tissue, thinner than media, with vasa vasorum | Conduct blood from heart and with elastic recoil help move blood forward under steady pressure |
| **Muscular arteries** | 10-1 mm | Endothelium; connective tissue with smooth muscle, internal elastic lamina prominent | Many smooth muscle layers, with much less elastic material | Connective tissue, thinner than media; vasa vasorum maybe present | Distribute blood to all organs and maintain steady blood pressure and flow with vasodilation and constriction |
| **Small arteries** | 1-0.1 mm | Endothelium; connective tissue less smooth muscle | 3-10 layers of smooth muscle | Connective tissue, thinner than media; no vasa vasorum | Distribute blood to arterioles, adjusting flow with vasodilation and constriction |
| **Arterioles** | 100-10 µm | Endothelium; no connective tissue or smooth muscle | 1-3 layers of smooth muscle | Very thin connective tissue layer | Resist and control blood flow to capillaries; major determinant of systemic blood pressure |
| **Capillaries** | 10-4 µm | Endothelium only | A few pericytes only | None | Exchange metabolites by diffusion to and from cells |
| **Venules (postcapillary, collecting, and muscular)** | 10-100 µm | Endothelium; no valves | Pericytes and scattered smooth muscle cells | None | Drain capillary beds; site of leukocyte exit from vasculature |
| **Small veins** | 0.1-1 mm | Endothelium; connective tissue with scattered smooth muscle fibers | Thin, 2-3 loose layers of smooth muscle cells | Connective tissue, thicker than media | Collect blood from venules |
| **Medium veins** | 1-10 mm | Endothelium; connective tissue, with valves | 3-5 more distinct layers of smooth muscle | Thicker than media; longitudinal smooth muscle may be present | Carry blood to larger veins, with no backflow |
| **Large veins** | > 10 mm | Endothelium; connective tissue, smooth muscle cells; prominent valves | > 5 layers of smooth muscle, with much collagen | Thickest layer, with bundled longitudinal smooth muscle | Return blood to heart |

these indicate the beginning of an organ's **microvasculature** (Figures 11–12 and 11–13) where exchanges between blood and tissue fluid occur. Arterioles are generally less than 0.1 mm in diameter, with lumens approximately as wide as the wall is thick (Figure 11–14). The subendothelial layer is very thin, elastic laminae are absent, and the media consists of the circularly arranged smooth muscle cells. In both small arteries and arterioles the adventitia is very thin and inconspicuous.

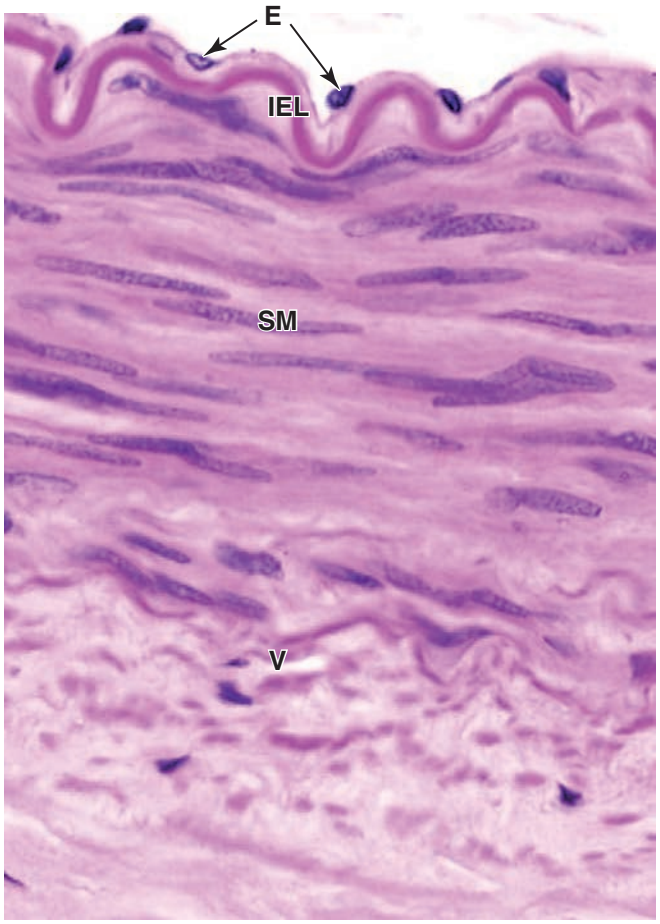
Arterioles almost always branch to form anastomosing networks of capillaries that surround the parenchymal cells of the organ. At the ends of arterioles the smooth muscle fibers act as sphincters and produce periodic blood flow into capillaries (Figure 11–13). Muscle tone normally keeps arterioles partially closed, resisting blood flow, which makes these vessels the major determinants of systemic blood pressure.

## FIGURE 11–10 Cells and capillaries in a glomus body.




Specialized regions in the walls of certain elastic arteries contain tissues acting as chemoreceptors that provide information to the brain regarding blood chemistry. The glomus bodies are two small (0.5-5 mm diameter) ganglion-like structures found near the common carotid arteries. They contain many large capillaries (**C**) intermingled with clusters of large glomus cells (**G**) filled with vesicles of various neurotransmitters. Supportive satellite cells (**S**) with elongated nuclei ensheath each glomus cell. Glomus cells form synaptic connections with sensory fibers. Significant changes in the blood $CO_2$, $O_2$, or $H^+$ concentrations are detected by the chemoreceptive glomus cells, which then release a neurotransmitter that activates the sensory nerve to relay this information to the brain. (X400; PT)

## 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 the muscular type. A transverse section through a muscular (medium-caliber) artery shows a slightly folded intima with only sparse connective tissue between the endothelial cells (**E**) and internal elastic lamina (**IEL**). Multiple layers of smooth muscle (**SM**) in the media are thicker than the elastic lamellae and fibers with which they intersperse. Vasa vasorum (**V**) are seen in the adventitia. (X100; H&E)

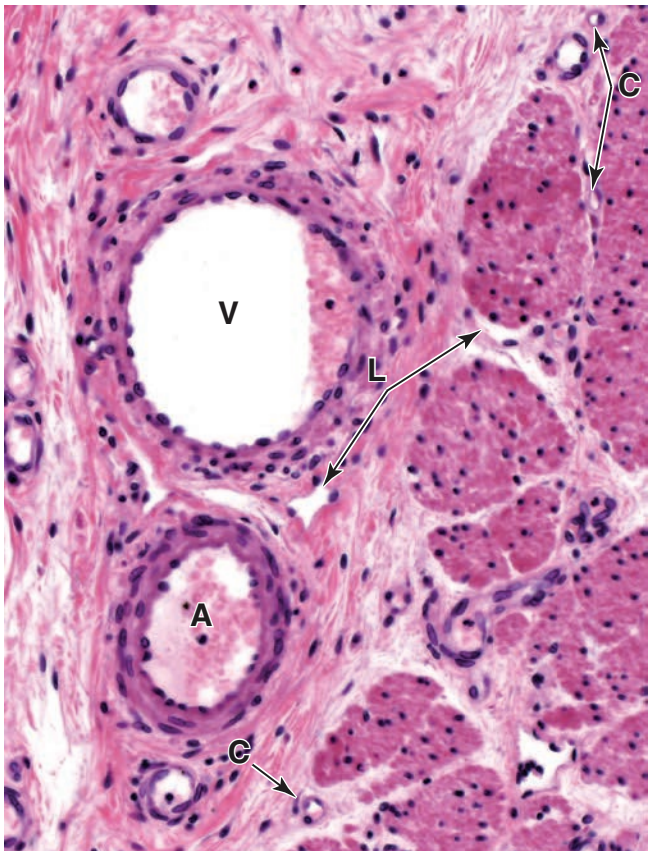
### ›› MEDICAL APPLICATION

Blood pressure depends on cardiac output and the total peripheral resistance to blood flow, which is mostly due to the resistance of arterioles. **Hypertension** or elevated blood pressure may occur secondarily to renal or endocrine problems, but is more commonly essential hypertension, due to a wide variety of mechanisms that increase arteriolar constriction.

