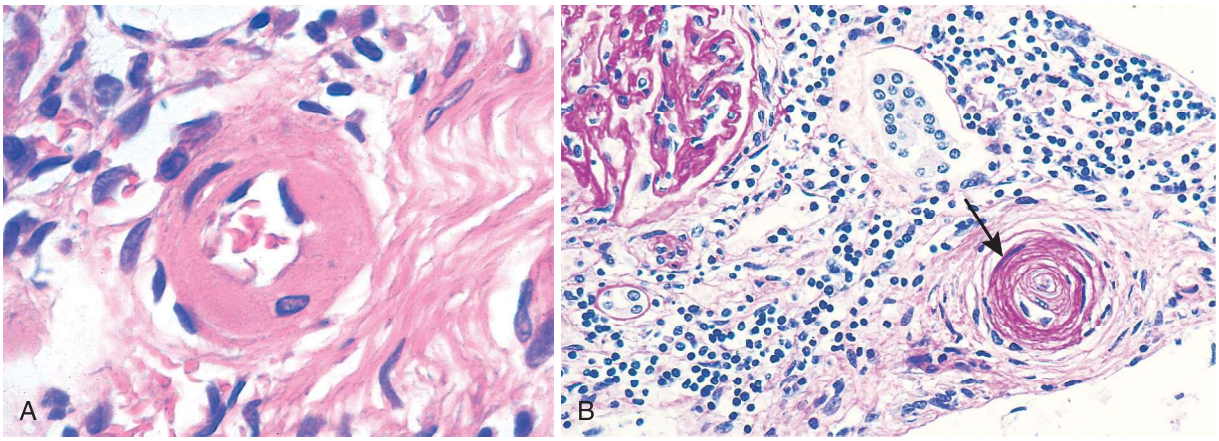

Figure 11.6 Vascular pathology in hypertension. (A) Hyaline arteriolosclerosis. The arteriolar wall is thickened with increased protein deposition (hyalinized), and the lumen is markedly narrowed. (B) Hyperplastic arteriolosclerosis (onion-skinning) causing luminal obliteration *(arrow)* (periodic acid-Schiff stain). (B, Courtesy Helmut Rennke, MD, Brigham and Women's Hospital, Boston, Mass.)

narrowing causes diffuse impairment of renal blood supply and glomerular scarring (Chapter 20).

Hyperplastic arteriolosclerosis. This lesion occurs in severe hypertension; vessels exhibit concentric, **laminated ("onion-skin")** thickening of the walls with luminal narrowing (Fig. 11.6B). The laminations consist of SMCs with thickened, reduplicated basement membrane; in malignant hypertension, they are accompanied by fibrinoid deposits and vessel wall necrosis **(necrotizing arteriolitis)**, particularly in the kidney (Chapter 20).

Pulmonary hypertension can be caused by several entities including left heart failure, congenital heart disease, valve disorders, obstructive or interstitial lung disease, and recurrent thromboemboli. The arterioles in such affected lungs typically show histologic changes ranging from fibrotic intimal thickening to medial hyperplasia. These are described in greater detail in Chapter 15.

KEY CONCEPTS
HYPERTENSION

- Hypertension is a common disorder affecting roughly half of adults in the United States; it is a major risk factor for atherosclerosis, congestive heart failure, and renal failure.
- Essential hypertension represents 90% to 95% of cases and is a complex, multifactorial disorder involving both environmental influences and genetic polymorphisms that influence sodium resorption, aldosterone pathways, and the renin-angiotensin-aldosterone system.
- Hypertension is occasionally caused by single-gene disorders or is secondary to diseases of the kidney, adrenal, or other endocrine organs.
- Sustained hypertension requires participation of the kidney, which normally responds to hypertension by eliminating salt and water. In established hypertension, both increased blood volume and increased peripheral resistance contribute to the increased pressure.
- Histologically, hypertension is associated with thickening of arterial walls caused by hyaline deposits and, in severe cases, by proliferation of ECs or SMCs and replication of the basement membrane.

ARTERIOSCLEROSIS

Arteriosclerosis literally means "hardening of the arteries"; it is a generic term for arterial wall thickening and loss of elasticity. There are four general patterns, with different clinical and pathologic consequences.

- *Arteriolosclerosis* affects small arteries and arterioles and may cause downstream ischemic injury. The two anatomic variants, hyaline and hyperplastic, were discussed earlier in relation to hypertension.
- *Mönckeberg medial sclerosis* is characterized by calcifications of the medial walls of muscular arteries, typically starting along the internal elastic membrane. Adults older than age 50 are most commonly affected. The calcifications do not encroach on the vessel lumen and are usually not clinically significant.
- *Fibromuscular intimal hyperplasia* occurs in muscular arteries larger than arterioles. It is driven by inflammation (as in a healed arteritis or transplant-associated arteriopathy; see Chapter 12) or by mechanical injury (e.g., associated with stents or balloon angioplasty; see later) and can be considered as a healing response. The affected vessels can become quite stenotic; indeed, such intimal hyperplasia underlies in-stent restenosis and is the major long-term limitation of solid-organ transplants.
- *Atherosclerosis,* from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern and is discussed here.

ATHEROSCLEROSIS

Atherosclerosis underlies the pathogenesis of coronary, cerebral, and peripheral vascular disease and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder. Because coronary artery disease is an important manifestation of the disease, epidemiologic data related to atherosclerosis mortality typically reflect deaths caused by ischemic heart disease (Chapter 12); indeed, myocardial infarction is responsible for almost a quarter of all deaths in the United

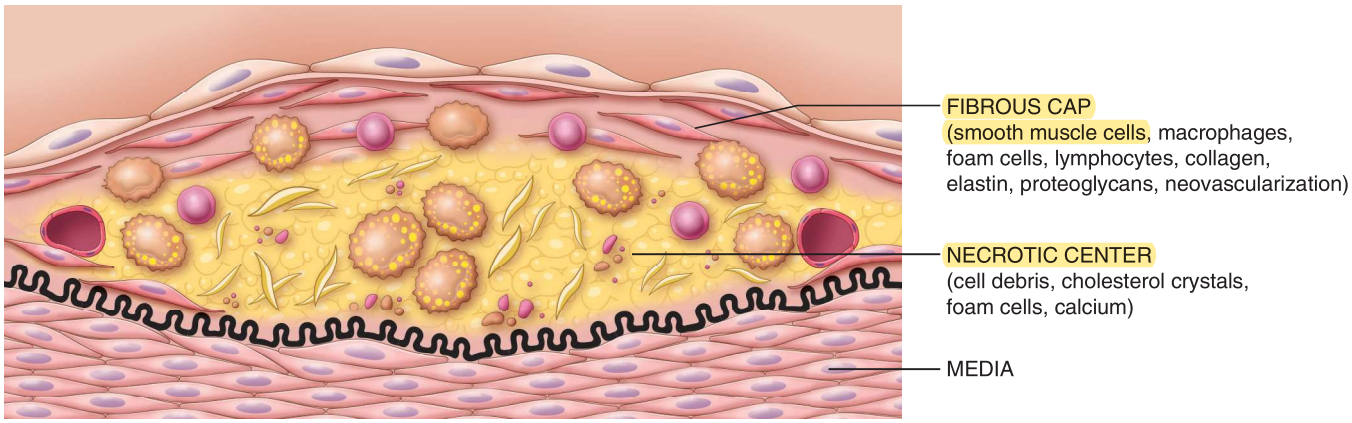

Figure 11.7 Basic structure of an atherosclerotic plaque. Note that atherosclerosis is an intimal-based process with a complex interplay of cells and extracellular materials. Plaques can have secondary effects on the underlying media including a reduction in smooth muscle cells.

States. Significant morbidity and mortality are also caused by aortic and carotid atherosclerotic disease and stroke.

The likelihood of atherosclerosis is determined by the combination of acquired (e.g., cholesterol levels, smoking, hypertension), inherited (e.g., low-density lipoprotein [LDL] receptor gene mutations), and gender- and age-associated risk factors. Acting in concert, they cause intimal lesions called *atheromas* (also called *atheromatous* or *atherosclerotic plaques*) that protrude into vessel lumens. An atheromatous plaque typically consists of a raised lesion with a soft grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a fibrous cap (Fig. 11.7). Besides mechanically obstructing blood flow, atherosclerotic plaques can rupture leading to catastrophic obstructive vascular thrombosis. Atherosclerotic plaques can also increase the diffusion distance from the lumen to the media, leading to ischemic injury and weakening of the vessel wall, changes that can result in aneurysm formation.

Epidemiology. Although atherosclerosis-associated ischemic heart disease is ubiquitous among most developed nations, risk reduction and improved therapies have combined to moderate the associated mortality. At the same time, reduced mortality from infectious diseases and the adoption of Western lifestyles has led to the increased prevalence of ischemic heart disease in low income nations. As a result, the death rate for coronary artery disease in Africa, India, and Southeast Asia now exceeds that in the United States; eastern European countries have rates 3 to 5 times higher than the United States and 7 to 12 times higher than Japan.

