Atherosclerotic Stenosis. In small arteries, atherosclerotic plaques can gradually occlude vessel lumina, 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. *Critical stenosis* is the stage at which the occlusion is sufficiently severe to produce tissue ischemia. In the coronary (and other) circulations, this typically occurs at when the occlusion produces a 70% 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) are all consequences of flow-limiting stenoses. The effects of vascular occlusion ultimately depend on arterial supply and the metabolic demand of the affected tissue.

Acute Plaque Change. Plaque erosion or rupture is typically promptly followed by partial or complete vascular thrombosis (Fig. 11-15), resulting in acute tissue infarction (e.g., myocardial or cerebral infarction) (Fig. 11-16). Plaque changes fall into three general categories:

- *Rupture/fissuring*, exposing highly thrombogenic plaque constituents
- *Erosion/ulceration*, exposing the thrombogenic subendothelial basement membrane to blood
- *Hemorrhage into the atheroma*, expanding its volume

It is now recognized that plaques that are responsible for myocardial infarction and other acute coronary syndromes are often asymptomatic before the acute 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. The worrisome conclusion is that a large number of now asymptomatic adults may be at risk for a catastrophic coronary event. Unfortunately, it is presently impossible to identify such individuals.

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, vessel spasm).

The composition of plaques is dynamic and can contribute to risk of rupture. Thus, plaques that contain large areas of foam cells and extracellular lipid, and those in which the fibrous caps are thin or contain few smooth muscle cells or have clusters of inflammatory cells, are more likely to rupture; these are referred to as "vulnerable plaques" (Fig. 11-17).

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

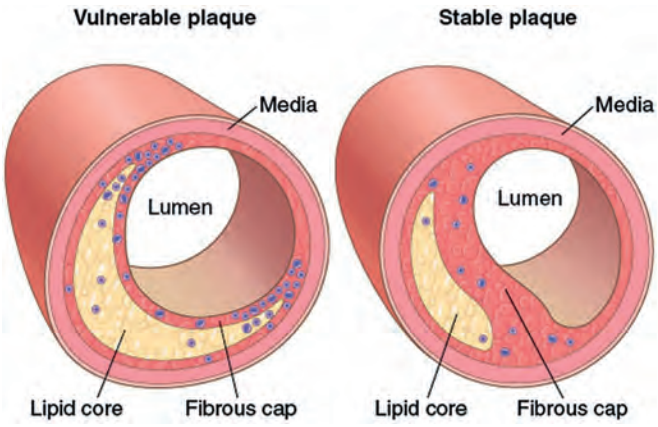

Figure 11-17 Vulnerable and stable atherosclerotic plaque. *Vulnerable plaques* have thin fibrous caps, large lipid cores, and greater inflammation. Stable plaques have thickened and densely collagenous fibrous caps with minimal inflammation and underlying atheromatous core. (Adapted from Libby P: Circulation 91:2844, 1995.)

stability. Thus, the balance of collagen synthesis versus degradation affects cap integrity. Collagen in atherosclerotic plaque is produced primarily by smooth muscle cells 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 smooth muscle cells within the atheromatous plaque; conversely, tissue inhibitors of metalloproteinases (TIMPs) produced by endothelial cells, smooth muscle cells, 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 the fibrous cap (see later). The inflammatiion 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. Thus, 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 wakening 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 MI (peaking between 6 AM and 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 resorption of their overlying thrombi—is an important mechanism in the growth of atherosclerotic lesions.