In certain tissues and organs, arterioles deviate from this simple path to accommodate various specialized functions (Figure 11–15). For example, thermoregulation by the skin involves arterioles that can bypass capillary networks and connect directly to venules. The media and adventitia are thicker in these **arteriovenous shunts** (or arteriovenous anastomoses) and richly innervated by sympathetic and parasympathetic nerve fibers. The autonomic fibers control the degree of vasoconstriction at the shunts, regulating blood flow through the capillary beds. High capillary blood flow in the skin allows more heat dissipation from the body, while reduced capillary blood flow conserves heat—important functions when the environmental temperature is hot or cold, respectively.

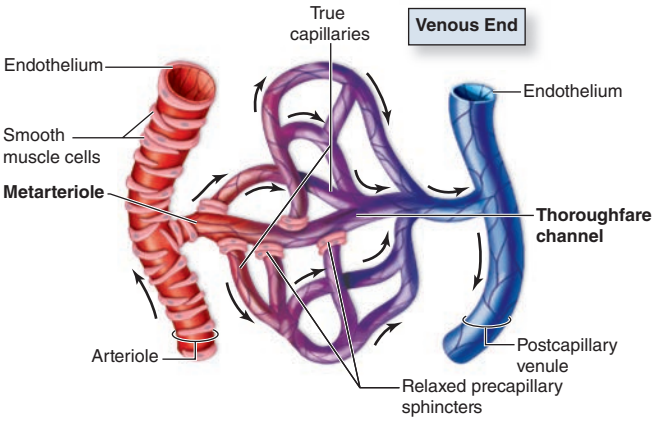
Another important alternative microvascular pathway is a venous **portal system** (Figure 11–15), in which blood flows through two successive capillary beds separated by a **portal vein**. This arrangement allows for hormones or nutrients picked up by

## FIGURE 11–12 Microvasculature.

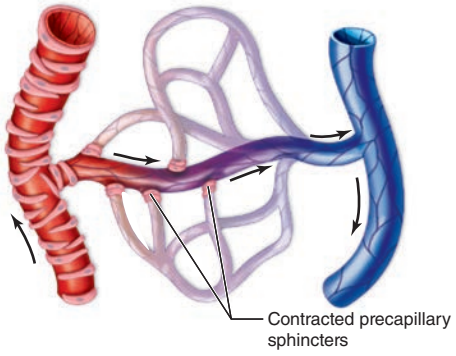



Arterioles (**A**), capillaries (**C**), and venules (**V**) comprise the microvasculature where, in almost every organ, molecular exchange takes place between blood and the interstitial fluid of the surrounding tissues. Lacking media and adventitia tunics and with diameters of only 4-10 µm, capillaries (**C**) in paraffin sections can be recognized by nuclei adjacent to small lumens or by highly eosinophilic red blood cells in the lumen. As described in Figure 5–20, not all interstitial fluid formed at capillary beds is drained into venules; the excess is called **lymph** and collects in thin-walled, irregularly shaped lymphatic vessels (**L**), such as those seen in connective tissue and smooth muscle here. (200X; H&E)

## FIGURE 11–13 Microvascular bed structure and perfusion.




**(a) Sphincters relaxed; capillary bed well perfused**




**(b) Sphincters contracted; blood bypasses capillary bed**

**Arterioles** supplying a capillary bed typically form smaller branches called **metarterioles** in which the **smooth muscle cells** are dispersed as bands which act as **precapillary sphincters**. The distal portion of the metarteriole, sometimes called a **thoroughfare channel**, lacks smooth muscle cells and merges with the **postcapillary venule**. Branching from the metarteriole and thoroughfare channel are the smallest vessels, **true capillaries**, which lack smooth muscle cells (although pericytes may be present). The precapillary sphincters regulate blood flow into the true capillaries.

Part **a** shows a well-perfused capillary bed with all the sphincters relaxed and open; part **b** shows a capillary bed with the blood shunted away by contracted sphincters. At any given moment, most sphincters are at least partially closed and blood enters the capillary bed in a pulsatile manner for maximally efficient exchange of nutrients, wastes, $O_2$, and $CO_2$ across the endothelium. Except in the pulmonary circulation (Figure 11–1), blood enters the microvasculature well oxygenated and leaves poorly oxygenated.

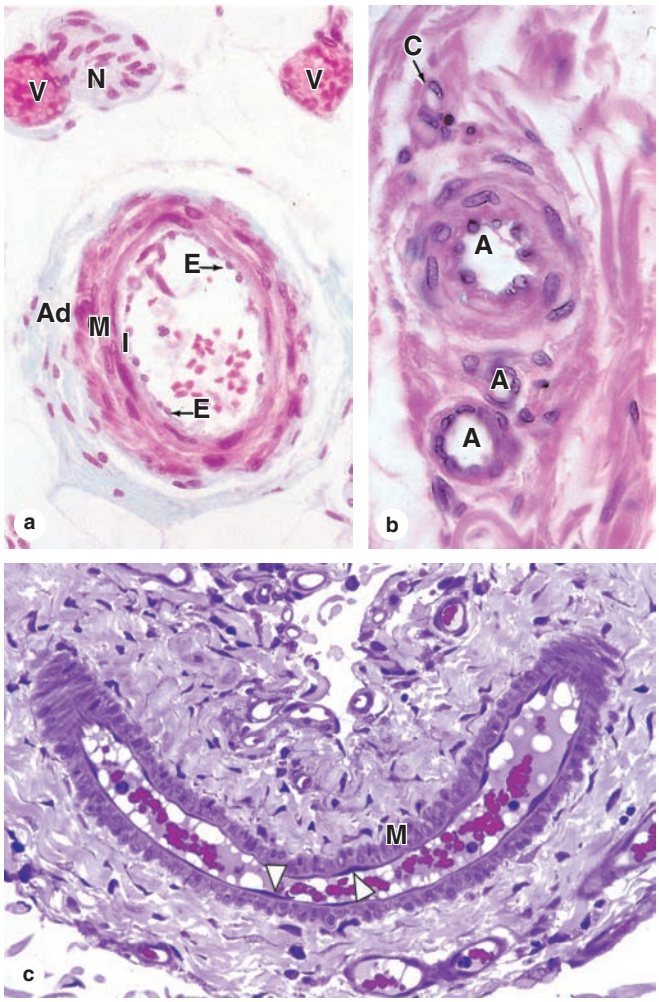
the blood in the first capillary network to be delivered most efficiently to cells around the second capillary bed before the blood is returned to the heart for general distribution. The best examples are the hepatic portal system of the liver and the hypothalamic-hypophyseal portal system in the anterior pituitary gland, both of which have major physiologic importance.

