the three-way street

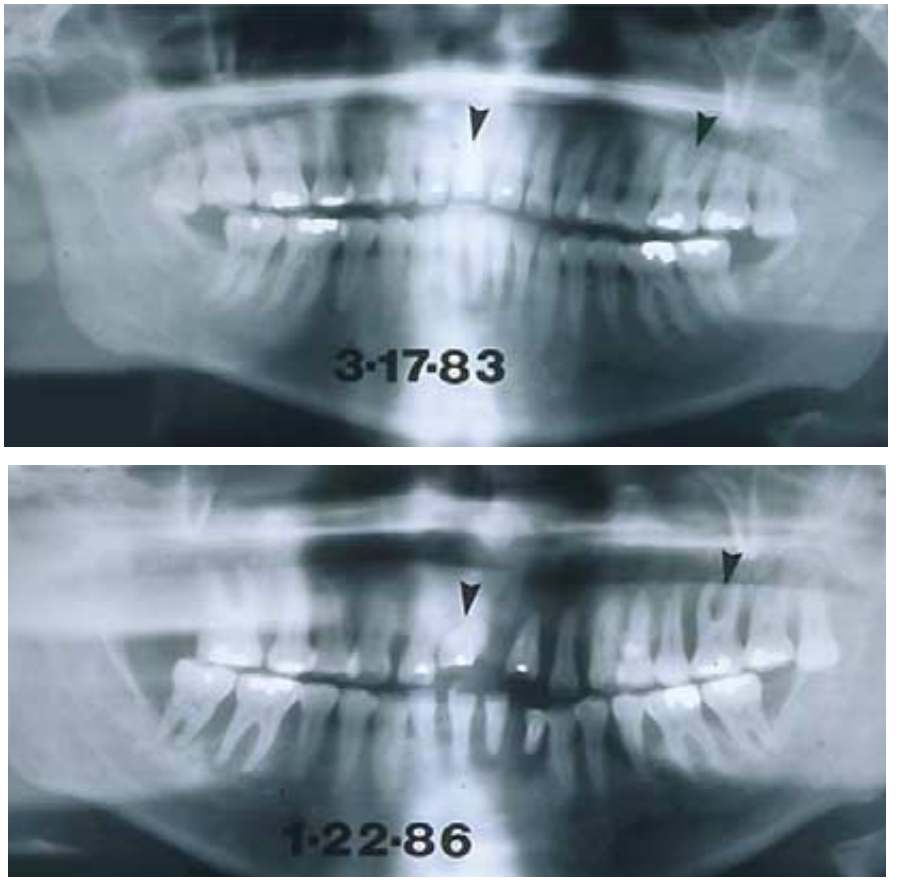
Two decades of biomedical and dental detective work have linked obesity, diabetes and periodontal disease

BY **ROBERT J. GENCO**

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. >>

NORTHWESTERN UNIVERSITY LIBRARY, *EDWARD S. CURTIS'S "THE NORTH AMERICAN INDIAN,"* 2003

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

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 (TNFα), 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 TNFα, 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.

the DIABETIC in the DENTAL CHAIR

BY BRIAN L. MEALEY

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. ●

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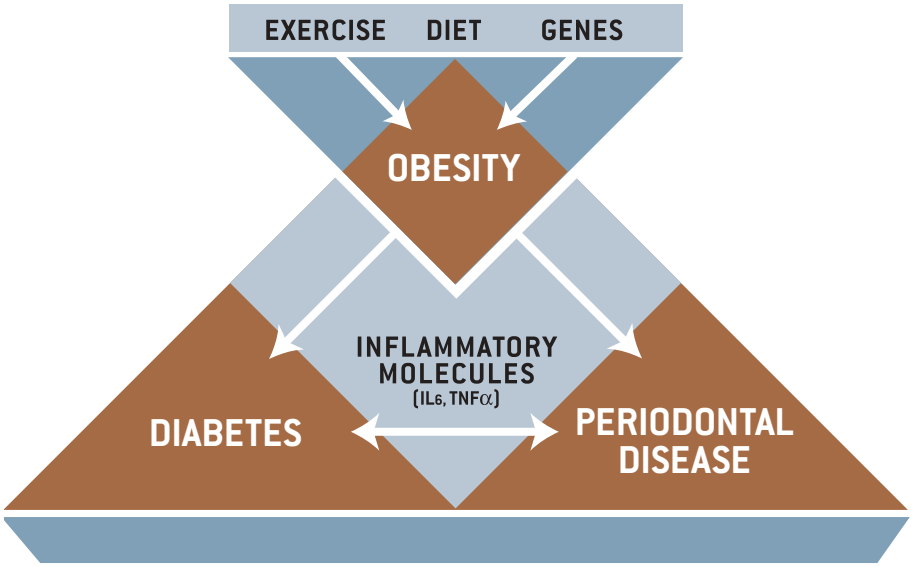

A TRIANGULAR RELATIONSHIP: Obesity can intensify infections, such as periodontal disease; cytokines produced by fat cells are known to trigger insulin resistance, which can lead to type 2 diabetes. Diabetes, in turn, is known to increase the risk for periodontal disease. New research suggests that periodontal 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 Country study subjects. All those who suffered from periodontal disease had elevated levels of soluable receptors for TNFα 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 TNFα and other cytokines in damaging tissue—and in predisposing an individual to diabetes. TNFα 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 exacerbate more dangerous, tenacious oral infections, their presence also helps explain why obesity is such a serious risk factor for diabetes and cardiovascular disease: TNFα 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.