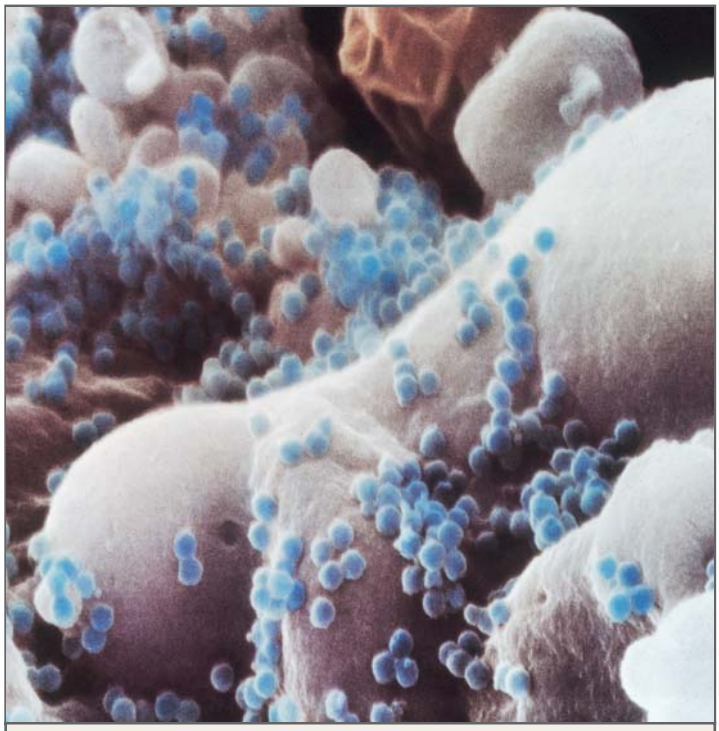

Surface of a T Lymphocyte Infected by HIV.
Photograph by Lennart Nilsson, M.D., Stockholm, Sweden, 1985.

similar viruses that cause AIDS in nonhuman primates (specifically, macaques). Thus, the causative relation between HIV and AIDS was accepted by the scientific and medical community in 1984 and was further verified through the later isolation of HIV type 2 in West African patients with AIDS. The relation was also supported by the clinical efficacy of drugs that specifically inhibit HIV enzymes and the demonstration that mutations in one of the coreceptors for HIV (CCR5) make some persons highly resistant to HIV infection and AIDS.

Many lessons can be drawn from this early intense period, and most suggest that science requires greater modesty. Our experience with AIDS underscores the importance of basic research, which gave us the technical and conceptual tools to find the cause less than three years after the disease was first described. The work of numerous researchers is required for such efforts, and we have described the contributions of many scientists in other publications.[1,2] It has also become clear that finding the cause of an infectious disease is the alpha but not the omega of its eradication. The identification of HIV has allowed us to eliminate transmission of the disease through the transfusion of blood and blood products, create rational policies for prevention, and design efficient antiretroviral therapies. These therapies are not a cure, however, and the epidemic is still growing in many countries for lack of accessible treatments and preventive vaccines. Moreover, we must recognize that we are still far from having exhausted the list of potential new pathogens. Finally, one lesson that should be clear is that effective collaboration among groups of scientists and clinicians is essential — and that it is possible to achieve such collaboration without excluding a certain dose of the competitive spirit as a stimulant.

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Unstable Coronary-Artery Plaques

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It is ironic and instructive that in the age of cellular and molecular biology, great advances in our understanding of the pathophysiology of cardiovascular disease continue to be made by pathologists who perform meticulous and imaginative studies. The concept of stable and unstable atherosclerotic plaques and implications for coronary thrombosis and myocardial infarction can be attributed to several great cardiovascular pathologists during the past century.

What characterizes an arterial plaque that is vulnerable to rupture? What causes the vulnerable plaque to rupture? How can plaque rupture be prevented? These are critically important questions in

cardiovascular medicine, because if the causes and treatment of the unstable plaque are identified, we may greatly reduce the enormous numbers of myocardial infarctions that occur each year.