## Capillary Beds

**Capillaries** permit and regulate metabolic exchange between blood and surrounding tissues. These smallest blood vessels always function in networks called **capillary beds**, whose size and overall shape conforms to that of the structure supplied. The density of the capillary bed 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 abundant capillaries; the opposite is true of tissues with low metabolic rates, such as smooth muscle and dense connective tissue.

Capillary beds are supplied preferentially by one or more terminal arteriole branches called **metarterioles**, which

## FIGURE 11–14 Arterioles.

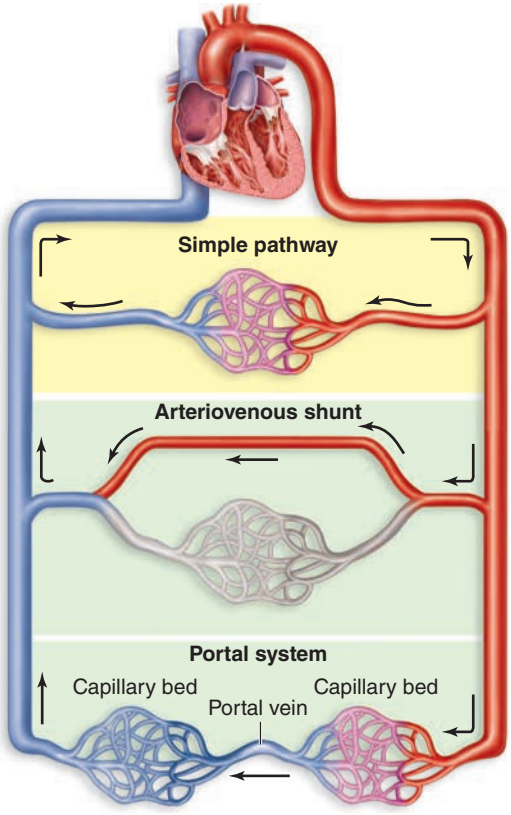



**(a)** Arterioles are microvessels with an intima (**I**) consisting only of endothelium (**E**), in which the cells may have rounded nuclei. They have media (**M**) tunics with only one or two layers of smooth muscle, and usually thin, inconspicuous adventitia (**Ad**). (X350; Masson trichrome)

**(b)** Three arterioles (**A**) of various sizes and a capillary (**C**) are shown here. (X400; H&E)

**(c)** A large mesenteric arteriole cut obliquely and longitudinally 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)

## FIGURE 11–15 Comparison of the simple microvascular pathway with arteriovenous shunts and portal systems.




Most capillary beds are supplied by arterioles and drain into venules, but alternative pathways are found in certain organs. In skin blood flow can be varied according to external conditions by **arteriovenous (AV) shunts**, or anastomoses, commonly coiled, which directly connect the arterial and venous systems and temporarily bypass capillaries.

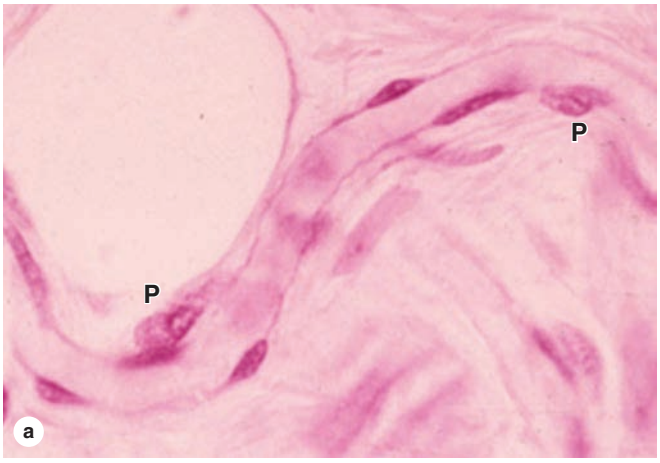
In **venous portal systems** one capillary bed drains into a vein that then branches again into another capillary bed. This arrangement allows molecules entering the blood in the first set of capillaries to be delivered quickly and at high concentrations to surrounding tissues at the second capillary bed, which is important in the anterior pituitary gland and liver.

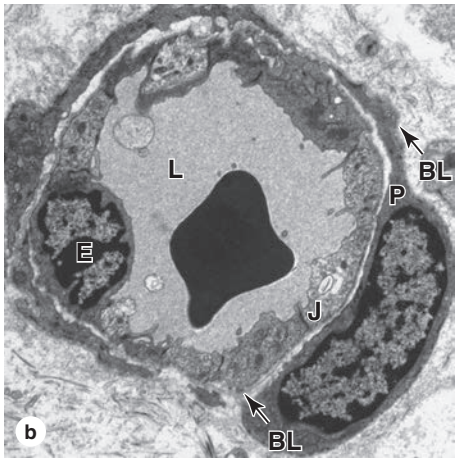
Not shown are **arterial portal systems** (afferent arteriole → capillaries → efferent arteriole) which occur in the kidney.

are continuous with **thoroughfare channels** connected with the **postcapillary venules** (Figure 11–13). Capillaries branch from the metarterioles, which are encircled by scattered smooth muscle cells, and converge into the thoroughfare channels, which lack muscle. The metarteriole muscle cells act as **precapillary sphincters** that control blood flow into the capillaries. These sphincters contract and relax cyclically, with 5-10 cycles per minute, causing blood to pass through capillaries in a pulsatile manner. When the sphincters are closed, blood flows directly from the metarterioles and thoroughfare channels into postcapillary venules.

Capillaries are composed of the simple layer of **endothelial cells** rolled up as a tube surrounded by basement membrane (Figure 11–16). The average diameter of capillaries varies from 4 to 10 μm, which allows transit of blood cells only one at a time, and their individual length is usually not more than 50 μm. These minute vessels make up over 90% of the body's vasculature, with a total length of more than 100,000 km and

## FIGURE 11–16 Capillary with pericytes.




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 of a spread mesentery preparation)

**(b)** TEM of a capillary cut transversely, showing the nucleus of one thin capillary endothelial cell (**E**). Endothelial cells form the capillary lumen (**L**), are covered by a basal lamina (**BL**), and are bound tightly together with junctional complexes (**J**). One pericyte (**P**) is shown, surrounded by its own basal lamina (**BL**) and with cytoplasmic extensions which surround the endothelial cells. (X13,000)

