It is clear that inflammation is linked to heart disease, and that one of the body's most common sources of inflammation is periodontal disease. Does poor oral health contribute to heart disease risk? Although the jury is still out while scientists investigate this link, here is what we know about inflammation's role in atherosclerosis. | BY **PETER LIBBY**

Heart Health in the INFLAMMATION AGE

ONLY A DECADE AGO, most physicians would have confidently described atherosclerosis as a plumbing problem: Fat-laden gunk gradually builds up on artery walls. If a deposit (plaque) grows large enough, it closes off an affected "pipe," preventing blood flow. Eventually, the blood-starved tissue dies. If that happens in the heart or the brain, a heart attack or stroke occurs.

Few believe that tidy explanation anymore. Twenty years of research show that arteries bear little resemblance to pipes. They contain living cells that communicate with one another and their environment. They also participate in the development of the fatty deposits that grow within vessel walls—few which actually shrink vessels to a pinpoint. Most heart attacks and many strokes stem from interior plaques that rupture suddenly, spawning a blood clot that blocks blood flow.

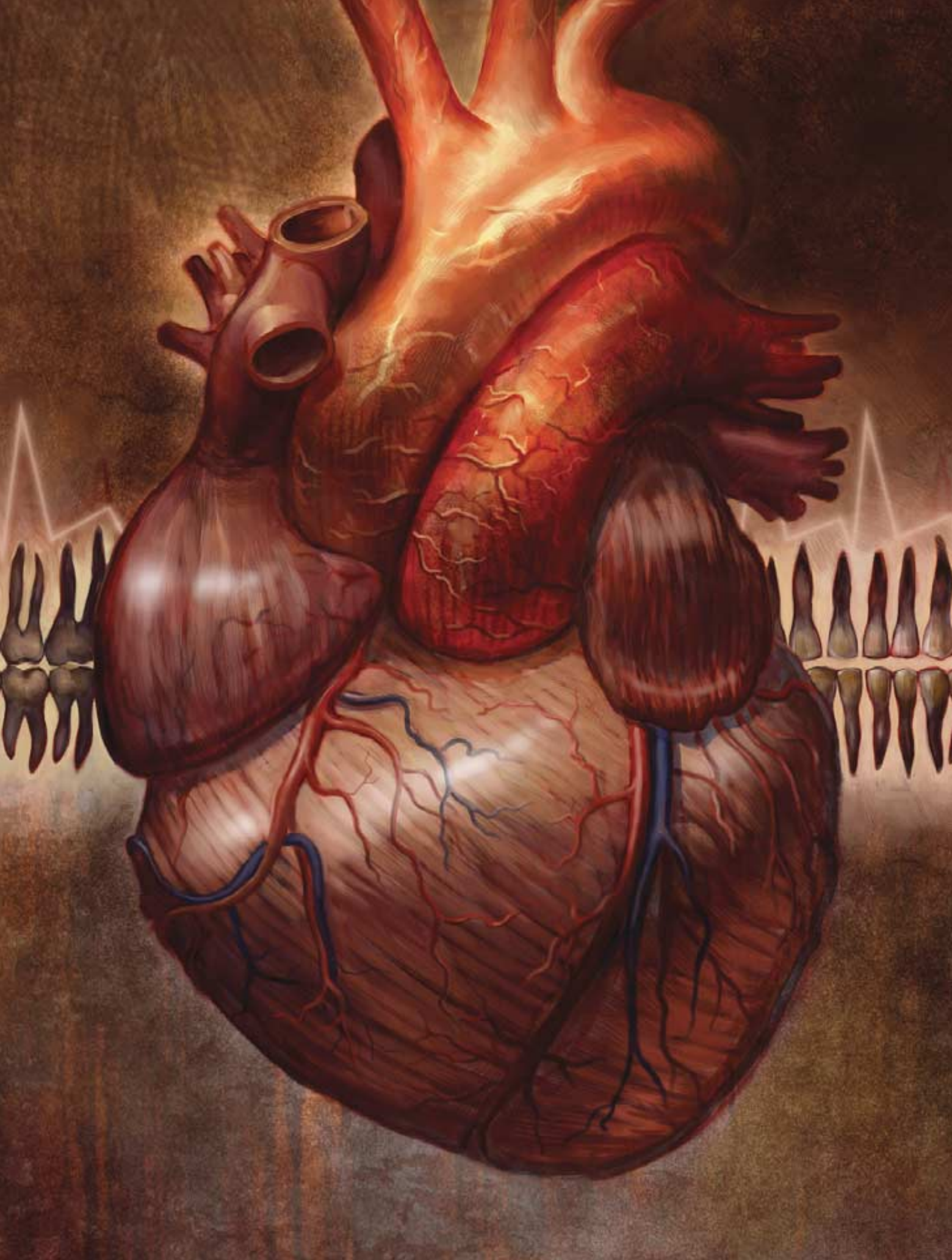
Such research has established inflammation's key role in atherosclerosis. This process—the same one that causes infected cuts to become swollen, hot and painful—underlies everything from the creation of plaques to their growth and rupture.

