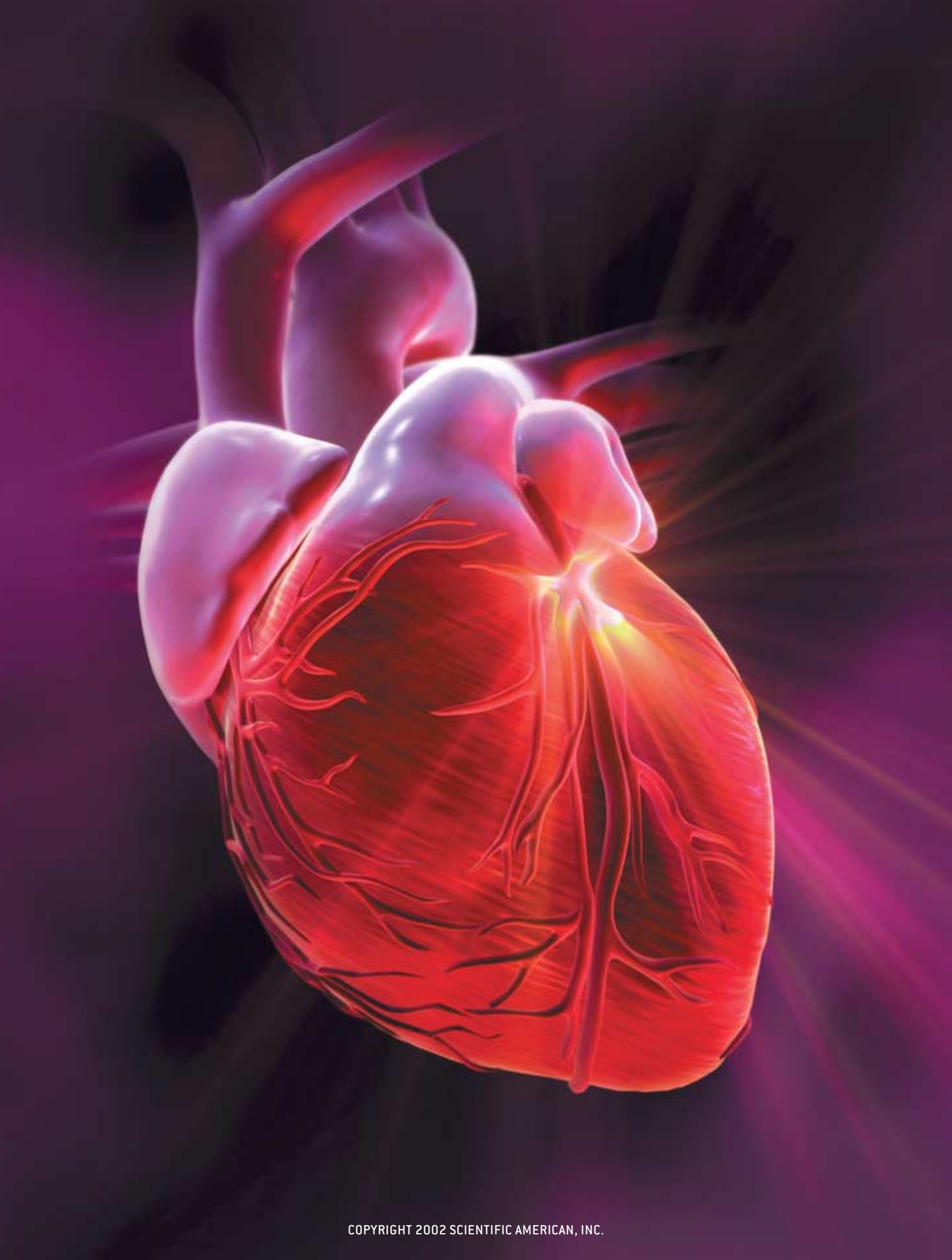




ATHEROSCLEROSIS: THE NEW VIEW

It causes chest pain, heart attack and stroke, leading to more deaths every year than cancer. The long-held conception of how the disease develops turns out to be wrong

By Peter Libby

JEFF JOHNSON Hybrid Medical Animation

ATHEROSCLEROSIS in an artery feeding the heart can set the stage for a heart attack.

AS RECENTLY AS FIVE YEARS AGO, most physicians would have confidently described atherosclerosis as a straight plumbing problem: Fat-laden gunk gradually builds up on the surface of passive artery walls. If a deposit (plaque) grows large enough, it eventually closes off an affected “pipe,” preventing blood from reaching its intended tissue. After a while the blood-starved tissue dies. When a part of the cardiac muscle or the brain succumbs, a heart attack or stroke occurs.

Few believe that tidy explanation anymore. Investigations begun more than 20 years ago have now demonstrated that arteries bear little resemblance to inanimate pipes. They contain living cells that communicate constantly with one another and their environment. These cells participate in the development and growth of atherosclerotic deposits, which arise in, not on, vessel walls. Further, relatively few of the deposits expand so much that they shrink the bloodstream to a pinpoint. Most heart attacks and many strokes stem instead from less obtrusive plaques that rupture suddenly, triggering the

emergence of a blood clot, or thrombus, that blocks blood flow.

The research has, moreover, established a key role for inflammation in atherosclerosis. This process—the same one that causes infected cuts to become red, swollen, hot and painful—underlies all phases of the disorder, from the creation of plaques to their growth and rupture. When microbial invaders threaten to hurt us, inflammation (literally meaning “on fire”) helps to ward off infection. In the case of atherosclerosis, though, the inflammation proves harmful. In other words, our own defenses bombard us

with friendly fire, just as happens in more famously inflammatory conditions, such as rheumatoid arthritis.

This revised conception suggests new ideas for detecting and treating atherosclerosis. It also resolves some disturbing mysteries—notably, why many heart attacks strike without warning and why certain therapies meant to avert heart attacks frequently fail. Society sorely needs advances in prevention, detection and therapy of atherosclerosis. Contrary to public perception, the heart attacks and strokes that result from this condition exceed cancer as a cause of death in industrial nations and are growing more prevalent in developing countries as well.