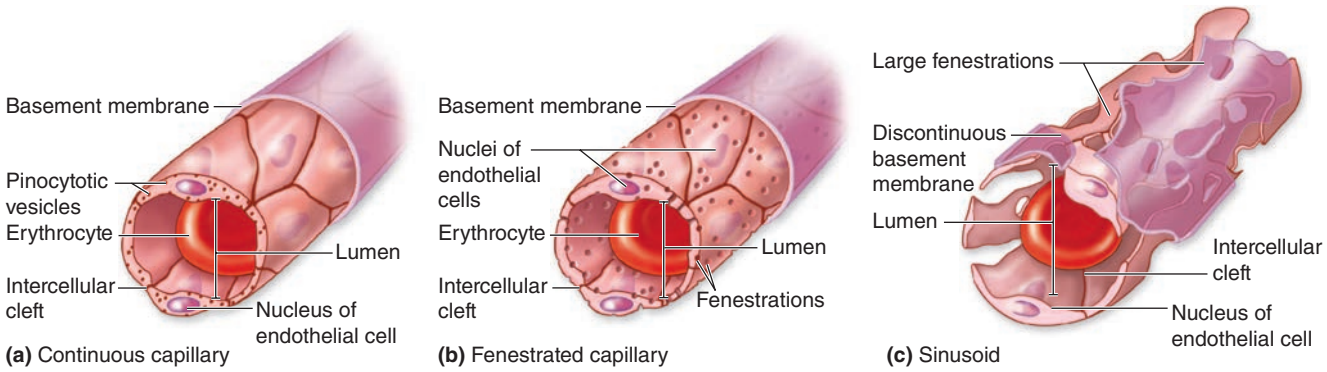
a total surface area of approximately 5000 $m^2$. Because of the cyclical opening and closing of the sphincters, most capillaries are essentially empty at any given time, with only about 5% (~300 mL in an adult) of the total blood volume moving through these structures. Their thin walls, extensive surface area, and slow, pulsatile blood flow optimize capillaries for the exchange of water and solutes between blood and tissues.

In addition to the endothelial properties mentioned earlier in this chapter, capillary cells have many features specialized for molecular transfer by mechanisms ranging from simple diffusion to transcytosis. The average thickness of the cells is only 0.25 μm and their nuclei are often distinctively curved to accommodate the very small tubular structure (Figure 11–10). The cytoplasm contains mitochondria and most other organelles, as well as a large population of membranous vesicles typically. Along with the basal lamina, junctional complexes between the cells maintain the tubular structure, with variable numbers of tight junctions having an important role in capillary permeability.

Major structural variations in capillaries occur in organs with various functions that permit very different levels of metabolic exchange. Capillaries are generally grouped into three histologic types, depending on the continuity of the endothelial cells and their basement membrane (Figures 11–17 through 11–20).

- **Continuous capillaries** (Figure 11–17a) have many tight, well-developed occluding junctions between slightly overlapping endothelial cells, which provide for continuity along the endothelium and well-regulated metabolic exchange across the cells. This is the most common type of capillary and is found in muscle, connective tissue, lungs, exocrine glands, and nervous tissue. Ultrastructural studies show numerous vesicles indicating transcytosis of macromolecules in both directions across the endothelial cell cytoplasm.
- **Fenestrated capillaries** (Figure 11–17b) have a sieve-like structure that allows more extensive molecular exchange across the endothelium. The endothelial cells are penetrated by numerous small circular openings or fenestrations (L. *fenestra*, perforation), approximately 80 nm in diameter. Some fenestrations are covered by very thin diaphragms of proteoglycans (Figure 11–19); others may represent membrane invaginations during transcytosis that temporarily involve both sides of the very thin cells. The basement membrane however is continuous and covers the fenestrations. Fenestrated capillaries are found in organs with rapid interchange of substances between tissues and the blood, such as the kidneys, intestine, choroid plexus, and endocrine glands.
- **Discontinuous capillaries**, commonly called **sinusoids** (Figure 11–17c), permit maximal exchange of macromolecules as well as allow easier movement of cells between tissues and blood. The endothelium here has large perforations without diaphragms and irregular intercellular clefts, forming a discontinuous layer with spaces between and through the cells. Unlike other capillaries sinusoids also have highly discontinuous basement membranes and much larger diameters, often 30-40 μm, which slows blood flow. Sinusoidal capillaries of this type are found in the liver, spleen, some endocrine organs, and bone marrow (Figure 11–20).

## FIGURE 11–17 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 (fenestrations) through the endothelial cells allow greater exchange across the endothelium. The basement membrane 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**, or discontinuous capillaries, usually have a wider diameter than the other types and have discontinuities between the endothelial cells, large fenestrations 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.

At various locations along continuous capillaries and postcapillary venules are mesenchymal cells called **pericytes** (Gr. *peri*, around + *kytos*, cell), with long cytoplasmic processes partly surrounding the endothelial layer. Pericytes secrete many ECM components and form their own basal lamina, which fuses with the basement membrane of the endothelial cells (Figure 11–16). Well-developed cytoskeletal networks of myosin, actin, and tropomyosin indicate that pericytes also dilate or constrict capillaries, helping to regulate blood flow in some organs. Within the CNS pericytes are important for maintaining the endothelial blood-brain barrier. After injuries pericytes proliferate and differentiate to form smooth muscle and other cells in new vessels as the microvasculature is reestablished. In many organs the pericyte population also includes mesenchymal stem cells important for regeneration of other tissues.

### ›› MEDICAL APPLICATION

The **hyperglycemia** or excessive blood sugar that occurs with diabetes commonly leads to **diabetic microangiopathy**, a diffuse thickening of capillary basal laminae and concomitant decrease in metabolic exchange at these vessels, particularly in the kidneys, retina, skeletal muscle, and skin.

## Venules

The transition from capillaries to venules occurs gradually. Postcapillary venules (Figure 11–21a) are similar to capillaries with pericytes but larger, ranging in diameter from 15 to 20 μm. As described with blood in Chapter 12, postcapillary venules are the primary site at which white blood cells adhere to endothelium and leave the circulation at sites of infection or tissue damage.

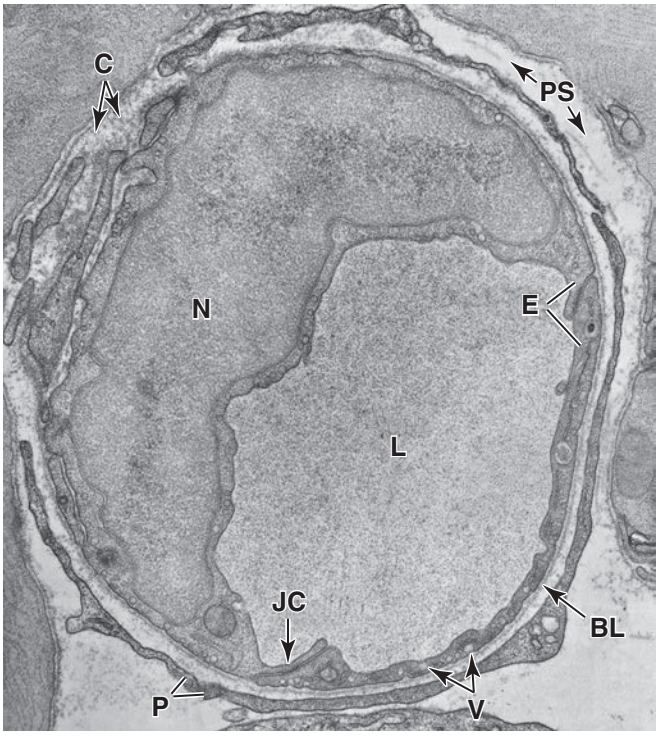
Postcapillary venules converge into larger **collecting venules** that have more distinct contractile cells. With increasing size venules become surrounded by a recognizable tunica media with two or three smooth muscle layers and are called **muscular venules**. A characteristic feature of all venules is the large diameter of the lumen compared to the overall thinness of the wall (Figure 11–21).

