Gum disease illustrates how local infections may have systemic consequences

INVADERS & THE BODY'S DEFENSES

BY PHILIP E. ROSS

IF EVER THERE WAS A MAGIC BULLET —a drug so discriminating that it attacked microbes while sparing healthy tissue— it would be the monoclonal antibody, a human-tuned form of an immune molecule honed by eons of natural selection. Yet, as the world learned this spring, when such an antibody nearly killed several subjects in a British clinical trial, even these drugs can cause serious side effects. No one should have been too surprised; the natural immune response also causes damage, which is why it fully mobilizes—in a process called inflammation—only when the enemy is at the gates.

In recent years, a lot of media attention has been lavished upon the process of inflammation (including a cover story in *Time* magazine on this "silent killer") as researchers continue to uncover evidence linking it with other serious diseases. Whether or not inflammation turns out to be the "holy grail" of medicine is yet to be seen. But inflammation's problem of friendly fire and potential systemic effects are nowhere better illustrated than in chronic gum disease. Although it originates in a bacterial assault, some two thirds of the damage is caused by the inflammatory response to the perceived invader. What is worse, inflammation somehow communicates itself to distant points, explaining the possible association of gum disease with other conditions: adult-onset (or type 2) diabetes, premature birth, stroke and cardiovascular disease. However infection travels from the mouth to inflame distant organs, it is clear that it turns the body against itself. In the words of the cartoon character Pogo, "We have met the enemy and he is us."

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JOHN SOARES

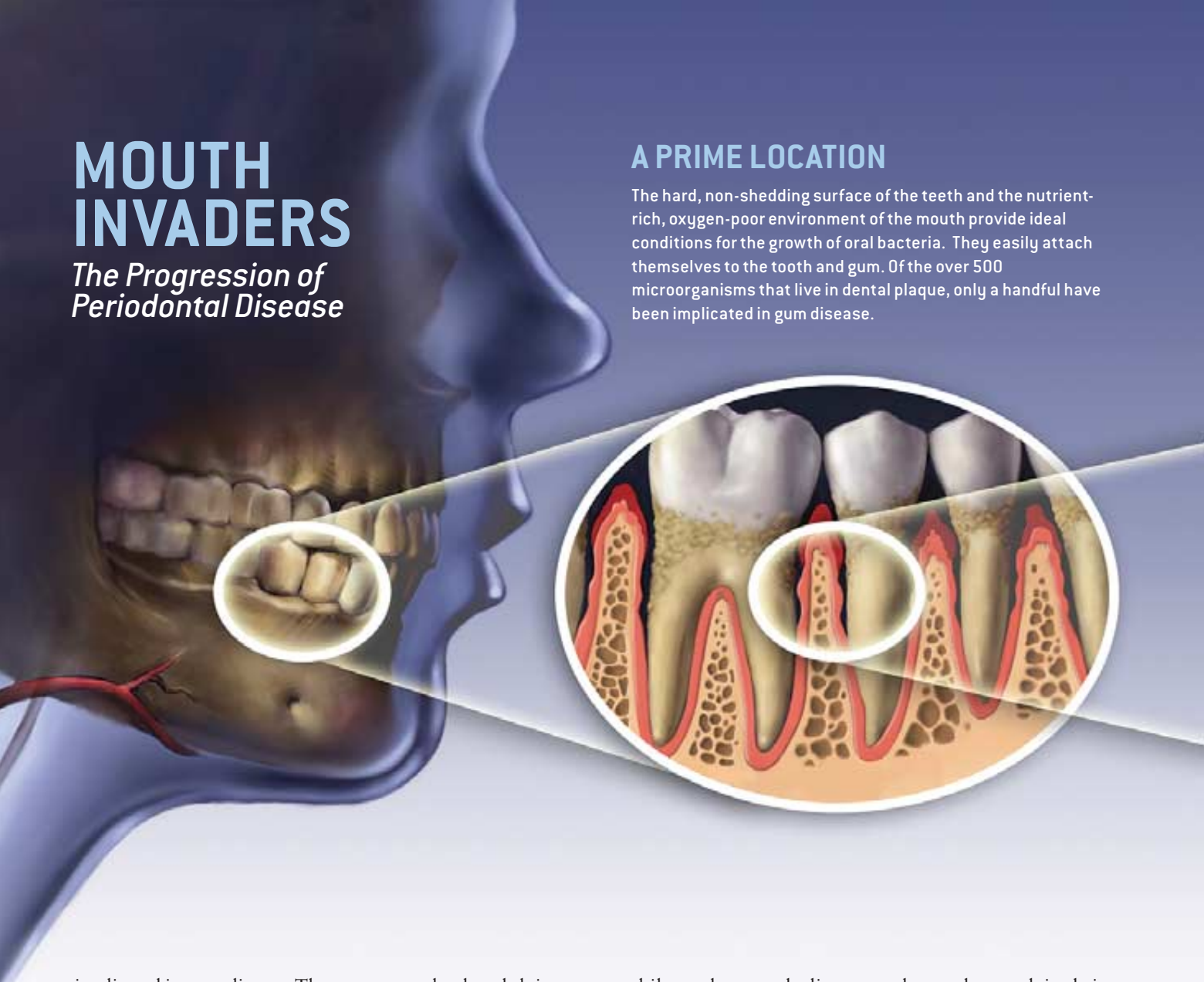
INFECTION AND INFLAMMATION in the mouth have been linked to a variety of systemic conditions, including pregnancy complications, type 2 diabetes, heart disease and stroke. While recent national media coverage spotlighting inflammation has spawned much interest in the topic, more research is needed to uncover exactly how infection and inflammation affect the body.