Risk Factors

The prevalence and severity of atherosclerosis and ischemic heart disease among individuals and groups are related to a number of risk factors identified through several prospective analyses (e.g., the Framingham Heart Study); some of these are constitutional (and therefore less controllable), but others are acquired or related to specific behaviors and potentially amenable to intervention (Table 11.3). These risk factors typically have greater than additive effects, but treatment (even less than optimal) can mitigate some of the risk (Fig. 11.8).

Constitutional Risk Factors

- *Genetics.* Family history is the most important independent risk factor for atherosclerosis. Certain Mendelian disorders are strongly associated with atherosclerosis (e.g., familial hypercholesterolemia; see Chapter 5), but they account for only a small percentage of cases. The well-established familial predisposition to atherosclerosis and ischemic heart disease is usually polygenic, relating to small effects of many shared alleles common to a family or population.
- *Age is a dominant influence.* The development of atherosclerotic plaque is a progressive process that usually becomes clinically manifest in middle age or later (see later). Thus between ages 40 and 60, the incidence of myocardial infarction increases fivefold. Death rates from ischemic heart disease rise with each decade even into advanced age. Increasingly, however, this age association is being recognized as perhaps more than just the accumulated slings and arrows of vascular injury over the years. Indeed, with aging, there is a tendency for the outgrowth of hematopoietic clones (so-called *clonal hematopoiesis of indeterminate potential [CHIP]*) carrying mutations that confer a proliferative advantage. Many of these affect DNA modifications and transcriptional regulation (e.g., *TET2* encoding an enzyme that converts methylcytosine to 5-hydroxymethylcytosine); as expected, these can ultimately influence the risk of developing hematologic malignancies. Perhaps more remarkable, however, is that such clonal hematopoiesis is even more

Table 11.3 Major Risk Factors for Atherosclerosis

Nonmodifiable (Constitutional)
Genetic abnormalities
Family history
Increasing age
Male gender
Modifiable
Hyperlipidemia
Hypertension
Cigarette smoking
Diabetes
Inflammation

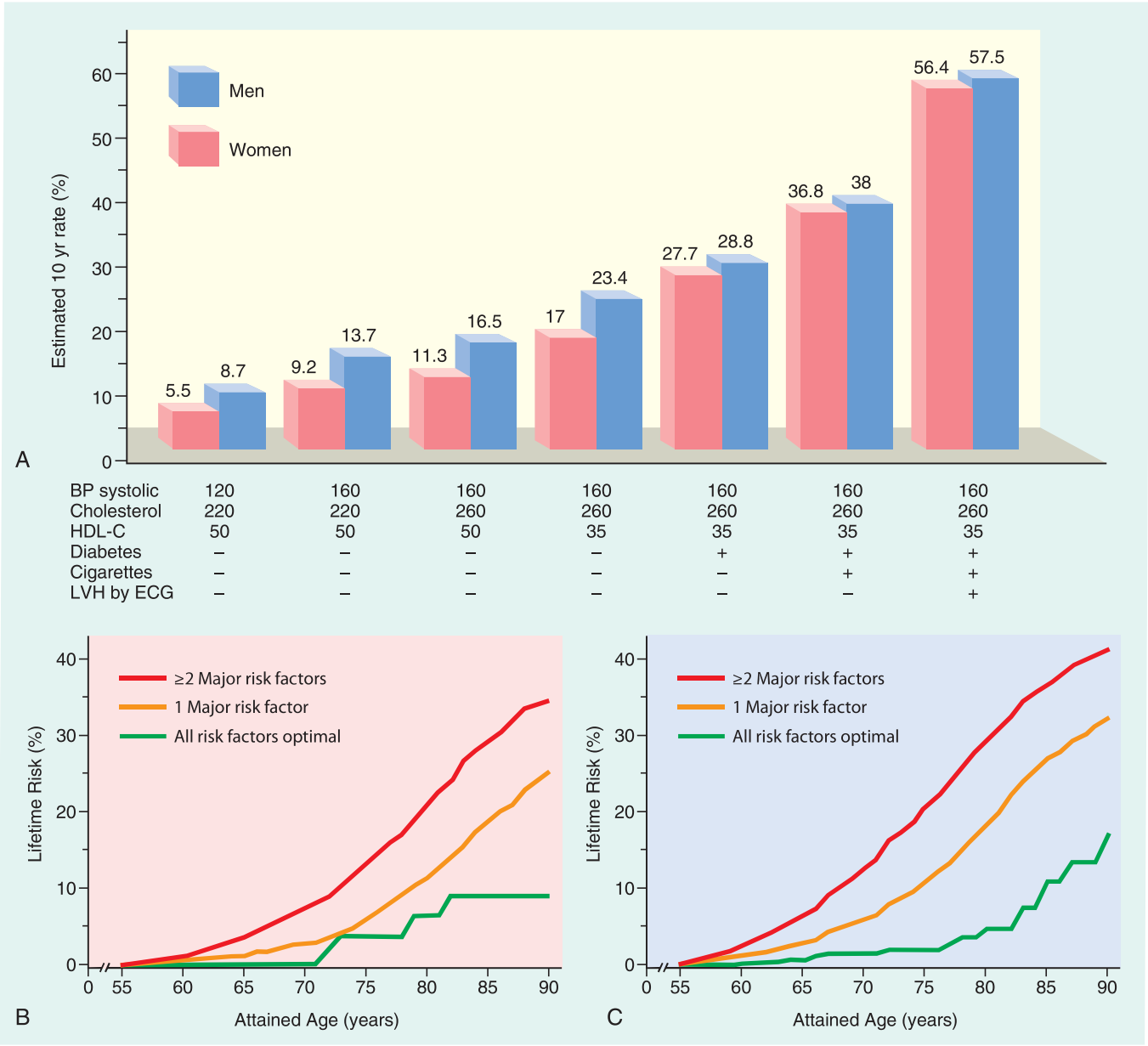

Figure 11.8 Lifetime risk of death from cardiovascular disease. (A) Estimated 10-year risk of coronary artery disease in hypothetical 55-year-old men and women as a function of traditional risk factors (hyperlipidemia, hypertension, smoking, and diabetes). *BP,* Blood pressure; *ECG,* electrocardiogram; *HDL-C,* high-density lipoprotein cholesterol; *LVH,* left ventricular hypertrophy. In women (B) and men (C), one or more risk factors of blood pressure, cholesterol, diabetes, and cigarettes significantly increases the lifetime risk of a cardiovascular event. (A, From O'Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: lessons from observational studies, *J Hypertens Suppl* 16(6):S3–S7, 1998, with permission from Lippincott Williams & Wilkins; B and C, Modified from Berry JD, Dyer A, Cai X, et al: Lifetime risks of cardiovascular disease, *N Eng J Med* 366:321–329, 2012.)

significantly associated with increased all-cause cardiovascular mortality. An explanation is beginning to emerge that the same CHIP mutations that affect cellular proliferation (e.g., *TET2*) can also impact the inflammatory response of mononuclear cells and thereby influence atherogenesis (see also later).

- *Gender.* Premenopausal women are relatively protected against atherosclerosis and its consequences compared with age-matched men. Thus myocardial infarction and other complications of atherosclerosis are uncommon in premenopausal women unless they are otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension. After menopause, however, the incidence of atherosclerosis-related diseases increases and at older ages exceeds that of men. Although a favorable influence of estrogen has been proposed to explain this effect, clinical trials of estrogen replacement did not show any benefit; indeed, postmenopausal estrogen therapy actually increased cardiovascular risk in some older women.

Modifiable Major Risk Factors

- *Hyperlipidemia*—and more specifically hypercholesterolemia—is a major risk factor for atherosclerosis; even in the absence of other risk factors, hypercholesterolemia is sufficient to initiate lesion development. The major component of serum cholesterol associated with increased risk is LDL cholesterol

("bad cholesterol"). LDL is the lipid-cholesterol-protein complex that delivers cholesterol to peripheral tissues; in contrast, high-density lipoprotein (HDL) is the complex that mobilizes cholesterol from the periphery (including atheromas) and transports it to the liver for catabolism and biliary excretion. Higher levels of HDL ("good cholesterol") correlate with reduced risk.

Understandably, dietary and pharmacologic interventions that lower LDL or total serum cholesterol are of considerable interest. Interestingly, approaches that exclusively raise HDL are not effective. Although previously considered important, the contribution of most dietary fats to atherosclerosis is now viewed as minimal. Nevertheless, omega-3 fatty acids (abundant in fish oils) are considered beneficial, whereas trans unsaturated fats produced by artificial hydrogenation of polyunsaturated oils (used in baked goods and margarine) can adversely affect cholesterol profiles. *Statins* are a class of drugs that lower circulating cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis (Chapter 5). Statins are widely used to lower serum cholesterol levels, lowering rates of myocardial infarctions, arguably one of the most significant success stories of translational research. Interestingly, some of the benefit of the statins may be due to "off-target" effects on reducing inflammation (see also later).

