

SCIENTIFIC
AMERICAN
P R E S E N T S

ORAL AND **WHOLE BODY** HEALTH

- Mouth - Body CONNECTIONS
- The Facts and Fictions of INFLAMMATION
- PREGNANCY and PERIODONTAL DISEASE
- Linking DIABETES, OBESITY and INFECTION
- Reflections from a SURGEON GENERAL
- HEALTH POLICY of the Future
- Blurring the DOCTOR-DENTIST Barrier

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SCIENTIFIC AMERICAN PRESENTS

ORAL AND WHOLE BODY HEALTH



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**RESEARCH SNAPSHOT »
A NOVEL APPROACH TO
INFLAMMATION**

Understanding how the body “turns off” inflammation may yield new treatments for periodontal disease and other inflammatory conditions.

**BY THOMAS E. VAN DYKE
& CHARLES N. SERHAN**



**PATH TO PREVENTION »
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Pathogenic bacteria are a way of life. So, too, must be brushing and flossing.

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How the American Dental Association, the world's leading dental organization, views the growing connections between a healthy mouth and a healthy body — a conversation with Daniel M. Meyer.

A Message from the AMERICAN ACADEMY OF PERIODONTOLOGY

THE AMERICAN ACADEMY OF PERIODONTOLOGY (AAP) congratulates Procter & Gamble Professional Oral Health, Scientific American and all of the contributors to this special supplement for providing in-depth and balanced information on the association between periodontal diseases and general health conditions.

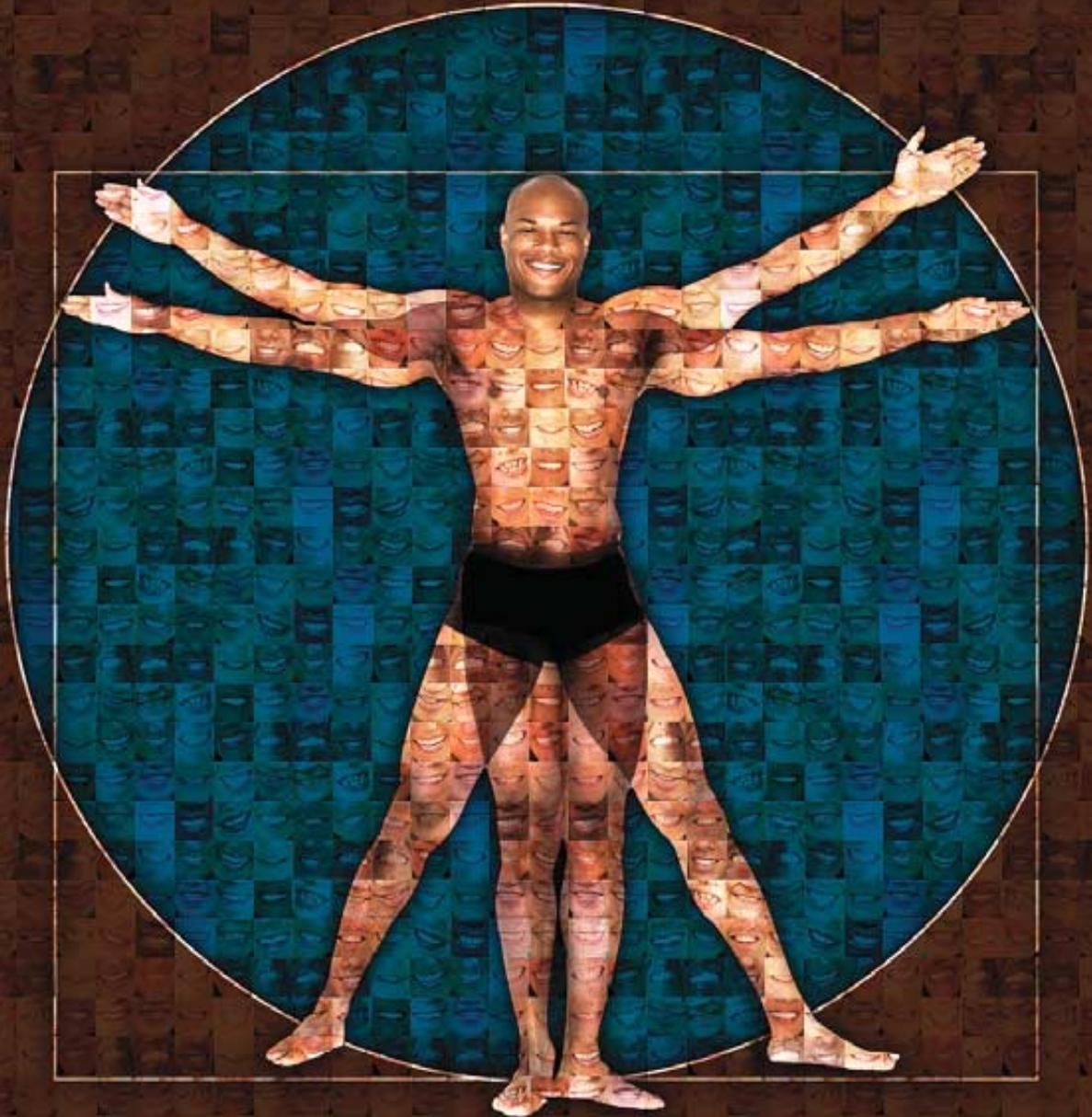
The AAP has been a leader in tracking periodontal and systemic research for over a decade. The research results to date have been promising, and the prospect that periodontal treatment may significantly improve general health outcomes is exciting. However, there is still a great deal to learn about the impact of periodontal infection and inflammation on general health. Additional research into these complex associations is essential if patients are to reap the benefits of improved health.

Given the potential impact on diabetes, pre-term low birthweight, cardiovascular disease and other conditions, we believe this research merits the investment and should be prioritized by the National Institutes of Health and other funding agencies.

The Academy and its member periodontists are proud to collaborate to advance oral and systemic health. Readers are encouraged to visit www.perio.org for more information about periodontists and periodontal health.

— **KENNETH A. KREBS, D.M.D.**
President, American Academy of Periodontology

INTRODUCTION



OUR MOUTHS, OURSELVES

As the interrelationship between the mouth and the rest of the body becomes clearer, dental professionals, doctors and patients will need to rethink the term “oral health”

BY SHARON GUYNUP

SINCE TIME IMMEMORIAL, people have struggled to maintain adequate oral health. As far back as A.D. 250, Kemetic Egyptians used myrrh and other antiseptic herbs to treat infected gums. The Nubians that dwelt in the Nile River valley two centuries later drank beer as a palliative for unhealthy teeth; it may have worked well, as it was brewed from grain contaminated with the same bacteria that produces tetracycline.

Lengthening teeth and receding gums have historically been considered a consequence of surviving into adulthood. (In his 1852 novel *The History of Henry Esmond, Esq.*, William Thackeray used the expression “long in the tooth” to describe a middle-aged person.) The few teeth that didn’t decay in youth usually loosened with the passing years, as the tissues supporting them were eroded by periodontal disease. Those teeth ultimately fell out.

Today, people are living longer, and gum disease has supplanted tooth decay as the most common cause of tooth loss in adults. The disease affects about 80 percent of Americans over age 65, according to the American Dental Association. At the turn of the last millennium, then—U.S. surgeon general David Satcher called periodontal disease the “silent epidemic” in his landmark report, *Oral Health in America*. Given the state of public health, good oral hygiene may prove to be more critical than just preserving your smile. A growing body of research suggests that periodontal disease may play a role in a variety of systemic health problems as wide ranging as diabetes, respiratory illness, pregnancy complications, and heart disease.

It is this body of research—and the attendant health policy implications it engenders—that is the subject of this custom publication from Scientific American, *Oral and Whole Body Health*, produced with the generous support of the Procter & Gamble Company. Here we present, for the benefit of both health professionals and patients, the latest pieces in the ever-growing puzzle of oral disease’s connection to systemic health. You’ll hear from some of the pioneering researchers themselves about their ongoing explorations into the mouth-body relationship.

Like any new area of scientific inquiry, some data paint a very clear picture while other results are still inconclusive. Several studies, for example, have found that blood-sugar levels in diabetics with periodontal disease were significantly reduced when the patients’ gum disease was treated. Others, like the ones examining the connection between periodontal disease and heart conditions, have not yet uncovered a definitive causal relationship. But new information on this

“oral-systemic link” emerges almost daily. For example, in May 2006 it was announced at an American Society for Microbiology meeting that researchers have identified genes in certain oral bacteria that allow the organisms to invade and infect human arterial cells. This certainly expands to the discussion of the possible biologic pathways that might link the mouth and the heart (or other parts of the body). Additionally, this year will see the results of two major studies examining the relationship between oral disease and pregnancy complications in expectant mothers.

So what exactly is the connection between what happens in your mouth and your overall health? Some of the millions of bacteria that lurk in our mouths (numbering more than all the cells in our bodies) are the primary culprits—along with the subsequent inflammation they cause. These microorganisms form complex colonies of sticky plaque. This tenacious plaque — what microbiologists call a “biofilm” — is composed of durable, coral reef–like structures, building up at the gum line and in between teeth.

Some of the approximately 500 species of bacteria in your mouth are not innocuous flora. They cause gingivitis, infecting gums. Your immune system steps in to fight these invaders—gums become inflamed, and may bleed when you brush.

The fields of dentistry and medicine have traditionally been worlds apart. But in light of the growing evidence pointing to links between oral and whole body health, this separation of disciplines is slowly beginning to change.

Interestingly, if this same type of infection appeared on a person’s arm or another body part, they would no doubt go running to the doctor for treatment—but bleeding, tender gums are often ignored.

Untreated, this tenderness progresses into full-blown periodontitis, and here the immune system shows its dark side. This simmering inflammation ulcerates gums and summarily destroys the soft tissue and bone that anchors your teeth. It also sends inflammatory substances throughout the body.

Researchers are discovering that out-of-control inflammation may prove to be the engine that drives an ever-growing list of greatly feared, chronic illnesses from clogged arteries

and heart attacks to arthritis and cancer. This inflammation link is just one of a number of hypotheses explaining how chronic oral infection may trigger or intensify systemic diseases.

Another concern is that the microbial ecosystem in your mouth doesn't just stay there. Stealthy, virulent bacteria overgrow in inflamed gum tissues; with each bite of food or stroke of a toothbrush, some of those microbes can seep into your bloodstream, traveling to distant parts of your body. The question is: can they set up shop elsewhere and cause harm? It is known that some of these bad bugs, when inhaled, can cause pneumonia, particularly in the elderly. Some are also able to move through arteries to the uterus and have been found in the placenta.

CLEARLY THE MOUTH is in many ways the “gateway” to the rest of the body. However, this connection is often overlooked. In the U.S., the fields of dentistry and medicine have traditionally been worlds apart. But in light of the growing evidence pointing to links between oral and whole body health, this separation of disciplines is slowly beginning to break down. The notion that dentists care for only gums and teeth, while doctors look after everything else is being rethought.

There is a dawning realization that often it is a dentist or periodontist who first discovers a larger health problem, because of what they see in a patient's mouth—and that doctors need to look at more than the tonsils when a patient opens wide and says “ah.” For example, diabetics tend to develop periodontal disease at three to four times the rate of nondiabetics. If a dental professional sees gum inflammation in someone who brushes and flosses regularly, they need to ask, “Have you checked your blood sugar lately?” Or, conversely, the doctor of a patient with uncontrolled blood sugar may need to refer them to a dental professional.

There is already a ripple effect in some sectors of the insurance industry. Some insurers are finding it more cost-effective to include periodontal treatment among covered services for diabetics and pregnant women. But if additional research solidifies the links between gum disease and other chronic illnesses, sweeping changes will be needed to provide access to care. This will be crucial for the segments of society—the poor and the elderly—who are most at risk for oral disease as well as conditions such as heart disease and diabetes. It is a huge public health issue: periodontal treatment and prevention can cost between \$100 and \$1,000 annually per patient.

Over the past few years, newspapers, magazines and other national media outlets have hyped numerous stories about the possible systemic health risks of periodontal disease as well as inflammation's general link to a broad range of diseases. Some articles have greatly exaggerated or oversimplified the connection, enough so that the expression “floss or die” has become a standing joke among researchers.

Even some opportunistic law firms have jumped on the bandwagon. One in Arizona solicits potential malpractice cas-



BUGS WITH STAYING POWER:

Once thought to be a mere congregation of pathogens, dental plaque is now known to be a dynamic – and tenacious – microbiological community called a biofilm.

es on their Web site, warning: “if you or someone you know had periodontal disease, diagnosed or undiagnosed, and either ignored or treated unsuccessfully, before or during the same time as any of the mentioned systemic diseases, you may be eligible for damages caused by these systemic diseases.” Although an extreme example, it embodies the confusion and hype surrounding this topic and underscores the need for objective, credible analysis. And it ignores the fact that oral disease is complex.

For example, changing hormone levels can cause flare-ups in women during pregnancy and while premenstrual—or in those taking oral contraceptives. Other medications can also make gums more susceptible to infection, including antihistamines, antidepressants, cancer drugs, steroids, and especially those that cause “dry mouth,” disrupting the mouth's bacterial ecosystem. Genetic, microbial, immunological and environmental factors influence both the risk and progression of infection. For example, the American Academy of Periodontology says that perhaps one third of Americans may be genetically susceptible—making them up to six times more likely to develop periodontal disease. It could be that in some cases these same factors or susceptibility might independently cause harm elsewhere in the body, creating a mere illusion of oral-systemic causality.

Of course, one of the most important differences between periodontal disease and other systemic conditions is that the former has a known cause and is quite treatable. Dental professionals should never lose sight of the fact that they are addressing a disease that significantly contributes to disability and a lack of well-being in the population. This fact alone makes it important to treat this condition, regardless of whether it might contribute to other serious illnesses. And although no one should overstate the oral-systemic link, proffers Robert Genco, a professor of oral medicine and microbiology at the University at Buffalo, no one should underestimate what can happen if it's ignored, either. While the mouth's relationship to the rest of the body will certainly be a matter of public health, of patient awareness and of the changing roles among caregivers, it will first and foremost be a matter of science. ●

SHARON GUYNUP is editorial director of *Oral and Whole Body Health*.



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

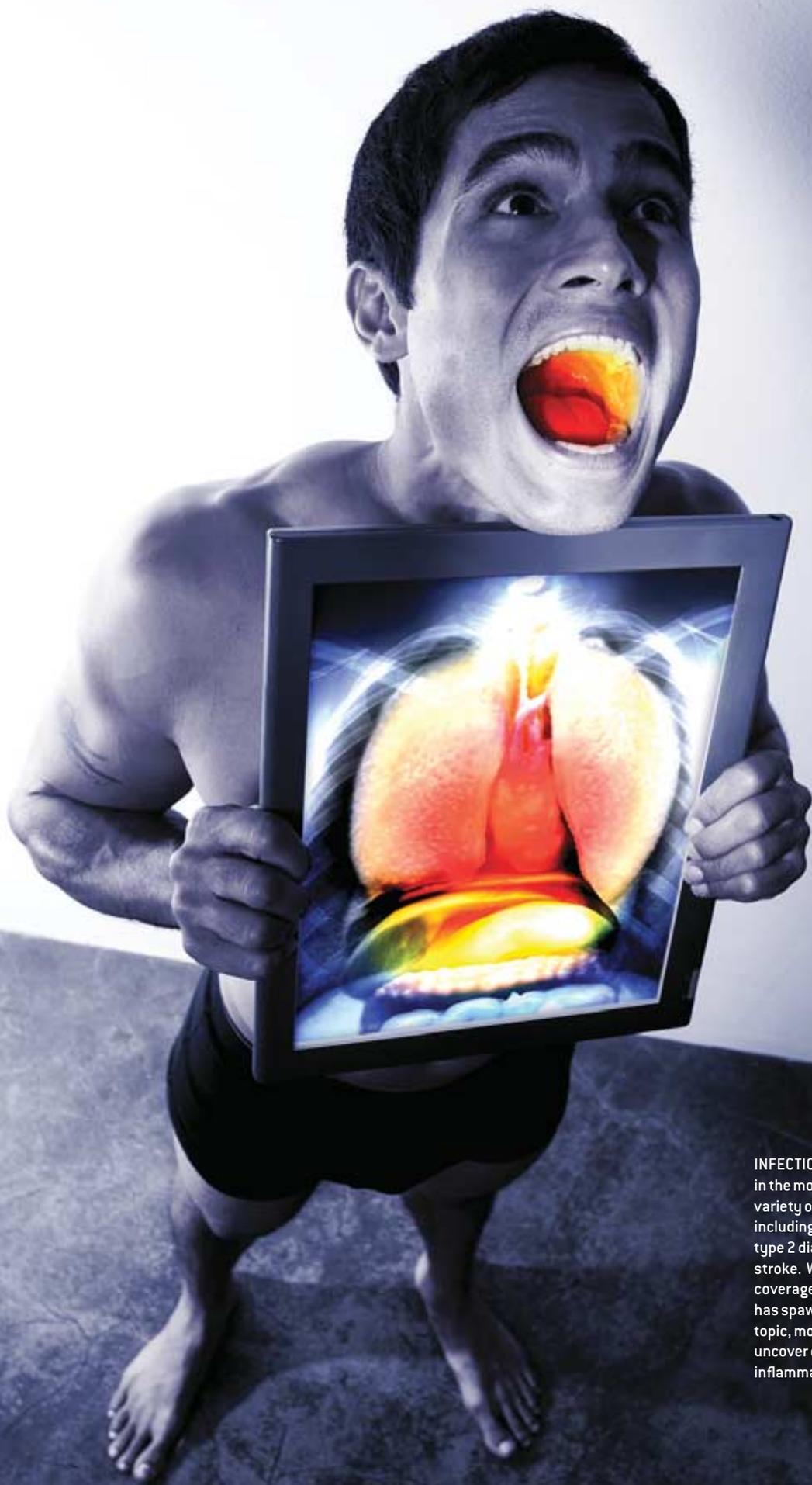
this spring, when such an antibody nearly killed several subjects in a British clinical trial, even these drugs can cause serious side effects. No one should have been too surprised; the natural immune response also causes damage, which is why it fully mobilizes—in a process called inflammation—only 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 system-

ic 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.”

