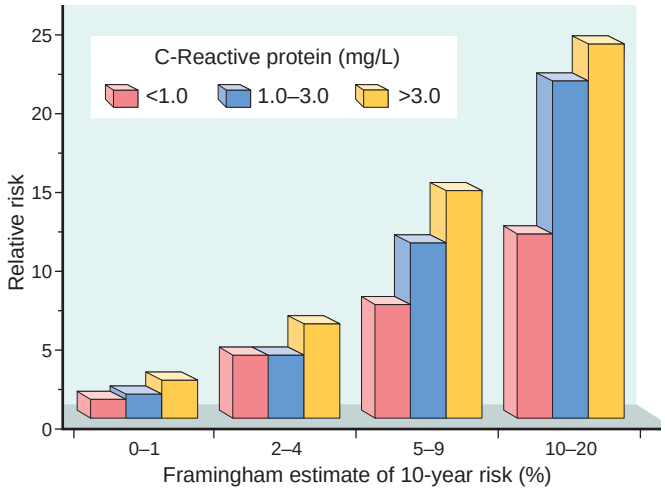

Figure 11-9 C reactive protein (CRP) predicts cardiovascular risk. Relative risk (y-axis) refers to the risk of a cardiovascular event (e.g., myocardial infarction). The x-axis is the 10-year risk of a cardiovascular event derived from established risk factors identified in the Framingham Heart Study. In each risk group, CRP values further stratify patients. (Data from Ridker PM, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347:1557, 2002.)

and sudden cardiac death, even among apparently healthy individuals (Fig. 11-9). Accordingly, CRP levels have been incorporated into risk stratification algorithms. CRP is also a useful marker for gauging the effects of risk reduction measures, such as smoking cessation, weight loss, exercise, and statins; each one of these reduce CRP levels.

- *Hyperhomocystinemia.* Serum homocysteine levels correlate with coronary atherosclerosis, peripheral vascular disease, stroke, and venous thrombosis. *Homocystinuria*, due to rare inborn errors of metabolism, results in elevated circulating homocysteine (>100 μmol/L) and is associated with premature vascular disease. Although low folate and vitamin B_{12} levels can increase homocysteine, supplemental vitamin ingestion does not affect the incidence of cardiovascular disease.
- *Metabolic syndrome.* Associated with central obesity (Chapter 9), this entity is characterized by insulin resistance, hypertension, dyslipidemia (elevated LDL and depressed HDL), hypercoagulability, and a proinflammatory state. The dyslipidemia, hyperglycemia, and hypertension are all cardiac risk factors, while the systemic hypercoagulable and proinflammatory state may contribute to endothelial dysfunction and/or thrombosis.
- *Lipoprotein a [Lp(a)]* is an altered form of LDL that contains the apolipoprotein B-100 portion of LDL linked to apolipoprotein A (apo A); Lp(a) levels are associated with coronary and cerebrovascular disease risk, independent of total cholesterol or LDL levels.
- *Factors affecting hemostasis*. Several markers of hemostatic and/or fibrinolytic function (e.g., elevated plasminogen activator inhibitor 1) are potent predictors of risk for major atherosclerotic events, including myocardial infarction and stroke. Platelet-derived factors, as well as thrombin—through both its procoagulant and proinflammatory effects—are increasingly recognized as major contributors to vascular pathology.
- *Other factors*. Factors associated with a less pronounced and/or difficult-to-quantitate risk include lack of exercise; competitive, stressful life style ("type A" personality); and obesity (the latter also being complicated by hypertension, diabetes, hypertriglyceridemia, and decreased HDL).

Pathogenesis of Atherosclerosis

The clinical importance of atherosclerosis has stimulated enormous interest in understanding the mechanisms that underlie its evolution and complications. The contemporary view of atherogenesis integrates the risk factors previously discussed and is called the "response to injury" hypothesis. **This model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury. Lesion progression occurs through interaction of modified lipoproteins, monocyte-derived macrophages, and T lymphocytes with endothelial cells and smooth muscle cells of the arterial wall** (Fig. 11-10). According to this schema, atherosclerosis progresses in the following sequence:

- *Endothelial injury and dysfunction*, causing (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis
- *Accumulation of lipoproteins* (mainly LDL and its oxidized forms) in the vessel wall
- *Monocyte adhesion to the endothelium*, followed by migration into the intima and transformation into *macrophages* and *foam cells*
- *Platelet adhesion*
- *Factor release* from activated platelets, macrophages, and vascular wall cells, inducing *smooth muscle cell recruitment,* either from the media or from circulating precursors
- *Smooth muscle cell proliferation, extracellular matrix production*, and *recruitment of T cells.*
- *Lipid accumulation* both extracellularly and within cells (macrophages and smooth muscle cell)

Endothelial Injury. Endothelial cell injury is the cornerstone of the response-to-injury hypothesis. Endothelial loss due to *any* kind of injury—induced experimentally by mechanical denudation, hemodynamic forces, immune complex deposition, irradiation, or chemicals—results in intimal thickening. However, *early human lesions begin at sites of morphologically intact endothelium.* Thus, nondenuding *endothelial dysfunction* underlies most human atherosclerosis; the intact but dysfunctional endothelial cells exhibit increased endothelial permeability, enhanced leukocyte adhesion, and altered gene expression.

The specific pathways of and factors contributing to endothelial cell dysfunction in early atherosclerosis are not completely understood: etiologic culprits include toxins from cigarette smoke, homocysteine, and even infectious agents, according to some (blame the bugs!). Inflammatory cytokines (e.g., tumor necrosis factor [TNF]) can also stimulate pro-atherogenic endothelial gene expression. However, **the two most important causes of endothelial dysfunction are hemodynamic disturbances and hypercholesterolemia.**