- *Hypertension* can increase the risk of ischemic heart disease by approximately 60% versus normotensive populations. Chronic hypertension is the most common cause of left ventricular hypertrophy, and hence the latter is also a surrogate marker for cardiovascular risk.
- *Cigarette smoking*, and in particular prolonged (years) use, doubles the death rate from ischemic heart disease. Smoking cessation reduces that risk substantially.
- *Diabetes mellitus* induces hypercholesterolemia (Chapter 24) and markedly increases the risk of atherosclerosis. Other factors being equal, the incidence of myocardial infarction is twice as high in diabetics relative to normoglycemic individuals. There is also an increased risk of strokes and a 100-fold increased risk of atherosclerosis-induced gangrene of the lower extremities.

Additional Risk Factors

As many as 20% of all cardiovascular events occur in the absence of major risk factors (e.g., hypertension, hyperlipidemia, smoking, or diabetes). Indeed, more than 75% of cardiovascular events in previously healthy women occur with LDL cholesterol levels below 160 mg/dL (levels generally considered to connote low risk). Clearly, other factors are contributory. Among those that are proven or suspected are the following:

- *Inflammation.* Inflammation is present during all stages of atherogenesis and is intimately linked with atherosclerotic plaque formation and rupture (see later). With the increasing recognition that inflammation plays a significant causal role in ischemic heart disease, assessment of systemic inflammation has become important in overall risk stratification. A number of circulating markers of inflammation correlate with ischemic heart disease, and *C-reactive protein (CRP)* has emerged as one of the most stable and simplest to measure.

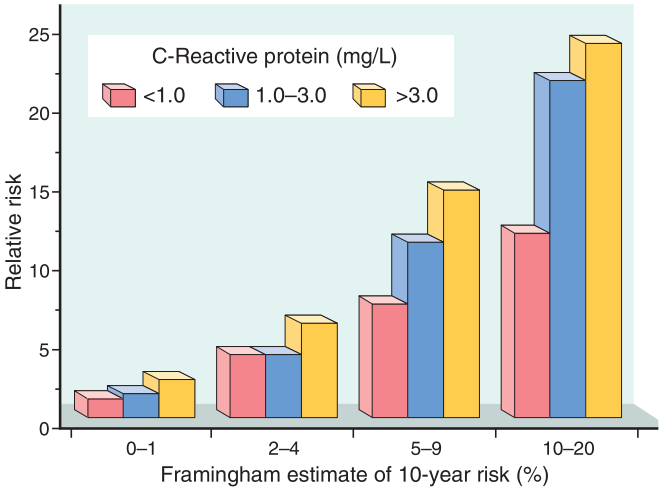

Figure 11.9 C-reactive protein adds prognostic information at all levels of traditional risk identified from the Framingham Heart Study. Relative risk (y-axis) refers to the risk of a cardiovascular event (e.g., myocardial infarction). The x-axis is the 10-year risk of a cardiovascular event derived from the traditional risk factors identified in the Framingham study. In each risk group, C-reactive protein values further stratify the patients. (Data from Ridker PM, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events, *N Engl J Med* 347:1557, 2002.)

CRP is an acute phase reactant synthesized primarily by the liver. Although CRP does not appear to be causally related to the development of atherosclerosis or its sequelae, it is well established that plasma CRP is a strong, independent marker of risk for myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals (Fig. 11.9). Accordingly, CRP levels are now incorporated into risk stratification algorithms. Interestingly, CRP levels are also typically lowered in concert with other risk reduction measures including smoking cessation, weight loss, exercise, and statin administration.

- *Hyperhomocysteinemia.* Serum homocysteine levels correlate with coronary atherosclerosis, peripheral vascular disease, stroke, and venous thrombosis. *Homocystinuria,* due to rare inborn errors of metabolism, results in elevated circulating homocysteine (>100 µmol/L) and is associated with premature vascular disease.
- *Metabolic syndrome.* Associated with central obesity (Chapter 9), this entity is characterized by insulin resistance, hypertension, dyslipidemia (elevated LDL and depressed HDL), hypercoagulability, and a proinflammatory state. Dyslipidemia, hyperglycemia, and hypertension all are cardiac risk factors, while the systemic hypercoagulable and proinflammatory state may contribute to endothelial dysfunction and/or thrombosis.
- *Lipoprotein a [Lp(a)]* is an altered form of LDL that contains the apolipoprotein B-100 portion of LDL linked to apolipoprotein A (apo A); Lp(a) levels are associated with coronary and cerebrovascular disease risk, independent of total cholesterol or LDL levels.
- *Factors affecting hemostasis.* Several markers of hemostatic and/or fibrinolytic function (e.g., elevated plasminogen activator inhibitor 1) are potent predictors of risk for

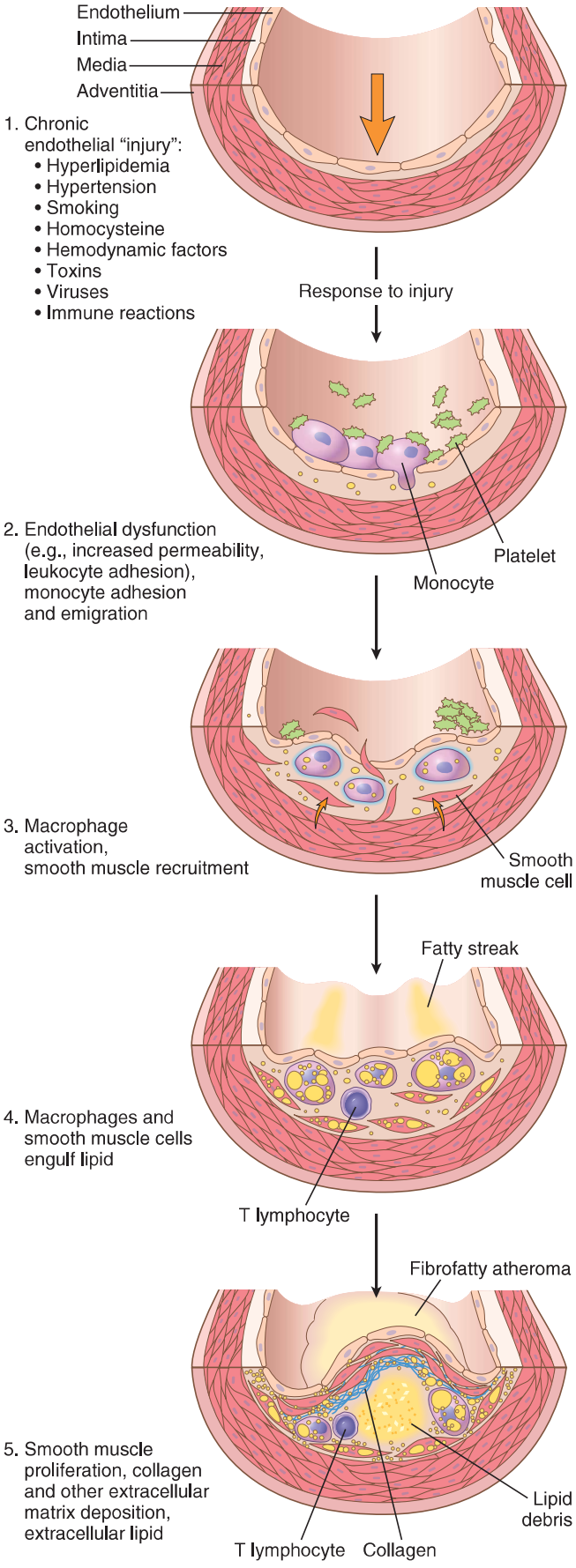

Figure 11.10 Evolution of arterial wall changes in the response to injury hypothesis. *1*, Normal. *2*, Endothelial injury with monocyte and platelet adhesion. *3*, Monocyte and smooth muscle cell migration into the intima, with macrophage activation. *4*, Macrophage and smooth muscle cell uptake of modified lipids, with further activation. *5*, Intimal smooth muscle cell proliferation with extracellular matrix production, forming a well-developed plaque.

major atherosclerotic events including myocardial infarction and stroke. Platelet-derived factors as well as thrombin—through both procoagulant and proinflammatory effects—are increasingly recognized as major contributors to local vascular pathology.

- *Other factors*. Factors associated with a less pronounced and/or difficult to quantitate risk include lack of exercise; competitive, stressful lifestyle (type A personality); and obesity (the last-mentioned also being complicated by hypertension, diabetes, hypertriglyceridemia, and decreased HDL).

Pathogenesis of Atherosclerosis

The clinical importance of atherosclerosis has stimulated enormous interest in understanding the mechanisms that underlie its evolution and complications. The contemporary view of atherogenesis integrates the risk factors previously discussed and is called the "response to injury" hypothesis. **This model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury. Lesion progression occurs through interaction of modified lipoproteins, macrophages, and T lymphocytes with ECs and SMCs of the arterial wall** (Fig. 11.10). According to this schema, atherosclerosis progresses in the following sequence:

- *Endothelial injury and dysfunction,* causing (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis.
- *Accumulation of lipoproteins* (mainly LDL and its oxidized forms) in the vessel wall.
- *Monocyte adhesion to the endothelium,* followed by migration into the intima and transformation into *macrophages* and *foam cells.*
- *Platelet adhesion.*
- *Factor release* from activated platelets, macrophages, and vascular wall cells, inducing *SMC* recruitment, either from the media or from circulating precursors.
- *SMC proliferation, ECM production, and recruitment of T cells.*
- *Lipid accumulation* both extracellularly and within cells (macrophages and SMCs).
- *Calcification* of ECM and necrotic debris late in the pathogenesis.