Only a handful of the more than 500 species of bacteria that live in the mouth are





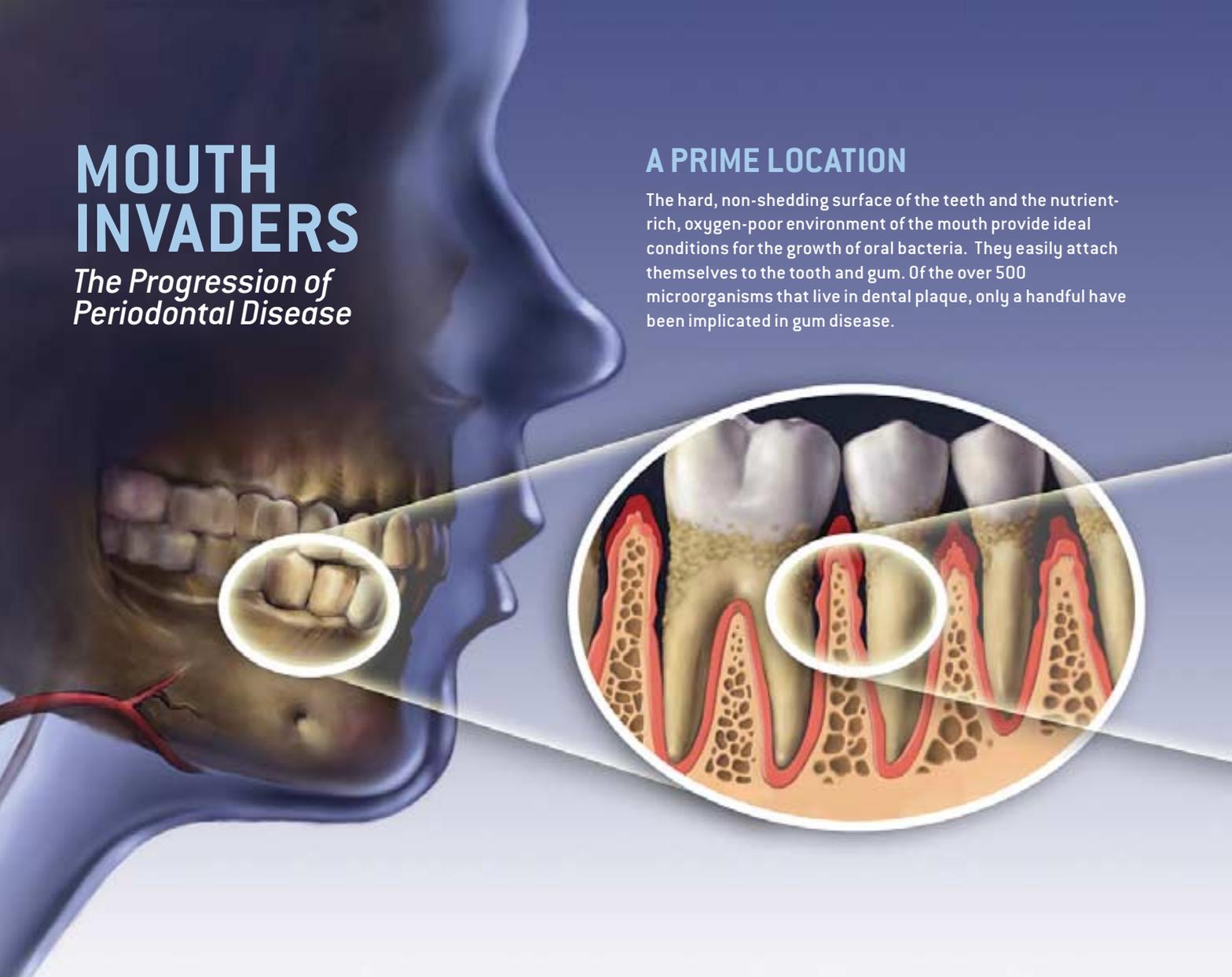
INFECTION AND INFLAMMATION in the mouth have been linked to a variety of systemic conditions, including pregnancy complications, type 2 diabetes, heart disease and stroke. While recent national media coverage spotlighting inflammation has spawned much interest in the topic, more research is needed to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

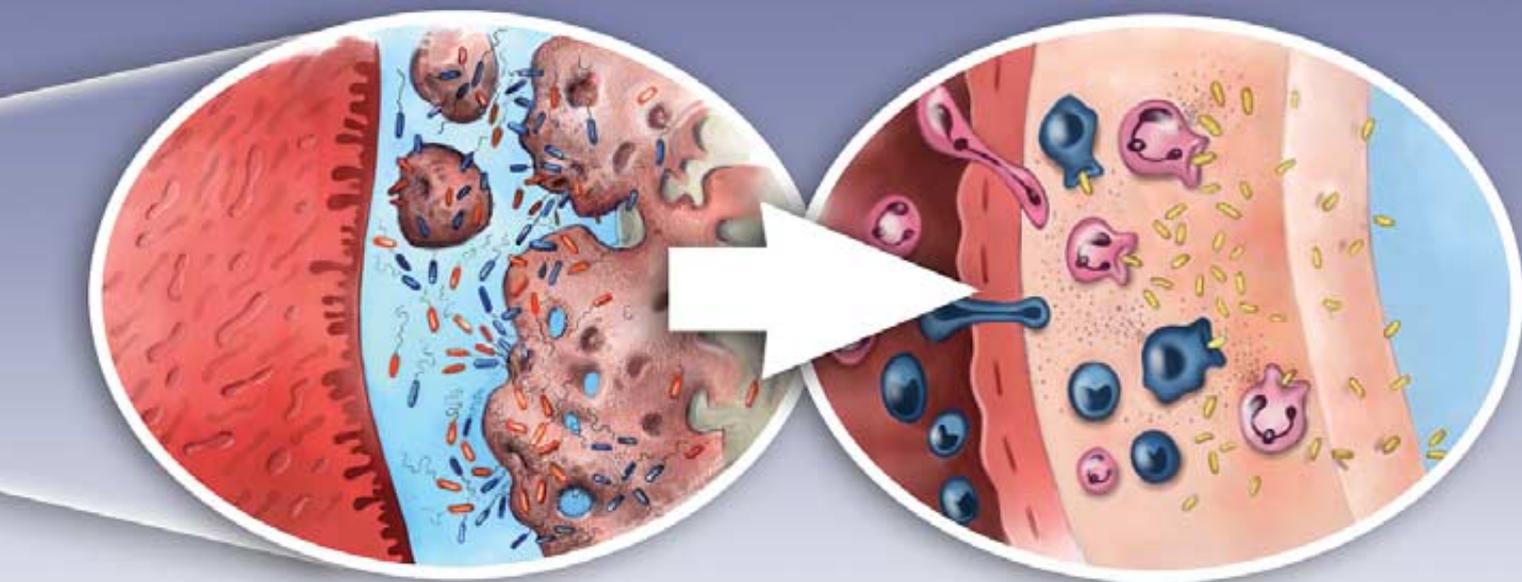
the ligaments that anchor teeth in their sockets, loosening them until they at last fall out. Nowadays this happens less frequently; the patient notices the bleeding and goes to a dentist. The dentist or dental hygienist scrapes away inflammation-riddled material and treats the infection with antibiotics. 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.



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 en-

tomb 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 *Porphyromonas gingivalis*, a main culprit in periodontal disease, under the skin of rodents and found that it

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 ex-

sidered 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

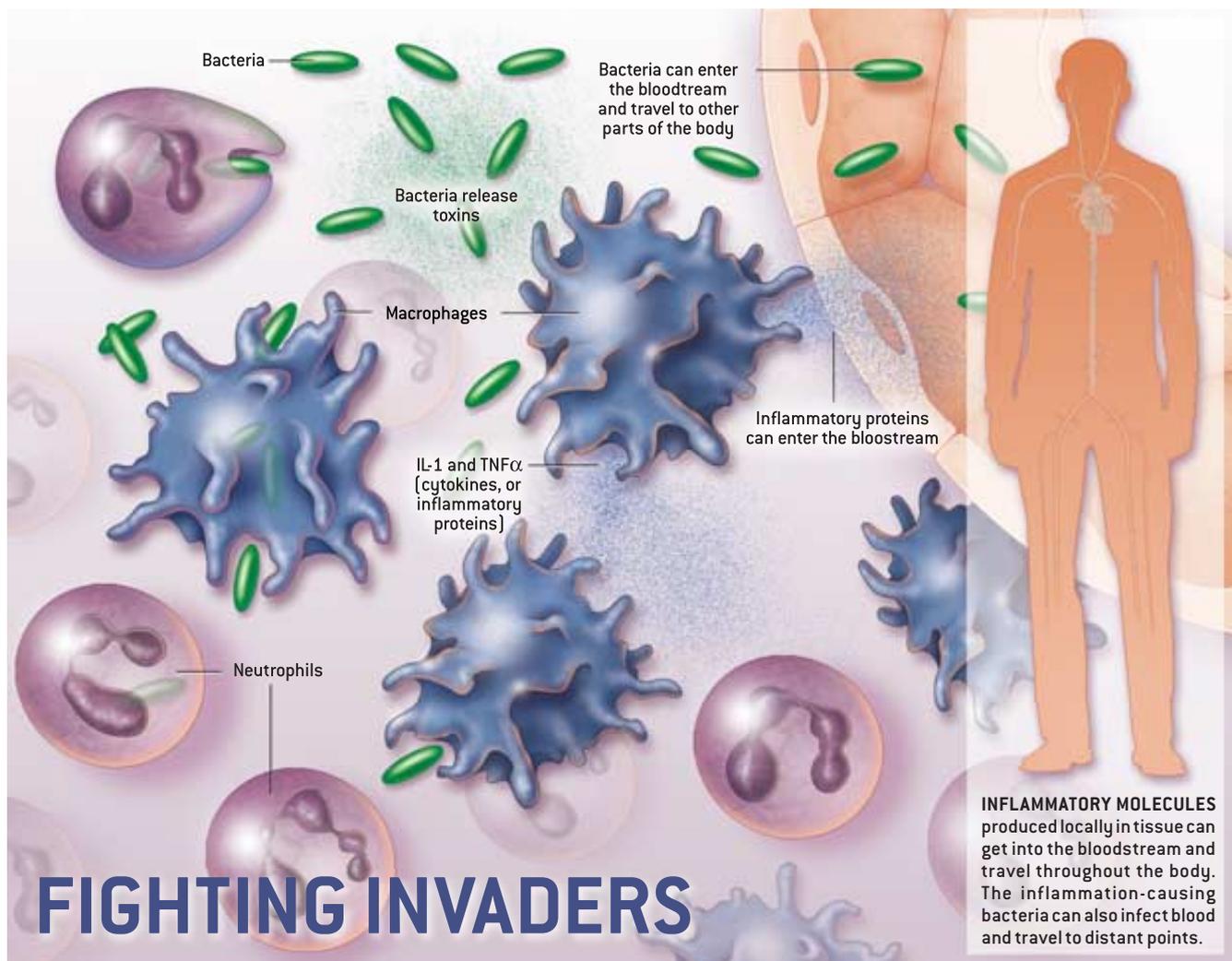
If infection in the gums not only precedes inflammation in the arteries, but encourages it, the question is how does it happen?

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

pect 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.

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 con-



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. ●

PHILIP E. ROSS, a former *SCIENTIFIC AMERICAN* contributing editor, is currently the online editor of *IEEE Spectrum*, the magazine of the Institute of Electrical and Electronic Engineers. He has written for *Forbes* and *Red Herring*.

TAMITOLFA

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**

HeartHealth

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.

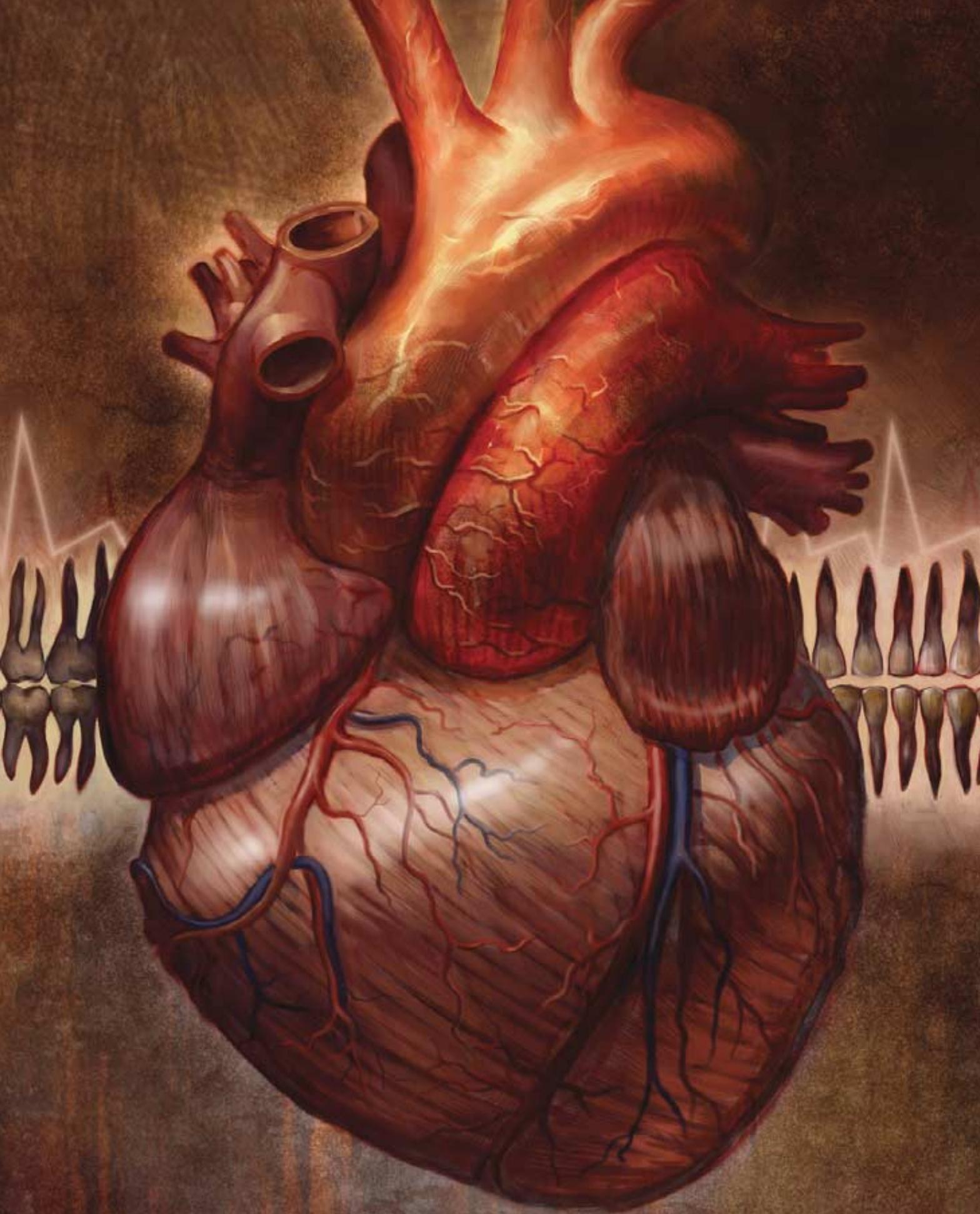
Such research has established inflammation's key role in atherosclerosis. This process—the same one that causes infected cuts to become swollen, hot and painful—underlies everything from the creation of plaques to their growth and rupture.

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.

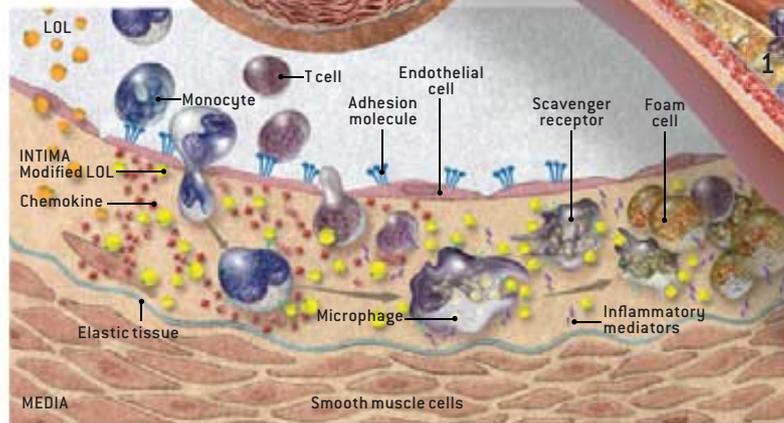
IGNITING TROUBLE

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. >>



CROSS-SECTION OF HEALTHY CORONARY ARTERY

Blood channel
Intima
Media
Adventitia



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.

