

Alterations in Blood Flow

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Blood vessels function in the delivery of oxygen and nutrients to the tissues and in the removal of waste products from the tissues. Unlike disorders of the respiratory system or central circulation that cause hypoxia and impair oxygenation of tissues throughout the body, the effects of blood vessel disease usually are limited to local tissues supplied by a particular vessel or group of vessels.

Disturbances in blood flow can result from pathologic changes in the vessel wall (*i.e.*, atherosclerosis, vasculitides), acute vessel obstruction caused by thrombus or embolus, vasospasm (*i.e.*, Raynaud's phenomenon), abnormal vessel dilation (*i.e.*, arterial aneurysms or varicose veins), or compression of blood vessels by extravascular forces (*i.e.*, tumors, edema, or firm surfaces such as those associated with pressure ulcers).

DISORDERS OF THE ARTERIAL CIRCULATION

The arterial system distributes blood to all the tissues in the body. There are three types of arteries: large arteries, including the aorta and its distal branches; medium-size arteries, such as the coronary and renal arteries; and small arteries and arterioles that pass through the tissues. Each of these different types of arteries tends to be affected by different disease processes.

Pathology of the arterial system affects body function by impairing blood flow. The effect of impaired blood flow on the body depends on the structures involved and the extent of altered flow. The term *ischemia* (*i.e.*, holding back of blood) denotes a reduction in arterial flow to a level that is insufficient to meet the oxygen demands of the tissues. *Infarction* refers to an area of ischemic necrosis in an organ produced by occlusion of its blood supply. The discussion in this section focuses on hyperlipidemia, atherosclerosis, arterial aneurysms, vasculitides, and arterial disease of the extremities.

Hyperlipidemia

Hyperlipidemia with elevated cholesterol levels is a major cause of atherosclerosis with its attendant risk of heart attack and stroke. An estimated 41.3 million Americans have high

KEY CONCEPTS

DISORDERS OF THE ARTERIAL CIRCULATION

- The arterial system delivers oxygen and nutrients to the tissues. Disorders of the arterial circulation produce ischemia owing to narrowing of blood vessels, thrombus formation associated with platelet adhesion, and weakening of the vessel wall.
- Atherosclerosis is a progressive disease characterized by the formation of fibrofatty plaques in the intima of large and medium-sized arteries, producing a decrease in blood flow due to a narrowing of the vessel lumen.
- Aneurysms represent an abnormal localized dilatation of an artery due to a weakness in the vessel wall. As the aneurysm increases in size, the tension in the wall of the vessel increases, predisposing it to rupture.

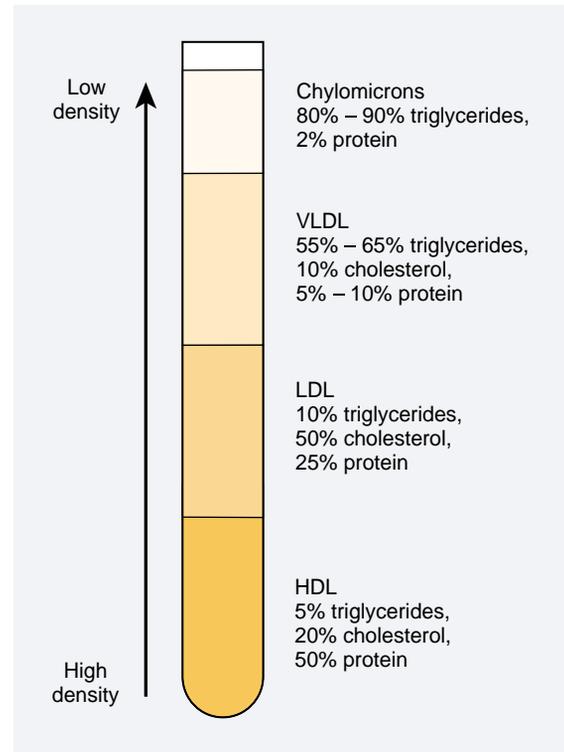
serum cholesterol levels that could contribute to a heart attack, stroke, or other cardiovascular event associated with atherosclerosis.¹

Lipoproteins

Because cholesterol and triglyceride are insoluble in plasma, they are encapsulated by special fat-carrying proteins called *lipoproteins* for transport in the blood. There are five types of lipoproteins, classified by their densities as measured by ultracentrifugation: chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) (see Fig. 15-1).

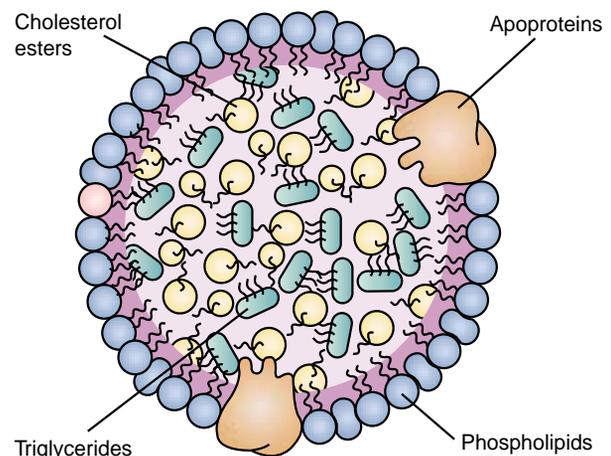
Each type of lipoprotein consists of a large molecular complex of lipids combined with proteins called *apoproteins*.^{2,3} The major lipid constituents are cholesterol esters, triglycerides, nonesterified cholesterol, and phospholipids. The insoluble cholesterol esters and triglycerides are located in the hydrophobic core of the lipoprotein macromolecule, surrounded by the soluble phospholipids, nonesterified cholesterol, and apoproteins (Fig. 15-2). Nonesterified cholesterol and phospholipids provide a negative charge that allows the lipoprotein to be soluble in plasma. The apoproteins control the interactions and ultimate metabolic fate of the lipoproteins. Some of the apoproteins activate the lipolytic enzymes that facilitate the removal of lipids from the lipoproteins; others serve as a reactive site that cellular receptors can recognize and use in the endocytosis and metabolism of the lipoproteins.

There are two sites of lipoprotein synthesis: the small intestine and the liver. The chylomicrons, which are the largest of the lipoprotein molecules, are synthesized in the wall of the small intestine. They are involved in the transport of dietary triglycerides and cholesterol that have been absorbed from the gastrointestinal tract. Chylomicrons transfer their triglycerides to the cells of adipose and skeletal muscle tissue. The remnant chylomicron particles, which contain cholesterol, are then taken up by the liver, and the cholesterol is used in the synthesis of VLDL or excreted in the bile.



■ **FIGURE 15-1** ■ Lipoproteins are named based on their protein content, which is measured as density. Because fats are less dense than proteins, as the proportion of triglycerides decreases, the density increases.

The liver synthesizes and releases VLDL and HDL. The VLDLs contain large amounts of triglycerides and lesser amounts of cholesterol esters.⁴ They provide the primary pathway for transport of the triglycerides produced in the liver, as opposed to those obtained from the diet. Like chylomicrons, VLDLs carry their triglycerides to fat and muscle cells, where the triglycerides are removed. The resulting IDL fragments are reduced in triglyceride content and enriched in cholesterol. They



■ **FIGURE 15-2** ■ General structure of a lipoprotein. The cholesterol esters and triglycerides are located in the hydrophobic core of the macromolecule, surrounded by phospholipids and apoproteins.

are taken to the liver and recycled to form VLDL, or converted to LDL in the vascular compartment. The pathways for triglyceride and cholesterol transport are shown in Figure 15-3.

LDL, sometimes called the *bad cholesterol*, is the main carrier of cholesterol. The IDLs are the main source of LDL. The LDL is removed from the circulation by either LDL receptors or by scavenger cells such as monocytes or macrophages. Approximately 70% of LDL is removed by way of the LDL receptor-dependent pathway.⁴ Although LDL receptors are widely distributed, approximately 75% are located on hepatocytes; thus the liver plays an extremely important role in LDL metabolism. Tissues with LDL receptors can control their cholesterol intake by adding or removing LDL receptors.

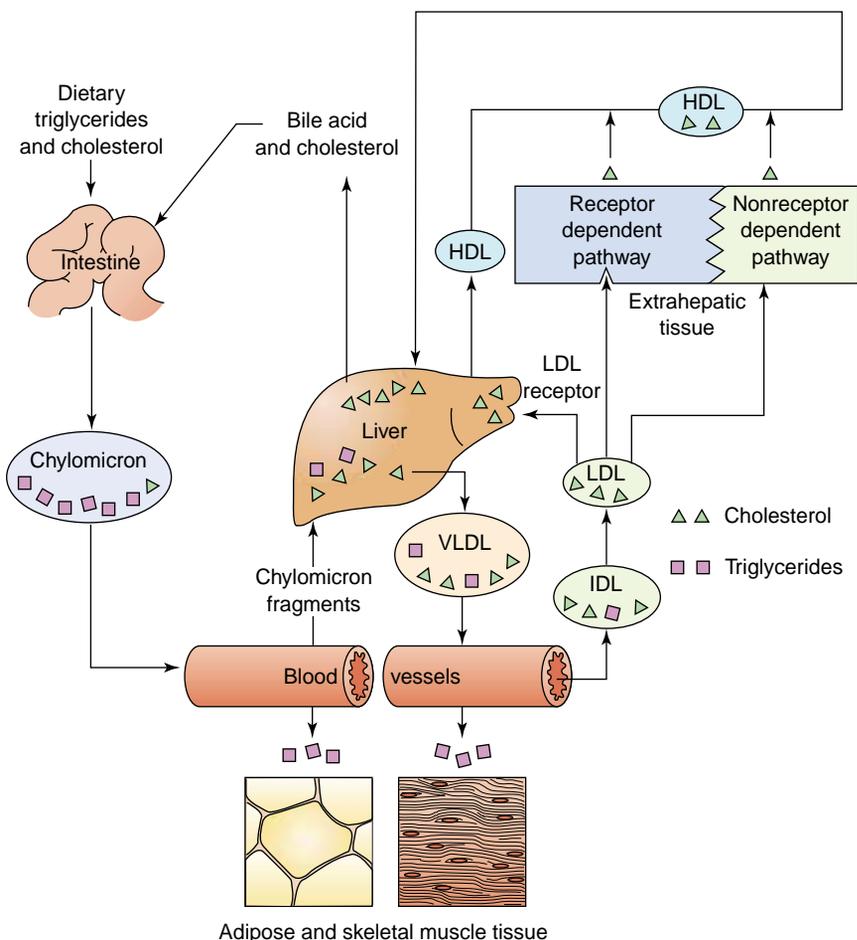
The scavenger cells, such as the monocytes and macrophages, have receptors that bind LDL that has been oxidized or chemically modified. The amount of LDL that is removed by the “scavenger pathway” is directly related to the plasma cholesterol level. When there is a decrease in LDL receptors or when LDL levels exceed receptor availability, the amount of LDL that is removed by scavenger cells is greatly increased. The uptake of LDL by macrophages in the arterial wall can result in the accumulation of insoluble cholesterol esters, the formation of foam cells, and the development of atherosclerosis.