When microbes invade, inflammation (literally meaning "on fire") fights infection. But with atherosclerosis, inflammation proves harmful; our own defenses bombard us with friendly fire, just as they do in lupus and other autoimmune disorders. This revised picture resolves two disturbing mysteries: why many heart attacks strike without warning and why preventative therapies sometimes fail. It also highlights the need for better prevention, detection and treatment. In industrialized nations, deaths from heart attacks and strokes exceed those from cancer—and they are also becoming more prevalent in developing countries.

IGNITING TROUBLE

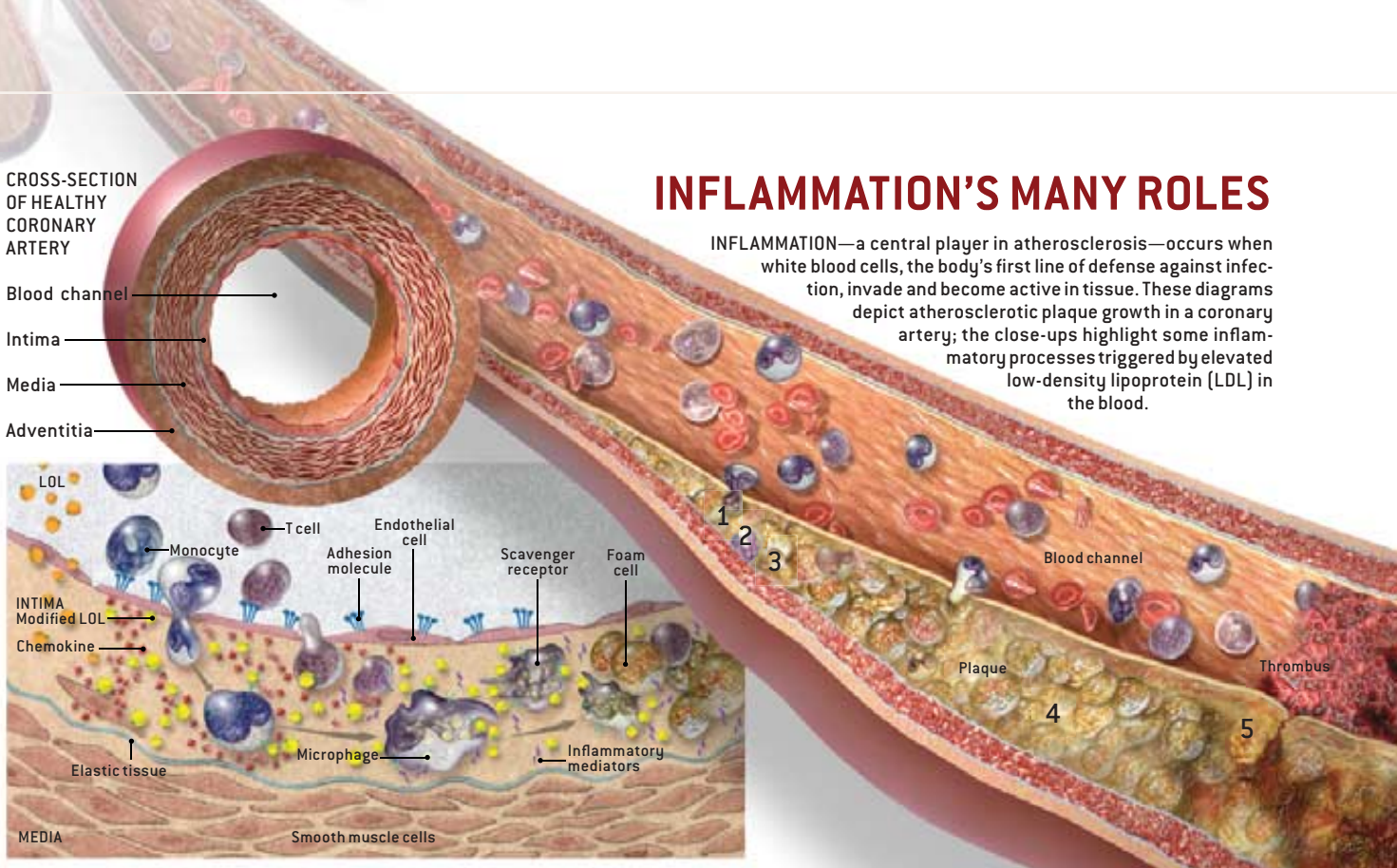
WE KNOW THAT inflammation symptoms reflect a pitched struggle on a microscopic battlefield. After sensing (rightly or wrongly) a microbial invasion, certain types of white blood cells—the immune system's frontline warriors—convene in the threatened tissue. There they secrete chemicals to limit infection: oxidants that damage invaders and signaling molecules (including proteins called cytokines) that orchestrate the activities of defensive cells. Their presence in tissue signifies an inflammatory response. >>

