understanding of the mechanisms that link risk factors to the pathogenesis of atherosclerosis and its complications.

PATHOPHYSIOLOGIC CONSEQUENCES OF ATHEROSCLEROSIS

Atherosclerotic lesions occur ubiquitously in Western societies, and the prevalence of this disease is on the rise globally. Most atheromata produce no symptoms, and many never cause clinical manifestations. Numerous patients with diffuse atherosclerosis may succumb to unrelated illnesses without ever having experienced a clinically significant manifestation of atherosclerosis. Arterial remodeling during atheroma formation accounts for some of this variability in the clinical expression of atherosclerotic disease (Fig. 291e-2*A*). During the initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as *compensatory enlargement*, a type of vascular remodeling. The growing atheroma does not encroach on the arterial lumen until the burden of atherosclerotic plaque exceeds ~40% of the area encompassed by the internal elastic lamina. Thus, during much of its life history, an atheroma will not cause stenosis that can limit tissue perfusion.

Flow-limiting stenoses commonly form later in the history of the plaque. Many such plaques cause stable syndromes such as demand-induced angina pectoris or intermittent claudication in the extremities. In the coronary circulation and other circulations, even total vascular occlusion by an atheroma does not invariably lead to infarction. The hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, mitigating the consequences of an acute occlusion of an epicardial coronary artery. By contrast, many lesions that cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation, may arise from atherosclerotic plaques that do not produce a flow-limiting stenosis. Such lesions may produce only minimal luminal irregularities on traditional angiograms and often do not meet the traditional criteria for "significance" by arteriography. Thrombi arising from such nonocclusive stenoses may explain the frequency of MI as an initial manifestation of coronary artery disease (CAD) (in at least one-third of cases) in patients who report no prior history of angina pectoris, a syndrome usually caused by flow-limiting stenoses.

Plaque Instability and Rupture Postmortem studies afford considerable insight into the microanatomic substrate underlying the "instability" of plaques that do not cause critical stenoses. A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus that causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute MI (Fig. 291e-2*B*). Rupture of the plaque's fibrous cap (Fig. 291e-2*C*) permits contact between coagulation factors in the blood and highly thrombogenic tissue factor expressed by macrophage foam cells in the plaque's lipid-rich core. If the ensuing thrombus is nonocclusive or transient, the episode of plaque disruption may not cause symptoms or may result in episodic ischemic symptoms such as rest angina. Occlusive thrombi that endure often cause acute MI, particularly in the absence of a well-developed collateral circulation that supplies the affected territory. Repetitive episodes of plaque disruption and healing provide one likely mechanism of transition of the fatty streak to a more complex fibrous lesion (Fig. 291e-2*D*). The healing process in arteries, as in skin wounds, involves the laying down of new extracellular matrix and fibrosis.

Not all atheromata exhibit the same propensity to rupture. Pathologic studies of culprit lesions that have caused acute MI reveal several characteristic features. Plaques that have caused thromboses tend to have thin fibrous caps, relatively large lipid cores, a high content of macrophages, outward remodeling, and spotty (rather than dense) calcification. Morphometric studies of such culprit lesions show that at sites of plaque rupture, macrophages and T lymphocytes predominate and contain relatively few smooth-muscle cells. The cells that concentrate at sites of plaque rupture bear markers of inflammatory activation. In addition, patients with active atherosclerosis and acute coronary syndromes display signs of disseminated inflammation. Inflammatory mediators regulate processes that govern the integrity of the plaque's fibrous cap and, hence, its propensity to rupture. For example, the T cell–derived cytokine IFN-γ, which is found in atherosclerotic plaques, can inhibit growth and collagen synthesis of smooth-muscle cells, as noted above. Cytokines derived from activated macrophages and lesional T cells can boost production of proteolytic enzymes that can degrade the extracellular matrix of the plaque's fibrous cap. Thus, inflammatory mediators can impair the collagen synthesis required for maintenance and repair of the fibrous cap and trigger degradation of extracellular matrix macromolecules, processes that weaken the plaque's fibrous cap and enhance its susceptibility to rupture (so-called vulnerable plaques, Fig. 291e-3). In contrast to plaques with these features of vulnerability, those with a dense extracellular matrix and relatively thick fibrous cap without substantial tissue factor–rich lipid cores seem generally resistant to rupture and unlikely to provoke thrombosis.

Functional features of the atheromatous plaque, in addition to its degree of luminal encroachment, influence the clinical manifestations of this disease. This enhanced understanding of plaque biology provides insight into the diverse ways in which atherosclerosis can present clinically and the reasons why the disease may remain silent or stable for prolonged periods, punctuated by acute complications at certain times. Increased understanding of atherogenesis provides new insight into the mechanisms linking it to the risk factors discussed below, indicates the ways in which current therapies may improve outcomes, and suggests new targets for future intervention.

PREVENTION AND TREATMENT

THE CONCEPT OF ATHEROSCLEROTIC RISK FACTORS

The systematic study of risk factors for atherosclerosis emerged from a coalescence of experimental results, as well as from cross-sectional and ultimately longitudinal studies in humans. The prospective, community-based Framingham Heart Study provided rigorous support for the concept that hypercholesterolemia, hypertension, and other factors correlate with cardiovascular risk. Similar observational studies performed worldwide bolstered the concept of "risk factors" for cardiovascular disease.

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy, and those that are immutable, such as age and sex. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly predict coronary risk, but the magnitude of the contributions of other so-called nontraditional risk factors, such as levels of homocysteine, levels of lipoprotein (a) [Lp(a)], and infection, remains controversial. Moreover, some biomarkers that predict cardiovascular risk may not participate in the causal pathway for the disease or its complications. Genetic studies using genome-wide association (GWAS) approaches and Mendelian randomization approaches have helped to distinguish between risk markers and factors that contribute causally to the disease. For example, recent genetic studies suggest that C-reactive protein (CRP) does not itself mediate atherogenesis, despite its ability to predict risk, whereas Lp(a) and apolipoprotein C3 have emerged as a causal risk factor. Table 291e-1 lists a number of risk factors implicated in atherosclerosis. The sections below will consider some of these factors and approaches to their modification.

Lipid Disorders

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank among the most firmly established and best understood risk factors for atherosclerosis. **Chapter 421 describes the lipoprotein classes and provides a detailed discussion of lipoprotein metabolism.**

The American College of Cardiology and American Heart Association (ACC/AHA) promulgated new guidelines on risk assessment, lifestyle measures, and cholesterol management in 2013. The panels that produced these guidelines followed an evidence-based approach.