291e The Pathogenesis, Prevention, and Treatment of Atherosclerosis

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PATHOGENESIS

Atherosclerosis remains the major cause of death and premature disability in developed societies. Moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and has distinct clinical manifestations that depend on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction (MI) (Chap. 295) and angina pectoris (Chap. 293). Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia (Chap. 446). In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability. Involvement of the splanchnic circulation can cause mesenteric ischemia. Atherosclerosis can affect the kidneys either directly (e.g., renal artery stenosis) or as a common site of atheroembolic disease (Chap. 301).

Even within a particular arterial bed, stenoses due to atherosclerosis tend to occur focally, typically in certain predisposed regions. In the coronary circulation, for example, the proximal left anterior descending coronary artery exhibits a particular predilection for developing atherosclerotic disease. Similarly, atherosclerosis preferentially affects the proximal portions of the renal arteries and, in the extracranial circulation to the brain, the carotid bifurcation. Indeed, atherosclerotic lesions often form at branch points of arteries, regions characterized disturbed hydrodynamics. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ectasia and the development of aneurysmal disease, for example, frequently occur in the aorta (Chap. 301). In addition to focal, flow-limiting stenoses, nonocclusive intimal atherosclerosis also occurs diffusely in affected arteries, as shown by intravascular imaging and postmortem studies.

Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth, linear fashion but discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be *chronic*, as in the development of stable, effort-induced angina pectoris or predictable and reproducible intermittent claudication. Alternatively, a dramatic *acute* clinical event such as MI, stroke, or sudden cardiac death may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated postmortem.

INITIATION OF ATHEROSCLEROSIS

An integrated view of experimental results in animals and studies of human atherosclerosis suggests that the "fatty streak" represents the initial lesion of atherosclerosis. These early lesions most often seem to arise from focal increases in the content of lipoproteins within regions of the intima. In particular, the fraction of lipoproteins related to low-density lipoprotein (LDL) that bear apolipoprotein B appear causally related to atherosclerosis. This accumulation of lipoprotein particles may not result simply from increased permeability, or

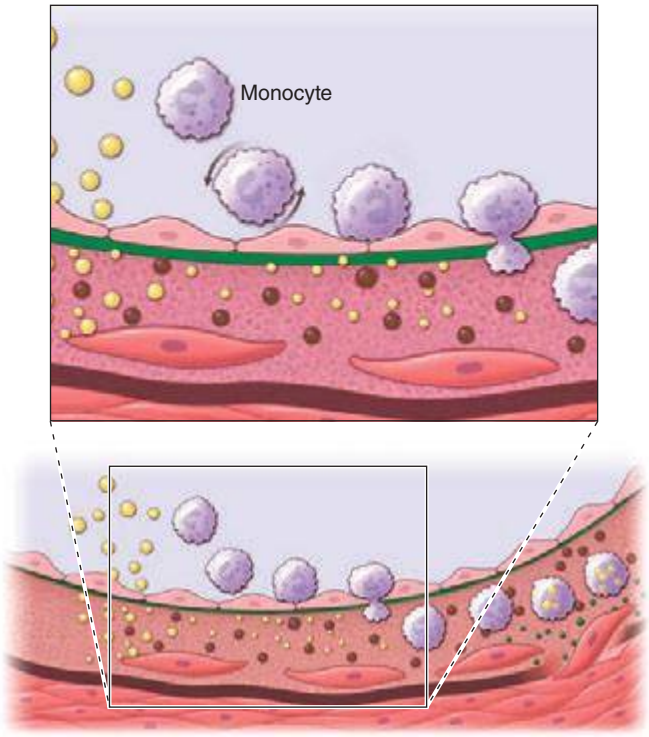

FIGURE 291e-1 Cross-sectional view of an artery depicting steps in development of an atheroma, from left to right. The *upper panel* shows a detail of the boxed area below. The endothelial monolayer overlying the intima contacts blood. Hypercholesterolemia promotes accumulation of low-density lipoprotein (LDL) particles (*yellow spheres*) in the intima. The lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans. Sequestration within the intima separates lipoproteins from some plasma antioxidants and favors oxidative modification. Such modified lipoprotein particles (*darker spheres*) may trigger a local inflammatory response that signals subsequent steps in lesion formation. The augmented expression of various adhesion molecules for leukocytes recruits monocytes to the site of a nascent arterial lesion.

Once adherent, some white blood cells migrate into the intima. The directed migration of leukocytes probably depends on chemoattractant factors, including modified lipoprotein particles themselves and chemoattractant cytokines (depicted by the smaller green spheres), such as the chemokine macrophage chemoattractant protein-1 produced by vascular wall cells in response to modified lipoproteins. Leukocytes in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins (scavenger receptors). These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate from the media (*bottom of lower panel hairline*) through the internal elastic membrane (*solid wavy line*) and accumulate within the expanding intima, where they lay down extracellular matrix that forms the bulk of the advanced lesion (*bottom panel, right side*).

"leakiness," of the overlying endothelium (Fig. 291e-1). Rather, the lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall. Lipoproteins that accumulate in the extracellular space of the intima of arteries often associate with proteoglycans of the arterial extracellular matrix, an interaction that may slow the egress of these lipid-rich particles from