MATT COLLINS



INFLAMMATION'S MANY ROLES

INFLAMMATION—a central player in atherosclerosis—occurs when white blood cells, the body's first line of defense against infection, invade and become active in tissue. These diagrams depict atherosclerotic plaque growth in a coronary artery; the close-ups highlight some inflammatory processes triggered by elevated low-density lipoprotein (LDL) in the blood.



BIRTH OF A PLAQUE

1 Excess LDL accumulates in artery walls, undergoing chemical changes. Modified LDLs stimulate endothelial cells to display adhesion molecules, which capture circulating monocytes (key players in inflammation) and T cells (immune cells). Endothelial cells also secrete "chemokines," luring snared cells into the intima.

2 Monocytes mature into active macrophages in the intima; with T cells, they produce inflammatory mediators, including cytokines that carry signals between immune system cells and factors that promote cell division.

3 The macrophages display "scavenger receptors" to help ingest modified LDLs; macrophages feast on them, filling with frothy, fatty droplets. These "foam cells" combine with T cells, comprising the fatty streak—early atherosclerotic plaque.

PLAQUE PROGRESSION

4 Inflammatory molecules trigger further plaque growth. A fibrous cap develops over the lipid core when the molecules induce smooth muscle cells to migrate to the intima surface, multiplying and producing a tough, fibrous matrix that glues cells together. The cap makes the plaque larger and walls it off from the blood.

Cholesterol studies on both animals and cultured cells have elaborated inflammation's role in atherosclerosis. Scientists have long known that although we need cholesterol, excessive amounts clog arteries. But until recently, no one knew how this happened. Low-density lipoprotein (LDL)—also known as bad cholesterol—is composed of fatty molecules (lipids) and protein. Its job: transport cholesterol (another lipid) from its source in the liver and intestines to other organs. The trouble begins when LDLs from the blood collect in the intima, the interior wall of an artery. At low concentrations in the blood, LDLs can pass in and out of the intima; in excess, LDLs become stuck in the cell matrix.

As LDLs accumulate, their lipids oxidize—a corrosive process similar to the one that rusts pipes. Cells in the blood vessel wall react to these changes by calling for reinforcements from the body's defense system. Adhesion molecules on the endothelial cells that line vessels latch like Velcro onto monocytes, inflammatory cells that normally circulate in the blood, attaching them to artery walls. Endothelial and smooth muscle cells inside vessels then secrete chemokines—chemicals that attract monocytes. Much as hounds track the scent of their prey, more monocytes follow the chemical trail into the intima.

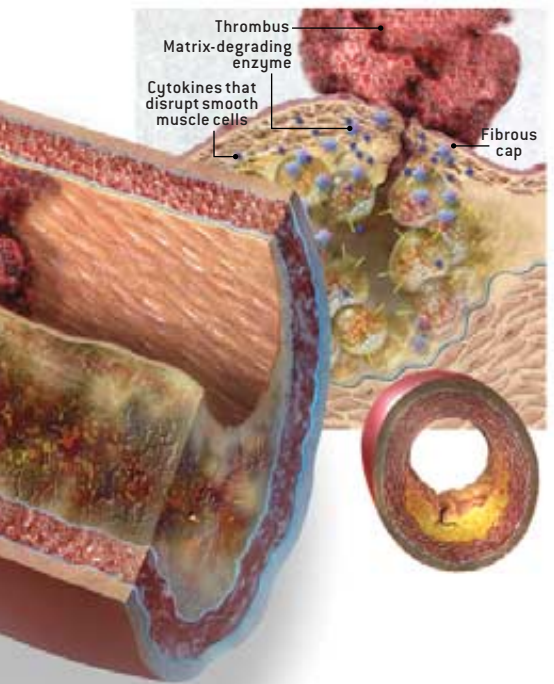
Stimulated by chemokines and other substances, the monocytes multiply and mature into active macrophages, ready to unleash their weapons against the body's enemies. These warriors set about clearing perceived invaders from vessel walls. Scavenger receptor molecules capture modified LDL particles and help macrophages "eat" them—until they're so full of fatty droplets that they look foamy under a microscope, giving them their "foam cell" nickname.