Overview/*Atherosclerosis*

- Scientists now agree that inflammation fuels the development and progression of atherosclerosis: the dangerous accumulation of fat-laden deposits, or plaques, in the arteries. The old view—that fat builds up on passive artery walls—is no longer tenable.
- Inflammation can also cause certain plaques to rupture. Blood clots tend to form over ruptured plaques and can then occlude arteries, leading to such atherosclerotic complications as heart attack and stroke.
- Excess low-density lipoprotein (LDL), or “bad cholesterol,” in the blood can trigger arterial inflammation. And cholesterol-lowering therapies—already cornerstones of treatment for atherosclerosis—can reduce it. Strategies that interfere with inflammation in other ways are under study as well.
- A blood test that detects ongoing inflammation might prove useful as an adjunct to the cholesterol tests that doctors now employ to assess risk for heart attack and stroke.

Igniting Trouble

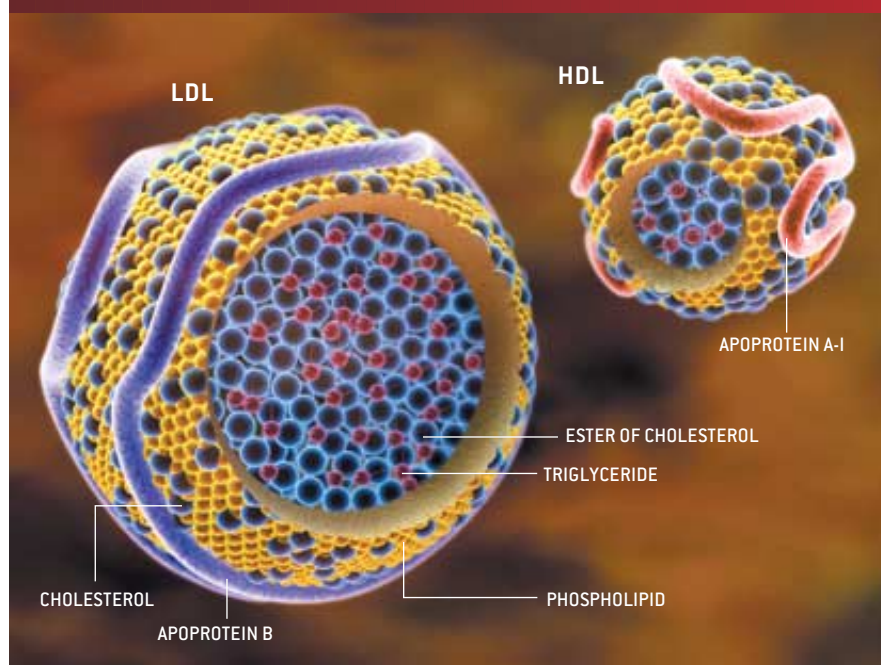
LACKING TOOLS to describe interactions among cells and molecules, the ancients who first defined inflammation had to focus on what they could see and feel. Today we know that the outward signs reflect a pitched struggle playing out on a microscopic battlefield. After sensing (rightly or wrongly) that a microbial attack has begun, certain white blood cells—the immune system’s frontline warriors—convene in the apparently threatened tissue. There they secrete an array of chemicals intended to limit any infection. These chemicals include oxidants (able to dam-

NEW ROLES FOR FAMILIAR ACTORS

POPULAR DESCRIPTIONS of atherosclerosis correctly cast low-density lipoprotein (LDL) as “bad” and high-density lipoprotein (HDL) as “good.” Yet these particles [shown in cutaway views] fulfill their roles in more ways than scientists once thought.

Lipoproteins transport cholesterol in the bloodstream. LDLs truck it from the liver and intestines to various tissues, which use it to repair membranes or produce steroids. HDLs haul cholesterol to the liver for excretion or recycling. The classic view of how atherosclerosis develops implies that excess LDL promotes the condition by accumulating on vessel walls. More recent work shows that it accumulates *within* vessel walls, where its components become oxidized and altered in other ways; the altered components then incite an inflammatory response that progressively—and dangerously—alters arteries.

Physicians also generally explain HDL’s protective effects as deriving from its removal of cholesterol from arteries. HDL certainly does that, but new findings indicate it can also combat atherosclerosis by interfering with LDL oxidation. —P.L.



age invaders) and signaling molecules, such as small proteins called cytokines, that orchestrate the activities of defensive cells. Researchers therefore document an inflammatory response by identifying inflammatory cells or mediators of their activities in a tissue.

The clearest picture of inflammation’s role in the onset of atherosclerosis comes from investigations into low-density lipoprotein, a.k.a. bad cholesterol. LDL particles, composed of fatty molecules (lipids) and protein, transport cholesterol (another lipid) from their source in the liver and intestines to other organs. Scientists have long known that although the body

needs LDL and cholesterol, excessive amounts promote atherosclerosis. Until recently, however, no one could explain how a surplus leads to plaque formation.

Experiments on cultured cells and animals now indicate that the trouble begins when LDLs from the blood collect in the intima, the part of the arterial wall closest to the bloodstream [see *illustration on next two pages*]. At reasonable concentrations in the blood, LDLs can pass in and out of the intima, which consists mainly of the endothelial cells that line vessel walls, the underlying extracellular matrix (connective tissue), and a smattering of smooth muscle cells (ma-

trix producers). But in excess, LDLs tend to become stuck in the matrix.

As the LDLs accumulate, their lipids undergo oxidation (similar to the processes that rust pipes and spoil butter) and their proteins undergo both oxidation and glycation (binding by sugars). Cells in the vessel wall seem to interpret the changes as a danger sign, and they call for reinforcements from the body’s defense system.