## Veins

**Veins** carry blood back to the heart from microvasculature all over the body. Blood entering veins is under very low pressure and moves toward the heart by contraction of the smooth muscle fibers in the media and by external compressions from surrounding skeletal muscles and other organs. Most veins are classified as **small** or **medium veins** (Figure 11–22), with diameters of 10 mm or less (Table 11–1). These veins are usually located close and parallel to corresponding muscular arteries. The tunica intima is usually thin, the media has small bundles of smooth muscle cells mixed with a network of reticular fibers and delicate elastic fibers, and the collagenous adventitial layer is thick and well developed.

The big venous trunks, paired with elastic arteries close to the heart, are the **large veins** (Figure 11–7b). These have well-developed intimal layers, but relatively thin media with alternating smooth muscle and connective tissue. The tunica adventitia is thicker than the media in large veins and

## FIGURE 11–18 Continuous capillary.




Continuous capillaries exert the tightest control over what molecules leave and enter the capillary lumen (**L**). The TEM shows a continuous capillary in transverse section. An endothelial cell nucleus (**N**) is prominent, and tight or occluding junctions are abundant in the junctional complexes (**JC**) at overlapping folds between the endothelial cells (**E**). Numerous transcytotic vesicles (**V**) are evident. All material that crosses continuous capillary endothelium must pass *through* the cells, usually by diffusion or transcytosis.

Around the capillary are a basal lamina (**BL**) and thin cytoplasmic extensions from pericytes (**P**). Collagen fibers (**C**) and other extracellular material are present in the perivascular space (**PS**). (X10,000)

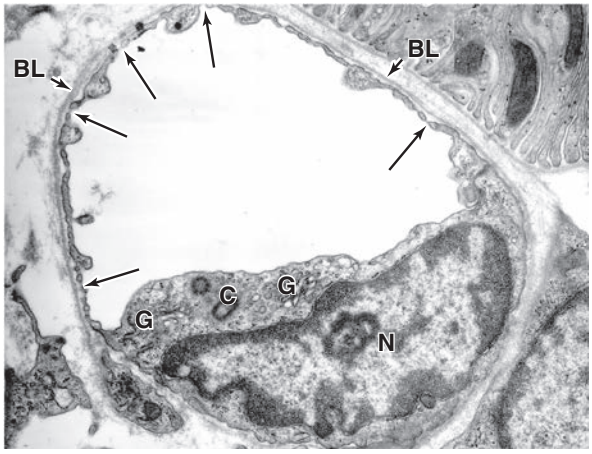
frequently contains longitudinal bundles of smooth muscle. Both the media and adventitia contain elastic fibers, and an internal elastic lamina like those of arteries may be present.

An important feature of large and medium veins are **valves**, which consist of thin, paired folds of the tunica intima projecting across the lumen, rich in elastic fibers and covered on both sides by endothelium (Figures 11–22 and 11–23). The valves, which are especially numerous in veins of the legs, help keep the flow of venous blood directed toward the heart.

### ›› MEDICAL APPLICATION

Junctions between endothelial cells of postcapillary venules are the loosest of the microvasculature. This facilitates transendothelial migration of leukocytes at these locations during **inflammation**, as well as a characteristic loss of fluid here during the inflammatory response, leading to tissue **edema**.

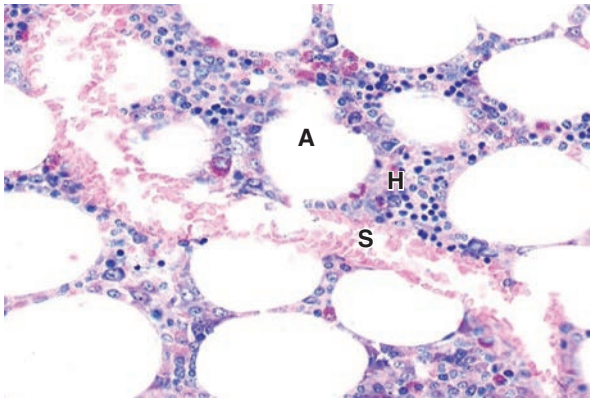
## FIGURE 11–19 Fenestrated capillary.




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 basal lamina surrounding the endothelial cell (**BL**). In this cell the Golgi apparatus (**G**), nucleus (**N**), and centrioles (**C**) can also 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)

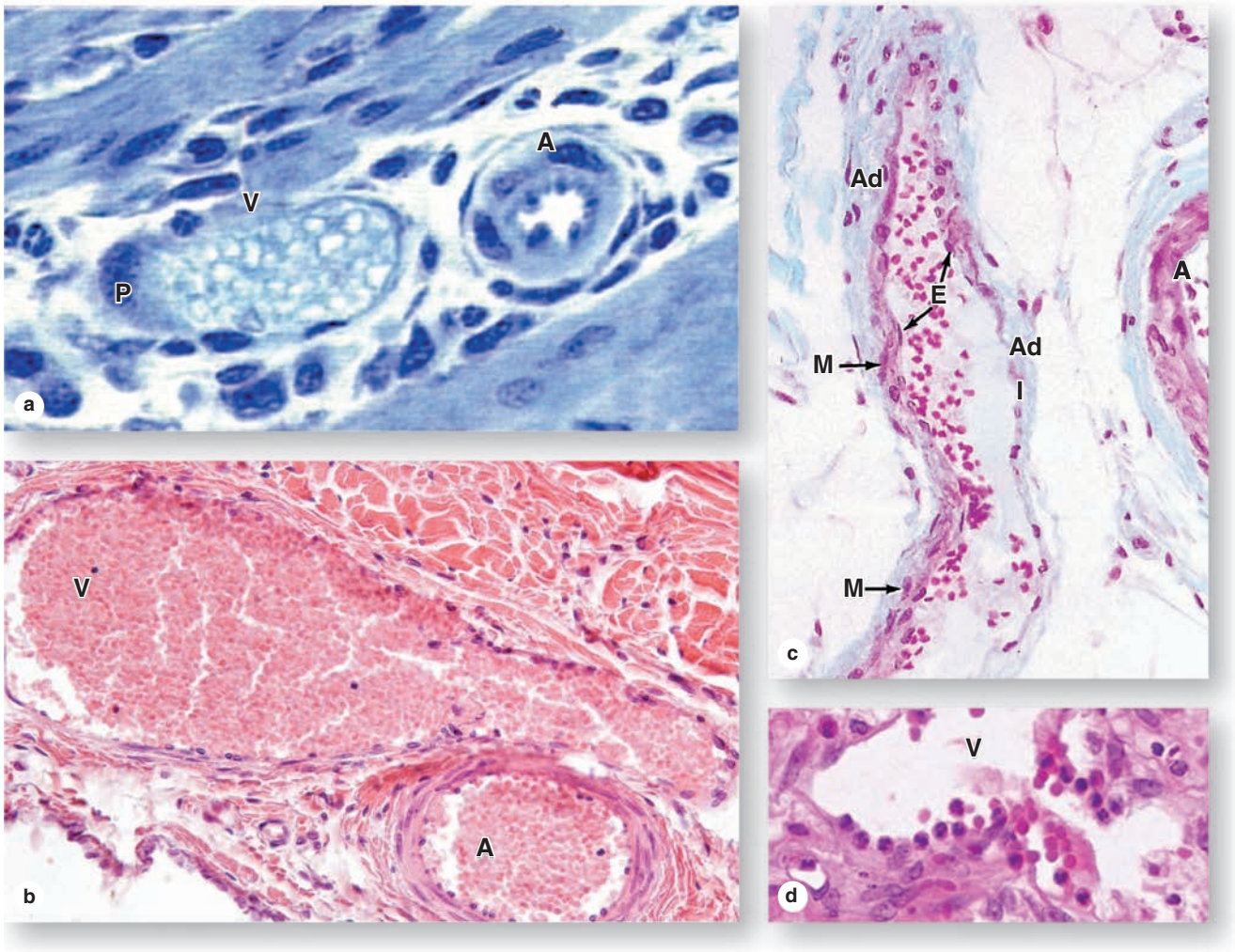
(*Used with permission from Dr Johannes Rhodin, Department of Cell Biology, New York University School of Medicine.*)