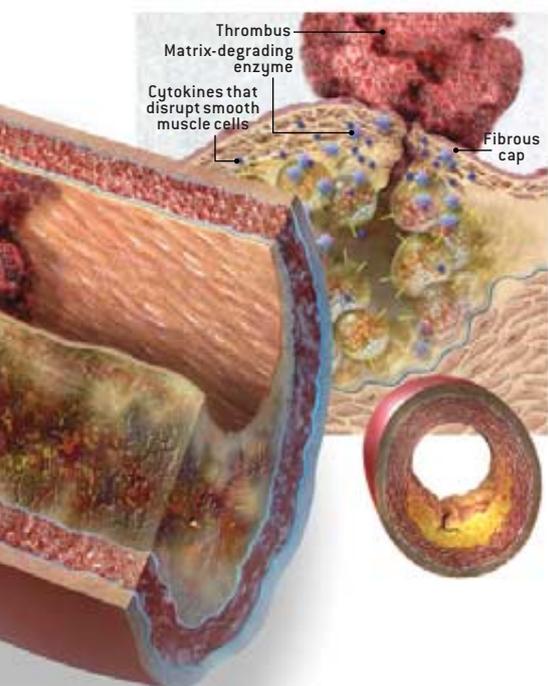
Stimulated by chemokines and other substances, the monocytes multiply and

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-

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 ves-

sel 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.

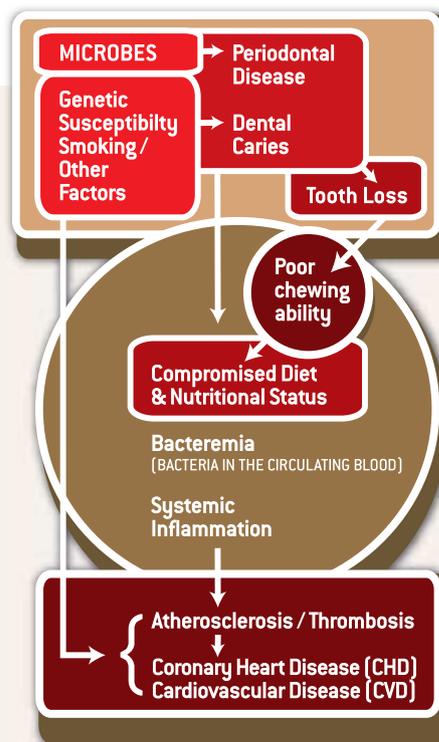
Other evidence comes from observational human studies. The largest such study, the National Health and Nutrition Examination Survey (NHANES), involved 10,000 Americans between the ages of 18 and 74. It found that people with periodontal disease were much more likely to be diagnosed with heart disease 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. ●



KAUMUDI JOSHIPURA is director of the Division of Dental Public Health at the University of Puerto Rico and also teaches at Harvard University.

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, inflamma-

tion’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. ●

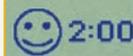
PETER LIBBY, who earned his M.D. from the University of California, San Diego, is chief of cardiovascular medicine at Brigham and Women’s Hospital, Mallinkrodt Professor of Medicine at Harvard Medical School, and co-editor of *Heart Disease*, a classic cardiology textbook (W.B. Saunders, 2001).

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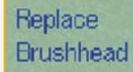
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the three-way street



Two decades of biomedical and dental detective work
have linked obesity, diabetes and periodontal disease

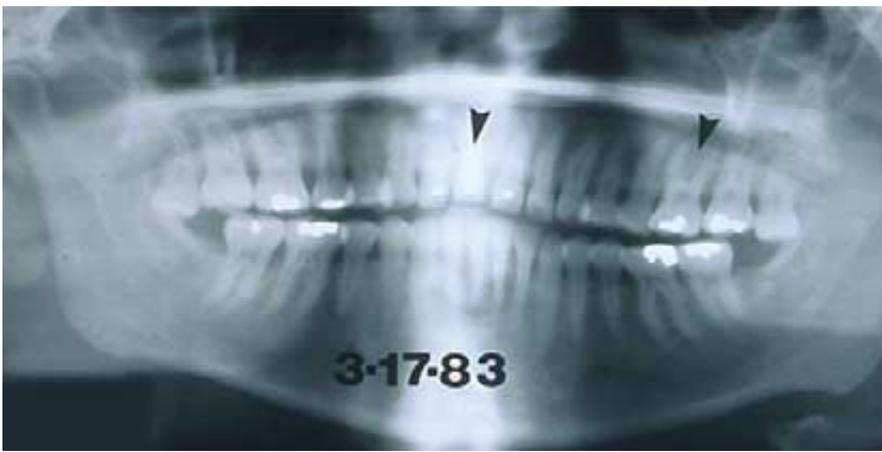
BY **ROBERT J. GENCO**

1 IN THE EARLY 1960S,
researchers from the National Institutes of Health (NIH) journeyed to the parched desert
lands of the Gila River Indian Community in central Arizona to study the health of the Pima

Indians. In the course of routine medical exams, they made a startling discovery: the Pima people proved to be fatter than any other group of people on Earth except for the Pacific Nauru islanders. Nearly half of those over the age of 35 had type 2, or adult-onset diabetes, eight times the national average. In order to survive in the desert, it seems that their thrifty genes may have evolved to carefully conserve fat through times of drought and famine. After World War II, when the tribe changed their traditional diet to an American one, their fat intake rose from about 15 percent to a whopping 40 percent of calories—and their genetic evolution backfired. >>



HISTORY INTERRUPTED:
When Arizona's Pima Indians adopted a fatty American diet, their thrifty desert genes backfired. Almost half of adults over 35 developed type 2 diabetes—and also contracted severe gum disease at twice the normal incidence.



IN 1983, H. was healthy. Three years later, she suffered from out-of-control type 2 diabetes and severe gum disease, with abscesses ulcerating her gums and loose, shifted teeth.

As the NIH studies continued over the following decades, the researchers delved into other health issues including kidney problems and heart disease. They also suspected that there might be a higher than normal incidence of gum disease. In 1981 the Dental Institute asked me to assess the periodontal health of the Pimas. At that time, I was in the midst of clinical studies at the University at Buffalo Periodontal Disease Research Center examining the body's response to bacterial infection in the mouth—so I welcomed the opportunity to examine a very different population. I spent three days at the Gila River reservation conducting several dozen clinical exams. Never before had I seen such severe, untreated periodontal disease.

In 1982 we established our first dental clinic in a trailer on the reservation, run by Dr. Marc Shlossman, and initiated a study to track the Pimas' oral health. Since then, we have examined 3,600 people, giving checkups every two years. (Regular dental care was provided by the reservation's dental

clinics.) Diabetics fared the worst, with twice the normal incidence of gum disease—and much more severe oral infection than nondiabetic patients.

In 1983 we examined H, a 32 year-old woman who was extremely overweight, but otherwise quite healthy. In her follow-up exam two years later we were shocked to discover that her health had deteriorated precipitously: she suffered from uncontrolled type 2 diabetes and had developed advanced gum disease. Abscesses ulcerated her gums, and her teeth were loose and had shifted out of position, leaving large gaps between her front teeth. Under normal circumstances, the progression of this condition would have taken 15 to 20 years to reach that level of infection.

Her case sparked a question that we couldn't answer. Could there possibly be a connection between obesity, diabetes and oral infection? It took 21 years of medical and dental detective work, piecing together data from many sources, to understand this triangular relationship. We gathered the results of type

2 diabetes research from our studies both on the Pimas and on the population of Erie County in New York State, along with research from around the globe—Japan, Brazil, Chile, Finland, Slovenia and other nations. In nearly all of the studies, it was found that diabetics suffered from more severe periodontal disease that often appeared years or even decades before it did in the general population—and once a diabetic patient had periodontal disease, their sugar control worsened and they suffered further complications, including nerve damage and kidney disease.

We combined the results of these studies and formulated a hypothesis that we and others could begin testing. This informational mosaic has given us a reasonable understanding of how obesity and diabetes are linked to infections such as periodontal disease. It also revealed a potential explanation of why diabetes is a significant risk factor for oral infection and inflammation—and why it often leads to periodontal disease at a much earlier age than normal. Patients with type 2 diabetes are twice as prone to periodontal disease as nondiabetics, all other factors being equal.

An important piece of this puzzle emerged 10 years ago during the Erie County study, conducted in metropolitan Buffalo, N.Y. We discovered that obesity and periodontal disease were related. We collected information on both the general and oral health of 1,250 adults. After statistical adjustment for other periodontal risk factors including age, gender, socioeconomic status, smoking, diabetes and dental plaque, the relationship remained strong: obesity appears to be an independent risk for periodontal disease. Investigations by Nabil Bissada and his colleagues at Case Western University in Cleveland and by Toshiyuki Saito of Kyushu University in Fukuoka, Japan, mirrored our findings.

Another important clue surfaced in the mid-1990s that helped to explain the role obesity plays in infection. We learned that fat tissue is not only a repository for fat cells but is increasingly viewed as a



the DIABETIC in the DENTAL CHAIR

BY BRIAN L. MEALEY

metabolically active endocrine organ. Scientists at the Dana Farber Institute in Boston found that fat tissue in the “obese mouse,” a species bred to be fat and diabetic, produced a protein called tumor necrosis factor (TNF). Fat cells produce and secrete several proteins—like TNF—that act in a hormonelike fashion, regulating the intake and expenditure of energy. These proteins, called proinflammatory cytokines, are powerful substances that mediate and regulate the body’s inflammatory process. The obese mice carried toxic concentrations of cytokines—immune response molecules—in their blood.

Human fat cells pump out tumor necrosis factor alpha (TNF α), which kills tumors and triggers production of other proinflammatory cytokines. But it also has a dark side: it can cause insulin resistance and high blood sugar levels (common diabetic symptoms) and break down bone as well as activate endothelial cells that line blood vessels, which can lead to heart disease and stroke. Interleukin-6 (IL-6), an immune protein, is another product of human fat cells. Like TNF α , it dissolves bones and causes inflammation—and prompts the liver to secrete C-reactive protein, whose presence signals high risk for heart attack. These are just two of the dozen or more cytokines produced by human fat tissue.

This relentless release of cytokines into the bloodstream provides a possible explanation of how obesity intensifies infections, including periodontal disease. The diverse colonies of bacteria that flourish in the mouth spark the inflammatory response that is so destructive to gum tissue. The infection intensifies as gum tissue produces its own cytokines. At the same time, fat tissue churns out cytokines that travel throughout the body. This cytokine overload heightens the overall inflammatory response, causing great tissue damage. Infected gums become chronically inflamed, the bone around the teeth dissolves, and the teeth loosen and eventually fall out.

CURRENTLY, 20.8 MILLION Americans have diabetes, according to the American Diabetes Association. About one third of those with the disease are unaware that they have it, and of those who have been diagnosed, only a little more than half have it under control.

Diabetes is a disease where the body does not produce or properly use insulin, a hormone made in the pancreas. Insulin “unlocks” cells, allowing sugars derived from carbohydrates and other food to enter. Sugar is the basic fuel for cells, providing energy for daily life.

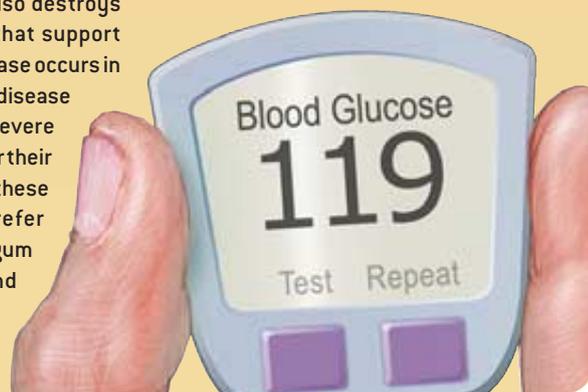
There are two types of diabetes: In type 1 diabetes, the pancreas no longer makes insulin. Sugar cannot enter the cells and builds up in the bloodstream. In type 2, the pancreas does not produce enough insulin, or the hormone does not function properly at the cellular level, a condition called insulin resistance. In this case, too, sugar is locked out of the cells, so it builds up in the blood. In both types of diabetes, cells may be starved for energy. Over time, high blood sugar can damage vision, even causing blindness. It can also trigger kidney failure, nerve damage and heart disease, and in people with diabetes wounds heal poorly.

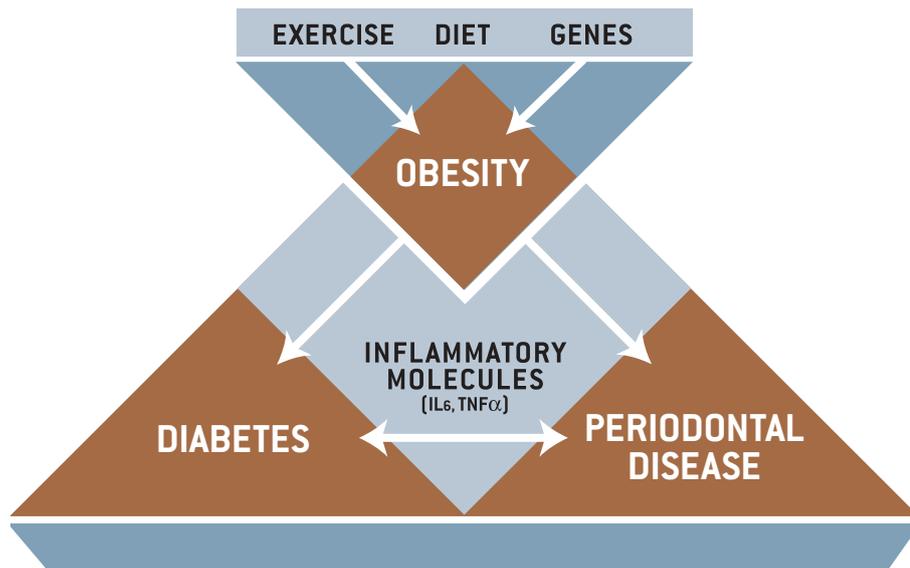
Diabetes also increases the risk for periodontal disease, an infectious process that inflames gum tissues, causing them to bleed; it also destroys the bone and soft tissues that support teeth. While periodontal disease occurs in nondiabetic people, too, gum disease is more common and more severe in diabetics. Dentists monitor their diabetic patients closely for these oral conditions and may refer patients to a periodontist (gum specialist) to diagnose and treat periodontal disease.

New research suggests that periodontal disease can also affect a diabetic patient’s ability to control his or her blood sugar levels, and can contribute to diabetic complications such as heart and kidney disease. Inflammatory diseases of many kinds—including those that affect the mouth—can increase insulin resistance. In people with type 2, increased resistance caused by gum disease can make blood sugar harder to control. However, periodontal treatment reduces the level of inflammation in the tissues around the teeth, thereby improving blood sugar control in many diabetics.

Thus, care of patients with diabetes poses a particular challenge to dental professionals. Diabetes often worsens oral health, particularly that of the gum tissues and bone, which, in turn, deteriorates blood sugar control. The patient and dental professional must work together to stop this vicious cycle before it begins by being attentive to daily oral hygiene: brushing and flossing, getting regular oral health checkups, and properly treating periodontal disease early on. •

BRIAN L. MEALEY is director of the Periodontics Postgraduate Program at the University of Texas Health Science Center at San Antonio





TRIANGULAR RELATIONSHIP: Obesity can intensify infections, such as periodontal disease; cytokines produced by fat cells are known to trigger insulin resistance, which can lead to type 2 diabetes. Diabetes, in turn, is known to increase the risk for periodontal disease. New research suggests that periodontal disease can affect a diabetic patient's ability to control blood sugar levels.

To test this hypothesis, we examined blood test results from the Erie County study subjects. All those who suffered from periodontal disease had elevated levels of soluble receptors for TNF α in their blood, but levels were highest in seriously overweight patients. Over the last decade, a large body of research from laboratories and clinics in many countries has highlighted the role of TNF α and other cytokines in damaging tissue—and in predisposing an individual to diabetes. TNF α triggers certain cells to produce tissue- or bone-dissolving enzymes. Other cytokines induce inflammation by increasing the amount of blood leaked from vessels and by stimulating the release of toxic substances (such as reactive oxygen species) from inflammatory cells in the region, damaging tissue. Another kind summons phagocytic cells to the site of the infection that then envelop and “devour” perceived invaders. At later stages of inflammation, antibodies (proteins that target and destroy specific bacteria and viruses) form. Although they are usually protective, they can also turn against cells, as in autoimmune disorders.

But proinflammatory cytokines manufactured by fat cells don't only ex-

acerbate more dangerous, tenacious oral infections, their presence also helps explain why obesity is such a serious risk factor for diabetes and cardiovascular disease: TNF α and other cytokines are known to trigger insulin resistance. This can ultimately lead to full-blown type 2 diabetes, which spikes blood sugar levels and elevates fats in the blood. This condition contributes to complications of diabetes, including heart, kidney and retinal disease, along with susceptibility to infection, and other complications.

It seems that inflammation creates a triangular interaction between obesity, diabetes and periodontal disease: Obesity is a risk factor for both type 2 diabetes and periodontal infection, and diabetes also heightens risk for gum disease. Inflammation links all three, triggered by the proinflammatory cytokines manufactured by fat tissue and produced locally by gum infection.

But fat tissue is complex, and further studies will likely illuminate the role of other substances secreted by these cells.