We will now discuss the role of these factors in the pathogenesis of atherosclerosis in some detail, starting with endothelial injury.

Endothelial Injury. EC injury is the cornerstone of the response-to-injury hypothesis. Early lesions begin at sites of morphologically intact endothelium that exhibit

features of endothelial dysfunction—increased permeability, enhanced leukocyte adhesion, and altered gene expression. Causes of EC dysfunction include toxins from cigarette smoke, homocysteine, and the local production of inflammatory cytokines. However, the **three most important causes of endothelial dysfunction are hemodynamic disturbances, hypercholesterolemia, and inflammation.**

Hemodynamic Disturbances. The importance of hemodynamic turbulence in atherogenesis is illustrated by the observation that plaques do not occur randomly, but rather tend to locate at the ostia of exiting vessels, branch points, and along the posterior abdominal aorta where flow patterns are disturbed and nonlaminar. This is explained by the fact that laminar nonturbulent flow increases the production of transcription factors and, in particular, Krüppel-like factor-2 (KLF2) that turn on atheroprotective genes and turn off inflammatory gene transcription. Conversely, turbulent, nonlaminar flow drives a repertoire of genetic transcription that makes those sites atheroprone. It is noteworthy that some of the atheroprotective effects of statins also occur through KLF2 upregulation.

Hypercholesterolemia. Lipids are transported in the bloodstream bound to specific apoproteins (forming lipoprotein complexes). *Dyslipoproteinemias* are lipoprotein abnormalities that may be present in the general population (and, indeed, are found in many myocardial infarction survivors). These include (1) increased LDL cholesterol levels, (2) decreased HDL cholesterol levels, and (3) increased levels of the abnormal Lp(a). These may result from mutations in apoproteins or lipoprotein receptors or arise from other underlying disorders that affect circulating lipid levels such as nephrotic syndrome, alcoholism, hypothyroidism, or diabetes mellitus. All of these abnormalities are associated with an increased risk of atherosclerosis.

The evidence implicating hypercholesterolemia in atherogenesis includes the following:

- *The dominant lipids in atheromatous plaques are cholesterol and cholesterol esters.*
- *Genetic defects in lipoprotein uptake and metabolism* that cause hyperlipoproteinemia are associated with accelerated atherosclerosis. Thus familial hypercholesterolemia, caused by mutations affecting the LDL receptors and consequent inadequate hepatic LDL uptake and catabolism (Chapter 5), can precipitate myocardial infarctions before age 20 in those homozygous for the mutation. Similarly, accelerated atherosclerosis occurs in animal models with engineered deficiencies in apolipoproteins or LDL receptors.
- *Epidemiologic analyses* demonstrate a significant correlation between the severity of atherosclerosis and the levels of total plasma cholesterol or LDL.
- *Lowering serum cholesterol* by diet or drugs slows the rate of progression of atherosclerosis, causes regression of some plaques, and reduces the risk of cardiovascular events.

The mechanisms by which hyperlipidemia contributes to atherogenesis include the following:

- *Impaired EC function.* Chronic hyperlipidemia, particularly hypercholesterolemia, can directly impair EC function by increasing local reactive oxygen species production; besides causing membrane and mitochondrial damage, oxygen free radicals accelerate NO decay, dampening its vasodilator activity.
- *Modified LDL.* With chronic hyperlipidemia, lipoproteins accumulate within the intima, where they may aggregate or become oxidized by free radicals produced by inflammatory cells. Such modified LDL is then accumulated by macrophages through a variety of scavenger receptors (distinct from the LDL receptor). Because the modified lipoproteins cannot be completely degraded, chronic ingestion leads to the formation of lipid-filled macrophages called *foam cells;* SMCs can similarly transform into lipid-laden foam cells by ingesting modified lipids through LDL receptor–related proteins. Not only are the modified lipoproteins toxic to ECs, SMCs, and macrophages, but their binding and uptake also stimulate the release of growth factors, cytokines, and chemokines that create a vicious inflammatory cycle of monocyte recruitment and activation. The early lesions containing lipid-filled macrophages are called *fatty streaks.*

Inflammation. **Chronic inflammation contributes to the initiation and progression of atherosclerotic lesions.** It is believed that inflammation is triggered by the accumulation of cholesterol crystals and free fatty acids in macrophages and other cells (Fig. 11.11). These cells sense the presence of abnormal materials via cytosolic innate immune receptors that are components of the inflammasome (Chapter 6). The resulting inflammasome activation leads to the production of the proinflammatory cytokine interleukin (IL)-1, which recruits and activates mononuclear cells including macrophages and T lymphocytes. Such mononuclear cell activation, in turn, leads to local production of cytokines and chemokines that recruit and activate more inflammatory cells. Activated macrophages produce reactive oxygen species that enhance LDL oxidation and elaborate growth factors that drive SMC proliferation. Activated T lymphocytes in the growing intimal lesions elaborate inflammatory cytokines, (e.g., interferon-γ), which, in turn, can activate macrophages as well as ECs and SMCs. Thus many of the lesions of atherosclerosis are attributable to the chronic inflammatory reaction in the vessel wall.

Infection. Although circumstantial evidence has been presented linking atherosclerosis to herpesvirus, cytomegalovirus, and *Chlamydophila pneumoniae,* there is not an established causal role for infection.

Smooth Muscle Proliferation and Matrix Synthesis. Intimal SMC proliferation and ECM deposition convert a fatty streak into a mature atheroma and contribute to the progressive growth of atherosclerotic lesions (see Fig. 11.10). Several growth factors are implicated in SMC proliferation and ECM synthesis, including platelet-derived growth factor (PDGF), released by locally adherent platelets, as well as macrophages, ECs and SMCs; fibroblast growth factor; and transforming growth factor-α (Chapter 1). These factors also stimulate SMCs to synthesize ECM (notably collagen), which stabilizes atherosclerotic plaques. In contrast, activated inflammatory cells in atheromas may increase the breakdown of ECM components resulting in unstable plaques (see later).

