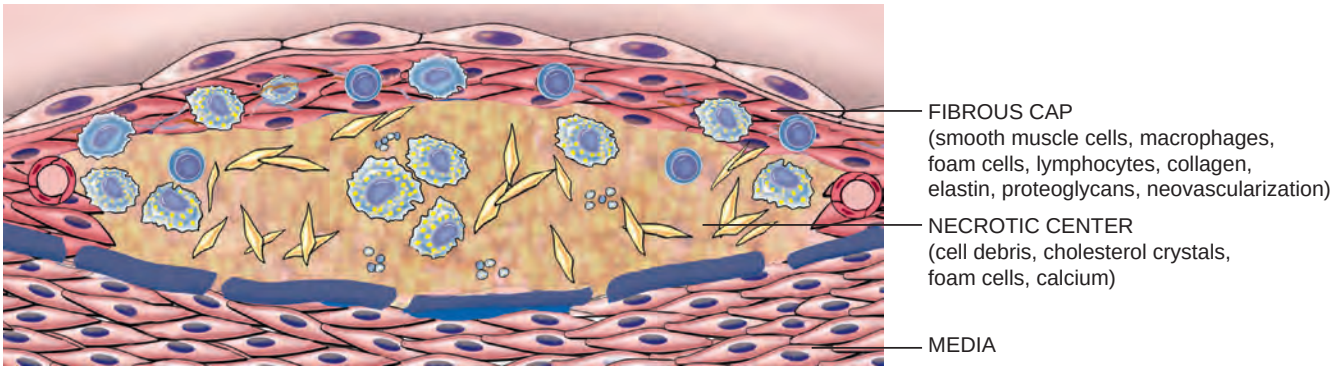

Figure 11-7 Basic structure of an atherosclerotic plaque. Note that atherosclerosis is an intimal-based process.

prevalence of ischemic heart disease in developing nations. As a result, the death rate for coronary artery disease in the United States now lags behind the death rates in most of Africa, India, and Southeast Asia. The countries of the former Soviet Union hold the dubious distinction of having the highest ischemic heart disease-associated mortality rates, three to five times higher than the United States, and seven to 12 times greater than Japan.

The prevalence and severity of atherosclerosis and ischemic heart disease among individuals and groups are related to a number of risk factors. Some of these factors are constitutional (and therefore less controllable), but others are acquired or related to specific behaviors and potentially amenable to intervention (Table 11-2). Risk factors have been identified through a number of prospective analyses (e.g., the Framingham Heart Study). *These risk factors have roughly multiplicative effect*. Thus, two factors increase risk approximately four-fold, and three (i.e., hyperlipidemia, hypertension, and smoking), increase risk by a factor of seven (Fig. 11-8).

Constitutional Risk Factors

- *Genetics*. Family history is the most important independent risk factor for atherosclerosis. Certain Mendelian disorders are strongly associated with atherosclerosis (e.g., familial hypercholesterolemia; Chapter 5), but these account for only a small percentage of cases. The well-established familial predisposition to atherosclerosis and ischemic heart disease is usually polygenic, relating to familial clustering of other established risk factors, such as hypertension or diabetes, or to inherited variants that influence other pathophysiologic processes, such as inflammation.

Table 11-2 Major Risk Factors for Atherosclerosis

Nonmodifiable (Constitutional)
Genetic abnormalities
Family history
Increasing age
Male gender
Modifiable
Hyperlipidemia
Hypertension
Cigarette smoking
Diabetes
Inflammation

- *Age* is a dominant influence. Although the development of atherosclerotic plaque is typically a progressive process, it does not usually become clinically manifest until lesions reach a critical threshold in middle age or later (see later). Thus, between ages 40 and 60, the incidence of myocardial infarction increases five-fold. Death rates from ischemic heart disease rise with each decade even into advanced age.
- *Gender*. Other factors being equal, premenopausal women are relatively protected against atherosclerosis and its consequences compared to age-matched men. Thus, myocardial infarction and other complications of atherosclerosis are uncommon in premenopausal women unless they are otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension. After menopause, however, the incidence of atherosclerosis-related diseases increases in women and at older ages actually exceeds that of men. Although a favorable influence of estrogen has long been proposed to explain this effect, clinical trials of estrogen replacement have not been shown to protect against vascular disease; indeed, in some studies, post-menopausal estrogen replacement actually *increased* cardiovascular risk. The atheroprotective effect of estrogens may be related to the age at which the therapy is initiated; in younger postmenopausal women, coronary atherosclerosis is diminished by estrogen therapy, while older women appear not to benefit.

Modifiable Major Risk Factors

- ***Hyperlipidemia*—and more specifically hypercholesterolemia—is a major risk factor for atherosclerosis; even in the absence of other risk factors, hypercholesterolemia is sufficient to initiate lesion development.** The major component of serum cholesterol associated with increased risk is low-density lipoprotein (LDL) cholesterol ("bad cholesterol"). LDL is the complex that delivers cholesterol to peripheral tissues; in contrast, high-density lipoprotein (HDL) is the complex that mobilizes cholesterol from the periphery (including atheromas) and transports it to the liver for excretion in the bile. Consequently, higher levels of HDL ("good cholesterol") correlate with reduced risk.

  Understandably, dietary and pharmacologic approaches that lower LDL or total serum cholesterol, or raise serum HDL, are of considerable interest. High