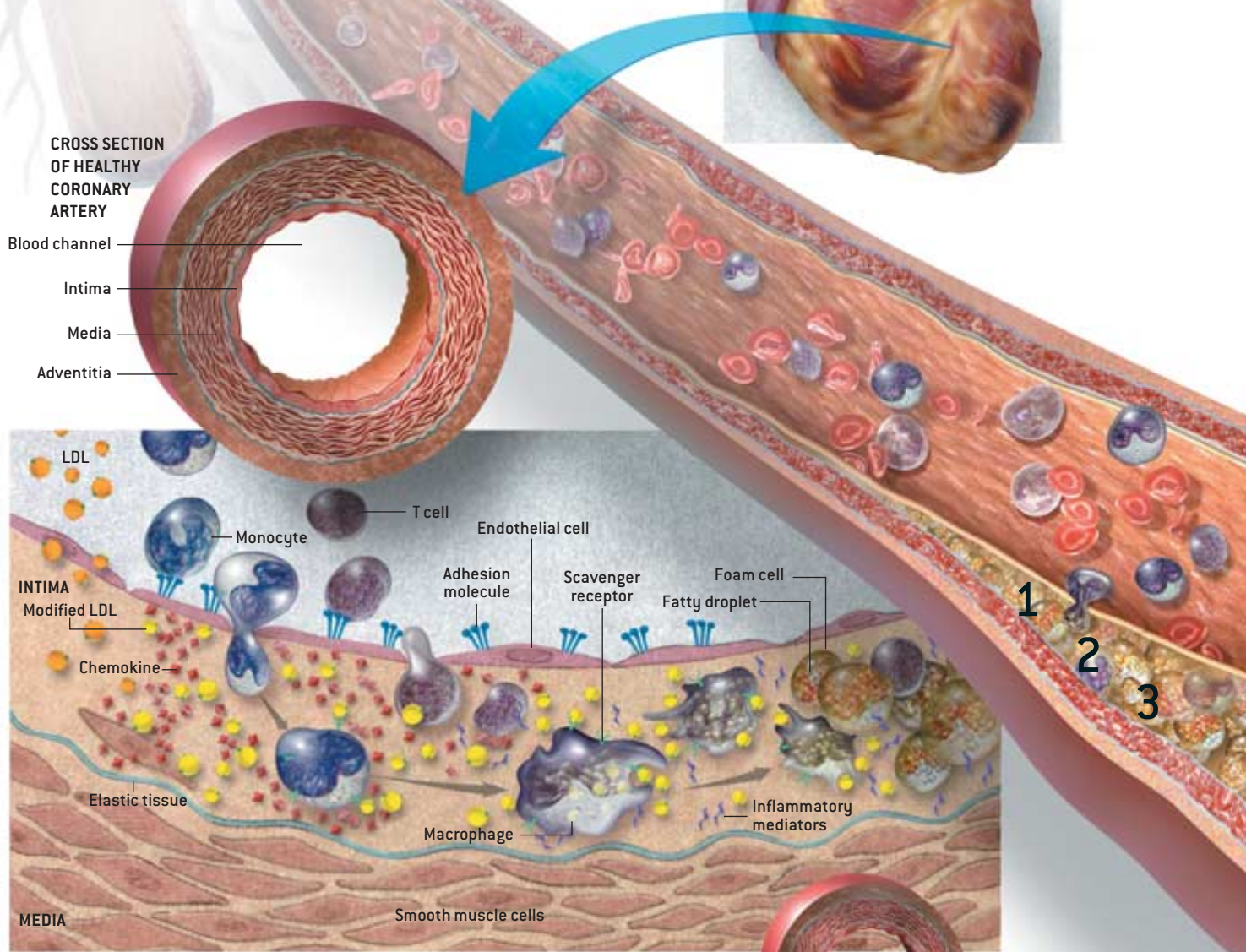
In particular, endothelial cells display adhesion molecules on their blood-facing surface. These molecules latch like Velcro onto quiescent inflammatory cells known as monocytes, which normally circulate in the blood. This interaction causes the cells to drop from the circulation and to roll along and attach to the artery wall. The modified LDLs also spur the endothelial cells and smooth muscle cells of the intima to secrete chemicals called chemokines, which attract monocytes. Much as hounds track the scent of their prey, the monocytes squeeze between endothelial cells and follow the chemical trail to the intima.

Chemokines and other substances elaborated by the endothelial and smooth muscle cells then induce the monocytes to multiply and mature into active macrophages: fully armed warriors, ready to unleash their various weapons against the body’s enemies. These warriors also set about clearing perceived invaders from the vessel wall. Reacting to proteins emitted by stimulated endothelial and intimal smooth muscle cells, the macrophages decorate their surface with molecules called scavenger receptors, which capture modified LDL particles and help the macrophages ingest them. The macrophages ultimately become so packed with fatty droplets that they look foamy when viewed under a microscope. Indeed, pathologists refer to the fat-filled macrophages as foam cells.

Just as monocytes follow adhesion molecules and chemokines into the intima, so do T lymphocytes, white blood cells that represent a different branch of the immune system. These lymphocytes also release cytokines that amplify inflammatory activities in artery walls. Together the foamy macrophages and a lesser number of T lymphocytes compose the so-called fatty streak, a precursor of the

Inflammation's Many Roles

INFLAMMATION—now recognized as a central player in atherosclerosis—occurs when certain white blood cells (those that normally constitute the first line of defense against infection) invade and become active in a tissue. These diagrams depict the growth of an atherosclerotic plaque in a coronary artery; the three close-up views highlight some of the inflammatory processes that can ensue when someone's blood carries too much low-density lipoprotein (LDL).