HDL is synthesized in the liver and often is referred to as the *good cholesterol*. Epidemiological studies show an inverse relation between HDL levels and the development of atherosclerosis.⁵ It

is thought that HDL, which is low in cholesterol and rich in surface phospholipids, facilitates the clearance of cholesterol from atheromatous plaques and transports it back to the liver, so that it can be excreted in the bile. HDL also is believed to inhibit the uptake of LDL into the arterial wall. It has been observed that regular exercise and moderate alcohol consumption increase HDL levels. Smoking and diabetes, which are in themselves risk factors for atherosclerosis, are associated with decreased levels of HDL.⁴

Hypercholesterolemia

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults has published a classification system for hyperlipidemia that list the laboratory values for optimal to very high levels of LDL cholesterol, desirable to high levels of total cholesterol, and low and high levels of HDL cholesterol (see Table 15-1).⁶ The NCEP recommends that all adults 20 years of age and older should have a fasting lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) measured once every 5 years.⁶ If testing is done in the nonfasting state, only the total cholesterol and HDL are considered useful. A follow-up lipoprotein profile should be done on persons with nonfasting total cholesterol levels ≥ 200 mg/dL or HDL levels < 40 mg/dL. Lipoprotein measurements are particularly important in persons at high risk for the development of coronary heart disease (CHD).



■ FIGURE 15-3 ■ Schematic representation of the exogenous and endogenous pathways for triglyceride and cholesterol transport.

TABLE 15-1 NCEP Adult Treatment Panel III Classification of LDL, Total, and HDL Cholesterol

Cholesterol Level (mg/dL)	Classification
LDL Cholesterol	
<100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

National Institutes of Health Expert Panel. (2001). *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. (NIH publication no. 01-3670). Bethesda, MD: National Institutes of Health.

Causes. Three factors—genetics, nutrition, and metabolic diseases—contribute to an increase in blood lipid levels. Many types of hyperlipidemia have a genetic basis. There may be a defective synthesis of the apoproteins, a lack of LDL receptors, defective LDL receptors, or defects in the intracellular handling of cholesterol.² The LDL receptor is deficient or defective in the genetic disorder known as *familial hypercholesterolemia*. This autosomal dominant type of hyperlipoproteinemia results from a mutation in the gene specifying the receptor for LDL. Because most of the circulating cholesterol is removed by receptor-

dependent mechanisms, blood cholesterol levels are markedly elevated in persons with this disorder. The disorder is probably one of the most common of all mendelian disorders; the frequency of heterozygotes is 1 in 500 persons in the general population.² Although heterozygotes commonly have an elevated cholesterol level from birth, they do not experience symptoms until adult life, when *xanthomas* (*i.e.*, cholesterol deposits) develop along the tendons and atherosclerosis occurs (Fig. 15-4). Myocardial infarction before the age of 40 years is common. Homozygotes are much more severely affected; they develop cutaneous xanthomas in childhood and may experience myocardial infarction by the age of 20 years.²

Secondary causes of hyperlipoproteinemia include diets high in saturated fats and cholesterol, obesity caused by high-calorie intake, and diabetes mellitus. Diets that are high in triglycerides and saturated fats increase cholesterol synthesis and suppress LDL receptor activity. Excess ingestion of cholesterol reduces the formation of LDL receptors and thereby decreases LDL removal. In diabetes mellitus, metabolic derangements cause an elevation of lipoproteins.⁷

The management of hyperlipidemia focuses on dietary and lifestyle modifications; when these are unsuccessful, pharmacologic treatment may be necessary. Lifestyle modification includes increased emphasis on physical activity, dietary measures to reduce LDL cholesterol levels, and weight reduction for people who are overweight. The aim of dietary therapy is to reduce total and LDL cholesterol levels and increase HDL levels. Three dietary elements affect serum cholesterol and its lipoprotein fractions: excess calorie intake, saturated fats, and cholesterol. High-calorie diets increase the production of VLDL, with triglyceride elevation and high conversion of VLDL to LDL. Saturated fats and cholesterol in the diet tend to increase LDL cholesterol levels.

The third report of the NCEP continues to identify reduction in LDL cholesterol as the primary target for cholesterol-lowering therapy, particularly in people at risk for CHD.⁶ Lipid-lowering drugs work mainly by decreasing cholesterol absorption from the intestine, decreasing cholesterol synthesis by the liver, or

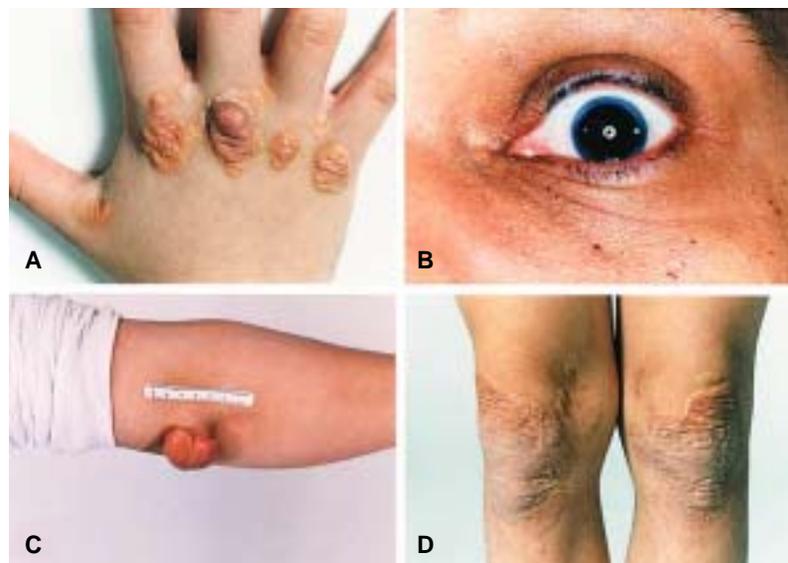


FIGURE 15-4 Xanthomas in the skin and tendons (A, C, D). Arcus lipoides represents the deposition of lipids in the peripheral cornea (B). (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 506]. Philadelphia: Lippincott Williams & Wilkins)

inhibiting VLDL release. Drugs that act directly to decrease cholesterol levels also have the beneficial effect of further lowering cholesterol levels by stimulating the production of additional LDL receptors. Because many of these drugs have significant adverse effects, they usually are used only in persons with significant hyperlipidemia that cannot be controlled by other means, such as diet.

Atherosclerosis

Atherosclerosis is a type of arteriosclerosis or hardening of the arteries. The term *atherosclerosis*, which comes from the Greek words *atheros* (meaning “gruel” or “paste”) and *sclerosis* (meaning “hardness”), denotes the formation of fibrofatty lesions in the intimal lining of the large and medium-size arteries such as the aorta and its branches, the coronary arteries, and the large vessels that supply the brain. Atherosclerosis contributes to more mortality and more serious morbidity than any other disorder in the western world.⁴ The major complications of atherosclerosis, including ischemic heart disease, stroke, and peripheral vascular disease, account for more than 40% of the deaths in the United States.⁸

Risk Factors

The cause or causes of atherosclerosis have not been determined with certainty. However, epidemiologic studies have identified predisposing risk factors, which are listed in Chart 15-1.^{2,4} Some risk factors can be affected by a change in health behavior and others cannot. Risk factors that cannot be changed in-

clude age, male gender, and family history of premature coronary heart disease.

The tendency to develop atherosclerosis appears to run in families. Persons who come from families with a strong history of heart disease or stroke caused by atherosclerosis are at greater risk for developing atherosclerosis than are those with a negative family history. Several genetically determined alterations in lipoprotein and cholesterol metabolism have been identified, and it seems likely that others will be identified in the future. The incidence of atherosclerosis also increases with age. Other factors being equal, men are at greater risk for coronary heart disease than are premenopausal women, probably because of the protective effects of natural estrogens. After menopause, the incidence of atherosclerotic-related diseases in women increases, and by the 7th to 8th decade of life, the frequency of myocardial infarction in the two sexes tends to equalize.⁴

The major risk factors that can be affected by a change in health behaviors include hyperlipidemia, cigarette smoking, hypertension, and diabetes mellitus. These risk factors can often be modified or controlled by a change in diet, exercise, health care practices, or medications. The presence of hyperlipidemia is the strongest risk factor for atherosclerosis in persons younger than 45 years of age. Both primary and secondary hyperlipidemia increase the risk. Cigarette smoking is closely linked with coronary heart disease and sudden death. Cessation of smoking reduces the risk substantially. High blood pressure produces mechanical stress on the vessel endothelium. It is a major risk factor for atherosclerosis in all age groups and may be as important or more important than hypercholesterolemia after the age of 45 years. Both systolic and diastolic pressures are important in increasing risk. Diabetes mellitus (type 2) typically develops in middle-aged persons and those who are overweight. Diabetes elevates blood lipid levels and otherwise increases the risk of atherosclerosis (see Chapter 32). Controlling other risk factors, such as hypertension and hypercholesterolemia, is particularly important in persons with diabetes.

Other factors, known as “soft” risk factors, are not as convincing as the established risk factors. These include insufficient physical activity, a stressful lifestyle, and obesity. These “soft” risk factors commonly are linked with the established and other contributing risk factors. For example, obesity and physical inactivity often are observed in the same person. Both conditions are reported to bring about elevations in blood lipid levels. Likewise, major risk factors such as cigarette smoking are closely associated with stress and personality patterns.

There are a number of other less well-established risk factors for atherosclerosis, including high serum homocysteine levels, elevated serum C-reactive protein, and infectious agents.^{9,10} Homocysteine is derived from the metabolism of dietary methionine, an amino acid that is abundant in animal protein. Homocysteine inhibits elements of the anticoagulant cascade and is associated with endothelial damage, which is thought to be an important first step in the development of atherosclerosis.¹⁰ Factors tending to increase plasma levels of homocysteine include lower serum levels of folate and vitamins B₆ and B₁₂; genetic defects in homocysteine metabolism; renal impairment; malignancies, increasing age; male gender; and female menopause.¹¹ *C-reactive protein* (CRP) is a serum marker for systemic inflammation. Several prospective studies have indicated that elevated CRP levels are associated with vascular dis-

CHART 15-1 Risk Factors in Coronary Heart Disease Other Than Low-Density Lipoproteins

Positive Risk Factors

Age

Men: ≥ 45 years

Women: ≥ 55 years or premature menopause without estrogen replacement therapy

Family history of premature coronary heart disease (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)

Current cigarette smoking

Hypertension ($\geq 140/90$ mm Hg* or on antihypertensive medication)

Low HDL cholesterol (< 40 mg/dL*)

Diabetes mellitus

Negative Risk Factor

High HDL cholesterol (≥ 60 mg/dL)

HDL, high-density lipoprotein.

*Confirmed by measurements on several occasions.

(Modified from National Institute of Health Expert Panel [2001]. *Third Report of the National Cholesterol Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]*. [NIH Publication No. 01-3670]. Bethesda, MD: National Institutes of Health.)

ease. The pathophysiological role of CRP in atherosclerosis has not been defined, but it may increase the likelihood of thrombus formation.¹⁰

Recently, there has been increased interest in the possible connection between infectious agents (*Chlamydia pneumoniae*, *herpesvirus hominis*, *cytomegalovirus*) and the development of vascular disease. The presence of these organisms in atheromatous lesions has been demonstrated by immunocytochemistry, but no cause-and-effect relationship has been established. The organisms may play a role in atherosclerotic development by initiating and enhancing the inflammatory response.¹²

Pathology and Pathogenesis

The lesions associated with atherosclerosis are of three types: the fatty streak, the fibrous atheromatous plaque, and the complicated lesion. The latter two are responsible for the clinically significant manifestations of the disease.

