failure and arrhythmias via left ventricular assist devices, implantable defibrillators, and cardiac resynchronization with pacemakers. Even a simple daily prophylactic aspirin can have therapeutic benefit.

Continuing this encouraging trend will be challenging, particularly in view of the increased longevity of "baby boomers" (which will lead to a doubling of individuals older than age 65 by 2050), the "obesity epidemic," and other factors. Increasingly, new therapeutic advances will depend on understanding the genetic determinants of coronary atherosclerosis and IHD. For example, the observation that MIs occur in only a fraction of individuals with coronary disease suggests that simple control of atherosclerotic risk factors is only part of the story. For example, MI risk—but not coronary atherosclerosis—is associated with genetic variants that modify leukotriene B4 metabolism.

Pathogenesis. **The dominant cause of IHD syndromes is insufficient coronary perfusion relative to myocardial demand; in the vast majority of cases, this is due to chronic, progressive atherosclerotic narrowing of the epicardial coronary arteries, and variable degrees of superimposed acute plaque change, thrombosis, and vasospasm.** The individual elements and their interactions are discussed next.

Chronic Vascular Occlusion. More than 90% of patients with IHD have atherosclerosis involving one or more of the epicardial coronary arteries (Chapter 11). The clinical manifestations of coronary atherosclerosis are generally due to progressive narrowing of the lumen leading to stenosis ("fixed" obstructions), or to acute plaque erosion or rupture with thrombosis, all of which compromise blood flow. A fixed lesion obstructing greater than 75% of vascular cross-sectional area defines significant coronary artery disease; this is generally the threshold for symptomatic ischemia precipitated by exercise (typically manifesting as angina). With this degree of obstruction, compensatory coronary arterial vasodilation is no longer sufficient to meet even moderate increases in myocardial demand. Obstruction of 90% of the cross-sectional area of the lumen can lead to inadequate coronary blood flow even at rest. Progressive myocardial ischemia induced by slowly developing occlusions may stimulate the formation of collateral vessels over time, which can often protect against myocardial ischemia and infarction and mitigate the effects of high-grade stenoses.

Although only a single major coronary epicardial vessel may be affected, two or all three—the LAD, LCX, and RCA—are often involved by obstructive atherosclerosis. Clinically significant plaques can be located anywhere along the course of the vessels, particularly the RCA, although they tend to predominate within the first several centimeters of the LAD and LCX. Sometimes the major epicardial branches are also involved (i.e., LAD diagonal branches, LCX obtuse marginal branches, or posterior descending branch of the RCA), but atherosclerosis of the intramural (penetrating) branches is rare.

Acute Plaque Change. The risk of an individual developing clinically important IHD depends in part on the number, distribution, structure, and degree of obstruction of atheromatous plaques. However, the varied clinical manifestations of IHD cannot be explained by the anatomic disease burden alone. This is particularly true for the so-called acute coronary syndromes, namely unstable angina, acute MI, and sudden death. These acute coronary syndromes are typically initiated by an unpredictable and abrupt conversion of a stable atherosclerotic plaque to an unstable and potentially life-threatening atherothrombotic lesion through rupture, superficial erosion, ulceration, fissuring, or deep hemorrhage (Chapter 11). In most instances, plaque changes—typically associated with intralesional inflammation—precipitate the formation of a superimposed thrombus that partially or completely occludes the artery.

Consequences of Myocardial Ischemia. The common feature of the acute coronary syndromes is downstream myocardial ischemia.

- *Stable angina* results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increase oxygen delivery; it is usually not associated with plaque disruption.
- *Unstable angina* is caused by plaque disruption that results in thrombosis and vasoconstriction, and leads to severe but transient reductions in coronary blood flow. In some cases, microinfarcts can occur distal to disrupted plaques due to thromboemboli.
- *Myocardial infarction (MI)* is often the result of acute plaque change that induces an abrupt thrombotic occlusion, resulting in myocardial necrosis.
- *Sudden cardiac death* may be caused by regional myocardial ischemia that induces a fatal ventricular arrhythmia.

Each of these important syndromes is discussed in detail next, followed by an examination of the important myocardial consequences.

Angina Pectoris

Angina pectoris is characterized by paroxysmal and usually recurrent attacks of substernal or precordial chest discomfort caused by transient (15 seconds to 15 minutes) myocardial ischemia that is insufficient to induce myocyte necrosis. The pain itself is likely a consequence of the ischemia-induced release of adenosine, bradykinin, and other molecules that stimulate sympathetic and vagal afferent nerves. There are three overlapping patterns of angina pectoris caused by varying combinations of decreased perfusion, increased demand, and coronary arterial pathology. Importantly, not all ischemic events are perceived by patients; silent ischemia is particularly common in the geriatric population and in the setting of diabetic neuropathy.

- *Stable (typical) angina* is the most common form of angina; it is *caused by an imbalance in coronary perfusion (due to chronic stenosing coronary atherosclerosis) relative to myocardial demand*, such as that produced by physical activity, emotional excitement or psychological stress. Typical angina pectoris is variously described as a deep, poorly localized pressure, squeezing, or burning sensation (like indigestion), but unusually as pain, and is