BIRTH OF A PLAQUE

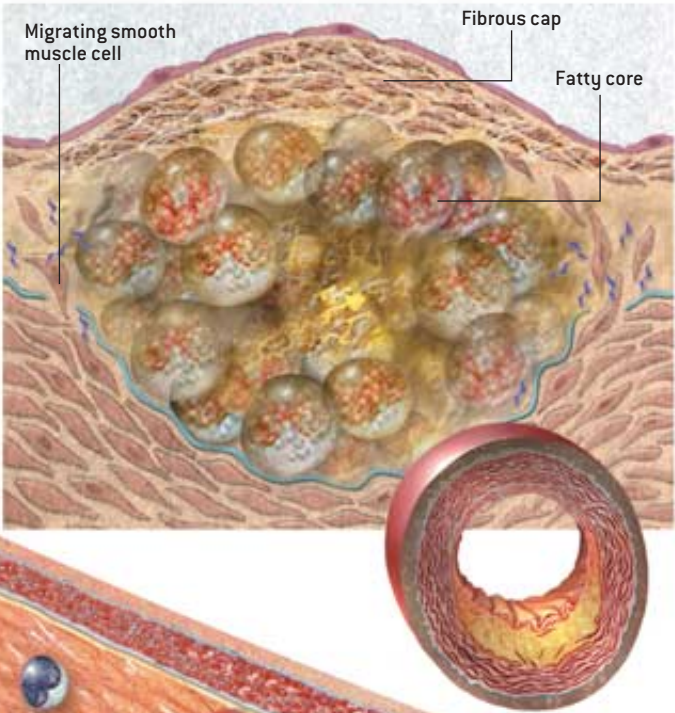
1 Excess LDL particles accumulate in the artery wall and undergo chemical alterations. The modified LDLs then stimulate endothelial cells to display adhesion molecules, which latch onto monocytes (central players in inflammation) and T cells (other immune system cells) in the blood. The endothelial cells also secrete “chemokines,” which lure the snared cells into the intima.

2 In the intima, the monocytes mature into active macrophages. The macrophages and T cells produce many inflammatory mediators, including cytokines (best known for carrying signals between immune system cells) and factors that promote cell division. The macrophages also display so-called scavenger receptors, which help them ingest modified LDLs.

3 The macrophages feast on LDLs, becoming filled with fatty droplets. These frothy-looking, fat-laden macrophages (called foam cells) and the T cells constitute the fatty streak, the earliest form of atherosclerotic plaque.

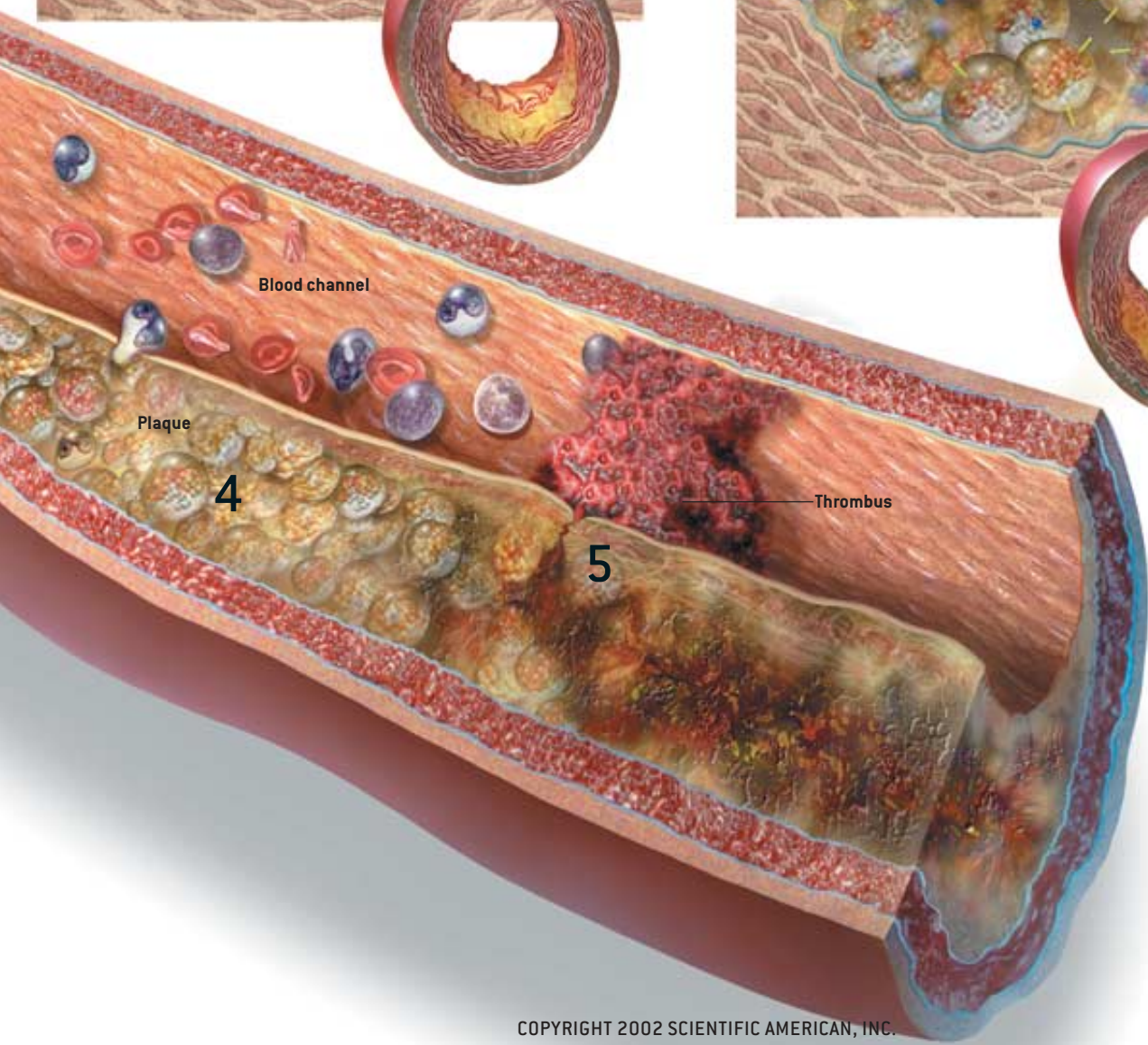
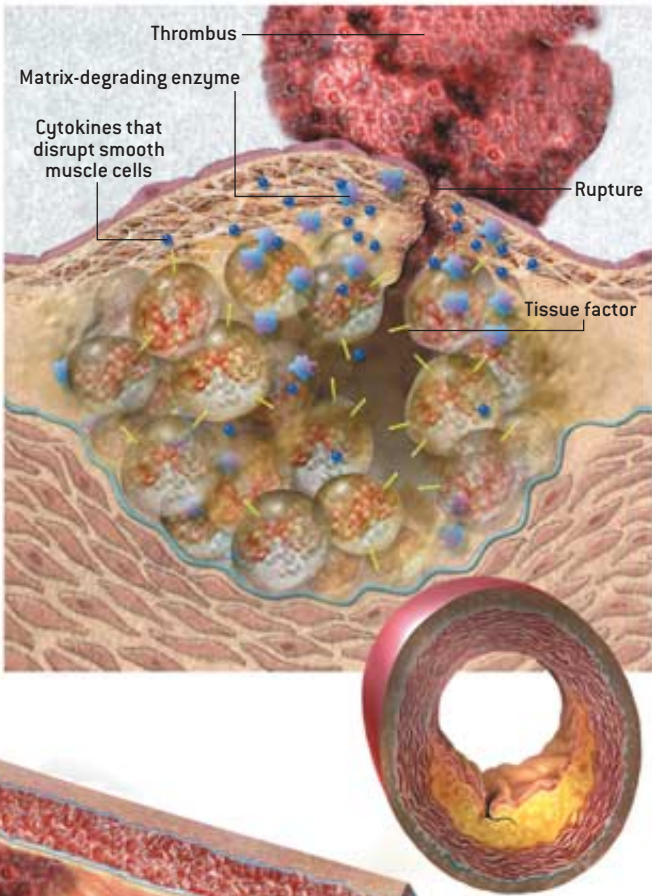
PLAQUE PROGRESSION