Fatty streaks are thin, flat yellow intimal discolorations that progressively enlarge by becoming thicker and slightly elevated as they grow in length (Fig. 15-5). Histologically, they consist of macrophages and smooth muscle cells that have become distended with lipid to form foam cells. Fatty streaks are present in children, often in the first year of life.^{2,4} This occurs regardless of geographic setting, gender, or race. They increase in number until about age 20 years, and then they remain static or regress. There is controversy about whether fatty streaks, in and of themselves, are precursors of atherosclerotic lesions.

The *fibrous atheromatous plaque* is the basic lesion of clinical atherosclerosis. It is characterized by the accumulation of intracellular and extracellular lipids, proliferation of vascular smooth muscle cells, and formation of scar tissue. The lesions begin as a gray to pearly white elevated thickening of the vessel intima with a core of extracellular lipid (mainly cholesterol, which usually is complexed to proteins) covered by a fibrous cap of connective tissue and smooth muscle (Fig. 15-6). As the lesions increase in size, they encroach on the lumen of the artery and eventually may occlude the vessel or predispose to throm-



■ **FIGURE 15-6** ■ Fatty plaque of atherosclerosis. The aorta shows discrete, raised, tan plaques. Focal ulcerations are also present. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 497]. Philadelphia: Lippincott Williams & Wilkins)

bus formation, causing a reduction of blood flow. Because blood flow is related to the fourth power of the radius, reduction in blood flow becomes more severe as the disease progresses.

The more advanced *complicated lesions* are characterized by hemorrhage, ulceration, and scar tissue deposits. Thrombosis is the most important complication of atherosclerosis. It is



■ **FIGURE 15-5** ■ Fatty streaks of atherosclerosis. The aorta of a young man shows numerous fatty streaks on the luminal surface when stained with Sudan red, shown on the left. The unstained specimen is shown on the right. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 496]. Philadelphia: Lippincott Williams & Wilkins)

caused by slowing and turbulence of blood flow in the region of the plaque and ulceration of the plaque. The thrombus may cause occlusion of small vessels in the heart and brain. Aneurysms may develop in arteries weakened by extensive plaque formation.

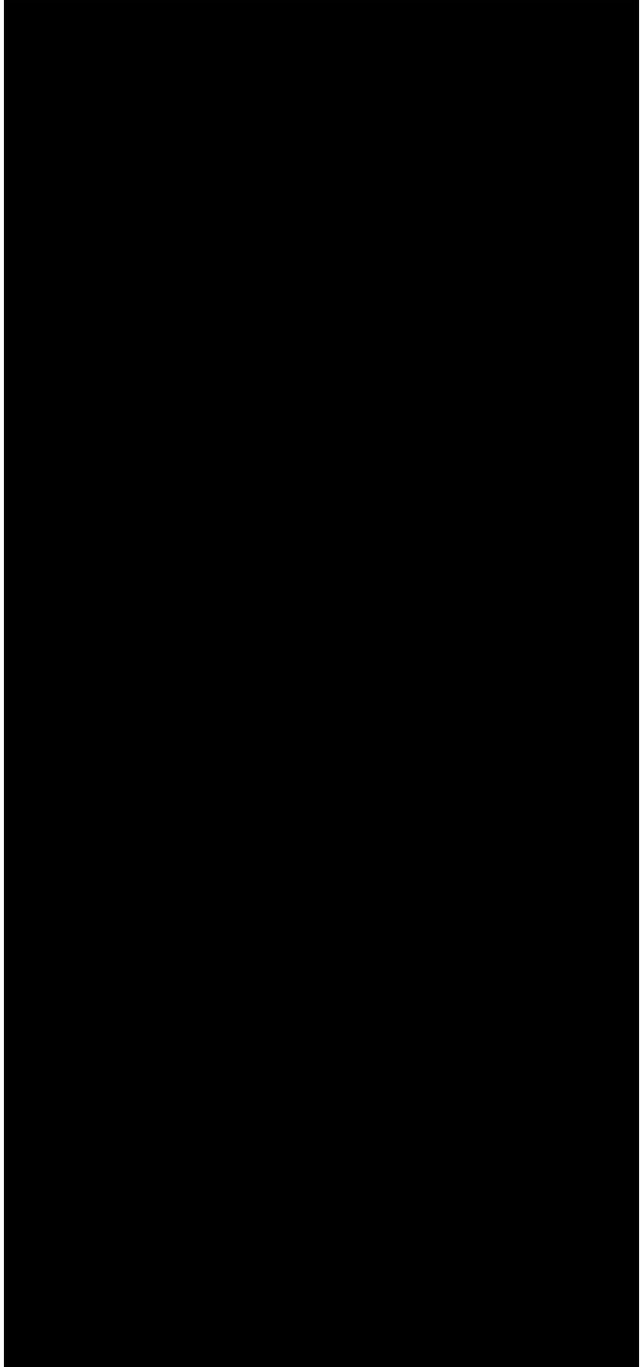
Although the risk factors associated with atherosclerosis have been identified through epidemiologic studies, many unanswered questions remain regarding the mechanisms by which these risk factors contribute to the development of atherosclerosis. There is increasing evidence that atherosclerosis is at least partially the result of (1) endothelial injury with leukocyte (lymphocyte and monocyte) adhesion and platelet adherence, (2) smooth muscle cell emigration and proliferation, (3) lipid engulfment of activated macrophages, and (4) subsequent development of an atherosclerotic plaque with lipid core (Fig. 15-7).

The vascular endothelial layer, which consists of a single layer of cells with cell-to-cell attachments, normally serves as a selective barrier that protects the subendothelial layers by interacting with blood cells and other blood components. One hypothesis of plaque formation suggests that injury to the endothelial vessel layer is the initiating factor in the development of atherosclerosis.^{2,4} A number of factors are regarded as possible injurious agents, including products associated with smoking, immune mechanisms, and mechanical stress, such as that associated with hypertension. The fact that atherosclerotic lesions tend to form where vessels branch or where there is turbulent flow suggests that hemodynamic factors also play a role.

Hyperlipidemia, particularly LDL with its high cholesterol content, is also believed to play an active role in the pathogenesis of the atherosclerotic lesion. Interactions between the endothelial layer of the vessel wall and white blood cells, particularly the macrophages (blood monocytes), normally occur throughout life; these interactions increase when blood cholesterol levels are elevated. One of the earliest responses to elevated cholesterol levels is the attachment of monocytes to the endothelium.¹⁰ The monocytes have been observed to emigrate through the cell-to-cell attachments of the endothelial layer into the subendothelial spaces, where they are transformed into macrophages. Activated macrophages release free radicals that oxidize LDL. Oxidized LDL is toxic to the endothelium, causing endothelial loss and exposure of the subendothelial tissue to blood components. This leads to platelet adhesion and aggregation and fibrin deposition. Platelets and activated macrophages release various factors that are thought to promote growth factors that modulate the proliferation of smooth muscle cells and deposition of extracellular matrix in the lesions.^{2,4} Activated macrophages also ingest oxidized LDL to become foam cells, which are present in all stages of atherosclerotic plaque formation. Lipids released from necrotic foam cells accumulate to form the lipid core of unstable plaques.

Clinical Manifestations

The clinical manifestations of atherosclerosis depend on the vessels involved and the extent of vessel obstruction. Atherosclerotic lesions produce their effects through narrowing of the vessel and production of ischemia; sudden vessel obstruction caused by plaque hemorrhage or rupture; thrombosis and formation of emboli resulting from damage to the vessel endothelium; and aneurysm formation caused by weakening of the vessel wall.⁴ In larger vessels such as the aorta, the important complications are those of thrombus formation and weakening of the vessel



wall. In medium-size arteries such as the coronary and cerebral arteries, ischemia and infarction caused by vessel occlusion are more common. Although atherosclerosis can affect any organ or tissue, the arteries supplying the heart, brain, kidneys, lower extremities, and small intestine are most frequently involved.

Aneurysms

An *aneurysm* is an abnormal localized dilatation of a blood vessel. Aneurysms can occur in different types of arterial vessels, but they are most common in the aorta. Aneurysms can assume

several forms and may be classified according to their cause, location, and anatomic features (Fig. 15-8). A *berry aneurysm* consists of a small spherical dilatation of the vessel at a bifurcation.² This type of aneurysm usually is found in the circle of Willis in the cerebral circulation. A *fusiform aneurysm* involves the entire circumference of the vessel and is characterized by a gradual and progressive dilatation of the vessel. These aneurysms, which vary in diameter (as large as 20 cm) and length, may involve the entire ascending and transverse portions of the thoracic aorta or may extend over large segments of the abdominal aorta.² A *saccular aneurysm* extends over part of the circumference of the vessel and appears saclike. An *aortic dissection* is a false aneurysm resulting from a tear in the intimal layer of the vessel that allows blood to enter the vessel wall, dissecting its layers to create a blood-filled cavity.

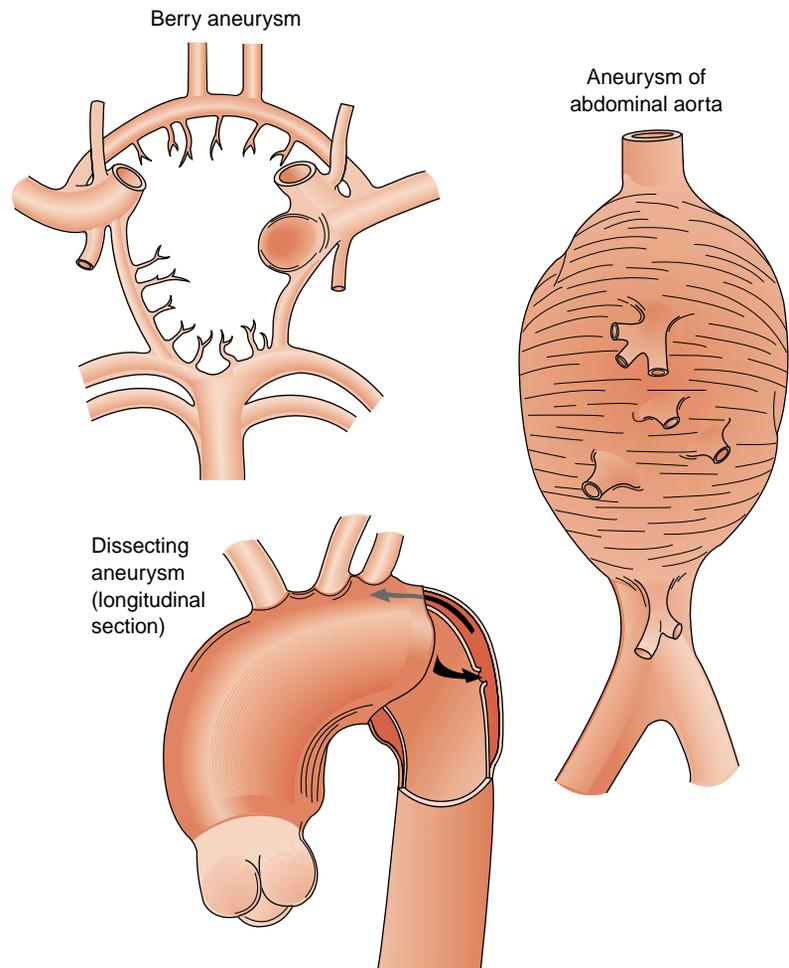
The weakness that leads to aneurysm formation may be caused by several factors, including congenital defects, trauma, infections, and atherosclerosis. Once initiated, the aneurysm grows larger as the tension in the vessel wall increases. As an aneurysm increases in diameter, the tension in the wall of the vessel increases in direct proportion to its increased size. If untreated, the aneurysm may rupture because of the increased tension. Even an unruptured aneurysm can cause damage by exerting pressure on adjacent structures and interrupting blood flow.