T lymphocytes (a type of white blood cell) also attach themselves to artery walls, releasing cytokines that intensify inflammation. The first visible atherosclerotic lesion, a yellow "fatty streak," is a mix of foamy macrophages and T lymphocytes. These lesions are a precursor of the complex plaques that later dis-

KEITH KASNOT

PLAQUE RUPTURE

5 Foam cells secrete inflammatory substances that weaken the cap, digesting matrix molecules and damaging smooth muscle cells that normally repair it. Foam cells may produce tissue factor, a potent clot-promoter. If the plaque ruptures, a clot forms. A large clot can halt blood flow to the heart, causing a heart attack—the death of cardiac tissue.



CUTAWAY VIEW OF ARTERY AFFLICTED BY ATHEROSCLEROSIS

figure arteries. Many Americans begin plaque buildup as early as their teens.

FUELING PLAQUE GROWTH

WHEN AN INFLAMMATORY RESPONSE in, say, a scraped knee successfully blocks infection, macrophages release molecules that promote healing. A "healing" process is also part of the chronic, low-level inflammation that operates in atherosclerosis. But instead of restoring artery walls, the process perversely remodels them, generating a bigger plaque.

Recently, biologists have learned that both macrophages and cells within an inflamed vessel wall secrete substances that create a kind of scar tissue. Smooth muscle cells migrate to the vessel surface. Once there, they form a fibrous covering over the original plaque. Underneath this cap, some foam cells die, releasing their load of lipids.

Atherosclerotic plaques usually expand outward, not inward to block an artery's blood-carrying channel. When they do push in, blood flow to tissues is restricted, especially when arteries would normally expand. During exercise or stress, blood flow through a compromised heart artery fails to meet the increased demand. This causes angina pectoris, a feeling of tightness or pressure usually under the breastbone. Narrowing in other arteries can cause painful cramping of the calves or buttocks during exertion.

CAUSING CRISES

ONLY ABOUT 15 PERCENT of heart attacks are caused by large plaques that block arteries. Autopsies have shown that most attacks occur after a plaque's fibrous cap ruptures, prompting a blood clot to develop over the break. Inflammation makes the cap vulnerable. My laboratory found that when stimulated by inflammatory chemicals, macrophages secrete enzymes that degrade a cap's strong collagen fibers and stop smooth muscle cells from extruding fresh collagen to repair and maintain it.

Clots form when blood seeps through a fissure in a cap and coagulates. Although our bodies produce substances that can prevent or degrade blood clots, inflamed plaques release chemicals that impede this clot-busting machinery. If a clot does clear naturally or with medication, the healing process may kick in once again, restoring the cap but also enlarging the plaque by forming scar tissue. Considerable evidence suggests that plaques grow in fits and starts as inflammation comes and goes and as clots emerge and dissolve.

This new picture of atherosclerosis explains why many heart attacks seem to come from out of the blue. Plaques that rupture may not protrude very far into a blood channel—and may not cause angina or appear on images of the channel. This also explains why bypass surgery or therapies such as angioplasty or stents that widen obstructed arteries can ease angina—yet often fail to prevent a heart attack. Even when blocked arteries are treated, they often clog up again fairly quickly—it seems that the treatment itself elicits a robust inflammatory response.

BEYOND BAD CHOLESTEROL

SEVERAL OTHER atherosclerosis risk factors exhibit intriguing inflammatory features: diabetes, for instance, elevates blood sugar levels, which can enhance LDL's inflammatory properties. Smoking causes oxidants to form, possibly hastening LDL oxidation—and fostering arterial inflammation even in people with average LDL levels. Obesity contributes to diabetes and vascular inflammation.

Conversely, high-density lipoprotein (HDL) seems beneficial; as levels of this "good cholesterol" decline, the likelihood of suffering a heart attack goes up. HDL may achieve its beneficial effects in part by reducing inflammation, because along with cholesterol, HDL transports antioxidant enzymes that break down oxidized lipids.

Given inflammation's usual responsibility in the body—blocking and eliminating infectious agents—biologists have wondered whether arterial infections might contribute to inflammation in the arteries. Recent studies suggest that atherosclerosis can develop in the absence of infection. However, circumstantial evidence suggests that certain microorganisms, such as herpes viruses or the bacterium *Chlamydia pneumoniae* could induce or aggravate atherosclerosis. *C. pneumoniae* appears in many atherosclerotic plaques—and can trigger inflammatory responses.