One of these, adiponectin, regulates insulin response and inhibits inflammation inside blood vessels. We need greater understanding of this and other regulatory chemicals manufactured both in fat tissue and in other parts of the body that could mitigate the chronic inflammation and insulin resistance sparked by cytokines.

We believe that the triangular interaction among obesity, type 2 diabetes and periodontal disease is mediated by the cytokines produced by both fat tissue throughout the body and by infected gums. More research is needed to evaluate other influences, like the impact of diet and the importance of genetics on inflammation and susceptibility to the aforementioned conditions. A more complete understanding should help physicians and dental professionals employ treatments or preventive measures to reduce the onset of diabetes and its potentially life-threatening complications such as heart and kidney disease.

Addressing obesity in the management of diabetes or periodontal disease is clearly important—as is tandem treatment in patients who have both conditions. Studies show that periodontal treatment leads to improved blood sugar control. Because periodontal disease in diabetics leads to a higher rate of complications, such as cardiovascular disease and diabetic kidney disease, we strongly suggest aggressive treatment and prevention of periodontal disease in patients with diabetes as part of the overall management of not only their oral health, but their diabetic state.

Current treatments for periodontal disease are effective. If maintained, recurrence can be, by and large, prevented—and of all the ways to mitigate diabetes risk in the first place, good oral hygiene is much easier to maintain than strict diet or exercise regimens. ●

ROBERT J. GENCO has studied periodontology and its relation to wider health conditions for over 30 years. He attended the University at Buffalo School of Dentistry and earned a Ph.D. in immunology from the University of Pennsylvania. He is currently a distinguished professor at the University at Buffalo and vice provost and director of the University's Office of Science, Technology Transfer and Economic Outreach.

SCIENTIFIC AMERICAN: Most of the buzz about the oral-systemic link has been among researchers. What should consumers or patients know about this topic at this stage?

JEFFCOAT: The consumer needs to know three things: First, oral disease is a disease like any other—and in and of itself is deserving of treatment. Number two, everything in the body is connected. Having a chronic infection is a serious problem that you should not ignore. It can indeed make you systemically sick. Three, patients should not think that treating periodontal disease will guarantee them lifetime health, but it is one step they can take to be healthier overall.

Consumers have to understand that all the data is not yet in. We cannot definitively say if



BUZZ TALK with MARJORIE K. JEFFCOAT

**THE DEAN OF THE UNIVERSITY OF PENNSYLVANIA SCHOOL OF DENTAL MEDICINE
—A PIONEERING DENTAL RESEARCHER HERSELF—ADDRESSES THE FACTS AND
FICTIONS ABOUT ORAL HEALTH'S RELATIONSHIP TO THE REST OF THE BODY**

treatment will affect one's susceptibility to other diseases—heart disease, stroke, diabetes, etc. We do know that it is one risk factor for preterm birth. But people act on these correlations because they want to feel they have control of their health. Professionals do, too. They want to provide every possible treatment avenue for the patient.

As a prominent researcher you must have a lot of people asking you about this topic? All the time. I don't know how many phone calls I took today—from patients, from doctors, from drug companies, from the media. They want to know the real scoop: what we really know at this time.

Has this issue spawned more collaboration between the fields of dentistry and medicine? Yes. And I have found that collaboration between the two fields comes quite easily. It is very important that both disciplines take ownership of these issues so that patients can get

the best information possible. We're already starting to see changes in reimbursement for some of these things. Insurance companies are taking notice. Cigna and others now cover periodontal treatment during pregnancy. It's a business decision; they feel it will help save money in the long run.

Do you hear a lot of misinformation? I do. Some people want information because they've heard a little bit about this topic—and some will believe anything they read on the Internet. Some media outlets do not provide the whole story or all of its complexities.

How is this topic – the mouth's relationship to the rest of the body – affecting dental education? I think more [dental] schools are integrating total health into their curriculum. Dental education can be a controversial topic, and I think some schools will probably not adopt this whole-body approach for some time. But I do feel that

eventually all curriculums will address this issue is some way or another.

So the patients, in your opinion, that would benefit most from this data would be expectant mothers? Right now, yes—pregnant women and diabetics. Although we have smaller studies on diabetics than we do on expectant mothers, we do know that any untreated infection in a diabetic can affect glucose control. So treating oral infection and oral inflammation is a reasonable thing to do until all the studies have finished.

What about the elderly and some of the data linking oral disease with respiratory problems in patients who are in intensive care units or hospitals? Getting care to these populations is still the biggest challenge. Often in a nursing home there are extra costs for dental care. Family members who monitor their elders' care should be made aware of the importance of good oral care. For many, it will help to reduce the risk of getting pneumonia.

Are consumers becoming more skeptical of health messages they see or read about in the media? We have two highly distinct populations: the "worried well"—those who are always looking for ways to improve their health, and those who are skeptical of everything they see or read—this population is very hard to deal with in terms of getting messages across. ●

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WHAT EVERY WOMAN NEEDS TO KNOW

Growing evidence suggests that poor oral hygiene during pregnancy can adversely affect the health of newborns

BY STEVEN OFFENBACHER

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In 1981 Judith F. was referred to me

for periodontal care. She was very upset, having just discovered why her front teeth were shifting: she had been diagnosed with severe gum disease. Her dentist had explained to her that periodontal disease is sometimes a “silent” infection that may be painless and without symptoms until very late in the disease process. She had also recently miscarried after having a very difficult time conceiving. She recounted how her gums had flared up after she became pregnant, which prompted her to go to the dentist. As crazy as it might have sounded at the time, she was convinced that the simmering infection in her gums was somehow related to her pregnancy complications.

I suspected that her intuition may have been correct—but told her that we really did not know scientifically whether periodontal disease could cause pregnancy problems. However, I did tell her that both her obstetrician and I were in agreement that any infection during pregnancy is a potential cause for concern.

Just before Judith came to me, my laboratory had begun what would become a 25-year scientific inquiry exploring the potential role of periodontal disease in pregnancy complications. This research has included a multitude of laboratory experiments, animal studies, and randomized human clinical trials.

Today, growing evidence supports the concept that gum infection may indeed play a role in pregnancy complications, possibly inducing miscarriage and premature birth as well as inhibiting the growth and development of the unborn child. Clearly, there are many causes for problems that can arise during pregnancy; but it now appears that with additional research, oral infection might be added to the list of possible risk factors. From a public health perspective, what is most important is that periodontal disease is both preventable and treatable. As a clinician who is trying to help patients, I know that it is critical to identify new causes of disease—and to find ways to prevent them.

In one of our earliest experiments at Emory University in 1981, we gave hamsters intravenous doses of the toxins gen-

erated by oral bacteria. The result: at low doses, about 15 percent miscarried and 30 percent of the surviving offspring were abnormally small. When given high doses, 100 percent of the mothers miscarried. We later induced gum disease in pregnant hamsters. Overall, the resulting babies weighed 18 percent less than normal. We also found elevated levels of prostaglandin-E₂ (PGE₂) in the hamsters’ placentas—similar to the human physiological response to preterm delivery and low-weight births. This chemical is produced as a response to infection; it mediates inflammation in both the placenta and the fetus—and also can induce labor. Around that time, obstetrics research had linked PGE₂ to premature and low-weight SGA (small for gestational age) births.

In a landmark paper published in 2002, Nestor Lopez in Chile reported the results of his study of 400 pregnant women with periodontal disease: half had scaling and root planing periodontal treatment during pregnancy; the other half were treated after their babies were born. Just 1.8 percent of the treated women gave birth early, compared with 10.1 percent in the delayed treatment group.

Marjorie Jeffcoat at the University of Alabama also saw similar benefits in a study of 123 mothers with periodontal disease. After treatment, their rate of preterm delivery (earlier than 37 weeks) was 4.1 percent, compared with 13.7 percent in another group of 733

mothers with untreated periodontal disease who were also being tracked.

These findings provided the rationale for the National Institute of Dental and Craniofacial Research to support two multicentered, randomized clinical trials. One of these, the Obstetrics and Periodontal Therapy (OPT) Study at the University of Minnesota, led by Bryan Michalowicz, tracked the pregnancies of more than 800 pregnant women following gum disease treatment. The second trial, run by our group at the University of North Carolina at Chapel Hill, is entitled MOTOR (Maternal Oral Therapy to Reduce Obstetric Risk) and will ultimately follow 1,800 women. The findings from these large, randomized and controlled trials should ultimately prove whether or not gum disease can cause pregnancy complications. Earlier estimates from pilot studies suggest that up to 18 percent of all preterm births may be attributable to gum disease.

Unfortunately, pregnancy complications are far too common, with about one in 10 babies being born too early in the U.S.—nearly double the rate of other industrialized countries. Improvements in prenatal care and neonatal intensive care medicine have improved the survival rates of these babies, but the rate of premature delivery has steadily climbed since the 1950s. The failure to prevent preterm deliveries is due in part to the fact that we do not understand all of the risk factors, which include race, smoking, alcohol and drug

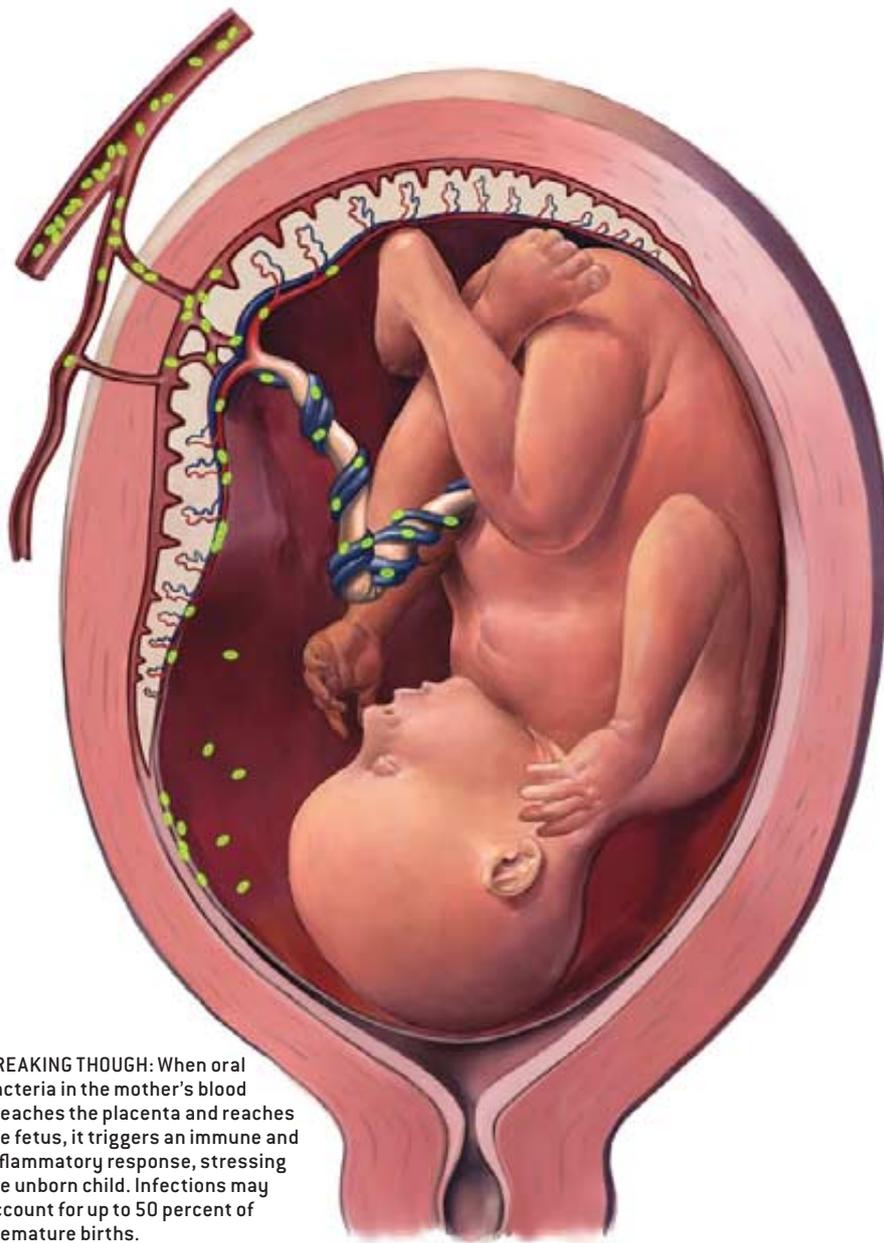
use, low income, and poor education, among others. More than one quarter of all complicated pregnancies occur for no known reason.

Periodontal disease may contribute to the common problems of pregnancy by presenting an infectious, inflammatory challenge to the fetus: when bacteria or their products slip through the placenta and reach the baby, they trigger an immune and inflammatory response—which stresses the fetus. Since pregnancy is such a critical time for human development, this could potentially have debilitating effects on an infant’s health, creating problems that could last a lifetime.

Infections are thought to account for between 30 and 50 percent of all premature deliveries. Maternal infections during pregnancy, especially when they spark a fever, have long been known to cause miscarriage, premature birth and babies that are born abnormally small for their gestational age. This is attributed to the fact that bacteria or viruses in the bloodstream trigger the production of infection-fighting chemicals that threaten the “mother-child unit” and impair fetal growth and development. The chemicals and hormones that mediate the inflammatory response can also dilate the cervix and trigger uterine contractions, leading to preterm labor.

But it’s not just infection and bacterial products that pose a threat—inflammation does, too. Inside the placenta, membranes normally remain intact, holding the fetus suspended in amniotic fluid until just hours before delivery when the water “breaks” to start labor. However, inflammation can make these membranes more fragile; their early rupture often initiates preterm labor.

When the placenta becomes inflamed, structural changes occur that can endanger the fetus and shorten gestation. Studies in mice have shown that placental inflammation causes edema and kills off tissue. It also can cause changes to the intertwined fetal/maternal blood vessels that resemble athero-



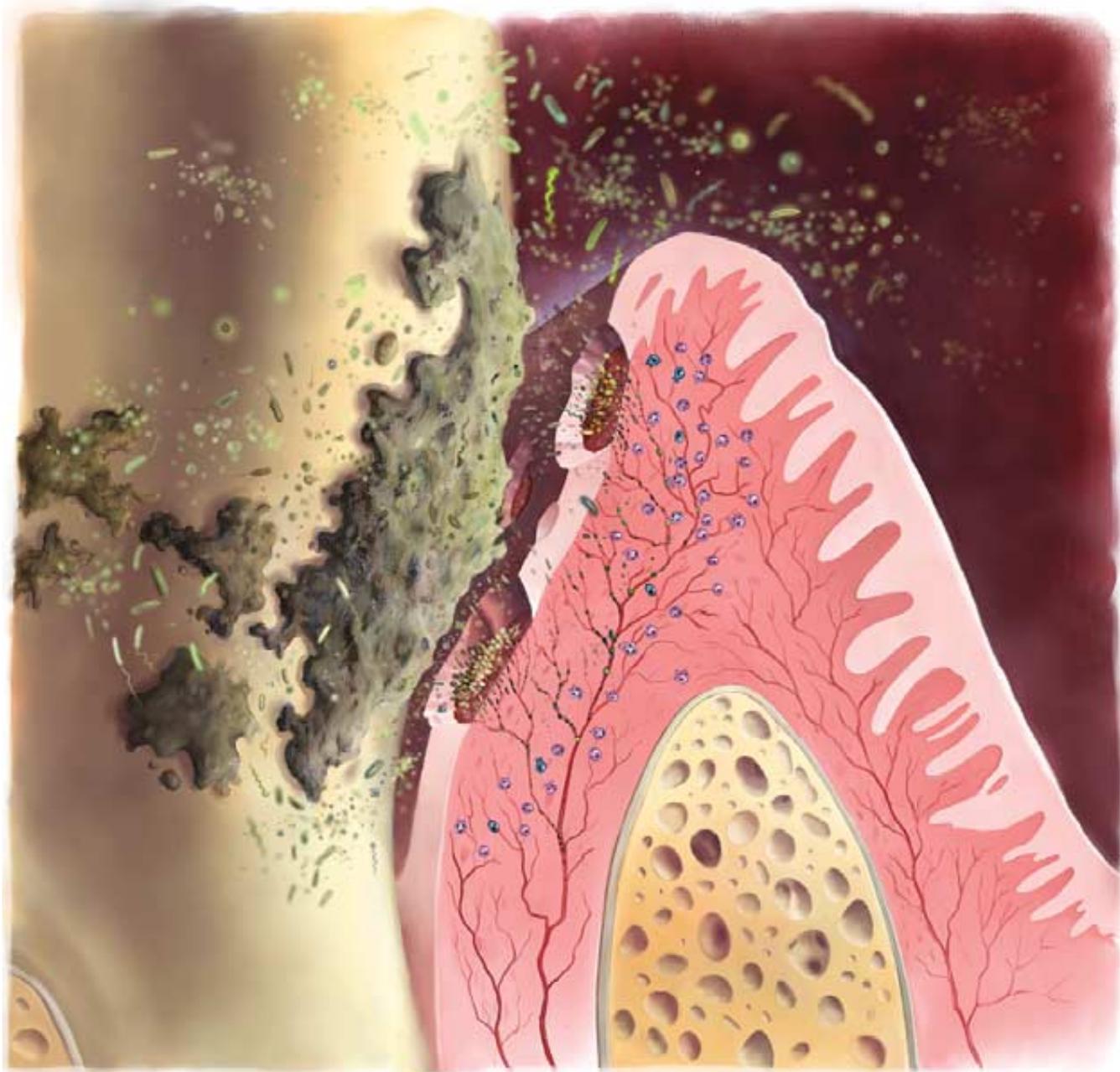
BREAKING THOUGH: When oral bacteria in the mother’s blood breaches the placenta and reaches the fetus, it triggers an immune and inflammatory response, stressing the unborn child. Infections may account for up to 50 percent of premature births.

sclerotic damage to heart arteries: the vessels shrink and do not function properly, compromising the flow of blood and nutrients to the fetus, and impairing growth. Abnormal blood flow in the placenta can also result in an imbalance in the mother’s blood pressure, causing preeclampsia, a mild kidney malfunction that can lead to life-threatening convulsions. This condition can only be cured by delivering the baby.