Aortic Aneurysms

Aortic aneurysms may involve any part of the thoracic or abdominal aorta. Aortic aneurysms occur more often in men than women. The two most common causes of aortic aneurysms are atherosclerosis and degeneration of the vessel media. Half of the people with aortic aneurysms have hypertension.² Population-based studies suggest that as many as 9% of persons older than 65 years have unsuspected and asymptomatic abdominal aortic aneurysms and that ruptured abdominal aortic aneurysms cause at least 15,000 deaths each year in the United States.¹³

Most abdominal aortic aneurysms are located below the level of the renal artery and involve the bifurcation of the aorta and proximal end of the common iliac arteries.^{2,4} They can involve any part of the vessel circumference (saccular) or extend to involve the entire circumference (fusiform). The greatest threat associated with abdominal aortic aneurysms is that of rupture. The risk of rupture rises from less than 2% for small abdominal aneurysms (those less than 4 cm in diameter) to 5% to 10% per year for aneurysms larger than 5 cm in diameter.⁴

The clinical manifestations of abdominal aortic aneurysms depend on its size and location. Most abdominal aneurysms are asymptomatic and are often discovered during a routine physical examination. Sometimes, the first evidence of an abdominal aneurysm is associated with vessel rupture. Because an aneurysm is of arterial origin, a pulsating mass may provide the



■ **FIGURE 15-8** ■ Three forms of aneurysms—berry aneurysm in the circle of Willis, fusiform-type aneurysm of the abdominal aorta, and aortic dissection.

first evidence of the disorder. As the aneurysm expands, it may compress the lumbar nerve roots, causing lower back pain that radiates to the posterior aspects of the legs. The aneurysm may extend to and produce obstruction of the renal, iliac, mesenteric arteries, or vertebral arteries that supply the spinal cord. Stasis of blood favors thrombus formation along the wall of the vessel (Fig. 15-9), and peripheral emboli may develop, causing symptomatic arterial insufficiency.

Aneurysms of the thoracic aorta are less common than abdominal aneurysms. They account for less than 10% of aortic aneurysms and may present with substernal, back, or neck pain. There also may be dyspnea, stridor, or a brassy cough caused by pressure on the trachea. Hoarseness may result from pressure on the recurrent laryngeal nerve, and there may be difficulty swallowing because of pressure on the esophagus.¹⁴

Diagnostic methods include use of ultrasound imaging, computed tomographic (CT) scans, and magnetic resonance imaging (MRI). Surgical repair, in which the involved section of the aorta is replaced with a synthetic graft of woven Dacron, frequently is the treatment of choice.¹⁵

Aortic dissection

Aortic dissection is an acute, life-threatening condition. It involves hemorrhage into the vessel wall with longitudinal tearing or separation (*i.e.*, dissection) of the vessel wall to form



■ **FIGURE 15-9** ■ Atherosclerotic aneurysm of the abdominal aorta. The aneurysm has been opened longitudinally to reveal a large thrombus in the lumen. The aorta and common iliac arteries display complicated lesions of atherosclerosis. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 521]. Philadelphia: Lippincott Williams & Wilkins)

a blood-filled channel. Unlike atherosclerotic aneurysms, aortic dissection often occurs without evidence of previous vessel dilatation. They can originate anywhere along the length of the aorta. Two thirds of dissections involve the ascending aorta.^{14,15} The second most common site is the thoracic aorta just distal to the origin of the subclavian artery.

Aortic dissections are caused by conditions that weaken or cause degenerative changes in the elastic and smooth muscle of the layers of the aorta. They are most common in the 40- to 60-year-old age group and more prevalent in men than in women.⁴ There are two risk factors that predispose to a dissection: hypertension and degeneration of the medial layer of the vessel wall. Aortic dissections also are associated with connective tissue diseases, such as Marfan's syndrome. Other factors that predispose to aortic dissection are congenital defects of the aortic valve (*i.e.*, bicuspid or unicuspid valve structures) and aortic coarctation.

Aortic dissections can originate at different sites in the aorta. When the ascending aorta is involved, expansion of the wall of the aorta may impair closure of the aortic valve. There also is risk of aortic rupture, with blood moving into the pericardium and compressing the heart. Although the length of dissection varies, it is possible for the abdominal aorta to be involved with progression into the renal, iliac, or femoral arteries. Partial or complete occlusion of the arteries that arise from the aortic arch or the intercostal or lumbar arteries may lead to stroke, ischemic peripheral neuropathy, or impaired blood flow to the spinal cord.

A major symptom of an aortic dissection is the abrupt presence of excruciating pain, described as tearing or ripping. The location of the pain may point to the site of dissection.⁴ Pain associated with dissection of the ascending aorta frequently is located in the anterior chest, and pain associated with dissection of the descending aorta often is located in the back. In the early stages, blood pressure typically is moderately or markedly elevated. Later, the blood pressure and the pulse rate become unobtainable in one or both arms as the dissection disrupts arterial flow to the arms. Syncope, hemiplegia, or paralysis of the lower extremities may occur because of occlusion of blood vessels that supply the brain or spinal cord. Heart failure may develop when the aortic valve is involved.

Diagnosis of aortic dissection is based on history and physical examination. Aortic angiography, transesophageal echocardiography, CT scans, and MRI studies aid in the diagnosis. The treatment may be medical or surgical. Aortic dissection is a life-threatening emergency situation; persons with a probable diagnosis are stabilized medically even before the diagnosis is confirmed. Two important factors that participate in propagating the dissection are high blood pressure and the steepness of the pulse wave. Without intervention, these forces continue to cause extension of the dissection. Thus, medical treatment focuses on control of hypertension and the use of drugs that lessen the force of systolic blood ejection from the heart. Surgical intervention may be indicated when there is threat of rupture or compromise of major aortic branches.

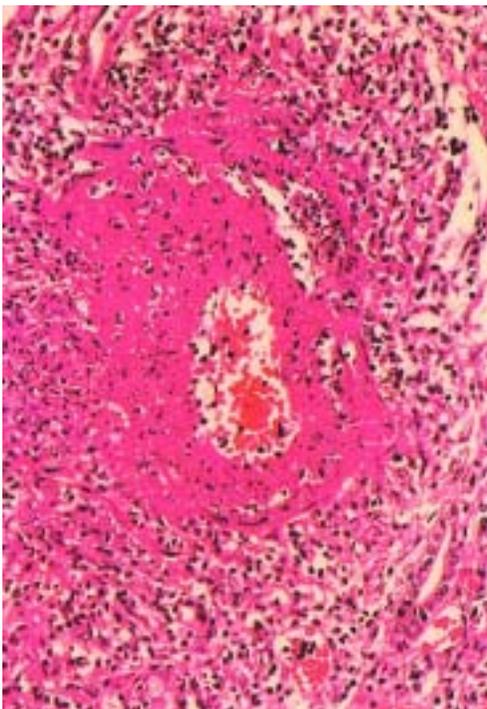
The Vasculitides

The vasculitides, which are a group of vascular disorders that cause inflammatory injury of blood vessels (vasculitis), are a common pathway for tissue and organ involvement in many

different disease conditions.^{16,17} Vessels of any type (arteries, veins, and capillaries) in virtually any organ can be affected. Clinical manifestations often include fever, myalgia, arthralgia, and malaise. Vasculitis may result from direct injury to the vessel, infectious agents, or immune processes, or may be secondary to other disease states such as systemic lupus erythematosus. Physical agents such as cold (*i.e.*, frostbite), irradiation (*i.e.*, sunburn), mechanical injury, and toxins may secondarily cause vessel damage, often leading to necrosis of the vessels.

The vasculitides are commonly classified based on etiology, pathologic findings, and prognosis. One classification system divides the conditions into three groups: (1) small vessel, (2) medium-size vessel, and (3) large vessel vasculitides.^{2,4} The small vessel vasculitides are involved in a number of different diseases, most of which are mediated by type III immune complex hypersensitivity reaction (see Chapter 10). They commonly involve the skin and are often a complication of an underlying disease (*i.e.*, vasculitis associated with neoplasms or connective tissue disease) and exposure to environmental agents (*i.e.*, serum sickness and urticarial vasculitis).

Medium-size vessel vasculitides produce necrotizing damage to medium-size muscular arteries of major organ systems. This group includes polyarteritis nodosa, Kawasaki's disease (discussed in Chapter 17), and thromboangiitis obliterans (discussed in the section on arterial diseases of the extremities). Polyarteritis nodosa is an uncommon acute multisystem inflammatory disease of small and medium-size blood vessels of the kidney, liver, intestine, peripheral nerves, skin, and muscles (Fig. 15-10). The usual course of the disease is progressive with various signs and symptoms according to the pattern of organ



■ **FIGURE 15-10** ■ Polyarteritis nodosa. The intense inflammatory cell infiltration in the arterial wall and surrounding connective tissue is mediated by fibrinoid necrosis and disruption of the vessel wall. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 515]. Philadelphia: Lippincott Williams & Wilkins)

involvement. Most cases were fatal before corticosteroid and immunosuppressant agents became available for use in treatment of the disorder.⁴

Large vessel vasculitides involve large elastic arteries; they are called *giant cell arteritides* because they involve infiltration of the vessel wall with giant cells and mononuclear cells. Giant cell (temporal) arteritis, the most common of the large vessel vasculitides, is an acute and chronic inflammation of large to small size arteries. It mainly affects arteries of the head—especially the temporal arteries—but may include the vertebral and ophthalmic arteries. About half of persons with the disease have an accompanying pain and stiffness of the shoulder and hip (polymyalgia rheumatica, see Chapter 43). The most common clinical presentation is with headache and tenderness over the superficial temporal artery. Diagnosis is by biopsy of the artery. Diagnosis followed by treatment with corticosteroid drugs is important because involvement of the ophthalmic artery can cause blindness.⁴

Arterial Disease of the Extremities

Disorders of the circulation in the extremities often are referred to as *peripheral vascular disorders*. In many respects, the disorders that affect arteries in the extremities are the same as those affecting the coronary and cerebral arteries in that they produce ischemia, pain, impaired function, and in some cases infarction and tissue necrosis. Not only are the effects similar, but the pathologic conditions that impair circulation in the extremities are identical. This section focuses on acute arterial occlusion of the extremities, atherosclerotic occlusive disease, thromboangiitis obliterans, and Raynaud's disease and phenomenon.

Acute Arterial Occlusion

Acute arterial occlusion is a sudden event that interrupts arterial flow to the affected tissues or organ. Most acute arterial occlusions are the result of an embolus or a thrombus. Although much less common than emboli and thrombi, trauma or arterial spasm caused by arterial cannulation can be another cause of acute arterial occlusion.

An embolus is a freely moving particle such as a blood clot that breaks loose and travels in the larger vessels of the circulation until lodging in a smaller vessel and occluding blood flow. Most arterial emboli arise in the heart and are caused by conditions that cause blood clots to develop on the wall of a heart chamber or valve surface. Arterial emboli usually are a complication of heart disease: ischemic heart disease with or without infarction, atrial fibrillation, or rheumatic heart disease. Prosthetic heart valves can be another source of emboli. Other types of emboli are fat emboli that originate from bone marrow of fractured bones or amniotic fluid emboli that develop during childbirth.

A thrombus is a blood clot that forms on the wall of a vessel and continues to grow until reaching a size that obstructs blood flow. These thrombi often arise as the result of rupture of the fibrous cap of an atherosclerotic plaque.