MOUTH INVADERS

The Progression of Periodontal Disease

A PRIME LOCATION

The hard, non-shedding surface of the teeth and the nutrient-rich, oxygen-poor environment of the mouth provide ideal conditions for the growth of oral bacteria. They easily attach themselves to the tooth and gum. Of the over 500 microorganisms that live in dental plaque, only a handful have been implicated in gum disease.



implicated in gum disease. They are particularly hard to eradicate because they form biofilms: tough, many layered, mineral encrusted communities. Huddling in the deepest layers are the oxygen-shunning, or anaerobic, bacteria that appear to cause the most damage.

When bacteria come in contact with gums, they secrete toxins that break down gum lining, creating a tiny ulcer. The body's bloodhounds, the neutrophil cells, then attack these invaders. If they keep the biofilm at bay, the battle reaches a standoff, termed gingivitis. If, however, the bacteria continue to advance into the gums, the immune system signals a higher state of alert, mobilizing macrophages (Greek for "big eaters"). These white blood cells swallow bacteria, along with the gorged, dead and dying neutrophils, and any cellular detritus that may litter the battlefield. Meanwhile, the macrophages secrete fatty acids and interleukin-1 (IL-1), a primary regulator of inflammatory and immune responses, as well as tumor necrosis factor alpha (TNFα), a protein that heightens inflammation. The resulting mayhem may be likened to urban warfare, with immune soldiers running from house to house, tossing in grenades, spraying rooms with machine-gun fire, all before asking who is friend and who is foe. No wonder the tissue breaks down. The ulcers sink deeper into the gum, creating a "periodontal pocket"; full-blown periodontitis begins.

