by increasing local reactive oxygen species production; besides causing membrane and mitochondrial damage, oxygen free radicals accelerate nitric oxide decay, damping its vasodilator activity.

- 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*; smooth muscle cells 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 endothelial cells, smooth muscle cells, and macrophages, but their binding and uptake also stimulates the release of growth factors, cytokines, and chemokines that create a vicious cycle of monocyte recruitment and activation.

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. 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 pro-inflammatory cytokine IL-1, which serves to recruit leukocytes, including monocytes. T lymphocytes are also activated, but what these T cells recognize and why these substances are detected as foreign "invaders" is not known. The net result of macrophage and T cell activation is the 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 smooth muscle cell proliferation. Activated T cells in the growing intimal lesions elaborate inflammatory cytokines, e.g., interferon-γ, which, in turn, can activate macrophages as well as endothelial cells and smooth muscle cells. These leukocytes and vascular wall cells release growth factors that promote smooth muscle cell proliferation and synthesis of extracellular matrix proteins. 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 no established causal role for infection.

Smooth Muscle Proliferation and Matrix Synthesis. Intimal smooth muscle cell proliferation and extracellular matrix deposition convert a fatty streak into a mature atheroma and contribute to the progressive growth of atherosclerotic lesions (Fig. 11-10). Intimal smooth muscle cells have a proliferative and synthetic phenotype distinct from the underlying medial smooth muscle cells. Several growth factors are implicated in smooth muscle cell proliferation, including platelet-derived growth factor (PDGF, released by locally adherent platelets, as well as macrophages, endothelial cells, and smooth muscle cells), fibroblast growth factor, and transforming growth factor-α (Chapter 1). These factors also stimulate smooth muscle cells to synthesize extracellular matrix (notably collagen), which stabilizes atherosclerotic plaques. In constrast, activated inflammatory cells in atheromas may increase the breakdown of extracellular matrix components, resulting in unstable plaques (see later).

Overview. Figure 11-11 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 endothelial cell injury, lipid oxidation and accumulation, and inflammation. Atheromas are dynamic lesions consisting of dysfunctional endothelial cells, proliferating smooth muscle cells, 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 smooth muscle cells, macrophages, and foam cells; death of these cells releases lipids and necrotic debris. With progression, the atheroma is modified by extracellular matrix synthesized by smooth muscle cells; connective tissue is particularly prominent on the intimal aspect forming a fibrous cap, although lesions also typically retain a central core of lipid-laden cells and fatty debris that can become calcified. The intimal plaque may progressively encroach on the vessel lumen, or may compress the underlying media, leading to its degeneration; this in turn may expose thrombogenic factors such as tissue factor, resulting in thrombus formation and acute vascular occlusion.

MORPHOLOGY

Fatty streaks. Fatty streaks are composed of lipid-filled foamy macrophages. Beginning as multiple minute flat yellow spots, they eventually coalesce into elongated streaks 1 cm long or longer. These lesions are not sufficiently raised to cause any significant flow disturbances (Fig. 11-12). 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. The observation 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, which together form plaques (Figs. 11-7, 11-10, and 11-11). Atheromatous plaques are white-yellow and encroach on the lumen of the artery; superimposed thrombus over ulcerated plaques is red-brown. Plaques vary in size but can coalesce to form larger masses (Fig. 11-13).

Atherosclerotic lesions are patchy, usually involving only a portion of any given arterial wall and are rarely circumferential; on cross-section, the lesions therefore appear "eccentric" (see Fig. 11-14*A*). The focality of atherosclerotic lesions—despite the uniform exposure of vessel walls to such factors as cigarette