The signs and symptoms of acute arterial occlusion depend on the artery involved and the adequacy of the collateral circulation. Emboli tend to lodge in bifurcations of the major arteries, including the aorta and iliac, femoral, and popliteal arteries. Occlusion in an extremity causes sudden onset of acute pain with numbness, tingling, weakness, pallor, and coldness.

There often is a sharp line of demarcation between the oxygenated tissue above the line of obstruction and that below the line of obstruction. Pulses are absent below the level of the occlusion. These changes are followed rapidly by cyanosis, mottling, and loss of sensory, reflex, and motor function. Tissue death occurs unless blood flow is restored.

Diagnosis of acute arterial occlusion is based on signs of impaired blood flow. It uses visual assessment, palpation of pulses, and methods to assess blood flow. Treatment of acute arterial occlusion is aimed at restoring blood flow. Thrombolytic therapy (*i.e.*, streptokinase or tissue plasminogen activator) may be used in an attempt to dissolve the clot. Anticoagulant therapy (*i.e.*, heparin) usually is given to prevent extension of the embolus. Application of heat and cold should be avoided, and the extremity should be protected from injury resulting from hard surfaces and overlying bedclothes. An embolectomy—surgical removal of the embolus—may be indicated.

Atherosclerotic Occlusive Disease

Atherosclerosis is an important cause of peripheral vascular disease and is seen most commonly in the vessels of the lower extremities. The condition is sometimes referred to as *arteriosclerosis obliterans*. The superficial femoral and popliteal arteries are the most commonly affected vessels. When lesions develop in the lower leg and foot, the tibial, common peroneal, or pedal vessels are the arteries most commonly affected. The disease is seen most commonly in men in their 60s and 70s.^{18,19} The risk factors for this disorder are similar to those for atherosclerosis. Cigarette smoking contributes to the progress of the atherosclerosis of the lower extremities and to the development of symptoms of ischemia. Persons with diabetes mellitus experience more extensive and rapidly progressive vascular disease than do individuals without diabetes.

As with atherosclerosis in other locations, the signs and symptoms of vessel occlusion are gradual. Usually, there is at least a 50% narrowing of the vessel before symptoms of ischemia arise. The primary symptom of chronic obstructive arterial disease is *intermittent claudication* or pain with walking.¹⁸ Typically, persons with the disorder report calf pain caused by ischemia of the gastrocnemius muscle, which has the highest oxygen consumption of any muscle group in the leg during walking. Some persons may report a vague aching feeling or numbness, rather than pain. Other signs of ischemia include atrophic changes and thinning of the skin and subcutaneous tissues of the lower leg and diminution in the size of the leg muscles. The foot often is cool, and the popliteal and pedal pulses are weak or absent. Limb color blanches with elevation of the leg because of the effects of gravity on perfusion pressure and becomes deep red when the leg is in the dependent position because of an autoregulatory increase in blood flow and a gravitational increase in perfusion pressure.

When blood flow is reduced to the extent that it no longer meets the minimal needs of resting muscle and nerves, ischemic pain at rest, ulceration, and gangrene develop. As tissue necrosis develops, there typically is severe pain in the region of skin breakdown, which is worse at night with limb elevation and is improved with standing.¹⁸

Diagnostic methods include inspection of the limbs for signs of chronic low-grade ischemia, such as subcutaneous atrophy, brittle toenails, hair loss, pallor, coolness, or dependent

rubor. Palpation of the femoral, popliteal, posterior tibial, and dorsalis pedis pulses allows for an estimation of the level and degree of obstruction. Blood pressures may be taken at various levels on the leg to determine the level of obstruction. A Doppler ultrasound stethoscope may be used for detecting pulses and measuring blood pressure. Ultrasound imaging, radionuclide imaging, and contrast angiography also may be used as diagnostic methods.¹⁸

The tissues of extremities affected by atherosclerosis are easily injured and slow to heal. Treatment includes measures directed at protection of the affected tissues and preservation of functional capacity. Walking (slowly) to the point of claudication usually is encouraged because it increases collateral circulation.

Surgery (*i.e.*, femoropopliteal bypass grafting using a section of saphenous vein) may be indicated in severe cases. In persons with diabetes, the peroneal arteries between the knees and ankles commonly are involved, making revascularization difficult. Thromboendarterectomy with removal of the occluding core of atherosclerotic tissue may be done if the section of diseased vessel is short. Percutaneous transluminal angioplasty, in which a balloon catheter is inserted into the area of stenosis and the balloon inflated to increase vessel diameter, is another form of treatment.^{18,19}

Thromboangiitis Obliterans

Thromboangiitis obliterans (*e.g.*, Buerger's disease) is a vasculitis affecting the medium-size arteries, usually the plantar and digital vessels in the foot and lower leg. Arteries in the arm and hand also may be affected. Although primarily an arterial disorder, the inflammatory process often extends to involve adjacent veins and nerves. It usually is a disease of men between the ages of 25 and 40 years who are heavy cigarette smokers, but it can occur in women. The pathogenesis of the disorder remains speculative, although cigarette smoking and in some instances tobacco chewing seem to be involved. It has been suggested that the tobacco may trigger an immune response in susceptible persons or it may unmask a clotting defect, either of which could incite an inflammatory reaction of the vessel wall.²⁰

Pain is the predominant symptom of the disorder. It usually is related to distal arterial ischemia. During the early stages of the disease, there is intermittent claudication in the arch of the foot and the digits. In severe cases, pain is present even when the person is at rest. The impaired circulation increases sensitivity to cold. The peripheral pulses are diminished or absent, and there are changes in the color of the extremity. In moderately advanced cases, the extremity becomes cyanotic when the person assumes a dependent position, and the digits may turn reddish blue even when in a nondependent position. With lack of blood flow, the skin assumes a thin, shiny look, and hair growth and skin nutrition suffer. Chronic ischemia causes thick, malformed nails. If the disease continues to progress, tissues eventually ulcerate and gangrenous changes arise that may necessitate amputation.

Diagnostic methods are similar to those for atherosclerotic disease of the lower extremities. It is essential that the person stop smoking cigarettes or using tobacco. Other treatment measures are of secondary importance and focus on methods for producing vasodilation and preventing tissue injury. Sympathectomy may be done to alleviate the vasospastic manifestations of the disease.

Raynaud's Disease and Phenomenon

Raynaud's disease or phenomenon is a functional disorder caused by intense vasospasm of the arteries and arterioles in the fingers and, less often, the toes. The disorder is divided into two types: the primary type, called *Raynaud's disease*, occurs without demonstrable cause, and the secondary type, called *Raynaud's phenomenon*, is associated with other disease states or known causes of vasospasm.^{21,22}

Vasospasm implies an excessive vasoconstrictor response to stimuli that normally produce only moderate vasoconstriction. In contrast to other regional circulations that are supplied by vasodilator and vasoconstrictor fibers, the cutaneous vessels of the fingers and toes are innervated only by sympathetic vasoconstrictor fibers. In these vessels, vasodilation depends on withdrawal of sympathetic stimulation. Cooling of specific body parts such as the head, neck, and trunk produces a sympathetic-mediated reduction in digital blood flow, as does emotional stress.

Raynaud's disease is usually seen in otherwise healthy young women. It often is precipitated by exposure to cold or by strong emotions and usually is limited to the fingers. It also follows a more benign course than Raynaud's phenomenon, seldom causing tissue necrosis. The cause of vasospasm in primary Raynaud's disease is unknown. Hyperreactivity of the sympathetic nervous system has been suggested as a contributing cause.²¹ Raynaud's phenomenon is associated with previous vessel injury, such as frostbite, occupational trauma associated with the use of heavy vibrating tools, collagen diseases, neurologic disorders, and chronic arterial occlusive disorders. Another occupation-related cause is the exposure to alternating hot and cold temperatures such as that experienced by butchers and food preparers.²¹ Raynaud's phenomenon often is the first symptom of collagen diseases. It occurs in persons with scleroderma and those with systemic lupus erythematosus.

In Raynaud's disease and Raynaud's phenomenon, ischemia caused by vasospasm causes changes in skin color that progress from pallor to cyanosis, a sensation of cold, and changes in sensory perception, such as numbness and tingling. The color changes usually are first noticed in the tips of the fingers, later moving into one or more of the distal phalanges (Fig. 15-11). After the ischemic episode, there is a period of



■ **FIGURE 15-11** ■ Raynaud's phenomenon. The tips of the fingers show marked pallor. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 514]. Philadelphia: Lippincott Williams & Wilkins)

hyperemia with intense redness, throbbing, and paresthesia. The period of hyperemia is followed by a return to normal color. Although all of the fingers usually are affected symmetrically, the involvement may affect only one or two digits. In some cases, only a portion of the digit is affected.

In severe, progressive cases usually associated with Raynaud's phenomenon, trophic changes may develop. The nails may become brittle, and the skin over the tips of the affected fingers may thicken. Nutritional impairment of these structures may give rise to arthritis. Ulceration and superficial gangrene of the fingers, although infrequent, may occur.

The initial diagnosis is based on history of vasospastic attacks supported by other evidence of the disorder. Immersion of the hand in cold water may be used to initiate an attack as an aid to diagnosis. Laser-Doppler velocimetry may be used to quantify digital blood flow during changes in temperature. Serial computed thermography (finger skin temperature) also may be a useful tool in diagnosing the extent of disease. Raynaud's disease is differentiated from Raynaud's phenomenon by excluding secondary disorders known to cause vasospasm.²²

Treatment measures are directed toward eliminating factors that cause vasospasm and protecting the digits from trauma during an ischemic episode. Abstinence from smoking and protection from cold are priorities. Avoidance of emotional stress is another important factor in controlling the disorder because anxiety and stress may precipitate a vascular spasm in predisposed persons. Vasoconstrictor medications, such as the decongestants contained in allergy and cold preparations, should be avoided. Drugs with a vasodilating action (*e.g.*, calcium channel blockers and α -adrenergic receptor blocking agents) may be indicated, particularly if episodes are frequent. Surgical interruption of sympathetic nerve pathways (sympathectomy) may be used for persons with severe symptoms.²²

In summary, the arterial system distributes blood to all the tissues of the body, and lesions of the arterial system exert their effects through ischemia or impaired blood flow.

Hyperlipidemia with elevated cholesterol levels play a major role in the development of atherosclerotic disorders of the arterial system. Because cholesterol and triglycerides are insoluble in plasma, they transported as lipoproteins. Elevated levels of LDLs, which carry large amounts of cholesterol, are a major risk factor for atherosclerosis. The HDLs, which are protective, remove cholesterol from the tissues and carry it back to the liver for disposal. LDL receptors play a major role in removing cholesterol from the blood; persons with reduced numbers of LDL receptors are at particularly high risk for the development of atherosclerosis.

Atherosclerosis affects large and medium-size arteries, such as the coronary and cerebral arteries. It has an insidious onset, and its lesions usually are far advanced before symptoms appear. Risk factors associated with its development include factors such as heredity, sex, and age, which cannot be controlled; factors such as smoking, high blood pressure, high serum cholesterol levels, and diabetes, which can be modified; and other contributing factors such as obesity, lack of exercise, and stress.

Aneurysms are localized areas of vessel dilation caused by weakness of the arterial wall. Abdominal aortic aneurysms are the most common type of aneurysm. They are characterized

by gradual and progressive enlargement of the abdominal aorta. The most serious consequence of abdominal aneurysms is rupture. Aortic dissection is an acute, life-threatening condition. It involves hemorrhage into the vessel wall with longitudinal tearing (dissection) of the vessel wall to form a blood-filled channel.