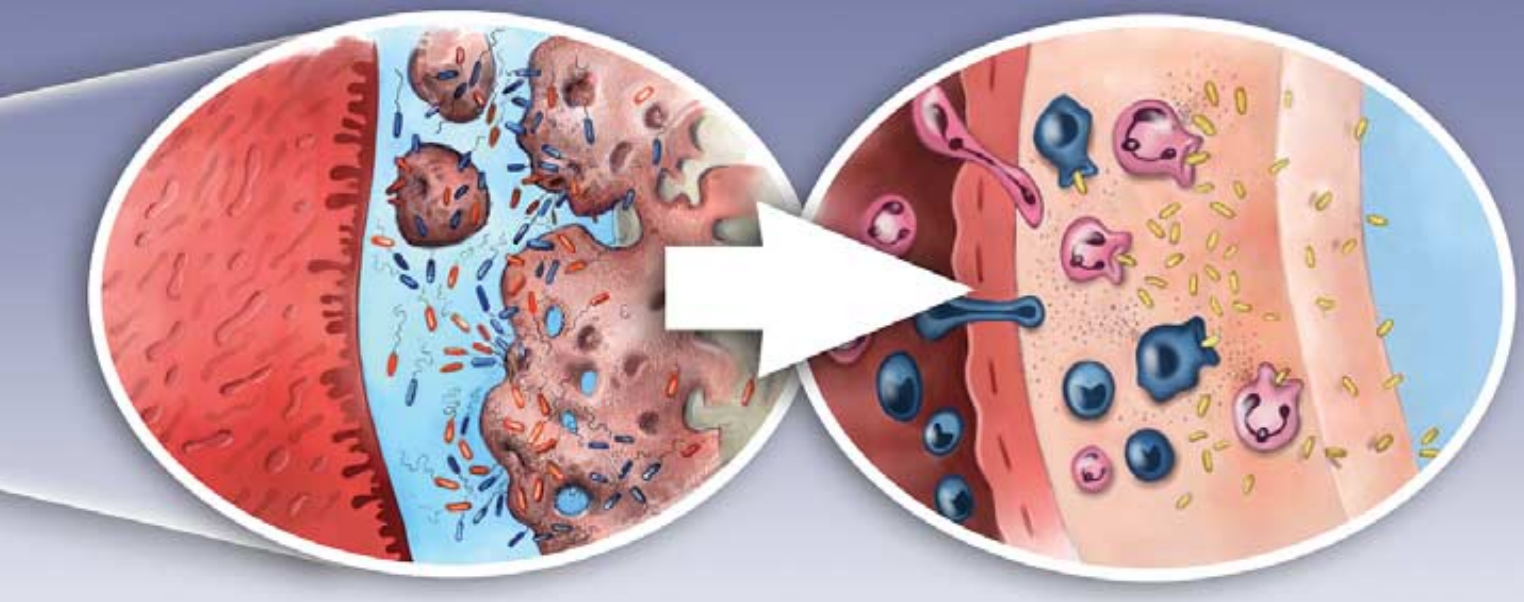
If the disease is allowed to progress, the advancing inflammation eats away the ligaments that anchor teeth in their sockets, loosening them until they at last fall out. Nowadays this happens less frequently; the patient notices the bleeding and goes to a dentist. The dentist or dental hygienist scrapes away inflammation-riddled material and treats the infection with antibiotics. Treatment, however, cannot prevent the influx of bacteria. The disease will recur if the patient does not stick to a rigorous routine of brushing, flossing, rinsing and dental cleanings. And although the damage in periodontal disease is primarily the result of the inflammatory process, it can only be prevented or treated by addressing the bacterial biofilm that is infecting the gums. What is worse, the chance of early detection is lessened in those who are most vulnerable—smokers. Just as to-

TENACIOUS BUGS

Oral bacteria are particularly hard to eradicate because they form tough, many-layered, mineral-encrusted communities, known as biofilms. If untreated, these biofilms become lodged in the gingival crevices around the tooth. The immune system launches a defensive strike against these bacterial invaders by dispatching neutrophils. The first signs of inflammation (redness, swelling) begin to appear.

A HEATED STRUGGLE

Continued defensive strikes by the immune system heighten inflammation as specialized white blood cells (macrophages, as well as others) secrete inflammatory substances. This intense inflammation can ultimately break down gum tissue, creating a periodontal pocket — the beginning of full-blown periodontal disease.



MATT COLLINS

bacco smoke irritates the gums, heightening inflammation, it also tends to mask telltale bleeding.