It now seems that oral infection may be one of a number of factors that can produce these pregnancy complications. Any oral disease, from mild gingivitis to severe periodontitis, causes infection and

inflammation in the mother. At first, the thought of a linkage between a distant oral infection and pregnancy complications was considered “preposterous,” but accumulating scientific evidence is unveiling its biological plausibility.

The increase in hormonal activity during pregnancy can cause gums to bleed more easily and may promote bacterial overgrowth. This bleeding is not normal and signals ulceration between the tooth and gum. In full-blown periodontal disease, the infected area around all 32 teeth becomes a huge ulcerated area—about the size of the palm of your hand. These infected areas no longer



HAVE INFECTION, WILL TRAVEL: Bacteria from dental plaque can enter the bloodstream through small ulcers in the gum and can then travel throughout the body. The increase in hormonal activity during pregnancy can cause gums to bleed more easily and promote bacterial overgrowth.

have the natural skin barrier between the bacteria in dental plaque and the mother's bloodstream. Bacteria enter the blood and travel to the placenta, which normally blocks penetration to the fetus.

For many years, doctors believed that the environment inside the uterus was relatively isolated and protected, with few organisms passing to the placenta or the fetus. But this infection barrier can be breached by a few organisms, including the rubella virus. A rubella (German measles) outbreak in 1964-65

caused at least 10,000 miscarriages and stillbirths, and more than 20,000 babies were born with birth defects. Rubella was first identified as a cause of birth defects several decades ago when researchers discovered the virus floating in amniotic fluid and that fetuses carried antibodies to it—proving that the virus had indeed entered the placenta to infect the growing baby inside.

We conducted studies at U.N.C., Chapel Hill to learn whether unborn babies would show antibody responses

to the organisms that normally live in our mouths with the first human findings being reported in 2001. Studies on mice reported in 2002 and later studies in rabbits proved that oral bacteria could cross the placenta and reach the fetus. Some recent work by Dr. **Yiping W. Han** at Case Western Reserve University demonstrated in 2006 that maternal oral bacteria have been found in human amniotic fluid providing proof of transmission. This strongly suggested fetal infection in

this study—but proving transmission to the fetus of a large population of oral bacteria will be difficult, as babies are not born in a sterile environment.

About eight years ago, we found that in utero exposure to the mother's oral bacteria is a fairly common event. Research conducted by Phoebus Madianos in our lab, published in 2001, showed that contact with enough periodontal bacteria to induce a fetal immune response resulted in a two- to three-fold increase in risk for preterm delivery.

It appears that if the magnitude of exposure is low, either because of a mild infection or effective protection from the mother's antibodies, then the fetus is shielded from these bacteria. But if oral bacteria cross the placental barrier early in gestation, the probability that they will cause problems is much higher than if the security breach occurs late-term. For example, about 28 percent of all unborn babies are exposed to the *Campylobacter rectus* (or *C. rectus*) bacteria—but evidence of exposure to the bacteria is found in 52 percent of infants born before 32 weeks gestation (eight weeks early).

When an unborn child's immune system kicks in to fight off those bacteria, the risk for preterm delivery increases between four- and seven-fold, after adjusting for traditional obstetric risk factors. Elevated levels of the chemicals and hormones that regulate the immune-inflammatory system create a toxic in utero environment that stresses the fetus. It was once thought that the mother's body determined when labor kicked in, but we now know that the baby also contributes to the timing of delivery. Stress may cause the fetus's adrenal glands to produce the hormones that help precipitate its own delivery.

At birth, these babies' umbilical cord blood carries higher-than-normal levels of C-reactive protein, a marker of inflammation which reflects liver activity in both mother and child. Other chemicals, like PGE2 and TNF α (tumor necrosis factor alpha), mediate the body's inflammatory response and act in con-

cert to trigger labor contractions, rupture the amniotic sac, and impair blood flow in the placenta. So the onset of labor is actually a naturally occurring inflammatory response—the mother's body uses inflammation to “reject” the baby—but labor can be triggered early by the abnormal presence of these inflammatory chemicals.

This mechanism—a silent infection leading to fetal inflammation—may also provide a possible explanation for the Barker hypothesis, developed in the early 1900s by David Barker and his colleagues in Southampton, England. They followed the health of low birth weight babies and discovered that prematurity harms health later in life. It seems that deficits in a baby's fetal and infant growth “programs in” risk factors for adult diseases and a lifetime of various disabilities and impairments, including diabetes, high blood pressure and cardiovascular disease. Preterm babies are particularly prone to long-term disability, because their respiratory and neurological systems are especially impacted by premature birth—and the earlier the delivery, the greater the risk of long-term conditions such as lung disease, asthma, mental retardation, cerebral palsy and impaired cognitive function. Preterm babies are also at high risk for neonatal death.

Studies in our laboratory demonstrated in 2004 that when pregnant mice were exposed to the *C. rectus* oral bacteria, brain damage in their offspring was similar to that seen in conditions such as cerebral palsy and mental retardation, which can be caused by in utero infections. But clearly, more research is needed, as animal models do not always reflect what happens in humans.

Certainly, there are many reasons for pregnancy complications that do

not involve infection. In fact, there may be underlying conditions, exposures or genetic traits that predispose mothers to abnormal pregnancy outcomes. Some of these risk factors may also predispose mothers to periodontal disease, such as susceptibility to severe inflammation. Nevertheless, the progression of periodontal disease during pregnancy can result in fetal exposure—and trigger a fetal inflammatory response—which may increase the risk for pregnancy complications. The potential importance of these linkages on health care costs and family well-being have not been lost on health insurance companies; some now provide coverage for periodontal care during pregnancy.

Although we do not yet have enough evidence to say unequivocally that periodontal infections can cause adverse pregnancy outcomes, the data supporting this idea are mounting quickly. According to our research, when oral bacteria breaches the “armed guard” of the placenta and reaches the fetus, that baby's risk of being born early rises to 2.8 times that of an unexposed baby. Perhaps in the future a vaccine will be developed to combat these organisms. But in the meantime, the good news is that we know how to prevent and manage periodontal disease—and treatment can be provided safely during pregnancy to improve a mother's oral health, reducing infection and inflammation that may harm her unborn child. An increased dialogue among expectant mothers, their obstetricians and their dental professionals to diagnose, prevent and manage maternal oral infections appears to be a promising strategy for optimizing maternal health during pregnancy. ●

STEVEN OFFENBACHER is director for Oral and Systemic Diseases and a distinguished professor at the Department of Periodontology, School of Dentistry at the University of North Carolina at Chapel Hill. He researches the mechanisms of periodontitis-associated pregnancy complications, risk factors for periodontitis, and bone regeneration. He holds D.D.S. Doctor of Dental Surgery and Ph.D. Biochemistry degrees from Virginia Commonwealth University.

When it comes to the complications of oral disease, the elderly are particularly vulnerable

AS THE BODY AGES

In the U.S., periodontal disease affects an estimated one in 10 adults, and one in five over the age of 65. It is the leading cause of tooth loss in adults. But emerging evidence linking periodontal disease to serious health problems, particularly in the elderly, is making diagnosis and treatment even more crucial. | BY FRANK A. SCANNAPIECO

EVELYN JONES, an 89-year-old woman, came to my office last year for a routine dental cleaning. She lived in a local nursing home and had not been to a dentist in over a year. Aside from high blood pressure, which was being treated with

diuretics, she apparently had no other medical problems. A dental exam revealed red, swollen gums and several loose teeth.

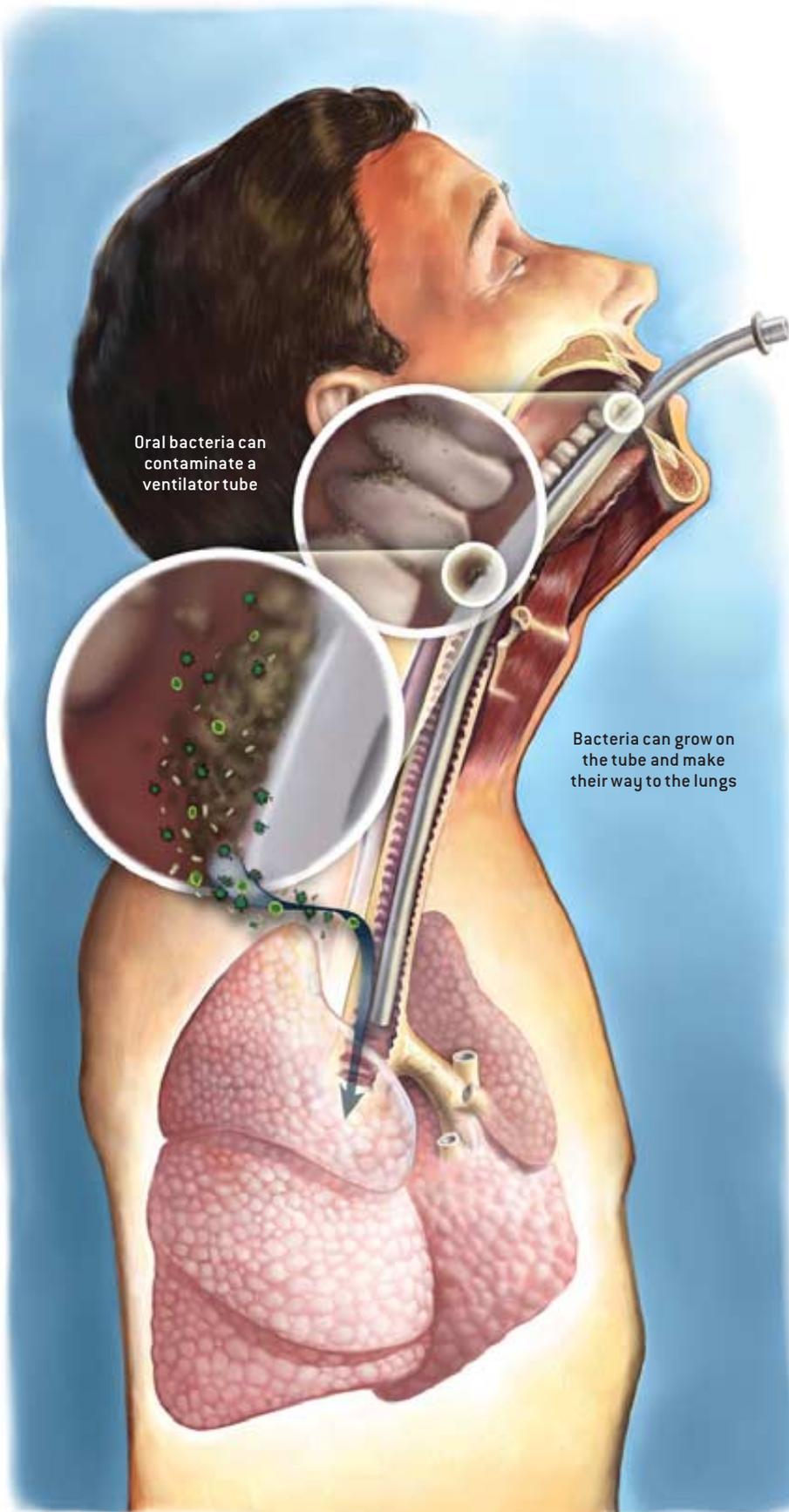
Mrs. Jones said she'd had a cold and felt tired. She also appeared short of breath, light-headed, and complained of chest pain. I took her blood pressure, which was elevated. Suspecting that she might have a heart problem, I urged her to see a physician immediately. Her caregiver drove her from my office to the hospital, where she was admitted with a diagnosis of pulmonary hypertension: high blood pressure had nar-

rowed and thickened the vessels carrying blood to her lungs, making her heart work harder and causing fluid to build up in her lungs.

After treatment with calcium channel blockers, which increase blood and oxygen flow to the heart, her condition improved. But on her third day in the hospital she developed a fever and cough, which proved to be pneumonia. She was placed on antibiotics. Two days later, lung cultures revealed that her pneumonia had been caused by the intestinal bacterium *Escherichia coli*, which was also found in her blood. She was switched to a different antibiotic on day six, but her condition worsened. She experienced kidney failure on day seven, and died on day nine. Believe it or not, Mrs. Jones's poor oral health may have contributed to her death.»



HEALTHY MOUTH, HEALTHY BODY:
Maintaining proper oral health is important at any age. Diseases that threaten the elderly can be exacerbated by poor oral care.



Oral bacteria can contaminate a ventilator tube

Bacteria can grow on the tube and make their way to the lungs

AN INFECTIOUS PATH: When patients are hooked to a ventilator, their risk of pneumonia can increase 20-fold, making it the leading killer among hospital-acquired infections. Oral bacteria in dental plaque can “jump” to the tube and begin to grow on it, eventually making their way down into the lungs.

Over the past several decades, researchers have found that tooth and gum health may influence the health of the entire body. Their provocative studies have shown that gum disease may increase a person’s risk for heart attack, stroke, diabetes and—as in Mrs. Jones’s case—pneumonia. These findings are especially pertinent to older people, because the likelihood of developing oral disease increases with age.

How poor oral health might affect overall health still is being actively investigated. Some researchers theorize that when the gums bleed, bacteria from the mouth enters the bloodstream and migrates to other parts of the body where they trigger health problems. For example, some heart valve infections are clearly linked to recent dental work. Among people with heart valve problems, oral bacteria that enter the blood may attach to the valves, causing a potentially fatal inflammatory disease called endocarditis. As a preventive measure, dentists since the 1950s have routinely prescribed antibiotics to patients with valve problems before even the simplest of procedures, such as a routine cleaning or filling a cavity.

To see if oral health might be associated with heart disease, in 1989 a team of Finnish investigators studied 100 recent heart attack patients and a similar number of closely matched people without a history of heart disease. The heart patients had substantially worse dental health, including a much higher prevalence of periodontal disease, than the control subjects. This finding sparked considerable interest. Numerous follow-up studies conducted since then have mostly supported a link between periodontal disease and an increased risk for heart disease. Other research has found a similar association between periodontal disease and stroke.

Both heart attack and stroke are caused by atherosclerosis, the buildup of fatty deposits within the arteries that channel blood to the heart and brain. With evidence now showing that inflammation helps fuel atherosclerosis, researchers are exploring whether cyto-

ORAL DISEASE & OSTEOPOROSIS

BY JEAN WACTAWSKI-WENDE

IS BONE LOSS from oral infection associated with osteoporosis? Research on osteoporosis and oral bone loss has shown a fairly consistent relationship, including a recent University at Buffalo study that linked osteoporosis and periodontal disease, which caused loss of both oral bone and teeth—especially in women aged 70 years and older. But other types of studies have produced inconsistent results, or have revealed no connection at all. This is due, in part, to study design variation. For example, several negative studies have included subjects in their 40s and 50s, when osteoporosis and low bone density prevalence is low. Assessment of both osteoporosis and periodontal disease can also differ across studies, which

sometimes makes comparison and interpretation difficult.

How does bone loss occur? Bones are living, growing tissues that undergo constant remodeling in response to the stress placed upon them. About 10 percent of the body's total bone mass is "remodeled" each year—removed and then replaced. Cells called osteoclasts lay on the bone surface, breaking down existing bone in a process known as resorption. Their counterparts, osteoblasts, then secrete collagen and minerals to lay down new, replacement bone.

In osteoporosis, there is an imbalance: Either too much bone is resorbed or too little bone is formed. This skeletal disorder decreases the quality, density (amount) and strength of bone, which becomes abnormally porous and spongy, and fractures easily. According to the National Osteoporosis Foundation, an estimated 10 million Americans have the disease; almost 34 million more have low bone mass. Three quarters of these are women.

Periodontitis, a bacterial infection in the mouth, is the primary cause of tooth loss in adults. It destroys both gum tissue and the

alveolar bone that supports the teeth. Researchers are exploring how alveolar bone is lost—and how it may be connected to osteoporosis and body-wide bone loss. Because osteoporosis is a systemic disease, it may affect bones in the mouth in a number of ways. Bone loss around teeth may occur independent of oral inflammation. Osteoporosis may lead to more

also more vulnerable to periodontal destruction. Lifestyle factors such as cigarette smoking and low calcium intake as well as the effects of aging may also put individuals at greater risk for low bone density and loss of alveolar bone.