## FIGURE 11–20 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 endothelial cells are very thin and cell nuclei are more difficult to find than in smaller capillaries. Ultrastructurally sinusoidal capillaries are seen to have large fenestrations through the cells and large discontinuities between the cells and through the basal lamina. (X200; H&E)

FIGURE **11–21** **Venules.**




A series of increasingly larger and more organized venules lie between capillaries and veins.

**(a)** Compared to arterioles (**A**), postcapillary venules (**V**) have large lumens and an intima of simple endothelial cells, with occasional pericytes (**P**). (X400; Toluidine blue [TB])

**(b)** Larger collecting venules (**V**) have much greater diameters than arterioles (**A**), but the wall is still very thin, consisting of an endothelium with more numerous pericytes or smooth muscle cells. (X200; H&E)

**(c)** The muscular venule cut lengthwise here 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 adventitia (**Ad**). Part of an arteriole (**A**) shows a thicker wall than the venule. (X200; Masson trichrome)

As discussed with white blood cells in Chapter 12, postcapillary venules are important as the site in the vasculature where these cells leave the circulation to become functional in the interstitial space of surrounding tissues when such tissues are inflamed or infected.

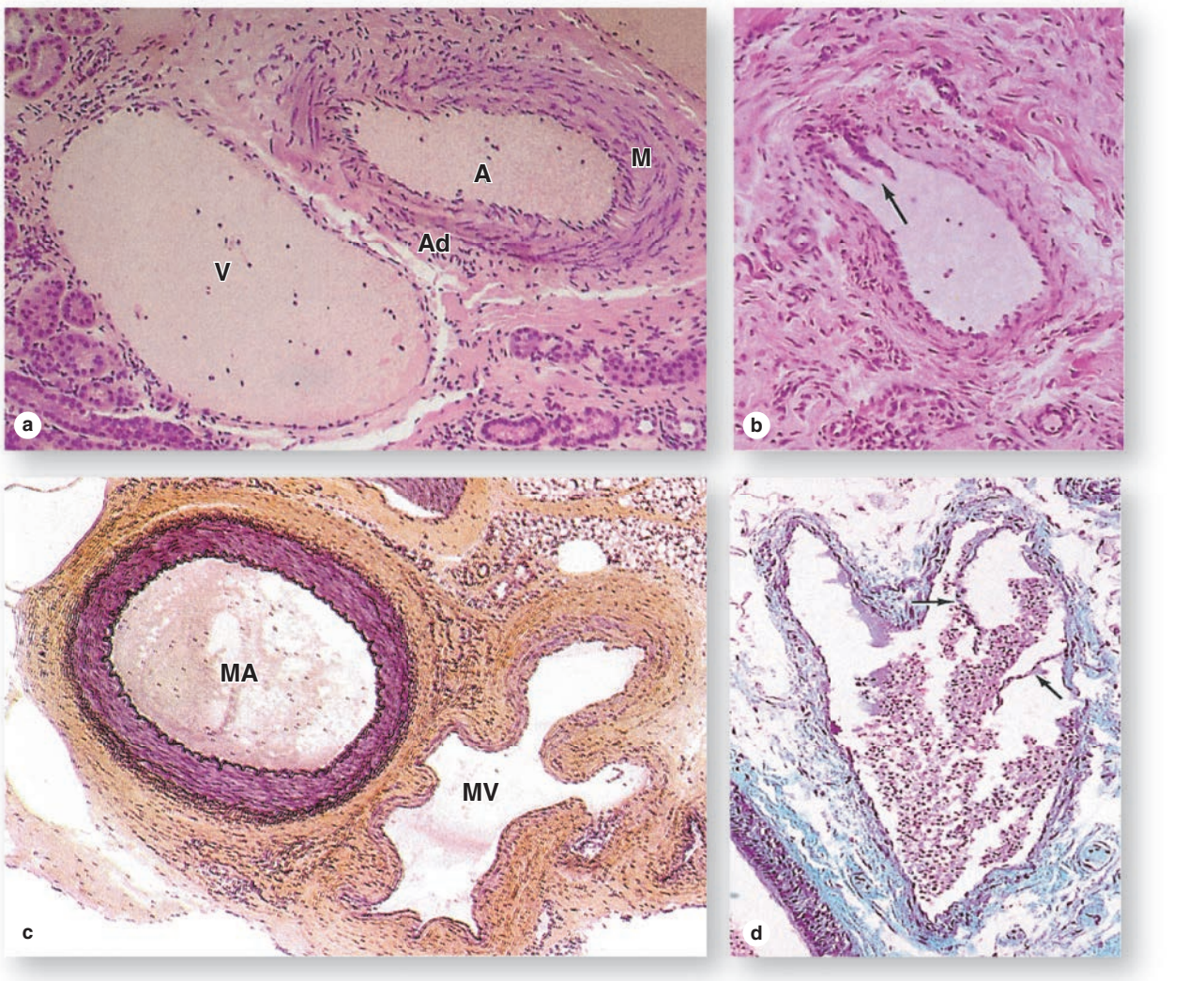
**(d)** Postcapillary venule (**V**) from an infected small intestine shows several leukocytes adhering to and migrating across the intima. (X200; H&E)

## › LYMPHATIC VASCULAR SYSTEM

In addition to the blood vasculature, the body has a system of very thin-walled channels, the **lymphatic capillaries**, which collect excess interstitial fluid from the tissue spaces as **lymph** and return it to the blood. Like the interstitial fluid, lymph is usually rich in lightly staining proteins but does not normally contain red blood cells, although lymphocytes and other white blood cells may normally be present (Figure 11–24a). With exceptions such as the bone marrow and most of the CNS, most tissues with blood microvasculature also contain lymphatic capillaries (or lymphatics).