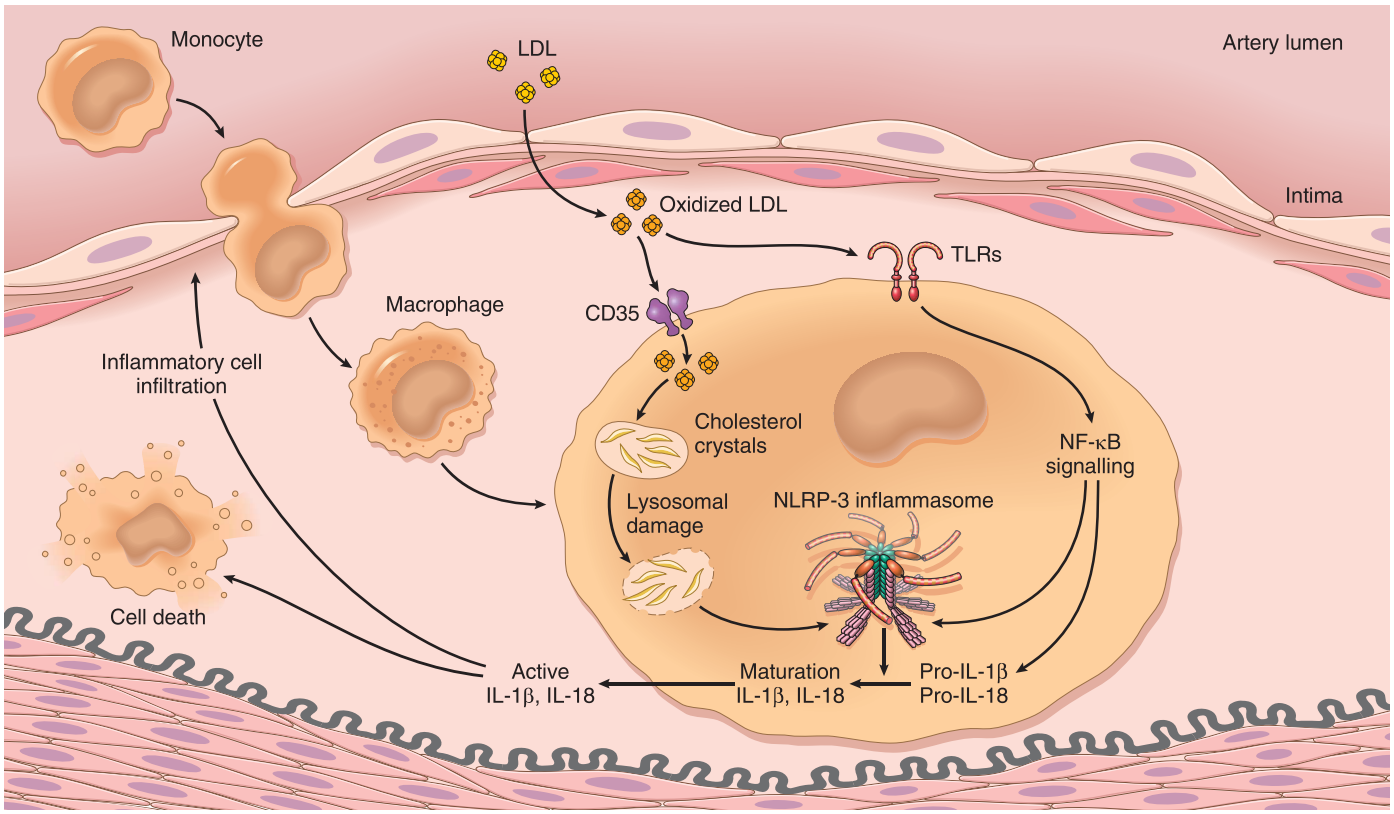

Figure 11.11 The role of cholesterol crystals in inflammasome activation and interleukin-1 production in atherosclerotic plaque. Oxidized low-density lipoprotein *(LDL)* leads to the activation of subendothelial macrophages through toll-like receptor *(TLR)* mediated initiation of downstream *NF-κB* transcription factor activation. The NF-κB complex then induces the production of a variety of proinflammatory mediators, including interleukin precursors and the components of the *NLRP3* inflammasome. Uptake of oxidized LDL and subsequent cholesterol crystallization results in assembly of the precursor components into an active inflammasome complex that proteolytically activates the pro-interleukin-1 beta *(IL-1β)* and interleukin-18 *(IL-18)* molecules. (Modified from Li X, Deroide N, Mallat Z: The role of the inflammasome in cardiovascular disease, *J Mol Med (Berl)* 92:307–319, 2014.)

Overview. Fig. 11.12 summarizes the major pathogenic pathways in atherogenesis, emphasizing the multifactorial nature of the disease. This schematic highlights the concept of atherosclerosis as a chronic inflammatory response—and ultimately an attempt at vascular "healing"—driven by a variety of insults including EC injury, lipid oxidation, lipid accumulation, and inflammation. Atheromas are dynamic lesions consisting of dysfunctional ECs, proliferating SMCs, and admixed T lymphocytes and macrophages. All four cell types are capable of liberating mediators that can influence atherogenesis. Thus at early stages, intimal plaques are little more than aggregates of SMCs, macrophages, and foam cells; death of these cells releases lipids and necrotic debris. With progression, the atheroma is modified by ECM synthesized by SMCs; connective tissue is particularly prominent on the intimal aspect forming a fibrous cap. Lesions typically retain a central core of lipid-laden cells and fatty debris that can become calcified. Although the intimal plaque can initially cause medial remodeling and outward expansion, the growing atherosclerotic plaque—with varying degrees of calcification depending on the nature of the surrounding matrix—eventually encroaches on the vessel lumen and compromises blood flow. The plaque can also compress the underlying media, leading to its degeneration, or can erode or rupture to expose thrombogenic factors resulting in thrombus formation and acute vascular occlusion.

MORPHOLOGY

Fatty streaks. Fatty streaks are composed primarily of lipid-filled foamy macrophages. Beginning as small flat yellow macules, these can eventually coalesce into elongated streaks 1 cm long or longer. The lesions are not particularly raised and do not cause any significant flow disturbance (Fig. 11.13). Although fatty streaks can evolve into plaques, not all are destined to become advanced lesions. Aortas of infants can exhibit fatty streaks, and such lesions are present in virtually all adolescents, even those without known risk factors. That coronary fatty streaks begin to form in adolescence at the same anatomic sites that later tend to develop plaques suggests a temporal evolution of these lesions.

Atherosclerotic plaque. The key processes in atherosclerosis are intimal thickening and lipid accumulation (see Figs. 11.7, 11.10, and 11.12). Atheromatous plaques are yellow-tan and are raised above the surrounding vessel wall; any superimposed thrombus over ulcerated plaques will be red-brown. Plaques vary in size but can coalesce to form larger masses (Fig. 11.14).

Atherosclerotic lesions are patchy and rarely circumferential, usually involving only a portion of any given arterial wall; on cross-section, the lesions therefore appear eccentric (Fig. 11.15A). The focality of atherosclerotic lesions—despite the uniform exposure of vessel walls to such factors as cigarette smoke toxins, elevated LDL, hyperglycemia, etc.—is attributable to the vagaries

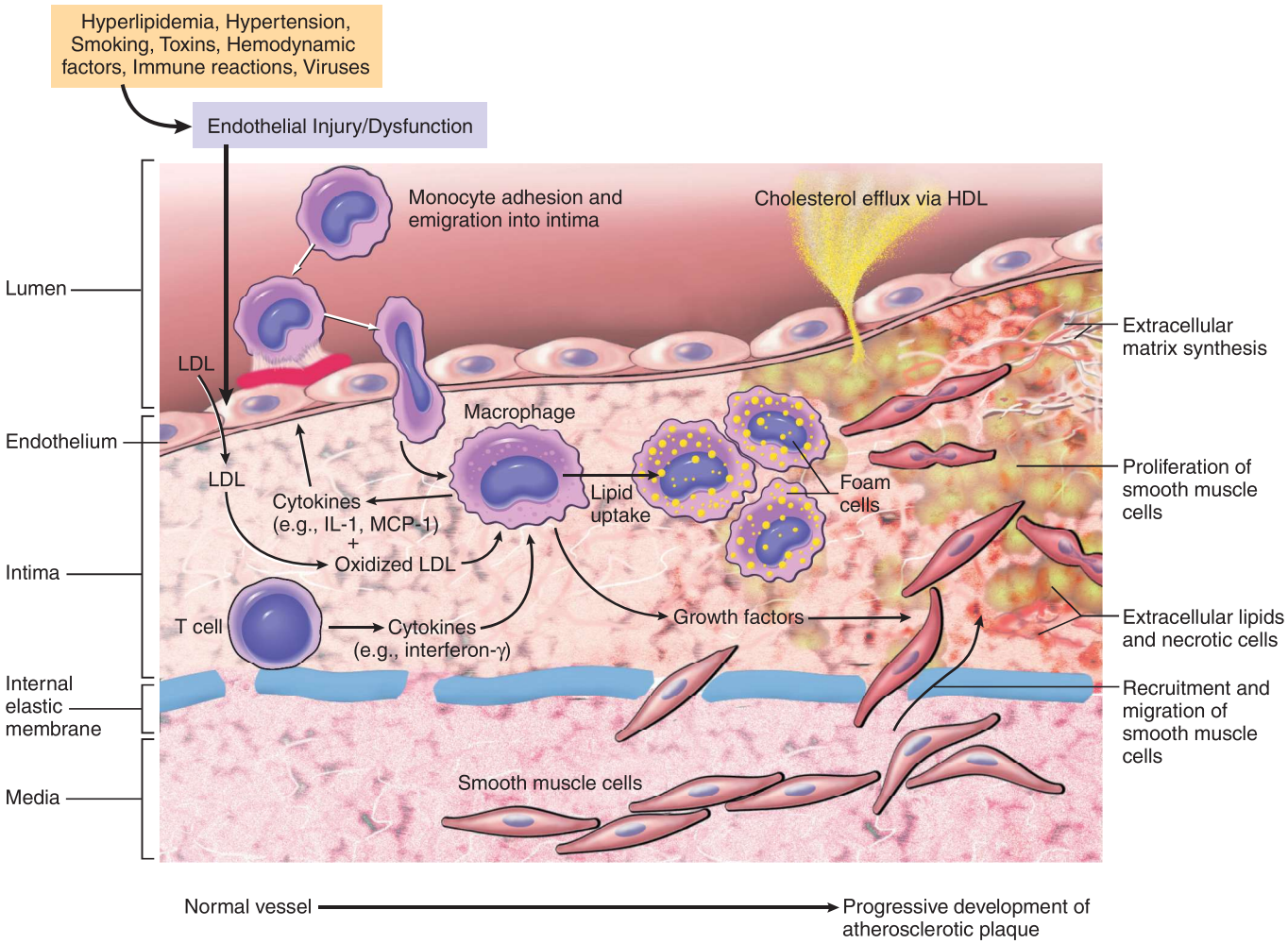

Figure 11.12 Sequence of cellular interactions in atherosclerosis. Hyperlipidemia, hyperglycemia, hypertension, and other influences cause endothelial dysfunction. This results in platelet and monocyte adhesion, with subsequent cytokine and growth factor release leading to smooth muscle cell migration and proliferation. Foam cells in atheromatous plaques derive from macrophages and smooth muscle cells that have accumulated modified lipids (e.g., oxidized and aggregated low-density lipoprotein *[LDL]*) via scavenger and LDL-receptor–related proteins. Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia, as well as from degenerating foam cells. Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux; high-density lipoprotein *(HDL)* likely helps clear cholesterol from these accumulations. In response to the elaborated cytokines and chemokines, smooth muscle cells migrate to the intima, proliferate, and produce extracellular matrix including collagen and proteoglycans. *IL-1,* Interleukin-1; *MCP-1,* monocyte chemoattractant protein-1.