Other factors that predispose people to gum disease include bad oral hygiene and an unlucky bequeathal of genes. One very invasive form of periodontal disease is found in just 0.1 percent of Americans, a distribution that indicates a genetic component. People with these and other predisposing genes must work extra hard to care not only for their teeth but even for the artificial implants that may replace those teeth. Periodontal disease can strike the tissues surrounding implants as well.

Genetic variation is of particular interest because it may illuminate the mechanisms that underlie all varieties of periodontal disease. In one invasive form, neutrophils have trouble homing in on bacteria, showering them with chemical grenades called superoxides. "But instead of destroying bacteria, they destroy the periodontal ligament that ties the tooth to the jaw," says Charles N. Serhan, professor of anesthesiology at Harvard Medical School. "It's like rheumatoid arthritis, an autoimmune disease where a lot of the degradation of the synovium [the lining of the joints] is done by neutrophils." Serhan is looking for ways to shut down this excessive immune response.

When inflammation strikes sites far from the gums, it progresses there much as it does in the mouth. In the lining of the heart's arterial wall, for instance, macrophages engulf whatever detritus they find, including fatty particles. When the macrophages die, they entomb fat in situ, creating atherosclerotic plaque. This buildup, combined with inflammation, fattens the arterial wall, gradually restricting blood flow to tissues. Sometimes, for reasons that are not well understood, the thin layer of tissue covering the plaque ruptures, spurring clots to form in a matter of minutes, often triggering a heart attack or stroke. This is why the most common first symptom of heart disease is sudden death.

If infection in the gums not only precedes inflammation in the arteries, but encourages it, the question is how does it happen. One theory holds that bacteria are the primary vehicles in communicating disease; another lays the blame on proinflammatory chemicals that leak out of the gums and into the blood-

stream. Direct inflammation currently holds sway, particularly in the popular press. Still, there is evidence supporting both theories, and each may explain part of the problem.

Oral bacteria can get into the bloodstream. Robert Genco, a professor of oral medicine and microbiology at the University at Buffalo, took moment-by-moment blood tests in healthy patients undergoing routine teeth cleaning. The bacterial count spiked when cleaning began, then fell back to normal less than a minute after it was over—that is how fast the body's immune system rousts such invaders. Yet in people with periodontal disease, such bacterial inundations of the blood occur every time a loosened tooth moves in its socket, providing many opportunities for a stray bacterium to relocate to some distant location.

Oral bacteria, once established elsewhere in the body, are bad news. Genco injected *Porphymonas gingivalis*, a main culprit in periodontal disease, under the skin of rodents and found that it invariably produced fatal infections. "It causes gross necrosis of skin and underlying tissue; if you inject into the belly, the intestines will be exposed," he says. A rare, analogous condition has been seen in humans, in which a dental infection spreads down the neck to the area surrounding the carotid artery, where it digests tissue.

Perhaps the most persuasive example of a secondary infection from oral sources comes from patients who have mitral valve heart defects. Such patients are warned to take antibiotics before their dental appointments so that tooth cleaning will not send bacteria to infect or inflame the valve, which could destroy it or produce clots that might block arteries. The critical element here is the vulnerability of the valve. What if a similar weakness exists in the arterial lining?

Researchers have, in fact, found traces of oral bacteria in arterial plaque. Yet as critics of the infection theory point out, the method they used to identify the bacteria—a highly potent DNA amplification tool—cannot tell how many bacteria were present in the plaque or whether any of them were alive when they entered it.

Paul Ewald, an evolutionary biologist at the University of Louisville, has been a leading advocate of the role of infectious agents in chronic illnesses. He argues that gum disease fits into the evolutionary model he has devised because it is chronic, widespread and of great antiquity, and therefore cannot be simply the result of defective genes.

