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DOES THE MOUTH PUT THE HEART AT RISK?

"A merry heart maketh a cheerful countenance," states the Book of Proverbs, "but by sorrow of the heart the spirit is broken." In language, hearts not only break; they sing, turn hard as stone, become heavy or light, cold or warm. In science, hearts are subject to assaults from a number of sources that are both known and unknown.

Louis Pasteur suggested at the close of the 19th century that specific microorganisms cause certain diseases. In the early 20th century, Sir William Osler observed that there were two types of bacterial endocarditis: an acute form that resulted in death within a few weeks, and a more subtle form that resulted in death after a much longer period. Osler fully appreciated what was killing his patients but did not have the therapeutics capable of preventing their deaths. It was not until 1940 that penicillin became available for the treatment of bacterial endocarditis. But the key question is this: What is the source of the microbes that invoke endocarditis or other cardiovascular diseases?

THE EMERGING CONNECTION BETWEEN ORAL INFECTION AND SYSTEMIC DISEASE

Today, we realize that oral infections are associated with a number of systemic diseases and disorders (Figure). The association between oral microbial infection and systemic disease is not a new concept. The effect of oral health on the rest of the body was proposed by the Assyrians as early as the seventh century B.C.[1] There was very little written about this correlation until the 18th century, when Benjamin Rush, a Pennsylvania doctor, was quoted as remarking that arthritis could be treated in some people after they had infected teeth extracted. However, there remains a skeptical reception to the 1989 work published by Finnish investigators that associated dental infections with cerebral and acute myocardial infarctions.[2,3] The authors took into consideration for their statistical analysis all of the common risk factors for stroke and heart attack, including age, smoking, high levels of serum lipids, diabetes and socioeconomic status. Accounting for all these factors, however, did not eliminate the statistically significant association between oral infections and cardiovascular disease.[2,3] The strength of this statistical evidence caused the research community to reconsider and investigate further the association between oral infections and systemic disease.

Pregnant women with oral infections have been found to have a substantially increased risk of giving birth to low-birthweight, premature babies.[4-7] People with certain heart problems or coagulation abnormalities and those with artificial joints are thought to be particularly vulnerable to some of the microbes that live in the oral cavity.[8-11] Such people often are advised to take antibiotics before they undergo dental procedures that might cause bleeding and possible transient bacteremia. Diseases such as diabetes are well-documented as affecting the pathogenesis of periodontal disease; indeed, periodontal disease affects the status of diabetes.[12,13]

The number of reports associating oral infections with systemic disease has been increasing steadily in the last few years. Most of the reports are based on epidemiological studies. A major confounding issue is that oral infections often are only one of the many important factors that can influence systemic diseases. Consequently, it is very difficult to achieve the time-honored proof of relationship by cause and effect. However, the increased number and

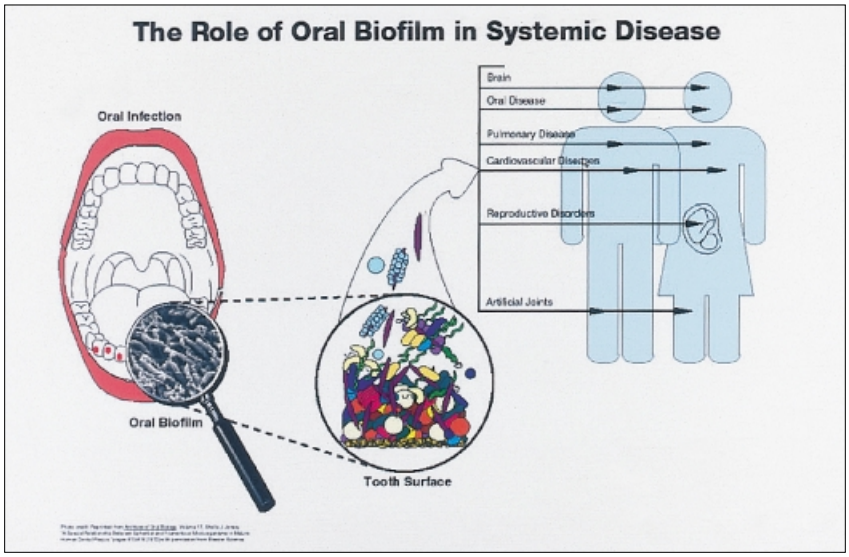

Figure. Oral biofilm is associated with disease in a number of the body's systems.

scope of study participants in epidemiological studies and further understanding of some of the putative mechanisms that support a connection between oral microbes and systemic disease have increased the evidence base supporting the hypothesis that microbes residing in the mouth can cause an array of systemic diseases if they move into the bloodstream and thus cause bacteremia. Transient bacteremia can occur for years in patients with chronic oral infections such as periodontal disease. Bacteria have been found in the blood after toothbrushing (40 percent of subjects), tooth extraction (60 percent) and periodontal surgery (88 percent).[1] The hypothesis is further supported by the statistical associations between periodontal diseases and systemic diseases, which identify periodontal diseases as risk factors in that relationship.[14] Obviously, rigorous and comprehensive scientific investigations are imperative. Scientific studies may reveal the evidence needed to understand these relationships and to aid in the development of preventive and interventional strategies to reduce cardiovascular disease.

