

Systemic Diseases Caused by Oral Infection

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INTRODUCTION

The theory of focal infection, which was promulgated during the 19th and early 20th centuries, stated that “foci” of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases such as arthritis, peptic ulcers, and appendicitis (120). In the oral cavity, therapeutic edentulation was common as a result of the popularity of the focal infection theory. Since many teeth were extracted without evidence of infection, thereby providing no relief of symptoms, the theory was discredited and largely ignored for many years. Recent progress in classification and identification of oral microorganisms and the realization that certain microorganisms are normally found only in the oral cavity have opened the way for a more realistic assessment of the importance of oral focal infection. It has become increasingly clear that the oral cavity can act as the site of origin for dissemination of pathogenic organisms to distant body sites, especially in immunocompromised hosts such as patients suffering from malignancies, diabetes, or rheumatoid arthritis or having corticosteroid or other immunosuppressive treatment. A number of epidemiological studies have suggested that oral infection, especially marginal and apical periodontitis, may be a risk factor for systemic diseases.

The teeth are the only nonshedding surfaces in the body, and bacterial levels can reach more than 10^{11} microorganisms per mg of dental plaque. Human endodontal and periodontal infections are associated with complex microfloras in which approximately 200 species (in apical periodontitis) (140) and more than 500 species (in marginal periodontitis) (97) have

been encountered. These infections are predominantly anaerobic, with gram-negative rods being the most common isolates. The anatomic closeness of these microfloras to the bloodstream can facilitate bacteremia and systemic spread of bacterial products, components, and immunocomplexes.

BACTEREMIA

The incidence of bacteremia following dental procedures such as tooth extraction, endodontic treatment, periodontal surgery, and root scaling has been well documented (4, 12, 25, 29, 33, 53, 75, 83, 100, 108). Bacteremia after dental extraction, third-molar surgery, dental scaling, endodontic treatment, and bilateral tonsillectomy has been studied by means of lysis-filtration of blood samples with subsequent aerobic and anaerobic incubation (53). Bacteremia was observed in 100% of the patients after dental extraction, in 70% after dental scaling, in 55% after third-molar surgery, in 20% after endodontic treatment, and in 55% after bilateral tonsillectomy. Anaerobes were isolated more frequently than facultative anaerobic bacteria. Another study (117) involving 735 children undergoing treatment for extensive dental decay found that 9% of the children had detectable bacteremias before the start of dental treatment. In addition, a variety of hygiene and conservative procedures, including brushing of the teeth, increased the prevalence of bacteremias from 17 to 40%. Anesthetic and surgical procedures increased the occurrence of bacteremias from 15 to 97%. One recent study by Debelian et al. (26) used phenotypic and genetic methods to trace microorganisms released into the bloodstream during and after endodontic treatment back to their presumed source, the root canal. Microbiological samples were taken from the root canals of 26 patients with asymptomatic apical periodontitis of single-rooted teeth. Blood was drawn from the patients during and 10 min after

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endodontic therapy. All root canals contained anaerobic bacteria. In group I, where the first three root canal reamers were used to a level 2 mm beyond the apical foramen of the tooth, *Propionibacterium acnes*, *Peptostreptococcus prevotii*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Saccharomyces cerevisiae* were recovered from the blood. In group 2, where instrumentation ended inside the root canal, *P. intermedia*, *Actinomyces israelii*, *Streptococcus intermedius*, and *Streptococcus sanguis* were isolated from the blood.

As stated above, dissemination of oral microorganisms into the bloodstream is common, and less than 1 min after an oral procedure, organisms from the infected site may have reached the heart, lungs, and peripheral blood capillary system (65).

There are more than 10^{13} microbes on all surfaces of the body, yet the underlying tissues and the bloodstream are usually sterile. In the oral cavity there are several barriers to bacterial penetration from dental plaque into the tissue: a physical barrier composed of the surface epithelium; defensins, which are host-derived peptide antibiotics, in the oral mucosal epithelium; an electrical barrier that reflects the E_h difference between the host cell and the microbial layer; an immunological barrier of antibody-forming cells; and the reticuloendothelial system (phagocyte barrier) (78, 81, 147). Under normal circumstances, these barrier systems work together to inhibit and eliminate penetrating bacteria. When this state of equilibrium is disturbed by an overt breach in the physical system (e.g., trauma), the electrical system (i.e., hypoxia), or immunological barriers (e.g., through neutropenia, AIDS, or immunosuppressant therapy), organisms can propagate and cause both acute and chronic infections with increased frequency and severity (79). With normal oral health and dental care, only small numbers of mostly facultative bacterial species gain access to the bloodstream. However, with poor oral hygiene, the numbers of bacteria colonizing the teeth, especially supragingivally, could increase 2- to 10-fold (80) and thus possibly introduce more bacteria into tissue and the bloodstream, leading to an increase in the prevalence and magnitude of bacteremia.

The purpose of this review is to evaluate the current status of oral infections, especially periodontitis, as a causal factor for systemic diseases.

PATHWAYS LINKING ORAL INFECTION TO SECONDARY NONORAL DISEASE

Three mechanisms or pathways linking oral infections to secondary systemic effects have been proposed (136). These are metastatic spread of infection from the oral cavity as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral microorganisms.

Metastatic infection. As previously discussed, oral infections and dental procedures can cause transient bacteremia. The microorganisms that gain entrance to the blood and circulate throughout the body are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia) and as a rule lead to no other clinical symptoms than possibly a slight increase in body temperature (65, 136). However, if the disseminated microorganisms find favorable conditions, they may settle at a given site and, after a certain time lag, start to multiply.