"If it were just a case of the immune system going haywire, you'd think that natural selection would have weeded it out," he says. "But if you are looking at actual combat between the immune system and [an] infectious agent, you'd expect it to be an evolutionary arms race, one that would never stabilize." That same arms race would have tuned the bacteria to a high pitch of virulence and invasiveness, hence their ferocious behavior when ensconced in another part of the body.

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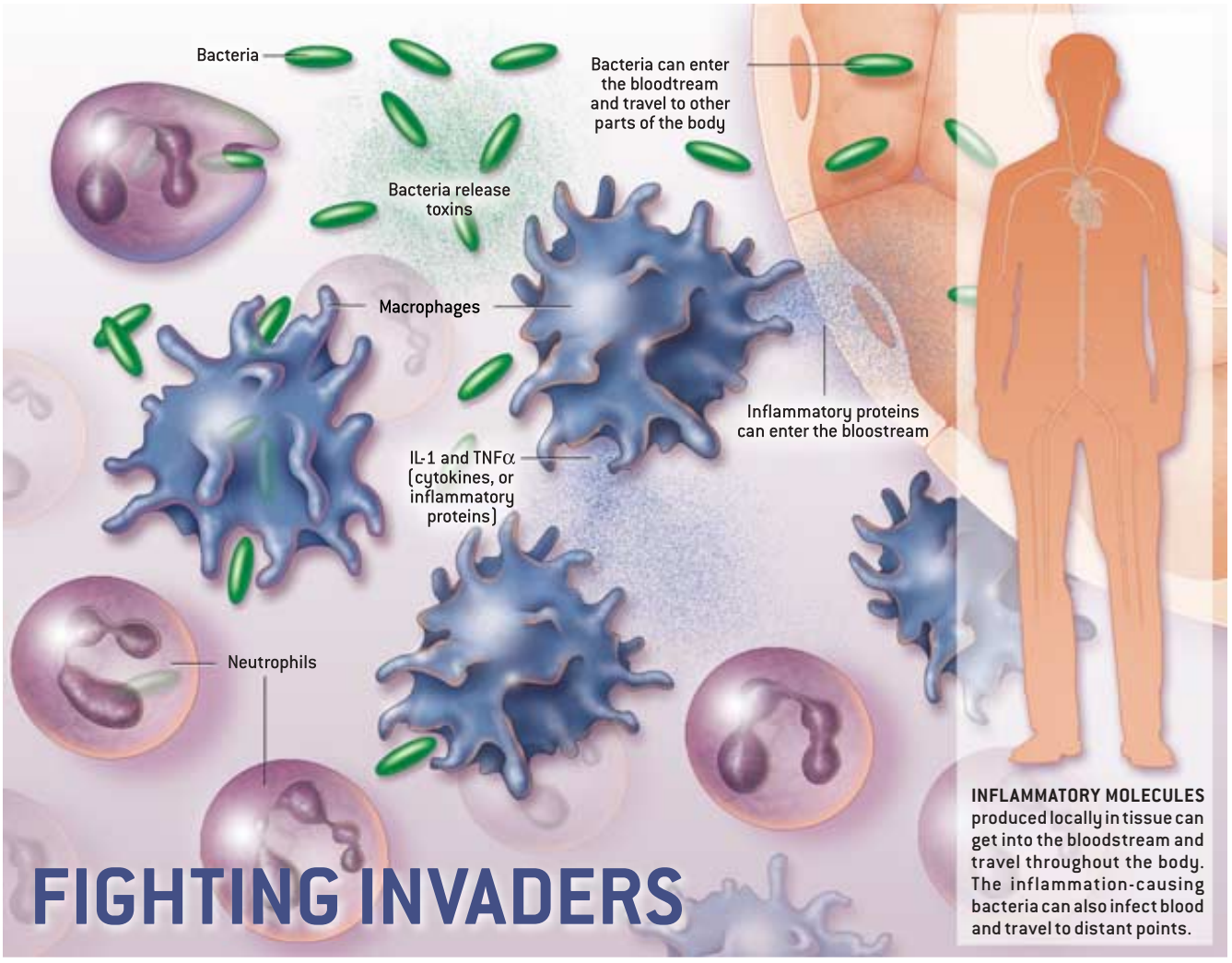
Biologists are now investigating the possibility that many chronic illnesses, once attributed to other causes, may in fact stem from infection. Several striking examples have been demonstrated in the past two decades: Stomach ulcers, long attributed to stress, spicy food and genes, turn out to derive, almost always, from the bacterium *Helicobacter pylori*. Cervical cancer, it is now known, can develop only in women who have been infected by certain varieties of the human papillomavirus (HPV), long considered innocuous. Yet critics of the bacterial-cause theory point out that oral bacteria survive poorly in the bloodstream. They also note that proinflammatory chemicals demonstrably leak from the gums into the bloodstream, adding to the body's inflammatory burden. In a test tube, proinflammatory agents from one group of cells can spark a response in another group. Injecting proinflammatories into animals also produces such a response. Some argue that these chemicals alone can explain the association of gum disease and systemic illness.