4 Inflammatory molecules can promote further growth of the plaque and formation of a fibrous cap over the lipid core. The cap develops when the molecules induce smooth muscle cells of the media to migrate to the top of the intima, multiply and produce a tough, fibrous matrix that glues the cells together. The cap adds to the size of the plaque but also walls it off safely from the blood.



PLAQUE RUPTURE

5 Later, inflammatory substances secreted by foam cells can dangerously weaken the cap by digesting matrix molecules and damaging smooth muscle cells, which then fail to repair the cap. Meanwhile the foam cells may display tissue factor, a potent clot promoter. If the weakened plaque ruptures, tissue factor will interact with clot-promoting elements in the blood, causing a thrombus, or clot, to form. If the clot is big enough, it will halt the flow of blood to the heart, producing a heart attack—the death of cardiac tissue.



CUTAWAY VIEW OF ARTERY AFFLICTED BY ATHEROSCLEROSIS

complex plaques that later disfigure arteries. Disturbingly, many Americans harbor nascent plaques as early as their teens.

Fueling Plaque Growth

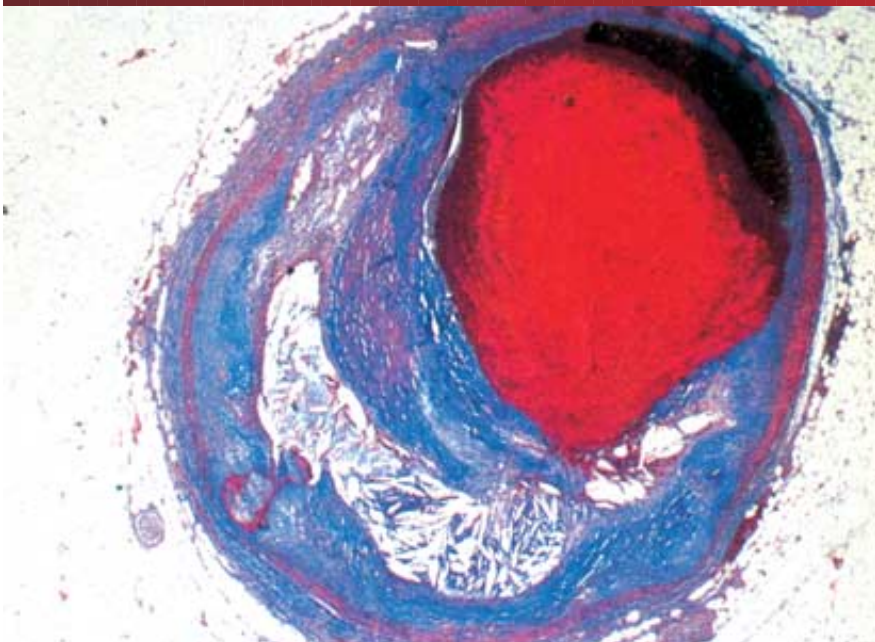
WHEN AN INFLAMMATORY response in, say, a scraped knee successfully blocks an infection, macrophages release molecules that facilitate healing. A “healing” process also accompanies the more chronic, low-level kind of inflammation that operates in atherosclerosis. Instead of restoring artery walls to their original state, though, the process perversely remodels—changes the character of—the wall, eventually generating a bigger, more complicated plaque.

In recent years, biologists have learned that macrophages, endothelial cells and smooth muscle cells of the inflamed intima secrete factors that prod smooth muscle cells of the media (the tissue under the intima) to migrate to the top of the intima, replicate and synthesize components of the extracellular matrix. The cells and matrix molecules coalesce into a fibrous covering overlying the original atherosclerotic zone. As this “cap” matures, the zone underneath generally changes somewhat. Most obviously, some fraction of the foam cells die, releasing lipids. For this reason, pathologists denote the region under the cap as the lipid or necrotic core.

Surprisingly, atherosclerotic plaques expand outward during much of their existence, rather than impinging on an artery’s blood-carrying channel. This pattern preserves blood flow for quite some time, often for decades. When the plaques do push inward, they restrict the blood channel—a condition called stenosis. Stenosis can impede blood delivery to tissues, especially at moments of greater need, when the arteries would usually expand. When a person exercises or experiences stress, for instance, blood flow through a compromised heart artery can fail to match the increased demand, causing angina pectoris: a feeling of tightness, squeezing or pressure usually under the breastbone. Narrowing in other arteries can cause painful cramping of the calves or buttocks during exertion, symptoms known as intermittent claudication.