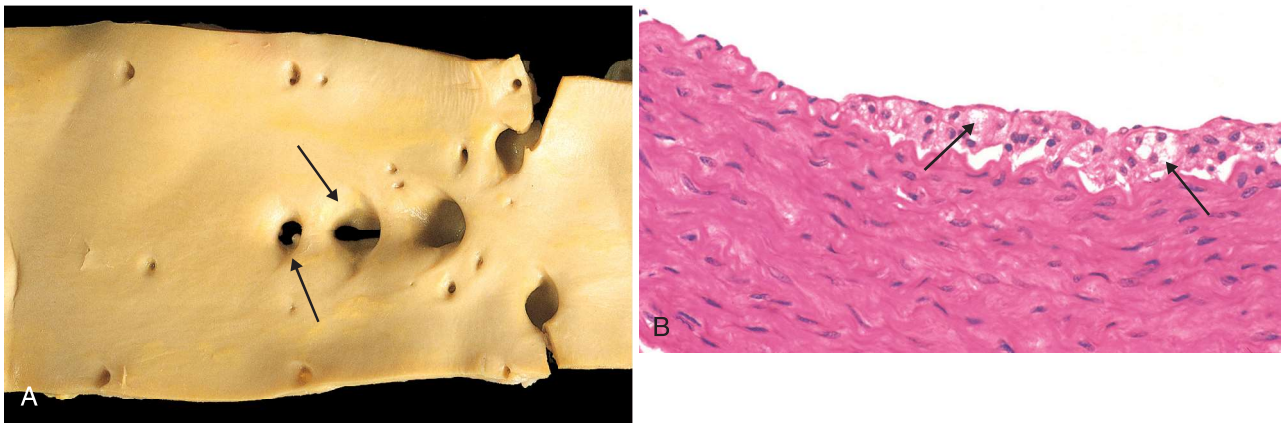

Figure 11.13 Fatty streak, a collection of foamy macrophages in the intima. (A) Aorta with fatty streaks *(arrows)*, associated largely with the ostia of branch vessels. (B) Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal, macrophage-derived foam cells *(arrows)*. (B, Courtesy Myron I. Cybulsky, MD, University of Toronto, Toronto, Ontario, Canada).

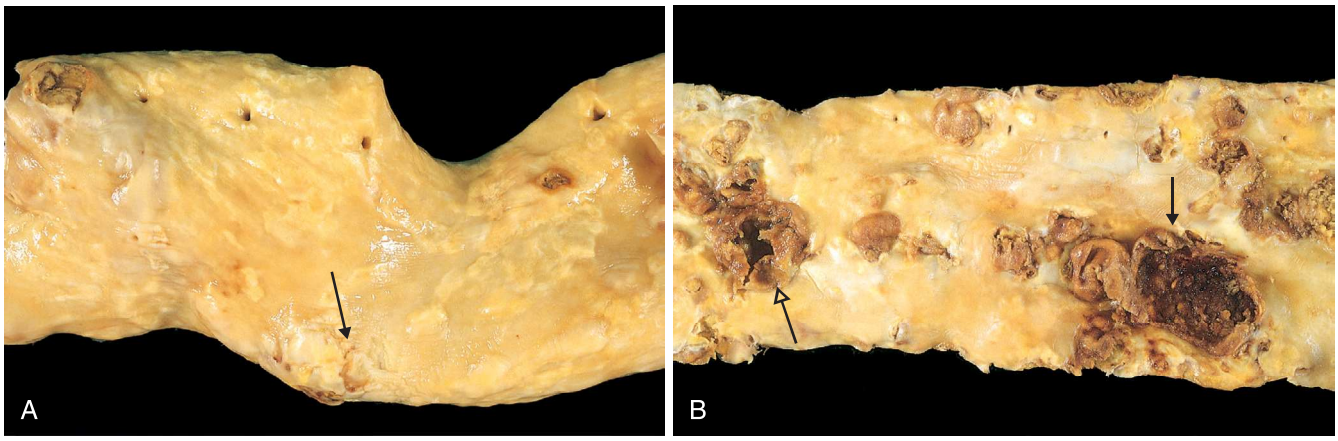

Figure 11.14 Gross views of atherosclerosis in the aorta. (A) Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the *arrow*. (B) Severe disease with diffuse, complicated lesions including an ulcerated plaque *(open arrow)* and a lesion with overlying thrombus *(closed arrow)*.

of vascular hemodynamics. Local flow disturbances, such as nonlaminar flow (turbulence) at branch points, make certain portions of a vessel wall more susceptible to plaque formation. Although initially focal and sparsely distributed, atherosclerotic lesions tend to enlarge over time and become more numerous and broadly distributed. Moreover, in any given vessel, lesions at various stages often coexist.

In descending order, **the most extensively involved vessels are the lower abdominal aorta and iliac arteries, the coronary arteries, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis.** Vessels of the upper extremities are usually relatively spared, as are the mesenteric and renal arteries except at their ostia. Although most individuals tend to have a consistent degree of atherosclerotic burden in the affected vasculature, the severity of disease in one arterial distribution does not necessarily predict severity in another.

Atherosclerotic plaques have four principal components: (1) cells including variable numbers of SMCs, macrophages, and T lymphocytes; (2) ECM including collagen, elastic fibers, and proteoglycans; (3) intracellular and extracellular lipids; and (4) calcifications in later stage plaques (Fig. 11.15B and C). These components occur in varying proportions and configurations in different lesions. Typically, there is a superficial fibrous cap composed of SMCs and relatively dense collagen. Beneath and to the side of the cap (the "shoulder") is a more cellular area containing macrophages, T lymphocytes, and SMCs. Deep to the fibrous cap is a necrotic core containing lipid (primarily cholesterol and cholesterol esters), debris from dead cells, foam cells (lipid-laden macrophages and lipid-laden SMCs), fibrin, thrombus in varying degrees of organization, and other plasma proteins; the cholesterol content is frequently present as crystalline aggregates that are washed out during routine tissue processing

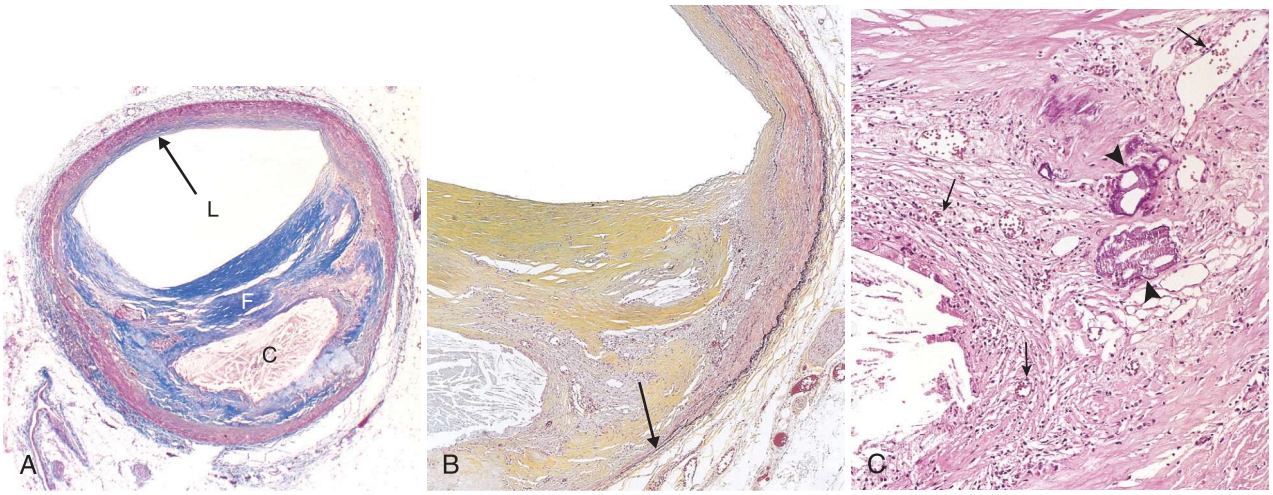

Figure 11.15 Histologic features of atheromatous plaque in the coronary artery. (A) Overall architecture demonstrating fibrous cap *(F)* and a central necrotic core *(C)* containing cholesterol and other lipids. The lumen *(L)* has been moderately compromised. Note that a segment of the wall is plaque-free *(arrow)*; the lesion is therefore "eccentric." In this section, collagen has been stained blue (Masson trichrome stain). (B) Higher power photograph of a section of the plaque shown in (A), stained for elastin (black), demonstrating that the internal and external elastic membranes are attenuated and the media of the artery is thinned under the most advanced plaque *(arrow)*. (C) Higher magnification photomicrograph at the junction of the fibrous cap and core showing scattered inflammatory cells, calcification *(arrowhead)*, and neovascularization *(small arrows)*.