The vasculitides are a group of vascular disorders characterized by inflammation and necrosis of blood vessels in various tissues and organs. They can be caused by injury, infectious agents, or immune processes, or can occur secondary to other disease conditions, such as systemic lupus erythematosus. Occlusive disorders interrupt arterial flow of blood and interfere with the delivery of oxygen and nutrients to the tissues. Occlusion of flow can result from a thrombus, embolus, vessel compression, vasospasm, or structural changes in the vessel. Peripheral arterial diseases affect blood vessels outside the heart and thorax. They include atherosclerotic occlusive disease, thromboangiitis obliterans, and Raynaud's disease or phenomenon, caused by vessel spasm.

DISORDERS OF THE VENOUS CIRCULATION

Veins are low-pressure, thin-walled vessels that rely on the ancillary action of skeletal muscle pumps and changes in abdominal and intrathoracic pressure to return blood to the heart. Unlike the arterial system, the venous system is equipped with valves that prevent retrograde flow of blood. Although its structure enables the venous system to serve as a storage area for blood, it also renders the system susceptible to problems related to stasis and venous insufficiency. This section focuses on three common problems of the venous system: varicose veins, venous insufficiency, and venous thrombosis.

Venous Circulation of the Lower Extremities

The venous system in the legs consists of two components: the superficial veins (*i.e.*, saphenous vein and its tributaries) and the deep venous channels (Fig. 15-12). Perforating or commu-

nicating veins connect these two systems. Blood from the skin and subcutaneous tissues in the leg collects in the superficial veins and is then transported across the communicating veins into the deeper venous channels for return to the heart. Venous valves prevent the retrograde flow of blood and play an important role in the function of the venous system. Although these valves are irregularly located along the length of the veins, they almost always are found at junctions where the communicating veins merge with the larger deep veins and where two veins meet. The number of venous valves differs somewhat from one person to another, as does the structural competence, factors that may help to explain the familial predisposition to development of varicose veins.

The action of the leg muscles assists in moving venous blood from the lower extremities back to the heart. When a person walks, the action of the leg muscles serves to increase flow in the deep venous channels and return venous blood to the heart (Fig. 15-13). The function of the so-called muscle pump, located in the gastrocnemius and soleus muscles of the lower extremities, can be compared with the pumping action of the heart.²³ During muscle contraction, which is similar to systole, valves in the communicating channels close to prevent backward flow of blood into the superficial system, as blood in the deep veins is moved forward by the action of the contracting muscles. During relaxation, which is similar to diastole, the communicating valves open, allowing blood from the superficial veins to move into the deep veins.

Varicose Veins

Varicose, or dilated, tortuous veins of the lower extremities are common and often lead to secondary problems of venous insufficiency (Fig. 15-12). Varicose veins are described as being primary or secondary. Primary varicose veins originate in the superficial saphenous veins, and secondary varicose veins result from impaired flow in the deep venous channels. Approximately 80% to 90% of venous blood from the lower extremities is transported through the deep channels. The development of secondary varicose veins becomes inevitable when flow in these deep channels is impaired or blocked. The most common cause of secondary varicose veins is deep vein thrombosis (DVT). Other causes include congenital or acquired arteriovenous fistulas, congenital venous malformations, and pressure on the abdominal veins caused by pregnancy or a tumor.

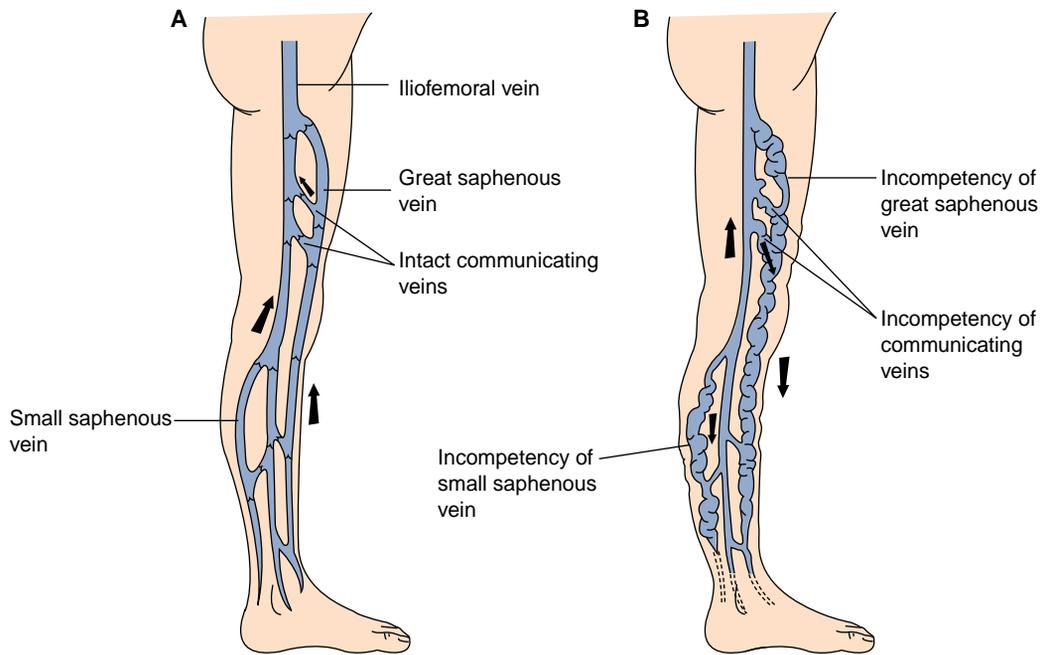
Primary varicose veins is more common after 50 years of age and in obese persons, and it occurs more often in women than men, probably because of venous stasis caused by pregnancy.² More than 50% of persons with primary varicose veins have a family history of the disorder, suggesting that heredity may play a role. Prolonged standing and increased intra-abdominal pressure are important contributing factors in the development of primary varicose veins. One of the most important factors in the elevation of venous pressure is the hydrostatic effect associated with the standing position. When a person is in the erect position, the full weight of the venous columns of blood is transmitted to the leg veins. The effects of gravity are compounded in persons who stand for long periods without using their leg muscles to assist in pumping blood back to the heart.

Because there are no valves in the inferior vena cava or common iliac veins, blood in the abdominal veins must be supported by the valves located in the external iliac or femoral

KEY CONCEPTS

DISORDERS OF THE VENOUS CIRCULATION

- The venous system is a low-pressure system that relies on the pumping action of the skeletal muscles to move blood forward and the presence of venous valves to prevent retrograde flow.
- Varicose veins are dilated and tortuous veins that result from a sustained increase in pressure that causes the venous valves to become incompetent, allowing for reflux of blood and vein engorgement.
- Thrombophlebitis refers to thrombus formation and the accompanying inflammatory response that occurs in veins. Deep vein thrombosis may be a precursor to pulmonary embolism.



■ **FIGURE 15-12** ■ Superficial and deep venous channels of the leg. (A) Normal venous structures and flow patterns. (B) Varicosities in the superficial venous system are the result of incompetent valves in the communicating veins. The arrows in both views indicate the direction of blood flow. (Modified from Abramson D.I. [1974]. *Vascular disorders of the extremities* [2nd ed.]. Philadelphia: Lippincott Williams & Wilkins)

veins. When intra-abdominal pressure increases, as it does during pregnancy, or when the valves in these two veins are absent or defective, the stress on the saphenofemoral junction is increased. Lifting also increases intra-abdominal pressure and decreases flow of blood through the abdominal veins. Occupations that require repeated heavy lifting predispose to development of varicose veins.

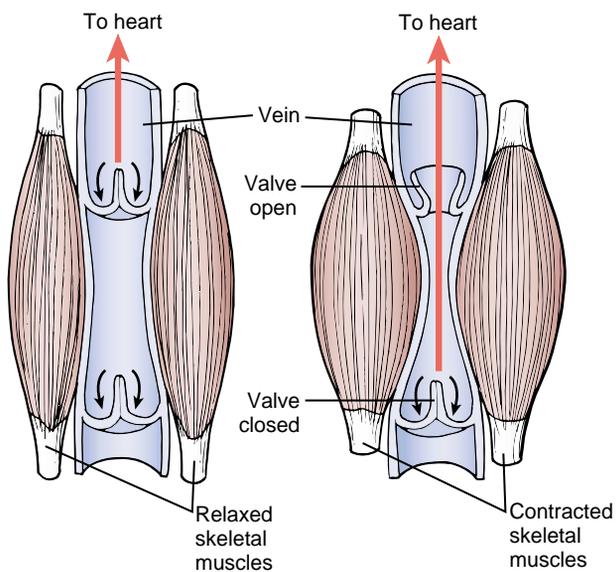
Prolonged exposure to increased pressure causes the venous valves to become incompetent so they no longer close properly. When this happens, the reflux of blood causes fur-

ther venous enlargement, pulling the valve leaflet apart and causing valvular incompetence in sections of adjacent distal veins. Another consideration in the development of varicose veins is the fact that the superficial veins have only subcutaneous fat and superficial fascia for support, but the deep venous channels are supported by muscle, bone, and connective tissue. Obesity reduces the support provided by the superficial fascia and tissues, increasing the risk for development of varicose veins.

The signs and symptoms associated with primary varicose veins vary. Most women with superficial varicose veins complain of their unsightly appearance. In many cases, aching in the lower extremities and edema, especially after long periods of standing, may occur. The edema usually subsides at night when the legs are elevated. When the communicating veins are incompetent, symptoms are more common.

The diagnosis of varicose veins often can be made after physical inspection. The Doppler ultrasonic flow probe also may be used to assess the flow in the large vessels. Angiographic studies using a radiopaque contrast medium also are used to assess venous function.

After the venous channels have been repeatedly stretched and the valves rendered incompetent, little can be done to restore normal venous tone and function. Ideally, measures should be taken to prevent the development and progression of varicose veins. These measures center on avoiding activities such as continued standing that produce prolonged elevation of venous pressure. Treatment measures for varicose veins focus on improving venous flow and preventing tissue injury. When correctly fitted, elastic support stockings or leggings compress the superficial veins and prevent distention. The most precise control is afforded by prescription stockings, measured to fit properly. These stockings should be applied before the standing position is assumed, when the leg veins are empty.



■ **FIGURE 15-13** ■ The skeletal muscle pumps and their function in promoting blood flow in the deep and superficial calf vessels of the leg.

Sclerotherapy, which often is used in the treatment of small residual varicosities, involves the injection of a sclerosing agent into the collapsed superficial veins to produce fibrosis of the vessel lumen. Surgical treatment consists of removing the varicosities and the incompetent perforating veins, but it is limited to persons with patent deep venous channels.

Chronic Venous Insufficiency

The term *venous insufficiency* refers to the physiologic consequences of DVT, valvular incompetence, or a combination of both conditions. The most common cause is DVT, which causes deformity of the valve leaflets, rendering them incapable of closure. In the presence of valvular incompetence, effective unidirectional flow of blood and emptying of the deep veins cannot occur. The muscle pumps also are ineffective, often driving blood in retrograde directions. Secondary failure of the communicating and superficial veins subjects the subcutaneous tissues to high pressures.