Lymphatic capillaries originate locally as tubes of very thin endothelial cells which lack tight junctions and rest on a

## FIGURE 11–22 Veins.




Veins usually travel as companions to 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 showing valve in an oblique section of a small vein (arrow). Valves are thin folds of intima projecting well into the lumen, which act to prevent backflow of blood. (X200; Aldehyde fuchsin & van Gieson)

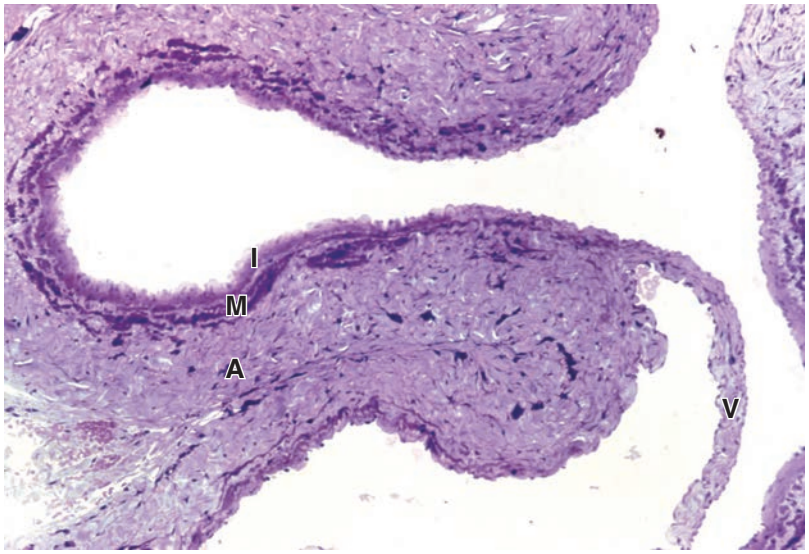
**(c)** Micrograph of a medium vein (**MV**) shows a thicker wall but still less prominent than that of the accompanying muscular artery (**MA**). Both the media and adventitia are better developed, but the wall is often folded around the relatively large lumen (X100; Aldehyde fuchsin & van Gieson).

**(d)** Micrograph of a medium vein contains blood and shows valve folds (arrows). (X200; Masson trichrome)

discontinuous basal lamina. Fine anchoring filaments of collagen extend from the basal lamina to the surrounding connective tissue, preventing collapse of the vessels. Interstitial fluid enters lymphatic capillaries by flowing between endothelial cells and by transcytosis. Specific domains of adjacent endothelial cells also lack hemidesmosome connections to the basal lamina and extend into the lumen to form leaflets of valves facilitating fluid entry and preventing most backflow of lymph (Figure 11–24b).

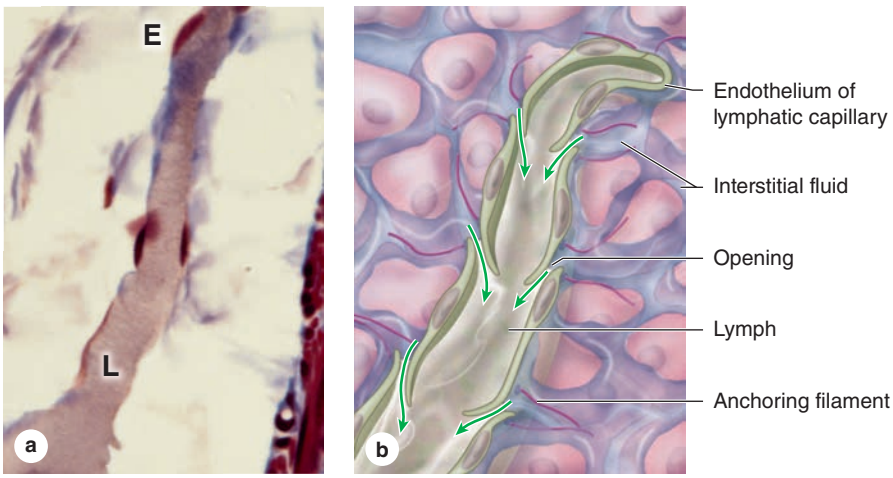
Lymphatic capillaries converge into larger **lymphatic vessels** with thin walls and increasing amounts of connective tissue and smooth muscle which never form clearly distinct outer tunics (Figure 11–25). Like veins lymphatic vessels have valves comprised of complete intimal folds. Interposed in the

## FIGURE 11–23 Wall of large vein with valve.




Large veins have a muscular media layer (**M**) which is very thin compared to the surrounding adventitia (**A**) of dense irregular connective tissue. The wall is often folded as shown here, with the intima (**I**) projecting into the lumen as a valve (**V**) composed of the subendothelial connective tissue with endothelium on both sides. (X100; PT)

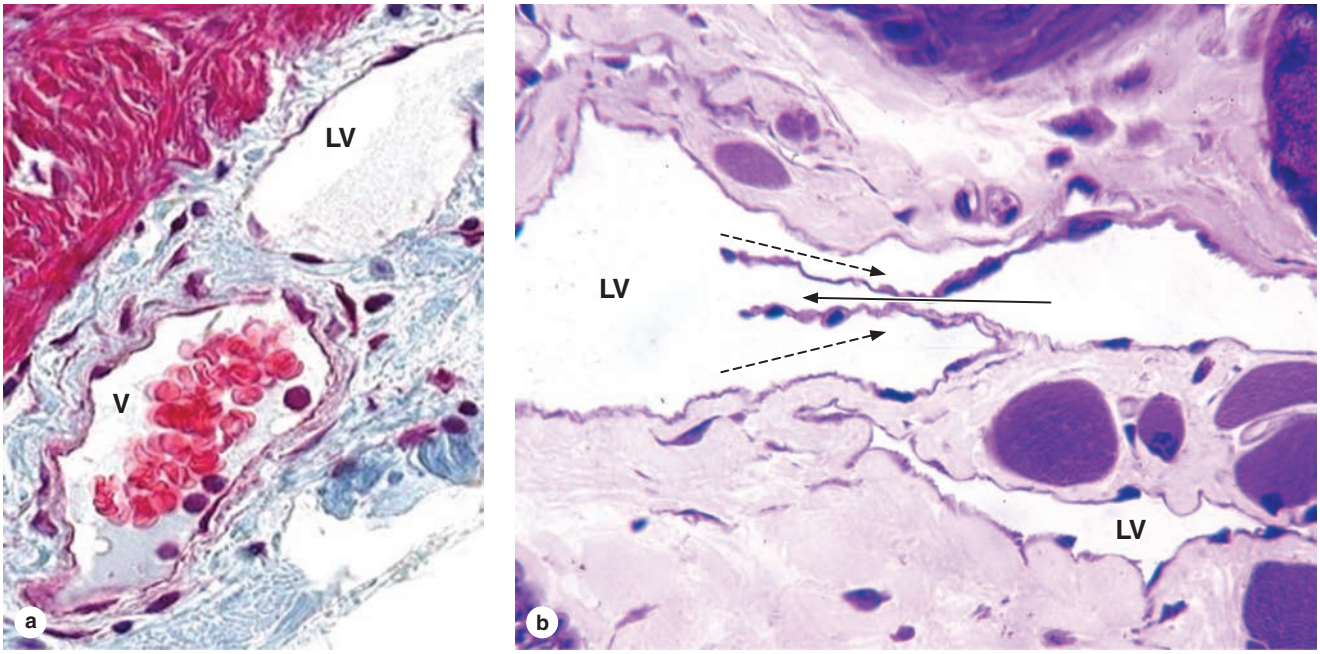
## FIGURE 11–24 Lymphatic capillary.