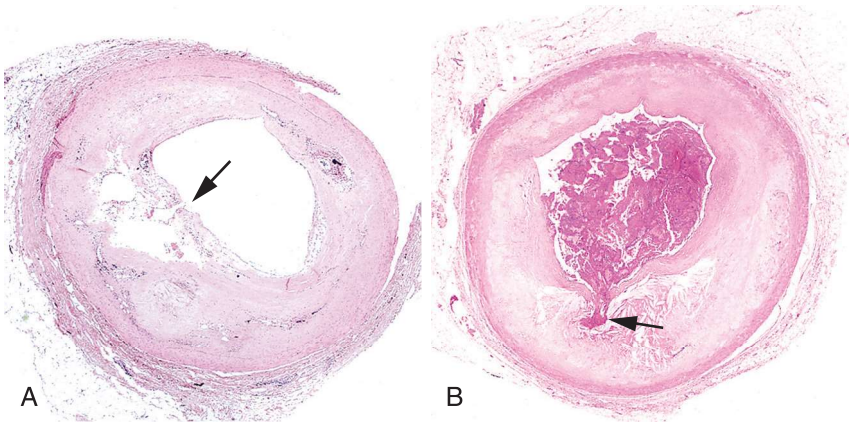

Figure 11.16 Atherosclerotic plaque rupture. (A) Plaque rupture without superimposed thrombus in a patient who died suddenly. (B) Acute coronary thrombosis superimposed on an atherosclerotic plaque with focal disruption of the fibrous cap, triggering fatal myocardial infarction. In both (A) and (B), an *arrow* points to the site of plaque rupture. (B, Reproduced from Schoen FJ: *Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles*, Philadelphia, 1989, WB Saunders, p 61.)

and leave behind only empty "clefts." The periphery of the lesions demonstrate **neovascularization** (proliferating small blood vessels) (Fig. 11.15C). Most atheromas contain abundant lipid, but some plaques ("fibrous plaques") are composed almost exclusively of SMCs and fibrous tissue, which can be heavily calcified.

Plaques generally continue to change and progressively enlarge as a consequence of cell death and degeneration, synthesis and degradation (remodeling) of ECM, organization of any superimposed thrombus, and secondary calcification of phospholipid or necrotic debris (see Fig. 11.15C).

Atherosclerotic plaques are susceptible to clinically important pathologic changes. As discussed further later, the thickness and ECM content of the overlying fibrous cap will impact the stability or fragility of the plaque and its tendency to undergo secondary changes.

- **Rupture, ulceration, or erosion** of the surface of atheromatous plaques exposes the blood stream to highly thrombogenic substances and leads to **thrombosis,** which can partially or completely occlude the vessel lumen (Fig. 11.16). If the patient survives, the thrombus may organize and become incorporated into the growing plaque.
- **Hemorrhage into a plaque.** Rupture of the overlying fibrous cap or of the thin-walled vessels in the areas of neovascularization can cause intraplaque hemorrhage; a contained hematoma may expand the plaque or induce plaque rupture.
- **Atheroembolism.** Plaque rupture can discharge atherosclerotic debris into the blood stream, producing microemboli.
- **Aneurysm formation.** Atherosclerosis-induced pressure or ischemic atrophy of the underlying media, with loss of elastic tissue, causes weakness and potential rupture.

Consequences of Atherosclerotic Disease

Myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease (gangrene of the legs) are the major consequences of atherosclerosis. Large elastic arteries (e.g., aorta, carotid, and iliac arteries) and large- and medium-sized muscular arteries (e.g., coronary and popliteal arteries) are the major targets of atherosclerosis. Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, kidneys, and lower extremities. The natural history, principal morphologic features, and main pathogenic events are schematized in Fig. 11.17.

We next describe the features of atherosclerotic lesions that are typically responsible for the clinicopathologic manifestations.

Atherosclerotic Stenosis. In small arteries, atherosclerotic plaques can gradually occlude vessel lumens, compromising blood flow and causing ischemic injury. At early stages of stenosis, outward remodeling of the vessel media tends to preserve the size of the lumen. However, there are limits on the extent of remodeling, and eventually the expanding atheroma impinges on the lumen to such a degree that blood flow is compromised (see Fig. 11.17). *Critical stenosis* is the stage at which the occlusion is sufficiently severe to cause tissue ischemia. In the coronary (and other) circulations, this typically occurs when the occlusion produces a 70% to 75% decrease in luminal cross-sectional area; with this degree of stenosis, chest pain may develop with exertion (so-called *stable angina;* see Chapter 12). Although acute plaque rupture (see later) is the most dangerous consequence, atherosclerosis also takes a toll through chronically diminished arterial perfusion. Mesenteric occlusion and bowel ischemia, sudden cardiac death, chronic ischemic heart disease, ischemic encephalopathy, and intermittent claudication (diminished perfusion of the extremities) all are consequences of flow-limiting stenoses. The effects of vascular occlusion ultimately depend on arterial supply and the metabolic demand of the affected tissue. If stenosis occurs slowly, smaller adjacent vessels can partially compensate by enlarging and creating collateral circulation to perfuse the organ.

Acute Plaque Change. Plaque erosion or rupture is typically promptly followed by partial or complete vascular thrombosis (see Fig. 11.16), resulting in acute tissue infarction (e.g., myocardial or cerebral infarction) (see Fig. 11.17). Plaque changes fall into three general categories:

- *Rupture/fissuring,* exposing highly thrombogenic plaque constituents that activate coagulation and induce thrombosis that is often completely occlusive
- *Erosion/ulceration,* exposing the thrombogenic subendothelial basement membrane to blood, less-frequently inducing fully occlusive thrombosis
- *Hemorrhage into the atheroma,* expanding its volume

It is now recognized that the plaques that are responsible for myocardial infarction and other acute coronary

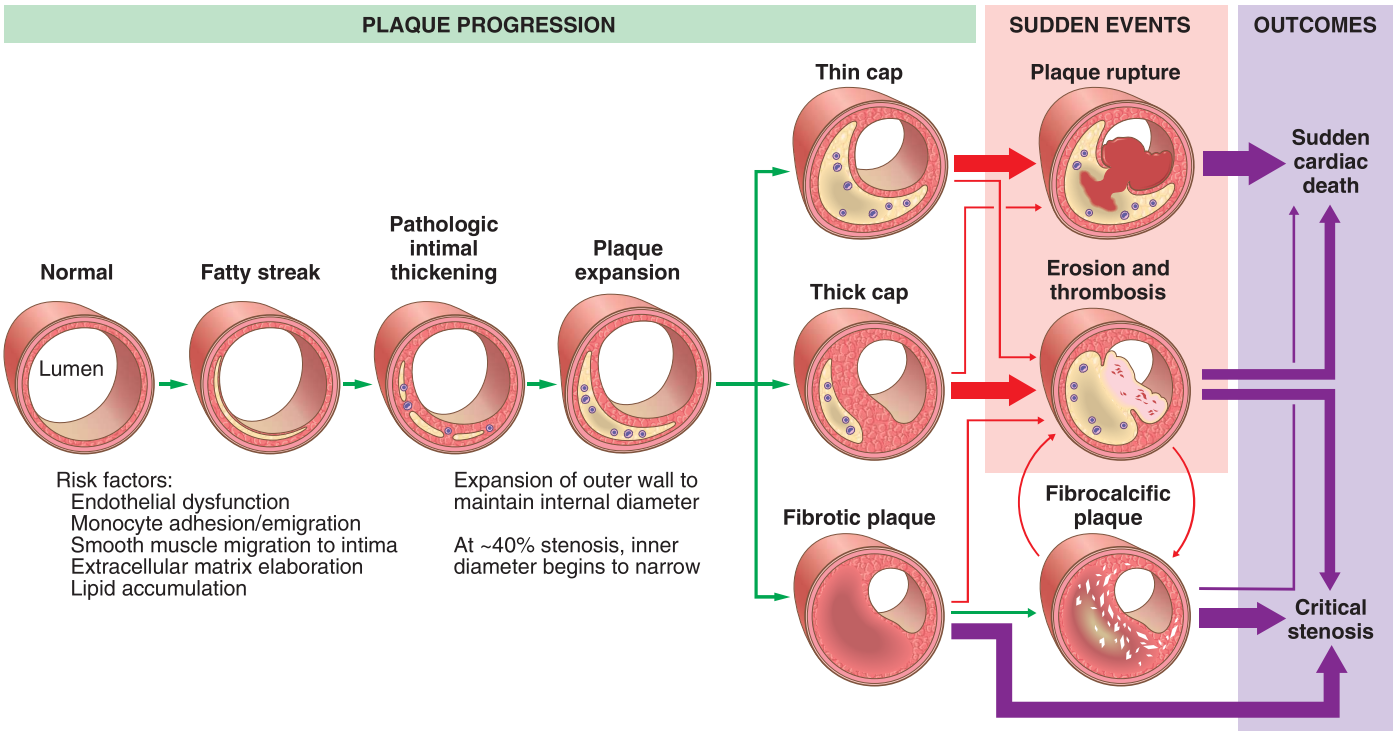

Figure 11.17 Atherosclerotic plaque formation, activities, and outcomes. In a lesion-prone area along with other risk factors, a reversible fatty streak is formed, which can progress to atherosclerosis. Compensatory enlargement initially prevents a reduction of blood flow through the vessel. A plaque can become a thin cap plaque (unstable, vulnerable), a thick cap plaque (stable), or a fibrotic plaque (stable). Thin cap plaques are the most prone to plaque rupture, generally leading to sudden cardiac death. Stable plaques can undergo surface erosion and thrombosis, rapidly expanding the plaque size and leading to more prominent calcifications. This event can lead to sudden cardiac death. Extensive narrowing of the luminal diameter from large plaques generally results in critical stenosis, reducing blood supply to the heart and resulting in angina.

syndromes are often asymptomatic before undergoing a sudden, typically unpredictable change. Thus pathologic and clinical studies show that the majority of plaques that undergo abrupt disruption and coronary occlusion previously showed only mild to moderate noncritical luminal stenosis. Thus a large number of asymptomatic adults may be at risk for a catastrophic coronary event. Although imaging modalities are being developed that could preemptively identify such lesions, it is clear that standard angiographic studies are woefully inadequate to visualize them until after the fact.