Ongoing studies will provide further insight into the interaction of osteoporosis and periodontal bone loss, which will be increas-



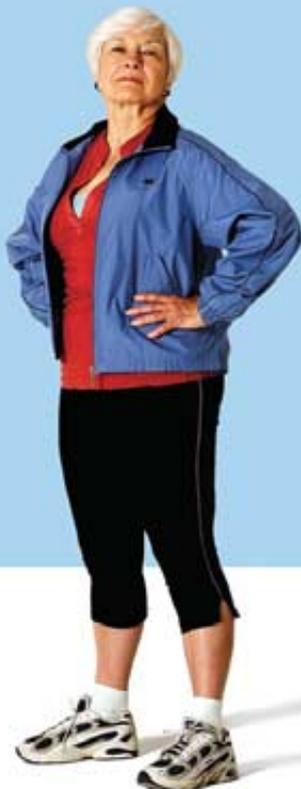
rapid breakdown of alveolar bone after oral bacteria invades.

Systemic factors that affect bone remodeling may also modify how local tissues respond to periodontal infection. Specifically, people with overall bone loss are known to have increased system-wide production of cytokines (specifically IL-1 and IL-6) that may impact bone quality throughout the body—including the bones of the oral cavity. Periodontal infection, in turn, increases local cytokine production that boosts local osteoclast activity—accelerating alveolar bone loss.

Both osteoporosis and gum disease share a number of risk factors. Individuals with a genetic predisposition to bone loss are

ingly important in the prevention of these two very prevalent disorders in older Americans. ●

JEAN WACTAWSKI-WENDE is associate chair of the Department of Social and Preventive Medicine at the State University of New York at Buffalo.



kines and other inflammatory chemicals from diseased gums may travel through the blood and contribute to the problem.

In Mrs. Jones's case, excess dental plaque and periodontal disease may have set the stage for nosocomial (hospital-acquired) pneumonia, a leading cause of death among older Americans. Elderly, institutionalized people like Mrs. Jones are at particular risk for de-

Clearly, more dedicated efforts to keep gums healthy may reap health dividends far beyond improving oral health and keeping your teeth.

veloping pneumonia while hospitalized because, along with other factors, they tend to have poor oral hygiene. So when they enter the hospital, their dental plaque—the bacterial biofilm that forms on teeth—is more likely to become colonized by the disease-causing bacteria that lurk in hospitals. The swallowing difficulty that often accompanies old age also increases the amount of bacteria in the mouth—it is not washed away by saliva, increasing the likelihood that it and other oral debris will inadvertently be inhaled into the lungs.

This risk is magnified if a mechanical ventilator is needed to assist patients who cannot breathe on their own by pumping air into the lungs via a tube inserted into the mouth or nose. Ventilated patients are up to 20 times more likely to develop pneumonia than those breathing on their own. Oral bacteria can grow on the tube and travel into the lungs. Not surprisingly, between 10 and 25 percent of these patients develop ventilator-associated pneumonia (VAP), making it the leading cause of death from hospital-acquired infections.

Improving oral hygiene among the institutionalized elderly would be a cost-effective way to reduce the risk of pneumonia caused by bacteria in the mouth. More than a dozen studies have shown that simple measures, such as supervised toothbrushing and regular use of antibacterial mouthwashes, can reduce by more than half the risk of pneumonia

in those people living in nursing homes or admitted to the hospital.

Chronic obstructive pulmonary disease (COPD), which limits the flow of air into the lungs, is also associated with poor oral hygiene and periodontal disease. COPD usually stems from long-term cigarette smoking and can involve a spectrum of conditions, including emphysema and chronic bronchitis. People

with COPD are at increased risk for periodontal disease, which, when present, seems to cause lung function to deteriorate further. Because smoking is also a major risk factor for periodontal disease, it is difficult to separate the roles that each of them plays in COPD. Preliminary studies by my colleagues and me indicate that, while smoking is clearly the major cause of COPD, periodontal disease may exacerbate it.

Other systemic diseases that affect older individuals may also be influenced by oral health status. For example, osteoporosis disproportionately affects postmenopausal women, thinning bones and often leading to bone fracture. Periodontal disease apparently does not increase one's vulnerability to osteoporosis, but people with the latter appear to face an increased risk of developing oral disease and tooth loss. My colleague Jean Wactawski-Wende and our research group at the University at Buffalo have found a strong and consistent association between osteoporosis and periodontal disease that causes both tooth and jawbone loss—especially among women ages 70 and older [see box on page 33].

Oral infection and the gum inflammation it causes may also contribute to

oral cancers. Researchers hypothesize that bacterial toxins, enzymes and the chemicals involved in inflammation may cause mutations in human cells that lead to uncontrolled growth and, ultimately, cancer. This work is still in its infancy, but results so far are provocative.

One recent study on the health status of a cross-section of the U.S. population included an assessment of the oral health of more than 13,000 people. People diagnosed with periodontal disease had a significantly higher risk of also having oral cancer compared with those who had healthy gums, even after controlling for age, a history of smoking and other factors that might have skewed the results.

Finally, periodontal disease has also been associated with rheumatoid arthritis (RA), an autoimmune disease that inflames joints and can cause destruction of cartilage, bone and ligaments. The two diseases share some basic characteristics: both the gum tissues affected by periodontal disease and the joints affected by RA contain similar cytokines and growth factors. These chemicals promote the dissolution of bone, a problem shared by both diseases. This suggests the presence of a common underlying inflammatory mechanism. People with advanced RA are known to be at increased risk for developing periodontal problems—and vice versa.

Clearly, more dedicated efforts to keep gums healthy may reap health dividends far beyond improving oral health and retaining your teeth. The good news is that controlling and even preventing periodontal disease is possible through relatively low-tech means: daily brushing and flossing, plus regular trips to your dentist's office for cleanings and check-ups. Knowing that maintaining oral hygiene could help prevent more serious conditions may be just the incentive both young and old need to make it a habit. ●

FRANK A. SCANNAPIECO studies oral microbiology and the interface between oral and systemic health—specifically, the role of oral conditions in the process of respiratory infection. He is professor and chair of the Department of Oral Biology, School of Dental Medicine at the State University of New York at Buffalo. He has been engaged in dental research and education for over 20 years.

ORAL HEALTH AROUND THE WORLD

WITH PROFESSIONAL EXPERIENCE IN FOUR DIFFERENT COUNTRIES—THE UNITED STATES, ITALY, SWITZERLAND AND THE UNITED KINGDOM, **MAURIZIO TONETTI**, CHAIR OF THE DIVISION OF PERIODONTOLOGY AT THE UNIVERSITY OF CONNECTICUT HEALTH SCIENCES CENTER HAS A TRULY GLOBAL PERSPECTIVE ON ORAL HEALTH. HERE HE OFFERS A FEW INSIGHTS ON ORAL HEALTH AND SYSTEMIC DISEASE:

ON EDUCATION AND THE CONVERGENCE OF DENTISTRY AND MEDICINE: A common biomedical curriculum is much more prevalent in Europe than in the U.S. Until 1980, in most countries, dentistry was a medical specialty, so you became a physician, and then specialized in dentistry—rather than, say, cardiology or orthopedics. So, the foundation of dentistry in the majority of European countries has very, very deep medical roots. In the United States most dental schools have their own faculty teaching such courses as anatomy, pharmacology and biology. In Europe it's not like this. There is a biomedical science faculty that includes medicine and dentistry.

A strong biomedical curriculum is needed not only because of the possible systemic implications of oral diseases, but also because of the fact that people are living longer. So all of a sudden, dentistry has become an important component of life expectancy, of the well-being of people.

ON RESEARCH ADDRESSING THE ORAL-SYSTEMIC LINK OUTSIDE THE U.S.: There's lots of enthusiasm and attention, but unfortunately all of this has translated into fragmented efforts. There is no body, no organization that has been able to catalyze and focus research activity in places as diverse as Africa, the Far East, Europe—even within Europe—and in the United States.

We are missing a tremendous opportunity because there are lots of people around the world that are doing research with

very, very few resources, but the usefulness of what they are doing is limited by the fact that there is no coordination or consistent methodology being employed. In Europe we have been—and in other areas of the world we are still—at the level of pilot [studies] involving a few hundred patients. The building blocks to be able to do the real clinical trial are there. Now it's time to do the real studies. We need to focus efforts and develop a vision in order to make a coordinated research effort happen.

ON PRESS COVERAGE OF THE ORAL CONNECTIONS TO OVERALL HEALTH: In Europe we have been much more cautious than in the U.S. We have kept the dental profession very well informed by making sure that these topics are discussed at professional meetings, but by and large we have not had major press releases on the topic. Over the last two years there has been an increased awareness, and the media has started to communicate. I think this is perhaps a better approach than the U.S. media hype; wait until you have enough data and then go to the people. Ideally, communication should include both the

problem and the recommendation of effective and accessible interventions or preventive measures.

Also, in Western society, these messages are likely to reach the portion of the population that could benefit least. The people you reach with these messages are the ones whose “health IQ,” or health awareness, is so developed that they are unlikely to be the ones harboring massive undetected disease.

ON CHANGES AT THE WORLD HEALTH ORGANIZATION (WHO) ON ORAL HEALTH: Historically, before a relatively recent reorganization in the 1990s, oral health was part of a WHO branch that focused on infections. Now, they have placed it with chronic noncommunicable diseases. They have grouped together areas where risk factors of the population base are similar because they think this is the best way to fight these diseases; many countries are following this approach.

ON ORAL HEALTH IN EUROPE: Europe is not a homogeneous reality. You have countries that are responsive to the needs of populations: they have public health systems that are probably the envy of the world—probably, I would say, better than the U.S. But Europe, being made of 25 states these days, has a wider discrepancy of care than between, say, Connecticut—which is probably one of the states with the best access to dental care and best health policy in the U.S.—and Louisiana, or rural Alabama. Health care is a state issue, not a European Union issue. Oral health care in traditional EU countries is generally good, but significant disparities among the various countries and disadvantaged groups and individuals exist. As in the U.S., in Europe the major burden of oral disease is to be found in a minority of the population. ●

“The foundation of dentistry in the majority of European countries has very, very deep medical roots.”

SUSAN HAD CAREFULLY MONITORED HER HEALTH IN

the months leading up to the delivery of her first child. She visited her obstetrician

for regular checkups, downed prenatal vitamins every morning, and stopped

smoking. Although she worked full time, she made sure to get plenty of rest. Many of her friends at work were parents and they gave her advice daily, telling her: keep exercising; don't jog, swim instead; don't eat too many tuna fish sandwiches. One thing she heard over and over again—an old wives' tale, really—was that she shouldn't go to the dentist because of “x-rays in the air.” So Susan skipped her annual dental check-up even though she was concerned by how her gums bled when she brushed her teeth. Everyone assured her that this was normal.

As she lay in her hospital bed after the premature delivery of her tiny little

daughter, she wondered what had gone wrong. Her baby had arrived just eight months into her pregnancy.

Susan is not alone. According to the March of Dimes, each day 1,300 babies in the U.S. are born prematurely for reasons linked to specific risk factors like smoking or high blood pressure. And if emerging research proves true, periodontal (gum) disease will be a new addition to that list. In fact, if the bacteria and inflammation from gum infection do indeed play a role in preterm deliveries—as well as other conditions such as pneumonia, stroke, heart disease and diabetes—the reverberations across our health care system will be seismic and transformative. “Medically necessary dentistry” will become the new slogan of our time.

PUBLIC POLICY & ORAL HEALTH:

A WHOLE NEW

game

Governments, insurers, clinicians & the public must all recognize the changing face of dental medicine.

BY SHEILA RIGGS



The generations-old barriers that inadvertently disconnect the mouth from the body in terms of patient care are substantial. Most of our physicians and dentists are trained in different schools, practice in different settings, and receive payment through different systems. When your physician asks you to “open wide,” he or she is examining your throat, not your mouth. Meanwhile, your dentist focuses on saving your teeth and gums; he or she doesn’t necessarily view periodontal treatment as a way to prevent inflammation that can cause harm throughout the rest of your body.

It takes an average of 17 years before Americans benefit from new knowledge gained from medical research, according to Carolyn Clancy, M.D., director of the Maryland-based Agency for Healthcare Research and Quality. This raises an important question: How long will the time lapse be

between what we know and what we do when it comes to an issue that crosses unusually hardened divides in our health care system?

A WHOLE NEW GAME

LET US ASSUME that all the research linking periodontal disease to many of our nation’s most prevalent and costly chronic health conditions reaches the same conclusion: the presence of active oral disease causes system-wide complications, and treatment and prevention will improve overall health. Our whole perception of dentistry will need to change, as will its role in our health care system.

In this new paradigm, dentists should be recognized as the physicians of one part of the body, not just the surgeons of a perfect smile. Dentists take blood pressures and health histories as well as gather insights from their patients on risk factors impacting oral health, like tobacco use and soda consumption. Now they must view this pre-

vious information through the lens of a primary care physician.

Dentists are usually the most accessible members of the medical team. Typically, Americans visit their dentist twice a year for preventive care. According to Dr. Michael Glick, editor of *The Journal of the American Dental Association*, “Dentists can play an important role in the primary prevention of cardiovascular disease...and refer patients for more in-depth evaluation.”

Referrals will come more easily when dentists and physicians train together in classrooms. It is also crucial that they work side by side in clinical settings during graduate school, for example, co-treating a pregnant patient. Defining and implementing a unified primary care team from day one in school will create a powerful new norm. Team members should include physicians, nurses, pharmacists, dentists and dental hygienists to both demystify the oral cavity for physicians and to empower the work of the dental team. >>



Curriculum changes, however, are not sufficient. This new knowledge ultimately must translate into the everyday practices of physicians and dentists and be covered by insurance companies—and there are precedents. Numerous “quality improvement initiatives” related to medical care are currently underway

If our assumption about periodontal disease proves true, such “pay for performance” programs should also include teeth cleaning and dental care. Likewise, when the federal government tracks how many Americans with diabetes receive essential monitoring and care in their annual National Healthcare Quality Re-

health plans in their “pay for performance programs”: insurance companies pay physicians a bonus for meeting or exceeding treatment metrics.

Another standard component of disease management is a program that connects pregnant Minnesotans or those suffering from chronic conditions with a registered nurse. In regular checkup phone calls, their nurse helps them improve lifestyle habits and coordinate care. These same nurses could also educate their patients on the importance of dental care.

Currently, more than 250,000 patients with diabetes, heart disease and other conditions are enrolled by two medical insurance companies who already partner with one of Minnesota’s largest dental insurers, Delta Dental. Broadening dental coverage for these populations with fewer co-pays would encourage preventive care.

Employers, consumers and innovators are also active in health improvement efforts in Minnesota. Companies are acting to lower health care expenses, which have spiraled dramatically upward over the past decade: The cost to employers in 2003 for a healthy newborn’s two-day hospital stay was about \$1,700, while a premature or underweight baby’s average 24.2-day stay was around \$77,000, according to the March of Dimes.

An employer coalition called the Buyers Health Care Action Group is in place to encourage and reward improvement initiatives in Minnesota’s health care. Recently, they issued a report comparing the performance of the state’s health plans in both clinical areas (such as prevention and chronic disease management) and in administrative practices (like extending personal digital assistant devices to physicians and nurse practitioners). In the future, employer coalitions should evaluate insurers’ efforts to encourage their employees with chronic conditions to seek dental care.

But it could be the entrepreneurs at one of Minnesota’s 450 medical device companies that offer the best solutions. For example, one company is developing a topical liquid for use by dentists that

It takes an average of 17 years before Americans benefit from medical research.

in clinics and hospitals nationwide. These initiatives implement standardized treatment guidelines to insure that patients receive proper care. They also establish who is responsible for carrying out each step outlined by these new guidelines. Hospitals and clinics using these new initiatives are examining their protocols to make sure no step in patient care is overlooked. For example, patients hospitalized with a heart attack should begin beta-blocker therapy (medication that lightens the heart’s workload) within seven days of discharge. New protocols dictate who is responsible for issuing the prescription.

These efforts are frequently sponsored by insurance companies or employers. Using financial incentives, they speed the time it takes for new research on health care practices to become everyday patient treatment. They must now also be injected with a healthy dose of dentistry, which would reconfigure programs to include gum disease as a preventable risk factor for several common health problems.

Some very large employers now directly pay bonuses to doctors; the “Bridges to Excellence” diabetes care program is one example. General Electric and other companies provide a bonus of \$80 per patient to physicians who meet National Committee for Quality Assurance standards in caring for their diabetic employees, with a focus on improving patients’ blood sugar levels, blood pressure and cholesterol levels. This saves employers about \$350 a year per patient.

port, a new dental component will need to be added to their survey.

MINNESOTA AS A PRACTICE FIELD

MINNESOTA, a state known for its health care reform, may be the ideal place to launch this revolution. All the major stakeholders currently working to improve the quality of the state’s health care are in place—and they are capable of getting this new research into practice sooner rather than later. Included in this group are educators, health care professionals, insurers, employers, consumers and entrepreneurs.

On the educational front, the deans of the University of Minnesota’s medical, dental, pharmacy, nursing and public health schools are discussing joint classes and a linked curriculum. “We are working through the details of launching on-campus and clinic-based educational opportunities, like at the Rice Memorial Hospital in Willmar,” said Patrick Lloyd, dean of the School of Dentistry.

Another important initiative is the Minnesota-based Institute for Clinical Systems Improvement (ICSI), a health insurance-funded think tank that establishes guidelines for medical treatment and improved care. For over a decade, ICSI has worked with virtually every medical group and hospital system throughout the state, designing ways to implement the best clinical practices. ICSI’s “collaboratives” are currently in place to improve care to pregnant women and to those suffering from diabetes and heart disease. The standards created by these collaboratives are rewarded by



THE BURDEN OF DISEASE: Poor oral health impacts individuals and whole communities and results in pain, suffering, impairment of function and reduced quality of life. According to the World Health Organization (WHO), oral disease is the fourth most expensive condition to treat in most industrialized countries. As more research links oral health to overall health, policymakers will need to address new models of prevention and treatment.

disrupts plaque biofilm, removing the harmful effects of the bacteria that cause periodontal disease in the first place. Ongoing research into oral-systemic health links will certainly spawn much more development among product makers and life sciences companies.