Oral infections such as dental caries and periodontal disease are the most common chronic diseases in the world. These infections lead to the destruction of enamel, dentin, root surfaces and the components of the periodontium (the periodontal ligament, gingiva, cementum and alveolar bone). More than 400 species of bacteria create an exquisite microbial ecological system in the form of a biofilm. We are learning that the early colonizers of this biofilm are the streptococci that help initiate dental caries. *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis* and *Treponema denticola* are significant gram-negative colonizers that are associated with periodontal disease. When these bacteria accumulate in large numbers (108 or 109 colony-forming units per milligram of dental plaque), they form biofilms on the surfaces of teeth and continuously shed virulent components and metabolites, especially lipopolysaccharide, or LPS. In response to these oral infections, the host responds by forming a dense infiltrate of inflammatory cells. Microbial products such as LPS invoke the host to produce a variety of prostaglandins and cytokines that destroy components of the extracellular matrix and mediate alveolar bone resorption. The engagement between infection and immunity has marked effects on the vascular endothelium. It results in platelet aggregation and adhesion, cholesterol deposition, and formation of lipid-laden cells both in the immediate area and in other cells distant from the periodontium. A chronic inflammatory response is a major component of oral microbes' invocation of periodontal diseases.

RELATIONSHIP OF PERIODONTAL DISEASE WITH CARDIOVASCULAR DISEASE

Cardiovascular diseases—myocardial infarction, endocarditis, coronary heart disease, atherosclerosis and other related vascular diseases—are very important to the health of a growing and aging United States population. Cardiovascular diseases as a group were reported in 1994 as the leading cause of death—954,720 people—in the United States for men and women of all ethnic groups. Some of the risk factors associated with these diseases—including smoking, hypertension, obesity, diabetes, elevated cholesterol levels and genetic factors—have been determined and studied extensively.[14]

Since 1989, a number of case studies and epidemiological reports have observed a strong relationship between oral in-

fections (including periodontal disease) and cardiovascular disease, suggesting that periodontal disease may be a risk factor for cardiovascular disease.[2,3,14] Studies of this association that eliminate as many other known risk factors as possible strengthen the interpretation that periodontal disease is a major risk factor for cardiovascular disease. Smoking is a known and well-documented risk factor for cardiovascular disease. A study involving the diabetes-prone Pima Indians, among whom smoking is at a very low level, reported that the risk of myocardial infarction was 2.7 times higher in subjects who had periodontal disease than in those who had little or no periodontal infection.[10] Researchers followed periodontal disease over a 10-year period in 1,372 people younger than 60 years old. Baseline periodontal disease measurements were available and previous studies had eliminated smoking as a factor in both periodontal and cardiovascular disease. Adjustments were made for other risk factors such as age, sex, high cholesterol levels, weight, high blood pressure, diabetes and insulin use.[10] These studies concluded that periodontal disease was an important indicator of cardiovascular disease among Pima Indians younger than 60 years of age. The researchers also found that the incidence of periodontal disease among the Pima Indians was second only to the presence of long-term diabetes.[10] This study supports the involvement of periodontal infection as a major risk factor for cardiovascular disease. Several other studies have correlated tooth loss, an indication of periodontal disease, with an increased risk of cardiovascular disease.

HOW ORAL MICROBES CAUSE SYSTEMIC DISEASE

The pulmonary pathogen *Chlamydia pneumoniae* and LPS-producing oral microbial pathogens in dental plaque can move through the circulation to infect the cardiovascular tissues and contribute to the development of atherosclerosis and the risk of myocardial ischemia and infarction. Several major bacterial species found in dental plaque or biofilms, including *Streptococcus sanguis* and *P. gingivalis,* induce platelets to aggregate in vitro, thereby providing a model of thrombosis.

Oral-infection–associated bacteremias can contribute to the risk of acute thromboembolic events associated with atherosclerosis and myocardial infarction.

Aggregation of platelets requires a surface protein found on both of these bacteria called platelet aggregation-associated protein, or PAAP. This protein is similar to a platelet-active site in type I collagen that is normally involved in platelet aggregation. In rabbits, PAAP causes dose-dependent electrocardiographic abnormalities, increased heart rate, alterations in blood pressure and reduced cardiac contractility.[1] These changes are consistent with the occurrence of myocardial infarction. In more than 60 percent of adults, dental plaque harbors PAAP and *S. sanguis* microbes. Platelets released through injured capillaries can interact with these and other bacteria and thereby can induce the inflammatory potential of the platelets through the expression of PAAP. Oral-infection–associated bacteremias can contribute to the risk of acute thromboembolic events associated with atherosclerosis and myocardial infarction. The scientific evidence for this suggested mechanism is accumulating.