AN INSIDE VIEW

THE BLOOD CLOT, or thrombus (red), captured in this micrograph has formed at the site of an atherosclerotic plaque in a coronary artery and has occluded the vessel. Some clots dissolve before they cause a heart attack or stroke, but they can foster trouble in another way—by stimulating plaque expansion.



Causing Crises

SOMETIMES A PLAQUE grows so large that it virtually halts blood flow in an artery and generates a heart attack or stroke. Yet only about 15 percent of heart attacks happen in this way. By carefully examining vessel walls of people who died from heart attacks, pathologists have demonstrated that most attacks occur after a plaque’s fibrous cap breaks open, prompting a blood clot to develop over the break. The plaques most likely to fracture possess a thinned cap, a large lipid pool and many macrophages, and their vulnerability stems, as in earlier stages of atherosclerosis, from inflammation.

The integrity of the fibrous covering depends largely on steel-strong collagen fibers made by smooth muscle cells. When something causes inflammation to flare in a relatively quiet plaque, mediators of the process can compromise the cap in at least two ways. My laboratory has shown that these inflammatory mediators can stimulate macrophages to secrete enzymes that degrade collagen, and

they can inhibit smooth muscle cells from extruding the fresh collagen required to repair and maintain the cap.

Clots form when blood seeps through a fissure in the cap and encounters a lipid core teeming with proteins able to facilitate blood coagulation. For example, molecules on T cells in the plaques spur foam cells to manufacture high levels of tissue factor, a potent clot inducer. Circulating blood itself contains precursors of the proteins involved in the cascade of reactions responsible for clot formation. When blood meets tissue factor and other coagulation promoters in a plaque’s core, the clotting precursors jump into action. Our bodies produce substances that can prevent a clot from materializing or can degrade it before it causes a heart attack or stroke, but inflamed plaques release chemicals that impede the innate clot-busting machinery.

If a clot does get cleared naturally or with the aid of drugs, the healing process may kick in once again, restoring the cap but also further enlarging the plaque by

forming scar tissue. Indeed, considerable evidence suggests that plaques grow in fits and starts, as triggers of inflammation come and go and as clots emerge and dissolve but leave scars.

The new picture of atherosclerosis explains why many heart attacks seem to come from out of the blue: the plaques that rupture do not necessarily protrude very far into the blood channel and so may not cause angina or appear prominently on images of the channel. The new view also clarifies why therapies that focus on widening the blood passage in semioccluded arteries (balloon angioplasty or insertion of wire-cage stents) or on surgically creating a bypass can ease angina yet frequently fail to prevent a future heart attack. In such cases, the danger may lurk elsewhere, where a plaque causes less narrowing but is more prone to rupturing. Sadly, even when stenosis is

ern society exceed by far the body's needs and can actually promote arterial disease.

Indeed, in response to new data correlating heart health with lipoprotein levels, public health experts have progressively refined the definition of "healthy" LDL levels. Guidelines released last year by an expert panel convened in cooperation with the National Institutes of Health now explicitly label LDL-cholesterol levels below 100 milligrams per deciliter of blood (mg/dL) as optimal. They also suggest considering drug treatment earlier than before—at 130 mg/dL instead of 160—for certain people with multiple risk factors. For adults with a relatively low risk of heart disease, the guidelines recommend (as before) initiating "lifestyle changes"—diet and exercise—at 160 mg/dL and considering drug treatment at 190 mg/dL.

Investigators have yet to explore the

sion and atherosclerosis simultaneously.

Conversely, high-density lipoprotein (HDL) seems beneficial; as levels of this "good cholesterol" decline, the likelihood of suffering a heart attack goes up. Accordingly, to fine-tune estimates of cardiovascular risk, many physicians today measure not only levels of LDL in the blood but also the level of HDL and the ratio of LDL (or LDL plus its various relatives) to HDL. HDL may achieve its beneficial effects in part by reducing inflammation: along with cholesterol, it can transport antioxidant enzymes able to break down oxidized lipids.

Given inflammation's usual responsibility in the body—blocking and eliminating infectious agents—biologists have naturally looked at whether arterial infections might contribute to inflammation in the arteries. Recent work suggests that atherosclerosis can develop in the

The ancients who first **DEFINED INFLAMMATION** had to focus on what they could see and feel. Today we know that the outward signs reflect a pitched struggle playing out on a **MICROSCOPIC BATTLEFIELD**.

the problem, treated arteries often become reoccluded fairly rapidly—apparently in part because the treatments can elicit a robust inflammatory response.

Beyond Bad Cholesterol

ALTHOUGH LDL frequently sparks the sequence of events I have outlined, scientists have identified several other factors that unequivocally increase a person's risk for atherosclerosis or its complications. Many of these risk factors, and a few still under study, exhibit intriguing inflammatory properties. Before I describe some of those features, I must first point out that LDL probably plays an even larger role in initiating and perpetuating atherosclerosis than is generally recognized.

A much repeated statistic says that half of all patients who have angina or have had a heart attack do not have above-average LDL levels—a finding frequently interpreted to mean that in such individuals, LDL exerts no influence on the atherosclerosis at the root of those disorders. But typical LDL levels in West-

connections between other risk factors and inflammation with the intensity accorded to LDL, but they have uncovered suggestive links. Diabetes, for instance, elevates glucose levels in the blood; this sugar can enhance the glycation, and thus the inflammatory properties, of LDL. Smoking causes oxidants to form and might hasten the oxidation of LDL's constituents, thereby fostering arterial inflammation even in individuals with average LDL levels. Obesity contributes to diabetes and vascular inflammation. High blood pressure may not exert direct inflammatory effects, but a hormone partly responsible for much human hypertension—angiotensin II—appears to incite inflammation as well; elevated levels of this hormone, then, might give rise to hyperten-

absence of infection. Nevertheless, circumstantial evidence suggests that certain microorganisms, such as herpesviruses or the bacterium *Chlamydia pneumonia* (a frequent cause of respiratory infections), could well induce or aggravate atherosclerosis at times. *C. pneumonia*, for instance, appears in many atherosclerotic plaques, and its constituents can evoke inflammatory responses by macrophages and by vascular endothelial and smooth muscle cells.