In the end, these solutions will be necessary to change the cultures of the medical and dental practices to embrace the new research findings on the connectedness of the mouth to the body.

FEDERAL GOVERNMENT'S ROLE

THE FEDERAL GOVERNMENT also has “skin in this game” both as a primary funder of medical research and as the provider of Medicaid and Medicare. Na-

tional policymakers should fund studies to confirm whether periodontal disease is indeed a risk factor for often preventable “medical” conditions that affect millions of Americans. “In order to move from uncovering an association between periodontal disease and various systemic diseases and conditions, to actually demonstrating causality, large-scale clinical trial research is needed,”

said Christopher H. Fox, executive director of the International and American Associations for Dental Research. “While the cost for these trials is high, it is pennies compared to the lifelong treatment costs for low birth weight babies or for patients with cardiovascular disease.” The landmark government report issued in 2000, “Oral Health in America: A Report of the Surgeon General,” made a similar call for future research.

When Medicare was established in 1965, Congress made a blanket exclusion of dental care. Medicaid coverage varies state to state, but adult periodontal services are covered in just nine states, according to a U.S. Government Accountability Office report to Congress. So although the poor and the elderly have some of the highest occurrences of heart conditions and diabetes, there is little public assistance available for periodontal treatment, which costs between \$100 and \$1,000 per year depending on its severity. In developed countries, 44 to 57 percent of adults have moderate periodontitis; 7 to 15 percent have an advanced form of the disease.

In their 2003 “Public Health Implications of Chronic Periodontal Infections in Adults” report, the Centers For Disease Control and Prevention (cdc) suggested restructuring benefits to provide dental infection control services to Medicaid and Medicare recipients. If preventing and treating periodontal disease does indeed avert preterm deliveries and decrease the illness burden of Americans with diabetes and heart disease, covering dental treatment for adults in our public entitlement health programs should be considered.

So that the next time Susan is pregnant, there will be a brand-new member on her health care team—her dentist. ●

SHEILA RIGGS received her dental degree (D.D.S.) from the University of Iowa College of Dentistry and went on to earn her doctorate of medical sciences (D.M.Sc.) in oral epidemiology from Harvard University. She was recently appointed president and CEO of Delta Dental Plan of Minnesota, one of the largest dental benefit providers in the upper Midwest, which serves more than 3.3 million individuals at 8,500 Minnesota-based companies and is leading the effort to integrate the latest dental and medical research into its dental offerings.

THE FORMER U.S. SURGEON GENERAL REFLECTS ON HIS SEMINAL REPORT THAT PUT ORAL HEALTH ON THE NATIONAL AGENDA, AND THE POLICY STEPS THAT STILL NEED TO BE TAKEN

SCIENTIFIC AMERICAN: “Oral Health in America” was a landmark report. What factors compelled you to issue it?

SATCHER: I think the request from the oral health community, including dentists and others, had probably been there for many

years. When I got to Washington—having come from the CDC [Centers for Disease Control and Prevention]—I was especially concerned about areas that had not been dealt with, like mental health and oral health, and obesity. So oral health was very high on our list because it had been neglected by the surgeon general’s office. We tried to make it very clear that this was not about the dental profession, it was about oral health, and that oral health was everybody’s business—everybody who was concerned about health and health care.

report—and how did it help mobilize efforts for better oral care and greater awareness? Both in the public and private sector, we’ve seen increased focus on oral health, funding programs and educating the population. The National Center for Dental and Craniofacial Research at NIH [National Institutes of Health] has now funded several Centers of Excellence on oral health research. In the private sector, the Robert Wood Johnson Foundation fund-

ed 19 dental schools to develop outreach programs into communities around them. Other foundations have also focused increased attention on oral health.

The other thing that I appreciate is that it’s led to new partnerships between doctors and dentists and other oral health professionals. I think [the report] rejuvenated the field in many ways.

As more evidence comes in linking oral health to other medical conditions, what further efforts do you feel need to be taken,

Were there specific issues around oral health that were of particular concern at that time, both to you and to the medical and dental communities? Well, one issue was disparities in health. If you go back to the “Healthy People 2010” report that we released in January 2000, we looked at two major areas. One was the quality of life of people as they get older; one of those issues was edentulousness [tooth loss]. The second was the issue of disparities in health among different racial and ethnic groups. I don’t think there is any area that demonstrates health disparities more than oral health—there are 108 million Americans who lack dental insurance.

Since that time, what steps have been taken toward addressing the issues outlined in the

in either clinical practice, public education or policy? I think in all of those areas there is a need for enhanced education and communication about the magnitude of the problem of oral disease—and its significance. Especially when you begin to tie periodontal disease to low birth weight or adverse pregnancy outcomes, increased risk for diabetes or cardiovascular disease and stroke. Those are the ones where there

is mounting evidence. We still don’t have that definitive, long-term study because those take a long time, but more and more studies support the associations.

And I don’t mean just public education. Clearly, in the future, it will be critical that medical students, dental students, nursing students and public health students be educated about the significance of oral disease as it relates to systemic disease—and about some of the things we can do to intervene.

In light of continued evidence linking oral and systemic health, is the mandate to address socioeconomic differences in oral health care access even more pressing?

I think it is. Our report stated that 20 percent of the population now suffers more than 80 percent of oral health disease. About one third of the elderly, by the time they’re 65, are edentulous. We know that periodontal disease is more common in African-American men in general, and that it’s more common in smokers. So I think we’re now in a position to begin to target populations [who are most adversely affected].

Many people without health care might go to a dentist, whereas they may not have had a medical checkup in some years. What kind of responsibility should fall on the dental profession in those cases, where perhaps they’re treating a diabetic patient that also

“We tried to make it very clear that this was not about the dental profession, it was about oral health, and that oral health was everybody’s business—everybody who was concerned about health and health care.”

has gum disease? Well, I think diabetes is a good example, because the association with periodontal disease is probably most clear. Since we know that people with diabetes are at greater risk for oral health disease, counseling patients about being tested for diabetes [or making sure that their diabetes is under control] is important. The education about diet that dentists give is important for both the health of the mouth and for the over-

DISCUSSION with DAVID SATCHER

all health of a person with diabetes: increasing fruits and vegetables, and decreasing sweets, meats and calories.

Dentists, by focusing on the mouth, have an opportunity to look at what's happening to the whole person. And by partnering with the health professional, they can work to make sure that the [patient] gets the care that he or she deserves. I was thinking about the role that dentists are playing in helping people [to] quit smoking, because they focus on how their teeth and gums look when they smoke. And so, in recent years a major avenue for smoking cessation has been to get dentists involved. I think that these [medical-dental] partnerships are being forged both ways. The mouth is an important mirror and a window to the body: it's not just what is going on in the mouth, it's what's reflected in the mouth about the state of health of the body.

What other comments do you have that you think would be good for both dental professionals and the general public to hear?

The overriding message that came out of that report is the importance of access to oral health care; the fact that so many Americans don't have access to oral health care is a major concern ... and that it disproportionately impacts low income families and minorities. Hopefully, as a nation, we should be moving towards universal access to oral health, as well as health care in general. I know that there were some states that significantly increased their Medicaid coverage for oral health after our report. [But] many of those states, after they had budget problems, cut back Medicaid again, which, of course, hurt all aspects of health care. ●

DAVID SATCHER completed his four-year term as the 16th surgeon general of the United States in February 2002. He also served as assistant secretary for health from February 1998 to January 2001, making him only the second person in history to have held both positions simultaneously

A Novel Approach to Resolving Inflammation

Understanding how the body naturally “turns off” inflammation may yield new treatments for periodontal disease and other inflammatory conditions

By Thomas E. Van Dyke and Charles N. Serhan

SCIENTISTS HAVE KNOWN FOR ALMOST 50 YEARS that periodontal disease is caused by bacterial infections. However, the tissue damage that occurs in periodontal disease—destruction

of the bone and ligaments that hold teeth in place—cannot entirely be explained by the action of infecting organisms. Instead, the real culprit seems to be the patient’s own inflammatory response to that infection.

Inflammation evolved as a protective response to infection and to traumas such as wounds and insect bites. Yet inflammation can also be deleterious—especially when it persists, instead of fading away as it should. Our research collaboration over the past nine years indicates

that periodontal disease results mainly from the body’s failure to turn off its inflammatory response to infection. The result is chronic inflammation, which causes much of the tissue damage that we observe in periodontal disease.

Why, for some of us, does this inflammatory response to oral bacteria persist rather than subside? The answer may lie in our genes: Studies indicate that much of our susceptibility to periodontal disease is genetically influenced. But fortunately, it may be pos-

sible to rein in runaway inflammation and the tissue destruction it causes.

We and our colleagues have identified powerful compounds, produced naturally by the body, that put the brakes on the inflammatory response. If we can manufacture these novel anti-inflammatory chemicals and use them as medicines, they might offer safe and effective treatments—not only for periodontal disease but also for heart disease, arthritis, Alzheimer’s disease and other health problems where chronic inflammation appears to play an important role.

Much of our work on inflammation in periodontal disease has focused on its cause: the immune reaction that the body mounts against infection. This attack triggers the classic signs of inflammation including heat, redness, swelling and pain. We’ve been particularly interested in the innate immune response—the body’s first line of defense. This response is initiated by neutrophils, a type of white blood cell crucially important in eliminating infectious organisms by engulfing them through a process called phagocytosis—which literally means “cell eating.”

As they congregate at the site of infection or trauma, neutrophils secrete “proinflammatory” chemicals that cause the first, or acute, phase of inflammation. Normally, in the next step, neutrophils cease their chemical onslaught and inflammation subsides. But in periodontal disease there is a glitch: neutrophils continue churning out proinflammatory chemicals, which create a complex, chronic lesion that destroys the gum and bone holding teeth in place.

Clearly, inflammation’s failure to enter its last or “resolution” phase can have serious consequences. This final

CAN GUM DISEASE CAUSE HEART DISEASE?

SEVERAL PROVOCATIVE STUDIES suggest that people with periodontal disease have an increased risk of heart disease. To further investigate this link, we induced periodontal disease in rabbits by tying a thread around some of their teeth and treating their gums and teeth with a bacterium known to cause periodontitis in humans. Six weeks later, after the rabbits had developed periodontal disease, we examined their major blood vessels. The rabbits with periodontal disease had much more atherosclerosis—fatty plaque deposits in their major blood vessels—than the healthy control rabbits.

But which component of periodontal disease—the infection or the inflammation—was the culprit? To find out which had caused the atherosclerosis, we once again tried inducing periodontal disease. This time, besides ordinary rabbits, we used “inflammation-resistant” rabbits that we genetically engineered with Larry Chan (Baylor Medical College) to have abnormally high lipoxin levels in their blood. The resistant rabbits not only failed to develop periodontal disease—their arteries were almost completely free of plaque, compared with the nonresistant rabbits that developed periodontal disease.

This study adds to mounting evidence that periodontal disease may contribute to atherosclerosis. It further suggests that periodontal inflammation plays a key role in the potential periodontal disease–heart disease connection.

—TVD

phase has traditionally been considered a passive event—a petering out of immune activity that paled in comparison to the acute phase’s neutrophil attack. That assumption required drastic revision after one of us (Serhan) carried out the first systematic study of the natural history of inflammation by examining inflammatory pus in skin lesions of rabbits and mice.

We observed that neutrophils, which lead the white cell onslaught during inflammation’s acute phase, secrete two compounds well known for provoking inflammation and attracting additional white cells to the area: leukotriene B₄, followed by prostaglandin E₂. But at the end of the acute phase, we saw something surprising: neutrophils stopped secreting classic inflammatory chemicals and instead began collaborating with other cells to synthesize compounds that halted inflammation.

We dubbed these anti-inflammatory compounds lipoxins, since they were derived from the lipids (fatty acids) released from neutrophils’ cell membranes and from other cells that congregate early in inflammation. If it is prostaglandins and leukotrienes that give the “green light” that accelerates tissue injury and inflamma-

tion, then it is lipoxins that can be considered the “red lights” that help bring inflammation to a halt.

The synthesis of these inflammation-stopping compounds starts late in the acute inflammatory response. Before that, inflammation is in full swing: enzymes from platelets and other cells attracted to the area metabolize arachidonic acid (a major fatty acid in cell membranes) to create leukotrienes and other proinflammatory compounds. Then, once these inflammatory chemicals have crowded together, an abrupt shift occurs, and enzymes induced in neutrophils convert arachidonic acid into inflammation-dampening lipoxins. The inflammatory response ceases as lipoxins increase in quantity at the expense of proinflammatory compounds.

SERHAN RECENTLY discovered yet another family of inflammation-resolving compounds that we’ve dubbed “resolvins.” In contrast to lipoxins, whose starting material is arachidonic acid, the resolvins are derived from fatty acids in the diet—specifically from omega-3 fatty acids that are especially plentiful in fish.

Several well-designed clinical studies indicate that diets rich in omega-3s help in treating and preventing arthri-



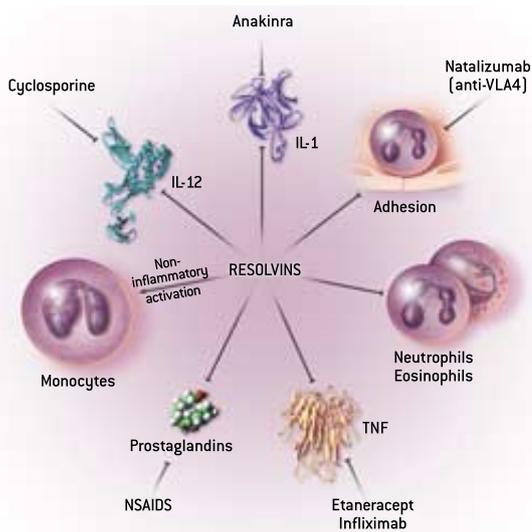
UPPER PHOTO shows inflammation and erosion of gums in rabbits with periodontitis. In lower photo, topical resolvins prevents inflammation and tissue destruction of periodontitis.

tis, cardiovascular disease and other inflammatory conditions. We now suspect that the resolvins formed from omega-3s may in part account for the anti-inflammatory properties of these dietary fatty acids.

The actions of lipoxins and resolvins in the body are similar but not identical. Their net effect is to rapidly halt inflammation and minimize tissue damage. Furthermore, taking aspirin results in more potent and longer-lasting lipoxins and resolvins [see box on page 45].

In our federally funded Specialized Center for Oral Inflammation and Resolution, we are studying how the structure of resolvins gives them their potent anti-inflammatory ability. Based on our findings, we reasoned that the topical application of lipoxins and resolvins as medicines might prove useful in treating or even preventing inflammatory diseases like periodontitis. We also wondered if these compounds might help against other inflammatory problems such as cardiovascular disease and the complications of diabetes.

To test resolvins’ ability to prevent periodontitis, we chose an established



ANTI-INFLAMMATORY DRUGS target only specific aspects of inflammation—and typically cause harmful side effects in doing so. Ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs), for example, curb prostaglandin production while increasing users’ risk for gastrointestinal bleeding. By contrast, naturally occurring inflammation-resolving compounds, such as resolvins and lipoxins, affect all aspects of inflammation. They create a coordinated cellular and molecular response that brings inflammation to a halt. Drugs mimicking these natural compounds could potentially treat inflammation “naturally” and without side effects.

model of human gum infection—the rabbit model. We tied silk thread around certain rabbit teeth to trap bacteria and then added a disease-causing human bacterium, *Porphyromonas gingivalis*, to induce periodontitis. After dividing the rabbits into two groups, we swabbed a resolvin-containing solution on the gums of one group and an inactive solution on the gums of the other. The results were striking: rabbits receiving the topical resolvin solution were completely protected against periodontitis, whereas the placebo group developed severe gum disease [see photos on page 44].

TO FURTHER EXPLORE this connection between inflammation and susceptibility to disease, we studied genetically engineered rabbits that have elevated levels of lipoxins when their white blood cells are activated. These rabbits also have a very low incidence of atherosclerosis [see box on page 42] in their major vessels. We tried to produce gum disease in these “inflammation-resistant” rabbits using the same silk thread and bacteria technique described above. With their elevated levels of circulating lipoxins, these rabbits proved resistant to periodontitis.

While we know that bacteria causes periodontal disease, it now appears that its progressive form may be primarily driven by inflammation—which could alter the way this condition is controlled and treated. In people susceptible to periodontal disease, for example, topical application of lipoxins or resolvins could possibly prevent or lessen its severity.

More broadly, our research has shown that inflammation involves the coordinated response of a large number of biochemical pathways. But today’s anti-inflammatory drugs defuse only one pathway or another and can be risky to use. Consider two examples: by far the largest class of anti-

REVVING UP LIPOXINS AND RESOLVINS WITH ASPIRIN

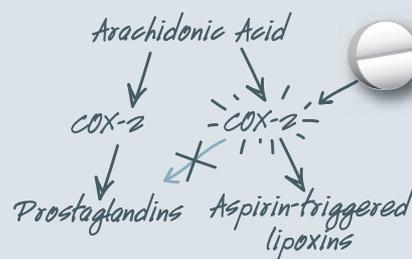
ASPIRIN’S POTENT ANTI-INFLAMMATORY PROPERTIES were recognized soon after it was introduced a century ago. But not until many decades later did Sir John Vane, Sune Bergström and Bengt Samuelsson—in research for which they shared a 1982 Nobel Prize—discover how aspirin actually works. Aspirin blocks the enzyme COX-2. This provides relief by preventing arachidonic acid in cell membranes from being converted into prostaglandins—the chemical messengers that cause the pain and swelling of inflammation.