With venous insufficiency, there are signs and symptoms associated with impaired blood flow. In contrast to the ischemia caused by arterial insufficiency, venous insufficiency leads to tissue congestion, edema, and eventual impairment of tissue nutrition.^{23,24} The edema is exacerbated by long periods of standing. Necrosis of subcutaneous fat deposits occurs, followed by skin atrophy. Brown pigmentation of the skin caused by hemosiderin deposits resulting from the breakdown of red blood cells is common. Secondary lymphatic insufficiency occurs, with progressive sclerosis of the lymph channels in the face of increased demand for clearance of interstitial fluid.

In advanced venous insufficiency, impaired tissue nutrition causes stasis dermatitis and the development of stasis or venous ulcers (Fig. 15-14).² Stasis dermatitis is characterized by the presence of thin, shiny, bluish brown, irregularly pigmented desquamative skin that lacks the support of the underlying subcutaneous tissues. Minor injury leads to relatively painless ulcerations that are difficult to heal. The lower part of the leg is particularly prone to development of stasis dermatitis and venous ulcers. Most lesions are located medially over the ankle and lower leg, with the highest frequency just above the medial malleolus. Persons with long-standing venous insufficiency may experience stiffening of the ankle joint and loss of muscle mass and strength.

Venous Thrombosis

The term *venous thrombosis*, or *thrombophlebitis*, describes the presence of thrombus in a vein and the accompanying inflammatory response in the vessel wall. Thrombi can develop in the superficial or the deep veins. DVT most commonly occurs in the lower extremities. DVT of the lower extremity is a serious disorder, complicated by pulmonary embolism (see Chapter 21), recurrent episodes of DVT, and development of chronic venous insufficiency.²⁵

In 1846, Virchow described the triad that has come to be associated with venous thrombosis: stasis of blood, increased blood coagulability, and vessel wall injury.²⁶ Risk factors for DVT are summarized in Chart 15-2. *Stasis of blood* occurs with immobility of an extremity or the entire body. Bed rest and immobilization are associated with decreased blood flow, venous pooling in the lower extremities, and increased risk of DVT.



■ **FIGURE 15-14** ■ Varicose veins of the legs. Severe varicosities of the superficial leg veins have led to stasis dermatitis and secondary ulcerations. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 525]. Philadelphia: Lippincott Williams & Wilkins)

CHART 15-2 Risk Factors Associated With Venous Thrombosis*

Venous Stasis

- Bed rest
- Immobility
- Spinal cord injury
- Acute myocardial infarction
- Congestive heart failure
- Shock
- Venous obstruction

Hyperreactivity of Blood Coagulation

- Stress and trauma
- Pregnancy
- Childbirth
- Oral contraceptive use
- Dehydration
- Cancer

Vascular Trauma

- Indwelling venous catheters
- Surgery
- Massive trauma or infection
- Fractured hip
- Orthopedic surgery

*Many of these disorders involve more than one mechanism.

Persons who are immobilized by a hip fracture, joint replacement, or spinal cord injury are particularly vulnerable to DVT. The risk of DVT is increased in situations of impaired cardiac function. This may account for the relatively high incidence in persons with acute myocardial infarction and congestive heart failure. Elderly persons are more susceptible than younger persons, probably because disorders that produce venous stasis occur more frequently in older persons. Long airplane travel poses a particular threat in persons predisposed to DVT because of prolonged sitting and increased blood viscosity caused by dehydration.

Hypercoagulability and conditions that increase the concentration or activation of clotting factors predispose to DVT. The postpartum state is associated with increased levels of fibrinogen, prothrombin, and other coagulation factors. The use of oral contraceptives appears to increase coagulability and predispose to venous thrombosis, especially in women older than 30 years and in those who smoke. Certain cancers are associated with increased clotting tendencies, and although the reason for this is largely unknown, substances that promote blood coagulation may be released from the tissues because of the cancerous growth.

Vessel injury can result from a trauma situation or from surgical intervention. It also may occur secondary to infection or inflammation of the vessel wall. Persons undergoing hip surgery and total hip replacement are at particular risk because of trauma to the femoral and iliac veins, and in the case of hip replacement, thermal damage from heat generated by the polymerization of the acrylic cement that is used in the procedure.²⁵ Venous catheters are another source of vascular injury.

Many persons with DVT are asymptomatic. The person may have experienced a pulmonary emboli with no previous signs or symptoms. When present, the most common signs and symptoms of DVT are those related to the inflammatory process: pain, swelling, and deep muscle tenderness. Fever, general malaise, and an elevated white blood cell count and sedimentation rate are accompanying indications of inflammation. There may be tenderness and pain along the vein. Swelling may vary from minimal to maximal. The site of thrombus formation determines the location of the physical findings. The most common site is in the venous sinuses in the soleus muscle and posterior tibial and peroneal veins. Swelling in these cases involves the foot and ankle, although it may be slight or absent. Calf pain and tenderness are common. Femoral vein thrombosis with calf thrombosis produces pain and tenderness in the distal thigh and popliteal area. Thrombi in iliofemoral veins produce the most profound manifestations, with swelling, pain, and tenderness of the entire extremity. With DVT in the calf veins, active dorsiflexion of the foot produces calf pain (Homans' sign).

The risk of pulmonary embolism emphasizes the need for early detection and treatment of DVT. Several tests are useful for this purpose: ascending venography, impedance plethysmography, and ultrasonography. The goals of treatment for DVT are to prevent formation of additional thrombi, prevent extension and embolization of existing thrombi, and to minimize venous valve damage. Anticoagulation therapy is used to treat and prevent venous thrombosis. A 15- to 20-degree elevation of the legs prevents stasis. Surgical removal of the thrombus may be undertaken in selected cases. Surgical interruption of the vena cava may be done in persons at high risk for experiencing pulmonary emboli.

This procedure involves ligating the vena cava with a suture or clamp or in creating a filter-like insertion to prevent large clots from moving through the vessel.

When possible, venous thrombosis should be prevented in preference to being treated. Early ambulation after childbirth and surgery is one measure that decreases the risk of thrombus formation. Exercising the legs and wearing support stockings improve venous flow. A further precautionary measure is to avoid assuming body positions that favor venous pooling. Antiembolism stockings of the proper fit and length should be used routinely in persons at risk for DVT. Another strategy used for immobile persons at risk for experiencing DVT is a sequential pneumatic compression device. This consists of a plastic sleeve that encircles the legs and provides alternating periods of compression on the lower extremity. When properly used, these devices enhance venous emptying to augment flow and reduce stasis.

In summary, the storage function of the venous system renders it susceptible to venous insufficiency, stasis, and thrombus formation. Varicose veins occur with prolonged distention and stretching of the superficial veins owing to venous insufficiency. Varicosities can arise because of defects in the superficial veins (*i.e.*, primary varicose veins) or because of impaired blood flow in the deep venous channels (*i.e.*, secondary varicose veins). Venous insufficiency reflects chronic venous stasis resulting from valvular incompetence. It is associated with stasis dermatitis and stasis or venous ulcers. Venous thrombosis describes the presence of thrombus in a vein and the accompanying inflammatory response in the vessel wall. It is associated with vessel injury, stasis of venous flow, and hypercoagulability states. Thrombi can develop in the superficial or the deep veins (*i.e.*, DVT). Thrombus formation in deep veins is a precursor to venous insufficiency and embolus formation.

DISORDERS OF BLOOD FLOW CAUSED BY EXTRAVASCULAR FORCES

Blood flow occurs along a pressure gradient, moving from the arterial to the venous side of the circulation. For blood to move through the vessels of the systemic circulation, arterial pressure must be greater than venous pressure, and the arterial and venous pressures must be greater than the external pressure of the surrounding tissues. Injury or infections that cause tissue swelling can compromise blood flow, particularly in parts of the body where the skin or other supporting tissues cannot expand to accommodate the increased volume. In other situations, external pressure may compress the tissues and the blood vessels. Two conditions resulting from compromised blood flow caused by extravascular forces are compartment syndrome and pressure ulcers.

Compartment Syndrome

The muscles and nerves of an extremity are enclosed in a tough, inelastic fascial envelope called a *muscle compartment* (Fig. 15-15). *Compartment syndrome* describes a condition of in-

KEY CONCEPTS**DISORDERS OF BLOOD FLOW DUE TO EXTRAVASCULAR FORCES**

- Blood flow requires that arterial pressure is greater than venous pressure and that arterial, venous, and capillary pressures are greater than the pressure surrounding the vessels.
- Compartment syndrome describes a condition of compromised blood flow resulting from pressure in an anatomic space that cannot expand. Causes include decreases in compartment size (*i.e.*, cast) or increases in compartment volume (*i.e.*, internal bleeding or edema).
- Pressure ulcers are ischemic lesions of the skin and underlying tissues caused by compression of blood vessels due to external pressure, such as that exerted by the weight of the body on the bed or chair surface. Prevention of pressure ulcers is preferable to treatment. Frequent position changes and meticulous skin care are essential components of prevention.

creased pressure in a limited anatomic space, usually a muscle compartment, that impairs circulation and produces ischemic tissue injury.²⁷ If the pressure in the compartment is sufficiently high, tissue circulation is compromised, causing death of nerve and muscle cells. Permanent loss of function may occur.

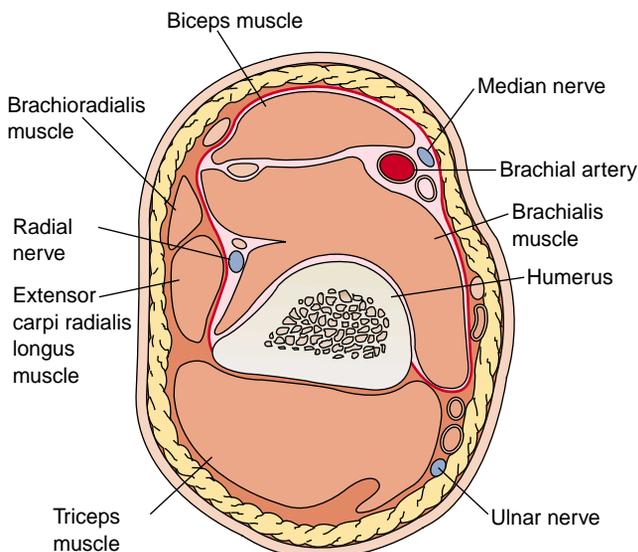
The amount of pressure required to produce a compartment syndrome depends on many factors, including the duration of the pressure elevation, the metabolic rate of the tissues, vascular tone, and local blood pressure. Less tissue pressure is re-

quired to stop circulation when hypotension or vasoconstriction is present. Intracompartmental pressures of 30 to 40 mm Hg (normal is approximately 6 mm Hg) are considered sufficient to impair capillary blood flow.²⁸

Compartment syndrome can result from: (1) a decrease in compartment size or (2) an increase in the volume of its contents (Chart 15-3). Among the causes of decreased compartment size are constrictive dressings and casts, closure of fascial defects, and thermal injuries or frostbite. In persons with circumferential third-degree burns, the inelastic and constricting eschar decreases the size of the underlying compartments. Burns also are associated with the formation of massive edema and an increase in compartment volume. The combination of the two problems may lead to necrosis of the underlying neuromuscular tissues. Frostbite produces neuromuscular injury for similar reasons.