Metastatic injury. Some gram-positive and gram-negative bacteria have the ability to produce diffusible proteins, or exotoxins, which include cytolytic enzymes and dimeric toxins with A and B subunits. The exotoxins have specific pharmacological actions and are considered the most powerful and lethal poi-

TABLE 1. Possible pathways of oral infections and nonoral diseases^a

Pathway for oral infection	Possible nonoral diseases
Metastatic infection from oral cavity via transient bacteremia.....	Subacute infective endocarditis, acute bacterial myocarditis, brain abscess, cavernous sinus thrombosis, sinusitis, lung abscess/infection, Ludwig's angina, orbital cellulitis, skin ulcer, osteomyelitis, prosthetic joint infection
Metastatic injury from circulation of oral microbial toxins	Cerebral infarction, acute myocardial infarction, abnormal pregnancy outcome, persistent pyrexia, idiopathic trigeminal neuralgia, toxic shock syndrome, systemic granulocytic cell defects, chronic meningitis
Metastatic inflammation caused by immunological injury from oral organisms	Behçet's syndrome, chronic urticaria, uveitis, inflammatory bowel disease, Crohn's disease

^a Compiled from references 109 and 115.

sons known (51). Conversely, endotoxins are part of the outer membranes released after cell death (51, 93). Endotoxin is compositionally a lipopolysaccharide (LPS) that, when introduced into the host, gives rise to a large number of pathological manifestations. LPS is continuously shed from periodontal gram-negative rods during their growth in vivo (93).

Metastatic inflammation. Soluble antigen may enter the bloodstream, react with circulating specific antibody, and form a macromolecular complex. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the sites of deposition (136, 145).

Possible pathways of oral infections and nonoral diseases are listed in Table 1.

PERIODONTAL DISEASE AFFECTS SUSCEPTIBILITY TO SYSTEMIC DISEASE

Most studies concerning the relationship between oral infection and systemic diseases are related to periodontal disease, by far the most common oral infection. The term periodontal disease is used to describe a group of conditions that cause inflammation and destruction of the attachment apparatus of the teeth (i.e., gingiva, periodontal ligament, root cementum, and alveolar bone). Periodontal disease is caused by bacteria found in dental plaque, and about 10 species have been identified as putative pathogens in periodontal disease, mainly gram-negative rods. *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Bacteroides forsythus* are the gram-negative bacteria most commonly associated with periodontitis (3, 50, 131). Periodontitis lesions exhibit gingival inflammation as well as destruction of the periodontal ligament and alveolar bone. This leads to bone loss and apical migration of the junctional epithelium, resulting in the formation of periodontal pockets.

In a recent review article (111), Page proposed that periodontitis may affect the host's susceptibility to systemic disease in three ways: by shared risk factors, by subgingival biofilms acting as reservoirs of gram-negative bacteria, and through the periodontium acting as a reservoir of inflammatory mediators.

Shared risk factors. Factors that place individuals at high risk for periodontitis may also place them at high risk for systemic diseases such as cardiovascular disease. Among the environmental risk factors and indicators shared by periodon-

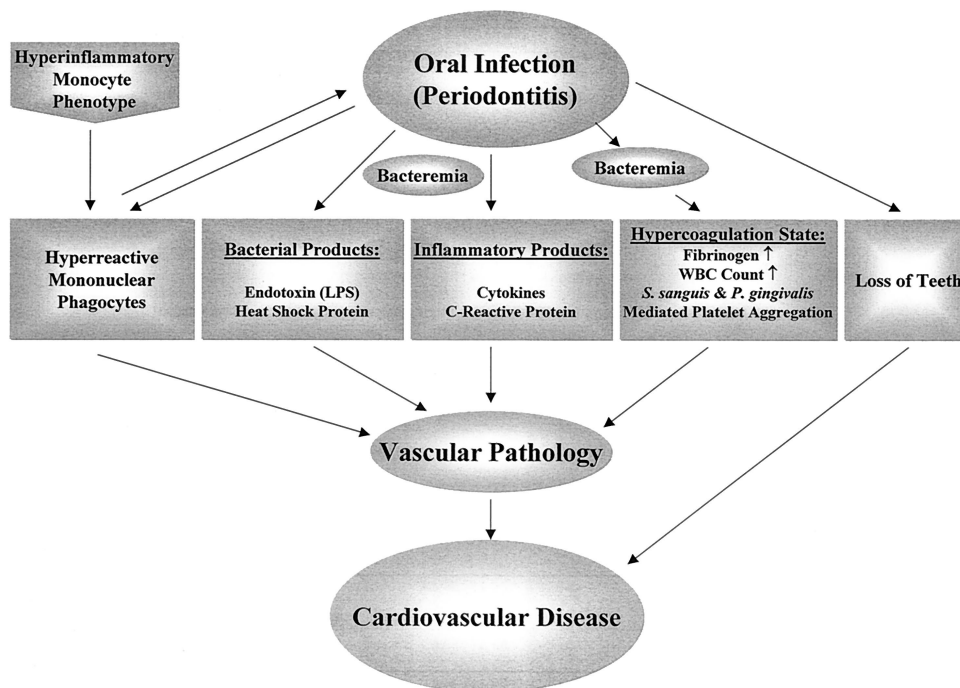


FIG. 1. Proposed mechanisms linking oral infection and periodontal disease to cardiovascular disease.

titis and systemic diseases, such as cardiovascular disease, are tobacco smoking, stress, aging, race or ethnicity, and male gender (111). Studies demonstrating genetic factors shared by periodontitis, cardiovascular disease, preterm labor, and osteoporosis have not yet been performed but may be fruitful (111).

Subgingival biofilms. Subgingival biofilms constitute an enormous and continuing bacterial load. They present continually renewing reservoirs of LPS and other gram-negative bacteria with ready access to the periodontal tissues and the circulation. Systemic challenge with gram-negative bacteria or LPS induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration, and intravascular coagulation (86, 87). LPS upregulates expression of endothelial cell adhesion molecules and secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), and thromboxane, which results in platelet aggregation and adhesion, formation of lipid-laden foam cells, and deposits of cholesterol and cholesterol esters.

Periodontium as cytokine reservoir. The proinflammatory cytokines TNF- α , IL-1 β , and gamma interferon as well as prostaglandin E₂ (PGE₂) reach high tissue concentrations in periodontitis (111). The periodontium can therefore serve as a renewing reservoir for spillover of these mediators, which can enter the circulation and induce and perpetuate systemic effects. IL-1 β favors coagulation and thrombosis and retards fibrinolysis (19). IL-1, TNF- α , and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells, and deposition of cholesterol. These same mediators emanating from the diseased periodontium may also account for preterm labor and low-birth-weight infants (111).