By blocking the COX-2 enzyme, aspirin and similar drugs do a good job of shutting off the prostaglandins that fuel the early, acute phase of inflammation. But they may also set the stage for chronic inflammation by hindering the body’s own attempt to heal: As the illustration on page 43 shows, prostaglandins are vital for producing the lipoxins that help to resolve inflammation.

This suggests a better strategy for quelling inflammation: Instead of halting acute inflammation, focus instead on helping the body in its effort to resolve the inflammatory response.

When we swallow aspirin, it not only inhibits COX-2 but also modifies its action. Research by one of us (C.S.) has shown that aspirin-modified COX-2 catalyzes the production of “new and improved” resolvin and lipoxin compounds that have more potent and longer-lasting anti-inflammatory effects than the naturally occurring variety.

These previously unappreciated aspects of aspirin’s activity may help researchers develop truly anti-inflammatory compounds that would not just muffle acute inflammation but would actively resolve inflammation and heal wounds. These drugs would be especially useful against periodontal disease, heart disease and other important health problems that arise from chronic inflammation.



— TVD

inflammatory drugs are the NSAIDs (nonsteroidal anti-inflammatory drugs), which include naproxen, ibuprofen and many other compounds. The NSAIDs short-circuit just one inflammatory pathway (the one that converts arachidonic acid into prostaglandins). Moreover, NSAIDs cause thousands of deaths annually in the U.S., mainly due to gastrointestinal bleeding. Other, more powerful anti-inflammatory drugs, such as Remicade for treating rheumatoid arthritis, do so by dampening the immune response, which may increase vulnerability to infections as well as to cancer.

By contrast, lipoxins and resolvins might offer major advantages over existing anti-inflammatory drugs. They act by “centrally” defus-

ing inflammation rather than just turning off one or another individual inflammatory pathway [see sidebar on page 44]. In addition, these natural compounds would be expected to produce few side effects.

Our studies have shown that lipoxins and resolvins may be ideally suited for treating periodontal disease. ●

THOMAS F. VAN DYKE studies the resolution of inflammation as a therapeutic target. He is a professor in the Department of Periodontology and Oral Biology at Boston University’s Goldman School of Dental Medicine, directs the Clinical Research Center, and is associate director at the BU School of Medicine General Clinical Research Center.

CHARLES N. GERHAN studies the cellular molecular mechanisms that resolve inflammation. He holds the Gelman Professorship at Harvard Medical School, is a senior biochemist and an endowed distinguished scientist at Brigham and Women’s Hospital. Dr. Gerhan is also chairman and professor of oral medicine, infection and immunity at the Harvard School of Dental Medicine.

MOUTHFUL of BUGS

Pathogenic bacteria are a way of life. So, too, must be brushing and flossing. | BY ROBERT H. KAGAN

THE MOUTH IS A CAULDRON OF BUGS.

On average, some 500 species sit in the oral cavity going about their daily business as their hosts sleep, talk, chew and swallow. “Bacteria are lurking in the tongue, nasal cavity, tonsil area, gingival pockets [and] floating in saliva,” explains John C. Gunsolley, a professor in the department of periodontics at Virginia Commonwealth University in Richmond. “Our skin has bacteria on it, we’re never completely sterile. Swab any external portion of the body, you will find bacteria. It’s nothing to be alarmed at. It’s what nature is.”

The body is constantly fighting these bacteria, and healthy bodies are able to keep them at bay. When our immune systems stop responding, however, our bodies become bacterial buffets. Within a day or two of dying, bodies start to smell, Gunsolley says. That’s the bacteria taking over. But we don’t have to

die for bacteria to find inroads: diseases, such as diabetes, can decrease the ability of the immune system to respond effectively to bacteria, and this can tilt the balance toward the latter, triggering the beginnings of oral disease. Localized neglect—not taking adequate care inside the mouth—can also lead to pathogenic bacterial overgrowth. This can occur when periodontal pathogens such as *Actinobacillus actinomycetemcomitans*, *Prophyromonas gingivalis* or *Tannerella forsythia* begin to increase their presence in the mouth and overcolonize soft tissue. When these bacteria expand in the pockets of the gums, they can trigger redness and inflammation from gingivitis, a warning sign for possible progression to periodontitis and the destruction of gum tissue and bone that can result.

Eliminating pathogenic bacteria completely might make the mouth safe from periodontal disease, Gunsolley explains. Experiments



*Grow
Good*

FEELIN' & HEALTH



BATTLING BACTERIA AND INFLAMMATION

Home Care

- Brushing & Flossing

Professional Care

- Scaling and root planing
- Flap surgery
- Grafts (BONE, SOFT TISSUE)
- Tissue regeneration surgery
- Bone (OSSEOUS) surgery

Chemotherapeutic

- Chlorhexidine
- Stannous flouride
- Cetylpyridium chloride
- Essential oils
- Triclosan
- Antimicrobial inserts into pockets
- Systemic antibiotics



ORAL ARSENAL: A variety of interventions are available to combat infection and inflammation in the mouth.

have been done with rats where periodontal pathogens were eliminated from parts of the mouth, and the rats resisted attempts to induce periodontitis as long as the areas stayed bacteria-free. But eventually, bacteria find their way back into the mouth, as humans (and rats) have bacterial reservoirs that make it impossible to completely eliminate the microbes for extended periods of time. The practical issue, then, is one of balance: oral disease can often be avoided or kept at bay if the number of bad bacteria are kept in check, Gunsolley says.

ZEN AND THE ART OF MOUTH MAINTENANCE

KEEPING MICROBES IN CHECK is an ongoing practice, and a goal met by two main approaches: mechanically sweeping away bacteria so they cannot take root in the mouth, and reducing their numbers through chemical means. The level of bacteria in a mouth will determine the types of tools to use under each approach.

A first step in addressing oral hygiene is to determine the amount of

pathogenic bacteria that populate a patient's mouth and how much damage they might do. Gunsolley points out that although there are no good metrics or devices to measure a mouth's bacterial load, the body's response to bacteria is effective in determining treatments. If a mouth appears healthy, with no inflammation or redness, then the main indication is mechanical: brushing and flossing. Both brushing, whether with a manual or electronic toothbrush, and flossing break up plaque—the mass of bacteria and food that forms a biofilm, which coats tooth and gum surfaces. The goal is break up biofilm on a daily basis before it adheres, Gunsolley says.

The next level of treatment is often chemotherapeutic, where chemicals in mouthwashes or antiplaque agents in some toothpastes are used to nonselectively combat bacteria in the mouth. This decreases the number of pathogenic bacteria and thus reduces inflammation. If there is serious gingivitis or periodontal disease, then other treatments are generally added, including scaling

and root planing as well as placing antimicrobial inserts into gum pockets, or additional interventions [see box above]. But first and foremost, Gunsolley emphasizes, is good mechanical oral hygiene: brushing and flossing. This, ultimately, is the ideal way to disrupt plaque, especially at the gum line.

Traci Portnoff, D.M.D., in private practice in Westborough, Mass., and a former instructor in oral medicine at the Harvard School of Dental Medicine, agrees: “The bottom line is if [someone is] not brushing, they are not doing anything. You need physical stimulation.” While Portnoff certainly employs advanced technologies to deal with indications of gingivitis or periodontal disease from pathogenic bacteria, her first line of defense and most important battle cry to patients remains the same. “Our main focus is hygiene instruction,” she emphasizes. “There’s no substitute for the brushing and flossing.” ●

ROBERT H. KAGAN is a science writer based in Boston, Mass.

DANIEL M. MEYER, ASSOCIATE EXECUTIVE DIRECTOR OF THE DIVISION OF SCIENCE AT THE AMERICAN DENTAL ASSOCIATION, SPEAKS WITH SCIENTIFIC AMERICAN ABOUT ORAL HEALTH, ETHICS, AND THE STATE OF THE SCIENCE LINKING GUM INFECTION WITH OTHER SERIOUS DISEASES.

SCIENTIFIC AMERICAN: What is the ADA's (American Dental Association) position on the science behind the possible links between periodontal disease and other systemic conditions?

DANIEL M. MEYER: The ADA is a science-based organization. It's had a rich history of basing its policies, clinical recommendations and guidance for providers, patients and the public on sound scientific principles. Oftentimes, the science is there and clearly sets a sense of direction, but at times we need more information. As far as oral-systemic relationships, we're dealing with new discoveries and new scientific information. The burden of proof of a causal relationship is not yet met; but research is ongoing and it looks promising. Inflammatory processes in the oral cavity could play a role in causing problems in other parts of the body.

It's important that we distinguish between sound science and pseudoscience—and between causal relationships and casual rela-

need to be clarified. It would be naive of us to think that the mouth is separate from the rest of the body; the mouth is an excellent location

THE ADA'S TAKE

How the world's leading dental organization views the growing connections between a healthy mouth and a healthy body.

to diagnose, prognose, treat and intervene on a whole host of disease processes. Oral health has to be a part of general health care, so it's not too early.

Which of the possible links do you feel are stronger and which do you feel will need considerably more research before there are any strong conclusions either way? The relationship to cardiovascular disease is less clear. Regarding the relationships to preterm births,

component of some of these conditions, or it may be a minor component.

Whether or not treating oral health conditions will affect systemic health depends on the disease—and we'll know more about that as future research unfolds. Until we have [intervention] studies, where we can measure results in consideration of other variables that may influence health, I think we have to be guarded in treatment recommendations. But treating oral conditions such as periodontal disease has its own undisputed benefits and may have broader systemic health outcomes.

I think it's going to be decades before we fully understand cardiovascular diseases. And again, I think we have to be very cautious about any of the oral health relationships, because they may pale in comparison to other risk factors. But good oral health makes sense, is appropriate to all cases, and contributes to good general health.

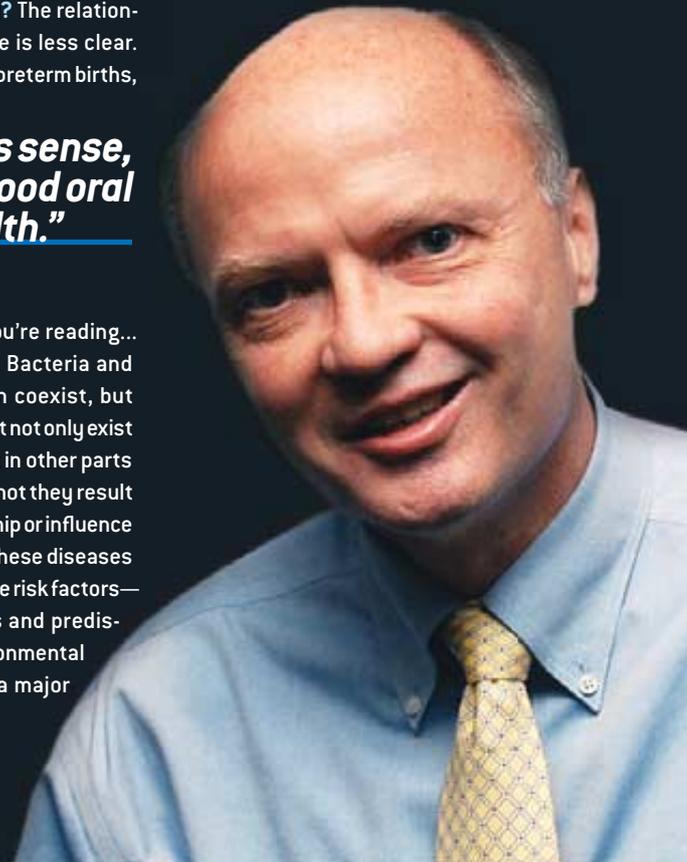
You make a good point. Regardless of periodontal health's relation to your heart, it still is important for your mouth and your teeth. We want patients to be focused on good oral health and oral hygiene, but we also want them to take care of their bodies. »

“Fundamental to it all, good oral health makes sense, it is appropriate to all cases, and certainly good oral health does contribute to good general health.”

tionships. We want to make sure that everyone has the best scientific information to make good treatment and clinical care decisions that will improve the quality of life and health for our patients.

Do you feel that it's too early for there to be clinical implications or do you feel that the evidence is solid enough in any of these areas to change either medical or dental care? Obviously there is a relationship between oral health and general health. Other relationships

depending on what studies you're reading... we're getting varying results. Bacteria and various health conditions can coexist, but we're talking about bacteria that not only exist in the oral cavity but may exist in other parts of the body as well. Whether or not they result in a cause-and-effect relationship or influence relative risk remains unclear. These diseases are complex. Some have multiple risk factors—behaviors, genetic conditions and predisposing factors, including environmental issues. So oral health can be a major



As more evidence links the health of the mouth to the health of the body, do you feel the role of the dentist needs to change, and if so, how?

I do. I think the role of the dentist, as well as any health care provider, needs to evolve as research evolves, expanding as information becomes available. In all of medicine and dentistry, the role of the provider has changed considerably over the last several decades. I see the dentist becoming much more integral to the general health care team. Dentists generally treat healthy, ambulatory patients rather than afflicted or debilitated patients so they can be involved in early intervention, early diagnosis, risk assessment and disease

an opportunity to work together with the AMA, to share information, to update the public and the profession on where we are at this time. We didn't want to overstate relationships, but we didn't want to understate them, either.

You mentioned that there is a lot of misinformation. What are some examples? There are those that would say that some of these are causal relationships, that there is a direct relationship between oral bacteria, and, for example, cardiovascular disease. That hasn't been demonstrated yet. There are still conflicting studies that call into question the strength of some of these relationships. Our

We've had patients calling up thinking that they can treat their heart conditions by simply going in and having their teeth cleaned or scale and root planed.

management of many diseases, and [they can] refer those individuals to appropriate health care providers. For example, to help detect cardiovascular conditions it would be beneficial for dentists to do blood pressure screenings, and we're looking at new technologies like salivary diagnostics. The chemicals that you see in blood should also be detected in saliva, and although this technology needs to be refined, it allows dentists to be part of the early diagnostic team. We need to take more of a medical approach to some of these conditions, and to align ourselves with other health care providers to address them.

Is the ADA promoting a closer relationship with the medical community? We are. We're working very closely with the American Medical Association, a variety of health organizations including the American College of Obstetricians and Gynecologists, the American Academy of Periodontology, and various professional and research organizations to address these issues collectively.

Specifically, the AMA and ADA had co-organized a press event on periodontal disease. What prompted that? The concern is that there is a lot of misinformation. We were receiving many requests from the public about these relationships and were concerned that they be put into proper perspective. We saw this as

concern is to keep things in the proper perspective—so when someone goes to a physician or a dentist, that the level of care is consistent with the quality and strength of scientific evidence.

Are there any other obvious myths around periodontal disease and general health that come to mind? There are misconceptions that need to be addressed. We've had patients calling up thinking that they can prevent or treat heart conditions by simply going in and having their teeth cleaned or scaled and root planed.

Getting your teeth cleaned wouldn't be the magic bullet there. No, it wouldn't be. We've had people call up asking, "If I brush my teeth with this certain toothpaste, will that help cure my heart disease?" No. Could utilizing an appropriate toothpaste improve oral health? Yes. Is oral health a component of general health? Yes. We do know how proper oral hygiene, proper lifestyles can influence health—and oral health; but to make huge extrapolations? We're very concerned about that.

I've heard a number of researchers use the expression "floss or die," and I've wondered where it originated. That mentality does frighten me a bit because some things that are said facetiously are taken to heart by

some people and by the media at times. I don't know who coined the phrase, but it does lend itself to the misconception that all you have to do is floss and you won't die.

If the role of the dentist does indeed need to shift to incorporate risk for—let's choose pregnancy outcomes—what would that mean regarding liabilities for dentists? We will have to wait and see. We're treating individuals, often with a host of prior medical conditions. People are living longer now, taking a variety of medications, many of which interact or cause dry mouth—which can cause other oral and health complications. So with care comes the concern for side effects and risks. You have to weigh the benefits against the risks. We are treating patients for complex diseases, but perhaps we don't fully understand all of the health implications, or all of the side effects, or all of the interactions. Along with that there certainly are medical and legal risks.

Which in the U.S. is a big issue. We are perhaps the most litigious society in the world. Right. And so, are dentists preyed upon? Yes. Are health care providers preyed upon? Are patients preyed upon? Yes. And so that's always a concern.

Do you think this new data could create a more complex legal matrix? It's already been brought to our attention. There are lawyers' Web sites saying, "If you've ever had a history of periodontal disease... and if you have any of the following conditions, then you may be eligible for legal action." Does concern us? Obviously we don't want harm done to patients, but we also recognize that there are individuals who may take advantage of the fact that some of these issues are still evolving. We don't yet know everything that we need to, and with that comes a level of risk and a real need to enlighten the public and the profession on relevant care—and the need for more research.

Does the ADA have a specific program or regimen approving dental care/dental procedures for specific problems? Yes. If you go to ada.org, you'll see that we do provide guidance on a whole host of topics related to patient/provider safety—including oral-systemic relationships. ●

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