Plaque rupture and fissures are the main causes of acute coronary syndromes. A remarkable finding, however, is that in many people (perhaps 10 percent) who die from noncardiac causes, acute plaque rupture is present in coronary arteries. This finding supports the concept that advanced plaques may undergo repeated, clinically silent rupture. Also, fatal myocardial infarction is not always associated with plaque rupture or superficial erosions. Thus, plaque rupture is strongly associated with (but is not equivalent to) vascular occlusion, myocardial ischemia, and infarction.

Although large plaques are more likely to rupture than small plaques, the greatest risk of myocardial infarction is from the rupture of small plaques. The most likely explanation for this paradox is that small plaques are far more common than large plaques.

What are the histologic characteristics of plaques that rupture (see Figure)? A thin fibrous cap, a large lipid core, and a high density of macrophages (which release many things, including matrix metalloproteinases) contribute to the structural instability of plaques and thus to their rupture. The lipid core results from the death of lipid-laden macrophages, or foam cells, and from the accumulation of lipids in extracellular matrix. Erythrocyte membranes, which have a very high cholesterol level, may also contribute to the inflammatory response[1] and to the accumulation of free cholesterol in plaques, as reported by Kolodgie et al. in this issue of the *Journal* (pages 2316–2325).

A plaque ruptures when the fibrous cap tears and the necrotic lipid core (which is extremely thrombogenic) is exposed to blood in the arterial lumen. The shoulders, or margins, of a complex plaque, which are especially prone to rupture, contain macrophages, T lymphocytes, and a paucity of smooth-muscle cells. Plaques whose lipid core exceeds 40 percent of the volume are especially vulnerable. Plaque rupture and fissuring account for the great majority of thrombi that cause acute coronary syndromes. Tissue factor, expressed by macrophages and smooth-muscle cells, and the activation of platelets are central to this thrombotic process.

In normal arteries, microvessels (vasa vasorum) are observed only in adventitia and in the outer media of the aorta and its largest branches. Neovascularization in atherosclerotic arteries occurs primarily by growth from the adventitia, as well as from the arterial lumen, into the intima of advanced plaques. New vasa in plaques appear fragile and may be susceptible to rupture (intraplaque hemorrhage) with a sudden increase in the size of the plaque. Repeated cycles of plaque rupture and healing probably explain the finding that there is layering in arterial plaques, which reflects the intermittent pattern of growth of the plaque.

There have been great advances in our knowledge of the cellular biology of the formation and progression of atherosclerotic plaques. Monocytes bind to adhesion molecules on endothelium, are transformed into macrophages in the vessel wall, and together with T lymphocytes have a central role in the inflammatory response and development of unstable plaques. Oxidized low-density lipoproteins appear to play a key part in the recruitment of mononuclear cells to the vessel wall.

Macrophages in plaques accumulate lipids in cytoplasmic droplets and become foam cells. Foam cells release a variety of growth factors and cytokines that modulate the characteristics of the atheroma. Some factors that are released locally (e.g., transforming growth factor β), which are antiinflammatory and stimulate the synthesis of matrix, help stabilize lesions. But local release of metalloproteinases and cathepsins, which digest collagen and elastin, may destabilize the plaque. Tissue inhibitors of metalloproteinases normally restrain the activity of metalloproteinases, and when this restraint is lost, the plaque may become less stable as matrix is digested. Although there are convincing data on the mechanisms underlying the initiation and growth of plaques, it is important to acknowledge that our understanding of the cellular biology of the unstable plaque remains speculative, because we do not have good experimental models of plaque destabilization.

A hot topic in vascular biology is the role of reactive oxygen species, especially oxygen radicals and hydrogen peroxide. High levels of reactive oxygen species are lethal to cells, but low levels are of great importance in cell signaling. Oxygen radicals from a variety of sources may have an important role in plaque disruption[2] — probably through direct destructive effects, oxidation of low-density lipoproteins, and signaling.