Infections might also act from a distance, in what I call an echo effect. When the body fights infections, inflammatory mediators can escape into the blood and travel to distant sites. These substances can, in theory, stimulate the white cells in atherosclerotic plaques, thereby prompt-

THE AUTHOR

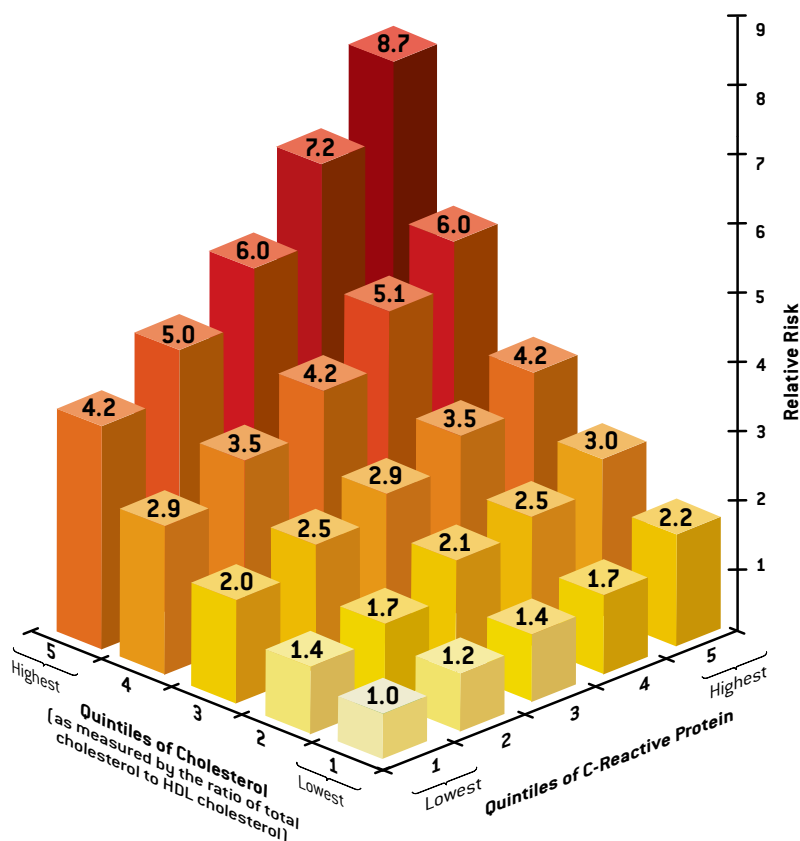
PETER LIBBY, who earned his M.D. from the University of California, San Diego, is chief of cardiovascular medicine at Brigham and Women's Hospital, Mallinckrodt Professor of Medicine at Harvard Medical School, and co-editor of the sixth edition of *Heart Disease*, a classic cardiology textbook (see "More to Explore," on page 55). He regards "lifestyle modification as the cornerstone of cardiovascular prevention" and practices what he preaches by running recreationally, albeit, he says, more avidly than swiftly.

A TELLING TEST

IN DECIDING WHETHER a patient requires therapy to prevent an atherosclerosis-related heart attack or stroke, physicians usually rely heavily on measurements of cholesterol in the person's blood. But that approach misses a great many vulnerable individuals. Several studies suggest that measuring blood concentrations of C-reactive protein—a marker of inflammation—could add useful information. Indeed, in one recent report, Paul M. Ridker of Brigham and Women's Hospital demonstrated that examining both C-reactive protein levels (which cannot be predicted from cholesterol measures) and cholesterol levels provides a more accurate indication of risk than assessing cholesterol alone (*graph*).

Ridker grouped cholesterol levels in the general adult population into five progressively rising ranges (quintiles) and, separately, divided C-reactive protein levels into quintiles as well. Then he determined the relative risk faced by people having different combinations of cholesterol and C-reactive protein values. That is, he assigned a danger level of "one" to individuals whose cholesterol and C-reactive values both fell in the lowest quintile (*front corner*) and calculated how much that risk multiplied in adults having other permutations of cholesterol and C-reactive protein measurements.

He found that high C-reactive protein values signify markedly elevated risk for heart attack or stroke even in individuals with seemingly reassuring cholesterol values. For instance, people with average (third-quintile) cholesterol levels and the highest C-reactive protein levels face much the same peril as those who have the highest cholesterol and lowest C-reactive protein levels. And subjects having the highest values for both cholesterol and C-reactive protein confronted the greatest risk of all. Encouraged by such results, researchers now hope to undertake a large study assessing whether basing treatment decisions on combined C-reactive protein and cholesterol testing will save lives. —P.L.



ing plaque growth or rupture. Clinical trials to see whether limited courses of antibiotics will prevent recurrent heart attacks are under way. A recently completed trial suggests, however, that antibiotics do not forestall recurrences in heart attack survivors.

Reducing Danger

INFLAMMATION'S essential role in atherosclerosis implies that anti-inflammatory medicines might slow this disease, and some (including aspirin) are already in use or under study. But logic and the investigations conducted so far suggest a need to look elsewhere as well.

Aspirin belongs to the class of drugs called NSAIDs (nonsteroidal anti-inflammatory drugs), a group that also claims such popular painkillers as ibuprofen and naproxen. Like other NSAIDs, aspirin can block the formation of certain lipid mediators of inflammation, including the prostaglandins, which generate pain and fever. Strong data from well-performed clinical trials indicate that aspirin shields against heart attacks and, in some patients, against mini strokes (technically, transient ischemic attacks, or TIAs). But the low doses that afford this protection probably reduce the clotting propensity of blood instead of quieting inflammation.