Infections might also act from a distance, in an "echo effect." When the body fights infections, inflammatory mediators can escape into the blood and travel to distant sites. Because the mouth can be a source of chronic infection, researchers are exploring the potential impact of gum disease. Infection from peri-

EVALUATING THE DATA:

Could Periodontal Disease Increase the Risk for Cardiovascular Disease? BY KAUMUDI JOSHIPURA

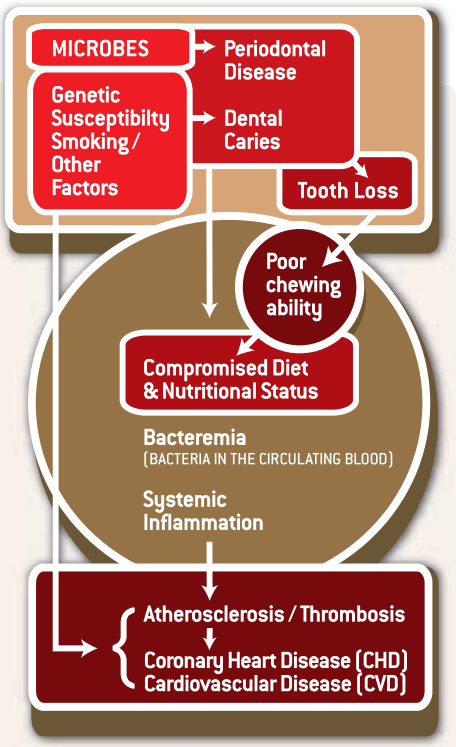
HEART DISEASE AND PERIODONTAL DISEASE have several things in common. One of them is inflammation, which both narrows coronary arteries and breaks down the tissues that hold teeth in place. Could periodontal disease increase your risk for developing heart disease, perhaps due to bacterial pathogens or inflammatory chemicals carried by the blood from the mouth to the heart? If so, could you reduce your heart disease risk by preventing or treating periodontal disease?

Research suggests that there may be links between the two conditions. Animal studies in particular offer provocative evidence that certain biologic pathways might allow one disease to influence the other. Periodontal bacteria are found in the plaque deposits that narrow coronary arteries; inducing periodontal disease in rabbits causes plaque accumulations in their coronary arteries.

Other evidence comes from observational human studies. The largest such study, the National Health and Nutrition Examination Survey (NHANES), involved 10,000 Americans between the ages of 18 and 74. It found that people with periodontal disease were much more likely to be diagnosed with heart disease than those without periodontal disease.

Not all studies have yielded similar results. For example, my colleagues and I examined a group of health care professionals and failed to find an overall association. Interestingly, our study and several others did detect a significant association between tooth loss (often a result of severe periodontal disease) and heart disease. So the "connection" between periodontal disease and heart disease may be indirect, involving tooth-loss-induced dietary changes (e.g., shunning fruits, vegetables and dietary fiber) that increase heart risks.

The link between the two diseases may derive from factors that influence both. For example, cigarette smoking is a major risk factor for heart disease and for periodontal disease, and a genetic susceptibility to inflammation might cause someone to develop both diseases (*see chart*).



Although periodontal disease seems to be associated with heart disease, more studies are needed before we can say with certainty that one disease actually causes the other. Meanwhile, everyone should be conscientious about treating gum disease, but it is not yet clear that doing so will protect you from heart disease. ●

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odontal disease pumps a continuous flow of bacteria and cytokines into the bloodstream. Bacteria also produce toxins that can trigger inflammatory responses. Cytokines and bacterial toxins can stimulate the white cells in atherosclerotic plaques, prompting plaque growth or rupture. Despite these links between infection and atherosclerosis, current clinical evidence does not support the use of antibiotics to prevent recurrent complications following a heart attack.

TOWARD EARLY DETECTION

NONINVASIVE METHODS for identifying vulnerable plaques might help pinpoint at-risk individuals who lack warning signs of potential heart attack or stroke. Ideas include testing for elevated levels of C-reactive protein, a substance in the blood that signifies acute inflammation; measuring the heat of blood vessels (because heat normally accompanies inflammation); and altering existing imaging technologies, such as MRI or CT scans, to improve their ability to peer inside vessel walls. Scientists are trying to develop molecular imaging techniques to "visualize" biological processes such as inflammation, looking beyond the anatomical features of blood vessels. Geneticists are hunting for genes that predispose some people to chronic inflammation and atherosclerosis so they 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 inflammation'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 intricate interactions that ignite and drive the inflammatory processes in the arteries. These insights should enable us to make further inroads against a disease with growing worldwide impact that causes extensive disability and takes far too many lives. ●

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