Stabilizing the unstable plaque is a key goal in reducing the risk of acute coronary syndromes. Treatment with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) reduces hypercholes-

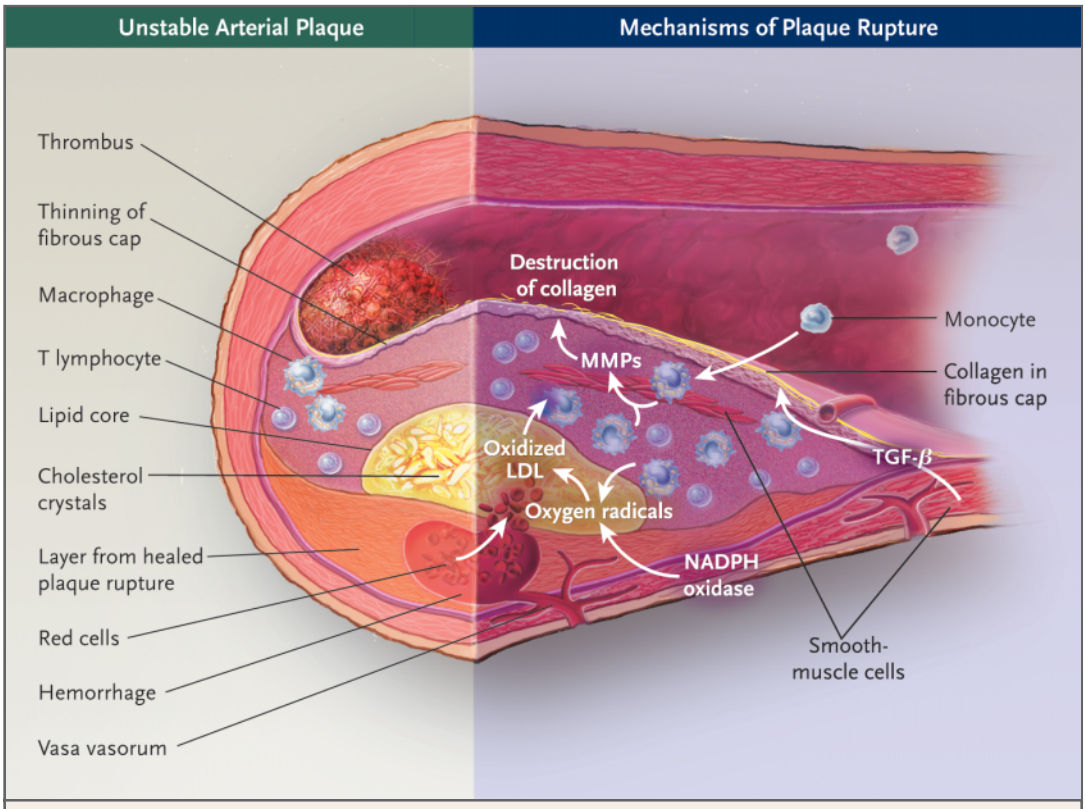

Figure. An Unstable Arterial Plaque and the Mechanisms of Plaque Rupture.

The stability of atherosclerotic plaques is provided by extracellular matrix and a thick fibrous cap. This unstable plaque has a thin fibrous cap and thrombus at the shoulder, many inflammatory cells, and a large lipid core. The synthesis of collagen by smooth-muscle cells is stimulated by growth factors, such as transforming growth factor β (TGF-β). Inflammation in plaques, with the accumulation of macrophages and T lymphocytes, leads to the release of matrix metalloproteinases (MMPs), which digest collagen and cause thinning of the fibrous cap. The necrotic lipid core grows as a result of the accumulation of lipids in extracellular matrix, the death of lipid-laden macrophages, and perhaps the accumulation of erythrocyte membranes after intraplaque hemorrhage from the vasa vasorum. Oxygen radicals, generated from many sources, including NADPH oxidase and inflammatory cells, oxidize low-density lipoproteins (LDL) and cause necrosis of cells. Repetitive cycles of plaque rupture and healing, which may be clinically silent, produce layers in the advanced plaque.

terolemia and inflammation and rapidly reduces the risk of cardiovascular events. It is likely that reduction of inflammation and lipid in lesions improves the stability of plaques by decreasing the lipid core and increasing collagen levels, thereby reducing the risk of cardiovascular events. Loss of vasa vasorum during regression of atherosclerotic lesions[3] may have a protective effect by reducing susceptibility to hemorrhage in the plaque.

The unstable atherosclerotic plaque is of great importance because it is the primary culprit in acute coronary syndromes. Diagnostic methods that improve our ability to identify the vulnerable plaque are needed. We can look forward to further advances in our understanding of the pathophysiology, identification, and treatment of the unstable plaque.

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