SYSTEMIC DISEASES ASSOCIATED WITH ORAL INFECTION

Cardiovascular Disease

Cardiovascular diseases such as atherosclerosis and myocardial infarction occur as a result of a complex set of genetic and environmental factors (56). The genetic factors include age, lipid metabolism, obesity, hypertension, diabetes, increased fibrinogen levels, and platelet-specific antigen Zw_b (P1^{A2}) polymorphism. Environmental risk factors include socioeconomic status, exercise stress, diet, nonsteroidal anti-inflammatory drugs, smoking, and chronic infection. The classical risk factors of cardiovascular disease such as hypertension, hypercholesterolemia, and cigarette smoking can only account for one-half to two-thirds of the variation in the incidence of cardiovascular disease (120).

Among other possible risk factors, evidence linking chronic infection and inflammation to cardiovascular disease has been accumulating (116, 134, 141). It is clear that periodontal disease is capable of predisposing individuals to cardiovascular disease, given the abundance of gram-negative species involved, the readily detectable levels of proinflammatory cytokines, the heavy immune and inflammatory infiltrates involved, the association of high peripheral fibrinogen, and the white blood cell (WBC) counts (66).

There are several proposed mechanisms (Fig. 1) by which periodontal disease may trigger pathways leading to cardiovascular disease through direct and indirect effects of oral bacteria. First, evidence indicates that oral bacteria such as *Streptococcus sanguis* and *Porphyromonas gingivalis* induce platelet aggregation, which leads to thrombus formation (55). These organisms have a collagen-like molecule, the platelet aggregation-associated protein, on their surface (57). When *S. sanguis* is injected intravenously into rabbits, a heart attack-like series

of events occur. Possibly, antibodies reactive to periodontal organisms localize in the heart and trigger complement activation, a series of events leading to sensitized T cells and heart disease (55). Furthermore, one or more periodontal pathogens have been found in 42% of the atheromas studied in patients with severe periodontal disease (V. I. Haraszthy, J. J. Zambon, M. Trevisan, R. Shah, M. Zeid, and R. J. Genco, *J. Dent. Res. Spec. Iss.* 77, p. 666, abstr. 273, 1998). In one recent study, Deshpande et al. (27) showed that *P. gingivalis* can actively adhere to and invade fetal bovine heart endothelial cells, bovine aortic endothelial cells, and human umbilical vein endothelial cells. Invasion efficiencies of 0.1, 0.2, and 0.3% were obtained with bovine aortic endothelial cells, human umbilical vein endothelial cells, and fetal bovine heart endothelial cells, respectively. Potempa et al. (J. Potempa, T. Imamura, and J. Travis, *J. Dent. Res. Spec. Iss.* 78, p. 180, abstr. 593, 1999) studied proteolytic enzymes referred to as gingipains R, which are released in large quantities from *P. gingivalis*. After entering the circulation, gingipains R can activate factor X, prothrombin, and protein C, promoting a thrombotic tendency through the ultimate release of thrombin, subsequent platelet aggregation, conversion of fibrinogen to fibrin, and intravascular clot formation.

The second factor in this process could be an exaggerated host response to a given microbial or LPS challenge, as reflected in the release of high levels of proinflammatory mediators such as PGE₂, TNF- α , and IL-1 β (54, 106). These mediators have been related to interindividual differences in the T-cell repertoire and the secretory capacity of monocytes. Typically, peripheral blood monocytes from these individuals with the hyperinflammatory monocyte phenotype secrete 3- to 10-fold-greater amounts of these mediators in response to LPS than those from normal monocyte phenotype individuals (54, 106). Several investigators have suggested that genes that regulate the T-cell monocyte response and the host-microbe environment can directly trigger and modulate the inflammatory response. Patients with certain forms of periodontal disease, such as early-onset periodontitis and refractory periodontitis, possess a hyperinflammatory monocyte phenotype (54, 106, 125).

A third mechanism possibly involves the relationship between bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS from periodontal organisms being transferred to the serum as a result of bacteremias or bacterial invasion may have a direct effect on endothelia so that atherosclerosis is promoted (113). LPS may also elicit recruitment of inflammatory cells into major blood vessels and stimulate proliferation of vascular smooth muscle, vascular fatty degeneration, intravascular coagulation, and blood platelet function. These changes are the result of the action of various biologic mediators, such as PGs, ILs, and TNF- α on vascular endothelium and smooth muscle (5, 137). Fibrinogen and WBC count increases noted in periodontitis patients may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis (71).

Periodontitis as an infection may stimulate the liver to produce C-reactive protein (CRP) (a marker of inflammation), which in turn will form deposits on injured blood vessels. CRP binds to cells that are damaged and fixes complement, which activates phagocytes, including neutrophils. These cells release nitric oxide, thereby contributing to atheroma formation (40; S. Al-Mubarak, S. G. Ciancio, A. Al-Suwied, W. Hamouda, and P. Dandona, *J. Dent. Res. Spec. Iss.* 77, p. 1030, abstr. 3192, 1998). In a study of 1,043 apparently healthy men, baseline plasma concentrations of CRP predicted the risk of

future myocardial infarction and stroke (116). Ebersole et al. (35) found that patients with adult periodontitis have higher levels of CRP and haptoglobin than subjects without periodontitis. Both CRP and haptoglobin levels decline significantly after periodontal therapy. Loos et al. (B. G. Loos, J. Hutter, A. Varoufaki, H. Bulthus, J. Craandijk, R. A. M. Huffels, F. J. Hoek, and U. Van Der Velden, *J. Dent. Res. Spec. Iss.* 77, p. 666, abstr. 274, 1998) described 153 systemically healthy subjects consisting of 108 untreated periodontitis patients and 45 control subjects. Mean plasma CRP levels were higher in the periodontitis patients. Patients with severe periodontitis had significantly higher CRP levels than mild-periodontitis patients, and both had significantly higher levels than the controls. Another recent study (41) evaluated the relationship of cardiovascular disease and CRP. Groups of adults who had neither periodontal nor cardiovascular disease, one of these diseases, or both of them were assembled. In those with both heart disease and periodontal disease, the mean level of CRP (8.7 g/ml) was significantly different from that (1.14 g/ml) in controls with neither disease. The authors also showed that treatment of the periodontal disease caused a 65% reduction in the level of CRP at 3 months. The level remained reduced for 6 months.