RELATIONSHIP OF ORAL INFECTIONS WITH OTHER SYSTEMIC DISEASES

The presence of chronic oral infections such as periodontitis has been associated with systemic diseases. There are several reports in the literature on the interaction between periodontal disease and diabetes mellitus.[12,15,16] The interaction between the two diseases is well-known. Diabetes influences the status of the oral cavity and is associated with increased occurrence and progression of periodontitis. The presence of moderate-to-advanced periodontal disease, on the other hand, is felt to directly influence a reduced glycemic control in diabetics.

Other reports in the literature have implicated oral infections as risk factors for other systemic diseases. *Helicobacter pylori* has been detected in subgingival plaque or biofilms in patients with periodontal disease. The relationship of this bacterium to gastric disease, with a possible source being the oral cavity, is being further investigated. Preliminary reports

FOR FURTHER INFORMATION

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have examined the association between pulmonary emphysema, other respiratory diseases and periodontal disease. These reports suggest similarities in general parameters and pathogenesis of these diseases, including recruitment of neutrophils to inflammatory sites, inactivation of protease inhibitors, increased exudate flow and connective tissue breakdown.

Infection and inflammation in the oral cavity also have been identified as risk factors for the development of other diseases in immunocompromised patients, especially those with cancer. A lesion in the oral cavity leads to the diagnosis of HIV-associated periodontitis—now known as necrotizing ulcerative periodontitis, or NUP. Research continues on both the causes of and therapeutic strategies for NUP.

Oral infections influence the pathogenesis of many diseases and conditions. An assessment of health status must include that of the oral cavity. Periodontitis has been reported to affect the successful outcome of joint and organ replacements and kidney dialysis. Since the presence and severity of oral infections such as periodontal disease often increase with age, it is of growing importance that we understand, prevent and control oral inflammatory diseases in the aging U.S. population.

Because of the enhanced awareness of the importance of maintaining good oral health at all ages, and the fact that approximately $6 billion is spent annually to treat periodontal disease, the amount of research on prevention has steadily increased. In the oral cavity, most of the organisms colonize as commensal organisms. When introduced into the circulation in bacteremias, they may behave as pathogens. There is a high prevalence of association between viridans streptococci and infectious endocarditis. Even in the era of modern antibiotics, this group of bacteria can selectively colonize on injured or defective heart valves and cause a life-threatening disease. In 1997, the American Heart Association, or AHA, updated its recommendations for the prevention of bacterial endocarditis in people at risk of developing this disease.[11] For oral and dental procedures, the AHA reduced the initial amoxicillin dose to 2 grams, and a follow-up antibiotic dose is no longer recommended. Erythromycin is no longer recommended for patients allergic to penicillin, but clindamycin and other alternatives are offered.[11]

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The increased interest in periodontitis also resulted in the FDA's recent approval of three new therapies. In October, CollaGenex Pharmaceuticals was given final marketing approval by the FDA for the doxycycline hyclate pill Periostat, which is to be prescribed by the dentist to help enhance and maintain the benefits of scaling and root planing for periodontal disease and to prevent the disease from spreading. In patients with periodontitis, the body overproduces the enzyme collagenase. Collagenase breaks down collagen, which forms the structural basis of the tissues of the periodontium. Periostat contains the drug doxycycline, which suppresses collagenase, thereby protecting the connective tissue from further destruction. This is the first drug that specifically inhibits a destructive aspect of the host inflammatory response.

Another new FDA-approved treatment for periodontitis is Atridox (10 percent doxycycline hyclate), developed by Atrix Laboratories. This product is administered with a syringe and blunt cannula in liquid form to infected periodontal pockets. Once administered, it

fills the pocket, solidifies and releases doxycycline hyclate (a collagenase suppressor) at a sustained rate for approximately one week. Unlike Periostat, it can be used as a stand-alone therapy.

A third approved product is PerioChip, marketed by Astra Pharmaceuticals L.P. It is a biodegradable chip soaked with the antibiotic chlorhexidine. Chlorhexidine is a broad-spectrum antibiotic that destroys the bacterial cell membrane and lyses the cell. It is released in a biphasic manner: 40 percent in 24 hours and then in a linear fashion for seven to 10 days. PerioChip is placed directly into the periodontal pocket.

CONCLUSION

The association of oral infections with systemic diseases is receiving increased interest in the research world.[8] A number of basic, translational and clinical research studies into this relationship are being supported. In the near future, interventional clinical studies will be needed to determine if the management of oral infections does in fact reduce systemic diseases and conditions. If these studies are successful, they will provide very compelling scientific evidence coupled with improved health outcomes, which can catalyze much-needed reforms in dental and medical education and practice. ■

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The views expressed are those of the author and do not necessarily reflect the opinions or official policies of the American Dental Association.

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