Plaques rupture when they are unable to withstand mechanical stresses generated by vascular shear forces. The events that trigger abrupt changes in plaques and subsequent thrombosis are complex and include both intrinsic factors (e.g., plaque structure and composition) and extrinsic elements (e.g., blood pressure, platelet reactivity, and vessel spasm).

The fibrous cap undergoes continuous remodeling that can stabilize the plaque or, conversely, render it more susceptible to rupture. Collagen is the major structural component of the fibrous cap and accounts for its mechanical strength and stability; the balance of collagen synthesis versus degradation affects cap integrity. Thus plaques with thin fibrous caps and active inflammatory cells over a necrotic core are more likely to rupture; these are referred to as "vulnerable plaques" (Fig. 11.18).

Collagen in atherosclerotic plaque is produced primarily by SMCs so that loss of these cells results in a less sturdy cap. Moreover, collagen turnover is controlled by metalloproteinases (MMPs), enzymes elaborated largely by macrophages and SMCs within the atheromatous plaque. Conversely, tissue inhibitors of metalloproteinases (TIMPs) produced by ECs, SMCs, and macrophages modulate MMP activity. In general, plaque inflammation results in a net increase in collagen degradation and reduced collagen synthesis, thereby destabilizing the mechanical integrity of

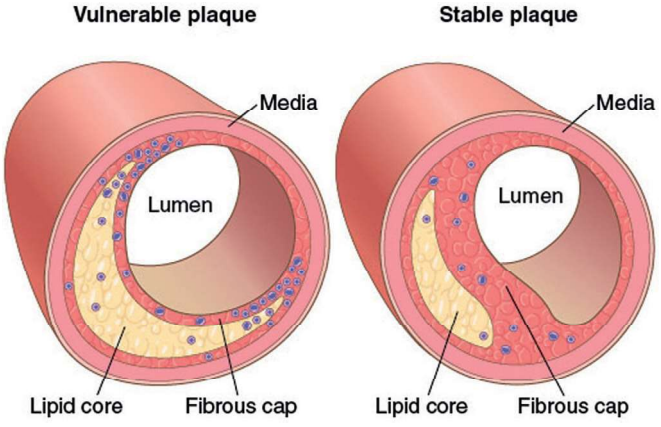

Figure 11.18 Vulnerable and stable atherosclerotic plaque. *Stable plaques* have thickened and densely collagenous fibrous caps with minimal inflammation and underlying atheromatous core. *Vulnerable plaques* have thin fibrous caps, large lipid cores, and increased inflammation. (Modified from Libby P: Molecular bases of the acute coronary syndromes, *Circulation* 91:2844, 1995.)

the fibrous cap (see later). The inflammation induced by cholesterol deposits themselves may contribute to plaque destabilization. Conversely, statins may have a beneficial therapeutic effect not only by reducing circulating cholesterol levels but also by stabilizing plaques through a reduction in plaque inflammation.

Influences extrinsic to plaques also contribute to acute plaque changes. Adrenergic stimulation can increase systemic blood pressure or induce local vasoconstriction, thereby increasing the physical stresses on a given plaque. Indeed, the adrenergic stimulation associated with awakening and rising can cause blood pressure spikes (followed by heightened platelet reactivity) that have been causally linked to the pronounced circadian periodicity for onset of acute myocardial infarction (peaking between 6 a.m. and 12 noon). Intense emotional stress can also contribute to plaque disruption; this is most dramatically illustrated by the uptick in the incidence of sudden death associated with natural or other disasters, such as earthquakes and the September 11, 2001, attack on the World Trade Center.

It is also important to note that not all plaque ruptures result in occlusive thromboses with catastrophic consequences. Indeed, plaque disruption and an ensuing superficial platelet aggregation and thrombosis are probably common, repetitive, and often clinically silent complications of atheroma. Healing of these subclinical plaque disruptions—and organization of their overlying thrombi—is an important mechanism in the growth of atherosclerotic lesions.

Thrombosis, partial or total, associated with a disrupted plaque is a central factor in acute coronary syndromes. In its most serious form, thrombus leads to total occlusion of the affected vessel. In contrast, in other coronary syndromes (Chapter 12), luminal obstruction by the thrombus is incomplete and may even wax and wane with time.

Mural thrombi in a coronary artery can also embolize. Small embolic fragments of thrombus can often be found in the distal intramyocardial circulation or in association with microinfarcts in patients with atherosclerosis who die suddenly. Thrombin and other factors associated with thrombosis are potent activators of SMCs and can thereby contribute to the growth of atherosclerotic lesions.

Vasoconstriction compromises lumen size and, by increasing the local mechanical forces, can potentiate plaque disruption. Vasoconstriction at sites of atheroma may be stimulated by (1) circulating adrenergic agonists, (2) locally released platelet contents, (3) EC dysfunction with impaired secretion of endothelial-derived relaxing factors (NO) relative to contracting factors (endothelin), and (4) mediators released from perivascular inflammatory cells.

KEY CONCEPTS

ATHEROSCLEROSIS

- Atherosclerosis is an intimal-based lesion composed of a fibrous cap and an atheromatous core; the constituents of the plaque include SMCs, ECM, inflammatory cells, calcifications, lipids, and necrotic debris.
- Atherogenesis is driven by an interplay of vessel wall injury and inflammation. The multiple risk factors for atherosclerosis all cause EC dysfunction and influence inflammatory cell and SMC recruitment and stimulation.
- Atherosclerotic plaques develop and generally grow slowly over decades. Stable plaques can produce symptoms related to chronic ischemia by narrowing vessel lumens, whereas unstable plaques can cause dramatic and potentially fatal ischemic complications related to acute plaque rupture, thrombosis, or embolization.
- Stable plaques tend to have a dense fibrous cap, minimal lipid accumulation and little inflammation, whereas "vulnerable" unstable plaques have thin caps, large lipid cores, and relatively dense inflammatory infiltrates.

ANEURYSMS AND DISSECTION

An aneurysm is a localized abnormal dilation of a blood vessel or the heart that may be congenital or acquired (Fig. 11.19). When an aneurysm involves all the layers of an intact (but attenuated) arterial wall or the thinned ventricular wall of the heart, it is called a true aneurysm. Atherosclerotic and congenital vascular aneurysms and ventricular aneurysms that follow transmural myocardial infarctions

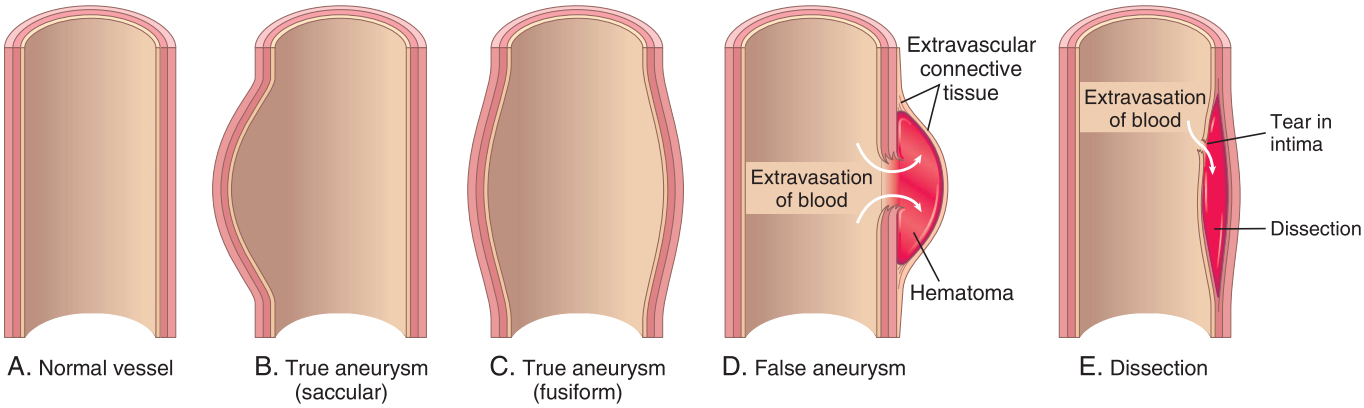

Figure 11.19 Aneurysms. (A) Normal vessel. (B) True aneurysm, saccular type. The wall focally bulges outward and may be attenuated but is otherwise intact. (C) True aneurysm, fusiform type. There is circumferential dilation of the vessel, without rupture. (D) False aneurysm. The wall is ruptured, and there is a collection of blood (hematoma) that is bounded externally by adherent extravascular tissues. (E) Dissection. Blood has entered *(dissected)* the wall of the vessel and separated the layers. Although this is shown as occurring through a tear in the lumen, dissections can also occur by rupture of the vessels of the *vasa vasorum* within the media.