Here is how it might play out. Imagine that there is some small irritation in the wall of the coronary artery, perhaps the result of chemicals absorbed from cigarette smoke or car exhaust. If the overall inflammatory burden is low, then perhaps these sites will remain quiescent. If, however, proinflammatory chemicals have leached from the periodontal pocket into the bloodstream, it might heighten local inflammation in the artery, beginning the process of atherosclerosis.

How do the two theories stack up? It is not easy to say from the evidence now in hand, which comes mainly from observing correlations between gum disease and other diseases; either or both of the proposed mechanisms could be responsible. Take the evidence linking periodontal disease with premature birth, which could be caused by the infection reaching the uterus or, alternatively, by the release into the bloodstream of such proinflammatories as prostaglandin E2, a drug used by obstetricians to induce labor. There is also evidence that oral disease destabilizes blood sugar control in diabetic patients, although the mechanism remains unclear. It is known that high blood sugar contributes to gum disease and that all kinds of stress badly impact diabetic control. Periodontal disease may put stress on the body by spreading bacteria, increasing the inflammatory burden, or both.

So, too, many treatments whose success may seem to confirm one theory or



THE IMMUNE SYSTEM INCLUDES, among other components, antimicrobial molecules and various phagocytes (cells that ingest and destroy pathogens). These cells, such as dendritic cells and macrophages, also activate an inflammatory response, secreting proteins called cytokines that trigger an influx of more defensive cells from the blood.

another turn out to be hard to interpret. Aspirin, an anti-inflammatory, is used to reduce the risk of heart attack, but again, no one can say that this proves that inflammation, pure and simple, is the culprit. It could be that aspirin merely limits clotting.

What is needed are large clinical trials in which patients are divided, at random, into two groups: one that gets treatment for periodontal disease, another that gets a placebo. Two such studies are trying to determine whether such treatment alleviates the risk of premature birth in women with gum disease. Another is testing whether antibiotic treatment can alleviate heart disease. Yet, even here, one must beware of the possibility that antibiotics themselves may exert a subtle anti-inflammatory effect. We need interventionist studies to learn whether treating oral disease unmistakably shows a preventative benefit against heart disease. Such trials are needed to justify any public investment in such treatment, and several are now planned and in line for funding.

In the meantime, insurance companies—which are used to basing policies on purely actuarial data—are responding. This year, Aetna Dental announced the results of a study of policyholders that had both dental and health insurance. It showed that treating periodontal disease in heart patients lowered the total cost of treating both conditions. Genco notes that "the insurance companies are driven by economics, and even though the science isn't absolutely there yet, they are taking action."

The smart money, therefore, is betting on healthy gums. To keep them that way, there are no magic bullets, no chemicals that can be added to drinking water, as fluoride was added to stave off tooth cavities. There is no substitute for brushing, flossing and regular dental visits. It should be easier to justify than in the past, for the dentist's or hygienist's ministrations may turn out to protect not only your teeth, but, quite possibly, the rest of you as well.

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