Recently, a specific heat shock protein, Hsp65, has been reported to link cardiovascular risks and host responses (67, 150–153). Heat shock proteins are important for the maintenance of normal cellular function and may have additional roles as virulence factors for many bacterial species (154). In animal studies, Xu et al. (153) demonstrated that immunization of rabbits with bacterial Hsp65 induces atherosclerotic lesions. A subsequent large-scale clinical study found a significant association between serum antibody levels to Hsp65 and the presence of cardiovascular disease (152). Their theory, consistent with their clinical findings, is that bacterial infection stimulates the host response to Hsp65, which is a major immunodominant antigen of many bacterial species. The interaction between expressed Hsp65 and the immune response induced by bacterial infection is hypothesized to be responsible for the initiation of the early atherosclerotic lesion (153). It has been suggested that chronic oral infection stimulates high levels of Hsp65 in subjects with high cardiovascular risk (81). Thus, if antibodies directed towards bacterial heat shock proteins cross-react with heat shock proteins expressed in the host tissue, especially if they are found in the lining of blood vessels, then some oral species might well be the link between oral infection and cardiovascular disease (81).

Finally, oral infection can also cause tooth loss. Evidence has shown that edentulous persons with and without dentures and dentate individuals with missing teeth change their eating habits (13, 14, 101, 143, 146). They may thereby avoid certain nutritious foods because of difficulty in chewing and select high-calorie, high-fat food. When the foods cannot be well pulverized, this has an adverse effect on the internal absorption of nutrients. Such dietary preferences would predispose such individuals to the type of high-fat foods that are recognized as risk factors for cardiovascular disease (148). In dentate individuals with many missing teeth, the diet-induced elevation of serum low-density lipoprotein has been shown to upregulate monocyte responses to LPS (96). In these subjects, one would have both the diet-induced sensitization of monocytes and the plaque-laden teeth that could provide the LPS challenge to these cells. Instead of having hyperresponsive monocytes reacting to any LPS introduced from the plaque, there would be elevated secretion of inflammatory cytokines by monocytes stimulated by elevated low-density lipoprotein levels. This interaction between LPS and monocytes may explain the severity

TABLE 2. Adjusted odds ratios for cardiovascular disease for patients with periodontal disease

Study	Yr	Odds ratio	
		Total cardiovascular disease	Fatal cardiovascular disease/stroke
DeStefano et al. (28)	1993	1.29	1.46
Beck et al. (5)	1996	1.5	1.9/2.8
Joshi-pura et al. (63)	1996	1.67	
Grau et al. (45)	1997		2.6

of gram-negative infections in certain diabetic patients (96), but it could also be operating in individuals who change to a high-fat diet because of missing teeth. Thus, all the mechanisms by which poor oral hygiene and periodontal disease may contribute to cardiovascular disease described above could also come into play as a result of certain dietary changes secondary to missing teeth (81).

Adjusted odds ratios for cardiovascular disease, fatal cardiovascular disease, and stroke for patients with periodontal disease are given in Table 2.

Coronary heart disease: atherosclerosis and myocardial infarction. Atherosclerosis has been defined as a progressive disease process that involves the large- to medium-sized muscular and large elastic arteries. The advanced lesion is the atheroma, which consists of elevated focal intimal plaques with a necrotic central core containing lysed cells, cholesterol ester crystals, lipid-laden foam cells, and surface plasma proteins, including fibrin and fibrinogen (9). The presence of atheroma tends to make the patient thrombosis prone because the associated surface enhances platelet aggregation and thrombus formation that can occlude the artery or be released to cause thrombosis, coronary heart disease, and stroke. Overall, about 50% of deaths in the United States are attributed to the complications of atherosclerosis and resulting cardiovascular diseases (5). A recent preliminary report indicates that atherosclerotic plaques are commonly infected with gram-negative periodontal pathogens, including *A. actinomycetemcomitans* and *P. gingivalis* (J. J. Zambon, V. I. Haraszthy, S. G. Grossi, and R. J. Genco, *J. Dent. Res. Spec. Iss.* 76, p. 408, abstr. 3159, 1997).

A myocardial infarction is the damaging or death of an area of the heart muscle resulting from a reduced blood supply to that area. Myocardial infarction is almost always due to the formation of an occlusive thrombus at the site of rupture of an atheromatous plaque in a coronary artery (9).

The associations between oral conditions and atherosclerosis and coronary heart disease are listed in Table 3.

Stroke. Stroke is a cerebrovascular disease that affects blood vessels supplying blood to the brain. It occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by local thrombus formation or by aggregates of bacteria and fibrin from other sources such as the heart. In an average population, the annual incidence of new strokes is 2 per 1,000 (21). Studies on the pathology of stroke indicate that 80 to 85% of these lesions are due to cerebral infarction; 15 to 20% are caused by hemorrhage (21).

The inflamed periodontium releases inflammatory cytokines, LPS, and bacteria into the systemic circulation, and they may promote atherosclerosis and affect blood coagulation, the function of platelets, and PG synthesis, thereby contributing to the onset of stroke. In a case-control study (135), 40 patients under the age of 50 with cerebral infarction and 40 randomly selected community controls matched for sex and age were compared for dental status. Poor oral health, as assessed by total dental index and orthopantomography, was more common in the patients with cerebral infarction than in individuals of the control group.

Another cross-sectional study of 401 veterans showed that several dental and oral conditions were significantly associated with the diagnosis of a cerebral vascular accident when included in a multivariate logistic regression model with and without many of the known risk factors for cerebral vascular accident (81).

Infective Endocarditis

Infective endocarditis is a bacterial infection of the heart valves or the endothelium of the heart. It occurs when bacteria in the bloodstream lodge on abnormal heart valves or damaged heart tissue. Endocarditis occurs rarely in people with normal hearts. However, people who have certain preexisting heart defects are at risk for developing endocarditis when a bacteremia occurs (9).

Infective endocarditis is a serious and often fatal systemic disease that has been associated with dental diseases and treatment. There are over 1,000 case reports associating dental procedures or disease with the onset of endocarditis (32). Three controlled studies have recently been conducted, all showing an association of dental procedures with bacterial endocarditis (31, 72, 144). In addition, multiple animal models (rats, rabbits, and pigs) have shown that oral bacteria and even dental extraction can create histologic evidence of endocarditis under experimental conditions (34, 110). It appears that dental procedures, especially extractions and possibly scaling, meet currently accepted epidemiological criteria for causation of endocarditis (58, 119). No other systemic diseases or condi-

TABLE 3. Associations between oral conditions and atherosclerosis/coronary heart disease^a

Study	Yr	Design	Association	Adjusted measure
Mattila et al. (88)	1989	Case-control	Total dental index and heart attack	OR = 1.3
Mattila et al. (89)	1993	Case-control	Total dental index and atheromatosis	OR = 1.4
DeStefano et al. (28)	1993	Cohort	PI, OHI, and admissions	RR = 1.2
			Death due to CHD	RR = 1.7
Mattila et al. (90)	1995	Follow-up	Total dental index and new events	HR = 1.2
Beck et al. (5)	1996	Cohort	PD, bone levels, and new CHD	OR = 1.5
			Fatal CHD	OR = 1.9
			Stroke	OR = 2.8
Joshi-pura et al. (63)	1996	Cohort	Tooth loss and CHD	RR = 1.7
Genco et al. ^b	1997	Cohort	Bone loss and new CHD	OR = 2.7

^a Abbreviations: CHD, coronary heart disease; PI, plaque index; PD, probing depth; OR, odds ratio; HR, hazard ratio; RR, relative risk.

^b R. Genco, S. Chadda, S. Grossi, R. Dunford, G. Taylor, W. Knowler, and D. Pettitt, *J. Dent. Res. Spec. Iss.* 76, p. 408, abstr. 3158, 1997.

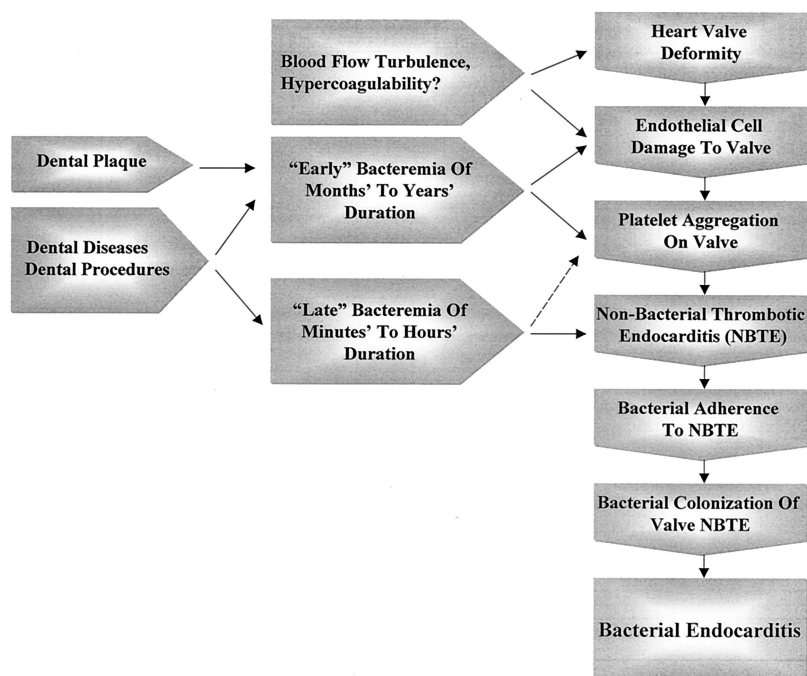


FIG. 2. Proposed causal model of dentally associated endocarditis (adapted from ref. 32 with permission of the publisher).

tions have been studied so extensively, although several other disorders may be linked to dental diseases.

Drangsholt (32) searched the world biomedical literature from 1930 to 1996 and concluded that the incidence of infective endocarditis varies between 0.70 and 6.8 per 100,000 person-years; over 50% of all infective endocarditis cases are not associated with either an obvious procedural or infectious event 3 months prior to developing symptoms; 8% of all infective endocarditis cases are associated with periodontal or dental disease without a dental procedure; the risk of infective endocarditis after a dental procedure is probably in the range of 1 per 3,000 to 5,000 procedures; and over 80% of all infective endocarditis cases are acquired in the community, and the associated bacteria are part of the host's endogenous flora. A new causal model (Fig. 2) of dental disease- and procedure-associated endocarditis has been proposed (32) that involves early and late bacteremia. The early bacteremia may "prime" the endothelial surface of the heart valves over many years and promote early valve thickening. This renders the valves susceptible to late adherence and colonization with bacteria. The late bacteremia may work over days to weeks and allows bacterial adherence and colonization of the valve, resulting in the characteristic fulminant infection.

Bacterial Pneumonia

Pneumonia is an infection of pulmonary parenchyma caused by a wide variety of infectious agents, including bacteria, fungi, parasites, and viruses. Pneumonia can be a life-threatening infection, especially in the old and immunocompromised patient, and is a significant cause of morbidity and mortality in patients of all ages. Total pneumonia mortality in low-risk individuals over 65 years of age is 9 per 100,000 (0.009%), whereas in high-risk individuals who are likely to aspirate, the mortality can be almost 1,000 per 100,000 (1%) or higher (102). Pneumonias can be broadly divided into two types, community ac-

quired and hospital acquired (nosocomial). These types of pneumonia differ in their causative agents.

The lung is composed of numerous units formed by the progressive branching of the airways. The lower respiratory tracts are normally sterile, despite the fact that secretions from upper respiratory tracts are heavily contaminated with microorganisms from the oral and nasal surfaces. Sterility in the lower respiratory tract is maintained by intact cough reflexes, by the action of tracheobronchial secretions, by mucociliary transport of inhaled microorganisms and particulate material from the lower respiratory tract to the oropharynx, and by immune and nonimmune defense factors (30, 73, 122). The defense factors are present in a secretion which also contains surfactant and other proteins such as fibronectin, complement, and immunoglobulins, which coat the pulmonary epithelium. The lung also contains a rich system of resident phagocytic cells which remove microorganisms and particulate debris (122).

Microorganisms can infect the lower respiratory tracts by four possible routes: aspiration of oropharyngeal contents (94), inhalation of infectious aerosols (139), spread of infection from contiguous sites (73), and hematogenous spread from extrapulmonary sites of infection (37).

Most commonly, bacterial pneumonia results from aspiration of oropharyngeal flora into the lower respiratory tract, failure of host defense mechanisms to eliminate them, multiplication of the microorganisms, and subsequent tissue destruction (8). It is likely that most pathogens first colonize the surfaces of the oral cavity or pharyngeal mucosa before aspiration (8). These pathogens can colonize from an exogenous source or emerge following overgrowth of the normal oral flora after antibiotic treatment. Common potential respiratory pathogens (PRPs) such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* can colonize the oropharynx and be aspirated into the lower airways. Other species thought to comprise the normal oral flora, including *A. actinomycetemcomitans* and anaerobes such as *P.*

gingivalis and *Fusobacterium* species, can also be aspirated into the lower airways and cause pneumonia (122).

Generally accepted risk factors that predispose an individual to nosocomial pneumonia include the presence of underlying diseases such as chronic lung disease, congestive heart failure, or diabetes mellitus; age >70 years; mechanical ventilation or intubation; a history of smoking; previous antibiotic treatment; immunosuppression; a long preoperative stay; and prolonged surgical procedures (20, 22, 129, 139).

Pneumonia can result from infection by anaerobic bacteria. Dental plaque would seem to be a logical source of these bacteria, especially in patients with periodontal disease. Such patients harbor a large number of subgingival bacteria, particularly anaerobic species. Among the oral bacterial species implicated in pneumonia are *A. actinomycetemcomitans* (155), *Actinomyces israelii* (98, 158), *Capnocytophaga* spp. (85), *Eikenella corrodens* (62), *Prevotella intermedia*, and *Streptococcus constellatus* (127).

There are several proposed mechanisms to explain the propensity for PRPs to colonize the oropharynx of susceptible patients. First, compromised individuals such as diabetics and alcoholics may be prone to oropharyngeal colonization by PRPs (122). These individuals are thought to be more likely to aspirate and are also known to be at greater risk of periodontal disease (48). Thus, the extensive dental plaque of these subjects may provide surfaces to which PRPs might adhere to provide a reservoir for infection to distal portions of the respiratory tract (69).

Second, the oral surface of subjects at high risk for pneumonia, such as hospitalized patients, may somehow become modified to provide receptors for the adhesion of PRPs (122). Poor oral hygiene increases the plaque load and therefore the level of hydrolytic enzymes in saliva. The source of these enzymes has been attributed to plaque bacteria (82, 99, 156) or polymorphonuclear leukocytes, which enter the saliva through the inflamed gingival sulcus (6, 7, 18, 44). These proteolytic enzymes may alter the characteristics of the mucosal surfaces, resulting in increased colonization by pathogenic bacteria (15, 43).

Limeback (74) noted a relationship between poor oral hygiene and aspiration pneumonia among elderly residents of chronic care facilities. He subsequently found that the nursing homes with the least number of dental visits had the most deaths due to pneumonia.

A study by Scannapieco et al. (123) has shown that individuals with respiratory disease ($n = 41$) have significantly higher oral hygiene index scores than subjects without respiratory disease ($n = 193$; $P = 0.044$). Logistic regression analysis of data from these subjects, which considers age, race, gender, smoking status, and simplified oral hygiene index (OHI), suggests that subjects having the median OHI value are 1.3 times more likely to have a respiratory disease than those with an OHI of 0. (OHI is a composite index which scores debris and calculus deposition on tooth surfaces.) Similarly, subjects with the maximum OHI value are 4.5 times more likely to have a chronic respiratory disease than those with an OHI of 0.

In another study, Scannapieco and Ho (F. A. Scannapieco and A. W. Ho, *J. Dent. Res. Spec. Iss.* 78, p. 542, abstr. 3491, 1999) examined data from the National Health and Nutrition Examination Survey III. The results showed that subjects ($n = 13,792$) with a mean periodontal attachment loss (which evaluates the loss of supporting tissues of the teeth) of 2.0 mm have a higher risk of chronic lung disease than those who have a mean attachment loss of <2.0 mm (odds ratio = 1.43, 95% confidence interval [CI] = 1.08 to 1.90), adjusting for age,

gender, race or ethnicity, education, income, frequency of dental visits, smoking, and alcohol consumption.

Loesche and Lopatin (81) have studied oral and dental conditions in over 350 elderly individuals that may predispose individuals for aspiration pneumonia. They used the periodontal disease score as the outcome and compared the upper tertile of the periodontal disease score with the lower tertiles. The individuals with "definite" aspiration pneumonia were 3.3 times more likely to have a higher periodontal disease score (95% CI = 1.06 to 10.3; $P = 0.05$) than the individuals without pneumonia. The odds ratio pattern and wide CIs suggest that an important association exists between poor periodontal status and aspiration pneumonia.

Low Birth Weight

Pregnancy can influence gingival health. Changes in hormone levels during pregnancy promote an inflammation termed pregnancy gingivitis (77). This type of gingivitis may occur without changes in plaque levels (70). Oral contraceptives may also produce changes in gingival health. Some birth control pill users have a high gingival inflammation level but a low plaque level. Birth control pills may cause changes such as alteration of the microvasculature, gingival permeability, and increased synthesis of estrogen PGs (64).

Oral infections also seem to increase the risk for or contribute to low birth weight in newborns. Low birth weight, defined as a birth weight of <2,500 g, is a major public health problem in both developed and developing countries. The incidence of preterm delivery and low birth weight has not decreased significantly over the last decade and remains at about 10% of all live births in the United States (105).

Low birth weight in preterm infants remains a significant cause of perinatal morbidity and mortality. Compared to normal-birth-weight infants, low-birth-weight infants are more likely to die during the neonatal period (92, 126), and low-birth-weight survivors face neurodevelopment disturbances (11, 38), respiratory problems (49, 91), and congenital anomalies (17, 142). They also demonstrate more behavioral abnormalities as preschoolers (133) and may have attention deficit hyperactivity disorder (10). For low birth weight, all these factors need further elucidation.

Risk factors for preterm low-birth-weight infants include older (>34 years) and younger (<17 years) maternal age, African-American ancestry, low socioeconomic status, inadequate prenatal care, drug, alcohol, and/or tobacco abuse, hypertension, genitourinary tract infection, diabetes, and multiple pregnancies. Although increasing efforts have been made to diminish the effects of these risk factors through preventive interventions during prenatal care, they have not reduced the frequency of preterm low-birth-weight infants (107).

Evidence of increased rates of amniotic fluid infection, chorioamnion infection, and chorioamnionitis supports an association between preterm birth or low birth weight and infection during pregnancy (105). Histologically, the chorioamnion is often inflamed, even in the absence of any bacterial infection in the vagina (vaginosis) or cervical area. This suggests that distant sites of infection or sepsis may be targeting the placental membranes. Vaginosis, caused by gram-negative, anaerobic bacteria, is a significant risk factor for prematurity and is usually associated with the smallest, most premature neonatal deliveries (59, 60). The biological mechanisms involve bacterially induced activation of cell-mediated immunity leading to cytokine production and the ensuing synthesis and release of PG, which appears to trigger preterm labor (59). Elevated levels of cytokines (IL-1, IL-6, and TNF- α) have been found in

the amniotic fluid of patients in preterm labor with amniotic fluid infection (118). These cytokines are all potent inducers of both PG synthesis and labor. Intra-amniotic levels of PGE₂ and TNF- α rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery (107).

As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome. During pregnancy, the ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaque in the second trimester (70). The gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that can directly affect the host. One microbial component, LPS, can activate macrophages and other cells to synthesize and secrete a wide array of molecules, including the cytokines IL-1 β , TNF- α , IL-6, and PGE₂ and matrix metalloproteinases (23, 105). If they escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of PGE₂ and TNF- α in the amniotic fluid and induce premature labor.

Human case-control studies have demonstrated that women who have low-birth-weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal-birth-weight infants (105).

A case-control study of 124 pregnant or postpartum mothers was performed, using mothers with normal-birth-weight babies as controls (107). Assessments included a broad range of known obstetric risk factors, such as tobacco and drug use, alcohol consumption, level of prenatal care, parity, genitourinary infections, and nutrition. Each subject received a periodontal examination to determine the clinical attachment level. Mothers of preterm low-birth-weight infants and primiparous mothers of preterm low-birth-weight infants ($n = 93$) had significantly worse periodontal disease than the respective mothers of normal-birth-weight infants (controls). Multivariate logistic regression models, controlling for other risk factors and covariates, demonstrated that periodontal disease is a statistically significant risk factor for preterm low birth weight, with adjusted odds ratios of 7.9 and 7.5 for all preterm low-birth-weight cases and primiparous preterm low-birth-weight cases, respectively. These data indicate that periodontal disease represents a previously unrecognized and clinically significant risk factor for preterm low birth weight as a consequence of either preterm labor or premature rupture of membranes.

In another 1:1 matched case-control study (55 pairs), the hypothesis that poor oral health of the pregnant woman is a risk factor for low birth weight was evaluated (24). The effect of the periodontal and dental caries status of the woman on the birth weight of the infant was evaluated at the time of delivery by conditional logistic regression analysis, while controlling for known risk factors for low birth weight. Mothers of low-birth-weight infants are shorter, less educated, and married to men of lower occupational class, have fewer areas of healthy gingiva and more areas with bleeding and calculus, and gain less weight during the pregnancy. Conditional logistic regression analyses indicate that mothers with more healthy areas of gingiva (odds ratio [OR] = 0.3, 95% CI = 0.12 to 0.72) and those who are taller (OR = 0.86, 95% CI = 0.75 to 0.98) have a lower risk of giving birth to a low-birth-weight infant. The authors conclude that poor periodontal health of the mother is a potential independent risk factor for low birth weight.

In a recent case-control study, 48 case-control subjects had their gingival crevicular fluid (GCF) levels of PGE₂ and IL-1 β measured to determine whether mediator levels are related to current pregnancy outcome (104). In addition, the levels of

four periodontal pathogens were measured by using microbe-specific DNA probes. The results indicate that GCF PGE₂ levels are significantly higher in mothers of preterm low-birth-weight infants than in mothers of normal-birth-weight infants (controls) (131.4 ± 21.8 versus 62.6 ± 10.3 ng/ml [mean \pm standard error], respectively, at $P = 0.02$). Furthermore, among the primiparous mothers of preterm low-birth weight infants, there is a significant inverse association between birth weight (as well as gestational age) and GCF PGE₂ levels at $P = 0.023$. These data suggest a dose-response relationship for increased GCF PGE₂ as a marker of current periodontal disease activity and decreasing birth weight. Four organisms associated with mature plaque and progressing periodontitis, *Bacteroides forsythus*, *P. gingivalis*, *A. actinomycetemcomitans*, and *Treponema denticola*, are detected at higher levels in mothers of preterm low-birth-weight infants than in controls. These data suggest that biochemical measures of maternal periodontal status and oral microbial burden are associated with preterm birth and low birth weight.

Offenbacher et al. (107) concluded that 18.2% of preterm low-birth-weight babies may result from periodontal disease—a previously unrecognized and clinically important risk factor for preterm birth and low birth weight.

However, it should be noted that periodontal disease pathogens are necessary but not sufficient for periodontal disease expression. The role of the host's inflammatory response appears to be the critical determinant of susceptibility and severity (103). The association between periodontal disease and low birth weight may reflect the patient's altered immune-inflammatory trait that places the patient at risk for both conditions. Thus, periodontitis may be a marker for preterm delivery susceptibility as well as a potential risk factor. Indeed, the data from animal models suggest that even if periodontal disease is not the primary cause of prematurity, in a subset of patients it may serve as a contributor to the morbidity of the condition.

Diabetes Mellitus

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to an absolute or relative deficiency of insulin. It affects more than 12 million people in the United States. Diabetes mellitus is characterized by metabolic abnormalities and long-term complications involving the eyes, kidneys, nervous system, vasculature, and periodontium (39, 76). Diabetes is commonly categorized as type 1, or insulin dependent, and type 2, non-insulin dependent. The fundamental derangement in insulin-dependent diabetes is the hypoproduction of insulin due to destruction of the beta cells of the pancreas. In non-insulin-dependent diabetes, the derangement involves resistance of target tissue to insulin action (120).

Although the precise etiology is still uncertain in both main types of primary diabetes, environmental factors interact with a genetic susceptibility to determine which of those with the genetic predisposition actually develop the clinical syndrome and the timing of its onset. Environmental factors in insulin-dependent diabetes include virus, diet, immunological factors, and pancreas disease. In non-insulin-dependent diabetes, environmental factors such as lifestyle, age, pregnancy, pancreas pathology, and insulin secretion and resistance are included (36).

Severe periodontal disease often coexists with severe diabetes mellitus. Diabetes is a risk factor for severe periodontal disease. The converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received more and more attention. Recently, a new model was presented by Grossi and Genco (46), in which severe periodon-

tal disease increases the severity of diabetes mellitus and complicates metabolic control. They propose that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from LPS and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end product (AGE)-mediated cytokine response that is operative in diabetes mellitus. The combination of these two pathways, infection and AGE-mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a two-way relationship between diabetes mellitus and periodontal disease or infection.

It is well established that diabetics are more likely to develop periodontal disease than nondiabetics (112) and that the disease severity is related to the duration of diabetes (61, 138). One plausible biologic mechanism for why diabetics have more severe periodontal disease is that glucose-mediated AGE accumulation affects the migration and phagocytic activity of mononuclear and polymorphonuclear phagocytic cells, resulting in the establishment of a more pathogenic subgingival flora. The maturation and gradual transformation of the subgingival microflora into an essentially gram-negative flora will in turn constitute, via the ulcerated pocket epithelium, a chronic source of systemic challenge. This in turn triggers both an "infection-mediated" pathway of cytokine upregulation, especially with secretion of TNF- α and IL-1, and a state of insulin resistance, affecting glucose-utilizing pathways. The interaction of mononuclear phagocytes with AGE-modified proteins induces upregulation of cytokine expression and induction of oxidative stress. Thus, monocytes in diabetic individuals may be "primed" by AGE-protein binding. Periodontal infection challenge to these primed phagocytic cells may, in turn, amplify the magnitude of the macrophage response to AGE-protein, enhancing cytokine production and oxidative stress. Simultaneously, periodontal infection may induce a chronic state of insulin resistance, contributing to the cycle of hyperglycemia, nonenzymatic irreversible glycation, and AGE-protein binding and accumulation, amplifying the classical pathway of diabetic connective tissue degradation, destruction, and proliferation. Hence, the relationship between diabetes mellitus and periodontal disease or infection becomes two way. A self-feeding two-way system of catabolic response and tissue destruction ensues, resulting in more severe periodontal disease and increased difficulty in controlling blood sugar (46).

Certain metabolic end products such as glycated hemoglobin are thought to contribute to the degenerative retinal and arterial changes commonly found in diabetic subjects. The concentration of glycated hemoglobin in serum is a direct function of the time that hemoglobin is exposed to elevated glucose levels (120). A longitudinal study (128) of diabetes and periodontal disease has been carried out in the Pima tribe, an Indian population in the United States having a prevalence of non-insulin-dependent diabetes of about 50%. This is the highest reported prevalence of non-insulin-dependent diabetes in the world (68). Poor glycemia control was defined as the occurrence of glycated hemoglobin of 9% or more at follow-up. The results indicated that severe periodontitis at baseline is associated with increased risk of poor glycemic control at follow-up 2 or more years later. These findings suggest that severe periodontitis may be an important risk factor in the progression of diabetes, and control of periodontal infection is essential to achieve long-term control of diabetes mellitus. Grossi and Genco (46) reexamined the studies that addressed the effect of periodontal treatment on metabolic control of diabe-

tes mellitus (1, 16, 47, 95, 124, 132, 149). Six of these studies included type 1 patients, and two studies (16, 47) included type 2 patients. Periodontal treatment was divided into two groups, mechanical treatment only and with systemic antibiotics as an adjunct to mechanical treatment. The results show that the effect of periodontal treatment on diabetic metabolic control is dependent on the mode of therapy. When mechanical periodontal treatment alone is provided, regardless of the severity of periodontal disease or degree of diabetes control, the treatment outcome is strict improvement in periodontal status or a local effect. On the contrary, when systemic antibiotics are included with mechanical therapy, an improvement in diabetes control, measured as a reduction in glycated hemoglobin or reduction in insulin requirements, is achieved. Therefore, one may propose that control of the chronic gram-negative periodontal infection should be part of the standard treatment of the diabetic patient.

RELATIONSHIP BETWEEN ORAL INFECTION AND SYSTEMIC DISEASES AND FUTURE STUDIES

As mentioned above, a large number of publications have suggested that oral infection, especially periodontitis, are a potential contributing factor to a variety of clinically important systemic diseases. Endocarditis has been studied most extensively. It appears that dental procedures and oral infection meet currently accepted epidemiological criteria for causation of endocarditis (58, 119). However, there is still not sufficient evidence to claim a causal association between oral infection and other systemic diseases.

Epidemiological research (cross-sectional and longitudinal studies) can identify relationships but not causation. If some types of periodontal disease merely constitute an oral component of a systemic disorder or have etiologic features in common with systemic diseases, periodontal and systemic diseases might frequently occur together without having a cause-effect relationship (130).

Therefore, further research must be done before the potential for oral infections to cause damage in other sites of the body can definitely be established. Slots (130) defined the criteria for causal links between periodontal disease and systemic diseases. These criteria also indicate the directions that future research in this area should take. The prevalence and incidence of the systemic disease in question should be significantly higher in periodontitis patients than in periodontally healthy ones (retrospective research); the onset of the systemic disease should follow the onset of periodontitis (prospective research); the removal or reduction of periodontitis should decrease the incidence of the medical disease (intervention research); the microorganism(s) of the systemic disease should be the same species, biotype, serotype, and genotype as the oral microorganism(s) (research on specific etiologic agents); appropriate experimental animals with periodontitis or with inoculated microorganism should develop more systemic disease than periodontally healthy animals (animal research); and the postulated association between periodontal disease and systemic disease should be biologically feasible (research on pathogenic mechanisms).

If the criteria listed above can be satisfied, then a causal relationship between periodontal disease and systemic disease is probable. Nevertheless, so much information is accessible at the moment that it seems justified to state that good oral health is important not only to prevent oral disease but also to maintain good general health.

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