An increase in compartment volume can be caused by trauma, vascular injury and bleeding, infiltration of intravenous infusions, postischemic swelling, and venous obstruction. One of the most important causes of compartment syndrome is bleeding and edema caused by fractures and osteotomies (see Chapter 42). Contusions and soft tissue injury also are common causes of compartment syndrome. Bleeding can occur as a complication of arterial punctures, particularly in persons with bleeding disorders or those who are receiving anticoagulant drugs. Infiltration of intravenous fluids also can restrict compartment size and cause compartment ischemia and postischemic swelling. Increased compartment volume may follow ischemic events, such as arterial occlusion, that are of sufficient duration to produce capillary damage, causing increased capillary permeability and edema. During unattended coma caused by drug overdose or carbon monoxide poisoning, high compartment pressures are produced when an extremity is compressed by the weight of the overlying head or torso. Exercise may produce acute or chronic elevations in compartment pressure.

The most important symptom of compartment syndrome is unrelenting pain, usually described as a deep, throbbing sensation, that is greater than that expected for the primary problem, such as fracture or contusion. Pain with passive stretch



■ **FIGURE 15-15** ■ Distal anterior arm muscle compartments, showing the location of fascia, muscles, nerves, and blood vessels.

CHART 15-3 Causes of Compartment Syndrome**Decreased Compartment Size**

- Constrictive dressings and casts
- Infiltration of intravenous fluids
- Thermal injury and frostbite
- Surgical closure of fascial defects

Increased Compartment Volume

- Fractures and orthopedic surgery
- Trauma and bleeding
- Postischemic injury
- Severe exercise
- Prolonged immobilization with limb compression (e.g., drug overdose)
- Thermal injury and frostbite
- Intravenous infiltration

is a common finding. Tenseness and tenderness of the involved compartment are specific symptoms of compartment syndrome. The skin over the compartment may become taut, shiny, warm, and red. Paresthesias progressing to anesthesia occur secondary to nerve involvement. Muscle weakness results from muscle ischemia.

It is important that persons at risk for compartment syndrome be identified and that proper assessment methods be instituted. Assessment should include pain assessment, examination of sensory (*i.e.*, light touch and two-point discrimination) and motor function (*i.e.*, movement and muscle strength), test of passive stretch, and palpation of the muscle compartments. Peripheral pulses frequently are normal in the presence of compartment syndrome because the major arteries are located outside the muscle compartments. Although edema may make it difficult to palpate the pulse, the increased compartment pressure seldom is sufficient to occlude flow in a major artery. Doppler methods usually confirm the existence of a pulse. Direct measurements of tissue pressure can be obtained using a needle or wick catheter inserted into the muscle compartment. This method is particularly useful in persons who are unresponsive and in those with nerve deficits. Compartment decompression is recommended when pressures rise to 30 mm Hg.

Treatment consists of reducing compartmental pressures. This entails cast splitting or removal of restrictive dressings. These procedures often are sufficient to relieve most of the underlying pressure and symptoms. When an extremity is elevated, its arterial pressure falls because of the effects of gravity. Therefore, limb elevation is not recommended when compartment syndrome is suspected. When compartment syndrome cannot be relieved by conservative measures, a fasciotomy may become necessary. During this procedure, the fascia is incised longitudinally and separated so that the compartment volume can expand and blood flow can be re-established. Because of potential problems with wound infection and closure, this procedure is performed as a last resort.

Pressure Ulcers

Pressure ulcers are ischemic lesions of the skin and underlying structures caused by external pressure that impairs the flow of blood and lymph. Pressure ulcers often are referred to as *decubitus ulcers* or *bedsores*. The word *decubitus* comes from the Latin

term meaning “lying down.” However, a pressure ulcer may result from pressure exerted in the seated or the lying position. Pressure ulcers are most likely to develop over a bony prominence, but they may occur on any part of the body that is subjected to external pressure, friction, or shearing forces.

Several subpopulations are at particular risk, including persons with quadriplegia, elderly persons with restricted activity and hip fractures, and persons in the critical care setting. The prevention and treatment of pressure ulcers is a public health issue and is addressed in *Healthy People 2010*, a national public health policy statement, which has set a target of a 50% decrease in prevalence of pressure ulcers in nursing home residents.²⁹

Mechanisms of Development

Two factors contribute to the development of pressure ulcers: (1) external pressure that compresses blood vessels and (2) friction and shearing forces that tear and injure blood vessels.

External pressure that exceeds capillary pressure interrupts blood flow in the capillary beds. When the pressure between a bony prominence and a support surface exceeds the normal capillary filling pressure of approximately 32 mm Hg, capillary flow essentially is obstructed.³⁰ If this pressure is applied constantly for 2 hours, oxygen deprivation coupled with an accumulation of metabolic end products leads to irreversible tissue damage. The same amount of pressure causes more damage when it is distributed over a small area than when it is distributed over a larger area. Approximately 7 lb of pressure per square inch of tissue surface is sufficient to obstruct blood flow.³¹

Whether a person is sitting or lying down, the weight of the body is borne by tissues covering the bony prominences. More than 90% of pressure ulcers are located on the lower part of the body, most often over the sacrum, the coccygeal areas, the ischial tuberosities, and the greater trochanter. Pressure over a bony area is transmitted from the surface to the underlying dense bone, compressing all of the intervening tissue. As a result, the greatest pressure occurs at the surface of the bone and dissipates outward in a conelike manner toward the surface of the skin (Fig. 15-16). Thus, extensive underlying tissue damage can be present when a small superficial skin lesion is first noticed.

Altering the distribution of pressure from one skin area to another prevents tissue injury. Pressure ulcers most commonly

occur in persons with conditions such as spinal cord injury in which normal sensation and movement to effect redistribution of body weight are impaired. Normally, persons unconsciously shift their weight to redistribute pressure on the skin and underlying tissues. For example, during the night, people turn in their sleep, preventing ischemic injury of tissues that overlie the bony prominences that support the weight of the body; the same is true for sitting for any length of time. The movements needed to shift the body weight are made unconsciously, and only when movement is restricted do people become aware of discomfort.

Shearing forces are caused by the sliding of one tissue layer over another with stretching and angulation of blood vessels, causing injury and thrombosis. For persons who are bedridden, injury commonly occurs when the head of the bed is elevated, causing the torso to slide down toward the foot of the bed. When this happens, friction and perspiration cause the skin and superficial fascia to remain fixed against the bed linens while the deep fascia and skeleton slide downward. The same thing can happen when a person sitting up in a chair slides downward. Another source of shearing forces is pulling, rather than lifting, the bedridden person up in bed. In this case, the skin remains fixed to the sheet while the fascia and muscles are pulled upward.

Prevention

The prevention of pressure ulcers is preferable to treatment. In 1992, a special panel of the Agency for Health Care Policy and Research (AHCPR; now the Agency for Healthcare Research and Quality), the Panel for the Prediction and Prevention of Pressure Ulcers in Adults, released the *Clinical Practice Guidelines for Pressure Ulcers in Adults*.³² The panel recommended four overall goals: (1) identifying at-risk persons who need preventative measures and the specific factors placing them at risk; (2) maintaining and improving tissue tolerance to prevent injury; (3) protecting against the adverse effects of external mechanical forces (*i.e.*, pressure, friction, and shear); and (4) reducing the incidence of pressure ulcers through educational programs.³² A 1994 publication of the AHCPR made specific recommendations for assessment of the person with pressure ulcers, management of tissue load, ulcer care, managing bacterial colonization and infection, operative repair, and education and quality control.³³

Risk factors identified as contributing to the development of pressure ulcers were those related to sensory perception (*i.e.*, ability to respond meaningfully to pressure-related discomfort), level of skin moisture, urine and fecal continence, nutrition and hydration status, mobility, circulatory status, and presence of shear and friction forces.

Methods for preventing pressure ulcers include frequent position change, meticulous skin care, and frequent and careful observation to detect early signs of skin breakdown. Adequate hydration of the stratum corneum appears to protect the skin against mechanical insult.³² The prevention of dehydration improves the circulation. It also decreases the concentration of urine, thereby minimizing skin irritation in persons who are incontinent, and it reduces urinary problems that contribute to incontinence. Maintenance of adequate nutrition is important. Anemia and malnutrition contribute to tissue breakdown and delay healing after tissue injury has occurred.

Staging and Treatment

Pressure ulcers can be staged using four categories.^{32,33} *Stage I ulcers* are characterized by a defined area of persistent redness in lightly pigmented skin or an area of persistent redness with blue or purple hues in darker pigmented skin. *Stage II ulcers* represent a partial-thickness loss of skin involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion, a blister, or a shallow crater. *Stage III ulcers* represent a full-thickness skin loss involving damage and necrosis of subcutaneous tissue that may extend down to but not through underlying fascia. The ulcer manifests as a deep crater with or without undermining of adjacent tissue. *Stage IV ulcers* involve full-thickness skin loss and necrosis with extensive destruction or damage to the underlying subcutaneous tissues that may extend to involve muscle, bone, and supporting structures (*e.g.*, tendon or joint capsule).

After skin breakdown has occurred, special treatment measures are needed to prevent further ischemic damage, reduce bacterial contamination and infection, and promote healing. Treatment methods are selected based on the stage of the ulcer.^{30,33} Stage I ulcers usually are treated with frequent turning and measures to remove pressure. Stage II or III ulcers with little exudate are treated with petroleum gauze, or semipermeable or occlusive dressings to maintain a moist healing environment. Stage III ulcers usually require debridement (*i.e.*, removal of necrotic tissue and eschar). This can be done surgically, with wet-to-dry dressings, or through the use of proteolytic enzymes.³⁰ Stage IV wounds often require packing to obliterate dead space and are covered with nonadherent dressings. Stage IV ulcers may require surgical interventions, such as skin grafts or myocutaneous flaps.

In summary, blood flow to the tissues is dependent upon a pressure gradient between the arterial and venous side of the circulation and a transmural pressure (*i.e.*, internal minus external) that holds the vessel open. Under certain conditions, such as compartment syndrome and pressure ulcers, increases in external pressures can exceed intravascular pressure and interrupt blood flow.

Compartment syndrome is a condition of increased pressure in a muscle compartment that compromises blood flow and potentially leads to death of nerve and muscle tissue. It can result from a decrease in compartment size (*e.g.*, constrictive dressings, closure of fascial defects, thermal injury, frostbite) or an increase in compartment volume (*e.g.*, postischemic swelling, fractures, contusion and soft tissue trauma, bleeding caused by vascular injury, venous congestion).

Pressure ulcers are caused by ischemia of the skin and underlying tissues. They result from external pressure, which disrupts blood flow, or shearing forces, which cause stretching and injury to blood vessels. Pressure ulcers are divided into four stages, according to the depth of tissue involvement. The prevention of pressure ulcers is preferable to treatment. The goals of prevention should include identifying at-risk persons who need prevention along with the specific factors placing them at risk; maintaining and improving tissue tolerance to pressure to prevent injury; and protecting against the adverse effects of external mechanical forces (*i.e.*, pressure, friction, and shear).

REVIEW QUESTIONS

- Characterize the role of LDL, HDL, and LDL receptors in the pathogenesis of atherosclerosis.
- List risk factors in atherosclerosis and relate them to the possible mechanisms associated with the development of atherosclerosis.
- Compare the mechanisms and manifestations of ischemia associated with atherosclerotic peripheral vascular disease and Raynaud's phenomenon.
- Compare the pathology and manifestations of thoracic or abdominal and aortic dissection.
- Describe the pathology of venous insufficiency and relate it to the development of stasis dermatitis and venous ulcers.
- Cite risk factors associated with venous thrombosis and describe the manifestation of the disorder and its treatment.
- Characterize the impairment of blood flow caused by external compression of blood vessels in compartment syndrome and relate it to five possible causes of compartment syndrome.
- Explain how pressure and shearing forces contribute to the development of pressure ulcers.



Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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