Scientists have little clinical data relating to the effects of other NSAIDs on atherosclerosis, and some evidence suggests that selective inhibitors of the prostaglandin-producing enzyme COX-2 might actually enhance thrombus development in some patients. Cortisone and related steroids could prove too toxic for long-term use, and no data support their utility in reducing atherosclerotic complications.

Even if anti-inflammatory drugs proved effective, they might have to be given for years on end to keep atherosclerosis at bay. That prospect worries me, because ongoing interference with inflammation could come at too high a price: increased risk of infection. One day someone could devise a way to halt the chronic, destructive inflammation of atherosclerosis without undermining overall immunity. But I suspect that a more practical strategy would concentrate on defusing the triggers at the root of arterial inflammation.

Fortunately, some means are at hand already. A heart-healthy diet, regular exercise and, for obese individuals, weight loss can reduce the risk of a heart attack and combat diabetes. In addition, since 1994 several impeccably designed and executed clinical trials have established beyond a doubt that lipid-lowering drugs can reduce the likelihood of atherosclerotic complications and can prolong life seemingly across the board—that is, in individuals with a broad range of risk levels. Researchers have not yet nailed down the mechanism behind the success of the lipid-lowering drugs, which do not seem to reduce arterial stenosis substantially. But studies of cells, whole animals and humans suggest that lipid lowering (as might be expected from the foregoing dis-

the large fraction of people whose lipid levels look too good to justify treatment. Recent findings suggest that blood tests combining lipid testing with monitoring of a substance called C-reactive protein might improve detection.

Toward Early Detection

THE PRESENCE of C-reactive protein in the blood signifies that inflammation is occurring somewhere in the body; highly elevated levels, even in the presence of LDL values too low to prompt treatment under current guidelines, indicate an increased risk of heart attack or stroke. What is more, in at least one study, delivery of statins to people with below-average LDL concentrations but high C-reactive protein levels reduced the incidence

stroke but who nonetheless are destined for disaster. Ideas include measuring the heat of blood vessels (because heat should accompany inflammation) and altering existing imaging technologies, such as MRI or CT scans, to improve their ability to visualize material inside vessel walls. Geneticists, meanwhile, hunt for gene variants that render some people more vulnerable to chronic inflammation and to atherosclerosis and its complications, so that individuals most prone to these disorders can seek more aggressive monitoring and treatment.

For most of human history, inflammation's ability to ward off infection outweighed its drawbacks. Today, as we live longer, exercise less, eat too much and smoke, many of us suffer from inflam-

THE NEW PICTURE of atherosclerosis explains why many heart attacks come from out of the blue: the plaques that rupture do not necessarily protrude very far into the blood channel and so **MAY NOT CAUSE ANGINA.**

cussion) might help by limiting inflammation, thereby minimizing plaque build-up and make existing plaques less likely to rupture.

Recent analyses of the statins (widely prescribed lipid-controlling drugs) support this notion. They confirm that the drugs can decrease inflammation in patients. Experiments on isolated cells and laboratory animals indicate as well that the drugs' anti-inflammatory effects may not depend entirely on changing the concentrations of lipids in the blood. Statins—which decrease the levels of LDL and related bad lipids by increasing their disposal in the body—also limit the availability of chemicals that enable cells to respond to inflammatory mediators.

Experimental drugs that aim at other risk factors for heart disease and stroke might exert useful anti-inflammatory effects as well. Agents that raise levels of HDL or limit the action of angiotensin II come to mind. But treatment with antioxidant vitamins has proved disappointing.

No matter how good a drug is, it will be of no value if it sits unused on pharmacy shelves. Doctors need better ways of detecting dangerous atherosclerosis in

of heart attack relative to the rate in a matched group of patients who received no treatment. Such results need to be confirmed in a much larger trial before doctors can confidently treat patients on the basis of the combined test, although some physicians already incorporate tests of C-reactive protein in their practices.

Noninvasive methods for specifically identifying vulnerable plaques might also help pinpoint individuals who lack strong warning signs of risk for heart attack or

mation's dark side—including its ability to contribute to atherosclerosis and other chronic disorders. Scientists continue to pursue a deeper understanding of inflammation's role in atherosclerosis and to decipher the devilishly intricate interactions that ignite and drive the inflammatory processes in the arteries. These insights should enable us to make further inroads against a disease of growing worldwide importance that causes extensive disability and takes far too many lives. SA

MORE TO EXPLORE

The Molecular Bases of Acute Coronary Syndromes. Peter Libby in *Circulation*, Vol. 91, No. 11, pages 2844–2850; June 1, 1995. Available at www.circulationaha.org

Stability and Instability: The Two Faces of Coronary Atherosclerosis. Paul Dudley White Lecture, 1995. M. J. Davies in *Circulation*, Vol. 94, No. 8, pages 2013–2020; October 15, 1996.

Oxidized Lipids in Atherogenesis: Formation, Destruction and Action. J. Berliner et al. in *Thrombosis and Haemostasis*, Vol. 78, No. 1, pages 195–199; July 1997.

Low Density Lipoprotein Oxidation and Its Pathobiological Significance. Daniel Steinberg in *Journal of Biological Chemistry*, Vol. 272, No. 34, pages 20963–20966; August 22, 1997. Available at www.jbc.org

Current Concepts of the Pathogenesis of the Acute Coronary Syndromes. Peter Libby in *Circulation*, Vol. 104, No. 3, pages 365–372; July 17, 2001.

The Vascular Biology of Atherosclerosis. Peter Libby in *Heart Disease: A Textbook of Cardiovascular Medicine*. Sixth edition. Edited by Eugene Braunwald, Douglas P. Zipes and Peter Libby. W. B. Saunders, 2001.

Inflammation and Atherosclerosis. Peter Libby, Paul M. Ridker and Attilio Maseri in *Circulation*, Vol. 105, No. 9, pages 1135–1143; March 5, 2002.

Current recommended LDL levels appear at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm