MOUTH IMMUNITY

An immune system deficiency is associated with a rare periodontal disease. This research progress promises understanding of the more widespread gum diseases.

White blood cells called neutrophils defend against periodontal diseases.

By JULIE ANN MILLER

The slogan "Look Mom! No cavities!" that advertised toothpaste in the 1950s was parodied by children who retorted, "Look Mom! No teeth!" The children's flippant response now turns out to have foreshadowed a serious concern of dental workers today. "We may be preserving teeth in children and young adults, only to have these teeth lost to periodontal diseases during adult life," says Harald Löe, director of the National Institute of Dental Research in Bethesda, Md. The American Association of Public Health Dentists recently called periodontal diseases the United States' "principal oral disease threat."

Periodontal diseases affect 94 million people in the United States. These infections of the soft tissues and bones that support teeth often lead to tooth loss. Research has been hindered by a lack of precise criteria for assessing the diseases and for identifying patients at risk. But for one periodontal disease, dental research has recently not only identified a disease-causing microbe but also implicated an immune system deficiency that seems to be hereditary. These findings allow dentists to predict who is likely to develop this disease and have triggered work on a new therapeutic approach — stimulation of a specific immune system function.

Whereas periodontal diseases are generally an adult problem, a particularly destructive form occurs in a small proportion of otherwise healthy children and adolescents. Called localized juvenile periodontitis (LJP), the disease develops rapidly in the tissues around specific teeth —the incisors and first molars. Untreated, it leads to extensive bone loss and the teeth fall out by the time the victim is 20 years old.

The microbe responsible for this disease is a bacterium called *Actinobacillus actinomycetemcomitans*, which may act in concert with other microorganisms. This bacterium can be identified at the disease sites of almost all patients with LJP, and most LJP patients have in their blood an elevated level of antibody to this microbe. But not all mouths harboring the microbe show periodontal disease. *A. actinomycetemcomitans* is also found in the mouths of about one-fifth of healthy people.

If *A. actinomycetemcomitans* is the organism responsible, why don't more people have the disease? Recent research suggests that an immune system defect also plays a role. Robert J. Genco of State University of New York at Buffalo described this research last month in the annual honorary lecture of the National Institute of Dental Research.

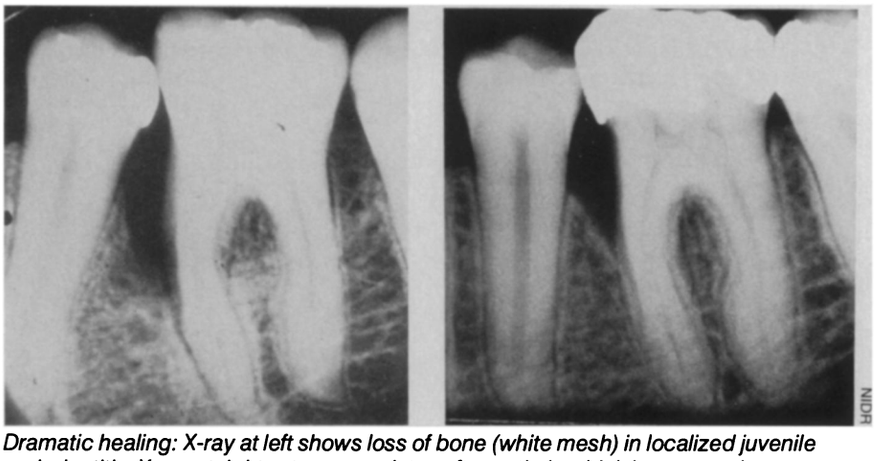
A major fighter of periodontal diseases is the immune system component known as a neutrophil. This white blood cell follows chemical trails to infecting bacteria and engulfs and destroys them. Researchers in about a dozen laboratories have examined the neutrophils of LJP patients. They find that the cells are able to move normally, but in about 70 percent of the patients the cells show little response to chemicals.

"The motor seems to be working but not the ability to sense and react to a chemical gradient," Genco says. "This neutrophil defect in LJP is one of the most highly documented findings in dental research."

This finding fits with observations that periodontal disease is common among persons having certain immune deficiency diseases characterized by abnormally low neutrophil number or function. But, LJP patients are not noticeably more susceptible to nonperiodontal diseases.

Depressed chemotaxis (the movement toward chemicals) appears to be an enduring, perhaps inborn, characteristic of LJP patients, rather than a response to infection. Low neutrophil chemotaxis is not reversed by successful treatment of LJP, and it is still observed in adults who had the disease when they were young. The basis for the defect appears to be that the neutrophils are deficient in a variety of membrane proteins, called receptors, that bind to attracting chemicals.

These abnormalities appear to be genetically determined, Genco says. Among 22 families containing LJP patients, 45 siblings of the patients also had the disease, 30 siblings had healthy periodontal tissues and 10 siblings were under the age of 12, so were still too young to be likely to show the disease. This study was performed by Genco and Thomas E. Van Dyke, now at Emory University in Atlanta. The incidence of LJP in these families is much higher than its incidence of about 1 percent in the general population of teenag-



Dramatic healing: X-ray at left shows loss of bone (white mesh) in localized juvenile periodontitis. X-ray at right —two years later, after antimicrobial therapy —shows restored bone and periodontal ligament, which appears as a white outline.

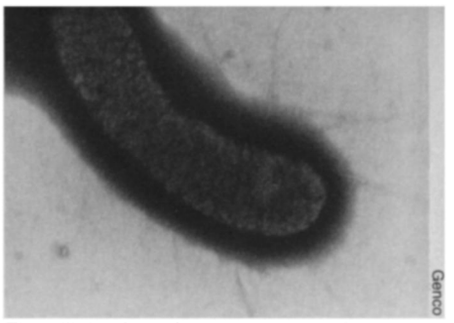
ers, so the researchers suggest there is a genetic basis.

The researchers examined neutrophils of the LJP patients and their siblings. In 19 families, the patients and all the siblings with LJP had abnormally low neutrophil chemotaxis. In the other three families, all had normal neutrophils.

"We were all startled by the finding that there are at least two forms of the disease," Genco says. Their genetic mechanisms are still controversial.

In families with LJP patients having abnormal neutrophils, it may be possible to predict which children will develop the disease. Of the 10 young siblings in the family study, nine were found to have depressed neutrophil chemotaxis. This finding further supports the idea that the neutrophil deficiency precedes and extends beyond the active LJP, rather than being caused by it. Dentists will closely observe the gum health of the youngsters showing low chemotaxis, and perhaps give antibiotics as a preventive measure.

The problem with the neutrophils that show abnormal chemotaxis may be that their development was arrested at an immature state, Genco suggests, although in microscope observations the cells appear to be fully developed. During the maturation process of the white blood cell, the number of specific membrane receptors increases and decreases. Genco and his colleague Mark Wilson have compared



The villain: A. actinomycetemcomitans *shows impressive virulence due in part to its release of toxins that damage neutrophils and other white blood cells.*

four types of receptors on the surface of LJP neutrophils with those of immature and of mature normal neutrophils. In the three cases where the number of receptors increases during maturation, the LJP cells had an abnormally low receptor population. But one type of receptor decreases on the cell surface during maturation, and in the LJP cell membranes that receptor is present at a concentration higher than normal.

These findings open up a new approach to treating LJP. The current therapy aims at eliminating *A. actinomycetemcomitans*. Clinicians usually give antibiotics while providing "mechanical therapy," the elimination of bacteria by scraping tooth and gum surfaces and sometimes surgically removing infected tissue. When this treatment is successful, it can lead to the regrowth of bone and gum in 6 to 18 months, according to studies by Lars Christersson of SUNY-Buffalo. "This is the most dramatic healing of any seen in periodontal therapy," Genco says. But the disease tends to recur — 25 percent of patients have a relapse within a year.

The new possibility is the enhancement of defective neutrophils. Genco and his colleagues have assessed in laboratory experiments the effect on neutrophils of an "immunomodulatory" chemical called bestatin. This chemical, which is produced by a microbe, can stimulate the human immune system at doses that do not seem to cause harmful side effects. Genco found that, in test tube experiments, bestatin does not affect chemotaxis in neutrophils from healthy subjects, but it almost doubles the chemotactic activity in neutrophils from LJP patients. Bestatin may increase the density of receptors on the cell membranes. Genco concludes, "Bestatin ... has potential for use as an adjunct in the treatment of juvenile periodontitis."

In addition to the usefulness of this research in developing therapy for LJP, the scientists hope it will provide insight into other periodontal diseases. Löe says, "It is most likely that research on juvenile periodontitis may throw additional light and give new clues to understanding the subtleties of the adult, slow-developing, chronic periodontitis." □