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 shows 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 more details about lymphatics, including the **openings between the endothelial cells**. The openings are held in place by **anchoring filaments** containing elastin and are covered by extensions of the endothelial cells. **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 capillaries.

## FIGURE 11–25 Lymphatic vessels and valve.




Lymphatic vessels are formed by the merger of lymphatic capillaries, but their walls remain extremely thin. **(a)** Cross section shows a lymphatic vessel (**LV**) near a venule (**V**), whose wall is thick by comparison. Lymphatic vessels normally do not contain red blood cells, which provide another characteristic distinguishing them from venules. (X200; Mallory trichrome)

**(b)** Lymphatic vessel (**LV**) in muscle cut longitudinally 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 lymphatic vessel is a lymphatic capillary with a wall consisting only of endothelium. (X200; PT)

path of these larger lymphatic vessels are **lymph nodes**, where lymph is processed by cells of the immune system (discussed in Chapter 14). In histological sections lymphatic vessels are often dilated with lymph. As in veins, lymphatic circulation is aided by external forces (eg, contraction of surrounding skeletal muscle) with the valves keeping lymph flow unidirectional.

Lymphatic vessels ultimately converge as two large trunks: the **thoracic duct** and the **right lymphatic duct**, which empty lymph back into the blood. The thoracic duct connects with the blood circulatory system near the junction of the left internal jugular vein with the left subclavian vein, whereas the right lymphatic duct enters near the confluence of the right subclavian vein and the right internal jugular vein. The structure of these largest lymphatic vessels is similar to that of small veins. 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 vascular system is a major distributor of lymphocytes, antibodies, and other immune components that are carried through many organs to and from lymph nodes and other lymphoid tissues.

### ›› MEDICAL APPLICATION

Lymphatics and larger lymphatic vessels are clinically important because (among other reasons) they facilitate the spread of pathogens, parasites, and malignant cells in the body. Surgical removal of lymph nodes, standard procedure to determine the occurrence of cancer metastasis, can disrupt the lymphatic drainage and produce swelling or **lymphedema**, in tissues of the affected region.

## The Circulatory System SUMMARY OF KEY POINTS

### Heart

- The heart has three major layers: (1) the inner **endocardium** of endothelium and subendothelial connective tissue; (2) the **myocardium** of cardiac muscle; and (3) the **epicardium**, connective tissue with many adipocytes and covered by mesothelium.
- The **cardiac conducting system** stimulates rhythmic contractions and consists of modified cardiac muscle fibers forming the **sinoatrial (SA) and atrioventricular (AV) nodes**, the **atrioventricular bundle (of His)**, left and right bundle branches, and **Purkinje fibers**.
- **Purkinje fibers**, located in the subendocardial layer of both ventricles, are distinguished from contractile fibers by their greater diameter, abundant glycogen, and more sparse bundles of myofibrils.
- Masses of dense irregular connective tissue make up the **cardiac skeleton**, which surrounds the bases of all heart valves, separates the atria from the ventricles, and provides insertions for cardiac muscle.

### Vasculature

- Macroscopically visible blood vessels have three major layers or **tunics**: (1) The **intima** includes the endothelium, connective tissue, and an internal elastic lamina in larger vessels; (2) the **media** contains alternating layers of smooth muscle and collagen or elastic lamellae; and (3) the **adventitia** (or externa) contains connective tissue, small vessels (**vasa vasorum**), and nerves.
- Through the vasculature, **endothelial cells** are not simply heart and vessel liners; they actively produce factors that prevent blood clotting, factors that cause adjacent smooth muscle cells to contract or relax, and factors that initiate inflammation at sites of damage or infection.
- Arteries are grouped by size and wall composition: (1) **large elastic arteries**, with fenestrated elastic laminae in the thick tunica media; (2) **muscular**, **medium-sized arteries**; and (3) **small arteries**, with fewer than 10 layers of smooth muscle in the media.
- A **microvasculature** too small for surgical manipulation permeates most organs and consists of (1) **arterioles**, with one to three smooth muscle layers; (2) **capillaries**, consisting only of an intima endothelial layer; and (3) **venules**, with large lumens and thin walls, which drain capillaries.
- Terminal arterioles branch into **metarterioles**, in which smooth muscle **sphincters** contract to resist blood flow and relax cyclically to allow pulsatile flow of blood into an anastomosing **capillary bed**, where **metabolic exchange** with surrounding cells occurs.
- Capillaries are classified as three structural and functional types, with features that allow different degrees of molecular or even cellular exchange: (1) **continuous capillaries** with many tight junctions so that all exchange must occur through the cells; (2) **fenestrated capillaries** with small pores or fenestrations through the cells; and (3) **discontinuous capillaries**, or **sinusoids**, with larger lumens, large spaces between the endothelial cells, and a discontinuous basal lamina.
- Capillary beds generally drain into **venules**, the last segment of the microvasculature; **postcapillary venules** are the sites at which white blood cells enter damaged or infected tissues.
- The endothelium of continuous capillaries and postcapillary venules is frequently surrounded by thin cells called **pericytes**, whose contractions facilitate blood flow and which can give rise to smooth muscle and connective tissue during microvascular remodeling or repair.
- Two alternative microvascular pathways include **arteriovenous anastomoses**, or **AV shunts**, in which arterioles can bypass a capillary bed, and **venous portal systems**, in which venules draining a capillary bed quickly branch again to form another capillary bed.
- **Small, medium, and large veins**, all with lumen diameters exceeding the thickness of the wall, carry blood back to the heart, with intimal **valves** preventing backflow, and have increasingly well-developed tunics.

### Lymphatic Vessels

- Interstitial fluid that is not pulled into venules by colloidal osmotic pressure drains as **lymph** into blind vessels called **lymphatics**, or **lymphatic capillaries**, which have very thin endothelial cell walls with spaces between the cells.
- Lymphatics converge into larger, thin-walled **lymphatic vessels** in which lymph is propelled by movements of surrounding muscles and organs, with intimal **valves** keeping the flow unidirectional.
- The largest lymphatic vessels, the **thoracic duct** and **right lymphatic duct**, both with walls having tunics like those of veins, return lymph to the circulatory system by joining veins near the heart.

## The Circulatory System ASSESS YOUR KNOWLEDGE

1. Vasa vasorum serve a function analogous to that of which of the following?
   a. Valves
   b. Basal lamina
   c. Coronary arteries
   d. Endothelial diaphragms
   e. Arterioles

2. What tissue is directly associated with and extends into the heart valves?
   a. Myocardium
   b. Epicardium
   c. Atrioventricular bundle of His
   d. Cardiac skeleton
   e. Pericardium

3. Which of the following is true for ventricles?
   a. Located at the base of the heart
   b. Myocardial cells contains abundant granules
   c. Receive blood directly from the venae cavae and pulmonary veins
   d. Walls contain Purkinje fibers of the right and left branches from the atrioventricular bundle
   e. Contain more elastic fibers than the atria

4. Individuals with Marfan syndrome have mutations in the fibrillin gene and commonly experience aortic aneurisms. What portion of the arterial wall is most likely to be affected by the malformed fibrillin?
   a. Endothelium
   b. Tunica intima
   c. Tunica media
   d. Tunica adventitia
   e. Vasa vasorum